Making Gastrointestinal Endoscopy Safer

Sanjay Ramrakha MBBS FRACGP FACEM

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CERTIFICATE OF AUTHORSHIP / ORIGINALITY

I hereby certify that the work in this thesis has not been previously submitted for a degree nor has it been submitted as part of requirements for a degree, except as fully acknowledged within the text.

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Dr Sanjay Ramrakha

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ABSTRACT

Endoscopic procedures have become the 'gold standard' of diagnosis and therapy in the alimentary tract and are frequently delivered in high volume centres. Given that the generic term ***endoscopy*** is broad, in this thesis, panendoscopy will refer to *"upper gastrointestinal"* procedure and colonoscopy will refer to "*lower gastrointestinal"* procedure.

In such procedures, complications can be attributed to the bowel preparation, the procedure itself and/or the effects of the sedative/anaesthesia. This thesis reports on an anonymous postal survey of Australian practice of endoscopic procedures and identifies system issues in the delivery of sedation. In particular, there is an unacceptable morbidity and mortality rate seen in some public endoscopy units. Therefore, there is scope to improve levels of safety in gastrointestinal endoscopy.

The first half of this thesis focuses on sedation-associated cardio respiratory embarrassment, a common cause of morbidity and mortality. This thesis examines the changes in cardio- respiratory parameters associated with sedation. Expanding on this knowledge the thesis describes the development of a novel oxygenating bite-block with capacity to sample carbon dioxide. The device, when tested against conventional delivery systems in a comparative clinical study shows, superiority in monitoring of ventilation.

The second half of this thesis focuses on the complications associated with bowel preparations relating to their palatability, their purgative effect and dehydration. Effective purgation is essential to reduce the missed pathology rate. The development of a novel bowel preparation to improve safety was trialled in a comparative clinical study against three other methods. Lessons learnt from this study led to the process of further enhancement to the development to formulate a capsule bowel preparation.

Improvements in oxygen delivery, ventilation monitoring and bowel preparation described in this thesis will significantly increase the safety of gastrointestinal endoscopy

CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1 HISTORY OF ENDOSCOPY

The Greek word endoscopy means to '*look inside'* and generically involves an optical instrument being introduced into a body cavity to allow direct visualisation of any region within a body cavity or joint (Wit, 2008) (Figure 1.1). The procedure has its roots firmly planted in history, with Egyptians the first to practice endoscopy, using bamboo reeds illuminated by candles. The father of modern medicine Hippocrates was the first to use a proctoscope in 370 BC (Simpson, 2004).

It was not until 1806 that Phillip Bozzini developed the first true endoscope. The 'Lichleiter' or light conductor consisted of various examining tubes coupled with a wax candle fashioned in a special holder to provide illumination. Technological advancements, including the invention of the light bulb by Thomas Edison in 1890 and the discovery of glass fibre optics by John Logie Baird in 1928, resulted in considerable progression in the field (Willingham and Brugge, 2009). In 1957 Basil Hirschowitz revolutionised the practice of endoscopy when he developed the first fibre-optic endoscope, which was clinically used from the 1960s onwards (Hirschowitz, 1988).

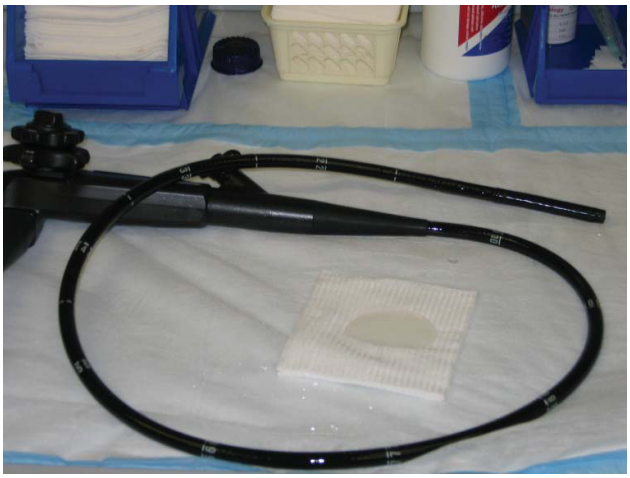


Figure 1.1 Pentax™ Gastroscope

These advances have greatly contributed to the state-of-the-art endoscopic devices available today with modern-day endoscopy using a flexible fibre optic tube with a minute television camera attached to the tip. This allows gastroenterologists to view previously inaccessible parts of the human body. With the advent of video technology, images on a colour monitor allow for superior resolution quality and increased diagnostic accuracy. The dramatic improvements in instrumentation and technique have cemented the role of endoscopy as the 'gold standard' of diagnosis and therapy in gastrointestinal disorders. Consequently, there has been a substantial increase in the volume of procedures performed (Classen, 2010). The 2006 Behavioural Risk Factor Surveillance estimates that approximately 56% of the U.S. population over the age of 50 years has had at least one lower gastrointestinal endoscopy in the 10 years (Singh et al., 2009). A National Health Statistics Report conducted on ambulatory surgery in the United States in 2006 found approximately 9.2 million endoscopic procedures performed of the lower bowel in the United States (Cullen et al., 2009). In Australia the number of colonoscopies performed during the 2005/06 period reached nearly 445,000 (21.48 colonoscopies per 1,000 people in that year) (St John, 2009).

In recent years, the increasing demand for greater volume and complexity of endoscopy has resulted in the design of purpose-specific units dedicated to gastrointestinal endoscopy. In the past, endoscopy has typically been carried out within hospital environments, frequently using existing wards and local expertise of general hospital personnel, often without the backup of anaesthetic staff. Endoscopy procedures are more likely to be performed on an outpatient basis at the hospital, in designated hospital day surgical units or day endoscopic units (Frakes, 2002) (Figure 1.2). Endoscopic suites are not always associated with an operating theatre and its available resources. As a consequence, the administration of sedation has largely evolved in an *ad hoc* manner, without clear guidelines. There is considerable variation in the administration of sedative agents and procedural monitoring in endoscopy (Burton et al., 1993). In the United States, approximately 35.8% of endoscopists consider *'day endoscopy centre'* as their primary location for performance of endoscopy (Cohen, 2006a). From the perspective of the anaesthetist, however, patient monitoring, resuscitation and availability of anaesthesia personnel, makes the operating room the ideal setting for caring for medically challenging patients.

Figure 1.2 Endoscopy room; Professor Thomas Borody at the Centre for Digestive Diseases, Five Dock, NSW, Australia

Endoscopy equipment has become more portable, which makes it possible for endoscopy cases to be conducted in various settings, to suit local system preference, which may be mutually advantageous to the endoscopist, the anaesthetist and the patient.

1.2 SAFETY ISSUES OF ENDOSCOPY

Any invasive procedure will inevitably encounter complications in spite of the highest standards of practice. Endoscopy is perceived to be a relatively safe procedure. The risks of endoscopy can be divided into three main areas: (a) those associated with the procedure itself, (b) those associated with sedation, and (c) those associated with the bowel preparation. Whilst obvious, it must be emphasized that prevention of complications in the first place is the best form of management (Green, 2006). This can be brought about by procedural system management or by development of new products aimed at reducing the risks associated with the procedure. Simple innovations can be applied in most cases to bring about significant reduction in the incidence of complications. It is also the professional responsibility of health providers to prevent avoidable risks by adhering to national standards for safe sedation such as those set down by the Australian New Zealand College of Anaesthetists (ANZCA)[i] , American Society of Anaesthesiologist (ASA)[ii], World Federation (WFSA)[iii] and the World Health Organisation (WHO)[iv].

This thesis will further expand on areas of risk associated with sedation and bowel preparation. The areas of risk directly attributable to the procedure, while falling outside the scope of this thesis is contributory to the overall safety of endoscopy and will be discussed in the following literature review for completeness.

1.2.1 Procedural Complications

1.2.1.1 Infection

Driven in part by the Acquired Immunodeficiency Disease (AIDS) epidemic, both physicians and patients have become increasingly aware of pathogens and are keenly interested in preventing their transmission. In response to the increasing prevalence of HIV infection and reports detailing transmission of infection via contaminated endoscopes (Spach et al., 1993), the Centre for Disease Control (USA) introduced recommendations for universal precautions in 1985. These recommendations specified standardised cleaning and disinfection after each patient to address risks of spread from patients harbouring currently undetected infections as well as in those with known infections (Mason, 1987).

Infectious complications during endoscopy can typically occur through the use of contaminated equipment or from the procedure itself. Endoscopes are made of fragile, heat sensitive material and therefore require routine decontamination by high-level disinfection instead of heat sterilisation. Endoscopes have multiple internal channels and valves that can serve as reservoirs for pathogenic microorganisms, which can be transmitted to subsequent patients after light or inadequate disinfection (Spach et al., 1993). Transfer of pathogens can also occur from contaminated equipment resulting from improper storage, contact with non-sterile water or via healthcare staff after disinfection procedures. The presence of spore forming pathogens can at times result in persistent contamination even with high-level sterilisation (Rey et al., 2005). Despite this, reports of pathogen transmission via contaminated endoscopes have been surprisingly uncommon in spite of the large volume of procedures performed (Spach et al., 1993, Nelson, 2003a, Muscarella, 2010).

During endoscopy, transmission of infection through cross contamination is rare in the USA, with only 35 documented cases at a rate of approximately 1 in 10 million procedures. All cases involved a breach in the accepted endoscope reprocessing technique. This purports that with observance of accepted guidelines, the risk of transmitted infection during endoscopy is greatly minimised (Nelson, 2007).

Aside from externally introduced infections, endogenous contamination can also transpire. Endogenous contamination occurs as a result of a breach of mucosa through polypectomy or biopsy collection allowing entry of a person's own intestinal micro flora into the bloodstream. Complications may lead to endocarditis, sepsis and increased mortality. The incidence of this occurring however is low for patients not at risk of endocarditis, such as those without valvular abnormalities with risks estimated at 1 in 5-10 million. For patients who are at risk of endocarditis such as those with cardiac valvular abnormality, antibiotic prophylaxis has previously been recommended (Nelson, 2003b).

A consensus statement released by the American Heart Association suggests a reduced risk of such transmission upon review of current literature. The statement concluded that only a few cases of infective endocarditis might be preventable by administration of antibiotics even in the event that prophylactic antibiotics were found to be 100% effective and administration of antibiotics solely as a prophylactic procedure for the prevention of endocarditis in gastrointestinal tract procedures was not recommended (Wilson et al., 2007)**.** Whilst important in safety consideration overall, this thesis shall not further expand on this area.

1.2.1.2 Perforation

Perforation is a serious complication of endoscopy and occurs when the bowel contents spill freely into the abdominal cavity (Green, 2006). Mechanisms leading to perforation are thought to be due to excessive mechanical pressure transmitted through the colonoscope to the anti-mesenteric border where the colon is non-adherent such as the sigmoid and the descending colon. Forced manipulations with torsion or straightening of the instrument, increased intra luminal pressure caused by excessive air insufflation and poor visibility due to inadequate bowel preparation are other important factors.

Perforation may also occur as a consequence of biopsy forceps in patients with impaired mucosal integrity although this is rare. Untreated perforations can lead to diffuse peritonitis, sepsis and death (Avgerinos et al., 2008). A survey conducted by the American Society for Gastrointestinal Endoscopy has determined the perforation rate as a complication of diagnostic endoscopy to be 0.03% with a mortality rate of 0.001% (Tham et al., 2008).

Therapeutic endoscopy, which is defined as a method of administering treatment via an endoscope, justifiably increases the risk of complications. Therapeutic procedures that involves resection or use of thermal ablation, increases the risk of perforation. On some occasions predisposing conditions such as presence of anterior cervical osteophytes, Zenker's diverticulum, oesophageal strictures, and malignancies are also known to increase the likelihood of perforation (Wolfsen et al., 2004). Rates of perforation during therapeutic endoscopy vary widely in different reports, with the rates ranging from 0.3% to 3.1% (Tham et al., 2008). Although quite uncommon, perforations of the oesophagus are associated with a relatively high mortality rate of 25% **(**Mathewson et al., 1962).

The most common and reproducible symptom related to perforation is abdominal pain with fever, pleuritic chest pain, leukocytosis, and pleural effusion as possible accompanying symptoms (Loh and Cooke, 2004). Patients presenting with equivocal signs and symptoms of a perforation can pose both a diagnostic and therapeutic dilemma. The presence of free extra luminal air in the abdominal cavity is the most common radiographic finding, observed in up to 67% of colonic perforations (Kim et al., 2009). Elevation of white blood cells and signs of abdominal distension is typically present (Loh and Cooke, 2004). Management will depend on the site of the perforation and the patient's premorbid health. In some select cases, non-operative treatment with nasogastric suction, intravenous antibiotics and parenteral hyper alimentation will be appropriate (Kremer et al., 1989). However, in most cases, surgery is used to repair the perforated colon. Although surgery is generally successful, morbidity depends on the extent of the perforation and the length of surgery required. In some cases intestinal resection is necessary (Kremer et al., 1989).

Endoscopy-related perforations while an important aspect of overall safety falls outside the scope of this thesis and will not be discussed further.

1.2.1.3 Bleeding

The average incidence of bleeding after a diagnostic colonoscopy has been reported to be 0.1% (Cappell and Abdullah, 2000). Distinctions must be made between diagnostic and therapeutic colonoscopy as the incidence of haemorrhage during therapeutic endoscopy is reported to be between 1-2%, and characteristically occurs from the site of either biopsy or polyp removal (Tham et al., 2008). It should be noted that the presence of blood in the stool after colonoscopy does not necessarily constitute a complication and haemorrhagic complication is more appropriately defined as bleeding that requires further medical attention (Kavic and Basson, 2001a). Whilst bleeding complications are uncommon, they are not rare. Individuals most at risk of bleeding complications are those with a history of clotting disorders such as thrombocytopenia and coagulopathy and/or those on anticoagulant therapy (Cappell and Abdullah, 2000). Bleeding may be immediate and evident on initial colonoscopy or delayed by several hours or even days. Immediate endoscopy induced bleeding is usually countered by intense effort during endoscopy to arrest or reduce the bleeding. Cauterisation or clipping of visible vessels or sites of active bleeding are usually performed to prevent excessive blood loss. Intensive care monitoring, transfusions, and surgery may be necessary in cases of post polypectomy haemorrhage (Sorbi et al., 2000).

Angiography and embolisation can be a useful strategy for controlling bleeds. Nevertheless, 80% of lower gastrointestinal bleed will resolve spontaneously (Sorbi et al., 2000).

Mallory-Weiss tears can also occur during endoscopy and usually as a consequence of severe retching or tearing of a hiatus hernia. Insufflation of air during the procedure can also cause breaks in the mucosal integrity and start minor spontaneous bleeding. In the majority of cases and in the absence of additional risk factors such as portal hypertension, endoscopic intervention is not usually required with extended patient observation as the primary conservative management implemented. In instances where active bleeding is observed, treatment is dependent on availability and familiarity of

intervention procedures such as argon plasma coagulation or multipolar electro coagulation (Song, 2011).

Endoscopy related bleeding while an important aspect of overall safety falls outside the scope of this thesis and will not be discussed further.

1.2.2 Complications Associated With Sedation

1.2.2.1 Definition

Sedation is defined as a state of *"dampened awareness"* where there is a reduction in response to external stimuli (Holder and Paladino, 2010). Sedation encompasses varying stages of consciousness and includes such terms as *"minimal sedation (anxiolysis), conscious (moderate) sedation, deep sedation and general anaesthesia*[i]*"* (Sedation and Non-Anesthesiologists, ASA 2002). When patients are minimally sedated, they continue to respond purposefully to verbal commands with or without light tactile stimulation and no intervention are needed to maintain a patent airway or spontaneous ventilation. When patients are moderately sedated, they cannot be roused easily but respond purposefully to repeated or painful stimulation. In deeply sedated patients ventilation may be inadequate and they may require ventilator assistance and maintenance of airway patency (Sedation and Non-Anesthesiologists, 2002, Waring et al., 2003, Faigel et al., 2002).

1.2.2.2 History of Sedation

Agents to induce sedation have been recorded in historical documents from a number of cultures including the Greeks, Romans, Incas and Chinese. The use of procedural anaesthesia in the Roman culture dates back as early as A.D 70, when Pedanius Dioscorides used natural anaesthetic agents such as opium and mandrake to relieve pain associated with procedures. Ancient medical texts of the Greeks and Romans reveal that Hippocrates, Theophrastus, Aulus Cornelius Celsus, and Pliny the Elder also discussed the use of opium and *Solanum* species. Later in 13th century Italian, Theodoric Borgognoni used mixtures combined with opiates to induce unconsciousness, and was

the anaesthesia of choice until the 19th century (Diz et al., 2002). The first recorded use of anaesthesia dates back to the ancient Incas where shamans used masticated coca leaves and sputum mixture as a numbing agent for drilling skulls, a common procedure implemented for sick patients to allow the release of bad spirits (Mendoza, 2003). Medical procedures in China used acupuncture and extreme cold methods to cause numbing of the nerves of certain areas of the body. Alcohol was also frequently used throughout history to induce apathy and decrease sensation of pain. However the amounts administered were sub-therapeutic and failed to induce true analgesia. Alcohol's vasodilatory properties were also unknown at that time (Jacob et al., 2010).

Anaesthetic agents did not experience further progression until the eighteenth century when a British chemist, Humphrey Davy first experimented with nitrous oxide (laughing gas) in 1795. However, the first recorded clinical practice use of nitrous oxide use was not achieved until 1845 by Horace Wells, a dentist, who performed the first painless tooth extraction witnessing the benefit at one of Davy's demonstrations at Massachusetts General Hospital (Diz et al., 2002).

The first medical operation to successfully utilise a modern chemical anaesthetic, diethyl ether was on March 30th, 1842, when Crawford Williamson Long, removed neck cysts after convincing the patient James Venable to inhale diethyl ether for pain relief. Boston dentist, William T. G. Morton became the first to practice painless surgery using an ether anaesthetic. At the Massachusetts General Hospital in 1846, Surgeon John Collins Warren removed a tumour from the neck of Edward Gilbert Abbott, after Morton had induced Diethyl Ether anaesthesia. Physician and writer Oliver Wendell Holmes penned a letter to Morton after the procedure proposing that the agents which produce these painless medical procedures be called *"anaesthetics"* from the Greek words meaning *an* (an)- *not*, or *without*, and aesthetos (aesqetos) meaning *to feel,* or *perceive* (Diz et al., 2002). Ether anaesthesia was used in the same year in Launceston, Australia (Hodge, 1989). Ether worked well, however it was soon replaced by chloroform in 1847, as it was seen to reduce the incidence of emesis and risk of spontaneous combustion (Jacob et al., 2010).

Karl Koller first used cocaine first isolated in 1859 from the coca leaves in 1884, at the suggestion of Sigmund Freud, in ophthalmic surgery (Fishbein, 1976). Following this,

German surgeon August Bier (1861–1949) used cocaine for intrathecal anaesthesia in 1898. A number of newer local anaesthetic agents, many of them derivatives of cocaine, were synthesized in the early 20th century, including procaine in 1905, Eucaine in 1900, Stovaine in 1904, and lignocaine in 1943 (Bett, 1956). Lignocaine is the most used local anaesthetic agent today due to its affordability, predictability of action and lack of allergic reaction (Brocmeyer DM, 1995).

During the next hundred years, anaesthesia became standard practice for almost all surgical procedures with agents directed in providing general anaesthesia and local anaesthesia utilising various techniques such as nerve, spinal and epidural blocks.

Despite the availability of anaesthetic agents and their frequent use in most surgical settings, early gastrointestinal endoscopy had largely been performed without the administration of conscious sedation. It is still not uncommon for diagnostic examination to occur without sedation throughout much of the world. In many parts of Europe, the United States of America and Australia, conscious sedation for upper endoscopy has become the standard of practice (Shaker, 1999). Patient and endoscopist acceptance of unsedated endoscopy vary widely with investigators reporting difficulty when recruiting patients into trials using unsedated endoscopy (Madan and Minocha, 2004).

The increased demand for endoscopic procedures has motivated endoscopists to focus on strategies designed to increase the efficiency and throughput in the endoscopy unit whilst maximising patient satisfaction (Cohen and Benson, 2009). Providing sedation has been a most effective strategy employed with most patients preferring the use of sedation and analgesia during colonoscopy (Subramanian et al., 2005). The use of sedatives has also been found to improve the performance of colonoscopy, enhancing completion and colonic polyp detection rates (Radaelli et al., 2008).

The term anaesthetist refers to any individual who is responsible for administering anaesthesia and who monitors the effect of that anaesthetic agent. However in the United Kingdom, Australia, New Zealand and Japan the administration of anaesthetic agents is primarily by physicians (McAuliffe and Henry, 2000). In the United States of America, physicians in solo practice provide 35% of procedural anaesthesia

administered. Approximately 55% is provided by *"anaesthesia care teams"* led by an anaesthesiologist with other qualified anaesthesiology trained staff, with Certified Registered Nurse Anaesthetists (CRNA) and anaesthesiologist assistants medically directed by anaesthesiologists accounting for approximately 10% in solo practice. According to the American Association of Nurse Anaesthetists, the 39,000 CRNAs in the USA administer approximately 30 million anaesthetics each year, equating to about two thirds of the USA total.[v] Nurse anaesthetists also administer anaesthesia in 109 nations (McAuliffe and Henry, 2000).

Both physician and patient satisfaction drive the use of sedation, with patient tolerance of the procedure crucial for not only the successful completion of a safe and thorough examination but also compliance with subsequent follow-up procedures (Van der Linden, 2010). Consequently, ensuring patient's clinical stability and delivering adequate sedation during endoscopic procedures through appropriate monitoring has become fundamental over the last decade.

The counter argument is that in patients undergoing colonoscopy transient decreases in oxygen saturation or systolic blood pressure occur commonly and while statistically significant in clinical studies, have little significance in clinical practice (Yilmaz et al., 2002). It is also argued that the initial problems with earlier sedative agents were responsible for profound over-sedation, have now been corrected given greater experience with such medications (Jacob et al., 2010). However other literature suggests that safety may still be an issue (Hankinks, 2001).

Patients under conscious sedation must have physiological monitoring to ensure safety. The Australia New Zealand College of Anaesthetists (ANZCA) have set minimum monitoring guidelines[vi] for conscious sedation during endoscopy which includes the monitoring of heart rate, oxygen saturation, blood pressure, and inspired and expired concentrations for oxygen and carbon dioxide. In spite of these recommendations and the availability of monitoring, cardiopulmonary complications continue to be responsible for the majority of morbidity and mortality associated with upper gastrointestinal endoscopy (Scheffer, 2004).

Benefits of the administration of sedation agents prior to endoscopy include the ability to complete the examination uninterrupted, an increase in patient and gastroenterologist satisfaction throughout the procedure and the willingness of the patient to undergo the procedure again in the future (Ristikankare M. H. J., 2004). However, these benefits are not without risks, with ventilatory compromise of primary concern.

Whilst variance in clinical practice standards occurs throughout the world, a general broad consensus exists with regards to sedation and its implementation during endoscopy. According to the Athens International Position Statement created from a consolidation of evidence based literature, expert opinion and consensus views; firstly, sedation has been shown to improve patient tolerance and compliance for endoscopy; secondly, the process of informed consent should take place between the endoscopist and patient before every endoscopic procedure and where possible, the option of an examination without sedation should be offered; thirdly, diligent observation of vital signs concurrent to monitoring of level of consciousness and pain/discomfort should be performed routinely; and lastly, *"endoscopists and nurses with appropriate training can safely and effectively administer propofol to low risk patients undergoing endoscopic procedures"* (Cohen et al., 2010).

In Australia, a tripartite working party involving ANZCA, Gastroenterological society of Australia and the Royal Australasian College of Surgeons promulgated the PS9 *"Guidelines on Sedation and/or Analgesia for Diagnostic and Interventional Medical or Surgical Procedure"*[vii] which allowed non-anaesthetists to administer sedation if an anaesthetist was unavailable if appropriate training was first undertake. This, however, is mainly a New South Wales based initiative for physicians who have not had previous airway training in a critical care/anaesthetic setting. It has four parts which includes a problem based learning/simulation course followed by observation of procedures undertaken by anaesthetists or experienced non anaesthetist, then a period of practice under supervision and finally assessment and approval[viiia] This is currently being developed and as yet there is insufficient data to determine its efficacy.

1.2.2.3 Sedation agents

Chemical Agents used to induce sedation are many and varied. They can be classed into groups based on their mode of action; traditional agents (benzodiazepine and narcotics), ketamine and propofol.

Traditional Agents

Medications referred to as traditional sedatives include drugs in the benzodiazepines class specifically diazepam or midazolam used alone or in combination with a narcotic (morphine, pethidine, fentanyl, remifentanil or alfentanyl).

Benzodiazepines

The mainstay of initial sedative agents in endoscopic practice has been the benzodiazepine group. The benzodiazepines produce significant sedation and amnesia. Midazolam, a shorter acting benzodiazepine with a greater potency but lower toxicity has largely replaced the longer acting, more astringent agent diazepam for pre-operative sedation (Stoelting and Tjeerdema, 2000). Midazolam is a lipophilic inhibitor of the gamma-amino butyric acid (GABA) with an onset in the intravenous form of 3-5 minutes, which decreases to 1.5 minutes with the addition of a narcotic agent. It has a half-life of 1.4-2.4 hours, undergoes hepatic metabolism via the CYP3A mechanism and is excreted in its conjugated forms in urine. Thus renal function, age and whether the patient is pregnant or lactating are of importance when considering use of this sedative agent. Midazolam is classed a Category C agent in pregnancy *("drugs which, owing to their pharmaceutical effects, have caused or may be suspected of causing harmful effects or neonate without causing malformation"*(MIMS, 2011). Breast milk excretion occurs in minute quantities, not enough to cause sedation in infants. Over-sedation with midazolam can be reversed with administration of flumenizil, a competitive inhibitor of $GABA_A$ in divided dosages of 200 mcg every 1-2 minute up to a total of 5mg. However caution is advised due to its short duration of action and association with seizures especially in the presence of a concurrent tricyclic antidepressant or when chronic dependency of benzodiazepine is an issue as midazolam can also prevent seizures (Hobbs et al., 1996).

The administration of midazolam must be carefully monitored in the presence of certain concurrent medications as these medications can affect midazolam metabolism. Some anti HIV drugs, macrolide antibiotics as well as other drugs such as verapamil, carbamazepines, phenytoin and natural remedies such as St. John's Wort and Echinacea can inhibit midazolam metabolism via the CYP3A mechanism leading to a prolonged or reduced action (Hobbs et al., 1996).

Narcotics

Older narcotic agents, while good for analgesia, generally have long duration of action. Opioids produce analgesia without generating amnesia, but can blunt airway reflex. Coughing and laryngospasm can cause significant respiratory depression (Fisher et al., 1991). Morphine is associated with histamine release although this does not preclude its use (Rosow et al., 1982). Synthetic agents used included pethidine and papaveretum however; newer agents such as fentanyl, alfentanil, sufentanil, and ramifentanil have largely replaced these. Because of rapid half-life and negligible histamine release potential, fentanyl with its relative hemodynamic stability and affordability, is the most popular agent in this group. Due to its high potency sufentinil can be difficult to titrate and can produce excessive sedation and respiratory depression. Moerman (2003) reported on the efficacy of a sole narcotic agent (remifentanil) in reduction of pain during endoscopy procedures however also advised caution given the frequency of hypoventilation observed with remifentanil (Moerman et al., 2003).

Ketamine

Ketamine is an interesting drug that has been widely used as a sedative agent in developing countries due to its ease of use and affordability. It is a dissociative anesthetic agent that causes a cataleptic state and exhibits potent analgesic and amnesic properties. This agent has cardiovascular stability, allowing ongoing ventilation as well as maintaining protective reflex of the airway (Reeves JG, 2005). It acts as an antagonist at the glutamate receptor stimulated by the agonist *N*-methyl-D-aspartate (NMDA) (Brocmeyer DM, 1995, Friesen RH, 1994). Ketamine exerts its sedative effects through a dissociation of the thalamocortical and limbic systems thereby preventing the central nervous system from receiving signals from external stimuli resulting in sensory deprivation state. This phenomenon does not appear to be dose-dependent and is observed at a dosing threshold of approximately 1.0 to 1.5mg/kg when

delivered intravenously or 3 to 5 mg/kg intramuscularly (Friesen RH, 1994). At a lower dose ketamine exhibits analgesia and disorientation. Ketamine does not augment or deepen sedation once the dissociative threshold is reached therefore ketamine-related respiratory complications is rare.

A re-emergence phenomenon has been described in patients recovering from ketamine sedation. Midazolam is not routinely required but may be titrated intravenously (0.05mg/kg) if an emergence reaction occurs (White PF, 1982). Laryngospasm associated with ketamine administration is relatively rare and transient (0.3%) and responds quickly to assisted ventilation and oxygen. Risks of laryngospasm increase upon stimulation of the upper oropharynx such as when commencing panendoscopy. Ketamine's inhibition of catecholamine reuptake results in a sympathomimetic effect by an increase in blood pressure and heart rate and therefore myocardial oxygen consumption. The data is not conclusively available to confirm whether there is increased coronary perfusion in parallel to the increase in oxygen demand in sedated patients (Green et al., 2011)**.**

Ketamine however can be a useful adjunct in patients who are difficult to sedate or who may have allergy to or adverse reactions to other sedative agents (Varadarajulu S, 2007).

Propofol

Propofol, (2, 6-di-isopropylphenol) typically used for general anaesthesia was initially introduced in 1989 and since has been used widely in critical care units and emergency departments as a primary sedation agent. In recent years Propofol has also been employed as an alternative sedative in endoscopy suites (Faulx et al., 2005)**.** A common side effect is pain upon injection which can occur in approximately a third of all patients (Tan CH, 1998) and may be countered by various strategies including use of a large vein, pre-treating with opioids, lignocaine or ketamine or warming or diluting the propofol solution (Scott RP, 1988). Additionally, hypotension can occur which responds to volume and vasopressors. Allergy to soya or egg products is a contra-indication to its use. Propofol produces moderate levels of sedation in sub-hypnotic doses (an average of 4mg/kg/hour) while it's comparatively narrow therapeutic window allow for relative ease of movement between levels of moderate sedation into deep

sedation or general anaesthesia (Mackenzie & Grant, 1987). This has resulted in a restrictive prescription of propofol to personnel trained in general anaesthesia administration and those with a proficiency in administering rescue procedures against unintended levels of deep sedation.[viii] This practice is consistent with the Joint Commission for the Accreditation of Health Care Organization's current approach to sedation. Their standards state that practitioners providing sedation should be able to rescue patients who slip into a *'deeper-than-desired'* level of sedation. Specifically, persons providing moderate sedation should be qualified to provide a rescue procedure for patients with unintended deep sedation and be competent to manage a compromised airway and provide adequate oxygenation and ventilation.[viiia]

A study comparing administration of propofol by anaesthesiologists to that by non-anaesthesiologists for sedation during colonoscopy reported no difference in procedure time or patient satisfaction, (Clarke et al., 2002). It has also been shown that propofol exhibits antiemetic activity, the mechanism for which is unclear (DeBalli, 2003). The motivation for the use of propofol as an adjunct to endoscopy has largely stemmed from an increased demand for endoscopic procedures and increased efficiency in the pre and post procedure patient care setting (Dinis-Ribeiro and Vargo, 2010, Fong et al., 2007). The advantages and disadvantages of propofol have been debated in several countries. A review on endoscopy unit developed training programs, for nurse-administered propofol for endoscopic procedures, determined safe administration of propofol by nurses and endoscopists (Rex, 2005). Another study found nurse-administered propofol in routine endoscopy cases to be safe and yielded rapid patient recovery post procedure (Walker et al., 2003). Previous trials comparing propofol with traditional agents for sedation during colonoscopy, reported no statistically significant variances in adverse events in a meta-analysis. This may have been partially attributed to inadequate sample sizes, as the reported incidence of adverse incidence is rare when considering the volume of procedures. Furthermore, whilst individual trials demonstrated earlier recovery time with propofol, the scale of positive benefit varied in the same trials (Singh et al., 2008).

Global experience reported with gastroenterologist-directed administration of propofol has now exceeded 200,000 without any mortality (Clarke et al., 2002, Rex et al., 2005). This, alongside an increased understanding of propofol dosages and titration for

moderate sedation has driven several professional medical societies to question the medical necessity of its restrictive use (Byrne and Baillie, 2005). It is prudent to state that with different competing interest, its use has remained controversial.

A consensus-based guideline proposed by the European Society of Gastroenterology (ESGE), European Society of Gastroenterology and Endoscopy Nurse and Associates (ESGENA) and European Society of Anaesthesiologists (ESA) included a meta-analysis on previous trials investigating the safety of propofol compared with traditional agents in colonoscopy procedures. The guideline reported an overall benefit for both patients and gastroenterologists when propofol-based sedation agents were utilised resulting in a decrease time to sedation, decrease recovery time and higher patient satisfaction post procedure. Adverse events associated with propofol-based sedatives were also found to be comparable to adverse events observed with the use of traditional sedation (Dumonceau et al., 2010).

Propofol has also been the preferred sedative agent for Patient Controlled Sedation (PCS), a novel means of administration of sedation, which involves a patient-operated machine allowing for intravenous self-administration of pre-determined doses of medication with a lock out, period to reduce the chance of over dosage. A Cochrane review on 20 studies found shorter recovery and discharge times with PCS using propofol and suggested higher patient satisfaction when propofol was used as a single agent or when used in combination with another sedation agent. The review found no significant difference in procedure time, caecal intubation rate or complications. However, whilst there was an overall higher patient satisfaction with PCS using propofol, pain control was superior with the use of traditional agents (Singh, 2008).

The advent of newer sedation agents and delivery options have misguided notion of *"safe"* agents versus *"unsafe"* agents. In trying to determine if an agent such as propofol falls into either category detracts from addressing system issues in particular *"safe"* versus *"unsafe"* practices.

The cardiopulmonary and hemodynamic changes associated with sedation and upper endoscopy shall be explored in detail in Chapter three.

1.2.2.4 Over-sedation

Hypoxemia occurs when the oxygen saturation in the arterial blood is less than 90%, whereas hypoxia is a pathological term for inadequate oxygen supply (Dark et al., 1990). Over sedation can occur in either *'deep sedation'* or general anaesthesia, with the patient frequently requiring an amount of time on mechanical ventilation (Rowe and Fletcher, 2008). The degree of depression of consciousness has been directly correlated with the percentage of benzodiazepines or narcotic receptor occupancy in the central nervous system (Bell, 1990b). Verbal and physical stimulation is usually implemented for patients who are too heavily sedated. Patients unresponsive to initial stimulation may be adminstered intravenous antagonists such as flumazenil and/or naloxone, however the reversal effects of these are generally shorter than the sedation effects and extended monitoring is recommended to recognise and prevent recurrence of deep sedation (Lightdale, 2010). Airway obstruction, aspiration of stomach content, hypoventilation and hypercarbia can result in respiratory depression, hypoxia and eventual cardio respiratory arrest (Kavic and Basson, 2001b)**.** Over sedation not only affects the safety of the patient but is associated in greater healthcare costs resulting in increased drug costs, and slower recovery time following the procedure (Devlin, 2008).

While the oft-used reason for restricting propofol use to anaesthetists is the ease in achieving deeper sedation and general anaesthesia. However this has not been supported by Devlin et al. who reported an increased incidence of over sedation with administration of benzodiazepines compared with administration of propofol (Devlin, 2008).

1.2.2.5 Paradoxical Reactions

Typically sedative medications are employed to produce a state of relaxation. However, rarely, patients may experience *"paradoxical"* behavioural reactions, characterized by combativeness, agitation, talkativeness, disorientation, and tachycardia. This occurs with the benzodiazepine group of drugs in particular midazolam and diazepam and is more common in children (Massanari et al., 1997, Mancuso et al., 2004)**.** Cerebral hypoxia or insufficient sedation may mimic paradoxical reactions, however use of pulse

oximetry can aid in the distinction of these two events (Jacob et al., 2010). Early recognition of paradoxical response is imperative for proper treatment. Additional doses of benzodiazepines and narcotics in the advent of a paradoxical reaction may exacerbate the effects, however administration of a benzodiazepine antagonist such as flumazenil, has been shown to be effective in managing these reactions with minimum side effects. Dispensation of droperidol in some cases, may provide resolution of a paradoxical reaction, however propofol may be frequently administered to allow increased control in patient management (Mancuso et al., 2004).

1.2.2.6 Allergic Reactions

Pre-sedation medication assessment also includes a comprehensive evaluation of the patient's allergy history to medications.[viiib] It is important not to confuse an increased sensitivity or side effect of a drug with that of a true allergy. Fortunately, true allergy reactions are usually transient such as an urticarial skin rash or symptoms such as nausea and vomiting and is rarely life threatening. When a life threatening anaphylaxis event does occur it simulates an acute cardiac, pulmonary and metabolic crisis and requires urgent acute critical care (Haupt 2000). Although rare, severe allergies can occur during anaesthesia. Anaphylaxis is a severe, rapid onset manifestation of an allergic reaction characterised by bronchospasms, acute onset respiratory distress and shock. Asphyxiation from airway oedema, angioedema and urticarial rash is common and cardiovascular effects of tachycardia and hypotension can occur. An anaphylactic reaction typically affects one patient in every 5,000 to 25,000 and carries a mortality of 3.4% (Sreevastava and Tarneja, 2003).

The history of drug allergy may be elicited from patient recollection and review of their previous chart, however close observation of all patients following administration of any medication is the most prudent course of action. A pre-sedation assessment of the patient with multiple allergies or documentation of a true anaphylactic reaction requires meticulous preparation and planning before administration of sedation. The initial step in the prevention of an allergic reaction includes identification of any allergen. When antibiotics, local anaesthetics, sedatives, hypnotics and analgesics have been combined and administered it may be difficult to deduce which was the inciting medication. A true

IgE-mediated allergy to narcotics is rare (Fisher et al., 1991). In the case of this rare phenomenon, a non-steroidal analgesic may offer the sedationist an alternative analgesia (Fisher et al., 1991). Anaphylaxis during sedation presents in a similar way but three features can complicate the picture. Firstly, the sedated patient cannot verbally communicate early warning symptoms such as breathlessness or light-headedness. Secondly, a typical general anaesthetic may consist of a combination of drugs making it difficult to ascertain which drug is responsible for the reaction. Thirdly, other potential causes may account for an acute hypotensive episode or advent of upper airway obstruction. A diagnosis of anaphylaxis is therefore not always easy to establish (Fisher et al., 1991). Treatment typically for both allergic and anaphylactic reaction includes the discontinuation of suspected allergen, parenteral administration of adrenaline, airway control, intravenous fluids resuscitation, anti-histamine blockade and steroids to reduce delayed histamine release.

1.2.2.7 Local Reactions

Intravenous administration of sedatives and analgesics is associated with a risk of local skin reactions and is observed in 2-37% of patients. Shafer reports immediate pain during the injection as a primary symptom, as well as thrombophlebitis with thrombosis occurring after the procedure (Shafer, 1998). The concentration and solubility characteristic of a drug largely impacts its likelihood of causing phlebitis. The risk appears to be lower with midazolam, a water-soluble drug. It has fewer local complications reported than diazepam, which has a predilection for developing phlebitis (Brouillette et al., 1989). Several precautions can be taken to reduce the risk of local injection reactions. These include slow infusion of sedation agents, careful placement of intravenous catheters to prevent leakage into the surrounding tissue and the selection of relatively large veins to administer the sedation. Pain upon injection of propofol may be lessened with the use of lignocaine, ketamine or simply using a larger more proximal vein (Canbay et al., 2008).

1.2.2.8 Monitoring

Monitoring procedures have evolved concurrently over the course of the history of sedation largely to augment the efficiency of clinical signs. In endoscopy practices standard monitoring procedures consist of pulse oximetry for observation of variance in oxygen and capnography to monitor ventilation.

Pulse Oximetry

Pulse oximetry involves the use of a photo detector that measures the amount of arterial oxygen via lights of two varying wavelengths (red light (660nm) and infrared (940nm)) emitted sequentially commonly through the patient's digit. Variance in the ratio of red light and infrared light absorbance is directly correlated with the percentage of oxygen present in pulsating arterial blood. False low readings occur with hypo-perfusion, reduced temperature, vasopressor agents, incorrect sensor application, highly calloused skin and movement (such as shivering). Methemoglobinemia characterised by unusually high concentrations of methemoglobins in the blood will also give falsely low oxygen saturation readings typically 85%. False high readings occur in the presence of carboxy hemoglobin (Mardirossian and Schneider, 1992).

The ease of use of pulse oximetry and its non-invasive advantages has resulted in its widespread acceptance in the clinical setting. In an earlier randomised trial, hypoxia detection increased twenty times in the pulse oximetry group although mortality benefit did not reach significance (Moller et al., 1993a)**.** A review conducted by the World Health Organisation (WHO) observed a significant decline in anaesthesia associated deaths during widespread adoption and application of monitoring standards during the 1980s. This has resulted in a WHO driven initiative to ensure that oximetry is mandatory for elective sedation.[ix] Indeed an independent review by Gibbs (2005) reported a significant decrease in anaesthesia mortalities over a twenty-year period after the advent of guidelines reporting a mortality rate of approximately 1 in 50,000 cases (Gibbs and Rodoreda, 2005). Lienhart (2004) also reported a ten-fold decline in anaesthesia-associated mortality since the 1980s. In the same period, there was a two-fold increase in anaesthetic procedures including an increase in the number of

procedures in patients considered high-risk. The implementation of standards and guidelines attributed the improvement in safety (Lienhart et al., 2004).

Capnography

Capnography was introduced to clinical practice by Smalhout and Kalenda in 1975, and involves the sampling of expired air to determine the partial pressure of carbon dioxide (CO_2) (Smalhout B, 1975). It has become an integral part of monitoring in anaesthesia, helping to provide a swift differential diagnosis of hypoxia before irreversible brain damage can occur (McCarter et al., 2008). The operating principle of capnography involves expired CO_2 being collected into sampling ports while a beam of infra-red light is passed across the gas sample to a photo detector. The presence of carbon dioxide in the gas causes a reduction in the amount of light falling on the sensor, which then changes the voltage in a circuit. Capnography measures the concentration of CO_2 continuously through an infrared spectrograph and displays end tidal CO_2, respiratory rate and a time-based waveform called a capnogram. Infrared spectroscopy relies on the property of selective proportional absorption of light of a wavelength emitted by a concentration of carbon dioxide. The concentration of CO_2 in the sample is directly correlated to the reduction of infrared levels detected (Nagler and Krauss, 2008). Normal capnogram assures the presence of effective ventilation (Szaflarski NL, 1991). Integrated nasal cannula for collecting CO_2 samples and oxygen delivery are available and oxygen delivery usually occurs close to the CO_2 sampling port. The 2009 ASA statement on respiratory monitoring during endoscopy states;*"Monitoring for exhaled carbon dioxide should be considered during endoscopic procedures in which sedation is provided with propofol alone or in combination with opioids and/or benzodiazepines, and especially during these procedures on the upper gastrointestinal tract.* [x] *"*

Capnography thus provides monitoring of the depth of ventilation, and therefore the overall quality of respiration. It is simple, non-invasive and provides the earliest warning of respiratory depression. Capnography is especially advantageous in early detection of abnormalities in ventilation, which are typically the first sign for most anaesthetic-related airway and respiratory adverse events. Oxygen desaturation frequently is the last manifestation of a respiratory adverse event particularly if supplemental oxygen is administered concurrently (Green and Pershad, 2010).

In infants undergoing a gastroenterological procedure a decrease in hypoxia by 13% was achieved with the use of capnography (hypoxia defined as oxygen saturation <95% for >5 sec) (Lightdale et al., 2006). In adults using a more liberal definition of hypoxia (i.e. oxygen saturation <90% for greater than 15 sec) there was a 23% decrease in the incidence of hypoxia. If the definition was extended to 85% then there was a 16% decrease in the incidence of hypoxia (Qadeer et al., 2009). Examining the use of capnography in emergency department procedural sedation showed a decrease in hypoxia with end tidal CO_2 (ETCO2) monitoring suggesting that this form of monitoring may improve safety (Deitch K., 2008).

In contrast, a review conducted by Webb et al (1993) on reported anaesthetic *incidents* in Australia and New Zealand stated the benefits of capnography were less compelling than those of pulse oximetry. In a review of 4,000 *'incidents'* in Australia and New Zealand, pulse oximetry detected adverse events more frequently. With respect to monitoring, oximetry alone would have detected 82% of the relevant incidents with 60% prior to organ damage whereas capnography alone would have detected 55% and 43%, respectively (Webb et al., 1993).

The early warning also can cause spurious warnings and up to 27% false positive were noted in the study by Deitch in which 37/64 developed capnographic evidence of respiratory depression but 10 of these resolved spontaneously without hypoxia (Deitch et al., 2008). Other studies report artefacts and false positive readings, caused by patient movement, nasal cannula displacement, or patient crying. The latter can be a particular problem in uncooperative children. In Lightdale's study all of the 163 children, in their study, exhibited loss of waveform at some point during their procedures mostly (96/163) attributed to patient verbalisation. There is however confusion from the current evidence of practical implications of these *"nuisance"* alarms (Lightdale et al., 2006). Similarly in the Emergency Department (ED) study of adult patients undergoing sedation, 27% of capnographic abnormalities did not lead to hypoxia and were thus falsely positive. However, this may underestimate the actual incidence of false alarms because the authors had to exclude an additional 12% (Deitch et al., 2008). Certainly there is scope to improve on detection to reduce nuisance alarms. This will be discussed in Chapter 4.

1.2.2.9 Aspiration

Aspiration is the regurgitation of stomach content up the oesophagus, and in the setting of loss of protective reflexes, into the upper airway then into the pulmonary space. The consequences of pulmonary aspiration of gastric contents can include pneumonia, adult respiratory distress syndrome, and cardiopulmonary arrest (Messahel and Al-Qahtani, 2009). Aspiration of gastric contents can carry a high-risk for mortality, with a survey in the United Kingdom reporting 5 deaths among 16 cases of inhalation of gastric contents during endoscopy (Colin-Jones et al.,1978). Aspiration is eminent when protective airway reflexes are blunted by excessive sedation and when significant amounts of fluid or food are still in the stomach, particularly in the setting of an emergency such as acute upper gastrointestinal bleeding (Messahel and Al-Qahtani, 2009). In a prospective study, 20% of patients undergoing endoscopy for acute upper gastrointestinal bleeding developed clinically apparent aspiration pneumonia (Farrell and Friedman, 2000). In a study on rhesus monkeys in 1974 critical values of gastric contents was extrapolated for an adult human as a pH value of < 2.5 and volume of > 0.4 ml/kg (Roberts and Shirley, 1974). Others have questioned the accuracy of these values in humans (Raidoo et al., 1990, James et al., 1984). The reason for fasting before general anaesthesia is to reduce the volume and acidity of stomach contents during surgery, to reduce the risk of regurgitation/aspiration. The American Society of Anaesthesiologists recommends that adults *"stop intake of solids for at least six hours, and clear fluids for two hours or more, prior to induction of anaesthesia"* (ASA 1999). The Canadian Anaesthetists' Society recommends a total fast of no less than five hours and suggests that policies be constructed within individual departments (Goresky and Maltby, 1990). The Norwegian clinical guidelines (NNCG 1993) also suggest a fast from solids of six hours and from clear fluids up to two hours before induction of anaesthesia (Splinter and Schreiner, 1999).

A Cochrane meta- analysis has questioned some of these assumptions based on a pooled study of 38 randomised controlled comparisons. These trials also looked indirect measures of patient safety i.e. intra-operative gastric volume and pH rather than morbidity. However they also showed that participants given fluids two to three hours preoperatively were not at increased risk of aspiration/regurgitation (as measured by their gastric volume and pH) than participants who had followed a standard *"nil by*

mouth from midnight" fast. In fact a drink during the preoperative period was noted to be beneficial in terms of patients' experience of thirst. In addition, there was no indication that participants given fluids up to 90 minutes before induction of anaesthesia were at increased risk of regurgitation/aspiration (Brady et al., 2003)**.** However most were of small numbers and comprised of *'healthy'* adult participants who were not considered to be at increased risk of regurgitation or aspiration during anaesthesia. One would assume that most patients undergoing gastrointestinal procedures, apart from those having colon cancer surveillance would fall into this group. Certainly patients who are pregnant and elderly and those on certain medications such as tricyclic antidepressants and anticholinergic agents may have delayed rates of gastric emptying. The issues to consider in relation to safe and optimum preoperative fasting time therefore are complex.

Based on clinical experience and on the available literature, the following precautions can be taken to avoid aspiration during upper endoscopy:

- A vigilant sedationist should be prepared to suction the oropharynx with a catheter.
- Excessive insufflation should be avoided if a full stomach is encountered and the procedure should be terminated unless essential.
- Sedation and topical anaesthetic sprays should be kept to a minimum.

1.2.2.10 Cardiac Complications

Clinically significant cardiac events such as myocardial ischemia and acute myocardial infarction may occur during endoscopic procedures, particularly in those patients with a history of cardiopulmonary disease. However, few prospective data regarding the incidence of clinically significant arrhythmias during gastrointestinal endoscopy exists (Kumura, 1975). Patient anxiety can cause increase in sympathetic tone can also cause an elevation in blood pressure and changes in cardiac rhythm, particularly tachyarrhythmia and vasovagal reactions. Cardiac ischemia may be a complication in patients with pre-existing cardiovascular disease in the context of hypoxia (Schenck J., 2000, Tham et al., 2008). Although the role of hypoxia in producing cardiac arrhythmias and ischemia is well accepted, other factors play an important role.

Tachycardia is frequent, and may be extreme, with heart rates reported up to 200 beats per minute during stressful, prolonged endoscopy procedures (Ristikankare M., 2006). Tachycardia occurs mostly during upper rather than lower gastrointestinal endoscopic procedures and more frequently in elderly patients and those with cardiac disease. Significant changes in blood pressure have also been reported during gastrointestinal endoscopy. This can put enormous strain on the cardiovascular system, particularly in frail and elderly patients often undergoing these procedures (Gu Q., 2009, Borgaonkar MR., 2012).

Atropine premedication and antispasmodic agents may also cause tachycardia (Marshall JB., 1999). On the other hand, two studies have shown that opioid premedication attenuates endoscopy-induced increase in pulse and blood pressure, suggesting that optimal safety to the patient is a balance between preventing hypoxia (which can ameliorated with supplemental oxygen) and preventing endoscopy-induced tachycardia and hypertension (Tham et al., 2009).

1.2.2.11 Hemodynamic Complications

Hemodynamic disturbances such as vasovagal reactions and fluctuations in blood pressure and pulse can occur during endoscopy. Vasovagal reactions commonly present clinically with perspiration and bradycardia and typically occur as a result of painful stimuli during colonoscopy. Although atropine is widely used to treat vasovagal reactions, few data support its routine use to prevent such events. Hypotension may result from vasodepressor effects of opioids, benzodiazepines, and other medications given during endoscopy (Herman et al., 1993, Heuss 2003).

