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Original Article

Remi-fent 1—A pragmatic randomised controlled study to evaluate the feasibility of using remifentanil or fentanyl as sedation adjuncts in mechanically ventilated patients☆

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ABSTRACT

Objective: To evaluate the feasibility of conducting a prospective randomised controlled trial (pRCT) comparing remifentanil and fentanyl as adjuncts to sedate mechanically ventilated patients.
Design: Single-center, open-labelled, pRCT with blinded analysis.
Setting: Australian tertiary intensive care unit (ICU).
Participants: Consecutive adults between June 2020 and August 2021 expected to receive invasive ventilation beyond the next day and requiring opioid infusion were included. Exclusion criteria were pregnant/lactating women, intubation >12 h, or study-drug hypersensitivity.
Interventions: Open-label fentanyl and remifentanil infusions per existing ICU protocols.
Outcomes: Primary outcomes were feasibility of recruiting ≥1 patient/week and >90 % compliance, namely no other opioid infusion used during the study period. Secondary outcomes included complications, ICU-, ventilator- and hospital-free days, and mortality (ICU, hospital). Blinded intention-to-treat analysis was performed concealing the allocation group.
Results: 208 patients were enrolled (mean 3.7 patients/week). Compliance was 80.6 %. More patients developed complications with fentanyl than remifentanil: bradycardia (n = 44 versus n = 21; p < 0.001); hypotension (n = 78 versus n = 53; p < 0.01); delirium (n = 28 versus n = 15; p = 0.001). No differences were seen in ICU (24.3 % versus 27.6 %,p = 0.60) and hospital mortalities (26.2 % versus 30.5 %; p = 0.50). Ventilator-free days were higher with remifentanil (p = 0.01).
Conclusions: We demonstrated the feasibility of enrolling patients for a pRCT comparing remifentanil and fentanyl as sedation adjuncts in mechanically ventilated patients. We failed to attain the study-opioid compliance target, likely because of patients with complex sedative/analgesic requirements. Secondary outcomes suggest that remifentanil may reduce mechanical ventilation duration and decrease

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the incidence of complications. An adequately powered multicentric phase 2 study is required to evaluate these results.

1. Introduction

Sedatives and opioids are commonly administered as infusions in intubated, mechanically ventilated patients in Intensive Care Units (ICU). Multiple studies, including the large analgosedation Australia-based ANALGESIC study, have confirmed that deep sedation has been associated with complications such as immobility, nosocomial infection, pressure injuries, ICU-acquired weakness, delirium, use of physical restraints, prolonged mechanical ventilation, need for tracheostomy, and increased mortality.[1–10]

Proposed solutions have predominantly focused on influencing good clinical practice by targeting “light sedation”, daily sedation cessation trials, titration protocols, and re-evaluating the need for ongoing sedation.[11,12] Despite this, recent trials suggest that deep sedation continues to be common,[13,14] implying the need to explore alternative strategies. For instance, a pharmaceutical strategy of using sedative infusions with shorter context-sensitive half-time such as propofol is associated with better outcomes, compared to sedatives with longer half-lives such as benzodiazepines.[12,15,16]

However, the opioids that are commonly used in Australian ICUs have a long duration of action, e.g., fentanyl, which has a long context-sensitive half-time and morphine, which is metabolized to active metabolites with long half-lives.[7,17–21] The largest ever ICU study on analgosedation (the ANALGESIC trial) demonstrated that for adult patients requiring mechanical ventilation, fentanyl infusion significantly increased the median number of ventilator-free days (VFD) at Day 28 compared with morphine. They concluded that the choice of opioid infusion agent may affect clinical outcomes and requires further investigation.[10]

However, since both fentanyl and morphine are opioid agents with long duration of action, they may contribute to complications from prolonged deep sedation.[6,11] In contrast, remifentanil is an ultra-short-acting opioid with a short context-sensitive half-life of 3–4 min.[22–27] Although clinical trials, systematic reviews, and meta-analyses have shown that the use of remifentanil may be associated with a reduction in the duration of mechanical ventilation and ICU length of stay,[28–30] its use in Australian ICUs is infrequent or rare.[31] While the reasons for this have not been explored, possible reasons could be attributed to the high cost of remifentanil until recently[7] and to the relative unfamiliarity with its use by intensivists with limited exposure to anaesthetic practice.

