Effect Analgo-Sedation with Morphine vs. Fentanyl on Ventilator-Free Days at Day 28 Among ICU Patients Receiving Invasive Mechanical Ventilation: The ANALGESIC randomized clinical trial

Statistical Analysis Plan

Andrew Casamento,[1] Ary Serpa Neto,[2] Rinaldo Bellomo[1,2]

1. Department of Intensive Care, Austin Hospital, Melbourne, Australia

2. Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Corresponding author:

Rinaldo Bellomo

Department of Intensive Care, Austin Hospital,

145 Studley Rd, Heidelberg, Victoria, Australia

Tel: +61-3-9496 5992

Fax: + 61-3-9496 3932

Email: rinaldo.bellomo@austin.org.au

INTRODUCTION

Pain and discomfort are common in mechanically ventilated intensive care unit (ICU) patients, being reported in up to 71% of patients.[1,2] Modern ICU practice focusses on managing unpleasant awareness with sedative agents, delirium with antipsychotic agents and pain with analgesic agents.[3-5] A multi-centred international prospective observational study of 703 mechanically ventilated patients revealed that 55% of the patients were prescribed morphine and 61% were prescribed fentanyl.[6] In 2015 and 2016, there were almost 150,000 ICU admissions to Australian and New Zealand ICUs of which 34.6% (approximately 52,000 patients) were mechanically ventilated.[7] The above data would suggest that equates to approximately 29,000 patients receiving morphine and approximately 32,000 patients receiving fentanyl per annum in Australian and New Zealand ICUs.

There are no direct comparative studies of morphine and fentanyl in mechanically ventilated, adult ICU patients. There is one small study in newborns[8] who were ventilated but most of the work is in the non-ICU population. There are a number of studies comparing effectiveness and side effects of intravenous morphine and fentanyl in the pre-hospital setting for analgesia,[9-11] for non-cardiac surgical patients for post-operative analgesia,[12-19] and in cardiac surgery for anaesthesia and analgesia.[20-25] Overall there is no strong evidence to favour the use of one agent over another in these patient groups.

The present study outlines the protocol and statistical analysis plan for a prospective cluster crossover randomized controlled trial comparing the effect of morphine with fentanyl on the ventilator-free days at day 28 in adult patients undergoing mechanical ventilation in the ICU. Recruitment for the trial has now

been completed but data collection is still running, and no data analysis has yet been undertaken. This trial is registered with ANZCTR (ACTRN12619000939190).

METHODS

Study design

National open-label, two centre cluster crossover, registry-embedded randomized clinical trial comparing two approaches for analgo-sedation implemented in the ICU among adult patients requiring mechanical ventilation. The protocol was approved by the Austin Health Human Research Ethics Committee (HREC), and informed consent was waived or an opt out process was followed according to local jurisdictions. No interim analyses were planned.

Study population

Patients aged 18 years or older requiring mechanical ventilation at any time during ICU admission were eligible for inclusion in the study. Patients who are allergic to any of the trial drugs, who have undergone cardiac surgery, who were deemed by the treating clinician not to require morphine or fentanyl to aid with sedation or who were treated as end of life care were excluded. Patients who were admitted and ventilated on more than one occasion had only their first admission included for analysis.

Randomization and masking

The study compared two standard approaches for analgo-sedation among adults requiring mechanical ventilation. One approach was to use morphine by default and the other was to use fentanyl by default when analgo-sedation was prescribed. Each ICU used one approach for a 6-month treatment period and then switched to the alternative approach for the next 6 months. The participating

units were randomized to the order of treatment (morphine - fentanyl or fentanyl - morphine). Clinicians, and investigators were aware of group assignments.

Intervention

Study treatments were administered open-label in this unblinded trial. Clinicians decided whether individual patients would receive analgo-sedation and the amount of sedative to be used. When clinicians chose to prescribe analgo-sedation, the default prescription of either morphine or fentanyl was determined by ICU randomization status. However, irrespective of the therapy assigned to the ICU, either morphine or fentanyl could be used for a particular patient if the treating physician considered this preferable. A protocol violation was defined if the non-allocated drug was administered for more than 4 hours after admission or if the non-allocated drug was commenced at any other time during the period of mechanical ventilation.