1.2.2.12 Respiration

Respiratory depression is most often defined as a reduced respiratory rate to below eight breaths per minute. Published data shows that arterial oxygen desaturation commonly occurs during gastrointestinal endoscopy. Up to 40% of patients undergoing upper endoscopy and 50% of patients undergoing colonoscopy experience respiratory depression (Bell, 1990a). Intravenous benzodiazepines, as a result of occupying

brainstem benzodiazepine receptor sites, can reduce respiratory drive. Intravenous opioids can similarly cause respiratory depression with resulting falls in tidal volume and respiratory rate. The sedative effects of these drugs used in combination are synergistic, so additional precaution is required (Murray AW., 1990).

The physical presence of the endoscope is also known to cause minor degrees of hypoxia, most often as a result of coughing or aspiration, or by a reflex mechanism. Splinting or looping during colonoscopy may cause transient desaturation. Endoscopy-induced oxygen desaturation is generally transient or minor however severe and prolonged desaturation, in association with drug-induced respiratory depression, can culminate in respiratory arrest (Tham et al., 2008).

Substantial data suggest that hypoxia during endoscopy may result in tachycardia, electrocardiographic ST-segment elevation or depression on cardiac monitoring, indicative of ischemia and both atrial and ventricular arrhythmias. Hypoxia is thought to cause most cardiac arrhythmias, which occur during endoscopy (Fisher et al., 2006). A few studies suggest that patient variables such as increased age, obesity, or pulmonary disease increase the likelihood of desaturation. Most studies, however, have shown that it is difficult to predict which patients will become hypoxic (Meiklejohn et al., 1987).

Although cardio respiratory complications are feared, sedative drugs by their usual action will cause levels of hypoxia, apnoea and respiratory depression, which will on occasions, require intervention to support breathing and ventilation.

1.2.2.13 Cardiopulmonary Complications

Four major types of cardiopulmonary complications can occur as a result of endoscopy. These include cardiac arrhythmia, hemodynamic compromise, pulmonary aspiration and respiratory depression.

Alterations in cardiac parameters may be observed before, during or after the procedure. The most common causes of death are cardiopulmonary complications, account for over 50% of all reported morbidity and 60% of mortality associated with endoscopy

(McCloy, 1992). The true incidence of complications is unknown with one major U.S. survey suggesting that approximately 0.5% of American Society for Gastroenterology (ASGE) members experienced cardiopulmonary complication annually, representing a complication rate of 0.01 per 1000 endoscopy procedures.[xi] In the controlled setting of medical research, examining safety in the use of propofol in ambulatory patients mortality rate of 0.0002% has been reported (Rex DK., 2009).

In contrast, a retrospective study based on data entered at endoscopy found that serious cardiopulmonary complications occurred in 5.4 per 1000 procedures, a 500-fold higher incidence. Mortality alone was reported at 0.3 per 1000 (Arrowsmith et al., 1991). Another ASGE database study reported one respiratory or cardiopulmonary arrest occurring per 1000 procedures (Iber et al., 1992). A prospective study from the U.K found a 30-day procedure-related cardiopulmonary mortality rate of 0.4 per 1000 diagnostic upper endoscopies (Quine et al., 1995). A Scottish study reported mortality rate of 153 out of 33,854 patients (Thompson AM., 2004).

The guidelines have been amended to recommend identifying risk factors including age, obesity, and co-morbidities prior to endoscopy and use of monitoring throughout the procedure (ANZCA, 2010). New methods are required to minimise the morbidity and mortality to reduce the significant rate of complications experienced.

1.2.2.14 Use of Supplemental Oxygen

Numerous studies have shown that the routine use of low-flow nasal oxygen during endoscopy can prevent or diminish hypoxia (Bell et al., 1987, Fennerty et al., 1990). One study demonstrated that administration of two litres/minute of nasal oxygen in patients sedated with midazolam whilst undergoing upper endoscopy prevented hypoxia (Bell et al., 1987). This was confirmed by Gross and Long who showed that three litres/minute of nasal oxygen reduced the incidence of hypoxia by more than 50% in patients undergoing colonoscopy with midazolam and pethidine (Gross and Long, 1990). In a study of patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP), patients found to have oxygen saturations below 90% had significantly faster pulse rates than patients receiving supplemental oxygen,

suggesting that corrections of oxygen in patients can alleviate tachycardia and associated myocardial stress in patients (Griffin et al., 1990). Based on these findings, and in keeping with standard practice in anaesthesia, the routine administration of oxygen for the majority of patients having sedation during endoscopy is recommended. Advantages to this approach include low cost and minimisation of cardio respiratory complications through prevention of hypoxia.

Prevention of hypoxia typically involves the delivery of supplemental oxygen by facemask or nasal cannula (Strachan and Noble, 2001). The question of whether preferential mouth breathing, nasal breathing or both has not been clearly resolved. There is however, a suggestion that patients change their breathing pattern after insertion of the endoscope from nasal to oral breathing and that this oral breathing continues until the endoscope tube is removed, making dual oxygenation a preferential delivery design to combat hypoxia (Bell et al., 1991a). Currently marketed oxygenating mouth guards have shown equivalent efficacy to nasal cannula for oxygenation. The Oxyguard® (Trawax P/L, Sydney) oxygen delivery system is one such device which combines oxygen delivery with a bite block. The Oxyguard® (Trawax P/L, Sydney) bite block directs the flow of oxygen to the nose and mouth simultaneously so the patients breathing pattern need not change. Supplemental oxygen during the recovery period has also shown to reduce the incidence of postoperative nausea and vomiting (Greif et al., 1999).

Supplemental oxygen can be administered by use of oxygen mask or nasal prongs. Current nasal prongs used are not ideal as they can shift, have sharp edges making them uncomfortable to wear and are visually unappealing. Additional equipment in and around the mouth and nose can, not only increase anxiety in a patient undergoing endoscopy, but can also complicate the procedure due to the additional equipment. There is scope for improvement in the delivery of oxygen and sampling of carbon dioxide which will be further explored in Chapter 4.

1.2.3 Complications Associated With Bowel Preparation

1.2.3.1 History of Bowel Preparations

Worldwide figures reveal that colorectal cancer is the third leading cause of cancer-related mortalities resulting in approximately 500,000 deaths per year (Bianchi et al 2011). Thus early detection and then removal of adenomatous polyps is of paramount importance in the early treatment and prevention of colon cancers (Figure 1.3). Detection of early-localised cancer is associated with a 90% survival rate however this is reduced to 39% when metastasis has occurred[xii].

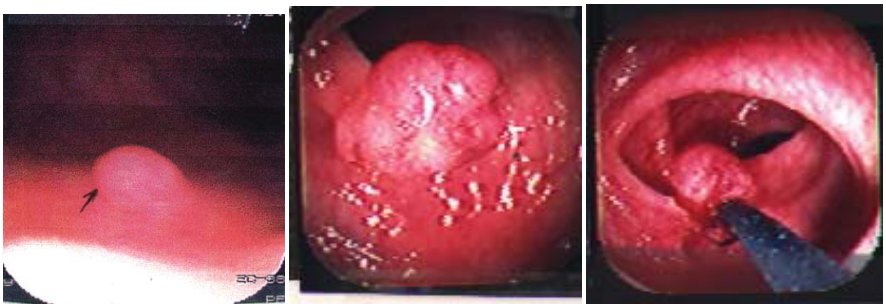


Figure 1.3 Examples of colonic polyps and removal using a snare

Whilst various screening methods are available, the use of colonoscopic surveillance has emerged as an effective method for detecting colonic polyps and bowel cancer and is considered the gold standard. Screening colonoscopy is effective for the early detection of colorectal cancer however it is largely dependent on the quality of bowel preparation. Poorly prepped bowels can lead to impaired visibility during the examination, increased potential for missed lesions, lengthy procedure time and repeat procedures (Cohen et al., 2009).

Results from randomised controlled trials have shown that 25% of bowel preparations are sub optimal (Harewood et al., 2003, Froehlich et al., 2005). Poor bowel preparation additionally leads to impaired detection rate of small polyps (Harewood et al., 2003) but more importantly there is an increased risk of bowel perforation which can be caused from blinded manoeuvres into faecally obscured diverticulae (Kim, 2000).

In an American study fewer than 43% of patients, older than 50 years of age, reported problems encountered in the bowel preparation due primarily to the administration of the preparation itself (Seeff et al., 2004). Effective bowel preparations as a general rule have poor palatability and frequently result in side effects such as nausea, vomiting, abdominal pain and bloating.

Effective bowel preparations have yet to achieve acceptance by both parties involved (gastroenterologist and patient). The initial use of phosphate enemas was associated with significant electrolyte and volume shifts. The introduction of isotonic solutions containing polyethylene glycol (PEG) resulted in safer bowel preparation than phosphate enemas, as these solutions generally result in lower electrolyte shifts. However, isotonic solutions still have significant compliance problems because of poor palatability and the large volume required to achieve adequate bowel preparation. Current preparations often sacrifice palatability and can cause severe electrolyte disturbances. Tolerability issues are a major factor in good bowel preparations, with the poor palatability of bowel preparation often leading to patients' trepidation in undergoing the screening colonoscopy procedure (Cohen et al., 2009). New preparations are therefore required that combine high efficacy with improved tolerability and palatability, whilst preventing electrolyte disturbances. Currently marketed bowel preparations utilise varying mechanisms to achieve bowel cleansing. However, the degree of adverse effects alongside lack of palatability often results in poor patient compliance and an inadequately prepped bowel with efficacy further compromised in cases where patients present with varying degrees of constipation (Figure 1.4).

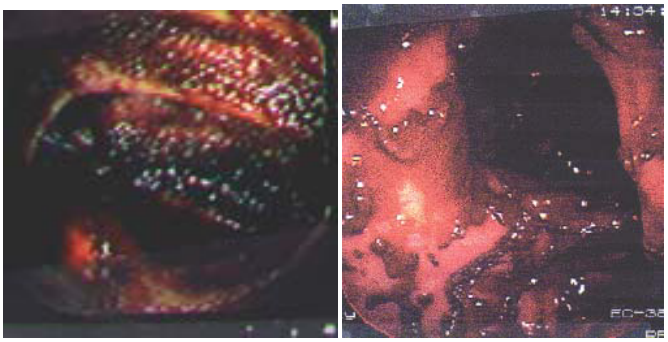


Figure 1.4 Examples of inadequate colonic preparation with faecal matter lining the mucosa.

A number of bowel preparations are currently on the market, with a variety of different mechanisms to achieve bowel washout[xiii]. When first developed gut lavage formulations using saline, mannitol or balanced electrolyte solutions which were effective but poorly tolerated because of large volumes (7–12 litres) and frequently required nasogastric administration for ingestion. In 1980, an osmotically balanced gut lavage formulation containing polyethylene glycol (PEG) and electrolytes (PEG-EL) was developed to provide a safer bowel-cleansing regimen with minimal fluid and electrolyte shifts (Davis et al., 1980). Polyethylene glycols (PEG)-based laxatives, such as GlycoPrep™, contain the non-absorbable macrogol polymer PEG and work by retaining water in the gastrointestinal tract. These laxatives are also composed of a dilute electrolyte solution, which remains in the colon due to PEG's osmotic affect. These preparations work effectively to cleanse the bowel and do not cause severe electrolyte disturbances due to little fluid exchange across the colonic mucosa. When compared with diet-cathartic regimens, PEG-EL formulations had improved efficacy and there was better patient acceptance (Davis et al., 1980, Ernstoff et al., 1983).

Hence PEG-based laxatives are considered safe to use in patients with electrolyte or fluid imbalances from conditions such as renal or liver insufficiencies, and congestive heart or liver failure. However these laxatives involve the consumption of large volumes of unpleasant tasting liquid. This lack of palatability can lead to a decrease in compliance, which can considerably alter bowel preparation efficacy (Dykes and Cash, 2008).

Stimulant laxatives, such as sodium picosulphate, work by stimulating the nerve endings in the walls of the large intestine and rectum, to increase peristalsis (Atchison WD., 1978). Compounds containing magnesium, such as magnesium citrate, also stimulate colonic cleansing by inducing cholecystokinin (CCK) release (Tedesco FJ., 1985). When this release occurs, fluid accumulates within the intestinal lumen and aids to purge the bowel. Preparations using stimulant laxatives are easy to use and have been shown to be as effective as PEG-based laxatives (Clarkston WK., 1996, Kastenberg D., 2001). However the consumption of large volumes of fluid is still required in order to prevent electrolyte disturbances. Tolerability can also be quite poor with many patients often complaining of headache, nausea, bloating, and abdominal pain (Greenberg JA.,

2008). It is also known to cause vomiting and does cause and anti-diuretic hormone (ADH) induced hyponatraemia (Cohen et al., 2001).

Preparations containing sodium phosphate, such as Fleet™ (C.B.Fleet Co.Inc, Lynchburg, Virginia) Phospho-Soda, are also very effective in bowel cleansing. However they are known to cause severe electrolyte disturbances that can lead to acute interstitial nephritis, subsequent kidney failure and occasional death (Ayus, 2003). Five times more significant adverse events have been reported in patients using sodium phosphate preparations compared with PEG preparations. For this reason, preparations containing sodium phosphate are not recommended for use in *"at risk"* patient groups, such as the elderly, children (Butan, 2005) or patients with a fluid or electrolyte imbalance (Ori Y., 2012). This includes patients with congestive heart failure, renal and hepatic insufficiency, and those patients taking diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (Greenberg JA, 2008). Thus palatability and side effects are major factors in the subject's acceptance of the preparation. Improving the process of bowel preparation involves administering patient-specific purgative with proper education to improve compliance, which may in turn reduce the risk of adverse events. Preparation of the bowel has been the most poorly tolerated aspect of colonoscopy procedures. Among the problems encountered are the dietary restrictions of a low residue diet, the period of fasting on the day of the procedure for aesthetic reasons. Most significantly, the effects of purgative solutions administered on the day prior. Therefore, favourable bowel prep experience combined with a safe and successful experience at endoscopy promotes compliance with repeat screening recommendation (Harewood et al., 2002). Problems encountered from inadequately prepped bowels, results in longer procedure times and increased risk of missed lesions of the colonic mucosa. Suboptimal bowel cleansing and inadequate visualization increase the risk of missed pathology (Froehlich et al., 2005, Harewood et al., 2003).

A separate issue but which is also an important safety consideration is that many of these purgatives have been available as over-the-counter products and therefore open to laxative abusers in the community.

Active Ingredient	Commercial preparations
Phosphate preparations	Fleet phospho-soda TM buffered Travad TM ready-to-use enema PhosphoprepTM
Polyethylene preparations (with electrolytes) Diphenylmethanes Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany)	ColonLytely TM GlycoPrepTM TM MiraLaxTM Bisalax TM Durolax TM
Sodium picosulphate (often combined with other laxatives)	Picolax TM PicoPrep TM
Magnesium preparations (combined with other laxatives)	PicoPrep TM

Table 1.1 Examples of some of the products available for bowel preparation

PicoPrepTM TM 15.546g sachet or 250mls 10mg sodium picosulphate 2.1g Magnesium 12g Citric Acid Total sodium 0.001 Require 2-3 sachets	**GlycoPrepTM** TM 200g sachet=3 litres Macrogol 3350 PEG 171.4g Sodium Chloride 4.4g potassium Chloride 2.25g sodium Bicarb 5.1g sodium sulphate 16.9g Total sodium =6.03g
Colon Prep Kit A TM PicoPrepTM and Colonlytely. 10mg. sodium picosulphate 2gm. magnesium 59gm PEG 1.46gm. NaCl 0.75gm. KCl 1.68gm. Na Bic 10.05 gm total sodium In 1 sachet	**Fleet** TM 2.4gm. Sodium Phosphate monobasic 0.9gm sodium phosphate dibasic per 5 mls Sodium benzoate Saccharin Na 45mls X 2 10-12hours apart

Table 1.2 Current bowel preparation products and their constituents

1.2.3.2 Hyponatraemia as a complication of Colonoscopy.

Hyponatraemia is defined as "*serum sodium under 135mmol/L"* and severe hyponatraemia is *"serum sodium less than 120mmol/L"*. Hyponatraemia occurs in 2.5-6% of in-patients and causes a 60-fold increase in morbidity and mortality (Reddy and Mooradian, 2009, Upadhyay et al., 2009).

Hyponatraemia can occur chronically when it is reasonably well-tolerated or acutely over less than 24 hours where it becomes symptomatic (Arieff AI, 1976)**.** Determination of euvolaemia, hypovolaemia or hypervolaemia helps guide treatment. The commonest cause is dilutional hyponatraemia due to retention of water in excess of sodium and is related to ADH being inadequately suppressed. Patients who are euvolaemic often have an underlying condition or drugs causing a syndrome of inappropriate anti-diuretic hormone (SIADH). Certain medications (Table 1.3) increase baseline ADH or the response to volume depletion such as thiazide diuretics and selective serotonin uptake inhibitors (SSRI) whereas non-steroidal anti-inflammatory drugs (NSAIDS) potentiate the renal ADH response. Patients with hypervolaemic disorder such as congestive cardiac failure or liver cirrhosis have a higher basal ADH level.

Diuretics Thiazide
Angiotensin Converting Enzyme Inhibitors/ Angiotensin Receptor Antagonists
Selective Serotonin Uptake Inhibitors, MAO Inhibitors
Monoamine Oxide Inhibitors
Antipsychotics
Antiepileptic Carbamazepine Valproate Lamotrigine
Antidiabetics Chorpropamide Tolbutamide
Antibiotics Ciprofloxacillin Trimethoprim –Sulfamethaxazole Rifabutin
Antiarrythmics – Amiodarone
Antihypertensive - Amilodipine
Anti-cancer - Vincristine/Vinblastine Cisplatin/Carboplatin,
Alkylating agents, - Methotrexate, levamisole Levamisole.
Proton Pump Inhibitors
Non-steroidal anti-inflammatory drugs
Oxytocin antidiuretic hormone analogues
Amphetamines MDMA (ecstasy)

Table 1.3 Drugs causing hyponatraemia

1.2.3.3 Polyethylene glycol electrolyte lavage solutions formulation

Osmolarity is normally low except when isotonic or hypertonic hyponatraemia occurs. In patients who are euvolaemic and hyponatraemic, the urine reaches maximal concentrated urine with an osmolarity >200mmol/kg. At the other end of the spectrum, the kidney is able to excrete 10-15 L/day of dilute urine with osmolarity of 100mosm/kg (Yeates KE, 2004). Hypertonic hyponatraemia can occur when an osmotically active compound such as glucose or mannitol enters the intravascular space pulls water in intra to extracellular space causing a fall in serum sodium while raising the serum osmolarity.

Excessive restoration of sodium can cause an osmotic demyelination syndrome *"Central Pontine Myelinolysis"*. It is irreversible and frequently fatal but may not be evident for several days (Sterns RH, 1989). In patients using polyethylene glycol and electrolytes (Schroppel et al., 2001) as well as those who used sodium phosphate or sodium picosulphate/magnesium citrate (Frizelle and Colls, 2005) colonoscopy induced hyponatraemic coma is a recognized complication. Researchers in Germany measured serum arginine vasopressin in 40 patients including 20 control patients who were only undergoing panendoscopy. They noted a 7.5% incidence of hyponatraemia associated with raised concentration of serum arginine vasopressin level. Patients in the study used 2-3 litres of polyethylene glycol solution and balanced electrolyte. These patients were sedated with midazolam. Three patients 7.5% had plasma sodium less than 130 and ten patients (25%) had raised serum arginine level after bowel prep and before the procedure (Cohen et al., 2001)**.**

Reports of hyponatraemia with six cases of convulsion have been reported from patients using sodium picosulphate (ADRAC, 2002). This followed form an earlier publication that reported on risks of severe electrolyte disturbance with use of oral sodium phosphate (ADRAC, 1997). Further reports by Mackey et al (2002) implicated the sodium phosphate solid bowel preparation Visicol^{TM} with acute hyponatraemia and thought to be due to water intoxication/dilutional hyponatraemia (Mackey et al., 2002). Purgative use can also cause hyponatraemia by various mechanism, anti-diuretic hormone (ADH) is the principal hormone in water clearance and when serum osmolarity increases >285mosm /kg thirst is stimulated in the posterior pituitary. Volume depletion also reduces the osmotic threshold for ADH and therefore release can

occur with volume depletion, nausea, pain and stress (Rowe et al., 1976, Schrier and Berl, 1975).

Other bowel preparation formulations including PEG-EL (Nagalar, 2006), oral sodium phosphate**,** MiraLax™ (Schering-Plough, Kenilworth, NJ) plus Gatorade ™ and sodium picosulphate (Frizelle and Colls, 2005, ADRAC, 1997) have also been known to cause hyponatraemia.

Seizures and hyponatraemic encephalopathy have been reported in patients taking polyethylene glycol solutions (Schroppel B., 2001). It is noted that manipulation of the gut organ, pain and nausea can all produce an increase in ADH hormone but this rise was seen prior to the procedure. It should be noted that the drowsiness normally attributable to sedation might be in part due to unnoticed hyponatraemia as an additive factor (Schroppel B., 2001). Severe hyponatraemic encephalopathy is more likely to be seen in young female patients. Early symptoms include nausea and vomiting followed by mental confusion, and with worsening hyponatraemia hypoxia, seizure and death (Arieff, 2006).

It is therefore crucial that the complication of dilutional hyponatraemia be considered when developing a novel bowel preparation. This will be further discussed in Chapter 6.

As polyethylene glycol comes mixed with balanced electrolytes, it is consumed, when mixed, in a large volume (3–4 litres) of water and often poorly tolerated because of its saltiness. Polyethylene glycol, due to its high molecular weight carbohydrate, allows retention of water in the gastrointestinal tract. The balanced electrolyte solution reduces the fluid shifts seen with the other osmotic and stimulant laxatives. There is not the same requirement to consume extra clear fluids and there is considerably less risk of dehydration or electrolyte disturbances. Because of the large volume, polyethylene glycol can cause nausea bloating and abdominal pain is not readily tolerated. It generally works within 1–4 hours.

Various studies have looked at the efficacy of oral versus rectal (Jensen VJ, 1988) Similarly several studies have compared sodium phosphate with polyethylene glycol and although the former is easier to take, it generally accepted that it was not as safe as

the latter (Marshall JB, 1993, Golub RW, 1995). A German study was carried out to compare the efficacy, safety, and tolerability of three most commonly used preparations; 1.) Standard polyethylene glycol-electrolyte solution based on the GoLytely™ formulation (PEG-EL1; Klean-Prep); 2.) Sulphate-free PEG-EL solution based on the NuLytely™ formulation (PEG-EL2, Endofalk); and 3.) Sodium phosphate preparation (sodium phosphate, Fleet Phospho-Soda™).

This was a blinded study and a total of 185 consecutive patients scheduled for elective colonoscopy were prospectively randomly assigned to undergo pre-colonoscopic bowel cleansing with either one of the above preparation. In this study PEG-EL1 was statistically significantly superior to the other treatments in relation to the *"worst cleansing"* and, visualisation and therefore was declared the *"gold standard"* for bowel cleansing. Adverse events (mainly nausea/vomiting and abdominal pain) and deviations in laboratory values occurred more frequently in the sodium phosphate group although patient satisfaction was similar in all groups (Ell C, 2003).

A newer 2L PEG-EL containing ascorbic acid does not require co administration of stimulant laxatives, achieves effective bowel cleansing and is well tolerated by patients (Bitoun et al., 2006, Ell C, 2003, Kastenberg et al., 2007) and when compared to other bowel preparation appears also to be more effective (Worthington J, 2008). Low volume PEG-EL solution of 2 litres was also compared with oral sodium phosphate again aiming for comparable efficacy and to reduce volume. This trial showed improved caecal cleansing by sodium phosphate (Poon CM, 2002). In a study evaluating 4 litres of PEG electrolytes a split dose PM/AM was more likely to get a good clean as opposed to drinking 4 litres at the one setting (44% vs. 6%) (Aoun et al., 2005). Another trial compared sodium phosphate and PEG electrolytes found that that sodium phosphate was a better preparation and also a longer split time of 12-24 hours rather than 6 hours was better tolerated, presumably due to greater fluid intake (Rostom et al., 2006). Studies comparing the time between preparation ingestion and procedure suggest this time may be more important than the actual compound (Parra-Blanco et al., 2006, Church, 1998, Poon CM, 2002).

1.2.3.4 Hyper osmotic purgatives- Sodium phosphate

Phosphate preparations have been used extensively and are highly effective and generally well tolerated. Phosphate preparations function largely through an osmotic mechanism, retaining fluid in the intestines thereby promoting peristalsis and evacuation of the colon. Sodium phosphate induces diarrhoea within 0.5 to 4 hours and within 10-15 minutes when administered orally and rectally respectively. Adequate amounts of extra fluids are essential. Nausea, abdominal pain and bloating are the most commonly observed adverse events associated with sodium phosphate formulations (Chan, 1997).

Studies have also found that sodium phosphate tablets may provide a more tolerable alternative to PEG-EL regimens and traditional, aqueous sodium phosphate products without compromising bowel-cleansing efficacy. Large reviews studies have shown that sodium phosphate has either equivalent efficacy (Hsu CW, 1998, Belsey, 2007) or is better than polyethylene glycol (Tan JJ, 2006). Meta-analysis of data pooled from 12 trials involving 3252 patients reported no significant difference in the incidence of adverse events experienced by patients taking PEG-EL preparations (63%) or sodium phosphate products (57%). These were in keeping with the previous studies on efficacy, however, abdominal pain was more common among patients who received PEG-EL ($p < 0.00001$), and dizziness was more common among patients who took Sodium phosphate preparations (p=0.008). While the previous studies (Hsu CW, 1998, Tan JJ, 2006) did not reveal any difference in adverse effect, this study suggested that fluid and electrolyte shifts could occur as a result of the hyper osmotic nature of sodium phosphate preparations (Hookey et al., 2002). Electrolyte shifts in patients taking sodium phosphate preparations have been reported as mild, and rarely cause clinical significance. However hyperphosphataemia does occur, even in patients without patients with renal insufficiency (Di Palma, 1996) and extreme caution should be exercised at the extremes of age (Beloosesky, 2003).

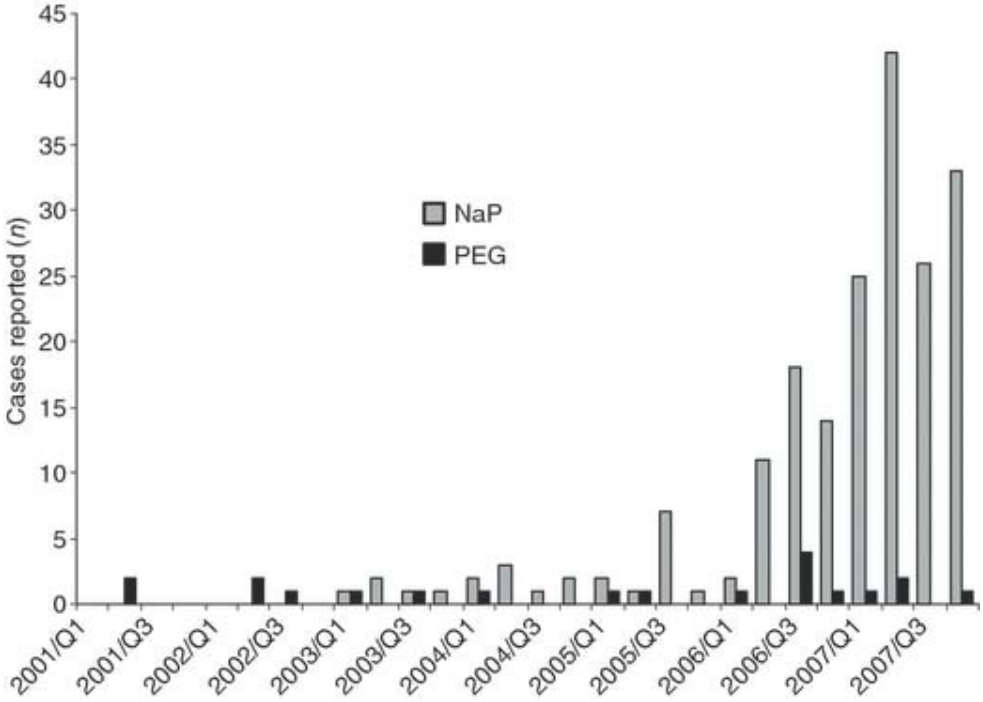


Figure 1.5 Cases of renal failure or nephrocalcinosis associated with sodium phosphate or polyethylene glycol. Reports to FDA January 2001-2007 (Belsey J, 2009)

Case studies between 1971 and 2006, reported 46 adverse events related to oral sodium phosphate solution including 11 fatalities (Belsey J., 2008). Although clinical experience with sodium phosphate tablets is less extensive, published clinical trials involving 1506 patients taking sodium phosphate tablets reported only three cases of serious adverse events (atrial fibrillation, ileus and ischaemic colitis). However seizures associated with hyponatraemia have also been reported rarely in patients taking sodium phosphate tablets (Ayus J.C. 2003). As seen in Figure 1.5, since 1998 when the US Food and Drug Administration (FDA) issued warnings of renal toxicity associated with the use of sodium phosphate, there has been a substantial increase in reporting (Belsey J, 2009).

The main reports are of hyperphosphataemia, which have been reported in the setting of acute renal failure, with or without hypocalcaemia and hypokalaemia (Ovias, 1999). The main renal side effect as shown in a retrospective study of more than 7000 renal biopsies were 21 cases of renal failure and acute phosphate nephropathy (nephrocalcinosis) due to the administration of oral Sodium phosphate solution (20

cases) or sodium phosphate tablets (one case) (Markowitz et al., 2005). Problems occurred with increased phosphate and possible exacerbation of hypocalcaemia and hypokalaemia; in a study on 32 patients 28% had some change from their baseline electrolyte profile (Liebermann DA, 1996). Problems in the bowel preparation phase also result from the physiological disturbance of fluid and electrolyte shift, which stem from the purgative effect (Heher EC., 2008). Side effects can occur as a result of clinically significant hyponatraemia and includes headache, confusion, seizure and coma. Such adverse effects prevent completion of the preparation in a significant proportion of patients who come to colonoscopy with insufficiently prepared bowel. Proper renal function plays a particularly important role in avoiding potential safety issues related to sodium phosphate-induced shifts in the fluid and electrolyte balance. Preventing dehydration in patients undergoing bowel preparation can prevent severe adverse events, regardless of the purgative administered.

1.2.3.5 Diphenylmethanes (Bisacodyl and Sodium Picosulphate)

Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) a diphenyl methane laxative, is locally acting, minimally absorbed from the gastrointestinal tract and is hydrolysed by bacteria in the colon to bis (para-hydroxyphenyl) pyridyl-2-methane. The two modes of action: stimulation of myoelectrical activity of the colon (Schang, 1986) and stimulation of intestinal secretion allows for peristalsis and promotes water and electrolyte accumulation within the colon (Ewe, 1995). The effect occurs 6–12 hours after oral ingestion and studies have shown that as little as 5mg of Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) can accelerate ascending colon emptying using colonic transit scintiscan technology (Manabe, 2009). Per rectal Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) is effective within 15–30 minutes. Stimulant laxatives are easy to administer and are commonly used in conjunction with other products (for example magnesium sulphate). In attempting to reduce the volume of polyethylene glycol Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) has been added to reduce the volume (Adams, 1994). However it is important that adequate fluids and electrolyte replacement of diarrhoeal losses occurs. A dose related ischaemic colitis has been linked to Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) (Baudet JS., 2010).

Small volume options have been the main stay of bowel cleaning. In Australia, this has been shared by sodium picosulphate (PicoPrep ^{TM} (Ferring Pharmaceuticals, Saint-Prex, Switzerland)) and sodium phosphate (Fleet ^{TM}). Oral sodium picosulphate/magnesium citrate acts locally in the colon as a stimulant laxative, (sodium picosulphate component), and an osmotic laxative, by retaining fluids in the colon (magnesium citrate component). It is not absorbed in any detectable quantities. Sodium picosulphate as a prodrug, is hydrolysed by bacteria in the colon to an active metabolite, 4, 4'-dihydroxydiphenyl-(2-pyridyl) methane (Hoy SM, 2009).

Oral sodium picosulphate/magnesium citrate is generally well tolerated in adult patients and adverse events usually mild to moderate in intensity and mainly gastrointestinal in nature (e.g. abdominal cramps/pain, nausea) is common. It has been shown to cause dehydration, as seen by a reduction in bodyweight and increased haemoglobin levels and patients may experience postural hypotension especially if they are older (Burke P., 1992). This combination is at least as well tolerated as oral sodium phosphate or oral polyethylene glycol, with moderate/severe nausea and vomiting occurring less frequently in sodium picosulphate/magnesium citrate recipients than in those receiving oral sodium phosphate (Regev A., 1998). Abdominal bloating/pain and nausea developed less often with sodium picosulphate/magnesium citrate than polyethylene glycol therapy (Hamilton D., 1996). The incidence of most adverse events was similar in recipients of sodium picosulphate/magnesium citrate and a sodium phosphate enema preparation. Patients receiving sodium picosulphate/magnesium citrate reported moderate/severe flatulence, incontinence and sleep disturbance, and patients receiving the enema preparation reported rectal soreness. The tolerability profile of sodium picosulphate/magnesium citrate in patients aged >70 years was reportedly similar to that in patients aged <70 years. Abdominal pain also occurred less frequently with sodium picosulphate/magnesium citrate than with oral Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) plus sodium phosphate enema preparation in children and adolescents (Hoy SM, 2009).

Comparison of sodium phosphate with sodium picosulphate was conducted in an Australian study of 225 outpatients. Both types of bowel preparation were associated with similar incidence of nausea, dizziness abdominal cramps although was sodium picosulphate significantly better tasting ($p = 0.03$) (Tan and Tjandra, 2006).

In summary, diphenylmethane containing products provide ease of administration. They have a lower risk of severe electrolyte disturbances than phosphate preparations; however they too are relatively contraindicated in the presence of renal impairment and cardiac failure.

1.2.3.6 Magnesium sulphate

Magnesium is a well-known laxative, which increases water in the gastrointestinal tract and stimulates peristalsis. A combination of magnesium sulphate and sodium picosulphate is a commonly prescribed oral bowel preparation, presented in two sachets. The contents of each sachet are mixed in a glass of water and taken approximately four hours apart. A laxative effect usually starts within 3–4 hours, but it is important to maintain an adequate oral intake of clear fluids during this time. Magnesium sulphate is relatively contraindicated in the presence of congestive cardiac failure and impaired renal function where the potential for dehydration and dangerous hypermagnesaemia exists (Kontani M., 2005).

1.2.3.7 Tablet Preparations

An alternative to poorly tolerated volumes of solution such as Fleet, PicoPrep™, Picolax™ and GlycoPrep™, has recently been the substitution of encapsulated active ingredients. These tablets which are sodium phosphate compounds have been shown to improve palatability and patient acceptance. However as the mode of action is the same as the aqueous form the side effects profile especially the renal and metabolic effects similar. In a study of 845 (420 and 425 in the tablet and PEG solution groups, respectively), there was greater compliance with the tablet 94% than with 57% completing the PEG solution regimen (p<0.0001). The tablets were easier to take (88.4% rated them *"easy"* versus 60.6% of patients taking the PEG solution) and side effects of nausea, vomiting, and bloating occurred significantly less often in patients taking sodium phosphate tablets (p<0.0001). Most (90.7%) patients taking the tablets indicated they would take the same preparation in the future, compared with 67.1% of patients taking the PEG solution (Kastenberg et al., 2007).

Similar trials have shown patient acceptance, preference and tolerability of bowel preparation. A randomised controlled trial compared 32-sodium phosphate tablets with 2 litre polyethylene glycol solution plus 4 Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) tablets for bowel preparation in 411 patients showed a superior tolerance with the tablets (77% vs. 42%), Nausea, vomiting, bloating and abdominal pain were reported less frequently with sodium phosphate (Lichtenstein et al., 2007).

A multicentre study compared the safety and efficacies of sodium phosphate with a 2 litre PEG plus Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) and concluded that the 32 capsules was more efficacious with fewer sides-effects however, both treatment arms caused changes in electrolyte and creatinine (Johanson, 2007).

Initial formulation of capsules had complaints of residue lining the walls of the colon however this was rectified by later formulation (Wruble, 2007). In a randomised trial comparing split dose small volume liquid and capsule sodium phosphate, liquid sodium phosphate was better tolerated and more effective. Patients were given 45 ml or 20 tablets as split dose 3-5 hours before colonoscopy. A total of 101 subjects were enrolled; bowel cleansing was rated *"Excellent"* or *"Good"* in 92% of liquid preparation subjects, compared with 74% of tablet preparation subjects (p=0.03). Subjects rated the liquid preparation easier to swallow (p<0.005) and more convenient to take (p<0.005) than tablets. Among liquid subjects, 45 of 50 reported a willingness to take their preparation for future colonoscopies, compared with 36 of 49 who took tablet sodium phosphate (p<0.04). Of note, compliance with split dosing and the drinking of small volume sodium phosphate was preferable to ingesting a large number of capsules in this study (Balaban et al., 2003).

1.2.3.8 Hydration during bowel preparation and split doses

Proper hydration throughout the bowel-preparation process may prevent intravascular volume depletion related complications. During the period of colonic cleansing, patients should be encouraged to drink fluids liberally. Studies suggest that a carbohydrate-electrolyte rehydration solution may be a superior alternative to clear liquids during

bowel preparation with oral sodium phosphate solution. Improved patient tolerability in terms of completion of preparation was seen in a study supplementing clear liquid intake with a carbohydrate-electrolyte rehydration solution. There was a decrease in the occurrence of dizziness and nausea thus resulting in significantly less intravascular volume contraction (p<0.03) (Barclay R., 2002).

A randomised controlled Australian study at the Royal Melbourne Hospital was designed to evaluate whether carbohydrate-electrolyte (E-Lyte™) solution enhanced bowel preparation and improved patient acceptance with oral sodium phosphate. In 187 subjects who received two packets of oral sodium phosphate (Fleet Phospho-soda™) with or without additional supplement of a carbohydrate-electrolyte (E-Lyte™) solution. Patients taking E-Lyte™ supplement had significantly less dizziness (none, 80% vs. 56%; p<0.001) and a trend toward less nausea (none, 70% vs. 56%; p=0.05). The group taking electrolytes were all able to complete the bowel preparation as opposed to 3 percent of the group without electrolytes. Side effects of hypokalaemia and dehydration requiring intravenous rehydration were reduced in the group taking supplementary electrolytes (11% vs. 4%). Differences in serum creatinine and urine-specific gravity suggested possibly a lesser degree of hypovolaemia in patients taking E-Lyte™ supplements. The quality of bowel cleansing in patients taking E-Lyte™ supplements was considered better by both the endoscopists and patients. Carbohydrate-electrolyte (E-Lyte™) solution protects against hypokalaemia, improves patient tolerability, and may enhance use of oral sodium phosphate as a bowel-preparation agent (Tan and Tjandra, 2006, Tjandra and Tagkalidis, 2004).

Thus, carbohydrate-electrolyte rehydration solutions may be more effective than clear liquids in restoring patients to baseline hemodynamic levels. Electrolyte composition in these solutions however varies widely, for example, potassium levels ranging from 1.2mmol (Gatorade) to 12.7 mmol (E-Lyte) per 350mls of solution and sports drink may have up to nine time less sodium than PEG-EL. The use of sports drinks has also been associated with seizures (Frizelle, 2005).

As the literature suggests, the efficacy and superiority of each type of bowel preparation is wholly dependent on the reviews that have been undertaken. Often this is due to the small study populations and the variable scales used to assess efficacy. The reviews are

also almost always conducted in single centres and analyses are often lacking sufficient power to be considered clinically significant. Authors may also have had conflicting interest with respect to funding by pharmaceutical companies. Conversely various trials have shown an improved effectiveness in split dosing and reduction in side effects and this was true for trials using sodium phosphate as well as polyethylene glycol (Park, 2007). The time to be taken, of the second split dose is 4-5 hours before the scheduled procedure (Atreja, 2006). However this has to be taken into consideration with fasting time as per the American Society of Anaesthesiologists guidelines for fasting prior to sedation or anaesthesia; patients may ingest clear liquids up to 2 hours and soft foods up to 4-6 hours before anaesthesia.

1.3 CONCLUSION

As the literature review has shown safety concerns in endoscopic procedures are broad ranging. In this thesis the main complications that arise during endoscopic procedures will be addressed with methods to reduce complications. Complications that will be addressed in detail for which solutions will be sought will be aiding of oxygen delivery and detecting carbon dioxide for monitoring of sedation and colonoscopy complications arising from bowel preparation.

This shall be done in two parts with the first part of the thesis concerned with oxygenation and detection of adequate ventilation. An opportunity exists to improve on current devices to deliver and monitor expired gas concentrations.
The aim of this project is to design a device that:

- Improves on the current methods of oxygenation to patients during endoscopy procedures and in recovery to reduce the risk of hypoxia in patients.
- Improves the look and ergonomics of current nasal prongs on the market.
- Includes a sampling port for measuring carbon dioxide and therefore monitor ventilation.

The second part of the thesis focuses on the development of a bowel preparation agent that addresses the problems currently associated with bowel preparations.

1. Unacceptable electrolyte shifts
2. Poor palatability
3. Unacceptable side effects
4. Effectiveness

However before embarking on the above, a survey of Australian endoscopic practices will be conducted to glean a general understanding of current practice in Australia. This type of survey has not previously been undertaken in Australia and the results will be presented in Chapter 2.

Sedation related cardio-respiratory complications are an important cause of morbidity and mortality. To understand the development of respiratory depression and

cardiovascular changes, Chapter 3 will concentrate on the physiological parameters affected during endoscopic sedation.

The Centre for Digestive Diseases developed an existing oxygenating bite-block Oxyguard^{TM}. The development of a new oxygenating device will form the basis of Chapter 4 and a comparative study of this device with nasal oxygenation and standard bite-block will be presented in Chapter 5.

Bowel preparations are an ongoing concern with issues of patient acceptance and adequate efficacy to satisfy the proceduralist. Chapter 6 will examine the effectiveness of a new bowel preparation and will demonstrate a strategy with use of hypertonic solution. The results of a trail involving fifty-nine patients will compare the safety and efficacy of four bowel-cleansing strategies.

Chapter 7 will discuss the process of formulating an encapsulated bowel preparation. The results of pilot trials in volunteer patients will be presented. The culmination of this exercise results in a final product ready for commercialisation and formal trials. However due to the constraints of time and finance, this thesis will not be able to explore this product any further.

Finally, the conclusions of Part A and B of this thesis will be presented in Chapter 8.

CHAPTER 2 AUSTRALIAN ENDOSCOPIC PRACTICE – SURVEY OF SEDATION PRACTICES IN ENDOSCOPIC UNITS IN AUSTRALIA

2.1 INTRODUCTION

Gastrointestinal procedures are common and according to Medicare in 2005-2006 there were 493,966 gastrointestinal procedures performed in private practice.[xiv] The practice of sedation, including drug selection, depth of sedation, drug delivery methods and personnel employed to administer sedation has evolved over the years. Largely determined by cultural, historical and economic factors, variation exists in the practice of sedation as practiced in Australia and elsewhere. Although professional bodies such as the Australian and New Zealand College of Anaesthetists (ANZCA) and the Australasian College for Emergency Medicine (ACEM) have developed standards for sedation and monitoring, preventable morbidity and mortality associated with sedation is still of concern.

Early survey studies report high complication rates of 1.4% and mortality of 3/10,000 (Arrowsmith et al., 1991). More recent figures report a rate of 0.9% unplanned cardiopulmonary events and a mortality of 0.8/10,000 predominantly due to cardiopulmonary causes (Sharma et al., 2007). The British Gastroenterology Society *"Scoping our practice-The 2004 Report of the National Confidential Enquiry into Patient Outcome and Death"* has also highlighted a range of inadequacies associated with endoscopy and in particular sedation related complications.[xv] These morbidity and mortality rates compares poorly with 1 in 63,000 deaths from all anaesthesia in Australia (Mackay, 1999). Notably, this figure does not take account of adverse events associated with sedation performed by non-anaesthetists. Non-anaesthetic sedations are not confined to the practice of gastroenterology. Radiological procedures such are magnetic resonance imaging (MRI) and interventional cardiac procedures are other

instances where sedation may be administered by non-anaesthetists. In areas such as the emergency department and intensive care, non-anaesthetists who have proficiency with regards to the administration of sedation and airway management routinely administer sedations.

By formalising standards, providing assistance in training of staff and delivering sedation to high-risk patients, most specialist sedationists and anaesthetists provide a more valuable role than simply providing sedation for uncomplicated endoscopies. Clinical practice guidelines including sedation guidelines have been shown to improve patient outcomes by standardising care in intensive care units (Elliott et al., 2006). Numerous surveys have been performed for sedation in gastrointestinal endoscopy in the United States of America, United Kingdom and Europe (Cohen, 2006b, Daneshmend, 1991, Heuss, 2005, Campo, 2004).

In Australia a profile of sedation practices and availability of anaesthetists and/or non-anaesthetists is currently unavailable. At present there isn't a reporting system for adverse outcomes associated with endoscopic sedation, nor is there a data collection system available to determine numbers of endoscopic procedures performed in Australia. This is the first nationwide survey performed in Australia that attempts to examine the practice of endoscopic sedation.

The aim of this survey is to:

- Gather data regarding current endoscopic practices in Australia.
- Ascertain complication rate associated with sedation.

2.2 METHODS

A voluntary postal survey method was used to obtain the data. The survey comprised a 17-item questionnaire developed specifically to examine demographics, anaesthetic responsibility, procedural fasting times, sedative used, bowel cleansing agents employed, and monitoring and reported complications as an estimate over the 2005-2006 financial years. The survey (Appendix 1) and a covering letter (Appendix 2) were addressed and mailed to the nurse unit manager/medical director of 60 private and 60 public centres/hospitals throughout Australia in November 2007. A reminder letter was

sent to 50 non-respondents in February 2008. Each survey had an allocated code number to maintain respondent anonymity. The survey was granted ethics approval as a voluntary survey.

Student t-test, non-parametric Wilcox and chi-squared difference were used to analyse the data.

2.3 RESULTS

The questionnaire survey attempted to clarify the broad range of practices pertinent to endoscopic practice. The results of each question or group of questions will be addressed and discussed separately followed by an overall conclusion.

A. Demography

1. Describe your practice 2. Number of proceduralists/endoscopist in your practice and approximate proportion of procedures done by each.

A total of 53 completed questionnaires were returned, 29 from public centres and 24 from private practices, representing a total of 421 practitioners (268 public, 153 private) throughout Australia. One survey returned was composed of both private and public sectors and was therefore dealt with independently as both public and private practice. Two surveys were returned unanswered and were therefore excluded from the analysis. The number of questionnaires returned were by no means entirely representative, however all states, and importantly both small volume and large volume centres, were represented. There was near equal representation of surveys from both private and public sectors.

The result of this survey provides national data on endoscopic sedation within Australia. According to Medicare figures the study represents approximately 25% of procedures in the year 2005-2006 in Australia. As the results were based on self-reporting, we sought to maximize confidentiality in order to encourage frank revelation.

The vastness of Australia and differences in the delivery of health care in regional and metropolitan areas were reflected in the diversity of endoscopic centres (Table 2.1 and

2.2). Respondents consisted of metropolitan (n=13) and larger regional locations (n=10) private centres; and small, regional (n=14) and metropolitan (n=13) public centres.

PUBLIC	**(N=28)**				
Location	**Number of procedures**	**Proceduralist¶**			**Percentage of sedation by Anaesthetist¶**
		Phy	**Surg**	**Other**	
Met Sydney	3100	**7**	**5**	**0**	100%
Met Sydney*	3376	**0.7**	**0.2**	**0**	Nil
Met Sydney	700	**5**	**5**	**0**	100%
Met Sydney	x	**8**	**5**	**0**	100%
Met Sydney*	2869	**0.6**	**.4**	**0**	100%
Reg NSW	4143	**5**	**12**	**2T**	100%
Reg NSW	1987	**8**	**7**	**0**	100%
Reg NSW	1841	**1**	**4**	**0**	10%/90% N
Reg NSW	5152	**4**	**2**	**0**	90%/10%N
Met Melbourne	1900	**3**	**11**	**0**	100%
Met Melbourne	500	**9**	**3**	**0**	X
Reg Victoria	300	**8**	**0**	**0**	100%
Reg Victoria	1163	**0**	**4**	**0**	100%
Reg Victoria	5600	**1**	**3**	**0**	50%/25%N
Met Melbourne	1146	**17**	**5**	**0**	100%
Met Melbourne	1131	**1**	**3**	**0**	25%
Met Brisbane	1999	**4**	**4**	**2T**	75%
Met Brisbane	800	**4**	**4**	**0**	100%
Met Brisbane	832	**3**	**2**	**0**	100%
Reg Qld	2650	**0**	**2**	**0**	11% N 89%
Reg Qld	2098	**10**	**3**	**2T**	Nil 20N80P
Reg Qld	276	**7**	**3**	**0**	100%
Reg SA	264	**0**	**4**	**0**	100%
Reg SA	116	**0**	**2**	**4G**	Nil 100%G
Reg WA	2086	**0**	**1**	**2T**	10%
Met Tas	135	**8**	**3**	**1G**	15%
Reg NT	x	**0**	**3**	**0**	20%
Total	**45,833**	**17**	**9**		

*(x= not provided *=Ratio provided P=physician T=trainee N=Registered Nurse G=General Practitioner)*

Table 2.1 Demographic details of public hospitals - Metropolitan (Met) and Regional (Reg)

PRIVATE	N=26			
Location	**Number of procedures/yr**	**Proceduralist¶ Phys**	**Surg**	**Percentage of sedation by Anaesthetist¶**
Reg NSW	2400	**2**	**3**	10% /90%G
Met Sydney	5466	**5**	**6**	100%
Met Sydney	2000	**2**	**0**	20%/ 80% G
Met Sydney	4915	**3**	**0**	60%/40%G
Met Sydney	4500	**6**	**6**	100%
Reg NSW	3000	**8**	**6**	100%
Reg NSW	1742	**6**	**3**	100%
Met ACT	3800	**5**	**2**	100% G
Reg NSW	500	**0**	**1**	100%
Reg NSW	954	**0**	**3**	100%
Reg NSW	2000	**0**	**6**	100%
Reg NSW	1450	**2**	**3**	80% /20%G
Met Melbourne	2056	**9**	**1**	100%
Met Melbourne	1700	**3**	**3**	50%/ 50% G
Met Melbourne	X	**6**	**2**	100%
Met Melbourne	1600	**3**	**0**	50% /50%G
Met Melbourne	2000	**0**	**1**	50%/ 50% G
Victoria	x	**5**	**3 (5 N)**	x
Reg Victoria	677	**0**	**2**	100%
Reg Victoria	1127	**0**	**4**	100%
Reg QLD	3960	**7**	**0**	100%
Met Brisbane	5000	**1**	**0**	100%
Met Perth	3845	**6**	**3**	100%
Met Perth	4000	**6**	**1**	40%/ 60% N
TOTAL	**60,280**			

Table 2.2 Demographic details of private hospitals - Metropolitan (Met) and Regional (Reg)

3. Number of proceduralists/endoscopists approximate proportion of procedures done by each.

In this cohort, a total of 106,113 procedures (45,833 public and 60,280 private procedures) were performed during the 2005-2006 financial year. Medicare rebates for colonoscopy-related and panendoscopy-related items for the 2005-2006 financial-years showed a total of 493,966 were performed annually in Australia alone. In this survey,

the proportion of procedures attributed to private and public were relatively similar, with private procedures accounting for 56.8% of all procedures performed and public procedures accounting for 43.2%. Notably the Australian Medicare figures do not take into account the number of hospital procedures (both in-patient and out-patient) performed so the actual number of procedures performed annually is likely to be much larger. There is currently no database available for the number of public hospital procedures.

