Original Article

Hospital and long-term opioid use according to analgosedation with fentanyl vs. morphine: Findings from the ANALGESIC trial[☆,☆☆]

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ARTICLE INFORMATION

ABSTRACT

Objectives: Opioid use disorder is extremely common. Many long-term opioid users will have their first exposure to opioids in hospitals. We aimed to compare long-term opioid use in patients who received fentanyl vs. morphine analgosedation and assess ICU related risk factors for long-term opioid use.

Design: We performed a post-hoc analysis of the Assessment of Opioid Administration to Lead to Analgesic Effects and Sedation in Intensive Care (ANALGESIC) cluster randomised crossover trial of fentanyl and morphine infusions for analgosedation in mechanically ventilated patients.

Setting: Two mixed, adult, university affiliated intensive care units in Melbourne, Australia.

Participants: Adult patients who were mechanically ventilated and received fentanyl or morphine for analgosedation in the ANALGESIC trial.

Main outcome measures: We assessed discharge and long-term (90—365 days) opioid use in opioid-naïve patients at hospital admission according to the agent used for analgosedation.

Results: We studied 477 patients (242 fentanyl and 235 morphine). There were no differences between discharge (16.5% vs. 14.0%, p = 0.45), 90—180 day post-discharge use (3.7% vs 2.1%, p = 0.30) or 180—365 day post-discharge use (3.4% vs 1.3%, p = 0.22) of opioids when comparing those patients who received fentanyl vs. those who received morphine. Surgical diagnosis and one chronic condition were associated with increased hospital discharge prescription of opioids, whereas increasing APACHE II score was associated with decreased discharge prescription. No ICU-related factors were associated with long-term opioid use.

Conclusions: Approximately one in seven opioid-naïve patients who receive analgosedation for mechanical ventilation in ICU will be prescribed opioid medications at hospital discharge. There was no difference in discharge prescription or long-term use of opioids depending on whether fentanyl or morphine was used for analgosedation.

1. Introduction

Opioid use disorder has reached epidemic proportions. It is estimated that in the United States (US) alone, three million (1/110) people had or currently suffer from opioid use disorder.[1] Alarmingly, in the year 2021 prescription opioid medications accounted for almost 17,000 deaths of the over 80,000 deaths due to opioid overdose in the US,[2] at a rate of approximately 51 deaths per million inhabitants.

In Australia, prescription opioid use is also a significant issue. In the 20 years from 1992 to 2011, total prescriptions of opioids increased from 4.86 million to 12.25 million.[3] In 2018, 794 of the 1123 opioid-related deaths in Australia were attributed to

prescription opioids, representing an estimated 32 deaths per million inhabitants.[4]

In-hospital initiation of opioids among opioid-naïve patients is associated with long-term opioid use disorder. Studies in general surgical patients, orthopaedic patients and cardiothoracic surgical patients show that the percentage of opioid-naïve patients at hospital admission who remain on prescription opioid medications between three and 12 months later is between 2.4% and 14%.[5−14] Moreover, chronic opioid use following hospital admission is associated with increased mortality 6−18 months following discharge.[15,16]

Over 80% of mechanically ventilated intensive care unit (ICU) patients receive opioid medications as infusion for analgosedation.[17] In opioid-naïve ICU patients who are mechanically ventilated, the reported rate of chronic opioid use in survivors is between 2.6% and 7.6%.[16,18−21] Despite fentanyl and morphine being the two most used agents worldwide as infusion for analgosedation, there are no data directly comparing the long-term risk of chronic opioid use in patients who received fentanyl vs. those who received morphine for analgosedation. It is also unclear if there are modifiable risk factors during the ICU stay that are associated with long-term opioid use following ICU admission.

2. Objectives

Accordingly, we performed a secondary analysis of patients enrolled in a prospective, cluster-randomised, cluster-crossover trial of fentanyl and morphine for analgosedation (the ANALGESIC trial).[22] We aimed to test the primary hypothesis that fentanyl vs. morphine for analgosedation in adults receiving mechanical ventilation would differentially impact the incidence of hospital discharge prescription of opioids and long-term opioid use. We further aimed to identify the risk factors associated with patients receiving hospital discharge prescription of opioids, and in those patients discharged on opioids, risk factors during the ICU stay associated with transition to long-term opioid use.