In our ICU, where fentanyl has historically been the default opioid adjunct for sedation, audits have shown a longstanding problem of over-sedation. In recent years, the use of remifentanil as a sedation adjunct for mechanically ventilated patients has become more common, initially in patients with brain injury and then more widely. We conducted an investigator-initiated, pragmatic, unblinded prospective randomised controlled trial comparing remifentanil and fentanyl infusions as adjuncts to sedate mechanically ventilated patients to evaluate feasibility.

2. Methods

Following approval by the Nepean Blue Mountains Ethics Committee (2020/ETH00311, 04/30/2020) and registration with the Australia New Zealand Clinical Trials Registry (ID: ACTRN12620000719932), the RCT was conducted between June 2020 and August 2021 in a tertiary Australian ICU.

The case-mix comprised medical and surgical patients, excepting postoperative cardiac surgery and solid organ transplantation. Prior informed consent or consent to continue to participate in the trial was obtained from all patients or their proxies. An independent data and safety monitoring committee provided oversight. Since no financial assistance/funding was received, a pragmatic study design was employed to ensure sustainable patient-enrolment, study-opioid preparation, administration and monitoring, and data collection. eTable 1 lists the features of a pragmatic study design in designing the study.

All consecutive endotracheally intubated patients aged ≥18 years were screened. Inclusion criteria included clinician expectation that the patient would require invasive mechanical ventilation beyond the next calendar day and immediate opioid analgesic continuous infusion to facilitate ventilation. Exclusion criteria were pregnancy, lactation, intubation duration ≥12 h in an ICU before randomisation (excluding time spent intubated within an operating theatre or transport) or known hypersensitivity to the study-opioids or constituents.

Using computer-generated block randomisation sequences with variable block sizes placed in sequential, sealed envelopes, patients were randomly assigned in a 1:1 ratio to receive remifentanil or fentanyl. Patients readmitted within Day-28 were reallocated to their original treatment group. Data collection ceased after Day-28.

The sedation target in the ICU was based on the Richmond Agitation and Sedation Scale (RASS), which ranges from −5 (unresponsive) to +4 (combative).[32] The default practice in our ICU was to aim for light sedation. Hence, the opioid infusions were titrated to maintain a sedation goal between a RASS of −2 (lightly sedated) to +1 (restless), unless another target was chosen by the treating clinician. Delirium was assessed daily using the Confusion Assessment Method when RASS≥ −2.[33] Pain was assessed 4th-hourly using Yes/No responses for self-reporting patients or using the Critical Care Pain Observation tool.[34]

For pragmatic reasons, open-label opioids were used for the study. The treating clinicians used existing ICU practices to prepare, administer, and monitor the effect of the opioids (drug protocols in eAppendix). All management decisions were left to the discretion of the treating clinician, including (but not limited to) using other sedatives/analgesics, titrating the opioid doses, weaning mechanical ventilation, and determining the readiness for extubation. The study opioid was continued until the patient was extubated or deemed no longer necessary by the treating clinician and/or until Day-28 post-enrolment. All research-related data were collected automatically from existing ICU data systems, minimizing the workload of research staff.

The primary outcome was the feasibility of enrolling patients, defined as[1] recruiting ≥1 patient/week; ≥90 % compliance, defined as the study-opioid being the sole opioid infusion for the duration of mechanical ventilation or Day-28, whichever was earlier. Secondary outcomes included the following (definitions in Table 1):[1] Safety outcomes (bradycardia and/or hypotension);[2] delirium;[3] physical restraints;[4] ICU-free-days to Day-28(35);[5] ventilator-free-days (VFD) to Day-28[10,35];[6] Hospital-free-days (HFD) to Day-

Table 1
Definition of secondary outcomes.