The cohort from this survey suggests that the number of procedures between private and public facility is approximately equal.

Using the numbered participants and number of procedures from this survey, the average practitioner's workload was calculated to be 171 procedures a year in public centres and 394 procedures a year in private practice. More physicians than surgeons were represented in both public and private hospitals (Figure 2.1). Out of 268 proceduralists in the public sector, physicians made up 50.2%, surgeons 42.3%, nurse endoscopists 0%, GPs 2.6% and trainees 4.9%. In the private sector, out of 153 proceduralists, physicians made up 56.1%, surgeons 38.6%, nurse endoscopists 3.3% and GPs 2%.

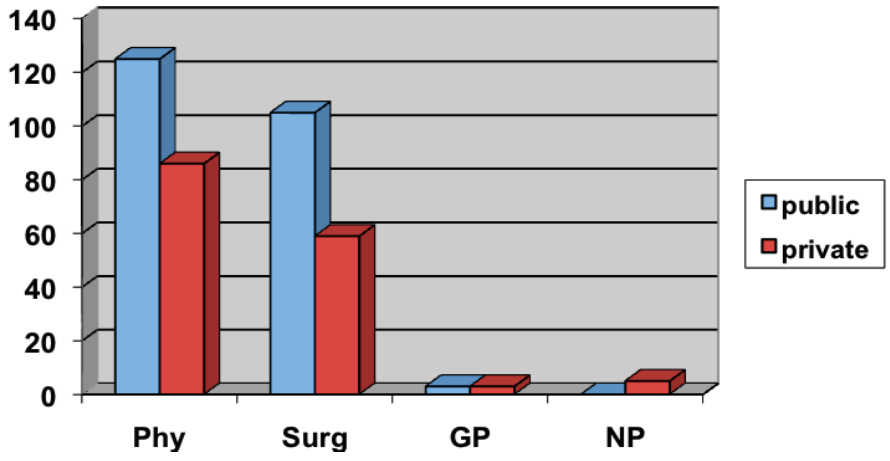


Figure 2.1: Number of proceduralists in private and public hospitals

General practitioner participation in both private and public centres was limited, with 7 reported in public centres and 3 reported in private centres. Public centres reported 13 trainees and no nurse endoscopists. In contrast, no trainees and 5 nurse endoscopists were reported in private centres.

4. Who administers sedation and approximately in which proportion (%)?

The overall participation of the different groups administering sedation is seen in Figure 2.2. In some centres there was differing anaesthetic support so further subdivisions were required to capture the percentage on non-anaesthetic participation in the provision of providing sedation.

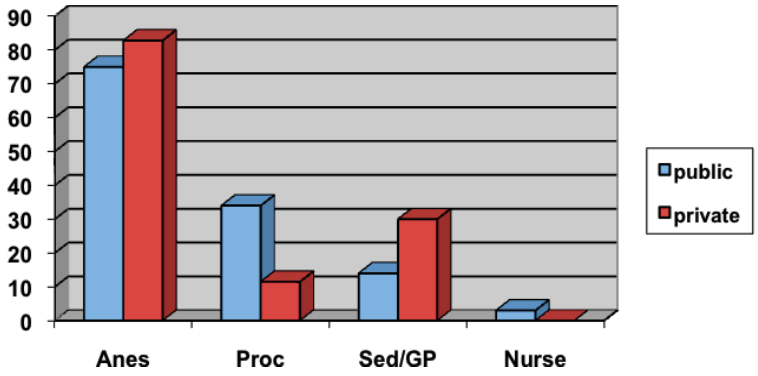


Figure 2.2 Percentage of participation in the provision of sedation in public and private units

Sedation in the public sector; was predominantly administered by anaesthetists (60.9%) followed by proceduralists (19.4%), GP/sedationists (13.8%), registered nurses (5%) and medical assistants (0.9%). In 53.3% of public practices, anaesthetists were fully responsible for administration of sedation and in 30% of centre they were responsible 10-90% of the time. In 10% of public practices, GP/sedationists were fully responsible for sedation administration and a further 3.3% were responsible for sedation administration 85% of the time. No proceduralists were responsible for 100% of sedation administration; however they were responsible for 5-90% of sedation in 33.3% of practices. Similarly no registered nurse was 100% responsible for sedation administration but was responsible for 20-80% of sedations in 10% of practices.

Medical assistants were rarely responsible for sedation, with none responsible for sedation 100% of the time and only 3.3% responsible for sedation 25% of the time.

In the private sector, sedation was predominantly administered by anaesthetists, (67.7%), followed by GP/seditionists (27.9%), proceduralists (3.53%) and Medical assistants (1.2%). In 56% of practices, anaesthetists were 100% responsible for administration of sedation, and a further 28% were responsible for sedation administration 10-90% of the time. In 4% of practices, GP/sedationists were 100% responsible for sedation administration, and a further 24% were responsible for sedation administration 40-90% of the time. No proceduralist was responsible for 100% of sedation administration, instead responsible for 10-60% of sedation in 8% of practices. Medical assistants were rarely responsible for sedation, with 4% responsible for sedation 20% of the time. Registered nurses were not responsible for sedation administration in any of the private centres.

5. Who performs airway management and approximately in which proportion (%)?

In public hospitals, airway management was conducted by anaesthetists (58.1%), nurses (25.6%), proceduralists (9.3%) and GP/sedationists (6.98%). Anaesthetists performed 100% of airway management in 53% of practices, while a further 26.7% of anaesthetists performed airway management 10-90% of the time. Nurses performed 100% of airway management in 10% of practices, while a further 26% performed airway management 10-90% of the time. GP/sedationists performed airway management 100% in 6.5% of practices while a further 3.2% performed airway management 50% of the time. No proceduralist was responsible for airway management 100% of the time in the public sector; however 12.9% of proceduralists in private centres performed airway management 75-90% of the time.

6. What is the recommended fasting time at your institution?

The recommended fasting times ranged from 3-12 hours, with median of 4 hours in all centres. The mean fasting times between public and private hospitals were 6.4 and 5.5 hours respectively. The discussion of optimal fasting times has received much attention in the anaesthetic and emergency medicine literature. There is a delicate balance for patient comfort and safety. Given that general anaesthetic reduces reflexes that prevent regurgitated gastric juices reaching the lungs, a 2009 Cochrane review reported that as a

result patients are often advised to eat or drink nothing from the midnight before surgery. However, the review of trials found that drinking clear fluids up to a few hours before surgery did not increase the risk of regurgitation during or after surgery. Patients at risk of regurgitation under anaesthetic include those who are pregnant, elderly, and obese or have stomach disorders. *"Additional research is required in these patient populations to determine whether it is also safe for them to drink up to a few hours before surgery"* (Cochrane 2009).

7. Is any form of topical local anaesthesia used routinely?

Local anaesthetic was routinely used in 67% of public centres. In contrast however, only 36% of private practices reported using local anaesthetic routinely ($p<0.05$).

It has been shown that sole use of local anaesthesia without intravenous sedation can be used effectively to carry out upper gastrointestinal procedures (Fisher and Baldo, 1993). Propofol however, is very effective in ameliorating the gag effect, which is the major impediment to performing an upper endoscopic procedure. The depth of sedation when performing an upper endoscopic procedure has to be maximal to overcome the initial gag phenomena. The difference in use of local anaesthetic agent in public and private hospital may be related to the universal use of propofol in private centres.

8. Which sedation agents are commonly used?

9. Are the above drugs used in combination?

Administration of sedation agents in combination was common in both public and private endoscopy centres, with 35.7% of public centres reporting that sedation agents were *"always"* used in combination, and a further 64.3% reporting that sedation agents were *"usually"* used in combination. In the private setting, 20.8% of practices reported *"always"* using sedation agents in combination, and a further 75% reported *"usually"* employing sedation agents in combination. Only one private centre, reported never using sedation agents in combination.

In the public sector, the sedation agents of choice were midazolam, propofol and fentanyl, used in 26/29 centres (89.7%), 26/29 centres (89.7%) and 25/29 centres (86.2%) respectively. Diazepam and alfentanil were less commonly employed, being

used in 3/29 centres (10.3%) in both cases. The use of other benzodiazepines, etomidate, ketamine or barbiturates as sedation agents was not reported.

In the private sector, propofol was used universally in 26/26 centres (100%), followed by midazolam (24/26 centres, 92.3%) and fentanyl (23/26 centres, 88.5%). Diazepam and pethidine were less commonly employed, used in 2/26 centres (7.7%) and 1/26 centre (3.8%) respectively. The use of other benzodiazepines, etomidate, ketamine or barbiturates was not used in any private centres.

In the USA a combination of a benzodiazepine and a narcotic is used in approximately three quarters of procedures with only 25% of procedures using propofol (Cohen et al., 2006).

Apart from safety, whether or not a patient is sedated appears to affect the success rate of the procedure. In a double blind, randomised trial of sedation versus placebo for panendoscopy, satisfaction and willingness to repeat the procedure were higher in the sedated group. Patient satisfaction was low in the placebo group (79% versus 47%) and was reflected in lower successful endoscopy rates in unsedated patients (success rate 76% in the sedation group versus 46% in the no sedation group. Further 10% of the placebo group crossing over to the sedation group, whereas none of the sedation group crossed over to placebo (Abraham et al., 2004).

10. Which of the following monitoring (BP, PR, pulse oximetry or capnography) are available?

In public centres, pulse oximetry was routinely monitored in 100% of practices; cardiac (rhythm) monitoring was routinely monitored in 54% of centres and in select cases in 32% of centres. Capnography was routinely monitored in 70% of centres and in select cases in 23.3% of centres; and blood pressure was routinely measured in 83.3% of centres and in select cases in 16.7% of centres.

In private centres, pulse oximetry was routinely monitored in 100% of practices; cardiac monitoring was routinely monitoring in 32% of centres and in select cases in 24% of centres. Capnography was routinely monitored in 30% and in select cases in 12.5% of

centres; and blood pressure was routinely measured in 87.5% of centres and in select cases in 12.5% of centres.

In this survey use of the pulse oximeter was universal while the regular use of capnography and cardiac monitoring was not. Routine capnography was used more in the public than private centres (70% vs. 30% p=0.02), as was cardiac monitoring (54% vs. 32%, p=0.007).

Pulse oximetry has had widespread acceptance with detection of hypoxia significantly increased 20 times than with clinical observation alone (Moller et al., 1993b)**.** In an interesting randomised control study looking at pulse oximetry and anaesthetic complications, cardiac arrest was less frequent 4 in 9578 cases with pulse oximetry and 11 in 9772 cases without pulse oximetry but p=0.06 was just out statistical significance (Moller et al., 1993b).

Capnographic signs of respiratory depression precede hypoxia in all patients. However, capnography exhibits imperfect specificity because not all patients with respiratory depression ultimately developed hypoxia (Wright, 1992, Miner and Burton, 2007). The benefits of capnography are not as widely accepted. This may be due to spurious warnings, lack of clinical significance as even evidence of respiratory depression resolution often occurred spontaneously without hypoxia (Deitch et al., 2008)**.** Although not explored in this survey, cost of disposables associated with capnography monitoring may be a further deterrent.

B. Oxygen and Monitoring

11. During the procedure, oxygenation is provided by which of the following devices?

In thirty public centres, oxygenation was provided during the procedure by Hudson® mask in 25 centres, nasal prongs in 24 centres, and an oral oxygenating bite block in 8 centres. Similarly in twenty-five private centres; Hudson® mask was used in 22 centres, 15 used nasal prongs, and an oral oxygenating bite block was used in 11 centres.

This result may be explained by the fact that facemask has been used since the origins of anaesthesia. The nasal cannula was invented by Wilfred Jones in 1949 and has long been regarded as essential and versatile equipment for the delivery of oxygen. The

oxygenating bite-block is comparatively a recent invention.

12. During recovery, is oxygen monitoring done?

Two public centres did not complete this question and were not included in the analysis. In twenty public centres, oxygen monitoring was performed *"routinely"* in 19 and in *"select cases"* in 1 centre.

One private centre did not complete this question and was not included in the analysis. In twenty-three private centres, oxygen monitoring was performed *"routinely"* in 18 and in *"select cases"* in 5 centres.

13. During recovery, is supplemental oxygen administered?

14. During recovery, which of the following devices administers oxygen?

One public centre did not complete the questionnaire component and was not included in the analysis. In twenty-nine public centres, during the recovery period supplemental oxygen was administered *"routinely"* in 28 (96.6%) centres, with only one (3.4%) centre using supplemental oxygen in *"select cases"*. Oxygen was administered by Hudson® mask in 26 (89.7%) public centres and nasal prongs in 18 (62%) centres. In 16 (55%) centres a Hudson® mask was used in combination with nasal prongs.

Six private centres did not complete the questionnaire component and were not included in the analysis. From the remaining twenty-four private centres, 23 reported routinely administering supplemental oxygen during recovery, with one centre reportedly using supplemental oxygen in select cases. Oxygen was administered during recovery by use of a Hudson® mask in 18 (75%) centres and by nasal prongs in 11 (45.8%) centres. Hudson® mask and nasal prongs were used in combination in 10 (41.7%) centres.

In an audit, describing a series of 9223 patients undergoing colonoscopy, in which 95% received intravenous sedation, oxygen saturation was not measured in 6%, and was not administered to 28% of sedated patients. In this audit 11.4% of sicker patients (ASA 3 and 4) did not have oxygen administered. Sedation-related complications (hypotension, hypoxia, nausea and vomiting), resulting in the termination of the examination occurred in 2.9% of patients. Ten deaths related to the colonoscopy occurred within 30 days, notably five in patients with normal pre-procedure medical examinations. The authors

also reported that, in many cases, patient comprehension and consent were inadequate (Bowles et al., 2004).

C. Bowel Prep

15. What is the preferred bowel preparation used for colonoscopy in your centre?

One centre left this question blank on the survey and was therefore not included in the analysis. Data from this survey showed the use of various bowel preparations, with some centres using up to four different bowel preparations. Sodium picosulphate products was the most common bowel preparation used in both public and private centres, employed in 43.2% and 45.7% of centres respectively. In public centres, other bowel preparations used were, Colonlytely™ (21.6%), GlycoPrep™ (13.5%), and Fleet™ (8.1%). Duralax™, Prepkit C™ and Golytley™ were used rarely, each used in 2.7% of centres. One centre left this question blank on the survey and was therefore not included in the analysis.

Private centres reported that GlycoPrep™ was the next most common bowel preparation, used in 31.4% of centres. There was less use of Fleet™ (8.6%) and Prepkit-C™ (5.7%). Colonlytely™ and Magnesium citrate were rarely used, only reported in 2.9% centres each.

Morbidity and Mortality

16. Approximate number of reported complications in the year 2005-2006

Complication	Public Sector*	Private Sector#
Aspiration	49	24
Assisted Ventilation	70	35
Endotracheal Intubation	103	2
Cardiac Arrests	3	0

*45,833 procedures #60,280 procedures

Table 2.3: Approximate number of reported complications in the year 2005-2006

In this study, during the year 2005-2006, the public sector reported a complication rate of 0.49% with endotracheal intubation representing the greatest complication (0.23%). Assisted ventilation was next, representing 0.15% of complications experienced, followed by aspiration at 0.10%. Cardiac arrests were the least reported complication, with a complication rate of 0.007%.

During the same period, the private sector reported an overall complication rate of 0.25% with assisted ventilation being the most frequently encountered complication at 0.16%. Aspiration was the next most frequently encountered complication, reported in 0.07% of cases. Endotracheal intubation represented the least common complication reported in private practice, with a complication rate of 0.015%. No cardiac arrests were reported.

The reported complication rates were determined as approximate numbers and in public areas the rate of endotracheal intubation was in some cases preventative rather than a result of complication. It is possible that there may be selection bias, as the survey did not look at the ASA classification of patients in public and private facilities. Additionally intubations may have been elective and thus represents a selection bias of sicker patients in public centres.

While infrequent, aspiration rates of 7.5/1,000 in public versus 4/1,000 in private centres and cardiac arrest rate of 1/15,000 procedures in public and nil in private centres are the most important results indicating a difference in safety.

16. *How many deaths have been associated with endoscopic procedures at your institution in the past 10 years? (Deaths that have been directly caused by endoscopic procedures)*

The reported death rate of thirteen patients in public centres and none in private centres (Table 2.4) is significant. Although this is retrospective data over a ten-year period and open to recall bias, the difference is striking. It can only be speculated that the increased mortality rate may because of sicker patients undergoing therapeutic endoscopy. It can also be speculated that inadequate supervision of sedation and airway management may also be a cause for the discrepancy in mortality rates.

	Private	Public
Deaths in 10 years	Nil	13

Table 2.4: Reported deaths associated with endoscopic procedures in the past 10 years

One prospective cohort study has reported on cardiopulmonary complications that occurred during nearly 12,000 colonoscopies or panendoscopies in which patients received monitored anaesthesia care with propofol. The overall rate of complications was 0.86% for colonoscopy and 1.01% for panendoscopy. The rate of serious adverse events was much lower, with 0.16% colonoscopies and 0.16% panendoscopies. They found the rate of complications was lower for both procedures when an anaesthetist, rather than a gastroenterologist, provided sedation (Vargo et al., 2006).

Further in an audit of 33,854 patients who underwent upper gastrointestinal endoscopy, of whom 153 (0.004%) died, 13% was directly attributable to endoscopy. Eighty-eight per cent of deceased patients received sedation, but an anaesthesiologist was only present in the 20% of patients who received general anaesthesia. In this group 90% of were monitored with pulse oximetry, 24% had cardiac and blood pressure monitoring however oxygen was administered to only 45% of patients. Sedation related morbidity occurred in 0.65% of cases and contributed to three out of 153 deaths (1.96%) (Thompson et al., 2004).

2.4 DISCUSSION

We acknowledge certain methodological problem with our study, one of which was that it was retrospective and thus subject to recall bias that may have resulted in under-reporting. A further limitation is that the survey was sent to 120 centres, which is by no means exhaustive. The 48% response of those we surveyed, however represented centres in all states, and overall there was equal representation between the two groups.

Given the diversity of medical delivery in Australia, there was a great range of practices. On one end of the spectrum small centres, mainly rural, which performed as little as 116 procedures, and on the other end, metropolitan private centres, which performed more than 5000 procedures in the year. Physician and surgeons did the majority of procedures however the involvement of nurse endoscopists in private centres was of interest as was the absence of trainees in private centres.

Sedation

In general, the practice of intravenous sedation was acceptable and in line with published guidelines in terms of oxygenation and monitoring. Departure from current guidelines occurred when nursing staff or the proceduralist was responsible for the sedation. This finding supports the guideline, which recommends that an experienced clinician be solely responsible for airway management and sedation. There is much written about the lack of anaesthetic support in endoscopy clinics however, an anaesthetist was responsible for 70% of private and 50% of public endoscopic examinations. There wasn't any nursing representation in the private sector yet 33% of public units had nurses being responsible for the airway. Certainly there was a greater involvement of nurses providing sedation then performing the procedure.

Monitoring

Supplemental oxygen therapy and use of automated monitoring is generally utilised, although the use of capnography is not universal. There was still a reported complication rate in the public clinics as opposed to private clinics that reported minimal complications. Deaths directly attributed to procedure were greater in public centre whereas none was reported in private clinics. This may have been due to patient selection or that private centres have appropriately assessed patients given their

resource. This survey falls short of identifying the link between deaths and predisposing factors as it was meant protect anonymity and thus questions were broadly based to reflect lack of prejudice.

In conclusion the results of this survey identify current sedation and monitoring practices in Australia. There is a trend to using deeper levels of sedations with use of propofol. There is greater involvement of anaesthetists/sedationists in both public and private endoscopy units then commonly perceived. These findings may help clarify policy debate especially from an Australian perspective. While there are few complications and even fewer deaths, patients are still at risk when undergoing endoscopy procedures in Australia.

The results of this survey were presented at the Australian Gastroenterology Week in October 2008, in Brisbane (Appendix 3).

PART A OXYGENATION AND VENTILATION ISSUES ASSOCIATED WITH SEDATION

CHAPTER 3 MONITORING CARDIO-RESPIRATORY PARAMETERS DURING SEDATION AND THE IMPACT OF ENDOSCOPY

3.1 INTRODUCTION

Sedation for upper gastrointestinal endoscopy is commonly administered in Australia and the USA. While it is possible to perform endoscopic examination in the non-sedated patient (Fisher et al., 1998), given the option, most patients are unwilling to undergo the procedure without sedation (Madan and Minocha, 2004). There have been various sedative techniques described which have been administered by either a gastroenterologist (Yusoff et al., 2004, Vargo et al., 2002), with a nurse assistant (Weston et al., 2003) or by a dedicated *'sedationist'*/anaesthetist (Clarke et al., 2002). Moderate levels of sedation can frequently be achieved by either *'monotherapy'* or combination use of benzodiazepines, narcotics and/or propofol (Cohen et al., 2004).

The level of sedation achieved in individual patients can be unpredictable. Recent use of propofol has enabled deeper levels of sedation and has been administered safely in studies reported by all groups (Rex DK., 2008). Bispectral index has been used in anaesthetised patients to quantify depth of anaesthesia; however, muscle twitch causes interference in the non-paralysed patient and therefore is not as sensitive in the sedated patients (Fatovich et al., 2004). The American Society of Anaesthesiology has defined

four levels of sedation (Table 3.1), this being just one of several sedation classifications, all of which are observational.[xvi]

	Minimal	Moderate	Deep
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Responds to repeated painful stimulus. Not easily aroused.
Airway	Unaffected	No intervention required	Intervention may be required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained

Table 3.1: Sedation level classification from American Anaesthesiologists Task Force on sedation and analgesia by Non Anaesthesiologist

An adequately sedated, cooperative patient is preferable to a disinhibited, partially sedated or gagging patient, seen at levels of light sedation. For panendoscopic intubation titration adjustments to deeper levels of sedation is often required. In exceptional situations general anaesthesia level may be necessary when difficulty is encountered at the initial attempts at oesophogastric intubation.

Hypoxia is common in routine panendoscopy and can be a potentially life threatening complication. This occurs generally in sedated patients however it has also been noticed in non-sedated patients (Wang et al., 2000) where it is thought to be due to the obstruction of the airway by the competing endoscope. Hence, the administration of supplemental oxygen has been widely accepted.[xvii]

A feature of upper endoscopic procedures is the need to successfully negotiate the tip of the endoscope into the oesophagus without initiating the gag reflex. During this process there is a period where the oropharyngeal space has competing interest between the maintenance of the airway and ensuring passage of the endoscope. Panendoscopy usually employs an unsecured airway, often without a facemask, with oxygenation via either the oral or nasal route. The anaesthetic practise of pre-oxygenation with a closed seal at 100% ensuring nitrogen washout therefore cannot be utilised in this situation (Wang et al., 2000).

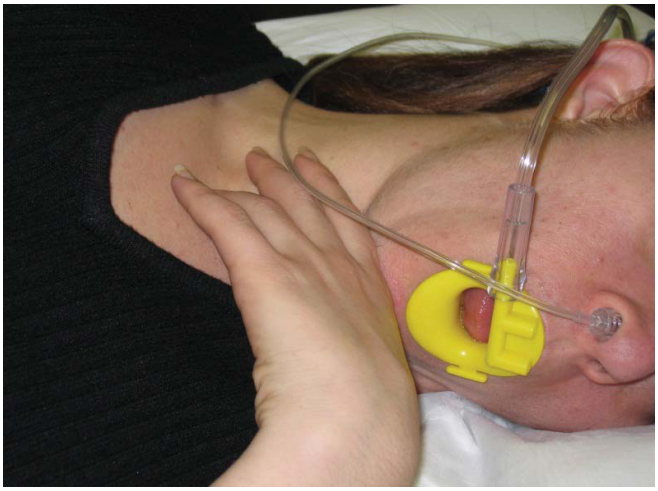


Figure 3.1 Patient with use of an oxygenating bite block and nasal carbon dioxide

Patient monitoring and prophylactic use of supplemental oxygen is generally used. Monitoring methods of oxygenation and ventilation are the pulse oximeter and capnography respectively (Figure 3.1). Use of an end tidal CO_2 monitor has been well established in anaesthetic practice and has been shown to be of benefit in sedation (Dark et al., 1990, Lightdale et al., 2006).

This clinical practice study aimed to examine the levels of sedation, associated oxygen requirement, and predictability of monitoring parameters in patients undergoing upper gastrointestinal endoscopic examination who were deeply sedated. To date there had not been a study that looked at the physiological parameters with the stages of endoscopy.

3.2 METHODS

A prospective clinical practice study was undertaken in patients undergoing endoscopic investigation of gastrointestinal symptoms in a single, private day endoscopy clinic (The Centre for Digestive Diseases, Five Dock, NSW, Australia). A single experienced endoscopist carried out endoscopic examinations. An emergency physician with advanced airway skills supervised administration of sedative agents and airway maintenance. As per standard clinical practice, prior to the procedure, demographic details and medical history was obtained. A physical examination was performed of the cardio respiratory system and the airway was assessed and given a Mallampati scores (Figure 3.2). Forced expiratory volume was performed using a peak flow meter. Patients

were assigned ASA classification (Table 3.2) and only patients who were ASA II and I was included in this study.

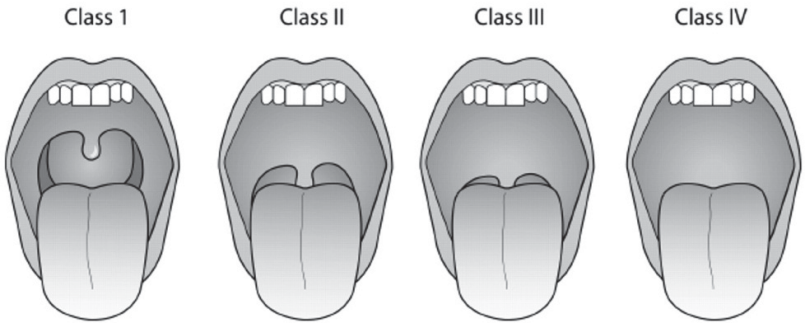


Figure 3.2 Mallampati score[xviii]

I	Normal healthy patients
II	Patients with mild systemic disease
III	Patients with severe systemic disease
IV	Patients with severe systemic - a constant threat to life.
V	Moribund patient, not expecting to survive without the operation

Table 3.2 ASA classification of physical status (circa 1941)[xix]

Spontaneously breathing patients were titrated to mild, then moderate, and finally deep sedation, in accordance with ASA sedation definition (Table 3.1), with the use of a combination of a midazolam, fentanyl and propofol.

Monitoring was commenced with baseline measures of non-invasive blood pressure, nasal side-stream capnography sampler and digital pulse oximeter using the Capnocheck^{TM} monitor (BCI Inc., Waukesha WI). Oxygen at 4 L/min was administered using the Oxyguard® (Trawax P/L, Sydney) oral oxygenating bite block. Blood pressure was measured with Omron5^{TM} (Omron Healthcare Co. Ltd, Kyoto, Japan). Airway maintenance was supervised ensuring spontaneous ventilation. Readings of the physiological parameters of pulse rate, oxygen saturation, capnography and blood pressure were obtained and plotted at baseline, prior to the commencement of sedation. Measurements were taken every 15 seconds as sedation level progressed from mild to deep as increasing levels of medication was administered. When the patient's oxygen saturation reached 90% supplemental oxygen at 4 L/minute was commenced via Oxyguard® (Trawax P/L, Sydney). Any under shoot of oxygen saturation less than 90%

(nadir) was noted. From this point, while airway patency was maintained to prevent airway obstruction, recordings were obtained at intervals of 15 sec, 30 sec, and then at 1 min. Data was recorded upon intubation, on entry into the duodenum, which was mid-procedure, and at the end of the procedure. Blood pressure readings were recorded at baseline, at the end of the procedure and at 15 minute intervals in recovery until the patient reached the second stage of recovery i.e. sitting in reclining chairs and having a drink and a snack.

Summary statistics of the one hundred patients were expressed as medians and ranges and means $\pm$ SD. Paired Student's *t*-test were used to assess the significance of changes in oxygen saturation and other cardiopulmonary variables over time. Using one-way ANOVA method, differences between oxygen saturations with regard to body weights and respiratory functions were assessed. Linear regression was used to examine the correlation of changes in oxygen saturation with cardiopulmonary variables where quoted *r* refers to Pearson's correlation coefficient.

3.3 RESULTS

One hundred patients were enrolled (49 males (52.9$\pm$13.6 yrs., range 23-78 yrs.) and 51 females (51.7$\pm$ 14.6 years, range 17-77 yrs.). All patients were able to complete the procedure. There was a single episode of laryngeal spasm, which occurred at the end of the procedure, but this resolved quickly with bag valve mask ventilation alone. There were no serious adverse events. As expected sedation-mediated hypoventilatory response occurred with increased doses of sedation and the oxygen saturation decreased towards 90%. The results for oxygen saturation for females and males are in Figure 3.3 and Figure 3.4 respectively. The increasing depth of sedation resulted in the mean pulse oximeter readings to decrease from pre-injection baseline oxygen saturation 95.7 ($\pm$1.9)% to mild 93.8 ($\pm$1.9)% (p<0.0001) and moderate sedation 92 ($\pm$2)% (p<0.0001) (Figure 3.3). This was seen in all patients. In seven patients oxygen saturation did not reach the threshold of 90% and supplemental oxygen was not commenced. In the remaining 93 patients, administration of oxygen at 4 L/min via the Oxyguard® (Trawax P/L, Sydney) oxygenating device increased the oxygen saturation from a nadir, which was the point of deepest sedation, of 88.6 ($\pm$ 2.38)% in a time-dependent fashion to 95.1

(± 2.7)% at 1 min (p<0.0001) (Fig. 3.3). A similar pattern was observed in males and females, whose age and body weights, were equally matched between the groups. However, males given supplemental oxygen had a trend towards slower increase in oxygen saturation rising from pre-oxygen saturation although this did not reach statistical significance 88.2 (±2.2)% to 89.4 (± 2.7)% (p=NS) at 15 sec (Figure 3.5) compared with 89.0(± 2.5)% to 90.6(± 2.5)% (p<0.0001) in females (Figure 3. 4).

Graph below demonstrating percentage oxygen saturation at each stage of sedation (mean and standard deviations, dark box=range)

(***= p <0.0001 compared with mean percentage oxygen saturation at nadir)

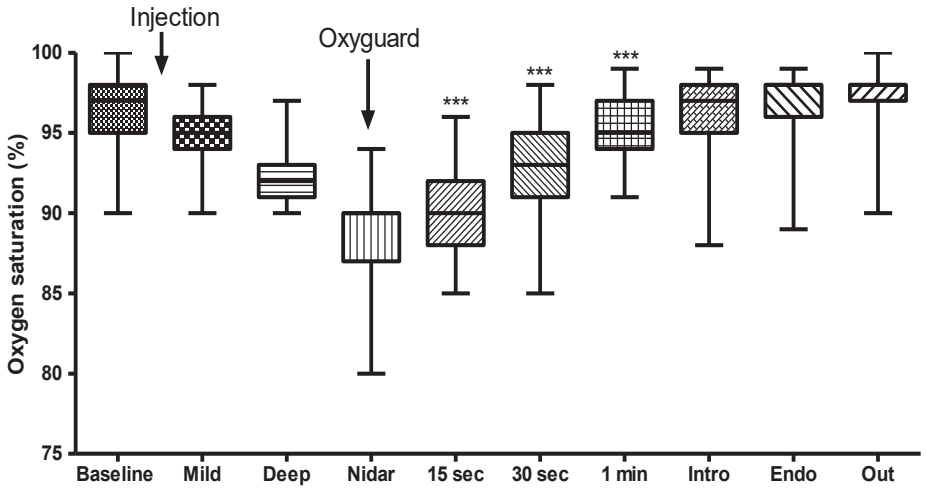


Figure 3.3. Effect of supplemental oxygen via oxygenating mouthguard (Oxyguard® (Trawax P/L, Sydney)) in 100 patients

Graph below demonstrating percentage oxygen saturation at each stage of sedation (mean and standard deviations, dark box=range)

(***= p <0.0001 compared with mean percentage oxygen saturation at nadir)

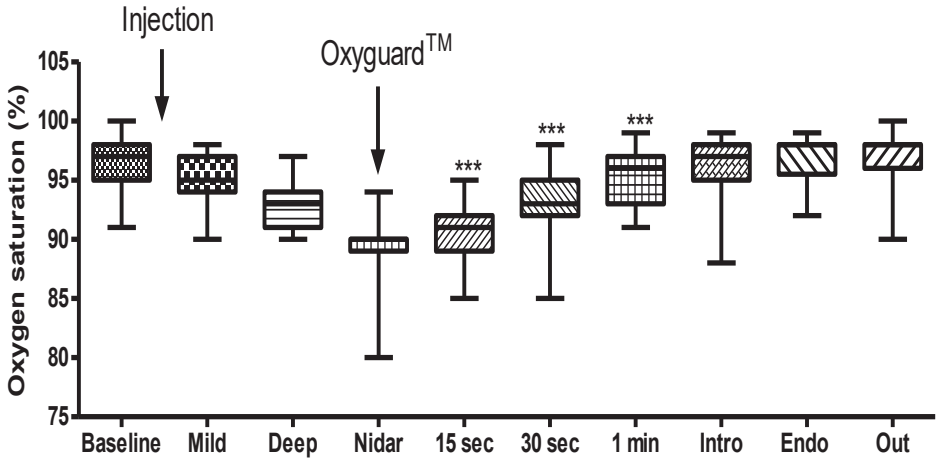


Figure 3.4 Oxygen saturation levels in 51 females undergoing panendoscopy on oxygen via Oxyguard® (Trawax P/L, Sydney).

Graph below demonstrating percentage oxygen saturation at each stage of sedation (mean and standard deviations, dark box=range)

(***= p <0.0001 compared with mean percentage oxygen saturation at nadir)

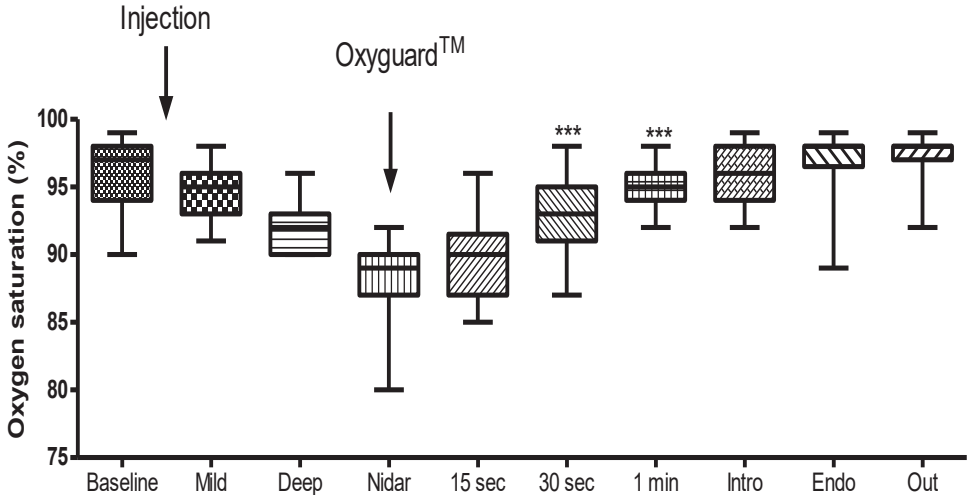


Figure 3.5. Oxygen saturation levels in 49 males undergoing panendoscopy on oxygen via Oxyguard® (Trawax P/L, Sydney).

There wasn't a correlation between Body Mass Index (BMI) and oxygen saturation in this study. The result however was not statistically significant and other studies have noted BMI to be a cause for anaesthetic and airway difficulties (Wani S., 2011) (Table 3.3).

	Body weight (kg)				***P* value**
	55.3 ± 5.3 (45-61)	66.2 ± 2.6 (62- 70)	77.4 ± 3.8 (72-84)	90.4 ± 6.2 (85-110)	
Baseline O_2 (%)	97.5 ± 1.5	96.8 ± 1.6	95.9 ± 2.4	95.9 ± 1.9	NS*
Sedation lowest O_2 (%)	89.3 ± 3.3	89.4 ± 3.1	88.3 ± 2.5	88.7 ± 1.7	NS*
Post-supplemental O_2 (%)	96.7 ± 1.8	96.0 ± 2.2	96.6 ± 1.8	95.6 ± 2.2	NS*
During endoscopy (%)	97.3 ± 1.6	96.8 ± 1.9	97.4 ± 1.9	96.9 ± 2.4	NS*

Table 3.3 Correlation of oxygen saturation and body weight (ANOVA)

As respiratory function reflects ventilation capacity, peak flow expiratory rates were measured. The data however shows that peak flow expiration rate does not predict which patients are likely to become hypoxic. The respiratory function as measured by peak flow meter is shown in (Table 3.4).

	Peak Flow Expiratory Rate			*p* value
	290 ± 54.11 (130-350)	432.3 ± 29.1 (360-480)	581.8 ± 59.8 (500-740)	
Patients (n)	33	30	28	NS*
Baseline O2 (%)	96.4 ± 1.9	96.7 ± 1.89	96.2 ± 2.2	
Sedation lowest O_2 (%)	89.2 ± 2	89.1 ± 2.97	88.3 ± 2.2	NS*
Post-supplemental O_2 (%)	95.7 ± 2.5	96.7 ± 1.9	96.4 ± 2.3	NS*
During endoscopy O_2 (%)	96.7 ± 2.2	97.2 ±1.6	96.9 ± 2.3	NS*

*, Comparison between PFER test groups (ANOVA)

Table 3.4 Effect of respiratory function on oxygen saturation a) following sedation b) with supplemental oxygen and c) during endoscopy

In contrast, there was a statistically significant correlation between respiratory rate (RR) and changes in oxygen saturation over time (Table 3.5). Pearson's correlation revealed a significant correlation of oxygen saturation with respiratory rate -0.084, (p=0.014). There was no correlation between end tidal carbon dioxide and oxygen saturation r=0.049, nor heart rate and oxygen saturation (p=0.15) (Table 3.5).

Pearson's Correlation	**HR**	**ETC02**	**RR**
R	-0.047	0.049	-0.084
P value	0.17	0.15	0.014

HR, Heart Rate; $ETCO_2$ arterial CO_2 tension; RR, Respiratory Rate

Table 3.5. Relationship between changes in oxygen saturation, HR, $ETCO_2$ and RR a) following sedation b) with supplemental oxygen and c) during endoscopy

3.4 DISCUSSION

In this study there was a predictable time-dependent improvement of oxygenation after reaching a nadir in spontaneously breathing patients undergoing sedated endoscopy. Oxygen saturation rose within one minute in most patients and in all patients at two minutes. In general, pre-oxygenation can be achieved in a closed circuit by eight deep breaths in sixty seconds, which is equivalent to three minutes tidal volume breathing (Baraka, 1999, Baraka, 2003). Since ventilation was measured by capnography in an open system, the ventilation rate and a trend when compared with the patient's baseline trace was all that was available to monitor adequate respiration. All patients had successful intubation by the endoscopist.

It is of note that at the point of introducing the endoscope into the oropharynx, there is a vulnerable period in which a combination of hypoventilation from sedation and/or obstruction by the endoscope could result in critical hypoxia. Furthermore, the time lag seen in this critical period must be considered, particularly in cases where levels of sedation are being increased to facilitate intubation in the case of a single operator who is responsible for the procedure and the administering of sedation.

Previous studies assessing apnoea have shown capnography to be superior to oxygen saturation levels or visual assessment in detecting apnoea and hypoventilation (Miner et al., 2003, Vargo et al., 2002). Similarly, studies in a paediatric population undergoing endoscopy and receiving oxygen via a nasal cannula found patients were less likely to experience a decrease in oxygen saturation, if capnography was used for monitoring ventilation (Lightdale et al., 2006). As ventilation and oxygenation are interrelated, not surprisingly there was a significant correlation between respiratory rate and oxygen saturation.

An unexpected finding in this study however was the lack of correlation between end tidal carbon dioxide and decreased oxygen saturation as capnography changes mirror respiratory rate. The dilution effect of gas sampling process or placement of expired carbon dioxide port in the presence of fluctuating breathing patterns between nasal and oral over the course of the procedure may be responsible for this discrepancy. Certainly

it should be noted that the paediatric population are obligate nasal breathers, therefore the findings of Lightindale's study may not be applicable to the adult population of this study.

The utility of capnography in such an open system with dilution effects is not as well established. It would thus appear that capnography monitoring of ventilatory status in patients undergoing sedation with an open system is not as reliable as seen in other sedation / anaesthetic situations using a closed seal system.

The respiratory rate, which was a secondary derivative of the capnography reading, and independent of whether the system was open or closed, however did correlate with falls in oxygen saturations. A decrease in the oxygen concentration with increasing depth of sedation occurs particularly with moderate to deep levels of sedation. The capnography tracing and absolute values obtained in this setting did not correlate with this fall.

This study was not able to demonstrate a correlation between peak flow expiratory rate and oxygen desaturation rates. The results confirm an early study using spirometry which also failed to correlate oxygen desaturation with functional expiratory to functional vital capacity ratio (Dark et al., 1990). The ability of monitoring devices to determine adequate ventilation, using capnography alone, may have a limited role when employed in adults using an open system of oxygen delivery.

In any case where the solo endoscopist is also responsible for the supervision and/or administration of sedation, it is quite possible the distraction of performing the procedure would impair vigilance of the patient's cardiovascular status. Safety concerns are relative in the setting of a short simple procedure. The general public have a perception that this diagnostic procedure should be completely safe and any measures to reduce sedation related cardio respiratory complications is warranted.

As seen from this study, while performing an endoscopic examination it is possible to use a single apparatus to deliver a 2-4L/min flow of oxygen. There is a need to sample expired carbon dioxide to improve monitoring of ventilation with both the use of an oral and a nasal device. Such a device forms the basis of the next chapter.

The results of this study were presented as a poster presentation at the 2005 Australian Gastroenterology Week (AGW) in 2005 (Appendix 4).

CHAPTER 4 DESIGN AND DEVELOPMENT OF TWINGUARD^{TM} FOR SEDATION MONITORING AND OXYGENATION

4.1 INTRODUCTION

Hypoxaemia occurs when the oxygen saturation in the arterial blood is less than 90%, whereas hypoxia is a pathological term for inadequate oxygen supply (Dark et al., 1990). Published data shows that decreased arterial oxygen saturation commonly occurs during gastrointestinal endoscopy (Murray et al., 1990, Dark et al., 1990). Desaturation can occur from intravenous sedation agents, which can have a direct effect on the respiratory centre, occupying brainstem benzodiazepine receptor sites and reducing respiratory drive (Bell, 1990b). The physical presence of the endoscope is also known to cause minor degrees of hypoxia, most often as a result of coughing or aspiration, or by a reflex mechanism (Bell et al., 1991b). Numerous studies suggest that hypoxia during endoscopy can result in tachycardia, electrocardiographic ST-segment elevation or depression indicative of ischemia and both atrial and ventricular arrhythmias (Lieberman et al., 1985). The majority of cardiac arrhythmias, which occur during endoscopy, are thought to be as a result of hypoxia (Bell et al., 1991b).

Administration of oxygen is an important intervention for maintaining safety during endoscopy by reversing and preventing complications from hypoxia. Prevention of hypoxia typically involves the delivery of supplemental oxygen by facemask or nasal cannula (Wang et al., 2000). It has been shown by using thermostats in the mouth and nostrils of patients undergoing routine endoscopy, that most patients breathe predominantly via the mouth rather than the nose following intubation of the oesophagus and that this oral breathing continues until the endoscope tube is removed (Bell et al., 1991a). This alternating breathing pattern makes dual oral-nasal oxygenation a preferential delivery design to combat hypoxia. Capnography has also become an integral part of monitoring in anaesthesia and involves the monitoring of the concentration or partial pressure of carbon dioxide (CO_2) in the respiratory gases,

helping to provide a swift differential diagnosis of hypoxia before irreversible brain damage can occur (Rushton and Gillbe, 1998).

The use of bite blocks in endoscopy has been common practice for decades. Bite blocks are intended to protect the patient and the instrument during upper-gastrointestinal endoscopy and typically consist of a one-part plastic molded design with a simple head strap to keep the device positioned in the patient's mouth.

Until 2007 the most popular bite-block in Australia was the Oxyguard® (Figure 4.1B). It consists of a bite block with included oxygen inlet and flow ports to allow supplemental oxygen to be delivered simultaneously to the nose and mouth during endoscopic procedures.

A. Conventional Bite Block **B. Oxyguard®**

Figure 4.1 Conventional bite block and Oxyguard® (Trawax P/L, Sydney)

Pictured is a conventional Bite Block compared to the Oxyguard® (Trawax P/L, Sydney). The similarity in *"bite block"* design of the Oxyguard® (Trawax P/L, Sydney) is substantially equivalent to traditional bite blocks and as such it inherits some of its limitations (Figure 4.2). Specifically the aperture width is limited to general endoscopy use and does not allow the entry of an oesophageal dilator as well as having ridging which can cause dental trauma. This device can only be used for panendoscopy. Patients going on to have a colonoscopy or being transported to recovery will require the use of an additional oxygenating device commonly a facemask with the associated consumable cost. Current devices are reusable however in the age of stringent infectious diseases protocol a single use device would be preferable.

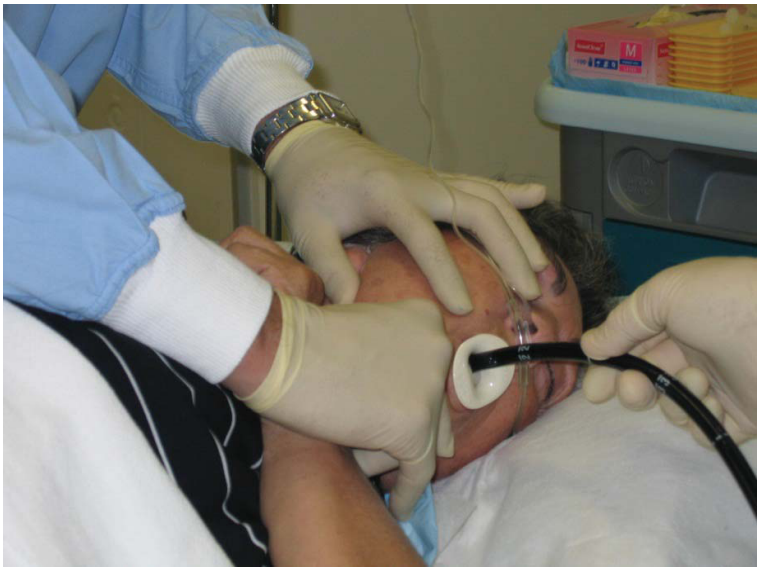


Figure 4.2 Conventional bite block in use

Currently marketed oxygenating mouth guards have shown equivalent efficacy to nasal cannula for oxygenation (Bell et al., 1992). The Oxyguard® (Trawax P/L, Sydney) oxygen delivery system combines oxygen delivery with a bite-block. The Oxyguard® (Trawax P/L, Sydney) is an open system with a bite block and nasal outlet which means that there is a large dilution effect in sampling as opposed to a closed ventilator circuit. With the Oxyguard® (Trawax P/L, Sydney) the flow of oxygen is directed to the nose and mouth simultaneously so the changes in patients breathing pattern is accommodated. However the Oxyguard® (Trawax P/L, Sydney) has the distinct disadvantage of being removed immediately after the procedure, at a time which maximal desaturation may occur. Supplemental oxygen during the recovery period has additionally been shown to reduce the incidence of postoperative nausea and vomiting (Greif et al., 1999). Prior to the availability of the Oxyguard®(Trawax P/L, Sydney) hypoxia would be treated by the use of either oxygen mask or nasal prongs. However currently marketed nasal prongs are not ideal for oxygenation. They can shift, resulting in impaired delivery of oxygen to the nasal passages; can cause physical irritation to the patient; they have sharp edges making them uncomfortable to wear; and are visually unappealing. For a patient undergoing endoscopy, additional equipment in and around the mouth and nose not only increases anxiety to the patient but also can further complicate the procedure due to additional gadgetry. An opportunity currently exists to improve on the mouth guard and oxygenating systems on the market.

4.2 AIM OF DESIGN

The aim of this project is to design a bite-block that:

- Improves on the current methods of oxygen delivery to patients during endoscopy to enable continuous flow of oxygen to patients before, during and after upper gastrointestinal endoscopic procedure.
- To enable oxygen to be delivered via both oral and nasal routes thereby reducing the risk of hypoxia in patients.
- To improve the aesthetics and ergonomics for current bite blocks
- To include capnography ports to allow for sampling of carbon dioxide and therefore enable ventilation measurements.
- To improve patient comfort.

4.3 PROTOTYPE DESIGN

The prototype was based on improving Oxyguard® (Trawax P/L, Sydney) bite block which in turn was modelled on existing bite blocks on the market, being of a similar size and shape to existing bite blocks. There is a paediatric size for smaller sized mouth opening. The Oxyguard® (Trawax P/L, Sydney) has been on the market since 1992. Over 1.5 million Oxyguard® (Trawax P/L, Sydney) products have been sold worldwide.

The design of a new device TwinGuard® to be used during endoscopy procedures was undertaken, in particular to address some of the limitations of Oxyguard® (Trawax P/L, Sydney) (Figure 4.3).

Unlike the Oxyguard® (Trawax P/L, Sydney) which is a single-piece moulded plastic held in place by the patient's teeth due to passive mouth closing, the new design would include the use of a pliable oxygenation device which would allow oxygenation. The main feature of the Oxyguard® (Trawax P/L, Sydney) is that it incorporates a port for connection of a gaseous oxygen supply line via channels moulded into the bite block.

