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ORIGINAL ARTICLE

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A randomised controlled phase II trial to examine the feasibility of using hyper-oxygenated fatty acids (HOFA) to prevent facial pressure injuries from medical devices among adults admitted to intensive care—A research protocol

Leanne Hunt[1,2] | **Jessica Ingleman**[3] | **Kathleen Brennen**[1,4] | **Karyn Armstrong**[4] | **Mariepaz Hazell**[1,5] | **Naomi Keith**[1,5,6] | **Brittany Bickford**[5] | **David Sanchez**[1,7] | **Souti Khalil**[7] | **Samara Geering**[8,9] | **Sabnam Acharya Sigdel**[8] | **Santhosh Skaria**[9] | **Sreeranjini Prabhakaran**[9] | **Joan Lynch**[1,2] | **Evan Alexandrou**[1,5,6,8] | **Peta Drury**[6] | **Thach Tran**[10,11] | **Steven A. Frost**[1,5,6,8]

[1]Critical Care Research in Collaboration and Evidence Translation, Liverpool, NSW, Australia

[2]School of Nursing and Midwifery, Western Sydney University, Sydney, NSW, Australia

[3]School of Nursing, Midwifery and Social Work, Queensland University, Brisbane, QLD, Australia

[4]Department of Intensive Care, Bankstown-Lidcombe Hospital, Bankstown, NSW, Australia

[5]Department of Intensive Care, Liverpool Hospital, Liverpool, NSW, Australia

[6]School of Nursing, University of Wollongong, Wollongong, NSW, Australia

[7]Department of Intensive Care, Campbelltown-Camden Hospital, Campbelltown, NSW, Australia

[8]South Western Sydney Nursing and Midwifery Research Alliance, Ingham Institute of Applied Medical Research, Liverpool Hospital, Liverpool, NSW, Australia

[9]Department of Intensive Care, Fairfield Hospital, Prairiewood, NSW, Australia

Abstract

One in three patients admitted to intensive care will sustain a pressure injury (PI) from a medical device. These injuries are painful and when on the face, head or neck they can result in permanent disfigurement. Preliminary evidence of the efficacy of hyper-oxygenated fatty acids (HOFAs) to prevent facial pressure injuries from medical devices is promising; however, the feasibility of incorporating HOFAs into current standard care to prevent PI from a medical device of the face, head and neck has not been extensively explored. It is intended that the findings from this phase II feasibility study will inform the design of a larger phase III trial, by addressing two primary aims: (1) to assess the feasibility of incorporating HOFAs into standard care to prevent device-related pressure ulcers of the skin associated with the face, head and neck assess the feasibility and (2) efficacy preliminary effectiveness of HOFA. This feasibility study is an investigator-initiated mixed method study incorporating a multi-centre randomised controlled trial of using HOFAs as an adjunct to standard pressure injury prevention and care, compared with standard care alone to prevent facial, head or neck from medical devices among adults admitted to intensive care. The primary outcome of interest is the incidence of facial, head or neck pressure injuries during the first 14 days in intensive care. Secondary outcomes include PI staging, medical device exposure and intensive care and hospital outcomes. The primary analysis will be undertaken using

[10]Bone and Osteoporosis, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

[11]School of Biomedical Engineering, University of Technology Sydney, Ultimo, NSW, Australia

Correspondence
Steven A. Frost, South Western Sydney Nursing and Midwifery Research Alliance, Ingham Institute of Applied Medical Research, Liverpool Hospital, Liverpool, NSW, Australia.
Email: steven.frost@health.nsw.gov.au

Cox's Proportional Hazards model, and due to the exploratory nature of this phase II trial, efficacy will be based on a one-sided *p*-value for superiority set at 0.10. Type I and Type II error rates are set at 20%; therefore, a total sample size of 196 study participants is planned. To explore the feasibility of incorporating HOFA into usual care and to design a larger phase III trial, we will aim to interview between 10 and 20 nurses across participating intensive care unit sites. Pressure injuries of the face, head or neck from medical devices, among adults admitted to intensive care, are considered preventable. This phase II study will investigate the feasibility and efficacy of HOFAs as an adjunct to standard care. Importantly, we aim to inform the development of a larger phase III trial.