Secondary Outcome	Definition
Bradycardia	Heart rate ≤50 after commencing the study-opioid infusion
Hypotension	Drop in mean arterial pressure by ≥ 20 % after commencing the study-opioid infusion
Delirium	Assessed daily in patients lightly sedated (i.e., RASS > -2 using the Confusion Assessment Method for Intensive Care (CAM-ICU)
ICU mortality	Death of an enrolled patient while still being admitted in the ICU
Hospital mortality	Death of an enrolled patient in the hospital ward after being discharged from the ICU
ICU-free days (up to Day 28)[1,10,35]	28 minus the number of days or part-days in ICU. Patients who died any time before or up to 28 days were deemed to have zero ICU-free days.
Ventilator-free days (VFD) up to Day 28[1,10,35]	28 minus the number of days in which a patient is alive and receives no assistance from invasive mechanical ventilation if any period of ventilator liberation lasts at least 48 consecutive hours. Patients who died any time before or up to 28 days were deemed to have zero ventilator-free days.
Hospital-free days (up to Day 90)[1,35]	90 minus the number of days or part-days in hospital. Patients who died any time before or up to 90 days were deemed to have zero hospital-free days.
ICU length of stay	Duration in days from the day of admission to the day when the patient was cleared to go to the ward by the treating intensivist.

90(35);[7] ICU and hospital mortality. Finally, the total pharmacy cost for the remifentanil given to patients in the remifentanil group and the total cost of the fentanyl given to patients in the fentanyl group was estimated based on the unit price of $2.40 for one ampoule (1 mg) of remifentanil and $2.25 for one ampoule (500 μg) of GH brand fentanyl.

Statistical analysis was performed using *R for Windows* (version 2022.07.1 + 554) as per the intention-to-treat. Categorical variables were reported as counts with percentages [*n*(%)] and compared using Fisher's exact test. Continuous data were reported as median [q1,q3] and group comparisons using the Mann–Whitney test. Two-tailed alpha <5 % was considered statistically significant. To account for the unblinded, open-label trial design, the statistical analysis was performed in a blinded manner with concealed opioid allocation groups coded as Group 1 and Group 2. The groups were unblinded only after every author approved the first draft manuscript.

3. Results

3.1. Study population

A total of 281 intubated and mechanically ventilated patients met the inclusion criteria. Of these, 208 patients were enrolled, with four patients being readmitted during their 28-day study period. Fig. 1 illustrates the CONSORT diagram with the enrolment details. There were no missing patients. The two groups were well matched in their reason for ICU admission, severity of illness, and baseline renal function. Patients in the remifentanil arm were more likely to be older and female. Table 2 summarizes the baseline characteristics.

3.2. Outcomes

As per our criteria for the primary outcome, we were able to recruit an average of 3.7 patients every week, exceeding our predefined target of at least one patient per week. For our second criterion (i.e., compliance with the study drug regimen during the study period), the study opioid was used as the sole opioid for 80.6 % patients overall (fentanyl arm 90 patients (84.1 %) versus remifentanil arm 81 (77.1 %). In both groups, the opioid change occurred typically in the second week between days 10 and 14. In the 17 patients in the fentanyl arm who had a change in opioid infusion, the choice of opioid was morphine (11 patients), remifentanil (4 patients), and hydromorphone (2 patients). In the 24 patients in the remifentanil arm who had a change in opioid infusion, the choice of opioid was morphine (12 patients), fentanyl (11 patients), and hydromorphone (1 patient). Of the 23 patients in whom the reason was documented, suboptimal analgesia was the reason in 17 post-abdominal surgical patients, suboptimal sedation (n = 2) and ventilator dysynchrony (n = 3). In 15 patients, the opioid switch occurred when the patient was palliatively extubated for comfort measures.