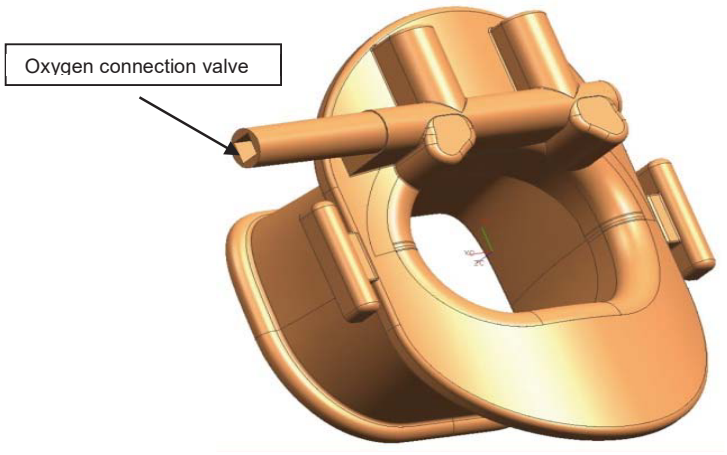
Oxygen supplied to the port is directed towards the patient's nares and into the patient's mouth (Figure 4.3). This dual flow mechanism would be again used in designing a new oxygenating device.

Oxyguard® (Trawax P/L, Sydney) has two versions, a reusable and a disposable version. The reusable version is intended to be disinfected (autoclaved) prior to each use and is discarded after 10 disinfection cycles. The disposable version is discarded after single-use. There are therefore associated issues of observing proper infection control protocols and efforts to have a single use device would ideal.

A further limitation was although the Oxyguard® (Trawax P/L, Sydney) device was adequate in providing passage of the endoscope there was insufficient space available for oesophageal dilatation device or addition of a second device such an oral suctioning device while performing endoscopy.

In summary, the Twin Guard® would aim to address the following:

- Protect the endoscope from mechanical damage, particularly by the patient's teeth.
- Protect the patient's mouth from injury by the endoscope during manipulation of the endoscope.
- To deliver oxygen to patients in low to medium concentrations 2-4litres/minute.
- To provide a means to sample carbon dioxide ($CO_{2)}$. (Measures of expired CO_2 are to be taken by an attached capnograph).
- Be a single-use device only.



A. Oxyguard® (Trawax P/L, Sydney) with oxygen valve

B. Oxyguard® (Trawax P/L, Sydney) with oxygen tubing attached

Figure 4.3 Oxyguard® (Trawax P/L, Sydney) with A) oxygen connecting valve and B) in use during endoscopy

The TwinGuard® prototype sample was designed to replace current nasal prongs and improve on current capnography sampling ports. The prototype was designed with three new key features;

1. A new nosepiece/nasal prong.
2. Capnography ports for oral and nasal attachment.
3. A modified mouthguard to allow for the detachment of the nasal component. The design therefore consists of a mouthpiece, a nosepiece and capnography ports.

The TwinGuard® is designed to maximise the delivery of supplemental oxygen, with delivery ports at close proximity to both the nose and mouth. Similarly by having the sampling ports close to both nose and mouth, the TwinGuard® is also designed to reduce dead space, allowing improved detection of carbon dioxide trends from baseline.

This forms the basis of detecting adequacy of ventilation so that earlier rescue interventions can be implemented thereby increasing safety.

Figure 4.4 Prototype diagram of TwinGuard®

The following considerations were taken into account when designing the new mouthguard (Figure 4.5 and 4.6);

1. The design shall consist of a mouthpiece, a nosepiece and capnography port.
2. The form/shape needs to accommodate facial features to ensure an ergonomic and comfortable fit across a wide variety of patients.
3. The design shall allow an oxygen flow rate over the range of 2-4 L/min.
4. The design shall look appealing.
5. The mouthpiece is to be designed without a rib to prevent potential dental adverse events such as the chipping of patient's teeth.

6. The design must also include fitment to the patient. When in use, the device must have minimal movement.
7. Consideration shall be given to the cable management of the oxygen and capnography tubing.
8. The mouthpiece shall be made of a hard plastic to withstand mechanical forces of teeth and endoscope and the nasal piece shall be made of soft flexible plastic to allow it to mould to various shaped faces.
9. The nasal piece shall suit the conventional off the shelf tubing commonly available.

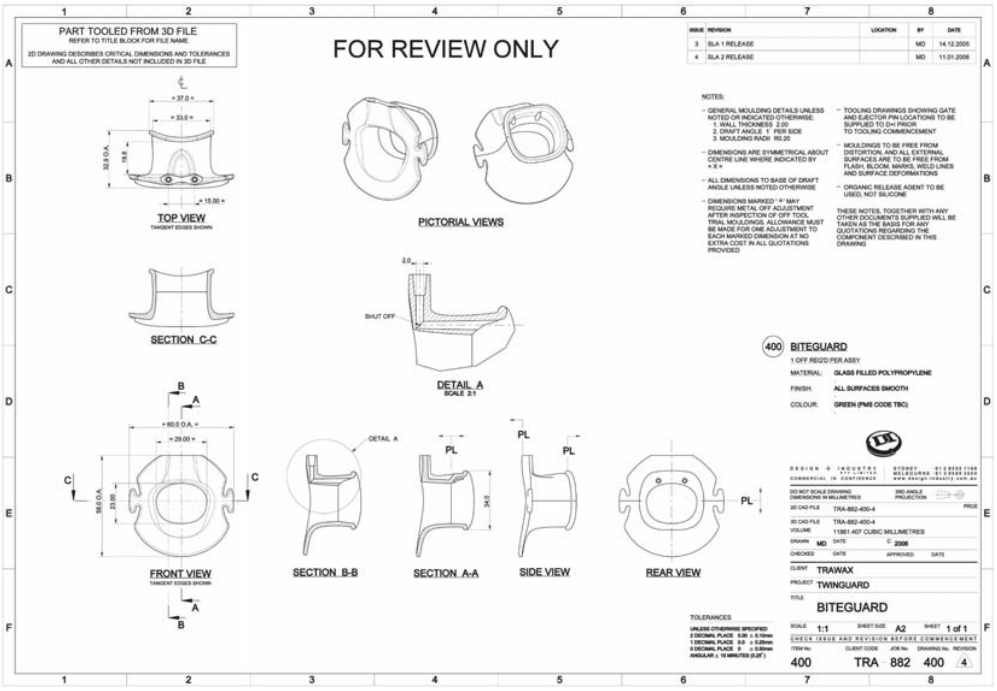


Figure 4.5 Description of TwinGuard® dimensions -general

The detachable TwinGuard® oxygenating piece was designed as a symmetrical, reversible part requiring no specific orientation during fitting to the main body of Twinguard®

A. TwinGuard bite block assembled with detachable oxygenating piece at the top of the bite block

B. Cross section of TwinGuard® oxygenating piece

C. Detached TwinGuard® oxygenating piece

Figure 4.6 TwinGuard with detachable oxygenation piece (schematic drawings)

Materials used were assembled in two parts; a soft translucent TPE-Soft (shore A hardness 60-80) polymer and a hard polypropylene compound. Figure 4.7 describes the interlock detail displays flow seen in the interlock detail as equally distributed so that the cross section within the area in red is equal to the narrowest cross section in the bite

block within the are yellow. Prototype development can be seen in the appendix section of this thesis (Appendix 5).

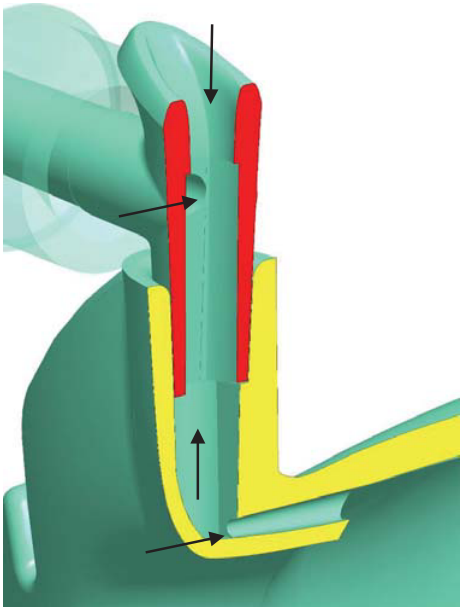


Figure 4.7 TwinGuard® schematic of interlock detail between detachable oxygenating piece and main body of TwinGuard®

The TwinGuard® device is designed to not only deliver oxygen as efficiently as a nasal cannula or the Oxyguard® (Trawax P/L, Sydney) but also allows the option to monitor carbon dioxide (capnography) both at the mouth and the nose. The TwinGuard® capnography accessory is designed to out-perform devices which simply measure carbon dioxide in the nares. Oxygen can be delivered seamlessly throughout the procedure and carbon dioxide detection can continue when the patient alternates between breathing through the nose and the mouth. The finished product (Figure 4.8) TwinGuard® oxygenation design incorporates a bite block with the functionality of a nasal cannula, delivering continuous oxygen to the mouth and the nose. After upper endoscopy is accomplished, the bite block is simply detached and discarded. The patient may then go straight to recovery or on to immediate colonoscopy allowing the patient to continue to receive oxygen without the need to fit another device, with the associated cost benefit.

Figure 4.8 TwinGuard® - The final product

The design was submitted to the Australian patent office and was granted and Australian patent in 2003 (Appendix 6). Following satisfying safety requirements and technical assessment the TwinGuard® was approved by the Food and Drug Administration in the USA for commercialisation (Appendix 8).

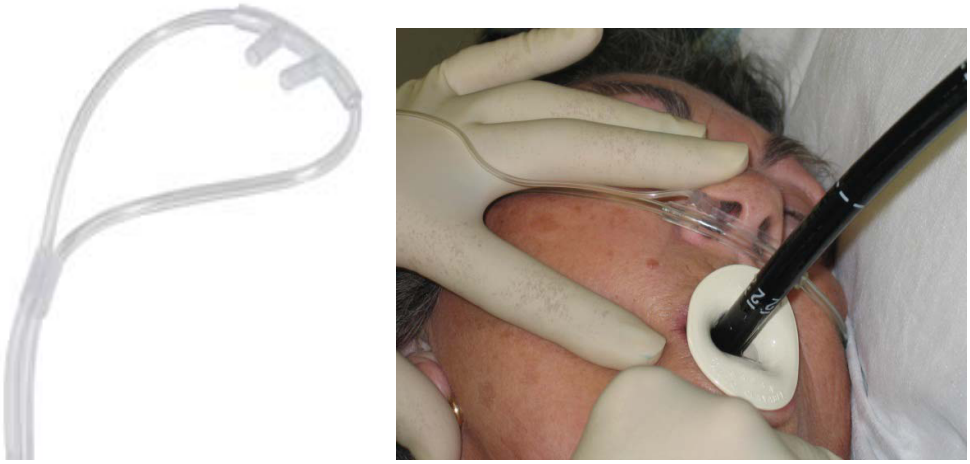
CHAPTER 5 TWINGUARD® VERSUS NASAL PRONG AND CONVENTIONAL BITE BLOCK - A COMPARATIVE STUDY

5.1 INTRODUCTION

The previous chapter dealt with the design and development of the innovative oxygenating bite block TwinGuard®. This chapter will explore whether the prototype TwinGuard® is capable of delivering an adequate supply of oxygen as well as being a superior alternative to the standard nasal prong and bite block. The study was designed to determine whether the new oral-nasal oxygenating device – TwinGuard® which is built as part of a bite block, is similarly effective in oxygen delivery during the procedure and during the recovery period when compared to existing methods such as Nasal Cannula. In providing an oral-nasal oxygenating mouth-guard that has a detachable nasal oxygenating apparatus, it is envisaged that costs will be minimised while maintaining safety and efficacy of oxygen delivery. The detachable portion bypasses the need for separate nasal annual and can provide comfort for the patient during recovery (post-procedure).

5.2 MATERIALS AND METHODS

A single centre, prospective, randomised, parallel study approved by the Centre for Digestive Diseases Human Research Ethics Committee (CDD HREC) was granted in February 2006 (CDD05/C05) and conducted to determine the safety and efficacy of the TwinGuard® oronasal (ON) device described in Chapter 4 compared to Nasal Cannula (NC) (Figure 5.1).



A. Nasal cannula **B. Nasal cannula in demonstrated use**

Figure 5.1 Nasal cannula oxygenation devices

The patient population base consisted of patients who presented to the Centre for Digestive Diseases (Five Dock, NSW, Australia) and were scheduled to undergo either a single procedure panendoscopy or double procedure with colonoscopy performed subsequently. The Investigator obtained informed consent from all patients who elected to participate in the study. Patients underwent a baseline medical assessment including cardiopulmonary examination. Eligible patients were determined by the following criteria:

Inclusion Criteria	Exclusion Criteria
Males and Females aged 18 to 80 years of age.	Patient who are unable to communicate well with the Investigators and to comply with the requirements of the entire trial.
Patients determined to be medically well-American Society of Anaesthesiology Grade I or II.	Patients considered high medical risk or patients suffering from cardio respiratory disease or ASA>III
Patients scheduled to undergo a panendoscopy.	Patients who have been involved in an experimental drug protocol within the past four weeks.
Patients who signed informed consent form to undergo the trial	Patient's non-consent to participate.
Patients without clinical evidence of any disease or which may interfere with the patient's ability to enter the trial.	Patients who are currently or have a history of drug or alcohol abuse.
Patients who have fasted for 4-6 hours prior to enrolment as per standard clinical practice for panendoscopy.	Patients who have not fasted for 4-6 hours.

Table 5.1 Inclusion/Exclusion Criteria

Eligible patients were randomised to receive either the nasal cannula (NC) or TwinGuard® (ON).

5.2.1 PRE- PROCEDURE ASSESSMENTS

An emergency physician was responsible for insertion of the intravenous cannula, administration of all drugs and airway monitoring and recording physiological parameters. Patients randomised to receive oxygenation via Nasal Cannula had sampling of carbon dioxide (CO_2) performed via the nasal route. Patients randomised to the TwinGuard® oxygenation had both oral and nasal sampling as per the sampling ports. A monitoring device, Capnocheck^{TM} (BCI Inc. Waukesha WI) (BCI Inc. Waukesha WI) was calibrated and used to measure O_2 saturation (SO_2), Heart Rate (HR), Respiratory Rate (RR) and side stream End Tidal CO_2 ($ETCO_2$) throughout the procedure for both groups. Both groups were attached to the same Capnocheck^{TM} (BCI Inc. Waukesha WI) machine which analysed all of the above perimeters, except systolic /diastolic blood pressure (BP) which was performed by the automated Omron M5^{TM} digital blood pressure monitor. Blood pressure monitoring was commenced at the onset of sedation and at the completion of the procedure, and then at 15-minute intervals during recovery.

5.2.2 PROCEDURAL ASSESSMENTS

Past history, current medications, presenting symptoms, physical examination and level of patient comfort were obtained from the patient's history and from data collected from the patient case report forms prior to the procedure. Other demographic details such as place of birth were obtained as well as respiratory consideration such as a cardio respiratory history and smoking status. Pre-procedure clinical respiratory examination with lung function was recorded with best of three attempts of peak expiratory flow rate measurement and a clinical cardiovascular examination was performed.

At the commencement of the procedure a 20G intravenous cannula was placed in the dorsal vein of the hand for the insertion of sedative agents. Sedation consisted of titrated doses of midazolam 2-5 mg and fentanyl 25-50 microgram, which were increased until

mild and moderate sedation was achieved, according to the ASA classification (Table 3.1). Incremental dose of propofol was administered to achieve deeper sedation. Periods of 30 seconds to 1 minute were allowed for initial sedative hypnotic agents to begin to take effect.

Adequate sedation was assessed by a loss of eyelash response, relaxation of the tongue and arms and ultimately suppression of the gag and cough reflex during oesophageal intubation. For most patients a single bolus of propofol was required for this to be achieved. An additional dose of propofol was administered during the procedure if there was movement, pain response or eye opening. The rate of decrease in oxygen saturation, from baseline during initial sedation was noted until it fell below 90%. The rate of rise in oxygen after commencement of supplemental oxygen from this minimal point was plotted in relation to time in 15-second intervals. The Ezi-Flow^{TM} meter controlled oxygen flow to a fixed rate of 4 litres. The change from baseline was expressed as the percentage of oxygen saturation. The secondary measurements were those related to changes in respiratory rate, heart rate and capnography occurring following sedation and during panendoscopy. The patient details including age, weight, initial measurements of lung function were compared to the variable of cardio respiratory parameters when using the oro-nasal TwinGuard® device as compared to Nasal Cannula.

As previously stated, carbon dioxide measurements were obtained nasally for the Nasal Cannula group and both orally and nasally in the TwinGuard® group. Apnoea, as opposed to detection failure, was noted if a capnographic trace was unobtainable after switching the sampling port from nasal to the oral route for between 15-30 seconds. This was confirmed by a decrease in chest movement and decrease in oxygen saturation following this adjustment. Post procedural oxygen saturation, blood pressure and heart rate were recorded by nursing staff in recovery.

As the TwinGuard's® nasal attachment was left to deliver oxygen recovery, comparison between the two devices with regards to oxygenation and comfort was sought while the patient was in recovery. The research staff noted any side effect.

5.2.3 DATA ANALYSES

As per standard statistical guidelines p value <0.05 was considered significant. The sample size of 150 patients with 75 patients in each group was determined to be of significant power for this study. Paired and unpaired t -tests and chi squared χ^2 tests were used to compare the two groups. Wilcox's sum rank test was used to determine the significance of changes in oxygen saturation. Linear regression was used to determine the correlation between falls in oxygen saturation and other patient factors such as age, weight and peak flow expiratory rate (PFER).

5.3 RESULTS

A total of 149 patients undergoing endoscopy were enrolled into the study. Table 5.2 contains data that the two groups were evenly matched demographically, although the TwinGuard® group had relatively more males than the Nasal Cannula group (M:F = 41:34 vs. 37:38 respectively). More Australian born participants was in the Nasal Cannula group compared to the TwinGuard® group (70 vs. 50 respectively) and were represented by fewer current smokers (8% vs. 13.3% respectively). Both groups were similarly matched for race, place of birth, height and weight results. These are known factors determining respiratory function (Arozollah AM., 2003).

Eighty-seven of 149 (58%) patients had both a colonoscopy as well as a panendoscopy performed. In these instances the panendoscopy was always the first procedure performed and sedation was maintained, with an interval allowing for the change of instruments and repositioning of the patient in preparation for the colonoscopy exam.

	TwinGuard® (ON)	Nasal Cannula (NC)
Number of patients	74	75
Age	24-80 (54)	20-78 (51)
M:F ratio	41:34	37:38
Race Caucasians Asian Unknown	 67 7 1	 70 4 1
Place of Birth	Australia 51	Australia 70
Smokers **Non smokers** **Ex-smokers**	8%: 61.3% 25.3% (Average11yrs since quitting)	13.3% 58.6% 26.6% (Average17yrs since quitting)
Daily Alcohol **Occasional** **Never Use**	30.6% 50.6% 14.6%	38.6% 45.3% 14.6%

Table 5.2 Characteristics of TwinGuard® (ON) and Nasal Cannula (NC) group

Twelve per cent of patients in the Nasal Cannula group were mild asthmatics, with one patient reporting previous asbestos exposure. The proportion of asthmatics in the TwinGuard® group was 7%. Other measurements such as height, weight, PFER and amount of sedation used were similar in both groups (Table 5.3 and 5.4). All patients had normal cardio respiratory examination noted in keeping with their ASA 1 and 11 medical states.

Twenty-nine subjects with Nasal Cannula and 31 with TwinGuard® underwent single panendoscopy procedure, while 45 with Nasal Cannula and 42 with TwinGuard® had additional colonoscopy examination.

	Age (yrs.)	Height (m)	Weight (kg)	PFER l/min	Midazolam (mg)
Median	55	1.7	74	440	5
Mean	50.9	1.7	74.1	441.6	4.92
Std Dev	13.8	0.1	13.3	114.7	1.11

Table 5.3 Pre procedure PFER height, weight, age and sedation requirements in the Nasal Cannula group

	Age (yrs.)	Height (m)	Weight (kg)	PFER (l/min)	Midazolam (mg)
Median	58	1.7	80	400	5
Mean	54.2	4.1	79.2	433.4	4.77
Std Dev	13.8	20.8	15.9	118.1	1.00

Table 5.4 Pre procedure PFER, height, weight, age and sedation requirements in the TwinGuard® group

5.3.1 EFFICACY RESULTS- OXYGEN SATURATION

The oxygenation levels as plotted along the phases of sedation, procedure and recovery were recorded in both groups (see Figure 5.2). The primary outcome measurement of oxygen delivery was measured as a rate in the rise of oxygenation saturation. This occurred after the pulse oxygenation detection reached a low point of around 90%. Often this was associated with an under shoot recorded as the lowest oxygen saturation (nadir). Both groups received identical source of oxygen, flow meter as well as length of oxygen delivery tubing. There wasn't a statistically significant difference in oxygen saturation levels between TwinGuard® (n=74) or Nasal Cannula (n=75) through all stages of panendoscopy.

No significant difference was noted in oxygen saturation, heart rate and respiratory rate between the TwinGuard® and Nasal Cannula group.

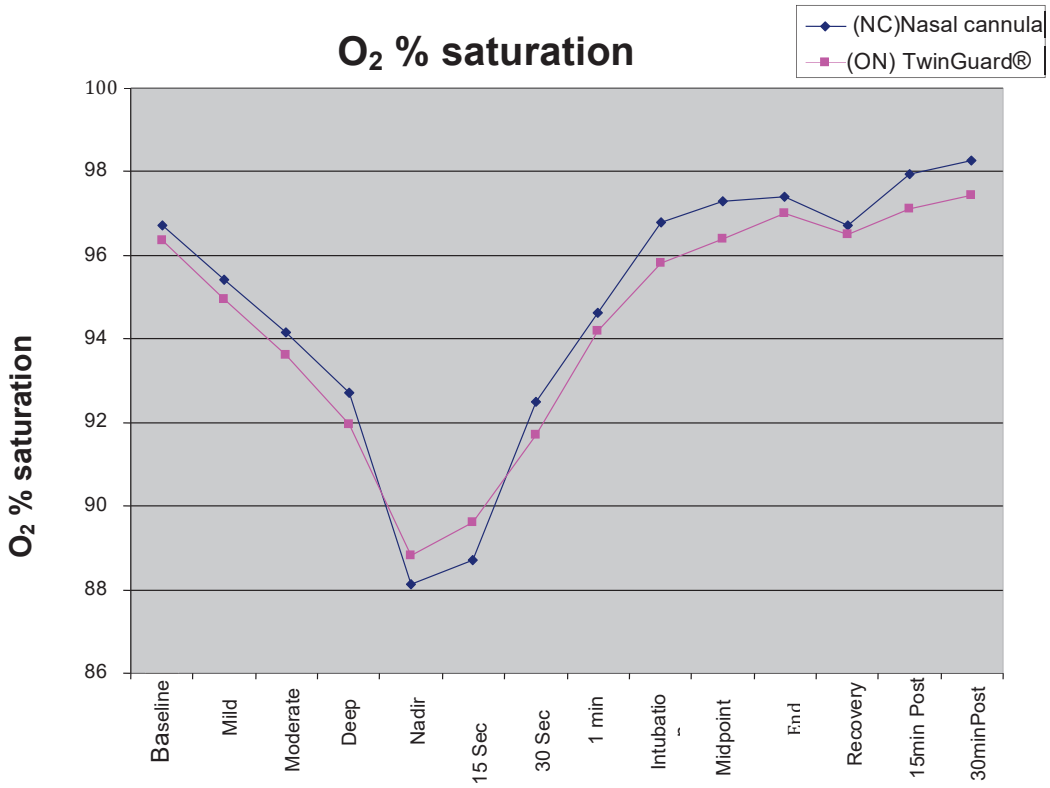


Figure 5.2 Relationship between oxygen saturation and phases of sedation, procedure and recovery

5.3.1.1 Capnography during initial sedation

As seen in Figure 5.3, at baseline, higher mean absolute $ETCO_2$ levels were observed with the Nasal Cannula group (mean=39.5mmHg, n=75) than with the TwinGuard® group (mean=29.7mmHg, n=74) (p=0.0005). At mild sedation, significantly higher $ETCO_2$ was observed with Nasal Cannula (mean=40.5mmHg; n=75) than with TwinGuard® (mean=30.9 mmHg; n=74) (p=0.0005) and again in moderate sedation $ETCO_2$ levels were significantly higher (mean=40.4 mmHg, n=75 with Nasal Cannula versus TwinGuard's ®mean=32.2 mmHg, n=74 (p=0.0005). At the point of deep sedation, higher $ETCO_2$ levels were detected with Nasal Cannula (mean=39.5mmHg, n=75) than with TwinGuard® mean=33.1mmHg, n=74, (p=0.0001).

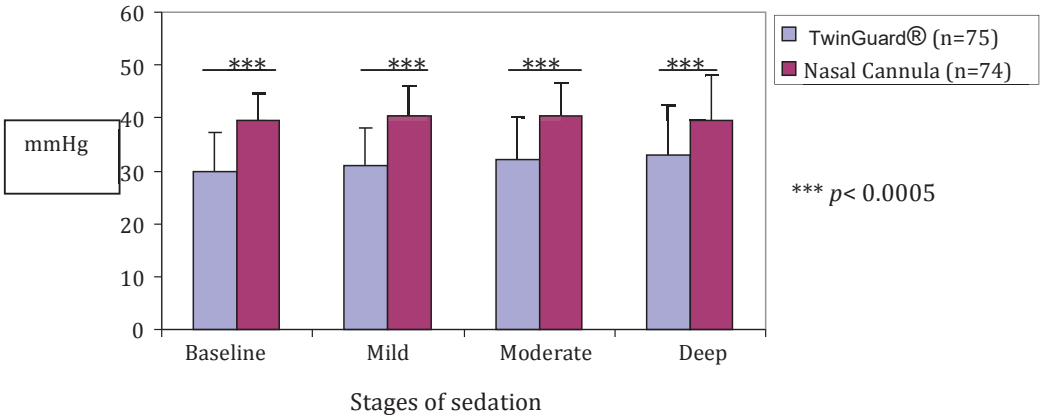


Figure 5.3 Comparison between TwinGuard® (ON) and Nasal Cannula (NC) for monitoring absolute $ETCO_2$ (mmHg) during sedation.

5.3.1.2 Capnography during Stages of Panendoscopy

Nasal Cannula also showed statistically higher $ETCO_2$ levels at the various stages of the procedure. At 30 seconds from the onset of sedation, at intubation, and on completion of the procedure (28.8 vs. 31.3mmHg (p =0.001), 32 vs. 30.3 mmHg (p =0.004), and 35.5 vs. 29.9mmHg (p=0.004) respectively the Nasal Cannula group consistently had higher $ETCO_2$ readings. Of note higher mean $ETCO_2$ levels were recorded with Nasal Cannula (59/75, 78.6%) at nadir and at 15 seconds after supplemental O_2 than with TwinGuard® (72/74) (39.2±9.9 vs. 31.4±9.3) and 29.5±9.9 vs. 35.7±10.4, p=0.0005, respectively). No significant difference in respiratory rate (RR) was observed between TwinGuard® and Nasal Cannula groups during the procedure (Figure 5.4).

Therefore nasal cannula is superior to TwinGuard® when absolute values of expired carbon dioxide are measured.

However, with sedation the relative change from base line in each individual case is of greater clinical significance and will be termed the delta change. When compared as a change from baseline, the TwinGuard® group revealed a significant trend difference during the initial sedation process (p <0.0001, (Figure 5.5 and 5.6).

No correlation was found between O_2 saturation and Heart Rate, Respiratory Rate or End Tidal CO_2 at any stage of the panendoscopy or sedation for TwinGuard®. However, a significant correlation between the parameters was obtained for nasal cannula in the following sub groups at the 0.05 level using Pearson's Correlation (2-tailed);

O_2 Sat and RR at intubation – r = -0.243, *p*= 0.039

O_2 Sat and $ETCO_2$ for mild sedation – r = 0.374, *p*= 0.001

O_2 Sat and $ETCO_2$ for moderate sedation – r = 0.299, *p*= 0.009

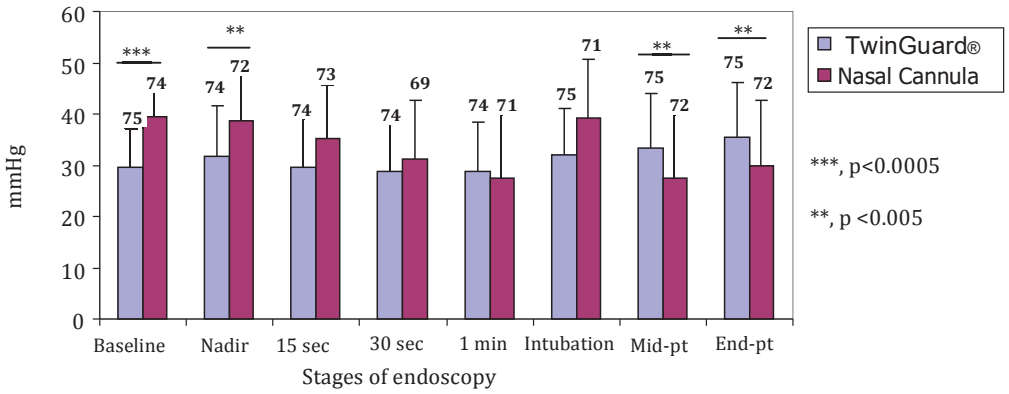


Figure 5.4 Comparison between TwinGuard® (ON) and Nasal Cannula (NC) for monitoring absolute $ETCO_2$ during endoscopy

(Numbers above bars denote number of readings for each group.)

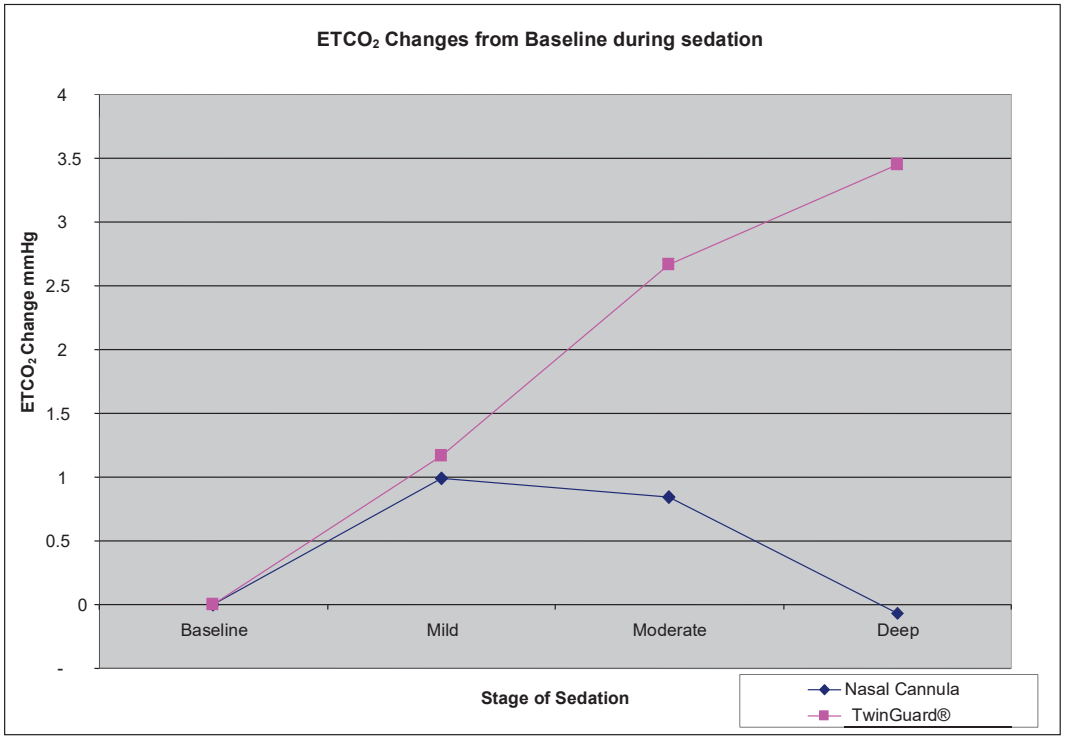


Figure 5.5 Comparison between TwinGuard® (ON) and Nasal Cannula (NC) for monitoring change from baseline in $ETCO_2$ (mmHg) during initial sedation.

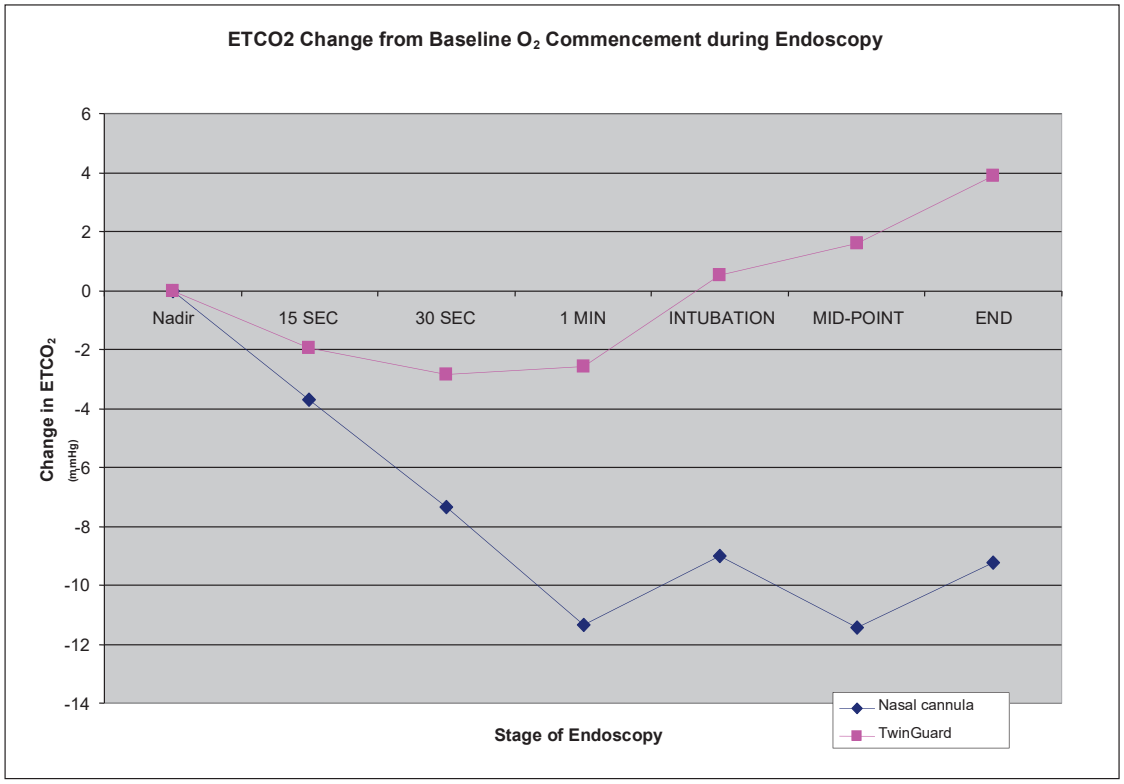


Figure 5.6 Comparison between TwinGuard® (ON) and Nasal Cannula (NC) for monitoring change from nadir in ETCO2 (mmHg) during endoscopy.

5.3.1.3 End Tidal CO_2 Detection

Consistent monitoring of $ETCO_2$ throughout the procedure was observed for 72/74 (96%) patients with TwinGuard®, compared to 58/75 (77.3%) patients in the NC group demonstrating inadequate $ETCO_2$ monitoring for 22.7% of these patients, where switching to oral sampling was required (p= 0.0005). This lack of detection was not due to apnoea but failure of detection as demonstrated by resumption of tracings after changing the detection port to the oral route. This switching led to a period of uncertainty regarding the possibility of true apnoea in the Nasal Cannula group however in the TwinGuard® group there was less nuisance alarms.

5.3.2 POST PROCEDURE

No significant difference in reported patient comfort was noted (Table 5.5). No significant adverse events were reported during this study. Only four possibly/probably related adverse events were recorded, 3 with Nasal Cannula and 1 with TwinGuard®. These were mild in nature and transient. Of note there was a lack of mechanical trauma from the use of either device and there wasn't any adverse effects related to the depth of sedation. None of the patients required rescue ventilation.

	TwinGuard® (n=74)	**Nasal Cannula (n=75)**
Unaware	32.4%	28.8%
Unaware but comfortable	24.3%	27.3%
Aware but comfortable	43.2%	41.1%
Discomfort	Nil	2.7%

Table 5.5 Patient comfort comparisons between TwinGuard™ and the Nasal Cannula group

5.4 DISCUSSION

It has been demonstrated that patients undergoing routine endoscopy breathe predominantly via the mouth rather than the nose following intubation of the oesophagus and that this oral breathing continues until the endoscope tube is removed (Bell et al., 1991a). Dual oral-nasal oxygenation would therefore be advantageous by providing an additional means of oxygenation to overcome the alternating breathing pattern. Capnography is also considered a valuable tool in recognising adverse ventilatory and circulatory events that potentially lead to serious complications. Capnography acts as a warning device by drawing attention to the events that can potentially lead to hypoxia if measures are not taken to correct the issue (Lightdale et al., 2006). Despite the American Society of Anaesthesiologist standards stipulating that continuous capnography is required for all patients undergoing general anaesthesia, it remains optional for sedation cases (Sedation and Non-Anesthesiologists, 2002). The need for CO_2 monitoring has been studied by other medical specialties that use procedural sedation, with many specialties now recommending capnography as a standard monitor (Miner, 2002). The development and validation of accurate non-invasive monitoring techniques are required to improve safety measures in endoscopy aimed at addressing potentially serious oxygenation complications. This has to be balanced with the ability to reduce false detection or nuisance alarms.

Based on the data of this trial, the combined oronasal TwinGuard® oxygen delivery system versus the nasal method of oxygenation is equivalent in terms of supplemental oxygen delivery during panendoscopy procedures. No significant difference was observed in the rates of oxygenation between the two groups. The results of the trial satisfy the hypothesis that the TwinGuard® device is at least equivalent to Nasal Cannula in providing supplemental oxygen to patients.

Although baseline detection of carbon dioxide was greater with the Nasal Cannula group, 22% had detection failure of carbon dioxide. The availability of ports available orally and nasally, in the TwinGuard® group would appear to increase the reliability in sampling $ETCO_2$, thereby improving patient care. In a paediatric study nasal capnography detection was superior in the detection of hypoventilation (Lightdale et al.,

2006), however as children are obligate nasal breathers this may not be extrapolated to an adult group. The failure of detection of carbon dioxide may be due to changes in pattern of breathing that occur in adults (Bell, 1995).

This study was not powered sufficiently to examine morbidity and mortality effect, which are rare events. Therefore secondary predictors such as the oxygen and carbon dioxide readings were used for comparison. An expected rise in carbon dioxide levels with increasing depths of sedation is a useful indicator of hypoventilation. However, when an open system is employed in panendoscopy, dilution effects from dead space provide a substantial challenge to accurately monitoring $ETCO_2$ levels. The limitations of capnography was seen in this trial where the absolute readings of carbon dioxide were higher in the Nasal Cannula group however better detection and individual‘s change from baseline was demonstrated with TwinGuard®. As a trend from baseline or delta change is generally of more use than absolute values, TwinGuard® demonstrated improved predictability in CO_2 detection over the Nasal Cannula. The improved predictability in CO_2 detection with the TwinGuard® group means that CO_2 can be reliably measured, which is particularly advantageous when contemplating use of deep sedation with agents such as propofol.

Oxygen administration via Nasal Cannula or TwinGuard® is equally effective. However, in providing an oral-nasal oxygenating mouth-guard that has a detachable nasal piece, it is envisaged that a single system can be employed from the onset of endoscopy to recovery. Continuous oxygen supplementation would maintain safe and efficacious oxygen delivery throughout the operative and postoperative period. The detachable portion bypasses the need for separate nasal oxygenating device, providing maximum comfort for the patient during recovery (post-procedure).

In conclusion this study showed the TwinGuard® gives more reliable monitoring of $ETCO_2$, less deviation of $ETCO_2$ from normal levels and a trend to improved patient comfort.

The results of this study were accepted as a poster presentation at the Digestive Diseases Week in San Diego, USA May 2008 (Appendix 9).

PART B:
SAFETY OF BOWEL PREPARATION

CHAPTER 6 DESIGN AND DEVELOPMENT OF NOVEL BOWEL PREPARATION

6.1 INTRODUCTION

While screening colonoscopy has been considered an effective method for early detection of colorectal malignancies, screening rates have remained significantly low. Many factors have contributed to low colonoscopy rates; though undergoing bowel preparations remains the major deterrent for patients (Harewood et al., 2002, Burke and Church, 2007).

Bowel purgatives established to date have been either hypertonic, sodium phosphate/sodium picosulphate based lavage known for their capacity to develop hyper-osmolar states and hyponatraemia (Cohen et al., 2001, Frizelle and Colls, 2005); or isotonic, large volume lavage that whilst better tolerated and generally free of homeostatic disturbances have nevertheless on occasions been implicated with the incidence of hyponatraemia (Fincher et al., 1999).

Hyponatraemia is an electrolyte disorder due to depleted serum sodium levels and increased fluid retention and can be facilitated by an increase in anti-diuretic hormone levels from stimulation of non-osmotic receptors by nausea, pain and intestinal hyperactivity (Marin et al., 2003). The use of polyethylene glycol (PEG) based bowel preparations and consequent excessive oral rehydration has been reported to promote the development of hyponatraemia in patients undergoing bowel-cleansing preparations (Frizelle and Colls, 2005, Chen et al., 2006).

Classic clinical features of hyponatraemia are highly variable and manifestations of symptoms appear to be correlated to levels of serum sodium. Life-threatening presentations of severe hyponatraemia such as grand mal epileptic seizures and cardiopulmonary events have been reported (Schrier, 2010). However hyponatraemia can also be characterised by lethargy and drowsiness, which have been observed post procedures and can mimic symptoms normally associated with endoscopic sedation (Cohen et al., 2001, Schrier, 2010).

Age and health status i.e. co-morbidities are factors to consider in patients undergoing bowel preparations as the risk of hyponatraemia increases in aged patients, perhaps due to decreasing efficiency in renal function or pre-existing concomitant conditions (Heymann et al., 1996, Marin et al., 2003).

Palatability and tolerability remain the most significant factors for patients' aversion to undergoing bowel preparations and a predictive indicator of patient compliance. A review conducted by Burke et al. reported greater patient compliance in patients undertaking sodium phosphate based bowel preparations than in PEG-based bowel preparations and a higher patient compliance with reduced-volume PEG based bowel preparations with comparable rates of adverse events (Burke and Church, 2007). Recently the incidence of acute phosphate nephropathy in patients who have undertaken oral phosphate based purgatives have resulted in removal or restricted use of oral phosphate purgatives from the market and the development of guidelines for aggressive treatment of acute and chronic renal failure detected in patients in susceptible or high risk categories (Markowitz and Perazella, 2009, Heher et al., 2008).

The tolerability of bowel purgatives has a direct correlation with the diagnostic efficacy of colonoscopic procedures, with inadequate or incomplete bowel preparations resulting in prolonged procedure times or higher incidence of aborted colonoscopies. Detection rate of neoplasm and polyps is reliant on the quality of bowel preparations. Burke et al. reported higher detection rates in adequate preparations in comparison with inadequate preparations thus impacting not only on the quality of the overall colonoscopy procedure but contributing to the overall increase in costs of the total colonoscopy experience (Burke and Church, 2007).

The ingestion scheduling or the administration of bowel purgatives is an important feature for a successful bowel preparation. Administrations of bowel purgatives vary depending on the instructions given by an individual proceduralist or institution. Previous day dosing and split dosing (half of bowel purgative is administered the day before the procedure and remaining half of the purgatives administered the day of the procedure) are the most commonly followed regimens. Split dosing has been has shown to be a more effective means of delivering an adequately prepared bowel when compared to previous day dosing, perhaps due to a more tolerable regimen, and greater patient compliance (Cohen et al., 2009). Certainly in a study comparing split dose and whole dose, Aoun et al (2005) observed a higher number of adequately prepared bowels and higher patient compliance under a split-dose regimen when compared to whole-dose regimen (Aoun et al., 2005).

Bowel purgative regimens often require a clear fluid diet 24 hours before the colonoscopy with a 48 hours pre-procedure exclusionary diet from high-residue foods. Developing an improved bowel purgative that takes into consideration the complications of undergoing bowel preparation and focuses on minimising those side effects while maximising patient comfort will increase the overall quality of cleansing and colonoscopy process.

6.2 DEVELOPMENT OF INITIAL CONCEPT

To date most products designed to induce purgation have relied on fluid replacement to balance fluid loss. But water may cause an intoxication syndrome causing serum hypo-osmolality with hyponatraemia with at times severe adverse effects. The effects are unpredictable and the symptoms vary widely to include headache, nausea and vomiting often resulting in both poor compliance and inadequate purgation. This leads to failed colonoscopic evaluation and increases the likelihood of missing significant pathology especially in the right side of the colon (Abela JE., 2009).

Apart from poor purgation, the clinical consequences of electrolyte disturbances may be serious and may include confusion, seizures and decreased consciousness resulting in

serious morbidity and occasionally mortality. This is seen more frequently due to the growing need of colonoscopy in an ageing population, particularly where many patients are taking numerous medications, especially diuretics, known to cause both fluid and electrolyte disturbances (McLaughlin P., 2010). Adverse effects are also seen in younger women, possibly due to total body water differences and increased propensity to dilution hyponatraemia and or sensitivity to anti-diuretic hormone effects (Liu J., 2011). Colonic orthostatic lavage is an iatrogenic phenomenon and therefore should be predictable in its action and side effects.

As a result of such accumulating experience in this field, there is acceptance that electrolyte replenishment fluids are beneficial while patients undergo preparation for colonoscopy. This poses a problem in that most oral rehydration solutions rely on glucose for co-transportation across the brush border of the small bowel utilising the glucose transporter GLUT1 mechanism (Fordtran JS., 1965). Sugars however are known to cause fermentation and production of combustible gases (Avgerinos et al., 1984). The development of the current novel bowel preparation began in response to patient complaints reported after preparation at colonoscopy. Patients emphasized an aversion to the taste of available marketed bowel purgatives contributing to poor compliance. Adverse effects included mostly nausea, vomiting and headaches of varying severities experienced during the purgative process. Particularly susceptible patients attended the emergency department due to dehydration, syncope and on occasions decreased level of consciousness.

In an initial attempt to determine the extent of the problem, biochemical tests were conducted on patients presenting to our unit for a colonoscopy after taking PicoPrep^{TM} who reported adverse symptoms. We found that that in these patients, approximately one in twenty patients suffered from significant hyponatraemia.

The aim of this chapter is to record and evaluate the development of a novel bowel purgative addressing the potential hyponatraemia and electrolyte disturbances found in existing bowel purgatives.

6.3 MATERIALS AND METHODS

This was a randomised, single blind, comparative study performed on patients scheduled to undergo a colonoscopy. The Centre for Digestive Diseases Human Research Ethics Committee granted ethics (CDD HREC) (CDD02/CO1). This study determined the efficacy, safety and tolerance of the novel bowel preparation and a currently marketed bowel purgative in encapsulated form compared with currently marketed bowel preparations. Patient population consisted of patients attending the Centre for Digestive Diseases, Five Dock, NSW Australia and inclusion criteria were male and female patients aged between 18-75 years of age scheduled to undergo a colonoscopy. The exclusion criteria included pre-existing conditions such as renal impairment or pulmonary disorders as well as use of any sodium lowering medication. Prohibited medications were those deemed to interfere with efficacy of the bowel purgatives and included diuretics and selective serotonin re-uptake inhibitors.

6.3.1 INVESTIGATIVE PRODUCTS

The four products evaluated were:
Arm 1) a purgative Hypertonic Solution with capsules (HYP)
Arm 2) encapsulated PicoPrep™ formulation (PCA)
Arm 3) 3 litres GlycoPrep™ formulation (GS)
Arm 4) two sachets of PicoPrep™ (PS)

The components comprising the Hypertonic Solution include:

- *Sodium picosulphate 20mg*
- *Xylose 10gm*
- *Magnesium sulphate 5gm*
- *Sodium chloride 5gm*
- *Potassium Gluconate 2gm*
- *Maggi™ Chicken flavour*

6.3.2 RANDOMIZATION AND BOWEL PURGATIVE GROUPS

Patients were randomised to one of four treatment groups with 15 patients per bowel purgative group:

	Arm 1 (HYP)	Arm 2 (PCA)	Arm 3 (GS)	Arm 4 (PS)
	Hypertonic Solution	PicoPrep™ Capsule	GlycoPrep™	PicoPrep™
First dose	25 grams dissolved in 350 ml water 10 capsules	15 capsules	1 sachet	1 sachet
Second dose *(3-6 hours after first dose)*	10 capsules	15 capsules		1 sachet

Table 6.1: Dosage schedule of the four treatment groups

Subjects in the standard PicoPrep™ and GlycoPrep™ arms followed the standard directions outlined on the packaging for each product. PicoPrep™ required drinking 6 glasses of water. This volume was similarly requested from Arm 1 and Arm 2 where ingestion of capsules was required.

6.3.3 EFFICACY AND SAFETY ANALYSES

Blinding in this study was restricted to two proceduralists and two sedationists who were assessing the quality of the bowel preparations (Table 6.2). Patients were not blinded to the study but were instructed not to disclose their assigned preparations to the admitting clinical staff during routine admission procedures. Tolerability, palatability and compliance were assessed through patient evaluation forms (Appendix 6), completion of investigational product data form and reported adverse events.

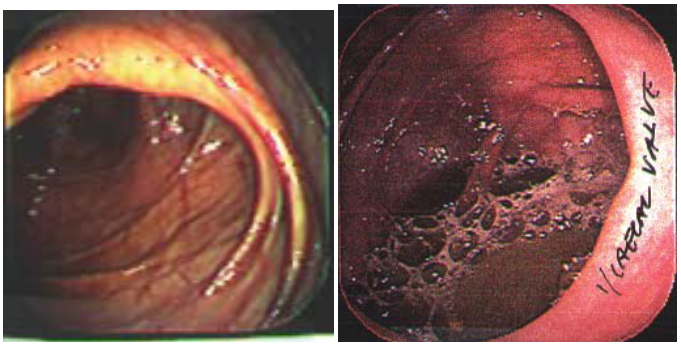
Patient evaluation forms assessed ease of completion, taste of preparation, ability to complete the bowel preparation, willingness to use the bowel purgative again and perceived efficacy of the bowel preparation.

Efficacy of the bowel purgatives were measured via doctor and sedationists evaluation forms using study specific formulated evaluation forms (Appendix 7) using a five-point rating scale ranging from *"unable to finish"* to *"excellent"* on the overall adequacy of the bowel cleansing (Figure 6.1). Doctors and Sedationists were also required to assign a numerical value based on a rating scale of 1 to 10 (with 1=not effective and 10= highly effective) as to the effectiveness of the bowel purgative in the four areas of the bowel; rectum, transverse colon, caecum and terminal ileum.

