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Alfentanil versus fentanyl for emergency department rapid sequence induction with ketamine: A-FAKT, a pilot randomized trial

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ABSTRACT

Background: Fentanyl is often administered during rapid sequence induction of anesthesia (RSI) in the emergency department (ED) to ameliorate the hypertensive response that may occur. Due to its more rapid onset, the use of alfentanil may be more consistent with both the onset time of the sedative and the commencement of laryngoscopy. As such, we compared the effect of alfentanil and fentanyl on post-induction hemodynamic changes when administered as part of a standardized induction regimen including ketamine and rocuronium in ED RSI.
Methods: This was a double-blind pilot randomized controlled trial of adult patients requiring RSI in the ED of three urban Australian hospitals. Patients were randomized to receive either alfentanil or fentanyl in addition to ketamine and rocuronium for RSI. Non-invasive blood pressure and heart rate were measured immediately before and at two, four, and six minutes after induction. The primary outcome was the occurrence of at least one post-induction systolic blood pressure outside the pre-specified range of 100-160mmHg (with adjustment for patients with baseline hypertension). Secondary outcomes included hypertension, hypotension, hypoxia, first-pass intubation success, 30-day mortality, and the pattern of hemodynamic changes.
Results: A total of 61 patients were included in the final analysis (31 in the alfentanil group and 30 in the fentanyl group). The primary outcome was met in 58% of the alfentanil group and 50% of the fentanyl group (difference 8%, 95% confidence interval: -17% to 33%). The 30-day mortality rate, first-pass success rate, and incidences of hypertension, hypotension, and hypoxia were similar between the groups. There were no significant differences in systolic blood pressure or heart rate between the groups at any of the measured time-points.
Conclusion: Alfentanil and fentanyl produced comparable post-induction hemodynamic changes when used as adjuncts to ketamine in ED RSI. Future studies could consider comparing different dosages of these opioids.

1. Introduction

Rapid sequence induction of anesthesia (RSI) is frequently used for definitive airway management in the emergency department (ED). Ketamine is increasingly used as the sedative drug in this setting as it reduces the risk of hypotension [1], an adverse event associated with increased mortality [2]. However, ketamine can lead to hypertension with reported rates ranging from 40% to 69% in recent prospective studies [3,4], which may in turn worsen patient outcomes through mechanisms such as accelerated hemorrhage and myocardial ischemia [5].

Fentanyl is sometimes administered prior to intubation to attenuate the hypertensive response that may result from a combination of the direct effect of ketamine, and the sympathetic response to laryngoscopy and intubation [6-9]. Although the adjunctive administration of fentanyl

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at induction may reduce the risk of hypertension following RSI with ketamine, there is a dose-dependent risk of hypotension [4,10].

Alfentanil is a fentanyl analogue with a faster onset (<60 s) and shorter time to peak effect (<90 s) than fentanyl (60 to 120 s and five minutes respectively) [11]. When clinicians decide to use an opioid to manage potential peri-induction hypertension, alfentanil may be temporally better suited to attenuate the associated hypertensive response given that ketamine has an onset time of 30 s and the first intubation attempt typically begins approximately two minutes after the commencement of induction [1]. Moreover, the shorter duration of effect of alfentanil may mitigate the risk of hypotension resulting from ongoing opioid action after the abatement of sympathetic stimulation [12,13].

Previous studies comparing alfentanil to fentanyl as induction adjuncts did not use ketamine as the sedative agent and were conducted in the setting of elective [14-18], obstetric [19], trauma [20], and pediatric anesthesia [21]. In these settings, co-induction with an opioid was linked to more favorable peri-intubation hemodynamics [14,17], and some studies observed greater stability with alfentanil than fentanyl due to either less pronounced hypotension or hypertension [15,17]. In different studies, alfentanil was found to produce similar [21], improved [16], or worse intubating conditions than fentanyl [19]. It would be useful to determine if alfentanil is better suited than fentanyl as an induction adjunct to ketamine for ED RSI in terms of hemodynamic changes and intubating conditions.

The aim of this study was to provide pilot data on post-induction hemodynamic changes seen when an equianalgesic dose of alfentanil or fentanyl is administered immediately before ketamine and rocuronium in an ED RSI protocol. The secondary aims were to compare intubating conditions and 30-day mortality.

2. Methods

2.1. Study design and setting

This double-blind randomized controlled trial was conducted between July 20, 2022, and February 13, 2023, in the ED of three urban teaching hospitals in Sydney, Australia: Liverpool Hospital (academic tertiary trauma center, 83,000 annual ED presentations), Campbelltown Hospital (community hospital, 85,000 annual ED presentations), and Northern Beaches Hospital (community hospital, 68,000 annual ED presentations). Ethical approval was granted by the South Western Sydney Local Health District Human Research Ethics Committee (2021/ETH12297) under a waiver of informed consent. The patient or their substitute decision-maker was subsequently informed of their inclusion in the study, and consent was obtained for the use of their data. This trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621001764820).