The mean (SD) dose of the opioid infusion in the fentanyl arm was 5.24 ± 2.08 mcg/kg/hour and in the remifentanil arm was 9.49 ± 2.69 mcg/kg/h (0.16 mcg/kg/min ±0.05 mcg/kg/min). The mean (SD) dose of propofol infusion (10 mg/ml concentration) in the fentanyl arm was 50 ± 57 mg/h and in the remifentanil arm was 48.2 ± 55.8 mg/h. The median RASS in both arms was −2 (Table 2). Overall, there were more episodes of complications in the fentanyl arm compared to the remifentanil arm (Table 3). The use of physical restraints was similar in both groups (16 episodes in the fentanyl arm versus 18 in the remifentanil arm). When these episodes were analyzed per patient per day, there were more episodes of these complications in the fentanyl arm than the remifentanil arm (Table 3). There was no significant difference in ICU or hospital mortality between the two groups. The ICU mortality rate in the remifentanil arm was 27.6 % versus 24.3 % in the fentanyl arm; p = 0.60. Hospital mortality rate was 30.5 % in the remifentanil arm versus 26.2 % in the fentanyl arm; p = 0.50 (eFig. 1).

However, patients in the remifentanil arm had a higher number of VFDs, ICU-free-days and HFDs, with the former being statistically significant (Table 3b).

The total pharmacy cost for the remifentanil given to the remifentanil group was $4401.6 ($41.9 per patient) and the total cost of all the fentanyl given in the trial to the fentanyl group was $3388.5 ($31.7 per patient).

4. Discussion

This single-center, pragmatic prospective RCT compared continuous infusions of remifentanil and fentanyl as sedation adjuncts in mechanically ventilated patients. It demonstrated the feasibility of enrolment but failed to attain the 90 % compliance target of the study-opioid being the sole opioid infusion throughout the patient's ventilation period. The remifentanil arm had an equivalent or better safety profile than the fentanyl arm with better clinically meaningful outcomes such as fewer complications, fewer delirium episodes, and more VFDs to Day-28.

Our results highlight both the benefits and drawbacks of using pragmatic criteria for enrolling patients in an analgesic-related study. Despite the tight 12-h recruitment window post-intubation, the pragmatic inclusion criteria helped achieve high enrolment rates, but at the expense of enrolling patients with