Patients who remained in the ICU through the crossover period continued to receive their originally assigned treatment. No washout occurred between crossover periods. The duration of the infusion of the study drug was until the patient no longer received mechanical ventilation or death, and the amount of drug was determined by the physician in charge. Following extubation, analgesia was prescribed at discretion of the treating physician, if required.

Data collection

All baseline demographic data, illness severity, and outcome of included patients are being collected from data submitted to the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult

Patient Database. These data are routinely collected by trained ICU staff for quality assurance purposes.

Individual patient-level data on the analgo-sedation used, and additional clinical and laboratory data are being collected for all included patients from electronic health records, medication charts, and electronic prescribing and pharmacy dispensing data. Data collection of patients who are still inpatients was ceased at 28 days after ICU admission.

Study outcomes

Primary outcome

The primary outcome is the number of ventilator-free days at day 28, defined as the number of days from day 1 to day 28 when the patient is alive and breathes without invasive assistance of the mechanical ventilator for at least 24 consecutive hours. To calculate this endpoint all relevant data will be taken into account and collected, including all additional periods of ventilation during the first 28 days. Patients who die or are still invasively ventilated after 28 days will be assigned zero ventilator–free days. The outcome is censored at hospital discharge, with patients discharged alive from the hospital before day 28 being considered alive at day 28.

Secondary outcomes

Secondary outcomes include:

- Duration of mechanical ventilation in survivors;
- Need of tracheostomy use;

- ICU-free days at day 28 (defined as the number of days from day 1 to day 28 when the patient is alive and outside the ICU, with patients who died or were at the ICU after 28 days assigned zero ICU–free days);
- ICU length of stay in survivors;
- Hospital-free days at day 28 (defined as the number of days from day 1 to day 28 when the patient is alive and outside the hospital, with patients who died or were at the hospital after 28 days assigned zero hospital–free days);
- Hospital length of stay in survivors;
- ICU mortality;
- Hospital mortality; and
- 28-day mortality.

Tertiary outcomes

The following tertiary and process-related outcomes are being collected:

- Mean daily dose of sedatives, including propofol, midazolam, dexmedetomidine and ketamine (cumulative, absolute, and dose adjusted by body weight, body surface area, body mass index, lean weight and ideal weight); and
- Adverse events.

Adverse event reporting

Since morphine and fentanyl have been in widespread use in ICUs for many years, and most of the adverse events are tolerated in this population, the more significant event assessed in the trial is if the trial drug needs to be stopped because of some significant adverse event.

Sample size

We estimate that, compared to morphine, analgo-sedation with fentanyl would increase the number of days alive and free of invasive mechanical ventilation by 2.5 days. Considering a standard deviation of 10, a fixed number of clusters per period of 2, a within-period intracluster correlation of 0.01, and a cluster auto-correlation of 0.8,[26] 660 patients are needed to have 80% power to detect such difference at an alpha of 0.05 (**Figure 1**). From previous ICU data, we estimated that a one-year period would be sufficient to study at least 330 patients in each group. Accordingly, we considered that 6 months of treatment with morphine vs. 6 months of treatment with fentanyl would deliver enough patients to achieve the desired power.

Statistical analyses

All statistical analyses will be conducted on an intention-to-treat basis, with patients analysed according to their assigned treatment arms, unless otherwise indicated (**Figure 2**). No or minimal losses to follow–up for the primary and secondary outcomes are anticipated. Complete–case analysis will be carried out for all the outcomes. However, if more than 5% of missing data were found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out.

Hypothesis tests will be two–sided with a significance level of 0.05. Analyses will be performed using the R v.4.0.2 (R Core Team, 2016, Vienna, Austria) program.