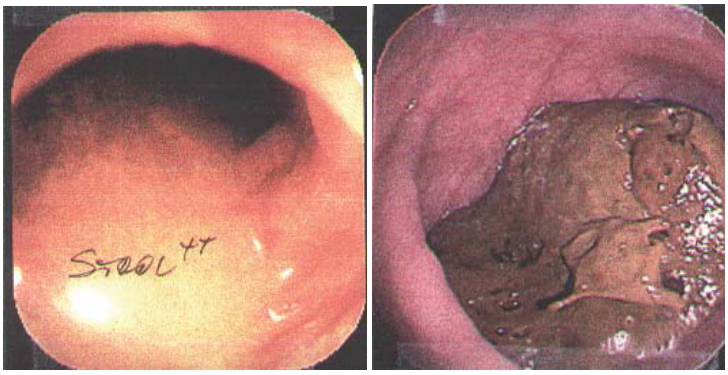
Safety of the bowel purgatives was assessed via physical examination, serum collection for laboratory studies (changes in biochemical and haematological parameters), patients' vital signs and adverse events.

Numerical value	Rating	Description
1	Excellent	Small volume of clear liquid or greater than 95% of surface seen
2	Good	Large volume of clear fluid covering 5% to 25% of the surface but greater than 90% of surface seen
3	Fair	Some semi-solid stool that could be suctioned or washed away but greater than 90% surface seen
4	Poor	Semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen
5	Unable to finish	Re-preparation needed

Table 6.2: Doctor/Sedationist evaluation scale of overall adequacy of colonic cleansing



Grade 1 **Grade 2**



Grade 3 **Grade 4**

Figure 6.1 Visual examples of the caecum - Grades 1=excellent cleaning to 4=poor cleaning

6.3.4 STATISTICAL ANALYSES

The study was specifically designed with a sample size to determine difference that would be clinically important for future studies. Fisher's exact test was used due to the small sample size and the Mann-Whitney non-parametric test was used to compare two mean scores. A *p* value of <0.05 was considered significant.

Statistical significance was examined in the following data sets:

1. Differences in proceduralists' ratings of the overall efficacy of the four bowel preparations and differences in efficacy of the four bowel preparations in the rectum, transverse colon, caecum and terminal ileum.

2. Differences in sedationists' ratings of the overall efficacy of the four bowel preparations and differences in efficacy of the four bowel preparations in the rectum, transverse colon, caecum and terminal ileum

3. Differences in ratings on ease of completion, taste of preparation, ability to complete preparation, willingness to use preparation in the future and perceived efficacy of the preparation, as reported by participants

4. Differences between bowel preparations in the type and severity of reported adverse events

6.4 RESULTS

6.4.1 PATIENTS

A total of 62 subjects were enrolled into the study. The eligible population comprised 32 females and 30 males ranging in age from 19-68 years (mean 45.7 years). Due to a delayed exclusion and two withdrawals, a total of 59 patients completed the study and were included in study analyses. Of these, 30 had not previously undergone a colonoscopy at this site.

6.4.2 RANDOMISATION AND TREATMENT ARMS

An initial sample size of 60 fully completed subjects was planned with 15 subjects per arm as per the randomisation schedule. Not all arms contained 15 subjects due to a delayed exclusion and patient withdrawals. Two subjects did not receive the correct IP as per the randomization schedule due to IP kit mislabeling. As a result an additional subject received PicoPrep™ capsules instead of the assigned PicoPrep™ sachet. As such the final patient disposition per treatment group is as follows:

Treatment Group	Number of Patients
Arm 1: Hypertonic Solution and PicoPrep™ capsules (HYP)	15
Arm 2: PicoPrep™ capsules (PCA)	16
Arm 3: One GlycoPrep™ sachet (GS)	14
Arm 4: PicoPrep™ sachet (PS)	14

Table 6.3: Number of patients per treatment arm

6.4.3 TREATMENT COMPLIANCE

Compliance was determined to be 100% for Arm 1(HYP), 94% for Arm 2 (PCA), 100% for Arm 3(GS) and 100% for Arm 4 (PS). It was noted that whilst the PS and GS treatment arms yielded 100% compliance rates, subjects frequently stated in their post procedure assessment form of poor palatability and difficulty with ingesting the preparation.

The PCA treatment arm commented on the size of the capsules used to encapsulate the PicoPrep™ formulation. Patients reported difficulties in swallowing the large capsules. Difficulty in completing the preparations were directly attributed to the amount of ingested solution such as the large volume of Hypertonic Solution and the large amount of PicoPrep™ capsules.

6.4.4 COMPARISON OF EFFICACY ACCORDING TO PROCEDURALIST EVALUATION

Figure 6.2 shows differences in doctors' ratings of general efficacy of the bowel purgatives. Arm 1 (HYP) (5/15, 33.3%) and Arm 4 (PS), (5/14, 35.7%) rated higher as *'excellent'* than Arm 2 (PCA) (3/16, 18.8%) and Arm 3 (GS) (3/14, 21.4%). In terms of general efficacy, Arm 2 (PCA) was the only group to have *"inadequate"* bowel preparation.

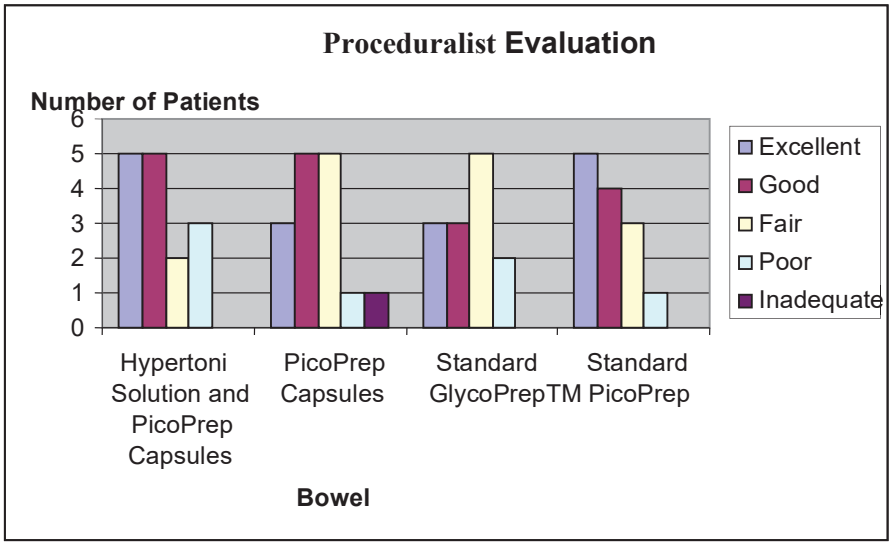


Figure 6.2 Proceduralist (N=2) evaluation of general efficacy

Proceduralists' ratings of degree of colonic cleansing in the specific bowel areas (rated on a scale of 1-10 with 1 being least effective and 10 being most effective) indicate that overall both Arm 1(HYP) and Arm 4(PS) were considered more efficacious in cleansing certain bowel areas than Arm 2(PCA) or Arm 3(GS) (Figure 6.3).

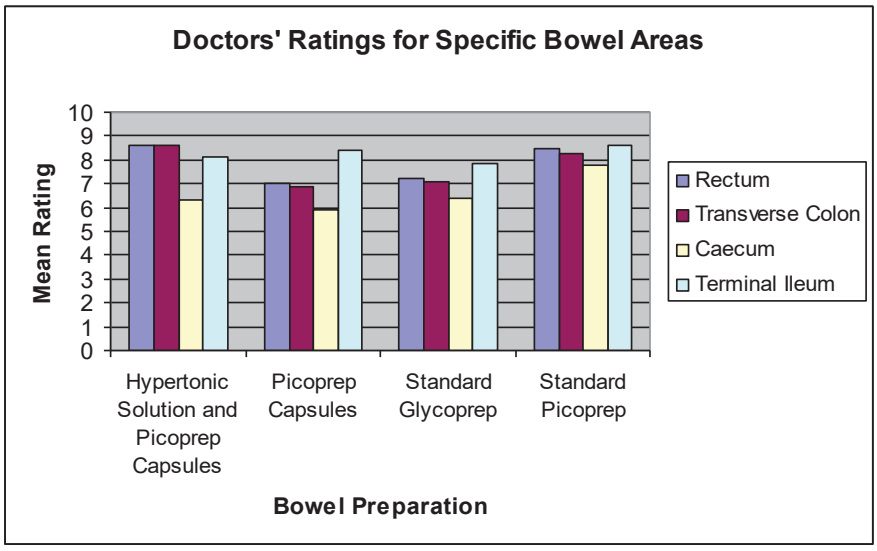


Figure 6.3 Proceduralists (N=2) evaluation and rating of specific bowel region

Differences between the arms in the specific bowel regions were noted:

Rectum - No significant differences were observed between the four bowel purgatives, however a non-significant trend was detected indicating that PicoPrep^{TM} in sachet form

(Arm 4) (mean rating 8.5 /10) was more effective in cleansing the rectum (p <0.06) than PicoPrep™ capsules (Arm 2) (mean rating 7.0/10).

Transverse colon - The *Hypertonic Solution* and PicoPrep™ capsules (Arm 1) were found to be significantly more effective in clearing the transverse colon than PicoPrep™ capsules alone (Arm 2) (mean rating 6.7 /10, p<0.03). PicoPrep™ sachet again was observed to be more effective than PicoPrep™ capsules in cleansing the transverse colon, however this was not considered statistically significant.

Caecum - PicoPrep™ sachet (Arm 4) (mean rating 7.8/10) was determined to be significantly better at cleansing the caecum than PicoPrep™ capsules (mean rating 5.9/10, p<0.03). Additionally, the Hypertonic Solution and PicoPrep™ capsule (mean rating 6.3/10) was found to be significantly more effective at cleansing the caecum than PicoPrep™ capsules alone (mean rating 5.9/10, p <0.03).

Terminal Ileum – No significant differences were observed between the bowel purgatives in cleansing the terminal ileum.

6.4.5 COMPARISON OF EFFICACY ACCORDING TO SEDATIONIST EVALUATION

No significant differences were seen in the overall efficacy of the entire colon between the four bowel purgative groups by the seditionists. There was greater *"excellent"* rating seen in Arm 1 (6/15, 40.0%) than in the other bowel purgative groups (Arm 2, 2/15, 13.3%; Arm 3- 2/15, 14.3% and Arm 4- 2/15, 13.3%) (See figure 6.4). This is also seen with the proceduralists' evaluation.

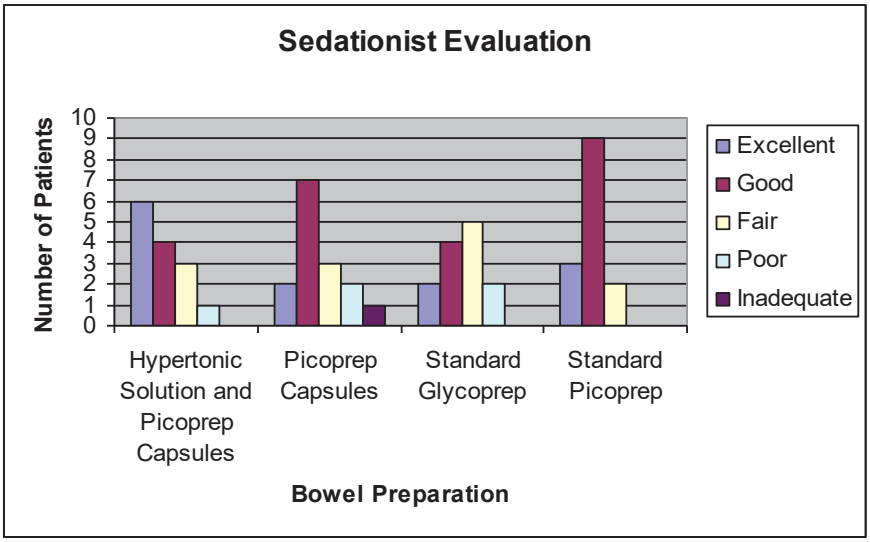


Figure 6.4 Sedationist (N=2) evaluation of general efficacy

The sedationists' assessment of colonic cleansing in the specific bowel regions were in concordance with the proceduralist' evaluations (Figure 6.5) Differences in cleansing the specific bowel areas were also noted. Arm 1(HYP) and Arm 4(PS) were more effective in cleansing certain bowel areas than either Arm 2(PCA) or Arm 3(GS).

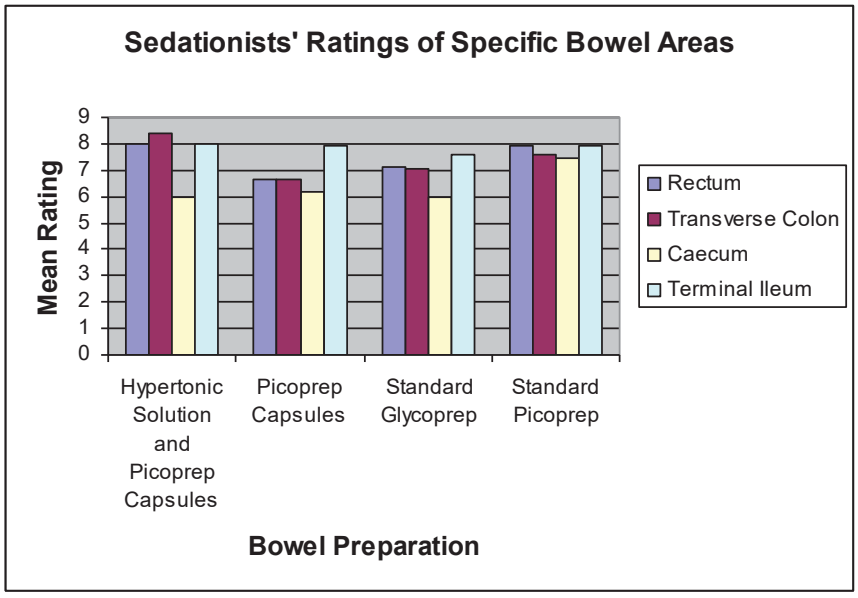


Figure 6.5 Sedationist (N=2) evaluation and rating of specific bowel region

Rectum - A non-significant trend was observed indicating a better cleanout of the rectum was achieved using PicoPrep™ sachets (mean rating 7.9/10) than PicoPrep™ capsules (mean rating 6.7/10) (p <0.058).

Transverse Colon - *Hypertonic Solution* and PicoPrep™ capsules (mean rating 8.40/10) was more effective in cleansing out the transverse colon than PicoPrep™ capsules alone (6.7/10, p<0.03) and GlycoPrep™ sachets (7.1/10, p<0.03).

Caecum – There were no significant differences or trends observed.

Terminal Ileum - No significant differences were observed.

6.4.6 Comparison of tolerability and Palatability

Patient evaluation from the one withdrawn subject was included as the subject had completed the bowel preparation and completed the evaluation forms.

Figures 6.6 and 6.7 show the data for patients. Overall, Treatment Arm 2 (PicoPrep™ capsules) yielded the highest scores for ease of completion (12/17, 70.9%) according to patient evaluations when compared with completion of other bowel purgative groups, in spite of concerns regarding capsule size and reports of difficulties in swallowing the capsules. In contrast only 5/14 subjects (35.7%) reported GlycoPrep™ (Arm 3) as easy to complete (p <0.03), No significant differences were observed in Treatment Arm 1 (Hypertonic Solution and PicoPrep™ capsules) and Arm 4 (PicoPrep™ sachet).

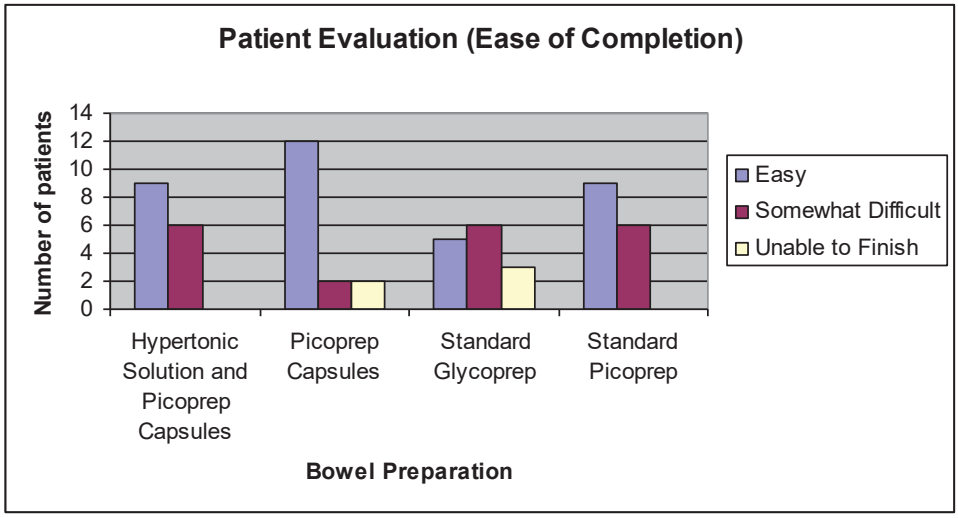


Figure 6.6 Ease of completion according to patient evaluation

Overall, PicoPrep^{TM} capsules were considered most palatable when compared with the other bowel purgative groups (14/17, 82.4%), in contrast, GlycoPrep^{TM} was considered barely tolerable (p <0.0009). Hypertonic Solution and PicoPrep^{TM} capsules were considered mostly as unpleasant but tolerable with 3/15 subjects rating the taste as pleasant (p <0.0002). Only 3/14 subjects rated PicoPrep^{TM} sachets as palatable.

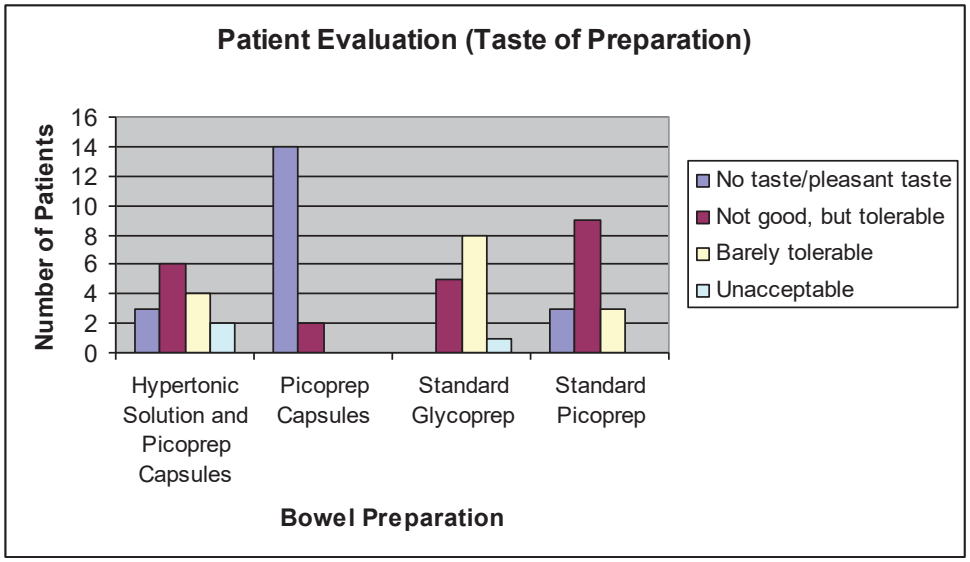


Figure 6.7 – Palatability of bowel purgative according to patient evaluation

6.5 EVALUATION ON SAFETY

6.5.1 ADVERSE EVENTS

A total of 30 subjects reported adverse events during their participation in the study with a total of 44 separate adverse events reported. The majority of the adverse events reported were determined as having a *"probable causal relationship"* to the bowel purgative taken (25/44, 55.7%) and 11/44 of adverse events reported were determined as having a *"possible causal relationship"* to the bowel purgative taken. Headaches were the most reported adverse event (21/44), which was in concordance with observations in clinical practice and reported clinical trials (Delegge and Kaplan, 2005, Macleod et al., 1998).

The Hypertonic Solution and PicoPrep™ capsules (Arm 1) reported only adverse events relating to headaches (8/15, 53.33%) or lightheadedness (1/15, 6.66%). In comparison PicoPrep™ capsules (Arm 2), GlycoPrep™ (Arm 3) and PicoPrep™ (Arm 4) reported vomiting, nausea or bloating in addition to headaches.

Adverse Events	***GlycoPrep™*** **(n = 16) n (%)**	***Hypertonic Solution and PicoPrepTM Capsules*** **(n = 15) n (%)**	***p values***
Moderate or severe adverse events			
Headache	1 (6)	4 (27)	0.17
Vomiting	1 (6)	0 (0)	-
Bloating	1 (6)	0 (0)	-
Mild adverse events			
Headache	4 (25)	4 (27)	-
Vomiting	1 (6)	0 (0)	-
Faint/Light headed	1 (6)	1 (7)	-
Total number of patients reporting adverse events	8 (50)	7 (47)	

Table 6.4 Adverse event comparisons GlycoPrep™ with Hypertonic Solution and PicoPrep™ capsules

Adverse Events	*GlycoPrep*™ **(n = 16)** **n (%)**	***PicoPrep Capsules* (n = 16)** **n (%)**	*p* value
	Moderate or severe adverse events		
Headache	1 (6)	2 (13)	-
Nausea	0 (0)	1 (6)	-
Vomiting	1 (6)	2 (13)	-
Bloating	1 (6)	0 (0)	-
Faint/Light headed	0 (0)	1 (6)	-
Anal irritation	0 (0)	1 (6)	-
	Mild adverse events		
Headache	4 (25)	1 (6)	0.33
Vomiting	1 (6)		-
Faint/Light headed	1 (6)		-
Total number of patients	8 (50)	8 (50)	

Table 6.5 Adverse event comparisons – GlycoPrep™ with PicoPrep™ capsules

Adverse Events	***Hypertonic Solution and PicoPrep Capsules* (n = 15) n (%)**	***PicoPrep Capsules* (n = 16) n (%)**	*p* value
	Moderate or severe adverse events		
Headache	4 (27)	2 (13)	0.39
Nausea	0 (0)	1 (6)	-
Vomiting	0 (0)	2 (13)	-
Faint/Light headed	0 (0)	1 (6)	-
Anal irritation	0 (0)	1 (6)	-
	Mild adverse events		
Headache	4 (27)	1 (6)	0.16
Faint/Light headed	1 (7)	0 (0)	-
Total number of patients	7 (47)	8 (50)	

Table 6.6 Adverse event comparisons – Hypertonic Solution and PicoPrep™ capsules with PicoPrep™ capsules alone

Adverse Events	***PicoPrep Sachets* (n = 15) n (%)**	***Hypertonic Solution and PicoPrep Capsules* (n = 15) n (%)**	*p* value
Moderate or severe adverse events			
Headache	1 (7)	4 (27)	0.32
Vomiting	1 (7)	0 (0)	-
Fainting/Light headed	2 (13)	0 (0)	0.48
Hyperventilating	1 (7)	0 (0)	-
Tremor	1 (7)	0 (0)	-
Mild adverse events			
Headache	4 (27)	4 (27)	-
Fainting/Light headed	0 (0)	1 (7)	-
Bloating	1 (7)	0 (0)	-
Dry mouth	1 (7)	0 (0)	-
Total number of patients	7 (47)	7 (47)	

Table 6.7 Adverse event comparisons - 'PicoPrep™ sachets' with Hypertonic Solution and PicoPrep™ capsules

Adverse Events	***PicoPrep Sachets* (n = 15) n (%)**	***PicoPrep Capsules* (n = 16) n (%)**	*p* value
Moderate or severe adverse events			
Headache	1 (7)	2 (13)	-
Nausea	0 (0)	1 (6)	-
Vomiting	1 (7)	2 (13)	-
Fainting/Light headed	2 (13)	1 (6)	-
Hyperventilating	1 (7)	0 (0)	-
Tremor	1 (7)		-
Anal irritation	0 (0)	1 (6)	-
Mild adverse events			
Headache	4 (27)	1 (6)	0.17
Bloating	1 (7)		-
Dry mouth	1 (7)		-
Total number of patients reporting adverse events	7 (47)	8 (50)	

Table 6.8 Adverse event comparisons -'PicoPrep™ Sachets' PicoPrep™ capsules

6.5.2 CLINICAL LABORATORY EVALUATION

Biochemistry (serum and urine) and haematological results were compared on the day of the procedure (Visit 2) from baseline taken on the day of recruitment into the study (Visit 1). No clinically significant differences were observed in the hematological analyses that were directly attributed to the bowel purgatives. No significant changes observed in serum osmolality or serum electrolyte levels, specifically serum sodium to indicate hyponatraemia in the patient population.

GlycoPrep™ (Arm 3) demonstrated a statistically significant change in chloride levels from Visit 1 (122.1±60.1) and Visit 2 (75.7±35.4) p=0.064, normal range being 122-135mmol/L. The mean chloride level reduced from the low end of normal range to a level significantly below the acceptable normal range.

When comparing results from recruitment (Visit1) with day of procedure (Visit2), urinalysis electrolyte changes were varied in each treatment arm. Sodium level (in mmol/l) comparisons in the treatment arms were not considered statistically significant (HYP Visit 1 92.7±36.8 and Visit 2 68.9±45.2; GS Visit 1 109.1±54.7 and Visit 2 126.5±62.1).

PicoPrep™ capsules (Arm 2) while demonstrating statistically and clinically significant decreases in urine potassium levels between Visit 1 (mean ± standard deviation) (86.8±51.6) and Visit 2 (42.1±38.3) p=0.016, levels were still within normal range (25-75mmol/L). Urine chloride levels also demonstrated a statistically and clinically significant decrease from Visit 1 (138.9±59.5) to Visit 2 (78.9146.1) p=0.014, normal range being 122-135mmol/L. The mean chloride level reduced from the normal range to a level significantly below the acceptable normal range.

Hypertonic Solution and PicoPrep™ capsules (Arm 1) demonstrated statistically and clinically significant decreases in urine potassium Visit 1 (69.1±29.9) to Visit 2 (42.4±27.4) p=0.013, normal range being 25-75 mmol/L. Urine chloride levels also demonstrated a statistically and clinically significant decrease from Visit 1 (122.7±47.0) to Visit 2 (73.1±41.0) p=0.032, normal range being 122-135 mmol/L. The mean urine

chloride level reduced from slightly below normal range to a level significantly below the acceptable normal range. This signifies chloride retention and therefore reduced urine chloride loss.

PicoPrep^{TM} sachets (Arm 4) demonstrated a statistically significant decrease in urine potassium levels from Visit 1 (76.0±53.0) and Visit 2 (27.7±25.8) p=0.017, normal range being 25-75mmol/L. Prior to intake of preparation urine excretion of potassium, while within the normal range, had variation across the range and above. No significant change was seen in serum potassium. However there was a significant decrease in excreted urine potassium following ingestions of preparation. It can be deduced that potassium is selectively reabsorbed in normally functioning kidneys, in an attempt to maintain serum potassium concentration.

Osmolarity measures the kidneys ability to concentrate/dilute urine in fluctuating conditions. Changes in specific gravity indicate a change in the concentration of urine. The subjects taking PicoPrep^{TM} capsules alone demonstrated statistically significant decreases in both. Changes in osmolarity from Visit 1 (736.1±220.2) to Visit 2 (539.1±199.0) p=0.011, with normal range being 100-800mmol/Kg. The specific gravity decreased from Visit 1 (1.019±0.006) to Visit 2 (1.015-0.005) p=0.017, with normal range being 1.005-1.030. These changes may be significant with a higher dose (equivalent to dose of PicoPrep^{TM} sachet). The subjects taking Hypertonic Solution and PicoPrep^{TM} capsules demonstrated statistically significant changes in both osmolarity and specific gravity. Changes in osmolarity from Visit 1 (655.0±227.88) to Visit 2 (442.7±229.1) p=0.013. The specific gravity from Visit 1 (1.018±0.006) to Visit 2 (1.013±0.007) p=0.091.

Changes were considered statistically and clinically significant and are indicative of intact renal function and a retained ability to alter the osmolarity concentration. The less osmolar, and less concentrated urine, were noted with associated decreases in urine chloride concentration in the above groups.

Subjects taking both PicoPrep^{TM} sachets and GlycoPrep^{TM} sachets showed neither statistical nor clinical significant changes in osmolarity or specific gravity, indicating that neither of these preparations affects these measures.

Differences in urine osmolarity and urine potassium and chloride levels in the Hypertonic Solution and PicoPrep™ capsules (Arm 1) was less than with PicoPrep™ capsules (Arm 2) alone although PicoPrep™ capsules (Arm 2) alone had higher than usual baseline values. In contrast PicoPrep™ sachets and GlycoPrep™ sachets, showed little change with the exception of a negative change in one of the electrolytes.

6.6 DISCUSSION

The results of this trial found no real difference in the overall adequacy of bowel purgatives used. However significant differences were observed when cleanliness of the bowel was compared in the different specific regions of the colon. Doctors rated PicoPrep™ sachet (Arm 4) and Hypertonic Solution and PicoPrep™ capsules (Arm 1) as more effective cleansing agent than PicoPrep™ capsules alone (Arm 2) on cleansing the caecum in the patient population. Caecal intubation is considered a measure of competence and an indicative measure of quality of colonoscopy (Aslinia et al., 2006, Harewood, 2005).

In general, PicoPrep™ sachet (Arm 4) and Hypertonic Solution and PicoPrep™ capsules (Arm 1) were considered superior to PicoPrep™ capsules alone (Arm 2) and GlycoPrep™ sachet (Arm 3) in achieving adequate bowel preparation. PicoPrep™ capsules (Arm 2) alone was considered the most tolerable of the four bowel purgatives and was also considered the most palatable when compared to Hypertonic Solution and PicoPrep™ capsules (Arm 1), PicoPrep™ sachet (Arm 4) and GlycoPrep™ sachet (Arm 3).

Overall however, Hypertonic Solution and PicoPrepTM capsule (Arm 1) was determined to be more efficacious when compared to PicoPrep™ capsules alone (Arm 2) and GlycoPrep™ sachet (Arm 3) and PicoPrep™ sachet (Arm 4).

Hypertonic Solution and PicoPrep™ capsules (Arm 1) reported adverse events in 50% of subjects that were attributable to the bowel preparation; these adverse effects were mostly mild in nature. Results of this trial also indicate milder adverse effects from PicoPrep™ capsules alone (Arm 2) and both Hypertonic Solution and PicoPrep™ capsules (Arm 1) and PicoPrep™ capsules alone (Arm 2) yielded insignificant clinical changes in laboratory results with the exception of urine chloride levels. GlycoPrep™ sachets (Arm 3) were considered least likely to cause shifts in laboratory values.

These results suggest that Hypertonic Solution and PicoPrep^{TM} capsules (Arm 1) are effective in achieving an adequately prepared colon. Modification of this product was necessary due to the incidence of adverse events, as well as aversion to the taste of the Hypertonic Solution. This has laid the basis for the next chapter with the development of an improved formulation and utilisation of a different delivery system for optimised provision of the bowel purgative.

The results of this study were presented as a poster presentation at the Australian Gastroenterology Week in Adelaide, in 2006 (Appendix 11).

CHAPTER 7 NEW FORMULATION OF A SOLID BOWEL PREPARATION

7.1 INTRODUCTION

The results of the trial described in Chapter 6 confirm that palatability and adverse effects are significant factors on the success of a bowel preparation. As shown in the patient evaluations, attitude on perceived efficacy is strongly dependent on patient experience during the bowel preparation. Patients reported a more positive experience when taking encapsulated PicoPrep^{TM} alone compared with taking Hypertonic Solution in addition to the PicoPrep^{TM} capsules. The electrolyte rich formulation whilst generally effective in resisting electrolyte changes was not palatable in spite of using masking agents in an attempt to overcome the heavy chemical taste.

Adequate bowel cleansing has also been observed to be generally reliant on bowel function in clinical practice. Patients with abnormal gastrointestinal function or pre-existing gastrointestinal conditions can also have less than adequate colonic cleansing. Bowel movement frequency is a predictive factor to determine those who were at risk of poor bowel preparations (Bloom et al., 2010).

Another issue that was not considered in the Phase II study in Chapter 6 was the time of difference between administration of a bowel purgative and procedure time. Previous studies report a greater quality overall in bowel preparation when bowel purgative administration was given on a split- dosing schedule versus same day dosing (Athreya et al., 2011, Ell et al., 2008). Athreya et al (2011) reported colonoscopy procedures conducted in the morning yielded better quality bowel preparations than those observed during afternoon procedures. In contrast a study conducted by Gurudu et al (2010) observed a better quality of bowel preparation in afternoon procedures that administered bowel purgatives on the same day as the colonoscopy (Athreya et al., 2011, Gurudu et al., 2010). Clinical experience has indicated that the quality of bowel preparations is

dependent on time of colonoscopy and tolerability of bowel preparations. Patient body mass index (BMI) has also identified as a predictive influence on adequacy of bowel preparations with Borg et al (2009) reporting a direct association between obesity and inadequate bowel preparations (Borg et al., 2009).

In Chapter 6 the formulation was composed of:

A. The use of flavourings of the liquid or capsules to improve tolerability.
B. The addition of electrolyte components, particularly to replenish sodium, potassium, magnesium and chloride losses.
C. The salts used were selected on the basis of compounds with purgative effects in their own right, which in a hypertonic form would have a synergistic effect.
D. The addition of a minimally degradable carbohydrate (sugar) to the lavage composition to facilitate the physiological balance of coupled transport of sodium in the small intestine. These carbohydrates have also had the ability to provided added purgative effect.

From clinical experience as well as feedback from the clinical study conducted, it was decided that the hypertonic solution be incorporated with an active bowel purgative and delivered as one formulation. It was also determined that the new hypertonic bowel purgative formulation would be delivered as a solid bowel preparation and would take the form of capsules or tablets that would be taken with a specified volume of fluid.

The previous chapter has also shown the hypertonic formulation to be effective in reducing the net amount of active substance needed to achieve bowel purgation. If all three PicoPrep^{TM} sachets were to be encapsulated, the resulting number of “00” capsules would exceed 90 capsules. In contrast the total number of “00” capsules when removing the flavouring for the Hypertonic Solution would number 32.

Currently, the only solid bowel purgative on the market using a similar delivery system is a sodium phosphate based purgative (sold as Visicol®, Salix Pharmaceuticals). This preparation requires patients to take 40 tablets of the bowel purgative with approximately 3 litres of clear fluid. Initial reports of white reside in the colon following bowel preparation using Visicol® were solved by improvement in formulation (Khasab M., 2005).

After extensive investigations into alternative components, a new formulation was devised in 2008 replacing xylose with mannitol and adjusting the ratios of existing components. Mannitol was chosen due to its long history of use in medical and clinical practice as well as its osmotic laxative characteristics. This was within the scope of a patent applied for in 2002 and granted in Australian in 2008 and in the United States in 2011 (Appendix 13).

Clinical Practice experience with various ratios of formulation was undertaken to assess effectiveness and side effects and will be discussed in this chapter. The quality of the bowel cleansing was then improved by changes in formulation or with changes in timing of administration.

As the inventors, we did the initial testing on ourselves looking at personal effect of each new modification, until a successful formulation was felt ready for clinical testing.

An example of use of modern telephony in this clinical exercise is seen in Figure 7.1where the two investigators with different gastrointestinal transit times compared the result of a formulation. This is the first time the iPhone® has been used in clinical experimentation of this form.

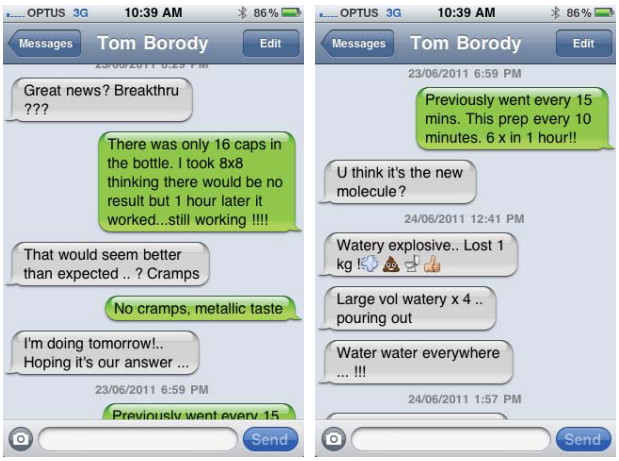


Figure 7.1 Example of modern telephony used in science

Formulation 2
Sodium picosulphate 38.4 mg
Mag sulphate 10.24gm
Sodium sulphate 5.76gm
Potassium Gluconate 4.48gm
Inulin 10.24gm
Formulation 3
Formulation with mannitol
Sodium Picosulphate
Magnesium sulphate5gm
Sodium sulphate 3gm
Potassium gluconate 2gm
Mannitol 10gm
Sodium Chloride 2gm
Total 22.02 gm in 32 capsules

Table 7.1 Formulation used in initial doctor observations

7.2 CLINICAL PRACTICE OBSERVATIONS

7.2.1 METHODOLOGY

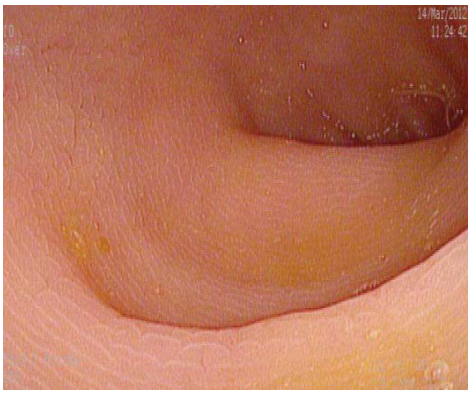
Clinical practice observations were conducted on a voluntary basis. Patients were self-selected in response to a notice placed at the booking desk at the Centre for Digestive Diseases (Five Dock; NSW Australia) seeking volunteers interested in trialling the new bowel preparation. Standard informed consent as per clinical practice guidelines was obtained to signify that the bowel purgative is a new formulation. Patients were given instructions on the bowel purgative administration and a general questionnaire to assess patient perception of new bowel purgative.

Patients then returned to the centre for their scheduled colonoscopy. Completed patient evaluation forms were collected and any adverse effects were reported in the pre procedure medical assessment (Appendix 14). Both the endoscopists and sedationists independently assessed the cleanliness of the bowel. The bowel preparation scoring

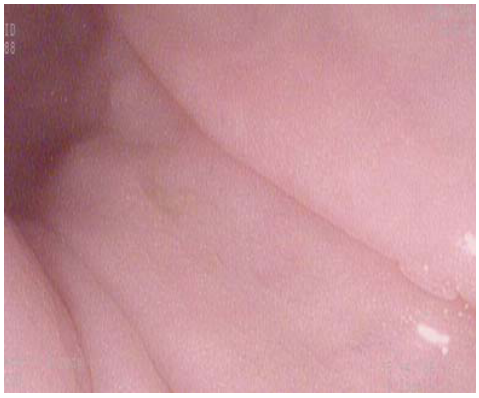
method employed were based on the Ottawa Bowel Preparation Scale (Rostom, 2004) modified to encompass five sections of the bowel; rectum, sigmoid/descending colon, transverse, ascending colon/hepatic flexure and caecum (Appendix 15). A five point rating system was used ranging from 0-4 (0=excellent, 1=Good, 2=Fair, 3=Poor, 4=Inadequate). The volume of residual fluid present in the entire colon was also assessed using a three point rating scale ranging from 0-2 (0=small volume, 1=medium volume, 2=large volume). Score ratings of each section of the bowel and scores of the presence of residual fluid were combined to produce a total score. Endoscopist rating and Sedationists' ratings were then averaged and given a general score and assigned a general evaluation grade based on the following grading system.

Average Total Score	General Evaluation Grade
0-5	EXCELLENT
6-9	GOOD
10-13	FAIR
14-19	POOR
20-22	INADEQUATE

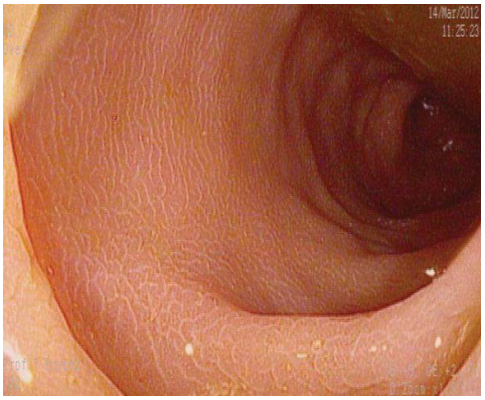
Table 7.2 - Evaluation grade used to assess quality of bowel preparation



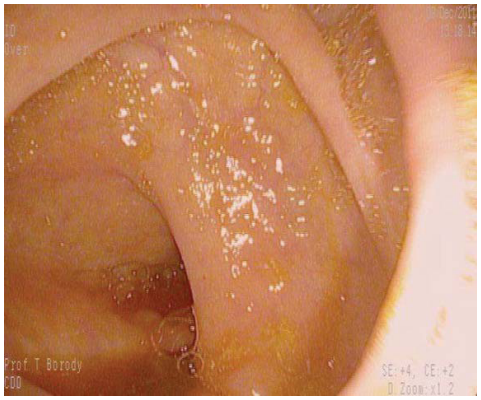
7.1(a) Rectum



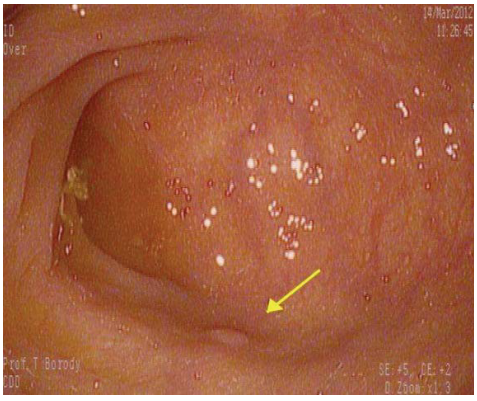
7.1(b) Sigmoid/Descending colon



7.1(c) Transverse



7.1(d) Ascending/hepatic



7.1(e) Caecum

Figure 7.2 – Depiction of "0" rating according to the Ottawa bowel scale in each of the five observed regions

7.3 RESULTS

7.3.1 Results using 20mg Picosulphate and 10g Mannitol

There were 29 patients who trialled the initial revised formulation consisting of 32 capsules, administered in four lots of eight capsules over a period of four hours with approximately 3 litres of fluid. Of these, 4 (13.8%) were rated *"excellent"*, 9 were rated *'good'*, 11 (37.9%) rated *'fair'* and 5 (17.2%) rated *'poor'* in overall quality of bowel preparation (Figure 7.3).

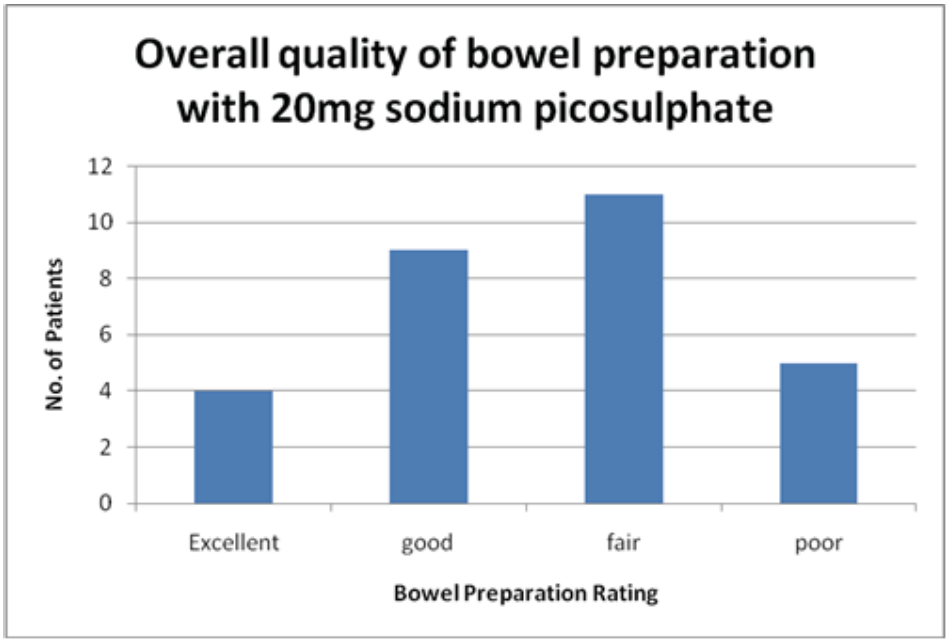


Figure 7.3 Mean rating scale for patient cohort using formulation containing 20mg sodium picosulphate, 10g mannitol (N=29)

In this initial formulation there wasn't any adverse effect in 15 (51.7%) patients taking the bowel preparation. The most common adverse effects reported were headaches (6) or nausea/vomiting (5) and both headaches and nausea/vomiting occurring concurrently in 3 patients (Table 7.3).

Adverse Symptoms	Number of patients
Headache	6
Abdominal pain	3
Nausea/Vomiting	5
Dizziness	2
Dry mouth	1
Heartburn	1

Table 7.3 Incidence and frequency of adverse effects in 20mg sodium picosulphate /10g mannitol cohort (N=29)

Twenty (69.0%) colonoscopies were conducted as morning procedures. Of these 8 (40.0%) achieved *'excellent'* or '*good'* rating and 3 (15.0%) was rated as *'poor'*. Overall 23 (79.3%) patients reported ease of completion with the bowel purgative and 27 (93.1%) patients reported willingness to take bowel purgative capsules for future colonoscopic investigations.

It was noted that 4/5 patients with *'poor'* ratings experienced their first bowel movement after the third or last dose of capsules, which suggested that earlier initiation of bowel movement improved overall bowel cleansing.

7.3.2 Results using 25mg Sodium Picosulphate with 10 g Mannitol

A revision was required in the formulation to increase the efficacy of the bowel preparation to improve the rating to achieve more *'excellent'* ratings. The second revised formulation containing 25mg sodium picosulphate, with the aim of increasing the quality of the bowel preparation, was trialled by 28 patients. The dose schedule consisted of 40 capsules administered in eight capsule doses over a period of five hours with approximately 3 litres of water.

From a 28 patient cohort, the bowel preparation, cleansing was rated *'excellent'* in 10 patients, *'good'* in 10 patients, *'fair'* in 5 patients and *'poor'* in 3 patients (Figure 7.4). Of the 19 (67.9%) scheduled colonoscopic procedures performed in the morning, 16 (84.2%) achieved an *'excellent'* or *'good'* rating and 2 (10.5%) a *'poor'* rating. 4

(44.4%) of the afternoon procedures were rated *'excellent'* or *'good'* in overall quality of bowel preparation. In this instance, there seems to be a strong correlation between procedure time and the quality of bowel preparation.

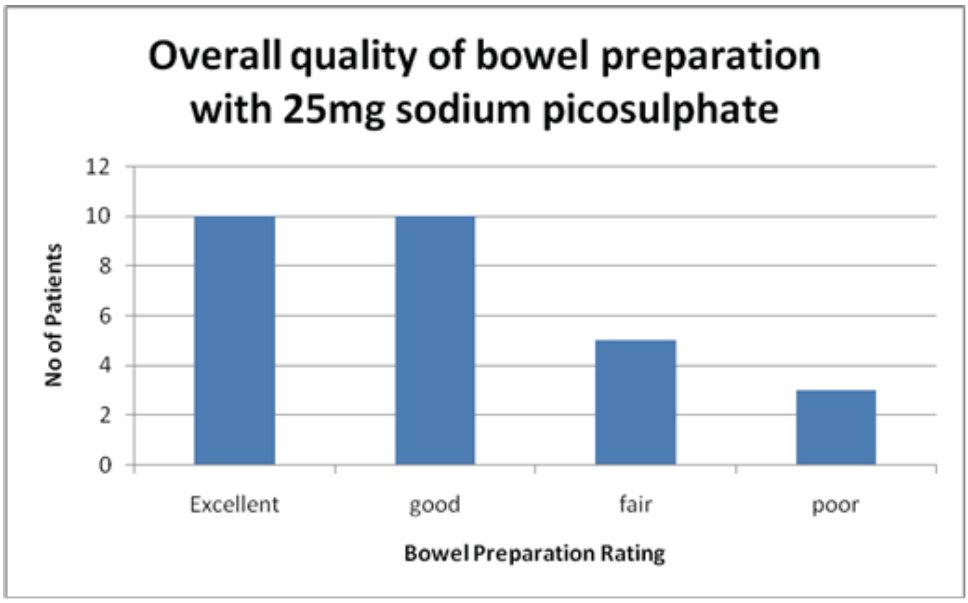


Figure 7.4 Mean rating scale for patient cohort using formulation with 25mg sodium picosulphate/10g mannitol (N=28)

Feedback on side effects was tabulated from 27 questionnaires returned. Twenty-three patients who returned patient questionnaire reported an overall ease of completion and all patients reported willingness to take the bowel purgatives again for future colonoscopic investigations. Fourteen patients reported adverse effects and 6 patients reported multiple symptoms. The most common adverse effects were abdominal pain (8), headaches (7) and nausea/vomiting (6), all of these were reported to be *"mild"* in nature (Table 7.4). From the earlier formulation, there was an increase in the incidence of abdominal pain. It could not be determined whether the reported abdominal pain is attributable to the intestinal hyperactivity induced by the bowel purgatives. These adverse effects were consistent with expected adverse effects of marketed bowel purgatives (Athreya et al., 2011).

It was noted as in previous patient cohort, that 2/3 patients with *'poor'* rated bowel preparation reported first bowel movement after undertaking a third or last dose of the bowel purgative.

Adverse Symptoms	Number of patients
Headache	7
Abdominal pain	8
Nausea/Vomiting	6

Table 7.4 Incidence and frequency of adverse effects in 25mg sodium picosulphate/10g mannitol cohort (N=28)

7.3.3 RESULTS USING 28.8MG SODIUM PICOSULPHATE WITH 10G MANNITOL

The standard accepted dosage for the commercially available PicoPrep™ prescribed for patients scheduled for colonoscopies in most centres is two sachets of PicoPrep™, which is equivalent to 20mg of sodium picosulphate. The recommended dosage prescribed in our clinic is three sachets of PicoPrep™ equivalent to 30mg of sodium picosulphate as we have found through clinical experience that three sachets of PicoPrep™ achieve a better quality of bowel preparation. The increase in Picosulphate to 25 mg demonstrated a greater quality in bowel preparation than the previous formulations. This appears to be in concordance with our experience of patients who have undertaken a greater amount of PicoPrep™ as compared to those patients who have only taken the standard accepted dosage of PicoPrep™ as their bowel purgative. Therefore further revision of the formulation was undertaken to increase the quantity of sodium picosulphate. This formulation also enabled the number of capsules to be reduced to 24 capsules.