KEYWORDS
clinical trial, critical care, equipment and supplies, pressure ulcer

Key Messages

- In the intensive care setting pressure injuries to the face, head and neck due to medical devices are common.
- The efficacy of interventions to prevent these types of pressure injuries has not been explored extensively in randomised controlled trials.
- There is a lack of early-phase studies to explore the feasibility, acceptability and fit-for-purpose nature of interventions, given the range of current approaches to preventing pressure injuries to the face, head, and neck due to medical devices.
- This protocol for a phase II trial to explore the feasibility of incorporating hyper-oxygenated fatty acids into current standard care to prevent pressure injury from a medical device of the face, head and neck describes a pragmatic approach to exploring efficacy in a complex clinical setting.
- The results of this study will inform the design of a phase III trial, that will understand the challenges of adding hyper-oxygenated fatty acids into current standard care in the adult intensive care setting.

1 | INTRODUCTION

1.1 | Background and rationale

One in three patients admitted to the intensive care unit (ICU) will sustain a pressure injury (PI) from a medical device.[1–4] These PIs can be painful, and when located on the face, head or neck, they can result in permanent disfigurement.[5,6] The economic burden of PI is significant,[7] representing approximately 1.9% of all public hospital expenditures.[4,8] The cost of treating a PI potentially diverts resources from other areas within the healthcare system.[9] Research has established that the cost of PI prevention in patients at risk is dwarfed by the costs of treating them.[10,11] Importantly, a PI is largely a preventable hospital-acquired adverse event.[9] Consequently, device-related pressure ulcers (DRPUs)[1] have become a key patient safety issue in the adult intensive care setting.[12]

DRPUs are localised injuries to the skin that are directly caused by a device and are generally classified by a staging system based on the severity.[1] These types of injuries can also occur in mucosal membranes that are in direct contact with a device but are not considered stageable, such as an endotracheal tube, orogastric or nasogastric tube,[1] with prone positioning being an added risk, highlighted by the COVID-19 pandemic.[13] The increased pressure and shearing load from the device on the skin, impacting skin microclimate are accepted as the causal pathways to the development of the DRPU.[14] A recent systematic review and meta-analysis reported that the estimated pooled incidence and prevalence of DRPU in over 126 000 patients in 29 studies was 12% and 10%, respectively.[1,12] From a cost–benefit perspective, the

prevention of DRPU is influenced by litigation costs, for example in English ICUs between 1995 and 2012, PI was among the harms that most led to substantial compensation following litigation.[15] Overall, ICU patients are over four times more likely to develop a severe PI than compared with the non-ICU acute patient population (Fulbrook et al., 2023).[16] The ICU setting has the added risk of patients with co-morbidities causing vulnerable skin and soft tissue, impaired nutrition and reduced level of consciousness which impact a patient's ability to sense the device and associated pressure combined with the need to tightly secure the device to a patient's face to ensure proper function or prevent dislodgement. Visual inspection of the underlying skin is often obstructed by the medical device itself or the anatomical location of the device prevents the identification of early warning signs, such as blanchable erythema. Consequently, awareness of the increased risks and differences for ICU patients is important and using targeted strategies is key to prevention.

Preliminary evidence of the efficacy of hyperoxygenated fatty acids (HOFAs) to prevent DRPUs has been promising.[14,17,18] The mechanism for the protective effect of HOFA has been suggested to be anti-radical activity in the oxidative stress process of cells in reactive hyperaemia,[18] an influence on the renewal of keratinocytes,[19] and enhanced microcirculation.[20] However, the evidence for the clinical efficacy in preventing pressure injuries has been based on a small number of studies, mostly single centres, with small sample sizes. Importantly, the feasibility of incorporating HOFA into standard care to prevent DRPUs to the face, head or neck has not been explored.

1.2 | Objectives

This feasibility study has been designed with the overall object of informing the design of a larger phase III trial, by addressing two primary aims: (1) to assess the feasibility of incorporating HOFA into standard care to prevent DRPU of the skin associated with the face, head and neck assess the feasibility and (2) efficacy of HOFAs in preventing DRPU (facial, head or neck) from medical devices in the adult ICU setting.

1.3 | Trial design

Due to our aim to explore the efficacy of HOFA and the challenge with blinding, a randomised open-label, phase II trial, with 1:1 allocation to treatment design has been chosen.