<u>Baseline characteristics</u>

A description of the baseline characteristics of the trial participants will be presented by treatment group and by period (**Table 1** and **2**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Additional baseline laboratory values and vital signs will be reported as in **Table 3** and **4**. Continuous variables will be summarized by either means and standard deviations (SD) or medians and interquartile ranges (IQR), according to the observed distribution of the variable.

Analgo-sedation characteristics

Analgo-sedation characteristics including dose of sedatives and analgesics will be reported according to the **Table 5** and **6**, and in the figures proposed below. The amount of sedatives will be presented in similar manner. Absolute differences between the groups with the respective 95% confidence interval will be calculated and presented.

Proposed additional figures

Figure X – Dose and Volume of Intravenous Analgesic Administered According to Group.

A four-panel figure showing the cumulative volume of fentanyl and morphine until day 7 in each group (panel A and B), and the mean daily dose of fentanyl and morphine (and a bar chart with the percentage of patients receiving the sedative) until day 7 in each group (panel C and D). Data will be presented as mean and 95% confidence interval.

General model for outcomes

All analyses for outcomes will use individual patient-level data, and all models will consider the ICU as the cluster unit (random effect), and will include as fixed effects the treatment group (morphine vs. fentanyl). Since only two clusters were included, the order of administration of the treatments (1st or 2nd period) will be consider in a sensitivity analysis only, to account for the order and secular time effect. This was chosen because due to the small number of clusters there may not be sufficient data to differentiate the order effect from the treatment effect. In addition, the intra-cluster correlation coefficient, the intra-period correlation coefficient, and the intra-cluster intra-period correlation coefficient will be calculated.

Primary outcome

The primary outcome of ventilator-free days at day 28 will be modelled considering a mixed-effect quantile models considering a T = 0.50 and an asymmetric Laplace distribution. *P* values will be extracted after 1,000 bootstrap samplings. Results will be reported as median difference with a 95% confidence interval.

Secondary outcomes

Binary secondary outcomes (need of tracheostomy, ICU and hospital mortality) will be modelled considering a mixed-effect generalized linear model with binomial distribution and presented as odds ratio and 95% confidence interval. ICU and hospital-free days at day 28 will be modelled considering a mixed-effect quantile models considering a T = 0.50 and an asymmetric Laplace distribution. *P* values will be extracted after 1,000 bootstrap samplings. Results will be reported as median difference with a 95% confidence interval. To further expand the findings for the primary outcome, and for the ICU- and hospital-free days, the

duration of ventilation, ICU, and hospital length of stay in survivors will be compared considering a Fine-Gray competing risk model with death before the event as a competing risk, and presented in cumulative incidence plots and with subdistribution hazard ratio and 95% confidence interval. The 28-day mortality will be compared using (shared-frailty) Cox proportional hazard models, and presented as hazard ratio with 95% confidence interval, and in Kaplan-Meier curves. The proportional hazard assumption will be assessed using Schoenfeld residuals. Outcomes will be reported in a specific table (**Table 7**).

Proposed additional figures

Figure X - Ventilator-Free Days at Day 28 According to Allocation Group

A two-panel figure with a cumulative distribution plot sowing the cumulative fraction of patients in each ventilator-free day at day 28. The spike at 0 represents the dead patients or those with duration of ventilation longer than 28 days, and the right part of the graph the duration of ventilation. The line most at right represents a shorter duration of ventilation in survivors (more ventilator-free days). The second panel will show a bar plot representing the percentage of patients in each category of the ventilator-free days at day 28.

Figure X - Duration of Ventilation, and ICU and Hospital Length of Stay, and 28-Day Mortality

A three-panel figure with cumulative incidence plots for duration of ventilation, ICU and hospital length of stay.

Figure X - 28-Day Mortality

A Kaplan-Meier curve.