3. Methods

3.1. Trial design and setting

This was a post-hoc analysis of a prospective, open label, multicentre, cluster-randomised, cluster cross-over registry-embedded clinical trial comparing fentanyl and morphine by continuous infusions for analgosedation among adult patients requiring invasive ventilation.

The protocol and statistical analysis plan,[23] and the original trial[22] have been published. The local human research ethics committee of the Austin Hospital approved the study (HREC approval number HREC/52656/Austin-2019). Informed consent was either waived (Austin Hospital) or obtained via an opt-out process (Northern Hospital). Both ICUs are in university-affiliated hospitals and located in Melbourne, Australia. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000939190).

3.2. Patients

Patients included in the primary trial were ≥18 years who received an opioid infusion whilst being mechanically ventilated during ICU admission. Patients allergic to either trial drug, who had undergone cardiac surgery (due to overall short duration of mechanical ventilation), who were deemed by the treating clinician not to require analgosedation or who were receiving end-of-life care (to facilitate organ donation or for palliative care therapy)

were excluded. Patients admitted and ventilated on more than one occasion had only their first (index) admission included for analysis. Time of enrollment into the study was the time of their index admission to the ICU. Time of observation was from enrollment to hospital discharge.

In this study, patients were considered opioid exposed and excluded if they had an opioid dispensed within 90 days prior to hospital admission or if an opioid was one of their admission medications. Other excluded patients were those who died in-hospital or those with missing data pertaining to hospital discharge opioid prescription.

3.3. Randomisation

The study compared two opioid infusions for analgosedation. One used fentanyl and the other used morphine whenever opioid infusions were prescribed. Each ICU used one opioid for a six-month period and then switched to the alternative opioid for the next six months. The participating units were randomised to a given order of treatment. The treatment was open label.

3.4. Intervention

Clinicians decided whether individual patients required opioid infusions for analgosedation and the dose of the allocated agent to be used. Patients who were on the non-allocated opioid on admission to ICU were changed to the allocated opioid within 4 h. Patients who remained in the ICU through the crossover period continued to receive their originally assigned treatment. There was no washout period.

Patients in both ICUs were under the constant care of an ICU specialist, who was board-certified with the College of Intensive Care Medicine of Australia and New Zealand and was responsible for all aspects of management. All ventilated patients were managed at a 1:1 nurse-to-patient ratio. All ICU specialists and nursing staff had similar familiarity with prescription and dosing of both drugs for analgosedation and had used both interchangeably.

Both ICUs used the Richmond Agitation Scoring System (RASS)[24,25] to assess sedation and aimed for a light sedation target (RASS -2 to +1) unless deep sedation was clinically required. Only the Austin Hospital used the Critical Care Pain Observation Tool (CPOT)[26] to assess pain in sedated patients, otherwise numerical pain scores or faces pain scale were used to assess pain.

3.5. Data collection and definitions

All baseline demographic data, illness severity, and outcomes of included patients were obtained from data submitted to the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database (ANZICS CORE APD). Trained ICU staff routinely collect these data for quality assurance purposes. Height and weight were measured on admission as part of regular nursing observations.

Individual patient-level data of the dose used, and additional clinical and laboratory data were collected from electronic medical records (EMRs), medication charts, and electronic prescribing data.

Patients were considered opioid naïve if they did not have an opioid dispensed in the 90 days prior to admission to hospital and did not have an opioid as part of their hospital admission medication list. Admission medications were recorded on all patients by pharmacy staff. Discharge medication data were collected from the EMR (Austin Hospital) and discharge medication charts (Northern Hospital).

Data relating to 90-day preadmission, 90−180 days and 180−365 days post-admission opioid dispensing data were

collected from SafeScript, a Victorian government computer software in compliance with obligations under the Privacy and Data Protection Act 2014 (Vic) and the Health Records Act 2001 (Vic)). The SafeScript system records all opioid prescriptions and opioid dispensing in the state of Victoria.

Patients were considered long-term opioid users if they had any opioid dispensed 90—365 days following hospital discharge. To study patients who had continual opioid use long-term following hospital discharge, patients who did not have an opioid dispensed between 90 and 180 days post discharge but did have opioids dispensed 180—365 days post hospital discharge were excluded from the 180—365 days analysis.