2 | METHODS

2.1 | Participants, interventions and outcomes

2.1.1 | Study setting

The study will enrol patients from four adult ICUs in South Western Sydney Local Health District (SWSLHD). The SWSLHD provides public hospital services for approximately a million residents, with five acute care hospitals, with approximately 230 000 separations each year. There are four adult ICUs, including a major trauma centre, across the local health district, that have between 80 to 250 admissions each month.

2.1.2 | Eligibility criteria

Inclusion criteria: All adults aged 18 years or older, admitted to intensive care, who can give explicit informed consent to participate in the trial. Exclusion criteria: Any patient who is not expected to stay in the ICU for 24 h, patients who are considered at the end-of-life, short-term toxicology admissions or short-term monitoring. Any patient with a pre-existing PI to the face, head or neck on admission to intensive care will not be considered for participation in the study.

2.2 | Interventions

2.2.1 | Trial intervention and routine care

Following a routine skin assessment of the head and neck, participants randomised to the intervention will have HOFA applied to any areas of the face, head or neck that are in contact with a medical device and not currently being protected with another form of pressure injury prevention (PIP) approach (i.e. foam dressing and barriers cream). This process will occur once per shift during routine skin assessment and hygiene care carried out by the bedside ICU nurse. More specific details of the intervention are reported using the Template for Intervention Description and Replication (TIDieR) checklist and guide[21,22] in the Appendix S2. Routine care includes the shift skin assessment by the bedside ICU nurse and the application of PIP, as per an ICU current protocol. The details of routine care, such as the routine use of foam dressings to protect the bridge of the nose or ears, when patients receive non-invasive ventilation via a mask, or high-flow oxygen via a nasal cannula will be collected as part of the study.

2.2.2 | HOFA application

The HOFA solution will be applied to all areas of the face, head and neck that are directly exposed to a medical device. HOFA will not be applied to any area that is already protected by a dressing to prevent a PI or to mucous membranes in contact with a medical device.

2.2.3 | Standard care (PIP)

Due to the aim to assess HOFA as an adjunct to standard care, standard PIP approaches for all study participants will continue as per local guidelines that are consistent with current national and international guideline recommendations. This includes the use of a protective hydrocolloid dressing which will continue to be placed on areas at risk of DRPUs. These standard PIP approaches generally advise that all medical devices must be fitted and placed correctly to achieve optimal patient comfort as well as proper securement of the device and that skin integrity is assessed as per local guidelines, with a full skin assessment of the face, head and neck being conducted each shift, with more frequent checks of the areas of concern when repositioning the device, changing interfaces or in response to patient discomfort. A flow diagram of the trial process is presented in the Appendix S1.

2.2.4 | Staff education on skin assessment and HOFA application

Each site will have investigators familiar with site-specific routines, equipment and practices. Site-specific investigators will provide education on the study protocol to the clinical team in the ICU before the commencement of the study.

2.3 | Outcomes

Primary outcomes measure: The primary outcome will be the development of an incident PI to the face, head or neck. Secondary outcome measures: The location and staging of PIs; the number of PI per patient; details of number and type of medical devices; ICU and hospital outcomes (length stay, discharge status and any return to ICU or hospital within 28 days of the primary discharge, hospital mortality); feasibility and process outcomes (how many times should it be applied, correct application versus incorrect application); and nurse survey barrier and facilitator results (to inform a Phase III protocol).

2.3.1 | Participants timeline

For a study participant, the study will commence after the randomisation process and continue to the time of a PI to the face, head or neck; 14 days; or discharge from the ICU (including death); the event occurring first after randomisation will be considered the censoring event for a given study participant.

2.3.2 | Sample size

Using a baseline rate of facial, head and neck PIs associated with the use of medical devices of 32%[3] and a 40% relative risk reduction to 19.2%, for preliminary effectiveness of the intervention,[14] approximately 98 patients would be required in each arm of the study (Type I and Type II error set at 20%).[23,24] To explore the feasibility of incorporating HOFA into usual care and to design a larger phase III trial, we will aim to interview between 10 and 20 nurses across participating ICU sites.