2.2. Participant selection

All adult patients (≥18 years old) who required RSI were screened for eligibility. Exclusion criteria were the need for an alternative induction regimen as deemed by the treating clinician, allergy to study drugs, known COVID-19 infection, unavailability of a specialist emergency physician trained in the protocol, or an overwhelmed ED as deemed by the treating physician. Patients with a systolic blood pressure (SBP) <100 mmHg or a shock index (heart rate [HR] / SBP) >1.0 were also excluded as previous data suggests these patients are less likely to develop post-intubation hypertension and may be at increased risk of shock [3].

2.3. Interventions

Patients were randomly allocated to either alfentanil or fentanyl using sequentially numbered, opaque sealed envelopes based on a computer-generated list with blocks of ten stratified for the three study sites. Each envelope contained instructions for drawing up either 200 μg fentanyl (Fentanyl B. Braun; B. Braun, Bella Vista, Australia) or 1000 μg alfentanil (Alfentanil GH; Generic Health, Box Hill, Australia) with water for injection into a 20 mL syringe so that the opioids would have theoretically equipotent concentrations of 10 μg/mL and 50 μg/mL respectively.

For each patient, the next sealed envelope in numerical sequence at the study site was opened by two non-treating clinicians who drew up the study opioid according to the enclosed instructions away from the treatment area, before labelling the syringe with the corresponding number. They then provided the labelled but masked syringe to the treating team and had no further involvement in the study. Patients were concurrently prepared for intubation in accordance with standard clinical practice, including continuous heart rate, pulse oximetry, waveform capnography, three-lead electrocardiography, and non-invasive blood pressure (NIBP) monitoring. Standardized checklists directed clinicians to optimize positioning, vascular access, oxygenation, and hemodynamics, although the method of achieving these was at clinician discretion and no specific resuscitation endpoints were mandated prior to intubation. The template for checklists used at the study sites can be found in the supplementary files.

The treating clinician calculated the study opioid dose by equating the volume administered to the volume of open label 10 μg/mL fentanyl that they would use for the enrolled patient, although they were aware that the masked syringe may instead contain alfentanil at an equipotent concentration. Induction was commenced by the intravenous administration of the calculated volume of the study opioid, followed immediately by intravenous boluses of ketamine 0.5–2.0 mg/kg and rocuronium 1.5–2.0 mg/kg. The three medications were administered as rapid sequential boluses.

Tracheal intubation was first attempted at least sixty seconds after completion of the rocuronium bolus with subsequent patient management at the discretion of the treating clinician. Post-intubation sedation was discouraged until the primary outcome data were collected at six minutes post-induction, unless in conflict with patient care, and subsequently consisted of standardized infusions of intravenous fentanyl and propofol.

2.4. Data collection

Dedicated, trained staff members collected all ED data using a standardized paper case-report form. Data collected included demographics, co-morbidities, regular medications, indication for intubation, baseline physiology, and pre-intubation interventions including oxygenation techniques, use of any vasopressor or intravenous fluids, as well as the administered doses of the study opioid, ketamine, and rocuronium.

Predictors of airway difficulty, intubator experience, use of cricoid pressure, laryngoscope type, need for external laryngeal manipulation and bougie or stylet use were also recorded, as were the need for manual in-line stabilization, number of intubation attempts, and the Cormack-Lehane grade of view. The first intubation attempt was made by a practicing specialist emergency medicine physician or resident. An intubation attempt was defined as one insertion of the laryngoscope past the teeth by a single operator.

Heart rate, NIBP, and oxygen saturations (SpO_2) were recorded immediately before induction to set a baseline and at two-minute intervals thereafter until six minutes after the commencement of induction. The effectiveness of blinding was assessed by recording the treating clinician's impression of which opioid was used.

Follow-up data, including the final diagnosis, vital status, and duration of mechanical ventilation at 30 days post-intubation, were collected from the patient's electronic medical record. All data were collated and managed in a bespoke Research Electronic Data Capture database hosted by the University of New South Wales [22,23].

2.5. Outcomes

The primary outcome was defined as the occurrence of at least one recorded SBP outside the range of 100-160 mmHg within six minutes of induction. For patients with a baseline SBP >160 mmHg, the upper limit of this range was changed to equal a 20% increase from their baseline.

There is no consensus definition of hemodynamic disturbance in the context of emergent intubation. The definition commonly used in the anesthetic literature, a change of >20% from baseline, may not be suitable in the ED setting as such a change towards normality may not be clinically relevant and may even be desirable (e.g., a rise in SBP from 104 mmHg to 130 mmHg represents an increase of 25%, but likely reflects improvement rather than a hypertensive emergency).

Although hypotension after intubation is often defined as SBP <90 mmHg in the literature, there is evidence that an SBP <100 mmHg at any time in the ED is an independent predictor of in-hospital mortality [24,25], and in the setting of brain injury, even higher thresholds may be relevant [26]. For hypertension, previous works regarding emergent intubation have used the threshold of SBP >160 mmHg [27,28], concordant with the anesthetic literature. Consequently, this study used 100 mmHg and 160 mmHg as the limits of normality as they appear to represent reasonable targets in a heterogenous ED patient mix.