Subgroup analysis

The interaction between the allocation group and the following pre-specified subgroups will be assessed in the model described above for the primary outcome:

- Age (≤ 65 vs. > 65 years);
- APACHE score (≤ median vs. > median);
- PaO_2 / FiO_2 (≤ median vs. > median);
- Admission type (medical vs. surgical);
- Sepsis (yes or no);
- Shock (yes or no);
- Serum creatinine at baseline (≤ 150 mcmol/L vs. > 150 mcmol/L);
- Liver dysfunction (yes or no, defined as bilirubin > 30 µmol/L or ALT > 70 U/L).

Sensitivity analysis

An additional analysis for the primary outcome will be carried out adjusting for APACHE and for any other imbalanced variable ($p < 0.01$) at baseline. An additional model for the primary outcome will be carried out including the order of administration of the treatments (1^{st} or 2^{nd} period) as fixed effect, to account for the order and secular time effect. Finally, due to overdispersion and excessive zeros, the primary outcome, ICU, and hospital-free days at day 28 will be reassessed considering a mixed-effect generalized linear model with zero-inflated negative binomial distribution.

REFERENCES

1. Puntillo KA. Pain experiences of intensive care unit patients. Heart Lung. 1990;19(5 Pt 1):526-33.

2. Stein-Parbury J, McKinley S. Patients' experiences of being in an intensive care unit: a select literature review. Am J Crit Care. 2000;9(1):20-7.

3. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med. 2014;370(5):444-54.

4. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263-306.

5. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. JAMA. 2016;315(14):1460-8.

6. Shehabi Y, Bellomo R, Kadiman S, et al. Sedation Intensity in the First 48 Hours of Mechanical Ventilation and 180-Day Mortality: A Multinational Prospective Longitudinal Cohort Study. Crit Care Med. 2018;46(6):850-9.

7. ANZICS CORE Annual Report 2017: Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation; 2017 [cited 2018 26th July]. Available from: http://www.anzics.com.au/www.anzics.com.au/Downloads/ANZICS CORE Annual Report 2017.pdf.

8. Saarenmaa E, Huttunen P, Leppaluoto J, et al. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial. J Pediatr. 1999;134(2):144-50.

9. Galinski M, Dolveck F, Borron SW, et al. A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia. Am J Emerg Med. 2005;23(2):114-9.

10. Weldon ER, Ariano RE, Grierson RA. Comparison of Fentanyl and Morphine in the Prehospital Treatment of Ischemic Type Chest Pain. Prehosp Emerg Care. 2016;20(1):45-51.

11. Smith MD, Wang Y, Cudnik M, et al. The effectiveness and adverse events of morphine versus fentanyl on a physician-staffed helicopter. J Emerg Med. 2012;43(1):69-75.

12. Scharonow M, Alberding T, Oltmanns W, Weilbach C. Project for the introduction of prehospital analgesia with fentanyl and morphine administered by specially trained paramedics in a rural service area in Germany. J Pain Res. 2017;10:2595-2599.

13. Howell PR, Gambling DR, Pavy T, et al. Patient-controlled analgesia following caesarean section under general anaesthesia: a comparison of fentanyl with morphine. Can J Anaesth. 1995;42(1):41-5.

14. Woodhouse A, Hobbes AF, Mather LE, Gibson M. A comparison of morphine, pethidine and fentanyl in the postsurgical patient-controlled analgesia environment. Pain. 1996;64(1):115-21.

15. Claxton AR, McGuire G, Chung F, Cruise C. Evaluation of morphine versus fentanyl for postoperative analgesia after ambulatory surgical procedures. Anesth Analg. 1997;84(3):509-14.

16. Woodhouse A, Ward ME, Mather LE. Intra-subject variability in post-operative patient-controlled analgesia (PCA): is the patient equally satisfied with morphine, pethidine and fentanyl? Pain. 1999;80(3):545-53.

17. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain. 2002;3(3):159-80.