2.3.3 | Recruitment

Potential study participation will be discussed with the clinical team before recruitment. After consent is obtained, the participant's details will be entered into the dedicated study Research Electronic Data Capture (REDCap) database (DB).[25]

2.3.4 | Assignment of intervention

Study participants will be randomised in a 1:1 ratio to receive either HOFA+ standard care or standard care via a study-specific REDCap DB using an uploaded randomisation scheme that was developed using R language.[26] Blocks alternating randomly between a size of 4 and 6 participants for each study site have been generated to ensure concealment.[27]

2.3.5 | Blinding

Due to the nature of the HOFA oil and the potential effect of a placebo agent that is oil-based,[17] the study will be open-label. The primary and secondary outcomes of interest will be confirmed by a blinded assessor.

2.4 | Data collection, management and analysis

2.4.1 | Data collection methods

Baseline variables: (1) Date and time of hospital admission; (2) Date and time of admission to ICU; (3) Source of ICU admission; (4) unplanned or emergency admission status to ICU; (5) admission type: cardiovascular, gastrointestinal, neurological, respiratory, sepsis, trauma and other (categorical); (6) APACHE III and SOFA score on admission; (7) age at the time of admission; (8) sex; (9) height and weight; (10) clinical biochemistry and haematology on admission to ICU; (11) comorbid conditions at admission; (12) Clinical Frailty Scale on admission; and (13) baseline skin assessment and any PIP on admission. All these baseline characteristics will be collected at the time of admission to ICU and subsequent entry into the study. The validity and reliability of these routinely collected adult ICU patient characteristics have been detailed previously[28]; however, any error is expected to be non-differential between the intervention and usual care groups, due to randomisation.

2.4.2 | Follow-up during ICU admission

During the first 14 days of ICU stay: (1) routine skin assessment; (2) medical device use; and (3) PIP strategies, along with HOFA application in the intervention group, will be assessed and documented in the dedicated study REDCap DB.

2.5 | Data management

All study data will reside in a dedicated REDCap Project DB, on our LHD secure server network. Data for final analysis will be exported to the R language[26] for cleaning and preparation for statistical analysis and preparation of reports of outcomes. The study database will only contain limited identifiable participant data (medical record number, hospital, date of birth and sex), participant-specific data will remain at each given study site.

2.6 | Statistical analysis

The overall trial design and analytic principles will be based on the concept of Good Clinical Practice.[29] The primary analysis will follow a prespecified statistical analysis plan (Gamble et al., 2017; Homer et al., 2022)[30,31] in the intention-to-treat (ITT) population defined as all consenting randomised participants. We will conduct unadjusted analyses and then, as prespecified, adjusted analysis for potential confounding factors (study site, sex and severity of illness at the time of admission to intensive care). Both analyses will be presented, though the conclusions will be based on the adjusted analyses. A predefined sensitivity analysis will be considered in the Per-Protocol Population, defined as the ITT population except those having one or more major protocol violations (defined as HOFA not being applied at least once per study day).

The characteristics of study participants will be presented using descriptive statistics. These statistics include a seven-point approach, frequency, per cent, mean, standard deviation, median and inter-quartile range (as 25th and 75th percentiles) based on the normal distribution status of continuous variables. Count data will be presented as frequencies and percentages.[29] The primary analysis of the effectiveness of HOFA in preventing facial, head or neck pressure injuries will be undertaken using an ITT approach. Rates of MDRPI to the face, head or neck will be compared between the HOFA and standard care groups using Cox's Proportional Hazards model, to incorporate exposure time at risk to medical devices in the ICU.[32] Estimates of effect will be presented as Hazard Ratios, with associated 95% confidence intervals.[32] The follow-up period for the primary outcome will commence on the day of enrolment and randomisation, until an incident PI on the face, head or neck, or discharge from the ICU or 14 days in the ICU, whichever comes first. Exposure time will be defined in hours. Due to the exploratory nature of this phase II feasibility trial, preliminary effectiveness will be based on a one-sided *p*-value for superiority set at 0.10.

The staging of PI, medical device exposure, intensive care and hospital outcomes (length of stay, readmission to ICU or hospital within 14 days of the primary discharge and survival) will be compared between HOFA and standard care groups. The perceptions of the feasibility, acceptability and fit-for-purpose nature of HOFA among clinical nursing staff will also be explored. All *p*-values from these secondary outcomes will be considered exploratory.