Dose equivalency for intravenous (IV) fentanyl and IV morphine was calculated according to the accepted conversion ratio of 1:100.[27] Thus, 10mcg of IV fentanyl was considered equivalent to 1,000mcg (1 mg) of IV morphine.

3.6. Outcome

The primary outcome was the difference in hospital discharge opioid prescription in adult patients who were mechanically ventilated according to treatment with continuous infusion of fentanyl vs. morphine for analgosedation in the ICU.

A key secondary outcome was to compare long-term opioid use according to fentanyl vs. morphine analgosedation in ICU.

Further secondary outcomes related to the identification of risk factors that may be associated with hospital discharge prescription, and long-term use, of opioid medications. Predefined factors examined based on clinical relevance and available evidence were age, sex, height, weight, BMI, Acute Physiology and Chronic Health Evaluation (APACHE) II score, number of chronic health conditions of APACHE II (either 0, 1, 2 or 3 - for definitions see eMethods in the Online Data Supplement), type of admission (surgical vs. medical), creatinine >150 μmol/L in first 24 h of ICU admission, highest creatinine in first 24 h of admission, need for renal replacement therapy, and liver dysfunction in first 24 h (defined as bilirubin >30 μmol/L or alanine transaminase >70 U/L.)

3.7. Statistical analysis

The statistical analysis plan for the original trial was posted online before data collection and locking of the database completion.[23] Given this was a post-hoc analysis limited by the original number of patients randomised to the trial, no power calculations were made.

Categorical variables are reported as counts and percentages, and continuous variables as mean (± standard deviation) or median (interquartile range). Patients were analysed according to randomisation group and according to whether they had opioids prescribed (at discharge) or dispensed (at 90—180 days or 180—365 days post discharge). Sample sizes for each analysis set are indicated. Categorical variables were compared using Fisher's exact test or χ^2 test, and continuous variables using independent student t test, Wilcoxon Rank Sum Test or ANOVA as appropriate. Multivariable analysis was performed by logistic regression adjusted by the following pre-defined variables: centre of enrolment, age, APACHE II score, number of chronic health conditions, surgical vs. medical diagnosis, and total opioid dose in morphine equivalents. The predictive model developed was tested for discrimination and calibration using the Hosmer—Lemeshow goodness-of-fit test. All analyses were performed using STATA (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP) and $p < 0.05$ was considered statistically significant.

4. Results

4.1. Patients

Between July 2019 and August 2020, 681 patients who received mechanical ventilation were enrolled in the ANALGESIC trial. The overall baseline characteristics have been previously published[22] and are presented in eTable 1 in the Online Data Supplement. After exclusions, there were 477 patients available for analysis. Of these, 73 (15.3%) were prescribed opioids at hospital discharge. Fourteen (2.9%) and 11 (2.3%) patients had opioids dispensed 90—180 days and 180—365 days post hospital discharge, respectively (Fig. 1). Baseline characteristics according to treatment group are presented in Table 1.

4.2. Primary outcome

There was no significant difference in the proportion of patients who were prescribed opioids at hospital discharge between treatment groups (16.5% [fentanyl] vs 14.0% [morphine], p = 0.45, Table 2).

4.3. Secondary outcomes

There was no significant difference in the proportion of patients who were dispensed opioids between 90-180 and 180—365 days post hospital discharge (Table 2).

A comparison of patients who were prescribed opioids at hospital discharge with those who were not is presented in Table 3. On univariable analysis, factors associated with decreased risk of hospital discharge of opioids include age >65 and female sex. Factors associated with increased risk were lower APACHE II score, surgical admission, liver dysfunction, shorter mechanical ventilation, and ICU length of stay. After multivariable analysis, only a higher APACHE II score (OR 0.95, 95% CI 0.90—0.99) remained significantly associated with decreased opioid prescription at hospital discharge, whereas having a surgical admission (OR 2.39, 95% CI 1.35—4.23) or one chronic comorbidity (OR 1.95, 95% CI 1.0—3.8) remained associated with increased opioid prescription (Table 4). Hourly or total opioid dose during ICU admission were not associated with hospital discharge opioid prescription.

Data comparing patients who were or were not dispensed opioid between 90-180 days and 180—365 days after hospital discharge are presented in Table 5 and eTable 2 in the Online Data Supplement. Factors associated with long-term opioid use on univariable analysis were creatinine >150 μmol/l, higher creatinine, and liver dysfunction in the first 24 h of ICU admission. Hourly or total opioid dose during ICU admission were not associated with long-term opioid prescription. However, the number of patients who were dispensed long-term opioids was too low to perform any meaningful multivariable analysis.