A total of 22 patients volunteered to undertake the third revised formulation consisting of 24 capsules administered in 6 capsule dosages over a 3-hour period with approximately 3 litres of fluids. Of these 12 (54.6%) were rated as *'excellent'*, 7 (31.8%) were rated as *'good'*, 2 (9.1%) were rated as *'fair'* and 1 (4.6%) was rated as *'poor'* (Figure 7.5). Fourteen of the 22 procedures were conducted in the morning. A strong correlation between procedure time and a higher quality of bowel preparation with all 14 morning procedures receiving either *'excellent'* or *'good'* rating when compared with a greater occurrence of lesser quality bowel preparation *('fair'* or *'poor'* rating) in the afternoon procedures. This was as a result of a longer time between capsule ingestion and procedure time for afternoon procedures.

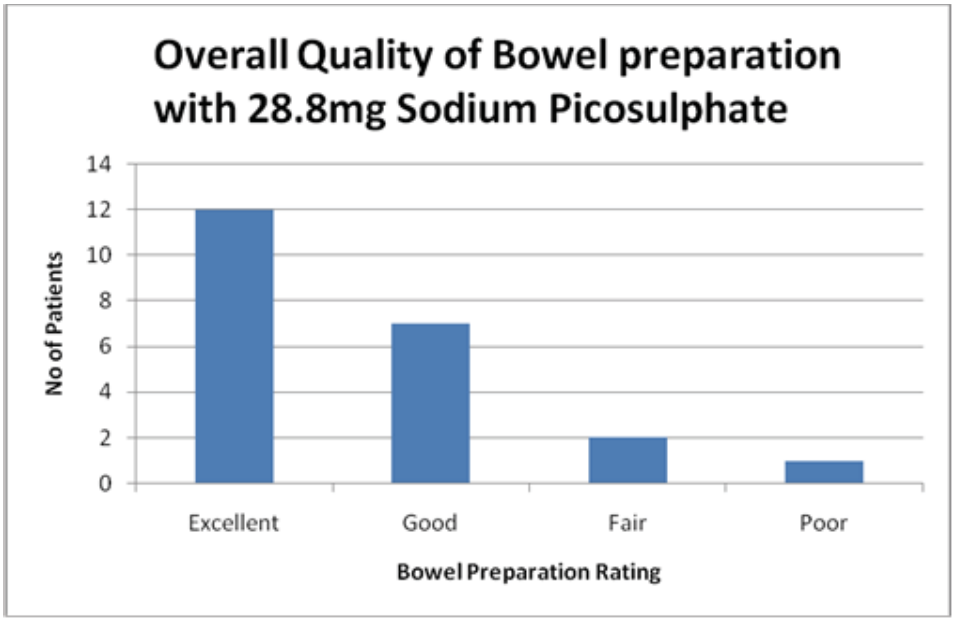


Figure 7.5 Mean rating scale for patient cohort using formulation with 28.8mg sodium picosulphate/10g mannitol cohort (N=22)

One patient failed to return the patient questionnaires. Of the remaining 21 patients, 2 patients did not report any adverse effects, 7 (22.6%) experienced only a single adverse effect and the remaining 12 (57.1%) reported experiencing more than one adverse effects. The most common adverse effect reported in this patient group was headaches of unspecified severity with 12 patients experiencing this whilst undergoing the bowel purgative regimen. The second most reported adverse effect was anal burning (21, 38.1%). However it could not be determined whether anal burning was a direct cause of the bowel purgative or a result of repeated wiping after each bowel movement. Nausea was again reported along with abdominal pain (6 (28.6%); 5 (23.8%) respectively). There were two instances of dizziness/light-headedness, which were reported to be transient and mild in nature (Table 7.5).

Adverse Symptoms	Number of patients
Headache	12
Abdominal pain	5
Nausea	6
Anal Burning	8
Dizziness / light-headedness	2

Table 7.5 Incidence and frequency of adverse effects in 28.8mg sodium picosulphate/10g mannitol cohort (N=22)

The majority of patients in this group found the bowel preparation schedule easy to complete and 19 patients indicated they were willing to take the bowel purgative for future colonoscopic investigations. Data in this group largely indicate that commencement of bowel movements after the first or second dose of the capsule purgatives were most likely to result in a good quality bowel preparation. The sole patient who rated *'poor'* reported experiencing first bowel movement after the last dose of capsules however two patients rated as having *'excellent'* bowel preparations reported experiencing their first bowel movement after ingesting the last dose of capsules. Of note three patients with a previous history of a colonoscopic procedure were intolerant to the commercially available bowel purgatives PicoPrep^{Tm}. They had also previously presented with such an inadequate bowel preparation with PicoPrep^{TM} that an additional enema purgative was necessary. In contrast, these three patients easily tolerated the purgative regime of 24 capsules and either achieved *'excellent'* (2/3) or *'good'* (1/3) rating in overall quality of bowel preparation.

7.3.4 Results using 38.5mg Sodium Picosulphate with 10g Mannitol

The final clinical practice observation was conducted using 32 capsules which contained 38.4mg of sodium picosulphate administered as two doses of 10 capsules each followed by two doses of 6 capsules each over approximately 3 hours with 3L of fluid. The reason for revision of the formulation was to improve the efficacy of the bowel purgative. This formulation group had the largest patient population totalling 81 patients. Of the 81 patients, 49 (60.5%) patients were considered to have an '*excellent'* bowel preparation, 22 (27.2%) patients were rated as having a *'good'* bowel

preparation, 7 (8.6%) achieved a *'fair'* rating and 3 (3.7%) were rated as being of '*poor'* quality (Figure 7.6).

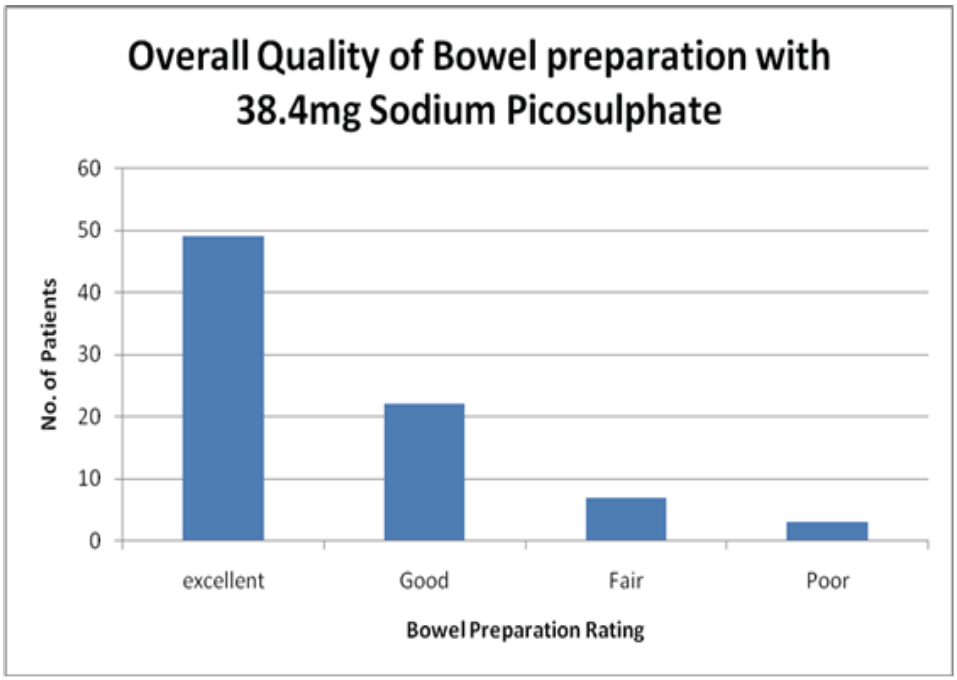


Figure 7.6 Mean rating scale for patient cohort using formulation with 38.4mg sodium picosulphate/10g mannitol cohort (N=81)

Three patients failed to return their questionnaires. Of the remaining 78 patients, 60 reported experiencing adverse effects while undergoing the bowel preparation procedure. The most common adverse effects were headaches (28, 35.9%), nausea (25, 32.1%) and abdominal pain (18, 23.1%) (Table 7.6) Two patients reported *'feeling cold'* an uncommon symptom, but one that has been reported by Cohen et al 1994 in a trial comparing bowel purgatives (Cohen et al., 1994). Seventeen patients reported experiencing anal burning as an adverse event, however again it could not be determined whether the anal burning was directly ascribed to the intake of the bowel purgative or occurred as a result of repeated wiping. One patient specifically wrote a comment that anal burning occurred from wiping rather than the bowel purgative. Sixty procedures were performed as morning procedures with 52 (86.7%) considered *"excellent"* or *'good'*, in comparison to 17 of the 21 (81%) procedures performed in the afternoon yielding an *'excellent'* or *'good'* rating.

Adverse Symptoms	Number of patients
Headache	28
Abdominal pain	18
Nausea	25
Anal Burning	17
Vomiting	6
Dizziness / light-headedness	4
Feeling Cold	2
Bloating	1
Dry Mouth	1
Increase in body temperature	1

Table 7.6 Incidence and frequency of adverse effects in 38.4mg sodium picosulphate /10g mannitol cohort (N=81)

Fifty three patients were able to complete the bowel purgative with ease; however 20 of the 25 patients, who found the bowel purgative regimen *'somewhat easy'* to complete, still achieved an *'excellent'* or *'good'* quality of bowel preparation. Time to first bowel movement may also be considered a good predictive factor for achieving an adequately prepared bowel, patients who reported experiencing their first bowel movement earlier had a greater incidence of higher quality of overall bowel preparation.

Seventy two patients reported willingness to take the bowel purgative capsules for future colonoscopic investigations, while three were uncertain as to whether they would take the capsules again.

7.4 COMBINED RESULTS

Combining the three different results, a total of 160 patients underwent the bowel purgative of differing formulations with 123 (76.9%) patients achieving an overall rating of *'excellent'* or *'good'* in their bowel preparations (Figure 7.7).

The 38.4mg picosulphate group yielded the greatest number of *'excellent'* scores; however the increased incidence of adverse events was correlated to the increase in the active purgative used in the clinical observation.

There was generally a poor correlation between co-existing conditions and the quality of bowel preparation. A trend towards patients undergoing morning procedures having a better quality bowel preparation has been observed. There have been studies that have examined timing of the bowel preparation compared to with that of the procedure and which report that the former is a more important factor when determining the cleanliness of the bowel (Gurudu, 2010, Eun, 2011).

The most significant factor observed in each of these groups is the positive correlation between quality of bowel preparation and procedure time with morning procedures achieving a greater quality of bowel preparation than those procedures performed in the afternoon previously reported similar findings (Athreya et al., 2011).

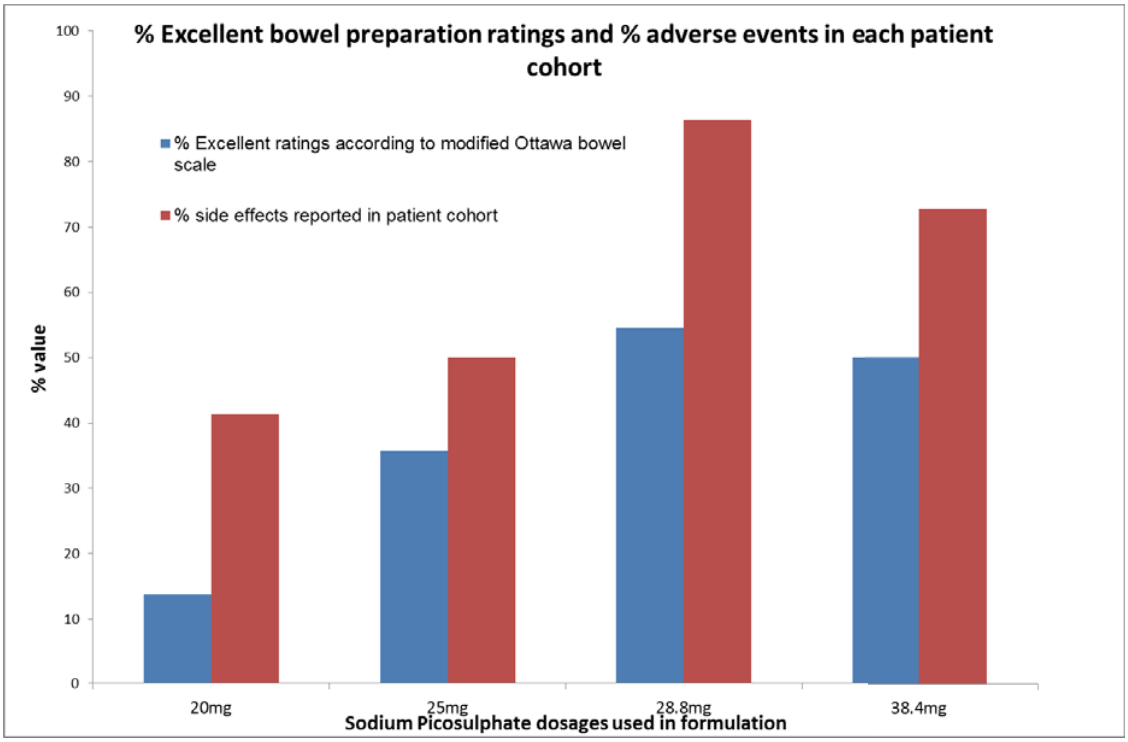


Figure 7.7 Incidence of excellence ratings and incidence of adverse events vs. increasing doses of sodium picosulphate

7.5 REDUCING EXPLOSIVE POTENTIAL

An important issue came to light during the trial process with the use of conventional sugars. Intra-colonic combustion secondary to fermentation of the sugars by colon bacteria has been previously described. Approximately 20 cases of colonic gas explosion have been reported in literature, 14 of which took mannitol solution exclusively as a purgative. The initial two cases were by Bigard 1979 and Raillat 1982 (Bigard et al., 1979, Raillat et al., 1982).

Colonic bacteria producing increased levels of hydrogen in the colonic environment ferment mannitol, a minimally degradable sugar. Studies have shown oral administration of mannitol increases levels of hydrogen in the colonic lumen resulting in high levels of combustive gas and increasing the risk of colonic gas explosion in the presence of an ignition source (La Brooy et al., 1981). For explosion to occur, combustible gases in sufficient concentration should be present along with oxygen and

an ignition source such as electro cauterisation during colonoscopic procedures (Avgerinos et al., 1984). Reduction of explosion can be achieved by using inert carbon dioxide for insufflation and reducing concentration of combustible gases hydrogen and methane at 4.1-72% and 5-15% and oxygen to have a concentration less than 5% (Levy, 1954, Taylor et al., 1981).

The three factors required to cause an explosion are a bacterial load, propensity to ferment products such as methane and hydrogen, and the use of an electro-cautery during colonoscopy. This complication remains a theoretical problem when small quantities of sugar have been incorporated into the purgative compositions described above. There remains, however, a perception that some such sugars that are non-absorbable such as mannitol or lactulose still, potentially pose an explosive potential.

In a study that measured intra-colonic gas samples of oxygen methane and hydrogen, 20 patients were found to have used either castor oil (N=10) or mannitol (N=10) as their bowel purgative. Six patients who had undergone a mannitol purgative had methane production greater than 4.1% and hydrogen greater than 5% with only one patient with oxygen concentration greater than 5%. The investigators concluded that suction and carbon dioxide for insufflation would have been a safe option in these patients (Avgerinos et al., 1984).

In spite of the mannitol concentration used in the formulation being below explosive levels, the potential for a negative perception of danger with the use of mannitol added further reason to steer clear of this component.

To minimize such adverse effects, the current invention has evolved considerably to overcome these challenges by utilising the unique and safe four-carbon chain polyol known as erythritol. This undergoes substantial absorption in the proximal small intestine (60-90%) utilising non-saturable kinetics, so allowing for both sodium and water re-absorption to prevent hypo-osmolar states that cause many of the undesired effects of orthostatic lavage. Other numerous improvements are also added by using this polyol.

Erythritol has many intrinsic advantages and is widely used as a food sweetener, with

evidence that erythritol exists in human tissues and body fluids. The taste is sweet and pleasant, it has no effect on blood sugar, it also no caloric value, but in particular, erythritol demonstrates none or minimal fermentation by colonic bacteria and only non-combustible short chain fatty acids and carbon dioxide are produced in small amounts. Furthermore, there are no recorded significant gastroenterological side effects at doses up to 1000mg/kg body weight/day (Tetzloff W., 1996).

In addition, the absorbed erythritol is not metabolised systemically and is excreted unchanged in urine (Bornet F.R., 1996). It is further safe as it will not cause interactions or cause metabolic disturbances and has no effect on 24-hour urine output of creatinine, urea or electrolytes (sodium, potassium, chloride, phosphate), which was in direct contrast to phosphate preparations.

Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany), another stimulant laxative has been used extensively as a colonic purgative and for the relief of constipation and it is anticipated that Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) in dosages of no more than 10mg will deliver the same quality prepped bowel demonstrated by sodium picosulphate in dosages exceeding 30mg. When erythritol is added to a purgative agent such as Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany), which promotes evacuation of the colon by altering intestinal fluid and electrolyte absorption and smooth muscle contractility, an unexpected enhanced purgative action occurs. Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) has on rare occasions been associated with ischaemic colitis in doses of 20mg, and less frequently with the 10mg tablet form in combination with HalfLytely^{TM} (Braintree Laboratories Inc., Braintree, MA). It has not been reported at a lower dosing range where it has been widely used on a daily basis for treatment of constipation over long periods. We have therefore incorporated Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) in our preparation in small doses.

The evolved formulation has also replaced sodium picosulphate with Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) with the aim of eliminating adverse effects associated with sodium picosulphate and yet uses a product in the dose range already approved for such use by the US Food and Drug Administration (FDA).

7.6 NEW FORMULATIONS

New formulations consisting of a new purgative Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) and erythritol were initially trialled by personal experience (example of reported observation 7.6.1.1) and compared with other staff volunteers. The examples of various formulations are shown below.

7.6.1 FORMULATION 1

Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) 10mg

Magnesium sulphate 10.24gm

Sodium Sulphate 5.76gm

Potassium Gluconate 4.4gm

Erythritol 10.24gm

7.6.1.1 Reported Observation

Documentation of individual response to capsule bowel prep 1st October 2010
Light breakfast Commenced @12:00 with 8 capsule & 8 capsules @ 12:30 with 2 large glasses of water Rpted 8 capsules @1:15 and then @2:15pm =24 capsules 13:50- Formed large stool 14:30- Large diarrhoeal stool (5min) 14:40 Large diarrhoeal stool (5min) 14:50 smaller longer diarrhoeal stool (10min) 2 glasses of water 15:00 Watery moderate (10min) 15:20 urine like stool 15:45 ditto 16:15 ditto Ate light meal cracker and cheese 18:00 –Still very watery “Number1s from Number 2” 19:30- dinner 20:00 Watery changing 0:400 Diarrhoea like 05:30 forming loose stool

7.6.2 FORMULATION 2

Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) 10mg

Magnesium sulphate 10.24gm

Sodium Sulphate 5.76gm

Potassium Gluconate4.4gm

Erythritol 10.24gm

7.6.3 OTHER FORMULATION

24 capsules

Magnesium Sulphate 6.42gm

Sodium Sulphate 7.47gm

Potassium Gluconate 1.89gm

Sodium Chloride 1.89gm

Erythritol 1.89gm

Bisoxatin 180mg

In a small series of patients the latest formulation using Bisoxitin as a stimulant laxative has been trialled and while acceptance and tolerability was unchanged from other forms of capsule preparations, the ability to clean the colon was greatly enhanced. In particular the ascending colon and caecum, which has been the most difficult part of the colon to be cleaned, had excellent scores. In Figure 7.8 images of the caecum of ten consecutive patients who trialled this formulation has been presented. This small series shows extremely clean bowel preparation with minimal mucosal wall matter and low incidence of bubbles.

This formulation with further enhancement will constitute the final product, which will be tested in comparative trial with currently marketed bowel preparations. In Australia, the market leaders are PicoPrep™ and GlycoPrep™. Two additional enhancement to the formulation will be required allow for commercialisation of this product and will be described below. Ideally the comparison would have been with another capsule preparation however the sodium phosphate bowel preparation has been *"black boxed"* by the FDA because of irreversible interstitial nephritis, which has been linked to its use. The comparative bowel preparation study proposed will not be part of this thesis although the preliminary efforts have been described in this body of work.

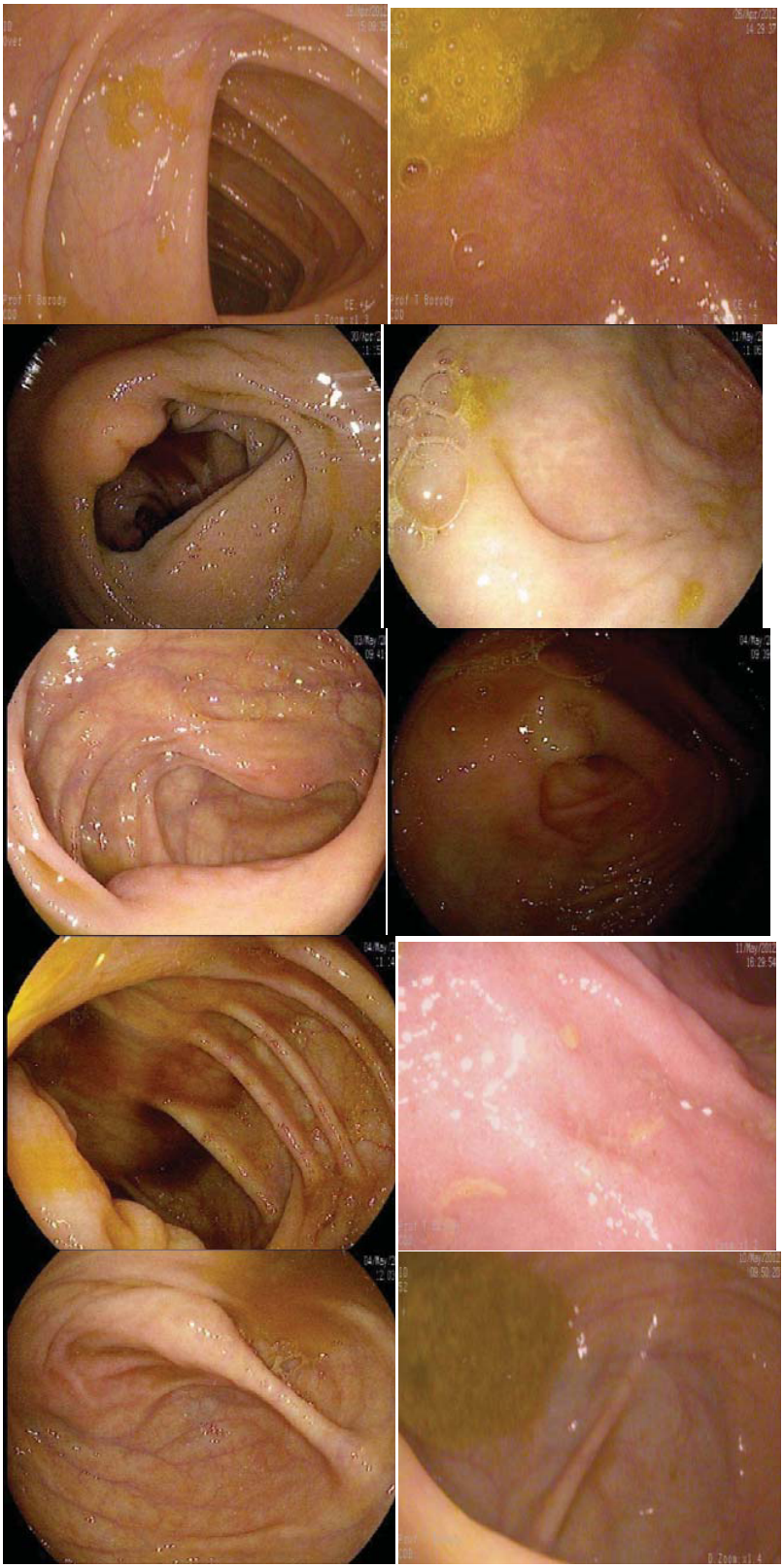


Figure 7.8 Images of caecum captured in ten patients during colonoscopy on Bisoxatin capsule preparation 26/4/2012 to 11/5/2012

7.7 ILLUMINATION

The aim of bowel preparations is to aid in better visualisation during colonoscopies; this in part has led to the evolution of the addition of simethicone or another surfactant. Simethicone is an anti-foaming agent designed to reduce the surface tension of gas bubbles and facilitating its exit from the body, thereby reducing bloating and discomfort associated with gas over- production. Addition of simethicone has improved visibility in a randomised placebo trial (McNally et al., 1988). Simethicone is anticipated to reduce the bubbling caused by bile, impeding visualisation. A randomised clinical trial involving 152 patients used addition of simethicone with improved visibility in all regions as well as shortened colonoscopy time (Kark W, 1995).

Various lubricants may also be added to the preparation so facilitating the passage of the colonoscope by reducing mucosal resistance. These include hyaluronic acid, glycerol or silicone. The encapsulating substance ideally would dissolve in the gut to form a lubricant as there will be between 20-40 capsules, the use of the encapsulating material will be advantageous as lubricant. Silicones are polymers that include silicon together with carbon, hydrogen, oxygen, and sometimes other chemical elements. It is thermally stable (constancy of properties over a wide operating range of, 100 to 250 °C) and although not a hydrophobe, it is able to repel water and does not stick. With low chemical reactivity, low toxicity, silicon does not support microbiological growth. During polymerization, this reaction evolves hazardous hydrogen chloride gas. For medical uses, a process was developed where the chlorine atoms in the silane precursor were replaced with acetate groups. Silicones are used as active compounds in defoamers due to the low water solubility and good spreading properties. Gelatin capsules in cooperating glycerol will further assist as a lubricant and defoamer.

Furthermore purgatives for colonic lavage are ideal vehicles for the delivery of certain markers that better highlight the presence of colonic polyps allowing for a higher detection rate of polyps at colonoscopy. We have proposed hexaminolevulinate to the present composition to mark polyps with fluorescence prior to colonoscopy so as facilitate enhanced polyp detection using the appropriate blue excitation light of 375-

440 nm. This preparation would therefore enhance the value of the bowel preparation by also improving the polyp detection rate, as has been found in the case of bladder cancers. Addition of other markers such as Indigo carbide methylene blue may similarly be in cooperated into the formulation.

These proposed changes to the formulation have not been tested as yet. The results of the pilot clinical study can only be compared to the individual formulations that we have developed and do not constitute a clinical study.

Collaboration with a pharmaceutical company will need to be undertaken in order to investigate the effects of the bowel preparations on a large-scale clinical trial. This thesis however will not be able to extend to this aspect of the development of the solid bowel preparation. Questions regarding safety of bowel preparation that arose during the process of this thesis have led to the realisation of what will eventually constitute a commercial product.

CHAPTER 8 GLOBAL CONCLUSION

In this thesis, which has been named '*Making Gastrointestinal Endoscopy Safer'*, I have scrutinised complications arising from upper and lower gastrointestinal endoscopic examinations and identified selected aspects of the procedures, which can be improved to increase safety.

SPECIFIC CONCLUSIONS

A. *The **survey conducted** in this thesis confirms there is regional variance in reported morbidity and mortality associated with gastrointestinal endoscopy and safety is an issue.*

   Patients may present for either or both procedures, which may be for a specific medical indication or commonly for colon cancer screening. The population presenting for these simple interventions are generally fit people and as such complications would be expected to be exceptionally rare. However, the literature shows an unacceptable morbidity and mortality rate associated with these procedures. Discussed in Chapter 2 the thesis showed increased morbidity in public institutions with a demonstrable mortality caused by the procedures. In public endoscopy units, there were twice as many cases of aspirations, twice as many cardio-respiratory complications and most importantly 13 deaths over the past 10 years. Safety in endoscopy is clearly an issue.

B. *In Australia, there is universal use of oxygen monitoring and administering of supplemental oxygen. However, use of **capnography monitoring is not widely adopted**. This will have implication in providing safety in endoscopy.*

   The survey revealed that 70% of public but only 30% of private centres routinely used capnography. However, pulse oximetry was universally utilised. Improvement in detecting carbon dioxide and reducing cost by incorporating it as an inbuilt feature, the TwinGuard® may improve adoption of capnography thereby increasing safety in endoscopy.

C. *Cardiovascular and respiratory parameters have a **predictable early lag** associated with sedation and the endoscopic procedures. This knowledge is crucial to providing safe sedation to patients.*

Sedation-related cardio respiratory complications are a major concern with regard to the overall complication rates. Chapter 3 concisely demonstrated cardiovascular and respiratory parameters associated with the sedation. There was a predictable early lag due to the pharmacokinetics of sedation, which causes a decrease in patients' oxygen saturation. With supplemental oxygen this is ameliorated within two minutes.

D. *There is a **requirement for a dedicated person** to provide sedation and maintain vigilance in monitoring patients' cardio-respiratory parameters. This person should have the ability to safely rescue any deterioration in the patient's condition.*

Understanding the lag effect and having a dedicated person in charge of sedation ensures that the proceduralist is not distracted and can safely perform the gastrointestinal endoscopic examination.

E. *The **novel respiratory device TwinGuard®** has been shown to safely deliver oxygen to patients and reliably detect carbon dioxide to ensure monitoring of ventilation.*

From the survey of Australian endoscopy centres, the leading oxygen delivery system is the Hudson mask with 89% public and 75% private centres using them. However, 55% public and 41.7% private centre used a combination of Hudson mask and nasal cannula. In Chapter 4 the development of the TwinGuard® is described. It provides oxygenation and carbon dioxide detection with a single device throughout upper endoscopy and colonoscopy without the need to replace or modify equipment. Oxygen delivery can continue to recovery with a detachable portion of this single use device.

F. *There were **fewer nuisance monitor alarms** with TwinGuard® when compared with nasal carbon dioxide detection systems.*

The utility of the TwinGuard® has been compared in Chapter 5 with nasal cannula oxygenation/sampling and was shown to be superior in detecting carbon

dioxide whilst being equivalent in delivering oxygen. This will assist in improving safety in sedated patients undergoing gastrointestinal endoscopy.

G. *The **TwinGuard® continued to effectively deliver oxygen through to recovery** by having a detachable soft, pliable, oronasal oxygenating device.*

In Chapter 4, the development of TwinGuard® allowed for provision of oxygenation with a single device throughout the upper endoscopy and lower colonoscopy without the need to replace or modify equipment. Oxygen delivery continued on to recovery with a detachable portion of the single use device. The utility of this device has been demonstrated in a comparative study in Chapter 5. Use of the TwinGuard® will improve safety in endoscopy by ensuring supplemental oxygen is continued into recovery.

H. *Colonoscopic examinations have similar concerns with regard to sedation as panendoscopy and the **TwinGuard® device can be used for patients who have a double procedure.***

If patients present for both procedures colonoscopy usually follows the panendoscopic examination. The TwinGuard® allowed for adequate oxygenation throughout the upper endoscopy and lower colonoscopy without the need to replace or modify equipment that would have been required specifically for each procedure.

I. *Colonoscopy carries the additional safety issue of bowel preparation. Use of **hypertonic bowel preparation** is a strategy to provide low volume preparation with attention to electrolyte replacement.*

The aim of this bowel preparation was to improve patient acceptance in reducing electrolyte depletion. In cases of unrecognized hyponatraemia, over-sedation may occur. The development of a new strategy of administering bowel preparations focused on electrolyte replacement and rehydration improves safety in administering bowel purgatives.

J. *The **efficacy and safety of hypertonic bowel preparation** has been demonstrated in a randomised clinical trial.*

The Phase II trial described in Chapter 5 showed that the hypertonic bowel preparation was of equal efficacy as conventional bowel preparations. There was no incidence of vomiting in this group neither was there abnormality in their biochemical profile.

K. *Lessons from comparative bowel preparation trial led to further enhancement of a purgative product. Improvement in safety and palatability led to the **development of a capsule bowel purgative**.*

In spite of the low volume of hypertonic bowel preparation the chemical taste was difficult to mask by the various sweet and savoury agents. Commercially available chicken flavouring was closest to tasting similar to consommé. To improve palatability a decision was made to encapsulate the active ingredients thereby preserving electrolyte replacement while increasing the purgative effect.

L. ***Pilot trials of the capsule purgative** saw improvement in cleansing and in patient tolerability with composition changes.*

Encapsulated bowel preparations in pilot trial showed dose dependent efficacy in bowel cleansing. However, increasing sodium picosulphate in the composition increased reported side effects. Generally tolerability was better than with previous commercial bowel preparations. There were patients in the past who were unable to complete the prescribed bowel preparations because of side effects. They were reluctant to undergo further colonoscopy fearing unpleasant preparation experience. This group of patients was able to complete the capsule bowel preparation safely.

M. *Scheduling the bowel preparation closer to the time of the procedure and using **split dose strategy improved the efficacy** of the bowel preparation.*

In the pilot trials searching for the ideal bowel preparation a positive correlation between quality of bowel preparation and procedure time was shown. It was noted that morning procedures achieved a better quality of bowel cleansing than

those procedures performed in the afternoon. The timing of bowel preparation is important when formulating a safe bowel purgative regimen.

N. *The **final purgative composition described in this thesis** safely improves bowel cleaning of the right colon, reduces bubbling and adds a 'staining' agent, which highlights subtle adenomatous polyps and detects cancer earlier.*
This final formulation improves on safety by improving patient tolerability and improving bowel cleansing, including the caecum and ascending colon. This is known to expedite colonoscopy and lead to improved polyp detection, further increasing safety.

In *'Making Gastrointestinal Endoscopy Sa*fer' solutions have been found to some common complications involving upper and lower gastrointestinal endoscopic examinations. I have concentrated on improving oxygenation and monitoring of ventilation for upper gastrointestinal endoscopy. For lower gastrointestinal endoscopy, the focus was on improving purgative agents' palatability and reducing electrolyte depletion. It is envisaged that these improvements will enhance the sedative experience and ultimately the safety of gastrointestinal endoscopy.

APPENDICES

APPENDIX 1 – SAFETY IN ENDOSCOPY SURVEY

It is likely that you may need to tick more than once.

Your post code_____. This has been requested for demographic purpose only.

1 Describe your practice

Hospital	Private	☐	Public	☐
Day surgical unit	Private	☐	Public	☐
Other		☐	_____	

2 Number of proceduralists/endoscopists in your practice and approximate proportion of procedures done by each

		Number	*Approximate %*
Physician	☐	_____	_____
Surgeon	☐	_____	_____
Trainee	☐	_____	_____
General Practitioner	☐	_____	_____
Nurse Practitioner	☐	_____	_____
Others	☐	_____	_____

3 Number of procedures performed in the 2005-2006 financial year.

Panendoscopy	_____
Colonoscopy	_____
ERCP	_____
Small bowel studies	_____

4 Who administers sedation and approximately in which proportion? (%)

Anaesthetist	☐	_____
Proceduralist	☐	_____
Medical assistant	☐	_____
GP anaesthetist	☐	_____
Nurse Practitioner	☐	_____

5 What is the recommended fasting time at your institution? _____hours

6 Who is in charge of the airway?

		Approximate %
Anaesthetist	☐	_____
Proceduralist	☐	_____
Medical assistant	☐	_____
GP/Sedationist	☐	_____
Nurse Practitioner	☐	_____

7 Is any form of topical local anaesthesia used routinely? Yes ☐ No ☐

8 What is the preferred bowel preparation used for colonoscopy in your centre?

_____

9 Which sedation agents are commonly used?

Benzodiazepine	☐	i.e. Diazepam	☐	Midazolam	☐	Other	☐
Narcotic	☐	i.e. Morphine	☐	Pethidine	☐	Fentanyl	☐
Propofol	☐	Etomidate	☐	Ketamine	☐	Barbiturate	☐

10 Are the above drugs used in combination?

Always ☐ Usually ☐ Occasionally ☐ Rarely ☐ Never ☐

11 Which of the following monitoring is available?

	Pulse oximetry	All cases ☐		Selected cases ☐	
	Cardiac monitor	All cases ☐		Selected cases ☐	
	Capnography	All cases ☐		Selected cases ☐	
	Blood Pressure	All cases ☐		Selected cases ☐	

12 During the procedure, oxygenation is provided by which of the following devices?

Nasal prongs ☐
Oral oxygenation device ☐
Hudson® mask ☐
Other ☐
Describe_____.

13 During recovery, is oxygen monitoring done?

Routinely on all patients ☐ Selected cases ☐

14 During recovery, is supplemental oxygen administered?

Routinely on all patients ☐ Selected cases ☐

15 During recovery oxygen is administered by which of the following devices?

Nasal prongs ☐
Oral oxygenation device ☐
Hudson® mask ☐
Other ☐
Describe_____

16 During the previous 12 months, what was the approximate number of complications?

Patients with aspiration ___
Requiring assisted ventilation ____
Patients requiring intubation ___
Cardiac arrest ___

17 How many deaths have been associated with endoscopic procedures at your institution in the past 10 years? (Deaths that have been directly caused by endoscopic procedures)

_____

We greatly appreciate your time. Thank you.

APPENDIX 2 – SAFETY IN ENDOSCOPY COVER LETTER

P O Box 123
Broadway, NSW 2007
Australia
Department of Health Sciences

University of Technology, Sydney

Date: 12th November 2007

"Safety in Endoscopy"

Dear Doctor/Practice Manager,

We would like you to take part in a questionnaire-based study to investigate current endoscopy practice in Australia. I am an emergency physician enrolled in a PhD program at the University of Technology Sydney and I am currently undertaking a research project entitled "**Safety in endoscopy**".

Your participation in the study is entirely voluntary and the time required to complete the survey should only be 5-10 minutes. The results of this data are strictly confidential, all data collected will be anonymous and no identification of yourself or your practice will be possible

Participants may withdraw from the study at any time without prejudice and without questions asked. If the study is completed as planned, the results of this survey will be presented at the next Australian Gastroenterology Week (AGW) meeting.

Your acknowledgement of this letter by returning the completed survey in the enclosed self addressed envelope by 1st of February 2008 is greatly appreciated.

Should you wish to discuss this study, please contact me [redacted] or Assoc. Prof Loraine Holley 02-9514 2180 at the Department of Health Science.

Thank you for your assistance in this study.

Yours sincerely

Sanjay Ramrakha, MB BS, FRACGP, FACEM
Department of Health Sciences
University of Technology Sydney

APPENDIX 3- AUSTRALIAN GASTROENTEROLOGY WEEK 2008 – POSTER PRESENTATION - ENDOSCOPIC SEDATION IN AUSTRALIA

University of Technology, Sydney

ENDOSCOPIC SEDATION IN AUSTRALIA: Results from a Nationwide Survey

Ramrakha SC, Holley L, Psilos M

INTRODUCTION

Wide variations exist around the world in the practice of sedation for endoscopy. The depth of sedation, drug choices, delivery methods and the practitioners involved are determined by historical, cultural and economic factors which in most instances have developed in a piecemeal fashion. Although professional bodies have promulgated standards for sedation and monitoring, preventable morbidity associated with sedation is of concern. The advent of widespread use of Propofol by non-anaesthesiologists has been studied and a US survey by Cohen[7] found that 25% of centres used Propofol as a major component of their sedation. Controlled studies by Rex[1] and Kulling[2] have also demonstrated safe use of nurse administered Propofol in study conditions with bag mask ventilation rates of 1.4 and .21 per thousand respectively with no deaths. However, survey studies by Arrowsmith[3] and Sharma[4] report higher complication rates of 1.4% and 0.9% unplanned cardiopulmonary events and procedure associated mortality rates of 3/10,000 and 0.8/10,000 respectively. This compares poorly with 1:63,000 rate of all deaths from anaesthesia in Australia[5]. While surveys have been done in the US[7], UK[8] and Europe[9], local factors such as reimbursement, distance and disproportionate delivery of medical/nursing personnel does not allow extrapolation of their findings. This is the first nationwide survey performed in Australia.

METHODS

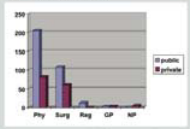
This voluntary, ethics approved, survey of public and private endoscopy centres was conducted to ascertain a national practicing pattern of sedation in endoscopy. The survey and a covering letter were mailed in November 2007 to 120 centres private and public in equal numbers all over Australia. A reminder was sent to 50 of the non respondents in February. A code number maintained anonymity. A two-page 17-item survey developed by the authors examined demographic, anaesthetic responsibility, fasting times, sedative and bowel cleansing agents employed, monitoring and reported complications as an estimate over the 2005-2006 financial year. A question on the number of deaths directly attributable to endoscopy procedures in the past ten years was included.

RESULTS

The response rate was 58/120 (48.3%) overall with 30/60 (50%) 'public' and 26/60 (43.3%) 'private clinics', from all states responding to the survey and only 2 non-responders. This represented 106,113 procedures, (43,986 public and 58720 private), which were performed by 421 proceduralists, an average of 171 and 393 per proceduralist respectively. During the year Medicare provided rebates for 493,966 procedures[10]. According to Medicare figures the study represents approximately 25% of procedures in the year 2005-2006 in Australia. An anaesthetist was solely responsible for 70% of private and 50% of public endoscopic examinations. There was no nursing representation in the private sector although 33% of public units had nurses responsible for the airway.

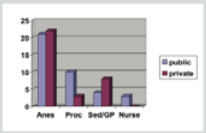
Fig 1. Distribution of Centres returning questionnaire; private ● public ●

Fig 2. Number of proceduralists who were represented in the survey



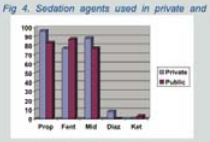
In the private sector, of 153 proceduralists, physicians made up 56% (p=0.66), surgeons 36%,(p=0.41) nurse endoscopists 3% (p=0.24)and GPs 2% (p=0.76). In the public sector, there were 268 proceduralists with physicians 51%, surgeons 43%, trainees 5% and GPs 3%.

Fig 3. Participation in the provision of sedation in public and private units



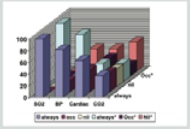
The number of procedures for which an anaesthetist was solely responsible was 60%(p=0.31) in the private sector; 24% and 12% when they shared the work with GP/sedationists and proceduralist respectively. In the public sector anaesthetists were solely employed in 50% of sedations. The sedation/airway was supervised 33% by nurses, 16% by proceduralist and 10% by GP/sedationist.

Fig 4. Sedation agents used in private and public



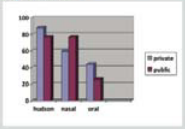
The vast majority of procedures were performed with combination of benzodiazepine, narcotic and Propofol, the latter used in 94% of centres.

*Fig 5. Percent monitoring used Public Vs Private **



Pulse oximeter was universal, capnography was used more in the public than private centres (70% vs 30% p=0.02)) as was cardiac monitoring (93% vs 53% p=0.0007)).

Fig 6. Percent of oxygenating devices used during the procedure



Supplemental oxygen pre- and post- procedure, monitoring of oxygen saturation and vital signs, were universal and fasting times were between 4-6 hours.

Table 1: During the previous 12 months, what were the approximate numbers of complications?

Complication	Private	Public
Aspiration	24	34
Assisted Ventilation	35	55
Endotracial Intubation	2	96
Cardiac Arrests	0	3

Table 2: How many deaths have been associated with endoscopic procedures at your institution in the past 10 years? (Deaths that have been directly caused by endoscopic procedures)

	Private	Public
Deaths in '0 years	Nil	8

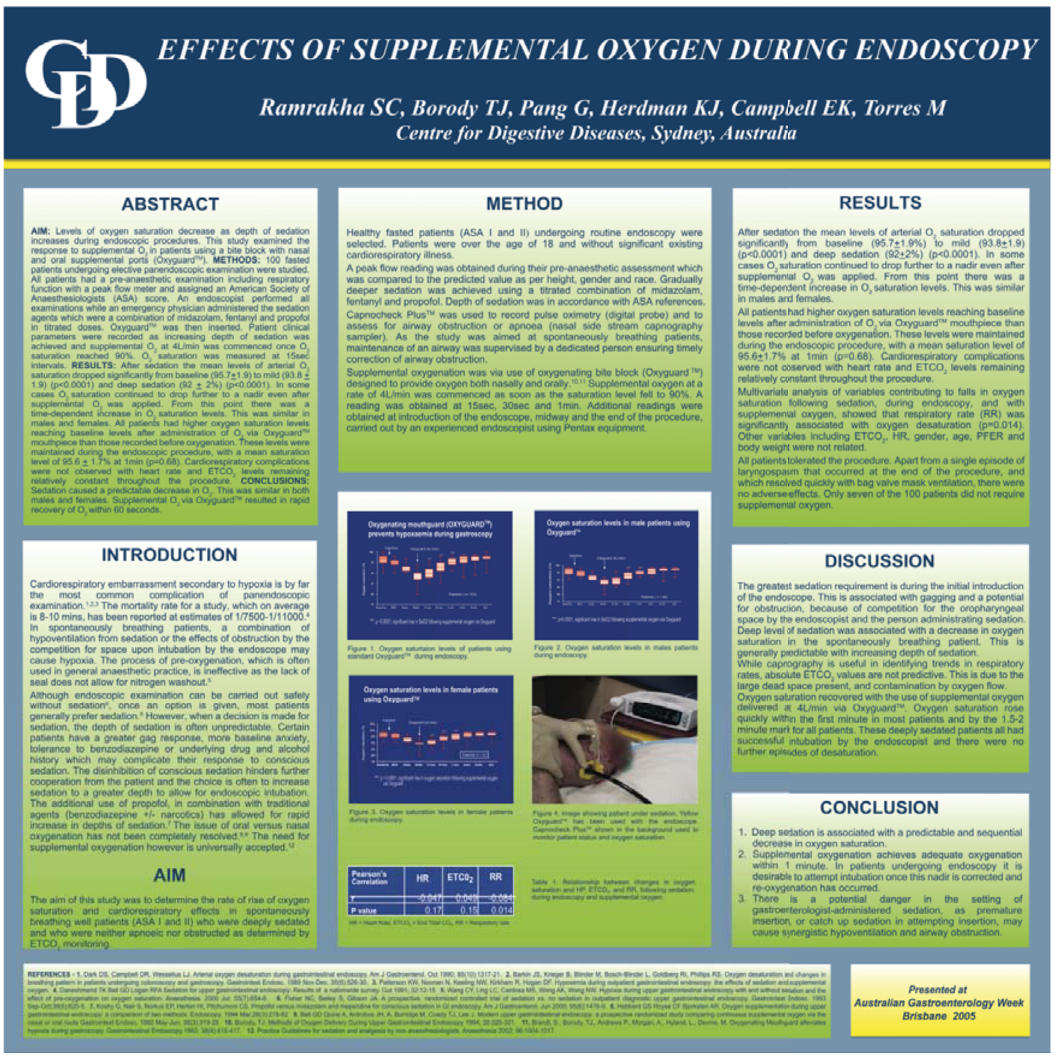
Reported complication rates were higher in the public sector with aspiration 0.11% vs. 0.08% (p=0.63), assisted ventilation 0.15% vs. 0.07% (p=0.77) ETT 0.22% vs. 0.01% (p=0.4). There were 3 cardiac arrests in that year, and 8 deaths within ten years due solely to the procedure - all in the public sector with none reported in the private sector.

CONCLUSIONS

The aim of this survey was to provide national data on endoscopic sedation within Australia. The survey revealed intravenous sedation during endoscopy to be the standard practice throughout Australia. In general, however, the administration of intravenous sedation by Australian endoscopy centres conforms to published guidelines. Supplemental oxygen therapy and use of automated monitoring is generally adopted although the use of capnography is not as popular. Public facilities also reported a higher incidence in complications and mortalities associated with endoscopies than private practices. While this retrospective survey has shown greater insight into the endoscopic sedation practices in Australia, it has encountered several limitations in particular recall bias.

The results of this survey identify current sedation and monitoring practices in Australia. There is greater involvement of anaesthetists/sedationists in endoscopy units than commonly perceived reflected in common use of Propofol. These findings should contribute to policy debate from an Australian perspective.

APPENDIX 4 – AUSTRALIAN GASTROENTEROLOGY WEEK 2005 – POSTER PRESENTATION - EFFECTS OF SUPPLEMENTAL OXYGEN DURING ENDOSCOPY.