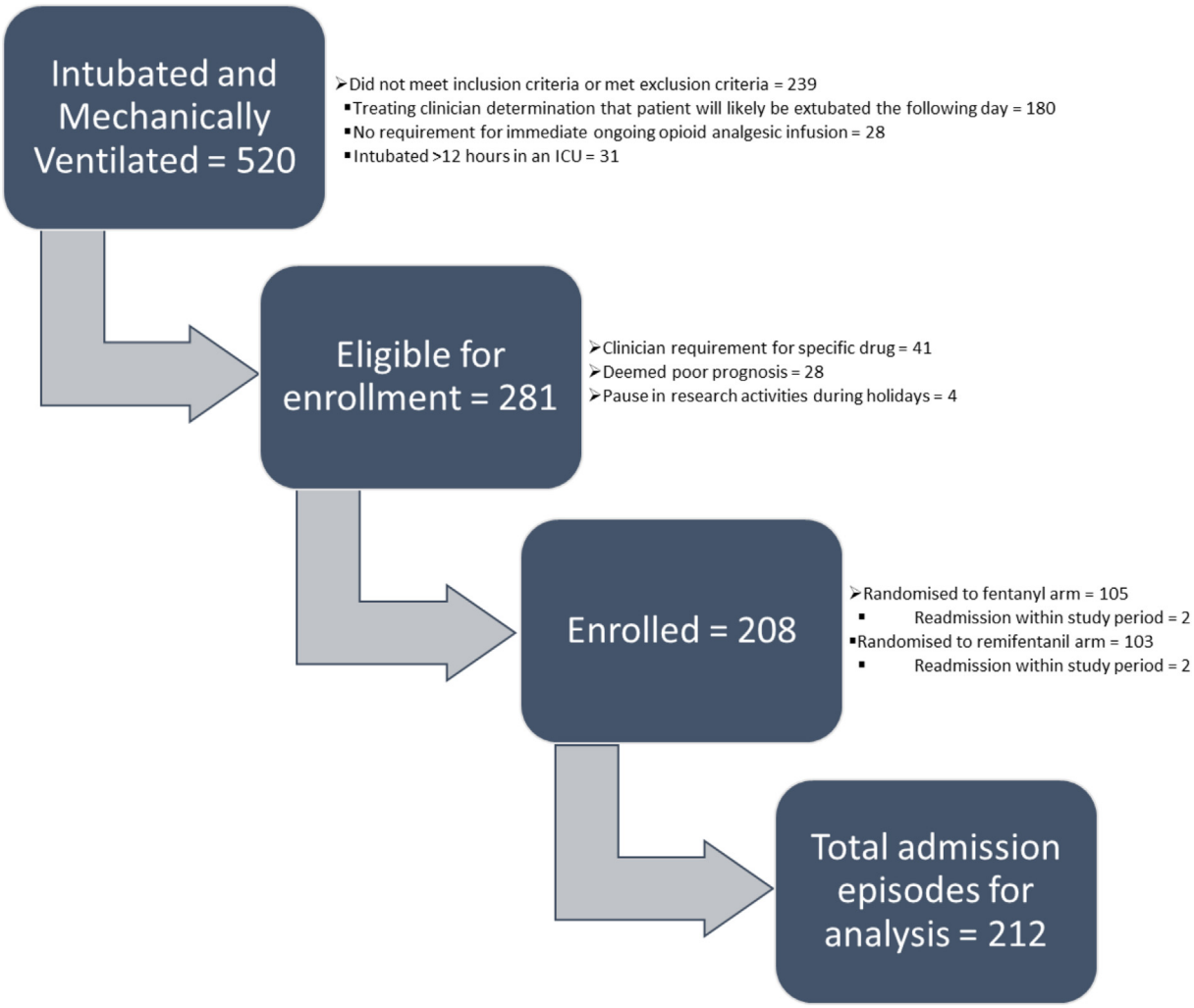

Fig. 1. CONSORT diagram.

Table 2
Baseline characteristics.

Parameter	Fentanyl Arm n = 107	Remifentanil Arm n = 105
Age (years)	60.50 (51.6, 73.6)	62.6 (52.6, 73.8)
Male gender, n (%)	68/107 (63.6 %)	57/105 (54.3 %)
APACHE-II	19[14,24]	18[13,24]
APACHE-III	71 (53, 91)	65 (49, 92)
Baseline creatinine (micromol/L)	96 (76, 176)	107 (70, 165)
Primary Reason for Admission		
Respiratory	13 (12.1 %)	11 (10.5 %)
Cardiovascular	21 (19.6 %)	16 (15.2 %)
Sepsis	25 (23.4 %)	25 (23.8 %)
Neurology	14 (13.1 %)	16 (15.2 %)
Gastrointestinal	20 (18.7 %)	25 (23.8 %)
Trauma	4 (3.7 %)	2 (1.9 %)
Other[a]	10 (9.3 %)	10 (9.5 %)
ICU Admission source		
Emergency department	30 (28 %)	40 (38.1 %)
Operation theatre/recovery	31 (29 %)	23 (21.9 %)
Ward	23 (21.5 %)	20 (19 %)
Miscellaneous[b]	23 (21.5 %)	22 (21 %)
Surgical patients	32 (29.9 %)	24 (22.9 %)
Unplanned/emergency surgery	19 (17.8 %)	8 (7.6 %)
Admission after MET call	24 (22.4 %)	19 (18.1 %)
Post cardiac arrest	11 (10.3 %)	6 (5.7 %)

Data are n (%).
[a] Other = endocrine, polypharmacy overdose, hematological.
[b] Other hospitals, direct admissions.