5. Discussion

5.1. Key findings

In this post-hoc study of the ANALGESIC randomised controlled trial, patients who were opioid naïve at hospital admission and received mechanical ventilation in the ICU were prescribed opioids on hospital discharge at a rate of 15.3%, with no difference between those who received fentanyl infusion vs. morphine infusion for analgosedation. A higher APACHE II score was associated with decreased risk of hospital discharge prescription of opioids whereas having a surgical admission or more chronic co-morbidities increased such risk. Approximately three in every 100
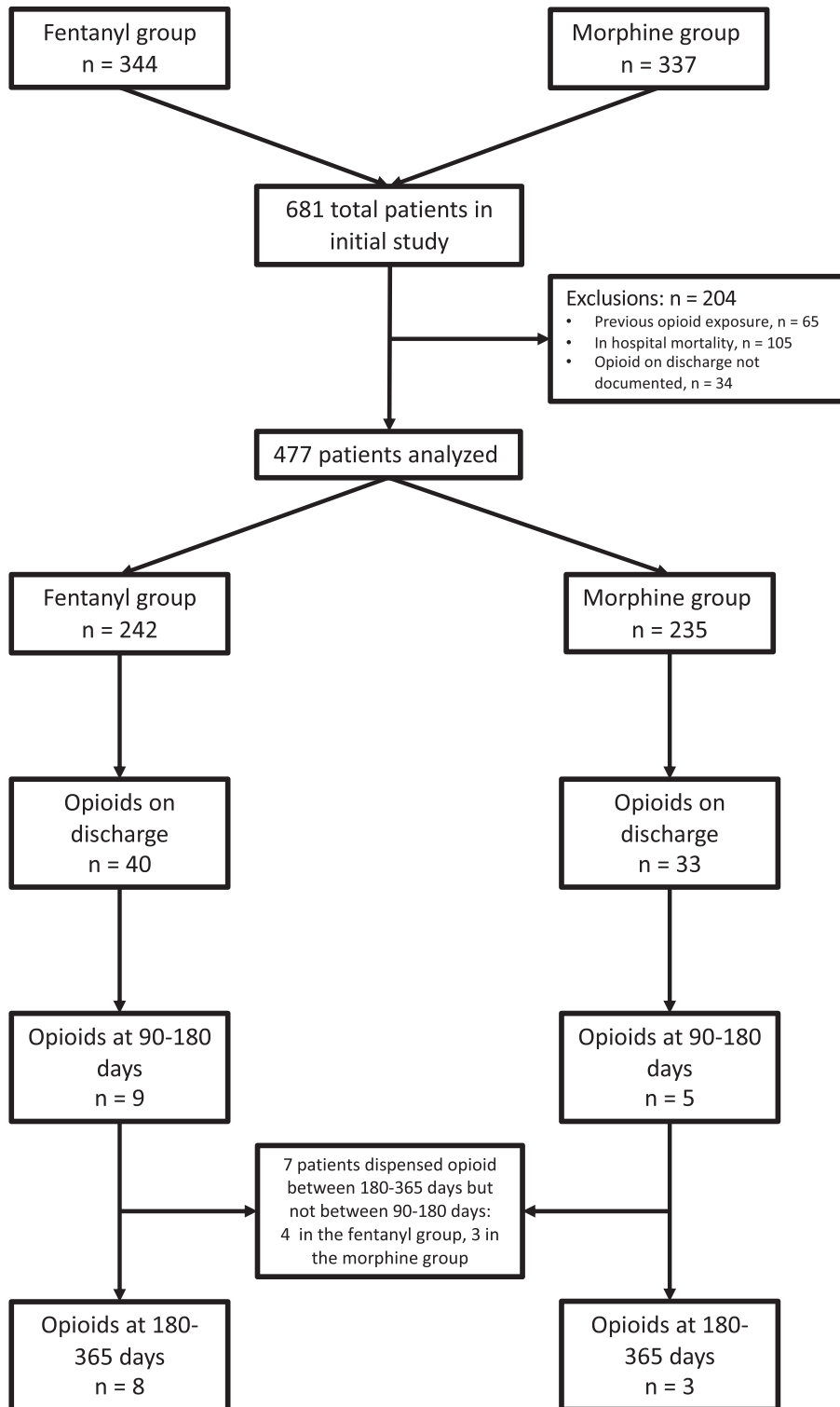
Fig. 1. Flow diagram of patients included in the opioid prescription after analgosedation study.

patients continued to used opioids 90–180 days following hospital discharge and most of these patients continued such opioid use from 180 to 365 days following discharge. On univariable analysis higher creatinine and liver dysfunction in the first 24 h were associated with long-term use of opioids. Hourly or total opioid dose during ICU admission were not associated with hospital discharge or long-term use of opioid medications.