Exploratory subgroup analyses will include (1) male versus female; (2) severity of illness at the time of admission to ICU (APACHE, SOFA score categorised); (3) type of admission (CVD, gastrointestinal, neurological, etc); (4) age group; and (5) types of medical device exposure to the head, neck and face. We will also explore the possible interaction between the intervention allocation and these subgroup indicators. The subgroup-specific findings will be reported regardless of whether the interaction term is

statistically significant (i.e., a *p*-value of the interaction term ≤0.05).

2.7 | Missing data

We will include data of study participants until the end of follow-up (discharge from ICU, death or 14 days, whichever occurs first) for the final analysis unless they have withdrawn consent to use their data. The approach to handling missing data (i.e., complete case analysis approach versus complete case analysis and multiple imputation approach), will be decided after an assessment of the amount of missing data during a blinded review.[33,34] The overall pattern of missingness, including amount, distribution across study groups and over different outcomes and covariates to be adjusted for will be examined. If the missingness is expected to have little impact on the results (<5% missing data), a complete case analysis will be performed. If the missingness is thought to have the potential to impact meaningfully on the results (>5% missing data), multiple imputation will be used to create 100 complete datasets for analysis. Imputation will be performed separately by treatment group using the fully conditional specification method (also known as chained equations).[34] Imputation models will include both baseline variables and outcomes. A complete case analysis will also be performed for comparison, but conclusions will be based on the imputed results.

2.8 | Monitoring

The overall conduct of the trial will be monitored by a trial steering committee, independent of the sponsor BBraun, who supplied the HOFA product. In terms of adverse events, all patient harms will be recorded in the dedicated study DB, and serious adverse events will be reported to the Chief Principal Investigators directly and the HREC office of our LHD.

2.9 | Data monitoring and safety committee

This phase II trial has no plans for IDMSC.[29]

2.10 | Interim analyses

Due to the phase II nature of the study, no interim analysis has been planned.

2.11 | Skin assessment and validation

Each study participant will have a skin assessment, that includes the face, head and neck conducted once per shift. If the participant required multiple skin assessments during the shift as part of their clinical management plan, the study would only require one of the skin assessments to be entered into the study database. The trial will be conducted up to day 14 of admission to ICU. A random subset of one or two blinded replicate skin assessments will be undertaken at each study site by a co-investigator (at most sites this is a hospital-wide wound Clinical Nurse Consultant). The skin assessments will include the classification of the skin as a normal colour, red (blanchable or non-blanchable) and staging of any incident PI to the face, head or neck using the European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance classification system.[35]

3 | DISCUSSION

DRPUs to the face, head or neck due to adults admitted to intensive care are considered preventable. Therefore, this phase II feasibility study aims to investigate the efficacy of HOFA as an adjunct to standard care. Importantly, we aim to inform the development of a larger phase III trial.

3.1 | Strengths

This trial aims to assess the feasibility of incorporating HOFA as an adjunct to standard care to prevent facial, head and neck PIs across six adult ICUs. We will explore current standard care skin assessment practices, baseline incidence of these PIs (via a control group) and current prevention approaches across these ICUs. Importantly, we will directly explore potential feasibility, acceptability and potential barriers and facilitators of the addition of HOFA to standard care, prior to initiating a larger phase III trial. All analyses will be undertaken using a preplanned SAP.

3.2 | Limitations

Our overall sample size is based on feasibility and potentially may be underpowered to assess small effect sizes; however, our Type I and Type II error rates have been both set at 20% by international standards for this phase of trial investigation.[29] Also, we have not attempted to

blind the intervention and control status, as any control (oil-based) substance may, in fact, have a potential protective effect, which has been suggested with the use of olive oil.[17]

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CONFLICT OF INTEREST STATEMENT

All authors have not actual or perceived conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All requests for data sharing will be considered on an individual basis.

ETHICS STATEMENT

The project will be undertaken in accordance with the principles of the Declaration of Helsinki.[36,37] The trial has been reviewed and approved by the SWSLHD Human Research Committee (HREC) (2020/ETH02833), and Research governance approval will be obtained from each study site. Adult patients who are conscious and capable of giving explicit informed consent will be approached to participate in the study. All amendments to the protocol have been and will be considered by our LHD HREC.

DISSEMINATION POLICY

After the completion of the trial, all trial results will be submitted to a peer-reviewed medical journal and conference presentations, irrespective of the direction of the results. We will adhere to the CONSORT statement including the accountability of all patients screened.[38]

ORCID

Steven A. Frost https://orcid.org/0000-0002-8879-0486

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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