Table 3
Secondary outcomes - Safety parameters and the parameters related to the length of stay.

	Statistic	Fentanyl Arm	Remifentanil Arm	p-value
Number of patients with bradycardia	n	44	21	0.001
Number of patients with hypotension	n	78	53	0.01
Number of patients with delirium	n	28	15	0.001
Number of 4-h blocks of deep sedation (RASS ≤2) per patient per day	mean [SD]	3.1 [4.6]	3.3 [6.1]	0.001
RASS score	Median [q1,q3]	−2 [-3.33,-1.2]	−2 [-3.37,-1.04]	0.55
ICU length of stay in days for all patients (survivors and non-survivors)	Median [q1,q3]	4.9 [3.0, 9.0]	3.1 [2.0,7.0]	0.003
ICU length of stay in days for survivors at ICU discharge	Median [q1,q3]	4.9 [2.9, 9.7]	3 [2.1, 5.7]	0.003
Hospital length of stay in days for all patients (survivors and non-survivors)	Median [q1,q3]	12.7 [7.0, 26.6]	9.49 [2.5, 20.2]	<0.001
Hospital length of stay in days for survivors at hospital discharge	Median [q1,q3]	16.9 [10.6, 33.5]	10.7 [3.9, 21.3]	<0.001
ICU-free days on Day 28	Median [q1,q3]	19.3 [0, 24.6]	22.5 [0, 26.4]	0.06
Hospital-free days at Day 90	Median [q1,q3]	60.5 [0, 76.2]	66.1 [0, 78.8]	0.59
Duration of ventilation in days for all patients (survivors and non-survivors)	Median [q1,q3]	3.1 [2.9, 7.6]	2.3 [1.6, 5.7]	0.001
Duration of ventilation in days for survivors at ICU discharge	Median [q1,q3]	3.1 [2.2, 7.5]	2.2 [1.6, 4.3]	0.001
Ventilator-free days (VFD) on Day 28	Median [q1,q3]	24.3 [20.8, 25.7]	26.2 [23.6, 27.4]	0.005

diverse analgesic requirements, ranging from sedation-adjuncts for endotracheal tube intolerance to deep sedation for respiratory failure to postoperative analgesia. Also, the open-label nature of the study may explain the lack of compliance with the study opioid regimen. Since fentanyl was the most common opioid used in our ICU, it is possible that clinical staff may have been less familiar/confident with the use and titration of remifentanil, which may have lowered the compliance in the remifentanil arm. With such broad inclusion criteria, our predefined 90 % compliance target was perhaps optimistic. Future studies may need to employ a blinded design and modify either the inclusion criteria or allow the co-administration of other opioids in patients with suboptimal analgesia.

Although both groups were sedated as per our default sedation target, the dose of fentanyl was slightly higher than the hourly doses reported in the ANALGESIC trial.[8,9] Perhaps due to the residual sedation arising from the long context-sensitive half-time of fentanyl used at high doses, patients in the fentanyl arm had a higher incidence of delirium. This may have contributed to more complications, fewer VFDs, and longer ICU stay. The potential for cost-savings from earlier extubation and/or ICU stay warrant evaluation in adequately powered multicenter phase-2 studies.