5.2. Comparisons to previous studies

Ours is the first study to compare the differential impact of fentanyl and morphine infusions for analgosedation in adult patients who are mechanically ventilated on discharge prescription of opioids and long-term opioid use. It is also the first study in Australia to explore the relationship between non-cardiac surgery

Table 1
Baseline characteristics and length of stay of study patients.

	Fentanyl (n = 242)	Morphine (n = 235)
Age, yr	59 (43–67)	58 (43–71)
Female, n (%)	84 (34.7)	92 (39.1)
APACHE II[a]	16 (12–20)	17 (12–21)
Type of Admission, n (%)		
Medical	146 (60.3)	143 (60.9)
Elective Surgical	34 (14.1)	29 (12.3)
Emergency Surgical	62 (25.6)	63 (26.8)
ICU Source of Admission, n (%)		
Emergency Department	82 (33.9)	75 (31.9)
Operating Suite	92 (38.0)	90 (38.3)
Ward	35 (14.5)	37 (15.7)
Other	33 (13.6)	33 (14.0)
Number of chronic conditions, n (%)		
0	179 (74)	155 (66.0)
1	50 (20.7)	66 (28.1)
2	11 (4.6)	11 (4.7)
3	2 (0.8)	3 (1.3)
Weight, kg[b]	85 (70–101)	80 (70–96)
Height, cm[c]	170 (162–178)	170 (162–178)
BMI, kg/m²[d]	30 (25–34)	29 (24–33)
ICU LOS, days	3.4 (1.8–7.8)	4.3 (1.9–8.4)
Hospital LOS, days	14.4 (8.2–27.7)	15.1 (8.0–25.8)

APACHE, Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit; LOS: length of stay.

  [a] APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death, e.g., an APACHE II score of 24 means 40% probability of mortality in a medical patient admitted due to a respiratory condition.

  [b] n = 229 (fentanyl), 222 (morphine).

  [c] n =184 (fentanyl), 201 (morphine).

  [d] n = 184 (fentanyl), 200 (morphine).

ICU admissions and long-term opioid use. There are a number of studies predominantly in the US, where per-capita death rates from prescription opioid overdose are 1.6 times that of Australia,[2,4] and Canada which have explored the relationship between ICU admission and long-term opioid use in both opioid exposed and opioid-naïve patients prior to hospital admission.[18–20,28–31] The reported rates of long-term opioid use (up to 12 months) in opioid-naïve adult patients who received mechanical ventilation in ICU varied from 2.6% to 7.6%.[16,18–21] Our findings fall at the lower end of such values.

Wunsch and colleagues[18] studied 25,085 opioid-naïve patients who received invasive mechanical ventilation in Ontario, Canada. Overall, 20% of patients filled a script within 7 days of discharge and 2.6% of patients had long-term opioid use, defined as having a script filled within 7 days of discharge as well as 10 or more prescriptions in total or more than 120 days' total supply in the first year after hospitalisation. Factors associated with such increased long-term use were being a surgical patient, being discharged home with additional care (compared with none) and a longer stay in the ICU. Our findings are broadly aligned with these observations using an alternate definition of long-term opioid use. However, although it is presumed that most patients in the above Canadian study received opioids for analgosedation, the study did not report the percentage exposed to such analgosedation during mechanical ventilation or any details about which opioid was used.