18. Hutchison RW, Chon EH, William F. Tucker J, et al. A Comparison of a Fentanyl, Morphine, and Hydromorphone Patient-Controlled Intravenous Delivery for Acute Postoperative Analgesia: A Multicenter Study of Opioid-Induced Adverse Reactions. Hospital Pharmacy. 2006;41(7):659-63.

19. Kim HS, Czuczman GJ, Nicholson WK, et al. Pain levels within 24 hours after UFE: a comparison of morphine and fentanyl patient-controlled analgesia. Cardiovasc Intervent Radiol. 2008;31(6):1100-7.

20. Russo A, Grieco DL, Bevilacqua F, et al. Continuous intravenous analgesia with fentanyl or morphine after gynecological surgery: a cohort study. J Anesth. 2017;31(1):51-7.

21. Sanford TJ, Jr., Smith NT, Dec-Silver H, Harrison WK. A comparison of morphine, fentanyl, and sufentanil anesthesia for cardiac surgery: induction, emergence, and extubation. Anesth Analg. 1986;65(3):259-66.

22. Yukioka H, Tanaka M, Fujimori M. Recovery of bowel motility after high dose fentanyl or morphine anaesthesia for cardiac surgery. Anaesthesia. 1990;45(5):353-6.

23. Gurbet A, Goren S, Sahin S, et al. Comparison of analgesic effects of morphine, fentanyl, and remifentanil with intravenous patient-controlled analgesia after cardiac surgery. J Cardiothorac Vasc Anesth. 2004;18(6):755-8.

24. Murphy GS, Szokol JW, Marymont JH, et al. The effects of morphine and fentanyl on the inflammatory response to cardiopulmonary bypass in patients

undergoing elective coronary artery bypass graft surgery. Anesth Analg. 2007;2007 Jun;104(6):1334-42.

25. Murphy GS, Szokol JW, Marymont JH, et al. Morphine-based cardiac anesthesia provides superior early recovery compared with fentanyl in elective cardiac surgery patients. Anesth Analg. 2009;109(2):311-9.

26. Giraudeau B, Ravaud P, Donner A. Sample size calculation for cluster randomized cross-over trials. Stat Med 2008; 27:5578-85.

Table 1 - Baseline Characteristics of the Included Patients		
	Morphine (*n* =)	**Fentanyl (*n* =)**
Age, years		
Female gender - no. (%)		
APACHE III score		
Type of admission - no. (%)		
Surgical		
Medical		
Acute respiratory failure - no. (%)		
Cardiac arrest - no. (%)		
Sepsis - no. (%)		
Shock - no. (%)		
ICU source of admission - no. (%)		
Operating room		
Emergency room		
Ward		
Other		
Admission diagnosis category - no. (%)		
Cardiovascular		
Respiratory		
Gastrointestinal		
Neurological		
Sepsis		
Trauma		
Surgical		
Other		
Co-existing disorders - no. (%)		
Diabetes		
Chronic respiratory failure		
Chronic cardiovascular disease		
Chronic kidney disease		
Immunosuppression		
Metastatic cancer		
Organ support in the first 24 hours - no. (%)		
Use of inotrope and/or vasopressor		
Renal replacement therapy		
Vital signs and laboratory tests in the first 24 hours		
Mean arterial pressure, mmHg		
Highest hear rate, bpm		
Urine output, millilitres		
pH		
PaO_2 / FiO_2		