APPENDIX 5 – DEVELOPMENT OF TWINGUARD™

Diagrams below depict early design concepts for TwinGuard™ and the proposed functionality of the new oxygenating bite block

Diagram A – Proposed oxygen route

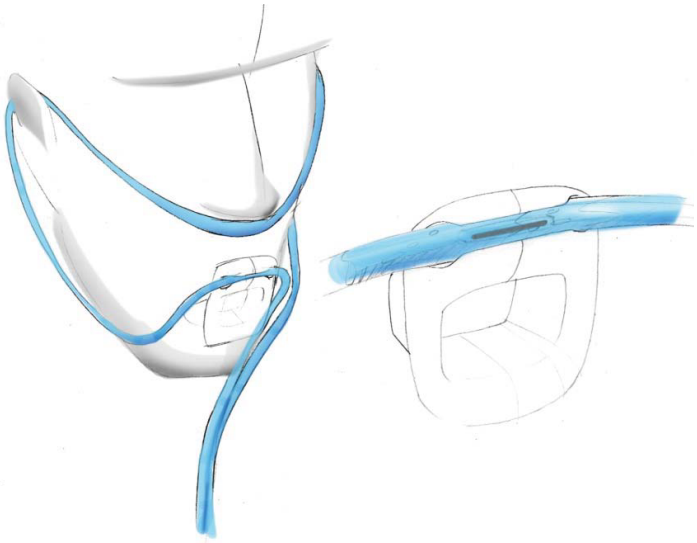


Diagram B (i) – Proposed alternative oxygen route B

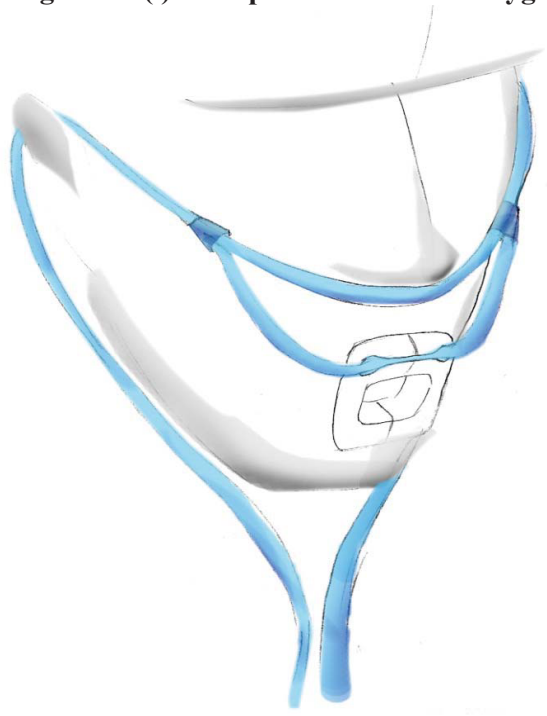
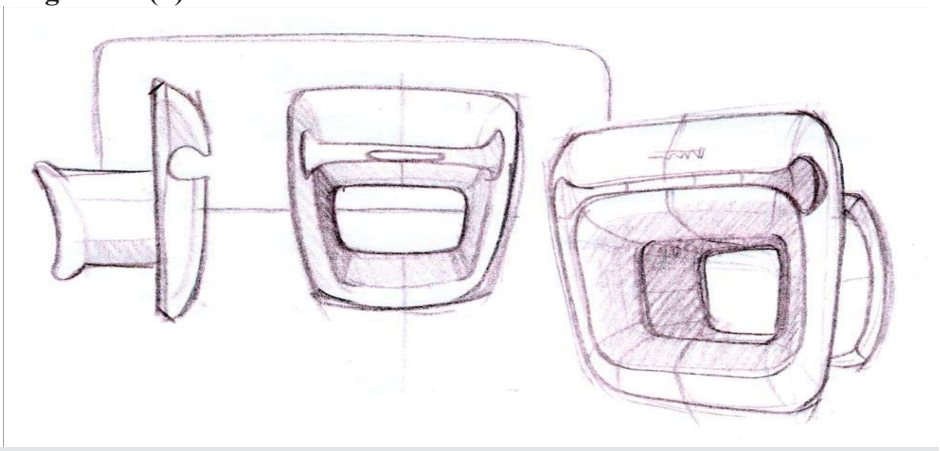
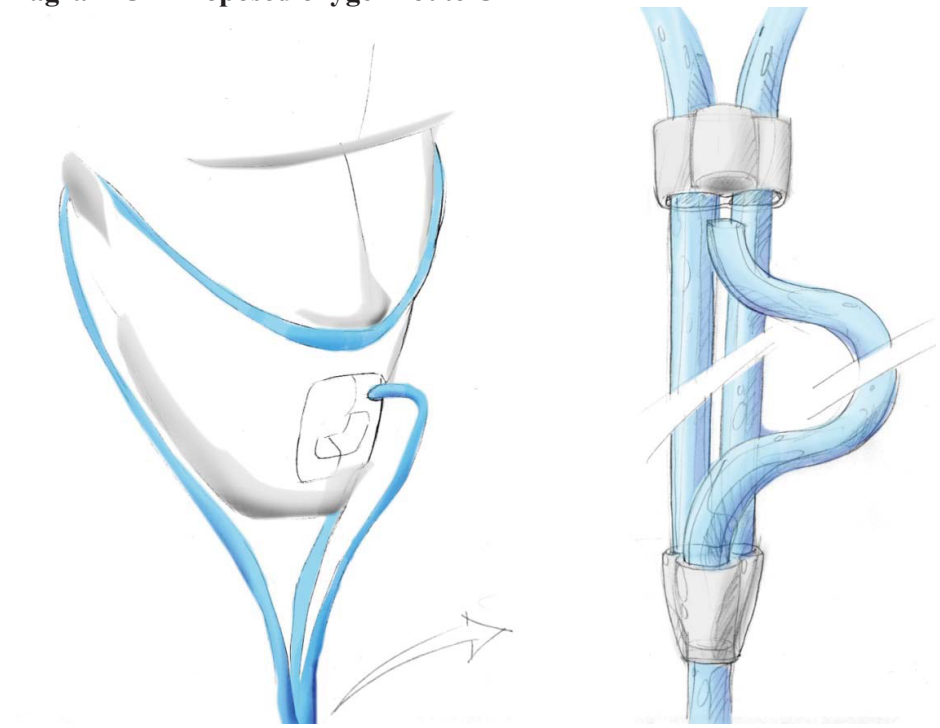


Diagram B (ii) – The bite block attachment



SNAP-IN AND PIERCED BITE GUARD CONCEPTS

Diagram C – Proposed oxygen route C



THREE WAY SPLITTER

Diagram D – Proposed oxygen route D using detachable oxygen tubing

Diagram E – Bite block with a single oxygenating port inlet

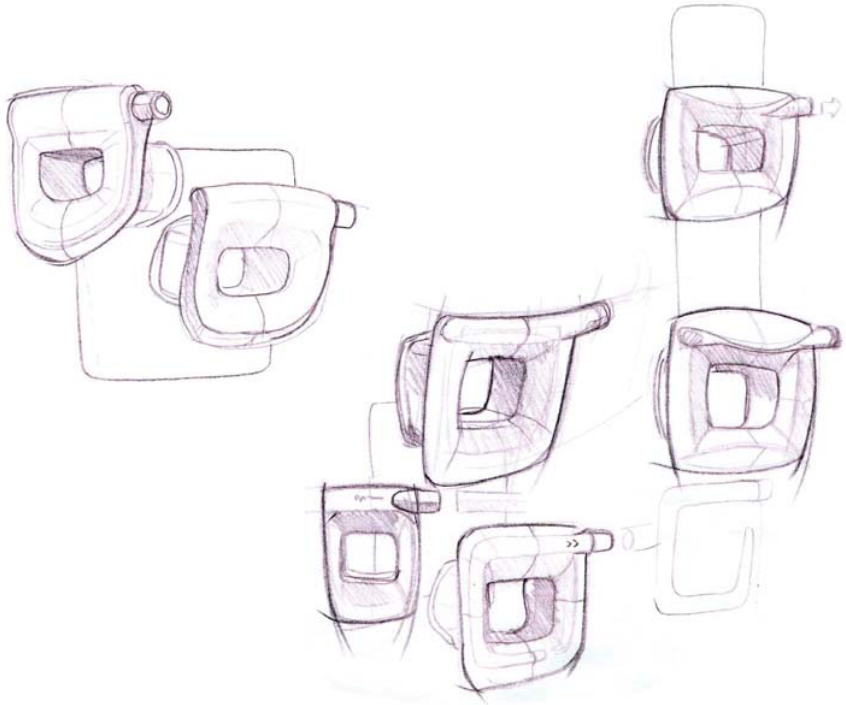


Diagram F – Bite block with a twin oxygenating port inlets

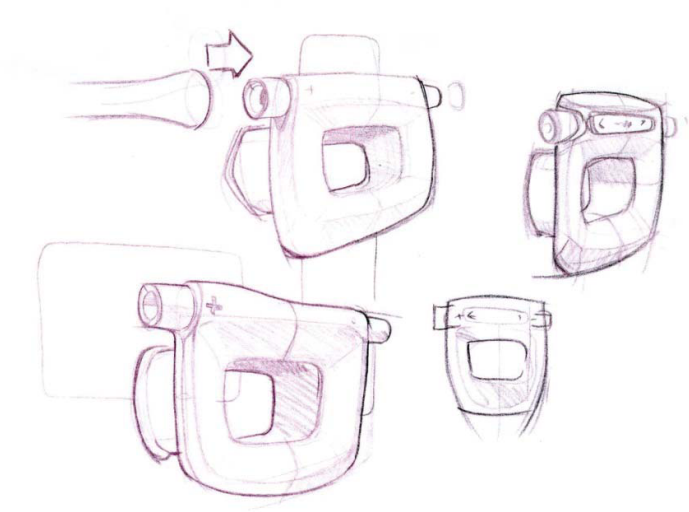


Diagram G – Bite block with a single oxygenating port situated at the top of the bite block

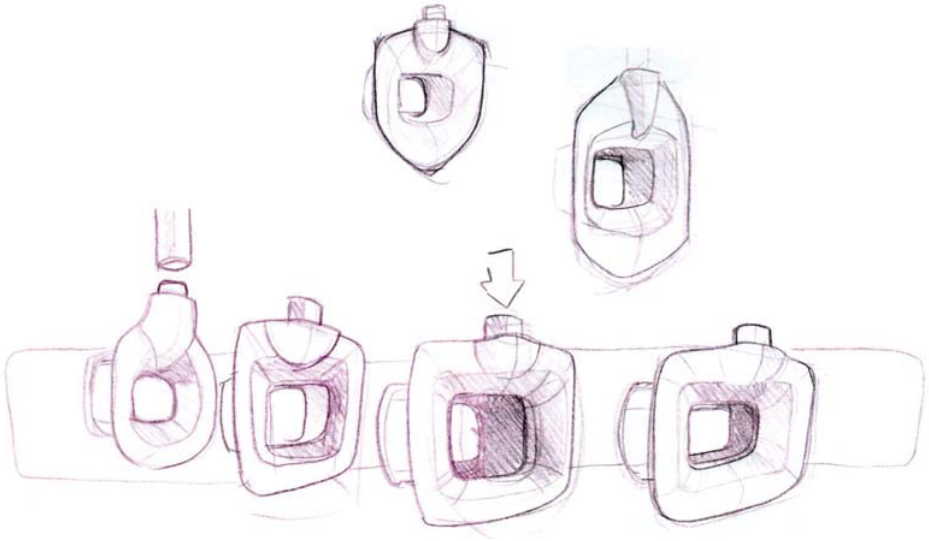


Diagram H – Proposed oxygen route Option E

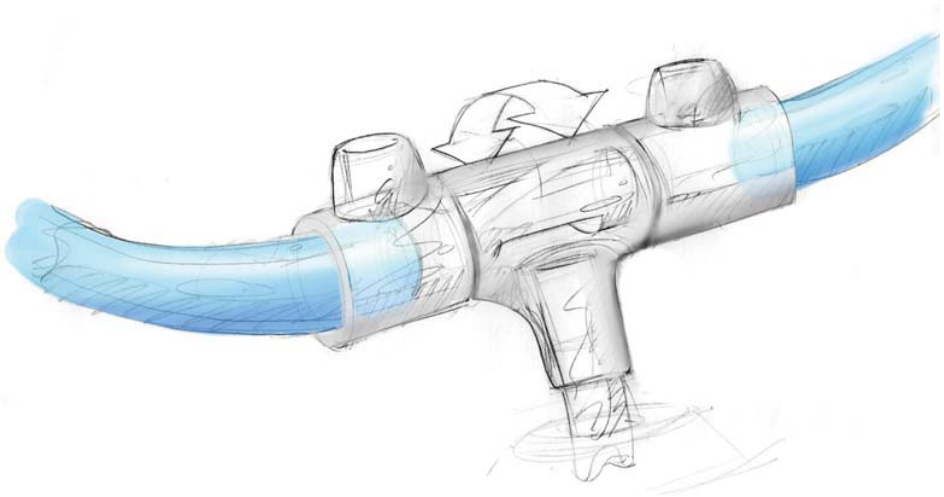


Diagram I – Looped Bite Guard concept

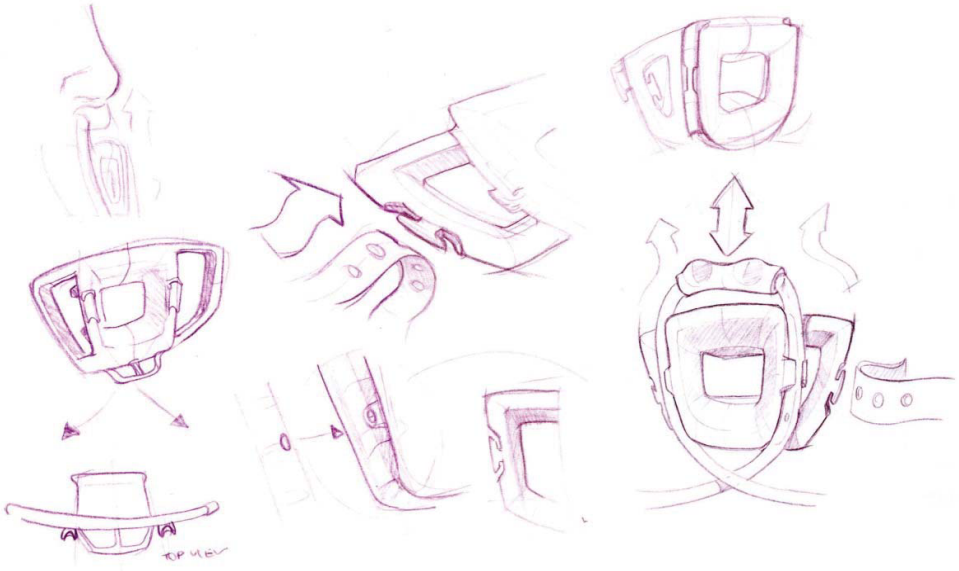


Diagram J – Clip and slide Bite Guard concept

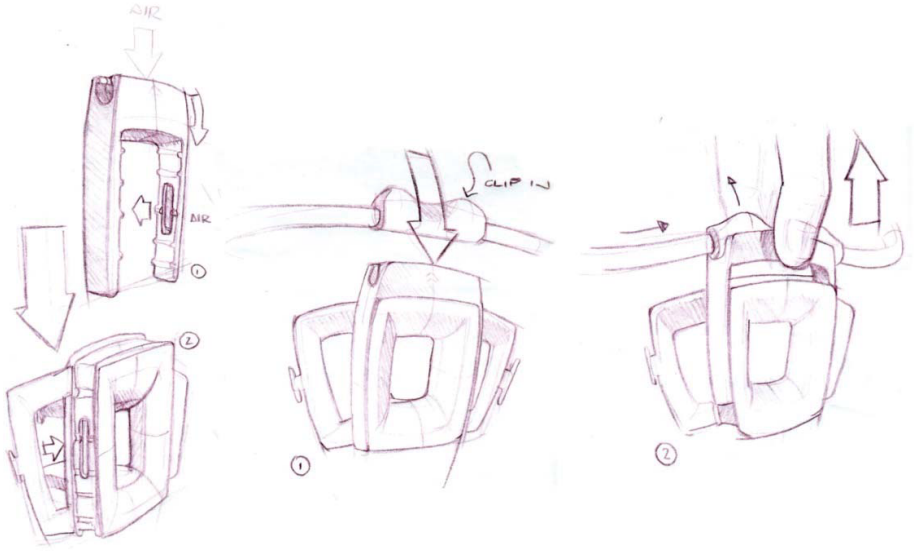


Diagram K – Adjustable clip-in foam Bite Guard concept

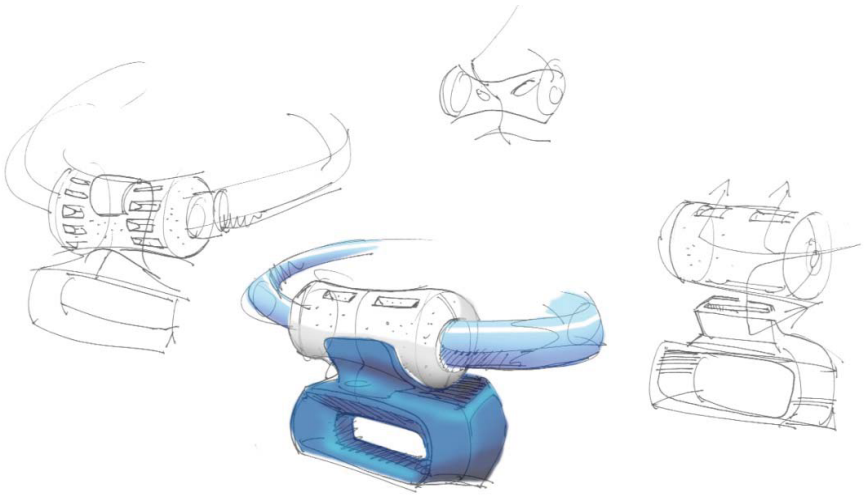


Diagram L – Height adjustable and clip-in Bite Guard concept

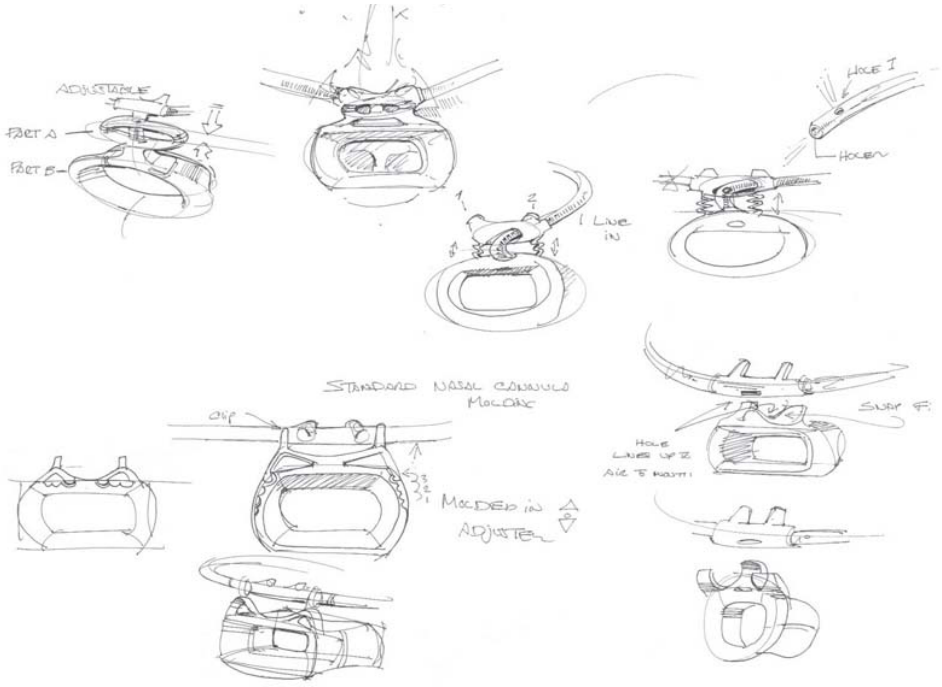


Diagram M – Pulp molded Bite Guard concept

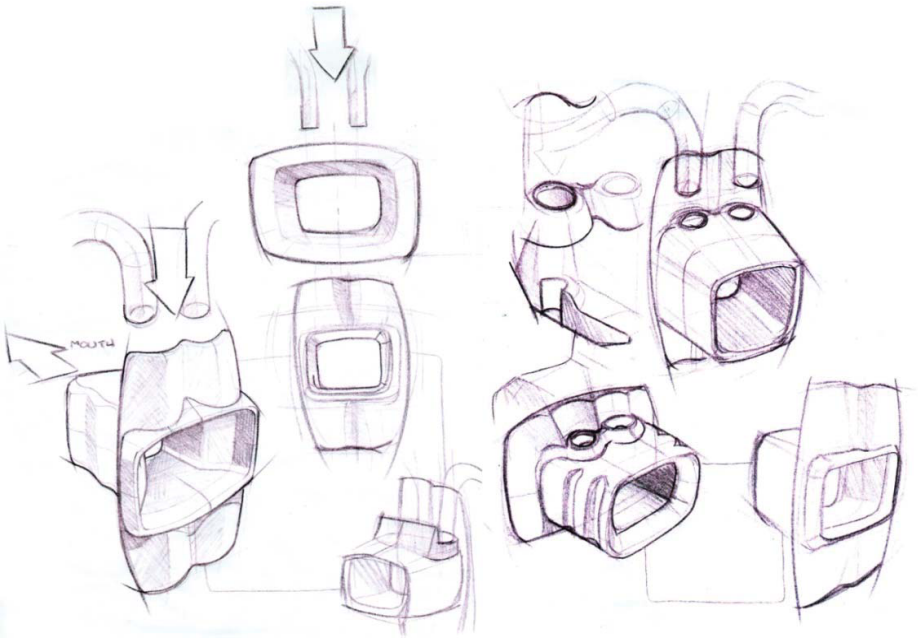


Diagram N (i) – Twin stakes oxygenating port concept

Diagram N (ii) – Preliminary geometry of Twin stakes oxygenating port concept

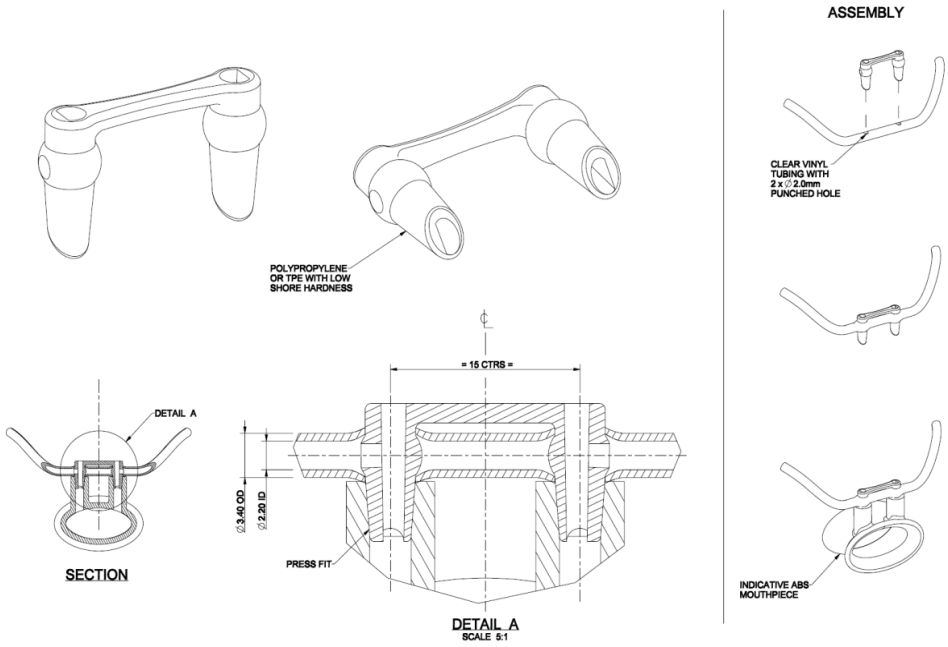


Diagram N – Connection of twin stakes oxygenating port to Bite block

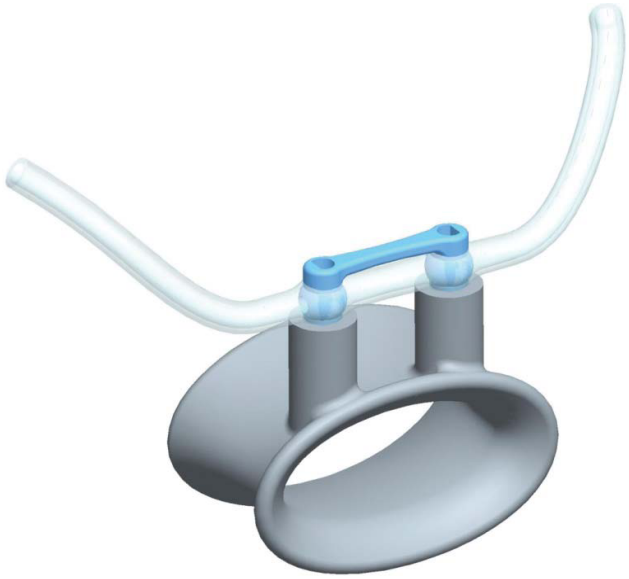


Diagram O – Revised nasal cannula

Diagram P (i) – Initial prototype using modified twin stakes oxygenating port on a modified Oxyguard® (Trawax P/L, Sydney) bite block

Diagram P (ii) – Initial prototype using modified twin stakes oxygenating port on a modified Oxyguard® (Trawax P/L, Sydney) bite block

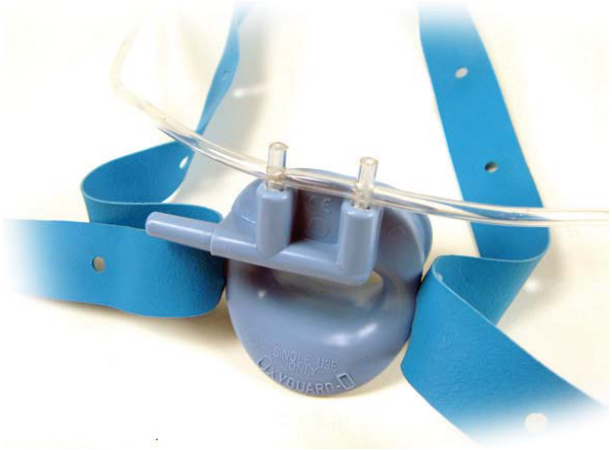


Diagram P (iii) – Initial prototype using modified twin stakes oxygenating port on a modified Oxyguard® (Trawax P/L, Sydney) bite block

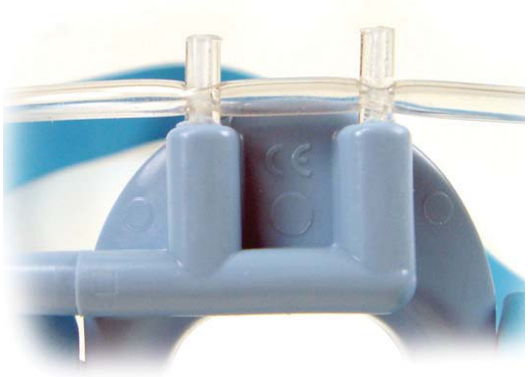


Diagram Q – Schematic of oxygen delivery for TwinGuard™

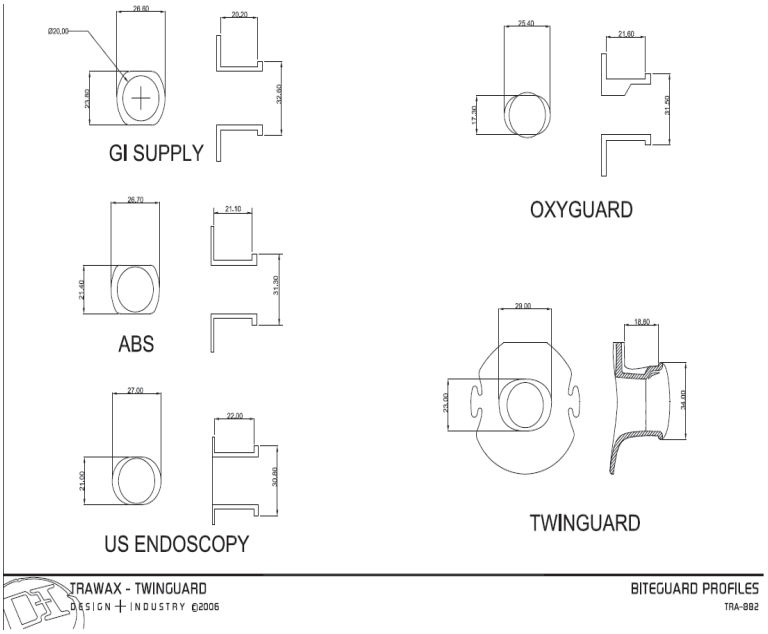
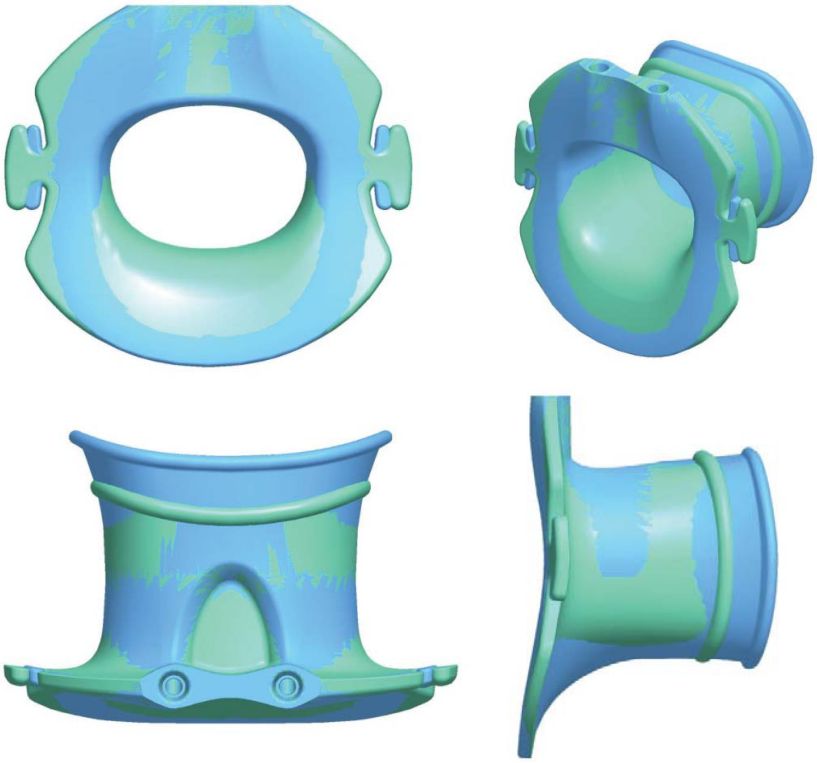


Diagram R – Final schematic prototype drawings for TwinGuard



APPENDIX 6 – AUSTRALIAN STANDARD PATENT ISSUED FOR TWINGUARD™

Australian Government
IP Australia

LETTERS PATENT

STANDARD PATENT

2004264256

I, Ian Goss, the Commissioner of Patents, grant a Standard Patent with the following particulars:

Name and Address of Patentee(s):

Thomas J. Borody
Level 1, 144 Great North Road, Five Dock, NSW, 2046, Australia

Name of Actual Inventor(s):

Borody, Thomas J..

Title of Invention:

Improved oral oxygenating appliance

Term of Letters Patent:

Twenty years from 9 August 2004

Priority Details :

Number	*Date*	*Filed with*
2003904278	13 August 2003	AU

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

Dated this 7th day of January 2010

Ian Goss
Commissioner of Patents

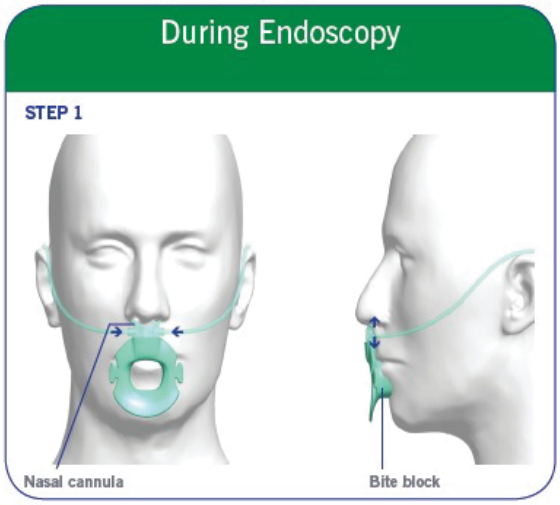
PATENTS ACT 1990

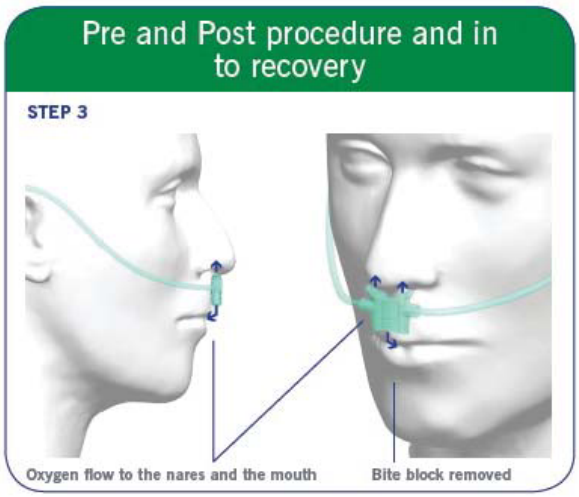
APPENDIX 7 – INSTRUCTIONS FOR TWINGUARD™ USE

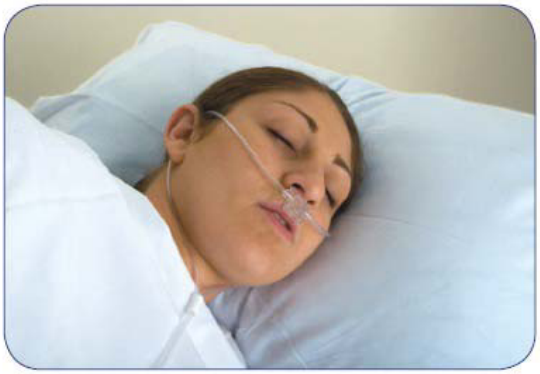
THE NASAL CANNULA MAY BE CHOSEN TO BE SECURED IN PLACE BEFORE CLIPPING THE BITE BLOCK TO THE NASAL PIECE.

1. Secure the nasal cannula in place as you would with conventional nasal prongs i.e. nasal piece under the nose, tubing hooked over the top of the ears and around the back of the ears, down under the chin. Slide the chin slide up under the chin to secure. The curved section of the nasal piece should sit towards the nostrils and the straight edge should point down towards the mouth.
2. Connect the end of the tubing to the oxygen source.
3. Position the bite block in the patient's mouth and clip the bite block to the nasal piece.
4. If required, attach a head strap to the notches on either side of the bite block.
5. Adjust the oxygen flow accordingly. Oxygen will then flow to the patient's mouth and nose.
6. Post procedure - If a head strap was required, detach the strap from the bite block first.
7. Removing the bite block from the patient's mouth and detach from the nasal cannula.

8. After use, dispose of products appropriately as a contaminated biohazard.







INSTRUCTIONS FOR USE – OPTIONAL CO_2 MONITORING ACCESSORY

FOR USE WITH SIDE-STREAM CAPNOGRAPHY IN CONJUNCTION WITH

A WATER TRAP DEVICE

1. Remove the CO_2 monitoring accessory from the packaging.
2. Attach the sample line luer lock to the water trap.
3. Connect the tube splitter to the TwinGuard nasal cannula at the patient's cheek.
4. Place the L shaped piece into the closest TwinGuard bite block hole.
5. Gently place the nosepiece into the patient's nostril.
6. Turn on the capnograph. CO_2 will then be detected at the mouth and nose
7. Post procedure-detach the CO_2 sample line from the nasal cannula.

APPENDIX 8 – FDA REGISTRATION ADVICE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 3 1 2008

Trawax Pty Limited
C/O Ms. Cindy Martin
Regulatory Affairs Associate II
29662 Avante
Laguna Niguel, California 92677

Re: K080527
Trade/Device Name: TwinGuard™ with Capnograph Accessory
Regulation Number: 21 CFR 876.1500
Regulation Name: Endoscope and Accessories
Regulatory Class: I
Product Code: MNK, CCK
Dated: October 22, 2008
Received: October 23, 2008

Dear Ms. Martin:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050. This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Center for Devices and Radiological Health's (CDRH's) Office of Compliance at (240) 276-0115. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

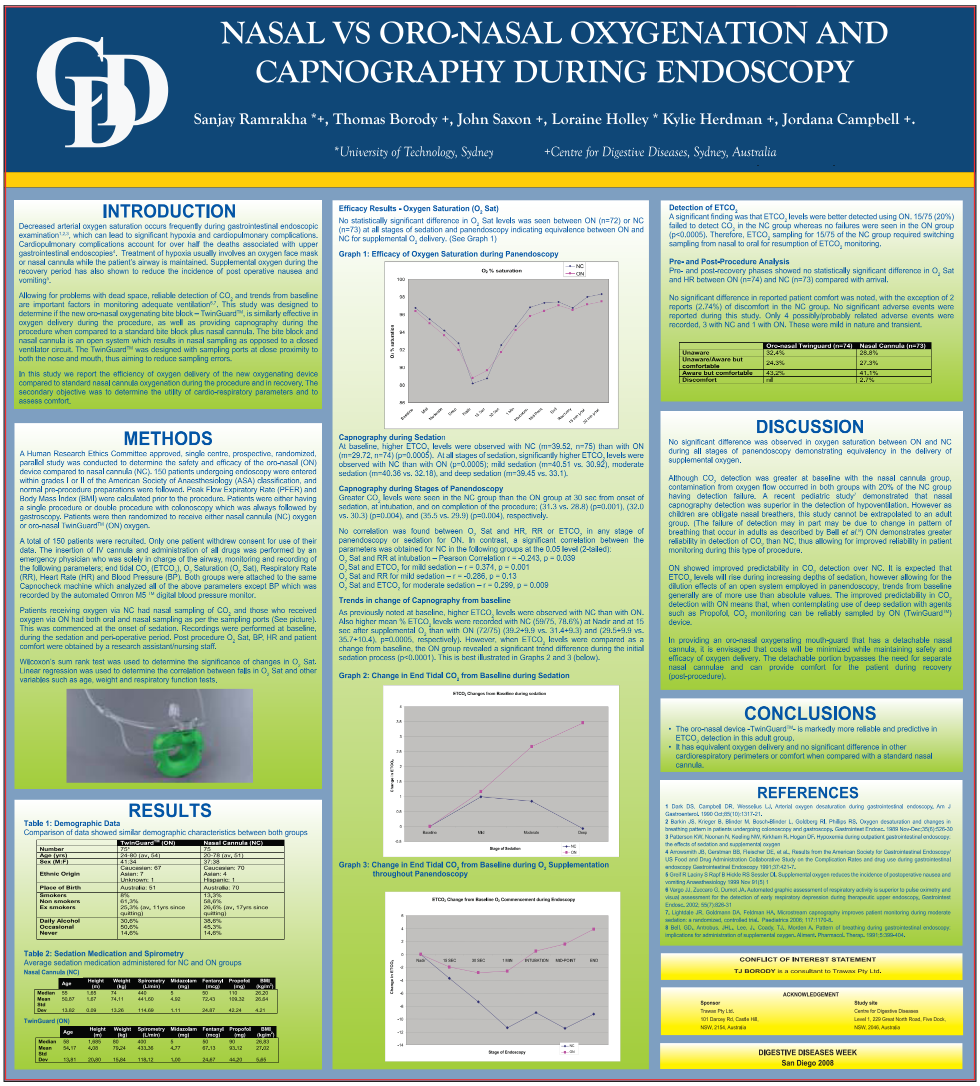
Sincerely yours,

Production Note:
Signature removed prior to publication.

Chiu Lin, Ph.D.
Director
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

APPENDIX 9 – DIGESTIVE DISEASES WEEK 2008 POSTER PRESENTATION TWINGUARD™ VS ORONASAL CAPNOGRAPHY



NASAL VS ORO-NASAL OXYGENATION AND CAPNOGRAPHY DURING ENDOSCOPY

Sanjay Ramrakha *+, Thomas Borody +, John Saxon +, Loraine Holley * Kylie Herdman +, Jordana Campbell +.

*University of Technology, Sydney +Centre for Digestive Diseases, Sydney, Australia

INTRODUCTION

Decreased arterial oxygen saturation occurs frequently during gastrointestinal endoscopic examination[1,2,3], which can lead to significant hypoxia and cardiopulmonary complications. Cardiopulmonary complications account for over half the deaths associated with upper gastrointestinal endoscopies[4]. Treatment of hypoxia usually involves an oxygen face mask or nasal cannula while the patient's airway is maintained. Supplemental oxygen during the recovery period has also shown to reduce the incidence of post operative nausea and vomiting[5].

Allowing for problems with dead space, reliable detection of CO_2 and trends from baseline are important factors in monitoring adequate ventilation[6,7]. This study was designed to determine if the new oro-nasal oxygenating bite block – TwinGuard™, is similarly effective in oxygen delivery during the procedure, as well as providing capnography during the procedure when compared to a standard bite block plus nasal cannula. The bite block and nasal cannula is an open system which results in nasal sampling as opposed to a closed ventilator circuit. The TwinGuard™ was designed with sampling ports at close proximity to both the nose and mouth, thus aiming to reduce sampling errors.

In this study we report the efficiency of oxygen delivery of the new oxygenating device compared to standard nasal cannula oxygenation during the procedure and in recovery. The secondary objective was to determine the utility of cardio-respiratory parameters and to assess comfort.

METHODS

A Human Research Ethics Committee approved, single centre, prospective, randomized, parallel study was conducted to determine the safety and efficacy of the oro-nasal (ON) device compared to nasal cannula (NC). 150 patients undergoing endoscopy were entered within grades I or II of the American Society of Anaesthesiology (ASA) classification, and normal pre-procedure preparations were followed. Peak Flow Expiratory Rate (PFER) and Body Mass Index (BMI) were calculated prior to the procedure. Patients were either having a single procedure or double procedure with colonoscopy which was always followed by gastroscopy. Patients were then randomized to receive either nasal cannula (NC) oxygen or oro-nasal TwinGuard™ (ON) oxygen.

A total of 150 patients were recruited. Only one patient withdrew consent for use of their data. The insertion of IV cannula and administration of all drugs was performed by an emergency physician who was solely in charge of the airway, monitoring and recording of the following parameters; end tidal CO_2 ($ETCO_2$), O_2 Saturation (O_2 Sat), Respiratory Rate (RR), Heart Rate (HR) and Blood Pressure (BP). Both groups were attached to the same Capnocheck machine which analyzed all of the above parameters except BP which was recorded by the automated Omron M5 ™ digital blood pressure monitor.

Patients receiving oxygen via NC had nasal sampling of CO_2 and those who received oxygen via ON had both oral and nasal sampling as per the sampling ports (See picture). This was commenced at the onset of sedation. Recordings were performed at baseline, during the sedation and peri-operative period. Post procedure O_2 Sat, BP, HR and patient comfort were obtained by a research assistant/nursing staff.

Wilcoxon's sum rank test was used to determine the significance of changes in O_2 Sat. Linear regression was used to determine the correlation between falls in O_2 Sat and other variables such as age, weight and respiratory function tests.

RESULTS

Table 1: Demographic Data

Comparison of data showed similar demographic characteristics between both groups

	TwinGuard™ (ON)	Nasal Cannula (NC)
Number	75*	75
Age (yrs)	24-80 (av. 54)	20-78 (av. 51)
Sex (M:F)	41:34	37:38
Ethnic Origin	Caucasian: 67 Asian: 7 Unknown: 1	Caucasian: 70 Asian: 4 Hispanic: 1
Place of Birth	Australia: 51	Australia: 70
Smokers Non smokers Ex smokers	8% 61.3% 25.3% (av. 11yrs since quitting)	13.3% 58.6% 26.6% (av. 17yrs since quitting)
Daily Alcohol Occasional Never	30.6% 50.6% 14.6%	38.6% 45.3% 14.6%

Table 2: Sedation Medication and Spirometry

Average sedation medication administered for NC and ON groups

Nasal Cannula (NC)

	Age	Height (m)	Weight (kg)	Spirometry (L/min)	Midazolam (mg)	Fentanyl (mcg)	Propofol (mg)	BMI (kg/m²)
Median	55	1.65	74	440	5	50	110	26.20
Mean	50.87	1.67	74.11	441.60	4.92	72.43	109.32	26.64
Std Dev	13.82	0.09	13.26	114.69	1.11	24.87	42.24	4.21

TwinGuard (ON)

	Age	Height (m)	Weight (kg)	Spirometry (L/min)	Midazolam (mg)	Fentanyl (mcg)	Propofol (mg)	BMI (kg/m²)
Median	58	1.685	80	400	5	50	90	26.83
Mean	54.17	4.08	79.24	433.36	4.77	67.13	93.12	27.02
Std Dev	13.81	20.80	15.84	118.12	1.00	24.67	44.20	5.65

Efficacy Results - Oxygen Saturation (O_2 Sat)

No statistically significant difference in O_2 Sat levels was seen between ON (n=72) or NC (n=73) at all stages of sedation and panendoscopy indicating equivalence between ON and NC for supplemental O_2 delivery. (See Graph 1)

Graph 1: Efficacy of Oxygen Saturation during Panendoscopy

Capnography during Sedation

At baseline, higher $ETCO_2$ levels were observed with NC (m=39.52, n=75) than with ON (m=29.72, n=74) (p=0.0005). At all stages of sedation, significantly higher $ETCO_2$ levels were observed with NC than with ON (p=0.0005); mild sedation (m=40.51 vs. 30.92), moderate sedation (m=40.36 vs. 32.18), and deep sedation (m=39.45 vs. 33.1).

Capnography during Stages of Panendoscopy

Greater CO_2 levels were seen in the NC group than the ON group at 30 sec from onset of sedation, at intubation, and on completion of the procedure; (31.3 vs. 28.8) (p=0.001), (32.0 vs. 30.3) (p=0.004), and (35.5 vs. 29.9) (p=0.004), respectively.

No correlation was found between O_2 Sat and HR, RR or $ETCO_2$ in any stage of panendoscopy or sedation for ON. In contrast, a significant correlation between the parameters was obtained for NC in the following groups at the 0.05 level (2-tailed):
O_2 Sat and RR at intubation – Pearson Correlation r = -0.243, p = 0.039
O_2 Sat and $ETCO_2$ for mild sedation – r = 0.374, p = 0.001
O_2 Sat and RR for mild sedation – r = -0.286, p = 0.13
O_2 Sat and $ETCO_2$ for moderate sedation – r = 0.299, p = 0.009

Trends in change of Capnography from baseline

As previously noted at baseline, higher $ETCO_2$ levels were observed with NC than with ON. Also higher mean % $ETCO_2$ levels were recorded with NC (59/75, 78.6%) at Nadir and at 15 sec after supplemental O_2 than with ON (72/75) (39.2+9.9 vs. 31.4+9.3) and (29.5+9.9 vs. 35.7+10.4), p=0.0005, respectively). However, when $ETCO_2$ levels were compared as a change from baseline, the ON group revealed a significant trend difference during the initial sedation process (p<0.0001). This is best illustrated in Graphs 2 and 3 (below).

Graph 2: Change in End Tidal CO_2 from Baseline during Sedation

Graph 3: Change in End Tidal CO_2 from Baseline during O_2 Supplementation throughout Panendoscopy

Detection of $ETCO_2$

A significant finding was that $ETCO_2$ levels were better detected using ON. 15/75 (20%) failed to detect CO_2 in the NC group whereas no failures were seen in the ON group (p<0.0005). Therefore, $ETCO_2$ sampling for 15/75 of the NC group required switching sampling from nasal to oral for resumption of $ETCO_2$ monitoring.

Pre- and Post-Procedure Analysis

Pre- and post-recovery phases showed no statistically significant difference in O_2 Sat and HR between ON (n=74) and NC (n=73) compared with arrival.

No significant difference in reported patient comfort was noted, with the exception of 2 reports (2.74%) of discomfort in the NC group. No significant adverse events were reported during this study. Only 4 possibly/probably related adverse events were recorded, 3 with NC and 1 with ON. These were mild in nature and transient.

	Oro-nasal Twinguard (n=74)	Nasal Cannula (n=73)
Unaware	32.4%	28.8%
Unaware/Aware but comfortable	24.3%	27.3%
Aware but comfortable	43.2%	41.1%
Discomfort	nil	2.7%

DISCUSSION

No significant difference was observed in oxygen saturation between ON and NC during all stages of panendoscopy demonstrating equivalency in the delivery of supplemental oxygen.

Although CO_2 detection was greater at baseline with the nasal cannula group, contamination from oxygen flow occurred in both groups with 20% of the NC group having detection failure. A recent pediatric study[7] demonstrated that nasal capnography detection was superior in the detection of hypoventilation. However as children are obligate nasal breathers, this study cannot be extrapolated to an adult group. (The failure of detection may in part may be due to change in pattern of breathing that occur in adults as described by Bell *et al.*[8]) ON demonstrates greater reliability in detection of CO_2 than NC, thus allowing for improved reliability in patient monitoring during this type of procedure.

ON showed improved predictability in CO_2 detection over NC. It is expected that $ETCO_2$ levels will rise during increasing depths of sedation, however allowing for the dilution effects of an open system employed in panendoscopy, trends from baseline generally are of more use than absolute values. The improved predictability in CO_2 detection with ON means that, when contemplating use of deep sedation with agents such as Propofol, CO_2 monitoring can be reliably sampled by ON (TwinGuard™) device.

In providing an oro-nasal oxygenating mouth-guard that has a detachable nasal cannula, it is envisaged that costs will be minimized while maintaining safety and efficacy of oxygen delivery. The detachable portion bypasses the need for separate nasal cannulae and can provide comfort for the patient during recovery (post-procedure).

CONCLUSIONS

- The oro-nasal device -TwinGuard™- is markedly more reliable and predictive in $ETCO_2$ detection in this adult group.
- It has equivalent oxygen delivery and no significant difference in other cardiorespiratory perimeters or comfort when compared with a standard nasal cannula.

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CONFLICT OF INTEREST STATEMENT

TJ BORODY is a consultant to Trawax Pty Ltd.

ACKNOWLEDGEMENT

Sponsor: Trawax Pty Ltd. 101 Darcey Rd, Castle Hill, NSW, 2154, Australia

Study site: Centre for Digestive Diseases, Level 1, 229 Great North Road, Five Dock, NSW, 2046, Australia

DIGESTIVE DISEASES WEEK
San Diego 2008

APPENDIX 10 – PATIENT EVALUATION FORM USED TO ASSESS COLONOSCOPY BOWEL PREPARATION IN CLINICAL TRIAL

Patient Initials:
_____

DOB: ___ / ___ / ___

Patient No : | | | |

Patient Evaluation Form
For Colonoscopy Bowel Preparation

Bowel Preparation used: _____

Please complete the form before you come in for your procedure. The completed questionnaire is to be given to research staff only and not reception or doctors.

Please circle the most appropriate answer

1. **How easy or difficult was it for you to complete the preparation you received?**

   a. Easy
   b. Somewhat difficult
   c. Unable to finish

2. **Please rate the taste of the preparation you took.**

   a. No taste or pleasant tasting
   b. Not good, but tolerable
   c. Barely tolerable
   d. Unacceptable

3. **Were you able to complete the prep?**

   a. Yes
   b. No

   If no, was this due to the taste of the preparation? YES / NO

4. **Would you refuse the same preparation again if you need another colonoscopy in future?**

   a. Yes
   b. No

5. **Did you feel that the preparation cleaned out your bowel effectively?**

   a. Yes
   b. No
   c. Unable to say

OFFICE USE ONLY -

APPENDIX 11 – DOCTOR AND SEDATIONIST EVALUATION FORMS USED IN CLINICAL TRIAL

Doctor Evaluation Form for Colonoscopy Bowel Preparation

The assessor is not to question the patient on the preparation taken prior to completion of this form. This form is to be completed during or immediately following the patient's colonoscopy.

NOTE: *This patient has been chosen randomly from both procedure lists. There is an equal possibility of this patient participating in the trial group or control group.*

Please circle the most appropriate description.

How would you evaluate the adequacy of colonic cleansing?

1. **Excellent:** Small volume of clear liquid or greater than 95% of surface seen
2. **Good:** Large volume of clear liquid covering 5% to 25% of the surface but greater than 90% of surface seen
3. **Fair:** Some semi-solid stool that could be suctioned or washed away but greater than 90% surface seen
4. **Poor:** Semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen
5. **Unable to finish:** Re-preparation needed

Please describe and rate the effectiveness of the bowel prep in the following regions. Rating "1" as the least effective and "10" as being the most effective.

REGION	DESCRIPTION	RATING 1-10
RECTUM		
TRANSVERSE		
CAECUM		
TERMINAL ILEUM		

Signature: _____

:

Sedationist Evaluation Form
for Colonoscopy Bowel Preparation

The assessor is <u>not</u> to question the patient on the preparation taken prior to completion of this form.
This form is to be completed during or immediately following the patients colonoscopy.

NOTE: *This patient has been chosen randomly from both procedure lists. There is an equal possibility of this patient participating in the trial group or control group.*

Please circle the most appropriate description

How would you evaluate the adequacy of colonic cleansing?