Adil et al.[19] performed a retrospective single centre review of 118 opioid-naïve veteran affairs patients who received mechanical ventilation and at least 12 h of opioid infusion for analgosedation in

Southwest Texas. Patients included were medical, surgical, and cardiovascular. All patients were male, the average duration of opioid infusion was 63 h, and 65% were surgical patients. Although not specifically documented, fentanyl appeared to be the only opioid used. The incidence of patients receiving opioids was 76.3% at three months, 19.5% at six months and 7.5% at 12 months, much higher than in our study. History of alcohol abuse and hospital length of stay were associated with decreased risk of use of opioids at 3 months, and being a surgical patient was associated with increased risk. At 12 months, only increasing age was associated with decreased risk of opioid use. It is possible the high incidence of surgical patients in this study compared with our study accounts for the difference in long-term use of opioids.

Krancevic and colleagues[20] performed a retrospective, multi-centre cohort study of 342 opioid-naïve patients in Michigan who received mechanical ventilation. Almost 80% of patients were admitted to the medical ICU and 98.7% received fentanyl via continuous infusion. Overall, 47.1% of patients were prescribed opioids at discharge and 5.0% had long term opioid use defined as 6 or more prescription in the 12 months following discharge., both significantly higher than in our cohort. Younger age, surgical diagnosis, trauma, malignancy, and increased non-icu length of stay were associated with increased risk of discharge prescription of opioid. Only discharge prescription of opioid medication was associated with increased long-term use of opioids. Given this relationship, it is possible the difference in long-term opioid use in our study is related to a smaller percentage of patients in our cohort who received a discharge opioid prescription. Like our study, this

Table 2
Comparison of opioid use at discharge and post-discharge follow-up according to randomisation group.

	Fentanyl (n = 242)	Morphine (n = 235)	OR (95% CI)	p value
Discharge prescription, n (%)	40 (16.5)	33 (14.0)	1.21 (0.71–2.07)	0.45
90–180 days post discharge, n (%)	9 (3.7)	5 (2.1)	1.78 (0.52–6.85)	0.30
180–365 days post discharge, n (%)[a]	8 (3.4)	3 (1.3)	2.65 (0.63–15.70)	0.22[b]

  [a] n = 238 (fentanyl), 232 (morphine).

  [b] Fisher's exact test.

Table 3
Comparison of patients prescribed opioids vs. no opioids at hospital discharge.

	Yes (N = 73)	No (N = 404)	OR (95% CI)	p value
Age, years	58 (44–64)	59 (43–69)		0.26
Age > 65 n (%)	15 (20.6)	150 (37.1)	0.44 (0.22–0.82)	**0.006**
Female, n (%)	19 (26.0)	157 (38.9)	0.55 (0.30–0.99)	**0.04**
Height, cm[a]	175 (164–180)	170 (162–178)		0.05
Weight, kg[b]	86 (70–107)	82 (70–99)		0.39
BMI, kg/m^{2c}	29 (24–34)	29 (25–33)		0.46
APACHE II[d]	13 (10–19)	17 (13–21)		**< 0.001**
Chronic conditions, n (%)				0.31
0	48 (65.8)	286 (70.8)		
1	23 (31.5)	93 (23.0)		
2	2 (2.7)	20 (5.0)		
3	0	5 (1.2)		
Surgical vs. Medical			2.93 (1.70–5.09)	**<0.001**
Type of admission, n (%)				
Medical	28 (38.4)	261 (64.6)		
Elective surgical	20 (27.4)	43 (10.6)		
Emergency surgical	25 (34.3)	100 (24.8)		
Creatinine > 150 μmol/l in first 24 h, n (%)	22 (30.1)	101 (25.1)	1.29 (0.71–2.29)	0.36
Highest creatinine first 24 h (μmol/l)	102 (76–171)	97 (72–152)		0.60
Need for RRT, n (%)	8 (11.0)	49 (12.1)	0.89 (0.35–2.01)	0.77
Liver dysfunction	37 (50.7)	138 (34.6)	1.94 (1.14–3.31)	**0.009**
Mechanical ventilation (days)	0.9 (0.4–2.7)	1.9 (0.8–5.4)		**<0.001**
Mean hourly opioid dose (ME)	8.8 (3.5–16.6)	6.6 (3.3–13.4)		0.19
Total opioid dose (ME), mg	165 (62–500)	219 (65–675)		0.30
ICU LOS	2.9 (1.7–5.5)	4.1 (2.0–8.5)		**0.02**
Hospital LOS	15.2 (9.2–28.0)	14.4 (8.0–26.1)		0.51

Data presented in median (IQR); APACHE: Acute Physiology and Chronic Health Evaluation; RRT: renal replacement therapy; ME: morphine equivalents; LOS: length of stay.
[a] n = 59 ("yes" group), 326 ("no" group).
[b] n = 71 ("yes" group), 380 ("no" group).
[c] n = 59 ("yes" group), 325 ("no" group).
[d] APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death, e.g., an APACHE II score of 24 means 40% probability of mortality in a medical patient admitted due to a respiratory condition.

study found that total or daily ICU opioid dose was not associated with discharge or long-term opioid use.