Highest creatinine, µmol/L		
Lactate, mmol/L		

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit

Table 2 - Baseline Characteristics of the Included Patients				
	Period 1 Morphine (*n* =)	**Period 2 Fentanyl (*n* =)**	**Period 1 Fentanyl (*n* =)**	**Period 2 Morphine (*n* =)**
Age, years				
Female gender - no. (%)				
APACHE III score				
Type of admission - no. (%)				
Surgical				
Medical				
Acute respiratory failure - no. (%)				
Cardiac arrest - no. (%)				
Sepsis - no. (%)				
Shock - no. (%)				
ICU source of admission - no. (%)				
Operating room				
Emergency room				
Ward				
Other				
Admission diagnosis category - no. (%)				
Cardiovascular				
Respiratory				
Gastrointestinal				
Neurological				
Sepsis				
Trauma				
Surgical				
Other				
Co-existing disorders - no. (%)				
Diabetes				
Chronic respiratory failure				
Chronic cardiovascular disease				
Chronic kidney disease				
Immunosuppression				
Metastatic cancer				
Organ support in the first 24 hours - no. (%)				
Use of inotrope and/or vasopressor				
Renal replacement therapy				
Vital signs and laboratory tests in the first 24 hours				
Mean arterial pressure, mmHg				
Highest hear rate, bpm				
Urine output, millilitres				
pH				
PaO_2 / FiO_2				

Highest creatinine, µmol/L				
Lactate, mmol/L				

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit

Table 3 - Baseline Laboratory Values in Included Patients		
	Morphine (*n* =)	**Fentanyl (*n* =)**
Albumin, g/dL		
Lowest		
Highest		
Bilirubin, mg/L		
Urea, mg/dL		
Creatinine, µmol/L		
Lowest		
Highest		
Glucose, mmol/L		
Lowest		
Highest		
Bicarbonate, mmol/L		
Lowest		
Highest		
Hemoglobin, g/dL		
Lowest		
Highest		
Hematocrit, %		
Lowest		
Highest		
White blood cell count, $x10^3$ cells/mm^3		
Lowest		
Highest		
Platelets, $x10^3$ cells/mm^3		
Lowest		
Highest		
Potassium, mEq/L		
Lowest		
Highest		
Sodium, mEq/L		
Lowest		
Highest		
Lactate, mmol/L		
Arterial blood gas		
pH		
PaO_2, mmHg		
$PaCO_2$, mmHg		
PaO_2 / FiO_2, mmHg		
Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.		

Table 4 - Baseline Vital Signs in Included Patients		
	Morphine (*n* =)	**Fentanyl (*n* =)**
Systolic blood pressure, mmHg		
Lowest		
Highest		
Diastolic blood pressure, mmHg		
Lowest		
Highest		
Mean arterial pressure, mmHg		
Lowest		
Highest		
Heart rate, bpm		
Lowest		
Highest		
Respiratory rate, mpm		
Lowest		
Highest		
Temperature, ºC		
Lowest		
Highest		
Urine output, millilitres		
Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.		

Table 5 - Cumulative Volume of Intravenous Analgo-Sedation in Included Patients				
	Morphine (*n* =)	**Fentanyl (*n* =)**	**Absolute Difference (95% CI)**	***p* value**
Total duration of study drug infusion, hours				
Median (IQR)				
Morphine, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Fentanyl, µg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Propofol, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Midazolam, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Ketamine, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Table 6 - Cumulative Volume of Intravenous Analgo-Sedation in Included Patients				
	Morphine (*n* =)	**Fentanyl (*n* =)**	**Absolute Difference (95% CI)**	***p* value**
Morphine, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Cumulative in the first five days				
Median (IQR)				
Cumulative in the first 14 days				
Median (IQR)				
Fentanyl, µg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Cumulative in the first five days				
Median (IQR)				
Cumulative in the first 14 days				
Median (IQR)				
Propofol, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Cumulative in the first five days				
Median (IQR)				
Cumulative in the first 14 days				
Median (IQR)				
Midazolam, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				