Our study has several strengths. This is the first such prospective RCT done in Australian ICUs. The results are broadly consistent with previous single-center studies from other countries that compared remifentanil to fentanyl, which have shown that remifentanil may be associated with shorter duration of mechanical ventilation, length of stay, and lower incidence of delirium.[26,29,30,36–42] However, our study has the largest sample size with a variable case-mix from a general ICU. Since it is the first study to be conducted in Australia, the results may be particularly relevant to Australian-New Zealand practice. The internal validity was robust, with clear research questions, inclusion/exclusion criteria, prospective design, consecutive screening, early enrolment, intention-to-treat analysis, and blinded statistical analysis to minimize the bias arising from the unblinded design. The pragmatic design allowed uninterrupted patient enrolment, clinical management within existing ICU practices and minimal additional burden on research staff due to automated data collection from existing ICU data systems.

There were several limitations. The pragmatic design chosen due to funding constraints led to advantages and disadvantages (eTable 1). A particular disadvantage is the lack of clinician-blinding of the opioid allocation group, as blinded opioid formulations would have overburdened nurses and/or the pharmacist. We took two steps to minimize bias: one, clinical staff were empowered to make management decisions completely independently without any need to consult the research team. The opioid change effected in almost 20 % of patients for clinical reasons is testament to the lack of interference by the research team. Also, blinded statistical analysis ensured data integrity. However, although the secondary outcomes suggest that remifentanil may reduce the duration of mechanical ventilation and decrease the incidence of complications, it is unclear if these differences were caused by clinician bias due to the open label trial design. The second limitation was the inadequate sample size to evaluate clinically meaningful outcomes (eTable 2). This may have exaggerated the treatment effect. Third, the differences in baseline characteristics (more patients from the emergency department in the remifentanil arm and more surgical patients in the fentanyl arm) may have had some impact on the differences in outcome. Fourth, the costing analysis was impacted by the increased cost of fentanyl during the study. Using the pre-COVID cost of $0.845 per fentanyl 500 μg ampoule (DBL brand), the cumulative pharmacy cost for fentanyl would be $1272.6 ($11.9 per patient) as opposed to our analysis of $3388.5 ($31.7 per patient). Whether remifentanil may be more economical by reducing ICU length of stay remains to be evaluated in future studies. Finally, the single-center design limits external validity to ICUs with similar case-mix and clinical management practices.

5. Conclusion

We demonstrated the feasibility of enrolling patients for a prospective RCT comparing remifentanil and fentanyl as sedation adjuncts in mechanically ventilated patients. We failed to attain the study-opioid compliance target, likely because of patients with complex sedative/analgesic requirements. Secondary outcomes suggest that remifentanil may reduce mechanical ventilation duration and decrease the incidence of complications. Since the study was not adequately powered to evaluate these outcomes, an adequately powered multicentric phase 2 study is required to validate these results.

CRediT authorship contribution statement

Arvind Rajamani: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, drafting the protocol, ethics application, Software, data analysis, Writing – original draft, Writing – review & editing.

Ashwin Subramaniam: Methodology, Software, data analysis, Writing – original draft, Writing – review & editing.

Brian Lung: Conceptualization, Methodology, drafting the protocol, ethics application, Writing – review & editing.

Kristy Masters: Investigation, Methodology, Project administration, Writing – review & editing.

Rebecca Gresham: Investigation, Methodology, Project administration, Writing – review & editing.

Christina Whitehead: Investigation, Methodology, Project administration, Writing – review & editing.

Julie Lowrey: Investigation, Methodology, Project administration, Writing – review & editing.

Ian Seppelt: Conceptualization, Methodology, ethics application, Writing – review & editing.

Hemant Kumar: Data curation, Software, Writing – review & editing.

Jayashree Kumar: Data curation, Software, Writing – review & editing.

Anwar Hassan: Methodology, Software, data analysis, Writing – original draft, Writing – review & editing.

Sam Orde: Conceptualization, Methodology, ethics application, Writing – review & editing.

Pranav Arun Bharadwaj: Data analysis of revised manuscript, review & editing.

Hemamalini Arvind: Methodology, Software, data analysis, Writing – original draft, Writing – review & editing.

Stephen Huang: Methodology, Software, data analysis, Writing – original draft, Writing – review & editing, Software, Supervision.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.10.012.

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