Finally, a large retrospective study of over 200,000 patients identified from the Swedish Intensive Care registry over 8 years[16] defined chronic opioid use as at least one prescription in 1–90 days and 91–180 days following ICU admission. In opioid-naïve patients, 4.3% became long-term opioid users. Factors associated with long-term use included increased age, Charlson co-morbidity index ≥1, increased ICU length of stay, and elective and emergency surgery. Factors associated with decreased risk included male sex and higher education level. Importantly, chronic opioid use was associated with an increased risk of 6–18-month mortality after admission in both opioid exposed and opioid-naïve patients.

Table 4
Factors associated with hospital discharge prescription of opioid by multivariable analysis.

Factor	Odds Ratio (95% CI)	p value
Centre[a]	1.5 (0.81–2.80)	0.19
Age	0.99 (0.98–1.01)	0.57
APACHE II[b]	0.95 (0.90–0.99)	0.03
Chronic conditions		
0	Reference	Reference
1	1.95 (1.0–3.8)	0.046
2	0.83 (0.18–3.93)	0.82
3	N/A	N/A
Surgical Admission	2.39 (1.35–4.23)	0.003
Total dose opioid (ME)	1.00 (1.00–1.00)	0.96

APACHE: Acute Physiology and Chronic Health Evaluation; ME: morphine equivalents.
[a] Austin Hospital as referent centre.
[b] APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death, e.g., an APACHE II score of 24 means 40% probability of mortality in a medical patient admitted due to a respiratory condition.

5.3. Implications

Our study implies that the choice of opioid medication for analgosedation in patients who are mechanically ventilated has no impact on either the hospital discharge prescription of opioid medication, or on long-term use of opioid medications. Overall, in our trial, the long-term use of opioid medications in opioid-naïve patents following analgosedation was relatively uncommon. Nevertheless, based on ANZICS CORE data[32] and data from our original trial,[22] this represents over 1000 opioid-naïve patients every year in Australia who continue to use opioids 3–12 months after hospital discharge following ICU admission. It is important to consider that, in most cases, their initial exposure to opioids will occur in the ICU. Finally, our study did not identify any modifiable risk factors for long-term opioid use during ICU admission or any relationship between overall opioid dose within the ICU and long-term opioid use.

5.4. Strengths and limitations

Our study has several strengths. It used data from a large randomised controlled trial comparing fentanyl and morphine for analgosedation. It is the first study to directly compare long-term opioid use in patients randomised to receive fentanyl vs. morphine for analgosedation. The case mix was broad and included general medical, general surgical, liver transplant, neurosurgical, obstetric, and traumatic spinal cord injury patients in two university affiliated ICUs located in distant suburbs of a large metropolitan area. We excluded patients who had been exposed to opioids in the 90 days prior to hospital admission. Our long-term opioid use data and risk factors, and failure to show an ICU dose relationship to long-term opioid use are similar to other studies suggesting a degree of external validity.

Table 5
Comparison of patients dispensed opioids vs. No opioids at 90−180 days post hospital discharge.