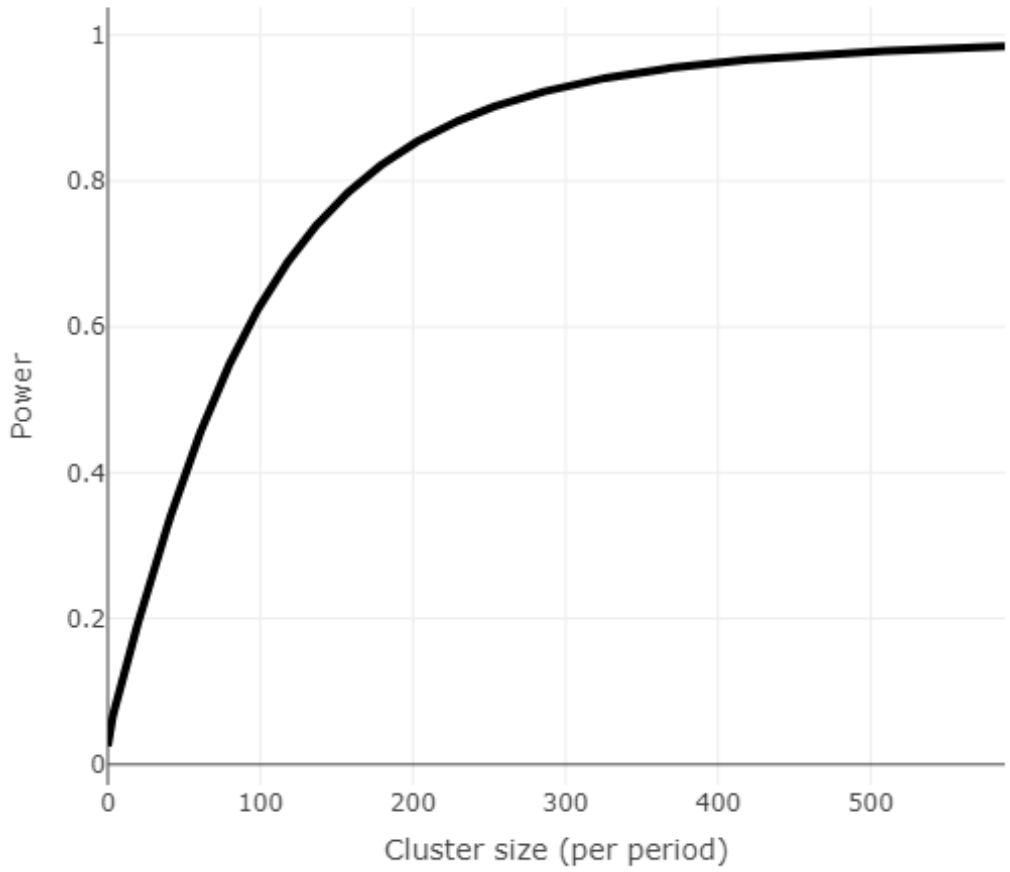
Cumulative in the first five days				
Median (IQR)				
Cumulative in the first 14 days				
Median (IQR)				
Ketamine, mg/kg				
Mean daily dose				
Median (IQR)				
Cumulative in the first 24 hours				
Median (IQR)				
Cumulative in the first three days				
Median (IQR)				
Cumulative in the first five days				
Median (IQR)				
Cumulative in the first 14 days				
Median (IQR)				

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Table 7 - Clinical Outcomes According to the Groups				
	Morphine (*n* =)	**Fentanyl (*n* =)**	**Effect Estimate (95% CI)**	***p* value**
Primary outcome				
Ventilator-free days at day 28			Median Difference	
Median (IQR)				
Secondary outcomes				
Duration of ventilation in survivors, days			Subdistribution Hazard Ratio	
Median (IQR)				
Need of tracheostomy use - no. (%)			Odds Ratio	
ICU-free days at day 28			Median Difference	
Median (IQR)				
Hospital-free days at day 28			Median Difference	
Median (IQR)				
ICU length of stay in survivors, days			Subdistribution Hazard Ratio	
Median (IQR)				
Hospital length of stay in survivors, days			Subdistribution Hazard Ratio	
Median (IQR)				
ICU mortality - no. (%)			Odds Ratio	
Hospital mortality - no. (%)			Odds Ratio	
28-day mortality - no. (%)			Hazard Ratio	

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Figure 1 - Power vs. Cluster Size Per Period



Within intracluster correlation is 0.01 and cluster auto-correlation is 0.8.

Figure 2 - Flowchart of Inclusion