Excellent: small volume of clear liquid or greater than 95% of surface seen

Good: large volume of clear liquid covering 5% to 25% of the surface but greater than 90% of surface seen

Fair: some semi-solid stool that could be suctioned or washed away but greater than 90% surface seen

Poor: semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen

Inadequate: re-preparation required

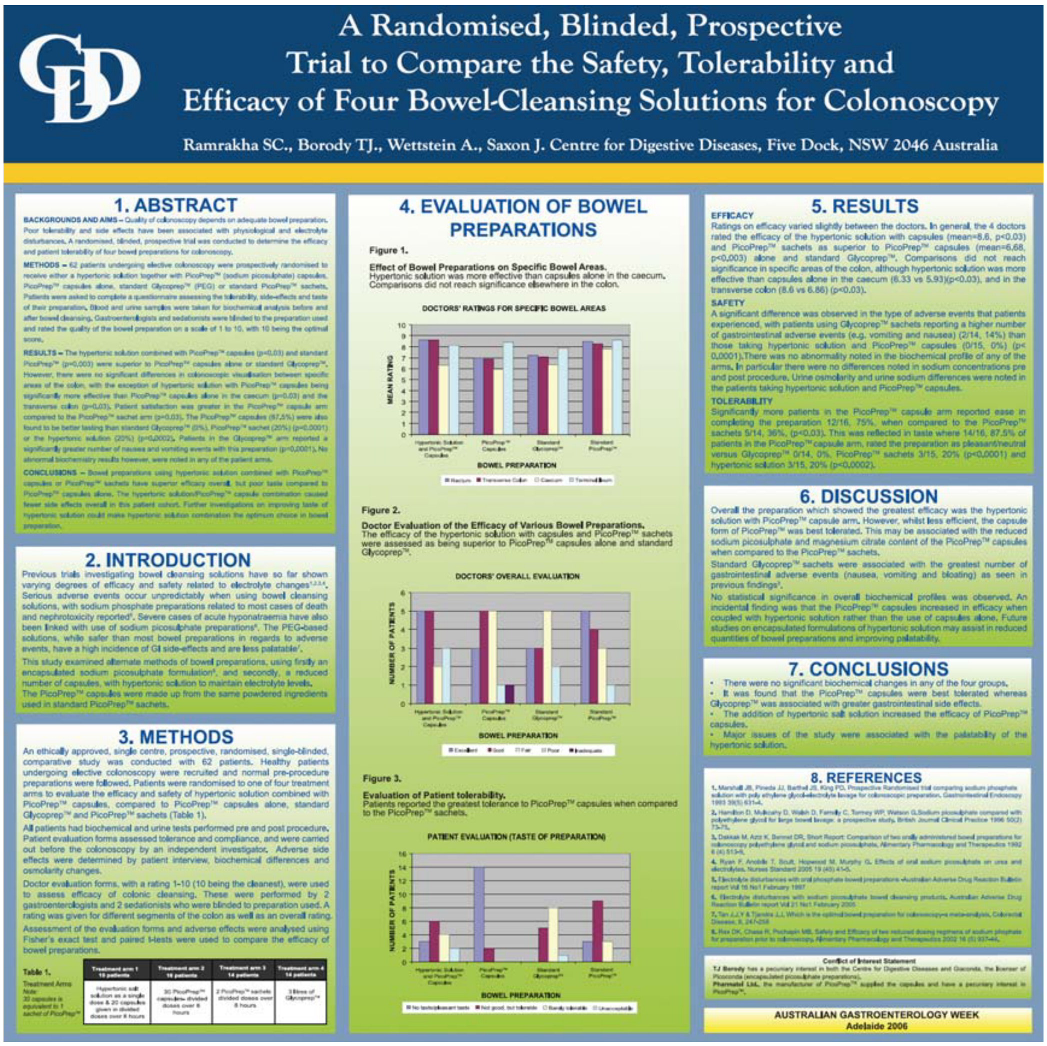
Please describe and rate the effectiveness of the bowel prep in the following regions. Rating "1" as the least effective and "10" as being the most effective.

REGION	DESCRIPTION	RATING 1-10
RECTUM		
TRANSVERSE		
CAECUM		
TERMINAL ILEUM		

Signature: _____

Name: _____ **Date:** _____

APPENDIX 12 – AUSTRALIAN GASTROENTEROLOGY WEEK 2006 POSTER PRESENTATION BOWEL PURGATIVE



APPENDIX 13 – AUSTRALIAN PATENT – ELECTROLYTE PURGATIVE

(11) Application No. AU 2003205450 C1

(19) AUSTRALIAN PATENT OFFICE

(54) Title

Electrolyte purgative

(51)[6] International Patent Classification(s)

A61K 33/14 (2006.01)
A61K 31/194 (2006.01)
A61K 31/7004 (2006.01)
A61K 33/00 (2006.01)
A61K 33/06 (2006.01)
A61P 1/10 (2006.01)
A61K 33/14 20060101AFI2005100
8BMEP **A61K** 31/194 20060101ALI2005100
8BMEP **A61K** 31/7004 20060101ALI2005100
8BMEP **A61K** 33/00 20060101ALI2005100
8BMEP **A61K** 33/06 20060101ALI2005100
8BMEP **A61P** 1/10 20060101ALI2006052
1BMWO PCT/AU03/00257

(21) Application No: 2003205450

(22) Application Date: 2003.03.04

(87) WIPO No: WO03/074061

(30) Priority Data

(31) Number	(32) Date	(33) Country
PS 0887	2002.03.04	AU

(43) Publication Date : 2003.09.16

(43) Publication Journal Date : 2003.10.23

(71) Applicant(s)

Thomas Borody; Sanjay Ramrakha; Antony Wettstein; John Saxon

(72) Inventor(s)

Borody, Thomas Julius; Ramrakha, Sanjay; Saxon, John; Wettstein, Antony

(74) Agent/Attorney

Spruson & Ferguson, Level 35 St Martins Tower 31 Market Street, Sydney, NSW, 2000

(56) Related Art

RU 2098100

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2003 (12.09.2003)

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(10) International Publication Number
WO 03/074061 A1

(51) International Patent Classification[7]: A61K 33/14, 33/06, 33/00, 31/7004, 31/194, A61P 1/10

(21) International Application Number: PCT/AU03/00257

(22) International Filing Date: 4 March 2003 (04.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PS 0887 4 March 2002 (04.03.2002) AU

(71) Applicants and
(72) Inventors: **BORODY, Thomas, Julius** [AU/AU]; 2-4 Cottonwood Place, Castle Hill, New South Wales 2154 (AU). **RAMRAKHA, Sanjay** [AU/AU]; 2 Forrest Street, Haberfield, New South Wales 2045 (AU). **SAXON, John** [AU/AU], 42 Arthur Street, Leichhardt, New South Wales 2040 (AU). **WETTSTEIN, Antony** [AU/AU]; 38 Gladstone Street, Chatswood, New South Wales 2067 (AU).

(74) Agent: **SPRUSON & FERGUSON**; GPO Box 3898, Sydney, NSW 2001 (AU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/074061 A1

(54) Title: ELECTROLYTE PURGATIVE

(57) Abstract: The invention relates to compositions for use in purgatives, to purgatives comprising such compositions, and to methods for inducing purgation of the colon. The composition may comprise at least one water-soluble sodium salt; at least one water-soluble minimally degradable sugar in an amount, by weight, of from about 1 to about 3 times the weight of sodium ions in said composition; at least one water-soluble potassium salt in an amount, by weight, of from about 0.05 to about 1 time the weight of said sodium salt in said composition; and at least one water-soluble magnesium salt, wherein the weight of magnesium ions in said composition is from 0.1 to about 10 times the weight of sodium ions in said composition.

ELECTROLYTE PURGATIVE

FIELD OF THE INVENTION

The invention relates to compositions for use in purgatives, to purgatives comprising such compositions, and to methods for inducing purgation of the colon.

BACKGROUND ART

Colonic orthostatic lavage is an iatrogenic phenomenon related to the administration of a purgative and therefore is predictable in its action and side effects. It is important to make the distinction between the use of iatrogenic purgation solutions and fluid/electrolyte replacement solutions used for treatment of vomiting and diarrhoea **associated** with gastroenteritis. The use of mainly hypotonic or isotonic solutions such as glucose-based 'Bangladesh' solution and rice-based solutions has been successful in patients with gastroenteritis and dehydration, a **highly** unpredictable disease. The physiological principle of coupled sodium and glucose transport in a **1:1** molar ratio in the intestine has been shown to be safe and effective. Purgatives developed to date for orthostatic lavage to clean the bowel of faecal matter prior to colonoscopy have taken the form of either an isotonic, large volume lavage (e.g. Braintree's Golytely) or more hypertonic lavage products such as Fleet's sodium phosphate or sodium picosulfate (Picolax) products. The former generally cause little homeostatic disturbance of intra-vascular sodium and other electrolytes or fluid shifts 20 because of their isotonic nature, which minimizes electrolyte absorption/secretion **by** the presence of high molecular weight polyethylene glycol **(PEG** mw **3350).** However, these preparations have recently been reported to **be** associated with hyponatremia (Clemens **D.C.** *et al., Lancet* **357(9252): 282-283** (2001)). Products with sodium phosphate and sodium picosulfate are felt to be better tolerated (Jayanthi V, *et al., **Am. J.** Gastroenterol.* **25** 94(8): **2122-7 (1999)).** However, these products have also been associated with a significant hypo-osmolar state and electrolyte imbalance, particularly hyponatremia.

This, to a large extent, is contributed to **by** a loss of electrolytes through the resultant diarrhoea caused **by** the lavage with concomitant replacement of this loss **by** water (without electrolytes) leading to hyponatremia and water intoxication associated with a **30** hypo-osmolar state.

The symptoms of headache, lethargy and nausea reported **by** patients undergoing orthostatic lavage are felt to **be** due to an osmotic shift with resultant dilutional hyponatremia that is induced **by** the various bowel preparation products such as "Fleet", Picolax etc. This effect appears to be more pronounced in adult females, perhaps as a result of relatively less total body water when compared to adult males and children (Fraser *et al., Am. **J.** Physiol.* **256: R880-5 (1989)).**

The clinical features of hyponatremia (hypoosmolality) are **highly** variable and their severity correlates poorly with the level of serum sodium. Classically, the clinical features of severe hyponatremia are confusion, seizures and obtundation. **A** decrease in plasma osmolality causes brain swelling (cerebral oedema) as water moves along osmotic gradients. In response, the brain loses solute from the intra and extra-cellular fluid spaces, which returns brain water content back towards normal. Once the brain has equilibrated (i.e. volume-adapted) through solute losses, neurological features will be less prominent or resolve.

The rate of fall of serum osmolality is generally better correlated with morbidity and mortality than the actual magnitude of the decrease (Arieff, **A.I.** *et al., Medicine*

(Baltimore) ***55:*** **121-9 (1976)),** and is somewhat arbitrarily defined as hypoosmolality developing over 24 to 48 hours. Mortality up to ***50%*** has been reported in patients with **acute** hyponatremia (Arieff, **A.I.** *et al.,* loc.cit.). Cerebral oedema develops when hypoosmolality exceeds the ability of the brain to regulate its volume **by** solute losses. In experimental models, acute hyponatraemia results in the loss of sodium and chloride from the brain within 30 minutes, whilst potassium loss is more delayed. **All** electrolyte losses are maximal **by 3** hours after initiation of hyponatraemia (Melton, **J.E.** *et al., Am.* ***J.*** 20 *Physiol.* **252: F661-9 (1987)).**

Hence in some situations the effects of the various bowel purgative formulations currently available can lead to the unpleasant side effects of headache, malaise and dizziness and hypotension. Additionally, life-threatening presentations of hypo-osmolar grand mal epileptic seizures, asphyxia and death have been reported.

Due to the accepted benefits of screening colonoscopic surveillance programs for the detection of colonic polyps and bowel cancer, the utilisation of colonic lavage **is** increasing rapidly. Indeed it is feasible that a large number of the population over the age of **50** years is likely to undergo colonoscopic examination. As a result, a considerable number of patients could potentially develop lavage-related hyponatraemia and hypo osmolar water intoxication with subsequent 'dilution' of other electrolytes leading to significant morbidity and potentially mortality.

Poor palatability leading to reduced patient compliance has been an important issue in the failure of some of the currently available products; either the volume is too large or the taste too objectionable for certain patients to comply with taking the prescribed bowel preparation. This leads to inadequate orthostatic lavage causing poor visibility at colonoscopy.

There is therefore a need for a purgative composition that reduces mortality and/or patient morbidity and/or which makes the procedure of purgation of the colon much more s pleasant for the patient so as to facilitate patient compliance.

The present invention therefore provides novel electrolyte-enhanced purgatives which may be administered in relatively small liquid volumes, suitably in the form of a palatable soup mixture, but which may also be formulated in various other forms such as capsules, powders or compressed tablets. Thus, the compositions and purgatives of the io present invention cause a purgative effect while ameliorating or overcoming the disadvantages associated with the administration of prior art purgatives, namely (a) symptoms associated with osmotic shifts and electrolyte imbalance; **(b)** hyponatraemia; and (c) poor patient compliance owing to unpalatibility and/or the need to consume large volumes of liquid.

SUMMARY OF THE INVENTION

In a first embodiment, the invention provides a composition for use in a purgative,

the composition comprising:

(i) At least one water-soluble sodium salt;

(ii) At least one water-soluble minimally degradable sugar in an amount, by weight, of from about 1 to about **3** times the weight of sodium salt in said composition;

(iii) At least one water-soluble potassium salt in an amount, **by** weight, of from

about **0.05** to about **I** times the weight of said sodium salt in said composition; and

(iv) At least one water-soluble magnesium salt, wherein the weight of magnesium **25** salt in said composition is from about **0.1** to about **10** times the weight of sodium salt in

said composition.

In a second embodiment, the invention provides a purgative, comprising a hypertonic aqueous solution of the composition of the first embodiment.

In a third embodiment, the invention provides a method of inducing purgation of the colon of a patient in need thereof, comprising administering to said patient a composition of the first embodiment or a purgative of the second embodiment in an amount effective to induce purgation of the patient's colon.

In a fourth embodiment, the invention provides the use of a composition of the first embodiment for the manufacture of a purgative for inducing purgation of the colon.

In a fifth embodiment, the invention provides a method for the treatment or prevention of one or more of a member selected from the group consisting of lavage associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions, comprising administering to a patient in need of such treatment a composition of the first embodiment or a purgative of the second embodiment.

In a sixth embodiment, the invention provides use of a composition of the first embodiment for the manufacture of a medicament for the treatment or prevention of one or more of a member selected from the group consisting of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions.

In a seventh embodiment, the invention provides a method for the treatment or prevention of acute gastrointestinal infections, comprising administering to a patient in need of such treatment a composition of the first embodiment or a purgative of the second embodiment.

In an eighth embodiment, the invention provides use of a composition of the first **embodiment** for the manufacture of a medicament for the treatment or prevention of acute gastrointestinal infections.

In a ninth embodiment, the invention provides a method for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome, comprising administering to a patient in need of such treatment a composition of the first embodiment or a purgative of the second embodiment.

In a tenth embodiment, the invention provides use of a composition of the first embodiment for the manufacture of a medicament for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant **irritable** bowel syndrome.

In an eleventh embodiment, the invention provides the composition of the first embodiment or the purgative of the second embodiment when used in pre-colonoscopic or pre-surgical lavage, as a simple purgative, as electrolyte replacement lavage, as a barium enema preparation, in **CT** "virtual colonoscopy", in radiological applications, as electrolyte replacement lavage solutions, as electrolyte replacement lavage solutions for acute gastrointestinal infections, for symptomatic treatment in patients suffering from acute or chronic constipation or related symptoms or constipation predominant irritable bowel syndrome, as a regular laxative, or for the treatment or prevention of lavage associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache or convulsions.

In a twelfth embodiment, the invention provides a composition for use in a purgative, the composition comprising:

(i) at least one water-soluble sodium salt; (ii) at least one water-soluble degradable sugar in an amount, **by** weight, of from s about 1 to about **3** times the weight of sodium salt in said composition;

(iii) at least one water-soluble potassium salt in an amount, **by** weight of from

about **0.05** to about 1 times the weight of said sodium salt in said composition; and

(iv) at least one water-soluble magnesium salt, wherein the weight of magnesium

salt in said composition is from about **0.1** to about **10** times the weight of sodium salt in Io said composition.

In a thirteenth embodiment, the invention provides a purgative, comprising a hypertonic aqueous solution of the composition of the twelfth embodiment.

In a fourteenth embodiment, the invention provides a method of inducing purgation of the colon of a patient in need thereof, comprising administering to said patient in the **15** absence of diathermy a composition of the twelfth embodiment or a purgative of the thirteenth embodiment in an amount effective to induce purgation of the patient's colon.

In a fifteenth embodiment, the invention provides the use of a composition of the twelfth embodiment for the manufacture of a purgative for inducing purgation of the colon in the absence of diathermy.

In the sixteenth embodiment, the invention provides a method for the treatment or prevention of one or more of a member selected from the group consisting of lavage associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions, comprising administering to a patient in need of such treatment in the absence of diathermy a composition of the twelfth embodiment or a purgative of the thirteenth embodiment.

In a seventeenth embodiment, the invention provides use of a composition of the twelfth embodiment for the manufacture of a medicament for the treatment or prevention in the absence of diathermy of one or more of a member selected from the group consisting of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions.

In an eighteenth embodiment, the invention provides a method for the treatment or prevention of acute gastrointestinal infections, comprising administering to a patient in need of such treatment in the absence of diathermy a composition of the twelfth embodiment or a purgative of the thirteenth embodiment.

In a nineteenth embodiment, the invention provides use of a composition of the twelfth embodiment for the manufacture of a medicament for the treatment or prevention of acute gastrointestinal infections in the absence of diathermy.

In a twentieth embodiment, the invention provides a method for the treatment or **prevention** of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome, comprising administering to a patient in need of such treatment in the absence of diathermy a composition of the twelfth embodiment or a purgative of the thirteenth embodiment.

In a twenty-first embodiment, the invention provides use of a composition of the twelfth embodiment for the manufacture of a medicament for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome in the absence of diathermy.

In a twenty-second embodiment, the invention provides the composition of the twelfth embodiment or the purgative of the thirteenth embodiment when used in the absence of diathermy in pre-colonoscopic or pre-surgical lavage, as a simple purgative, as electrolyte replacement lavage, as a barium enema preparation, in **CT** "virtual colonoscopy", in radiological applications, as electrolyte replacement lavage solutions, as electrolyte replacement lavage solutions for acute gastrointestinal infections, for

symptomatic treatment in patients suffering from acute or chronic constipation or related symptoms or constipation predominant irritable bowel syndrome, as a regular laxative, or for the treatment or prevention of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache or convulsions. As used herein, unless the context clearly indicates otherwise, the words "comprise", "comprises", "comprising" or other variations thereof shall **be** understood as **meaning** that the stated integer or integers is/are included and does not exclude other integers from being present even though those other integers are not explicitly stated.

The combined effects of the water-soluble sodium, potassium and magnesium salts and the minimally degradable sugar(s) in the compositions and purgatives of the invention cause a purgative effect which is surprisingly greater than the effect that would have been expected from the known effects of the same amounts of the individual components of the compositions. That is, the amounts of the salts required for simply performing their known purgative function would be significantly greater if they were used singly. Furthermore, the other benefits of the compositions and purgatives of the present invention are not provided **by** compositions of only a single component. Additionally, the increased tonicity of the present purgatives compared to existing products enables a reduction in the amount of each constituent while maintaining the desired purgative effect. Thus, the components of the purgatives of the invention cooperate to provide a purgative which is palatable and which causes purgation without the side effects seen with prior art compositions, in a way that could not have been predicted prior to the present invention.

The invention provides formulations, which safely achieve orthostatic bowel lavage without associated hypo-osmolar hyponatremia. Furthermore, the inventors have found that these formulations can achieve rapid resolution and symptom reversal together with electrolyte replacement in certain infective conditions of the gastrointestinal tract. The compositions of the invention may also be used for patients with either acute or chronic constipation, since their purgative effect, secondary to combined hypertonic effect, is not associated with melanosis seen particularly in patients taking senna containing faecal softening agents.

The additional function of the compositions is to combine sugar and sodium in amounts that assist in transluminal absorption of sodium and water. Individually, oral rehydration solutions (compositions) utilise this principle. However the compositions of the present invention have the unique and surprising feature of causing a purgative effect while performing the function of assisting in transluminal absorption of sodium and water.

Without wishing to be bound **by** theory, the present inventors believe that the administration of a hyperosmolar sodium load together with other electrolytes and sugar(s) and optionally trace elements at a time when the maximum effect of the iatrogenic purgative occurs reduces the gradient of change in serum osmolarity. The present inventors propose that preventing the osmolar and sodium shifts causes a reduction in the undesirable side effects seen with administration of prior art purgatives, as noted above.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the expression "minimally degradable sugar" is to **be** understood to mean a carbohydrate moiety that is substantially resistant to endogenous digestion in the gastrointestinal tract.

Typically, in the compositions of the invention, the minimally degradable sugar is xylose or xylotriose. However, other sugars including oligosaccharides such as other xylooligosaccharides, fructo oligosaccharides, fructosans, galacto oligosaccharides and the like may **be** used.

Glucose and other complex sugars used in standard oral rehydration therapy lead to intestinal decomposition with the formation of gases such as methane and hydrogen, which have been associated with explosion caused **by** diathermy (Altomare D.F. *et al., Dis Colon Rectum* **36: 291-2 (1993)).** The use of minimally degradable sugars in the **compositions** of the present invention prevents this from occurring and reduces the incidence of abdominal cramps. In situations however where diathermy is not to be used, the minimally degradable sugar can be replaced in the compositions of the invention with a degradable sugar such as glucose, L-glucose, sucrose, fructose, galactose, lactose, mannitol or lactulose.

The use of xylose (or other minimally degradable sugars) allows for transport of sodium into the alimentary cellular structure. The combination of xylose and sodium salts thus allows for replacement of electrolytes from the induced faecorrhoea, in particular sodium, potassium and chloride, and reduces the dilutional hyponatremia associated with other products such as PicoPrep, Fleet and recently reported with polyethylene glycol.

Typically, in the compositions of the invention, the water-soluble sodium salt is selected from the group consisting of sodium chloride, sodium gluconate, sodium citrate and sodium aspartate.

In one form of the compositions and purgatives of the invention, they include at 20 least one sodium salt other than sodium chloride, more preferably sodium gluconate, sodium citrate or sodium aspartate, which reduce the salty taste.

Typically, in the compositions of the invention, the water-soluble potassium salt is selected from the group consisting of potassium chloride and potassium tartrate. Usually, the ratio of potassium salt(s) to sodium salt(s) in the compositions of the invention is from about **1:1** to about **1:8,** more usually from about ***1:1.5*** to about **1:6,** still more usually from about 1:2 to about ***1:5,*** even more usually about **1:3,** on a weight basis.

Typically, in the compositions of the invention, the water-soluble magnesium salt is selected from the group consisting of magnesium sulfate, magnesium citrate and magnesium phosphate. Usually, the ratio of the weight of magnesium ions to the weight **30** of sodium ions in the compositions of the invention is from about ***1:5*** to about ***5:1,*** more usually from about **1:3** to about **3:1,** still more usually from about 1:2 to about 2:1, even more usually about **1:1.**

In the purgative of the second embodiment, the sodium salt or salts is/are typically present in an amount ranging from about **1-lOg,** more typically about **5g** per unit **35** dose of the purgative, which will usually **be** a volume of from about 0.2 to **0.5L.**

In one form, the composition of the invention comprises sodium chloride, potassium chloride, magnesium sulfate, and xylose or other minimally degradable sugars.

The composition of the invention may used for colonoscopic lavage, as a simple purgative or in electrolyte replacement therapy. The composition may be used with one **or** more known purgatives and in that case will complement the purgative effect of the other purgative(s) and thus reduce the amount required of these purgative agents. For example a

composition of the present invention may be administered with a half dose of Fleet, or a reduced number of PicoPrep capsules.

The composition may further comprise one or further additives selected **from** citrate, lactate, acetate, trace elements such as calcium and zinc, nutritional elements such as Vitamin B complex, thiamine, Vitamin **A,** Vitamin **C,** Vitamin **E,** folic acid, and biotin. These additives may be included in the compositions of the invention in amounts, which are based on the patient's daily dietary requirements. The ratio of minimally degradable sugar(s) to sodium ions in the compositions **15** and purgatives of the invention is from about **3:1** to **1:1** on a weight basis, and will more typically be about 2:1 to 1.4:1. The minimally degradable sugar or sugars is/are typically present in an amount ranging from about 2 to 20 **g,** more typically about **10 g** per unit dose.

In the purgative of the second embodiment, the potassium salt or salts is/are 20 typically present in an amount ranging from about **0.5** to **5 g** per unit dose, more typically about **1** to ***5*** **g** per unit dose, still more typically about ***1.5*** to **3 g** per unit dose.

In the purgative of the second embodiment, the magnesium salt or salts is/are typically present in an amount ranging from about 1 to about **10 g** per unit dose, more typically about **3** to ***5*** g per unit dose.

Typically, in a purgative of the second embodiment, sodium is present at a concentration of from about 200-700mosm. More typically, the purgative includes sodium at about three times the isotonic concentration (that is, about 270mosm).

In the methods of the third embodiment, the composition of the invention is typically administered in an amount sufficient to provide to the patient the following quantities of the components:

(i) Sodium in an amount of from about **0.01** to about **1.5g** per **kg** body weight, more usually about **0.05** to about 1 **g** per **kg,** still more usually about **0.08 g** per **kg,** in which case the administered dose of sodium will approximate ***5*** **g** for an individual weighing **60 -70 kg;**

(ii) The minimally degradable sugar or sugars in an amount of from about 0.02 to about **3g** per **kg** of body weight, more usually from about **0.1** to about 0.2 **g** per **kg,** still more usually about **0.15 g** per **kg** in which case the administered dose of minimally degradable sugar will approximate **10 g** for an individual weighing **60 - 70 kg; 5** (iii) potassium in an amount of from about **0.005** to about **0.1g** per **kg** body weight, more usually from about **0.01** to about **0.05 g** per **kg,** still more usually about **0.03 g** per **kg** in which case the administered dose approximates 2 **g** for an individual weighing **60 -70 kg;**

(iv) Magnesium in an amount of from about **0.01** to about ***1.5*** **g** per **kg** body **10** weight, more usually about **0.05** to about 1 **g** per **kg,** still more usually about **0.08 g** per **kg** in which case the administered dose approximates ***5*** **g** for an individual weighing **60 -70 kg.**

In a typical procedure, following the oral ingestion of the purgative of the invention, cool water in a volume greater than three times the volume of the purgative hypertonic solution is ingested.

The composition of the invention may further comprise a detergent stool-softening agent such as sodium picosulfate. Typically this will be present in an amount of from ***5-25*** mg; however more typically about **10-15** mg will be used, per unit dose of the composition.

The purgative of the second embodiment may suitably be prepared **by** dissolving a required amount of a composition of the first embodiment in a suitable quantity (typically from about 200mL to 500mL) of cold, warm or hot water.

In other forms the composition of the invention may be compressed into tablets, gel caps or capsules. In this form it is useful for pre-colonoscopic orthostatic lavage of the bowel, as preparation for barium enema, in **CT** "virtual colonoscopy" and for other radiological applications. It is also useful in pre-surgical lavage e.g. for removal of the bowel for cancer, diverticulitis etc. When formulated as tablets, the tablets may suitably comprise a core of the sodium, potassium and magnesium salts, surrounded **by** a coating of the minimally degradable sugar(s).

The composition or purgative of the invention may further comprise at least one flavouring ingredient, such as chicken, beef, vegetarian, Thai, seafood, spice or curry.

Suitably, the purgative of the second embodiment is formulated as a soup or soup-like composition.

The psychological advantage of an easily tolerated fluid with versatility of flavours is that it may be substituted for a meal for patients who are on a restricted low residue clear fluids regime. Using various flavours such as chicken, beef, vegetable, kosher, gluten free, Thai, Japanese (teriyaki), Indian (curry) etc. in a soup mix, which includes a composition of the first embodiment, allows for individual preference. **If** the purgative of the invention is administered as a clear soup, the purgative is typically made up using hot water rather than cool fluids. Improved tolerance and compliance is thereby achieved, in part **by** reducing the volume of the preparation to ***350*** ml and in part **by** providing a hypertonic "tasty" meal, as opposed to **3** litres of an unpalatable isotonic solution such as polyethylene glycol.

The purgative of the invention is an electrolyte replacement product, which may accompany and augment the action of other purgative agents such as products containing sodium picosulfate and sodium phosphate (e.g. Fleet and Pico lax/PicoPrep). The purgative of the invention, when administered in an effective amount to a patient, contributes to lavage but leads to fewer complications such as hyponatremia, and hypoosmolar dilutional state, and to fewer symptoms such as dizziness, nausea, headache and hypotension, than known purgative agents.

Although the ratio of individual salts in the compositions of the invention may vary within the ranges stated above, it is the combination of these salts added to a defined volume of water, which forms a hypertonic salt solution. The tonicity of fluid is the key to the electrolyte replacement and purgative effect of the purgatives of the invention.

As part of the preparation involves an intact thirst mechanism which is provided **by** the hypertonic load, patients for whom administration of compositions of the invention is to **be** used with caution include the very young, the infirmed and demented, those unable to self administer water or other fluids, and those patients in which a large sodium load is undesirable (that is, patients with LVEF **<25%),** renal failure patients, those with advanced cardiac or renal disease and those with pituitary adenoma/hypofunction.

The invention described herein provides an electrolyte replacement lavage solution, which can have several roles. It can be administered with hyper-osmolar solutions such as products containing sodium picosulfate and sodium phosphate (e.g. Fleet and Pico lax/PicoPrep). It can also be used as an electrolyte replacement lavage solution for acute gastrointestinal infections including salmonella, shigella, campylobacter or viral gastroenteritis. This is applicable in particular to viral gastritis or bacterial gastroenteritis so as to give patients a clearance of contents of the flora as well as replaces electrolytes that are being lost during the gastroenteritis. It can also provide symptomatic improvement in those patients suffering from acute or chronic constipation and related symptoms and for those with constipation predominant irritable bowel syndrome **(IBS). In** addition, the

product can be used alone as an effective orthostatic lavage for the following applications: prior to colonoscopy, **CT** scanning "virtual colonoscopy", barium enema examination, or intestinal surgery, or as a regular laxative.

This is due to the product allowing simultaneous lavage of the bowel and replacement of essential electrolytes with fewer complications such as hyponatremia, hypo-osmolar dilutional state, and fewer symptoms such as dizziness, nausea and headache. The product can be used as a treatment of constipation as a regular laxative since it does not cause electrolyte losses.

The effective hyper tonicity of the purgatives of the invention will cause purgation when administered to a patient undergoing a procedure for which purgation is required. These patients adhere to bowel preparation protocols, which commonly instruct a low residue diet and clear fluids for **1** to 2 days prior to the procedure for which they are being prepared. In administering the purgatives of this invention a smaller volume (approximately 200 **-500** ml) of hyperosmolar electrolyte enhanced fluid is required as opposed to larger volumes (3-4 litres) of isotonic balanced salt solution (GlycoPrepTM). The patients continue to consume clear fluids to maintain hydration. This is more palatable and acceptable to the patient. The volume of the purgatives of the present invention is much less (typically about one tenth) of the volume of solutions of prior art purgatives which are administered to a patient. Other fluid taken is part of a normal diet, and hence 20 is better tolerated and more palatable, with better patient compliance.

The compositions and purgatives of the invention are particularly useful for constipation and bloating, and as soup-like preparations the purgatives of the invention are acceptable to patients as a daily food product. As a flavoured medication they have particular use as simultaneous orthostatic lavage and electrolyte replacement products in patients suffering with acute gastroenteritis. When combined with added fluids they can be used in patients with diarrhoea without dehydration. This includes traveller's diarrhoea and similar acute bacterial gut infections. The compositions and purgatives of the invention are also gluten free and therefore acceptable to those with coeliac disease.

The contained xylose and/or other minimally degradable sugar(s) (being relatively inert as opposed to glucose) in compositions of the invention is particularly important in orthostatic lavage for colonoscopy as it will **help** to avoid fermentation and volatile explosive gas production (e.g. methane and hydrogen). The importance of this is that the potential of an explosion during diathermy polypectomy is reduced.

One aim of the present invention is to replace lost sodium as well as water resulting from bowel preparation in intact epithelial cells devoid of toxin-induced block such as with cholera toxin Na-K ATPase pump. The use of hypertonic solutions gives an opportunity to restore the osmotic equilibrium, which is altered **by** the induced water intoxication following replacement of fluid without electrolytes in patients undergoing some of the established bowel preparation protocols.

In a typical method of inducing purgation of the colon in a patient, a composition of the invention is provided in the form of a sachet, which includes flavouring. The contents (typically weighing about **25 g)** when mixed with water, preferably heated, in a quantity of 200-500mls **(1-10** ml/kg) will form a palatable soup, which may be cool or heated to form a hypertonic preparation with an osmolarity >350mosm/l.

After consuming the above purgative dose, the patient will be instructed to ingest cool water at least **3** times the volume, or in an adult greater than 750-1000mls of cool water.

EXAMPLES Formulation Examples

The following formulations illustrate the compositions of the invention. When dissolved in about ***350*** ml of water, they have osmolarity in the range 500-800mosm/l.

Suitably, the formulations maybe mixed with about half a sachet (about **3.2g)** of commercial powdered soup mix.

Formulation **1**

Xylose **10** ***g***

Sodium chloride ***5*** **g**

Potassium chloride **1.5 g**

Magnesium sulphate ***5*** **g**

Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) **10** mg

Formulation 2

Xylose 10 g

Sodium chloride **5 g**

Potassium chloride **1.5 g**

Magnesium sulphate ***5*** **g**

Formulation **3**

Xylose **10 g**

Sodium chloride **5 g**

Potassium chloride *1.5* **g**

Magnesium sulphate ***5*** **g**

Sodium picosulfate **10** mg

Formulation 4

Sodium chloride **10 g**

Xylose 14 **g**

Potassium chloride **3 g**

Magnesium sulphate **3 g**

Formulation **5**

Xylose **10 g**

Sodium citrate **3 g**

Sodium chloride 2 **g**

Potassium chloride 2 **g**

Magnesium sulphate **5 g**

Sodium picosulfate **15** mg

Formulation **6**

Xylose 8 g

Sodium chloride **3 g**

Sodium citrate 2 **g**

Potassium chloride 2 **g**

Magnesium sulphate **10 g**

Sodium picosulfate **15** mg

Examples of administration of compositions of the invention

Administration Example **1**

At time zero **3** Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) **5** mg tabs and **350** ml of soup containing Formulation **1** and **3.2 g** of a commercial powdered soup mix were taken **by** a normal male subject ***(75* kg)** in two doses spaced %2-1 hour apart. Alternatively, the Formulation 1 may **be** added to the Bisacodyl (Dulcolax, Boehringer Ingelheim, Germany) preparation in the form of a capsule.

At the time of taking the preparation, side effects experienced were irritability and indigestion. Two large cups of water were drunk freely **by** the patient before and after administration of the formulation. At **1.5** hour commenced watery diarrhoea with minimal gas, which continued about every **10** minutes for **1** hour (i.e. **6** occasions) with decreasing amounts of faecal matter. At 3-4 hours no adverse affects were observed.

Administration Example 2

350 ml of soup containing Formulation 2 and **3.2 g** of a commercial powdered soup mix were taken **by** a normal male subject ***(75* kg)** over **15** minutes followed **by** 1 litre of cold water. At 1 hour watery evacuation commenced with no flatulence and **5** continued at intervals of **10** minutes for 45 minutes then ceased. No cramps and no headaches are associated with the treatment.

Administration Example **3**

Formulations **5** and **6,** which include sodium citrate and have improved palatability, were administered as **350** ml of warm soup containing **3.2 g** of a commercial powdered soup mix, with similar results as above. That is, loose watery motions occurred over 1-1/2 hour duration after administration.

Administration Example 4:

Combination with Picosulfate in Patient Undergoing Colonoscopy

Formulation **3** above was used in a 40-year-old woman with previously good health. Two sachets, each containing formulation **3** and **3.2 g** of commercial powdered soup mix (one chicken flavoured and one beef flavoured) were given six hours apart and cleaned the bowel to enable colonoscopic evaluation without any complaints from the patient of side effects of headache or light-headedness.

Administration Example ***5:***

Combination with PicoPrep Capsules

A 72-year-old male with a history of right hemicolectomy for carcinoma of colon and constipation was given a single sachet containing formulation ***5*** and **3.2 g** of commercial powdered soup mix in **350** ml water at 3pm. This was followed **by** nine watery motions, which commenced fifteen minutes after drinking the soup. The instruction was to drink one litre of water following the soup. The patient then took five **25** one gram capsules of "PicoPrep" at **6** pm, again accompanied with one litre of water and had six further loose motions. Overnight he had three loose motions. **A** colonoscopy was successfully performed the next day at **11am.** There were no reported side effects.

Administration Example **6:**

Treatment of Gastroenteritis

A child of **8** years with symptoms of crampy abdominal pain was given a third of the amount of formulation 2 with onset of loose motions within 1-2 hours and resolution of symptoms and no untoward effect.

Administration Example **7:**

Treatment **of** Constipation

A 48 year lady with long standing constipation was given a single preparation of formulation **3** as a soup containing **3.2 g** of commercial powdered soup mix and developed a result after one to one and a half hours of taking the formulation. There were **5** four episodes in the space of ninety minutes when she had to evacuate her bowel and apart from complaining of the "saltiness" of the preparation it was well tolerated.

Administration Example **8:**

A 67-year-old lady with a family history of colonic carcinoma and single **polyp** removed three years prior was returning for her surveillance colonoscopy. At the previous colonoscopy she had used picosulfate **-**two sachets, which resulted in profound hyponatremia associated with nausea and vomiting, malaise and severe headache. She required intravenous fluids prior to colonoscopy. On return for surveillance colonoscopy three years later the patient was afraid to take the picosulfate because she was concerned about developing the same complications. As a result she was given the two sachets of picosulfate but this time also with two sachets of Formulation **3** mixed in beef flavoured soup. These were given six hours apart. The bowel was cleansed to the caecum with excellent mucosal views. This time the patient did not develop any nausea, vomiting, headaches, light-headedness or malaise. Her serum electrolytes were normal when tested.

INDUSTRIAL APPLICABILITY

The compositions of this invention are useful for colonoscopic lavage, as simple purgatives or in electrolyte replacement therapy, as preparations for barium enema, in **CT** "virtual colonoscopy" and for other radiological applications, as electrolyte replacement lavage solutions for acute gastrointestinal infections, for symptomatic improvement in those patients suffering from either acute or chronic constipation and related symptoms, or as a regular laxative.

The claims defining the invention are as follows:

1. A composition for use in a purgative, the composition comprising:

(i) At least one water-soluble sodium salt; (ii) at least one water-soluble minimally degradable sugar in an amount **by** weight, of from about 1 to about **3** times the weight of sodium salt in said composition;

(iii) At least one water-soluble potassium salt in an amount, **by** weight of from about **0.05** to about **I** times the weight of said sodium salt in said composition; and

(iv) At least one water-soluble magnesium salt, wherein the weight of magnesium salt in said composition is from about **0.1** to about **10** times the weight of sodium salt in said composition.

2. The composition of claim **1,** wherein the minimally degradable sugar is selected from the group consisting of xylose, xylotriose, xylo oligosaccharides, fructo oligosaccharides, fructosans, galacto oligosaccharides, other oligosaccharides, and mixtures thereof.

3. The composition of claim **1** or 2, wherein the water-soluble sodium salt is selected from the group consisting of sodium chloride, sodium gluconate, sodium citrate, sodium aspartate and mixtures thereof.

4. The composition of any one of claims **1** to **3,** wherein the water-soluble potassium salt is selected from the group consisting of potassium chloride and potassium tartrate.

5. The composition of any one of claims **1** to 4, wherein the water-soluble magnesium salt is selected from the group consisting of magnesium sulphate, magnesium citrate and magnesium phosphate.

6. The composition of any one of claims **1** to **5** further comprising at least one additive selected from the group consisting of a flavouring ingredient, a detergent stool softening agent, citrate, lactate, acetate, trace elements and nutritional elements.

7. The composition of any one of claims **1** to **6** in the form of a soup or soup-like composition, tablet, gel cap, capsule or sachet.

8. A composition as claimed in claim 1, substantially as hereinbefore described with reference to any one of the examples.

9. A purgative, comprising a hypertonic aqueous solution of the composition of any one of claims 1 to 8.

10. The purgative of claim **9** in the form of a unit dose having a volume from about 0.2 to 0.5L and wherein the sodium salt or salts are present in an amount from about 1 to about 10g per unit dose, the minimally degradable sugar or sugars in an amount of from about 2 to about **20g,** the potassium salt or salts in an amount of from about **0.5** to about **5g,** and the magnesium salt or salts in an amount of from about 1 to about 10g per unit dose of purgative.

11. A method of inducing purgation of the colon of a patient in need thereof, comprising administering to said patient a composition of any one of claims **1** to **8** or a purgative of claim **9** or **10** in an amount effective to induce purgation of the patient's colon.

12. The use of a composition of any one of claims **I** to **8** for the manufacture of a purgative for inducing purgation of the colon.

13. A method for the treatment or prevention of one or more of a member selected from the group consisting of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions, comprising administering to a patient in need of such treatment a composition of any one of claims **I** to **8** or a purgative of claim **9** or **10.**

14. Use of a composition of any one of claims 1 to **8** for the manufacture of a medicament for the treatment or prevention of one or more of a member selected from the group consisting of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions.

15. A method for the treatment or prevention of acute gastrointestinal infections, comprising administering to a patient in need of such treatment a composition of any one

of claims **I** to **8** or a purgative of claim **9** or **10.**

16. Use of a composition of any one of claims I to 8 for the manufacture of a medicament for the treatment or prevention of acute gastrointestinal infections.

17. A method for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome, comprising administering to a patient in need of such treatment a composition of any one of claims **1** to **9** or a purgative of claim 9 or 10.

18. Use of a composition of any one of claims 1 to **8** for the manufacture of a medicament for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome.

19. The composition of any one of claims 1 to **8** or the purgative of claim 9 or 10 when used in pre colonoscopic or pre-surgical lavage, as a simple purgative, as electrolyte replacement lavage, as a barium enema preparation, in **CT** "virtual colonoscopy", in radiological applications, as electrolyte replacement lavage solutions, as electrolyte replacement lavage solutions for acute gastrointestinal infections, for symptomatic treatment in patients suffering from acute or chronic constipation or related symptoms or constipation predominant irritable bowel syndrome, as a regular laxative, or for the treatment or prevention of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache or convulsions.

20. A composition for use in a purgative, the composition comprising:

(i) At least one water-soluble sodium salt; (ii) at least one water-soluble degradable sugar in an amount, **by** weight, of from about 1 to about **3** times the weight of sodium salt in said composition;

(iii) At least one water-soluble potassium salt in an amount, **by** weight, of io from about **0.05** to about 1 times the weight of said sodium salt in said composition; and

(iv) At least one water-soluble magnesium salt, wherein the weight of

Magnesium salt in said composition is from about **0.1** to about **10** times the weight of sodium salt in said composition.

21. A composition of claim 20 wherein the degradable sugar is selected from the **is** group consisting of glucose, L-glucose, sucrose, fructose, galactose, lactose, mannitol and lactulose.

22. A composition as claimed in claim 20, substantially as hereinbefore described with reference to any one of the examples.

23. A purgative, comprising a hypertonic aqueous solution of the composition of claim 20, 21 or 22.

24. A method of inducing purgation of the colon of a patient in need thereof, comprising administering to said patient in the absence of diathermy a composition of claim 20, 21 or 22 or a purgative of claim **23** in an amount effective to induce purgation of the patient's colon.

25. The use of a composition of claim 20, 21 or 22 for the manufacture of a purgative for inducing purgation of the colon in the absence of diathermy.

26. A method for the treatment or prevention of one or more of a member selected from the group consisting of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache and convulsions, comprising administering to a patient in need of such treatment in the absence of diathermy a composition of claim 20, 21 or 22 or a purgative of claim **23.**

27. Use of a composition of claim 20, 21 or 22 for the manufacture of a medicament for the treatment or prevention in the absence of diathermy of one or more of a member selected from the group consisting of lavage-associated hyponatremia, **35** hypoosmolality, nausea, malaise, vomiting headache and convulsions.

28. A method for the treatment or prevention of acute gastrointestinal infections, comprising administering to a patient in need of such treatment in the absence of diathermy a composition of claim 20, 21 or 22 or a purgative of claim **23.**

29. Use of a composition of claim 20, 21 or 22 for the manufacture of a s medicament for the treatment or prevention of acute gastrointestinal infections in the absence of diathermy.

30. A method for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome, comprising administering to a patient in need of such treatment in the absence of diathermy a **10** composition of claim 20, 21 or 22 or a purgative of claim **23.**

31. Use of a composition of claim 20, 21 or 22 for the manufacture of a medicament for the treatment or prevention of constipation, acute constipation, chronic constipation or constipation predominant irritable bowel syndrome in the absence of diathermy.

32. The composition of claim 20, 21 or 22 or the purgative of claim **23** when used in the absence of diathermy in pre-colonscopic or pre-surgical lavage, as a simple purgative, as electrolyte replacement lavage, as a barium enema preparation, in **CT** "virtual colonoscopy", in radiological applications, as electrolyte replacement lavage solutions, as electrolyte replacement lavage solutions for acute gastrointestinal infections, 20 for symptomatic treatment in patients suffering from acute or chronic constipation or related symptoms or constipation predominant irritable bowel syndrome, as a regular laxative, or for the treatment or prevention of lavage-associated hyponatremia, hypoosmolality, nausea, malaise, vomiting, headache or convulsions.

Dated 10 September, 2007

Thomas Julius Borody and Sanjay Ramrakha and John

Saxon and Antony Wettstein

APPENDIX 14 – SOLID BOWEL PURGATIVE EVALUATION FORMS

Bowel Preparation Capsules - Patient Questionnaire

Patient Name: _____

DOB: ____ / ____ / ____

Please complete this page BEFORE commencing the bowel preparation capsules. This page of the questionnaire concerns your usual bowel habit.

1. Stool Frequency _____ / **day** / **week** (circle selection)

Would you consider yourself :

- ☐ Normal bowel function
- ☐ Alternating constipated / diarrhea
- ☐ Constipated
- ☐ Diarrhea

2. Stool Consistency (tick all appropriate) (General appearance)

☐ 
Type 1 Separate hard lumps, like nuts

☐ 
Type 2 Sausage-like but lumpy

☐ 
Type 3 Like a sausage but with cracks in the surface

☐ 
Type 4 Like a sausage or snake, smooth and soft

☐ 
Type 5 Soft blobs with clear-cut edges

☐ 
Type 6 Fluffy pieces with ragged edges, a mushy stool

☐ 
Type 7 Watery, no solid pieces

Therefore, over a 7 day period what % are you?

___% Hard or lumpy

___% "Normal" soft with clear edges

___% Loose (mushy) or watery

3. Baseline Gastrointestinal Symptoms (please circle severity)

Symptom	Severity			
Straining	none	mild	moderate	severe
Urgency	none	mild	moderate	severe
Feeling of Incomplete Evacuation	none	mild	moderate	severe
Flatulence	none	mild	moderate	severe
Abdominal bloating or pain	none	mild	moderate	severe
Nausea	none	mild	moderate	severe
Vomiting	none	mild	moderate	severe

4. Other Symptoms (please include severity)

_____

5. Existing Gastrointestinal condition/s?

Eg.	Crohn's Disease	YES / NO
	Ulcerative Colitis	YES / NO
	Irritable Bowel Syndrome	YES / NO
	Other (please specify): _____	

6. Have you taken bowel preparations previously?

a) Yes ☐ Picoprep ☐ Glycoprep ☐ Other _____
b) No

7. Why are you having a colonoscopy performed?

☐ Screening

☐ Follow up due to pre-existing gastrointestinal condition

☐ Other _____

Time of last dose

____ : ____ am/pm

Bowel Preparation Capsules - Patient Questionnaire

Patient Name:

_____

DOB: ____ / ____ / ____

Please complete this page AFTER you finish the bowel preparation capsules. Please circle the most appropriate answer.

1. **How easy or difficult was it for you to complete the bowel preparation?**

   a) Easy
   b) Somewhat
   c) Unable to finish
   If unable to finish, why? _____

2. **When was your first bowel movement?**

   Time of first bowel movement: _____

3. **Did you feel the preparation cleaned out your bowel effectively?**

   a) Yes
   b) No
   c) Unable to say

4. **Did you experience any new symptoms after commencing the preparation?**
   a) No
   b) Yes (please complete the following table)

EVENT	SEVERITY	RESOLVED/ ONGOING
Event 1		
Event 2		
Event 3		
Event 4		

5. **Would you take the same preparation again in the future if you need another colonoscopy?**

   a) Yes
   b) No

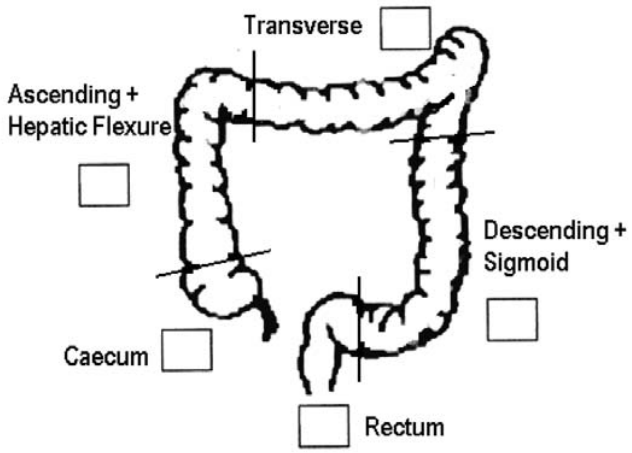
6. **Approximately how many bowel motions did you have on this bowel preparation?**

   _____ bowel motions

APPENDIX 15 – DOCTOR/SEDATIONIST EVALUATION FORM FOR SOLID BOWEL PREPARATION

The assessor is not to question the patient on the preparation taken prior to completion of this form. This form is to be completed during or immediately following the patient's colonoscopy.

A) Please score each part of colon according to scale below.



0.	**Excellent:**	Mucosal detail clearly visible. If fluid is present, it is clear. Almost no stool residue.
1.	**Good:**	Some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary.
2.	**Fair:**	Turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing is **not** necessary.
3.	**Poor:**	Presence of stool obscuring mucosal detail and contour. However, with suctioning **and** washing, a reasonable view is obtained.
4.	**Inadequate:**	Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

Please circle most appropriate description.

B) Fluid in whole colon: **Small (0)** **Moderate (1)** **Large (2)**

C) Total Score: C: _____ + A: _____ + T: _____ + D/S: _____ + R: _____ + Fluid: _____ =_____/22

Signature: _____

Name: _____ **Date:** _____

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FOOTNOTES

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