	Yes (N = 14)	No (N = 463)	Odds Ratio (95%CI)	p value
Age, years	62 (45−65)	58 (43−69)		0.87
Age > 65 n (%)	3 (21.4)	162 (35.0)	0.51 (0.09−1.95)	0.40[a]
Female, n (%)	4 (28.6)	172 (37.2)	0.68 (0.15−2.39)	0.59[a]
Height, cm[b]	175 (167−178)	170 (162−178)		0.43
Weight, kg[c]	102 (80−118)	82 (70−99)		0.06
BMI, kg/m^{2d}	31 (25−37)	29 (25−34)		0.62
APACHE II[e]	18 (14−25)	16 (12−21)		0.33
Chronic conditions, n (%)				0.12
0	6 (42.9)	328 (70.8)		
1	7 (50.0)	109 (23.5)		
2	1 (7.1)	21 (4.5)		
3	0	5 (1.1)		
Surgical vs. Medical			1.15 (0.33−3.88)	0.79
Type of admission, n (%)				
Medical	8 (57.1)	281 (60.7)		
Elective surgical	2 (14.3)	61 (13.7)		
Emergency surgical	4 (28.6)	121 (26.1))		
Creatinine > 150 μmol/l in first 24 h, n (%)	9 (64.3)	114 (24.7)	5.49 (1.61−21.22)	**<0.001**
Highest creatinine in first 24 h (μmol/l)	181 (118−328)	97 (72−150)		**0.001**
Need for RRT, n (%)	3 (21.4)	54 (11.7)	2.06 (0.36−8.14)	0.23[a]
Liver dysfunction	11 (78.6)	164 (35.8)	6.57 (1.69−37.06)	**0.001**
Mechanical ventilation (days)	1.4 (0.5−3.3)	1.8 (0.7−5.2)		0.52
Mean hourly opioid dose (ME)	9.7 (3.3−19.5)	6.7 (3.3−13.9)		0.51
Total opioid dose (ME), mg	236 (113−500)	203 (63−675)		0.94
ICU LOS	3.7 (11.5)	3.8 (1.8−8.0)		0.75
Hospital LOS	14.9 (7.2−35.2)	14.5 (8.2−26.2)		0.72

Data presented in median (IQR); APACHE: Acute Physiology and Chronic Health Evaluation; RRT: renal replacement therapy; ME: morphine equivalents; ICU: Intensive Care Unit; LOS: length of stay.
[a] Fisher's exact test.
[b] n = 9 ("yes" group),376 ("no" group).
[c] n = 14 ("yes" group), 437 ("no" group).
[d] n = 9 ("yes" group), 375 ("no" group).
[e] APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death, e.g., an APACHE II score of 24 means 40% probability of mortality in a medical patient admitted due to a respiratory condition.

We acknowledge several limitations. First, this is a post-hoc analysis of an unblinded clinical trial. However, hospital discharge prescription by ward doctors and long-term prescription and dispensing of opioids in the community are unlikely to be affected by knowledge of the agent the patient received in the ICU. Second, the number of patients who received opioids long-term was too low to perform any meaningful multivariable analysis. The results gained from univariable analysis are hypothesis-generating and require further exploration. Third, we have no data on the type and dose of opioids prescribed after the infusion of opioid was complete in ICU prior to ICU discharge, or on the wards post-ICU discharge, which may have confounded our results. However, we aimed to compare fentanyl and morphine infusions as analgosedation given that these infusions were the first opioid exposure in most of our patients. Fourth, we only explored whether the patients were prescribed opioids at hospital discharge or whether opioids were dispensed in the long term. We have no data on dose or frequency of opioid use in the short-term or long-term post discharge. Fifth, we only included data on patients originally included in the ANALGESIC trial. We have no comparable data on long term opioid use of those patients who were excluded from the original trial because they did not receive opioid infusions in ICU.

6. Conclusion

In adult patients who were mechanically ventilated and received either fentanyl or morphine for analgosedation with a randomised controlled trial, approximately one in seven received a discharge medication of opioids and three in a hundred became opioid-dependent. There was no difference in hospital discharge or long-term use of opioid medications according to which agent was used for analgosedation or dose of opioids prescribed for analgosedation in ICU. Surgical admission, lower APACHE II score and having one chronic co-morbidity were associated with hospital discharge prescription of opioids. No modifiable ICU risk factor for long-term opioid use could be identified. These observations provide indirect reassuring evidence that choice or dose of opioid-based analgosedation for mechanical ventilation is not a major contributor to long-term opioid dependence.

Author contributions

AC: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, writing − original draft, writing − review and editing.
AG: conceptualisation, formal analysis, investigation, methodology, project administration, writing − original draft, writing − review and editing.
VH: data curation, formal analysis, writing − review and editing.
ASN: data curation, formal analysis, investigation, methodology, writing − original draft, writing − review and editing.

Data availability statement

The data that support the findings of this study are available from the corresponding author, AC, upon reasonable request.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ary Serpa Neto reports a relationship with Drager that includes: consulting or advisory and speaking and lecture fees. Ary Serpa Neto is an Associate Editor of Critical Care and Resuscitation (voluntary role) If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.11.004.

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