Immediate secondary outcomes included the incidence of hypertension (SBP >160 mmHg), hypotension (SBP <100 mmHg), and hypoxia (SpO_2 ≤ 93%) occurring within six minutes of induction, the pattern of HR and SBP changes over this time, first-pass intubation success, and the laryngoscopic view obtained during the first intubation attempt. Laryngoscopic view was dichotomized as good (Cormack-Lehane grade I/II) and poor (Cormack-Lehane grade III/IV) due to the low incidence of grade III/IV views.

Delayed secondary outcomes included ventilator-free days during the 30 days following intubation and 30-day mortality. It was defined a priori that patients discharged from hospital at their baseline level of function within 30 days of intubation were deemed alive for the assessment of 30-day mortality.

2.6. Analysis

A sample size of 60 patients (30 in each arm) was determined based on this being the minimum required to generate results that represent appropriate estimates of effect size for the purpose of informing future study [29]. Due to prior experience demonstrating that some enrolled participants would not undergo intubation [4], and to guarantee our target sample size, it was decided in advance that recruitment would continue until at least 60 participants had completed the protocol to the point of collection of the primary outcome.

All outcomes were assessed through a modified intention-to-treat approach which excluded participants who had no available primary outcome data. Categorical data were compared with the chi-square test. Differences between groups over time were compared with two-way mixed ANOVA, with the Greenhouse-Geisser correction applied where the sphericity assumption was violated per Mauchly's test. Due to low numbers in this pilot study, further formal hypothesis testing was not conducted, and results are presented as descriptive statistics with between-group differences and the corresponding 95% confidence intervals (CIs).

The level of statistical significance was set at 0.05. ANOVA was performed using R version 4.2.3 (R Core Team, Vienna, Austria) with the rstatix package. All other analyses were performed using Stata version 17.0 (StataCorp, Texas, United States).

As the alfentanil and fentanyl syringes were visually identical, patients and all members of the treating team were blinded to the randomization. Additionally, the research staff were blinded until the data analysis was complete.

3. Results

3.1. Characteristics of study subjects

As a result of the enrollment methods, of the 120 patients who were screened for eligibility, 71 were enrolled and randomized with outcome data being available for 61 patients (31 in the alfentanil group and 30 in the fentanyl group) as shown in Fig. 1.

3.2. Results

Baseline characteristics are shown in Table 1 and Table S1. Patients in the alfentanil group had higher rates of previous cerebrovascular disease, were less likely to have a bougie used or a specialist emergency physician as the intubator during the first intubation attempt, and received a slightly larger median rocuronium dose. Baseline characteristics and peri-intubation interventions were otherwise similar between the groups. Drug overdose was the most common indication for intubation in both groups. No patients received additional sedation within six minutes of induction, and all were intubated within two attempts. All but one first intubation attempt was performed using a standard geometry CMAC video laryngoscope.

The primary outcome and immediate secondary outcomes are summarized in Table 2. The primary outcome was met by a similar proportion of patients in both groups (58% in the alfentanil group versus 50% in the fentanyl group, difference 8%, 95% CI: −17% to 33%). All immediate secondary outcomes listed in Table 2, including the incidence of hypertension and hypotension within six minutes of induction, were also similar between groups.

Figs. 2 and 3 depict the distribution of SBPs and HRs respectively in each group from induction to six minutes post-induction. There were no significant differences in mean SBP or mean HR between the groups at any of the recorded time-points (summary statistics and between-group differences with 95% CIs are listed in Table S2). The individual patient data are presented in Fig. 4. Visual inspection of this figure indicates that while alfentanil did not reduce the risk of hypertension, the magnitude of the hypertension (maximum SBP) that occurred appears lower than that with fentanyl and the range of blood pressures seen (i.e., the difference between the maximum and minimum) appears smaller.

To investigate this finding, we performed an exploratory post-hoc comparison of the post-induction SBP and HR range between fentanyl and alfentanil using a Wilcoxon rank-sum test. We examined both the raw range, and a scaled range to account for differences in baseline SBP and HR (range/baseline value). The SBP and HR range (raw or scaled) was smaller in the alfentanil group (Table S3, Fig. S1).

The 30-day mortality rate was similar between the groups at 16% (five deaths) in the alfentanil group and 20% (six deaths) in the fentanyl group (difference −4%, 95% CI: −23% to 15%), as was the number of ventilator-free days during the 30 days following intubation (median 28 [interquartile range 20 to 29] versus 28.5 [interquartile range 20 to 29], median difference 0, 95% CI: −5 to 5).

3.3. Assessment of blinding

The administered opioid was correctly predicted in 34 of the 61 cases (proportion 56%, 95% CI: 43% to 67%), suggesting effective blinding.

4. Discussion

In this pilot randomized trial of ED RSI with ketamine and rocuronium, the administration of alfentanil, as compared to fentanyl in equianalgesic doses, did not significantly alter the proportion of patients who had at least one recorded SBP outside the pre-specified range during the six minutes following induction. Both groups had

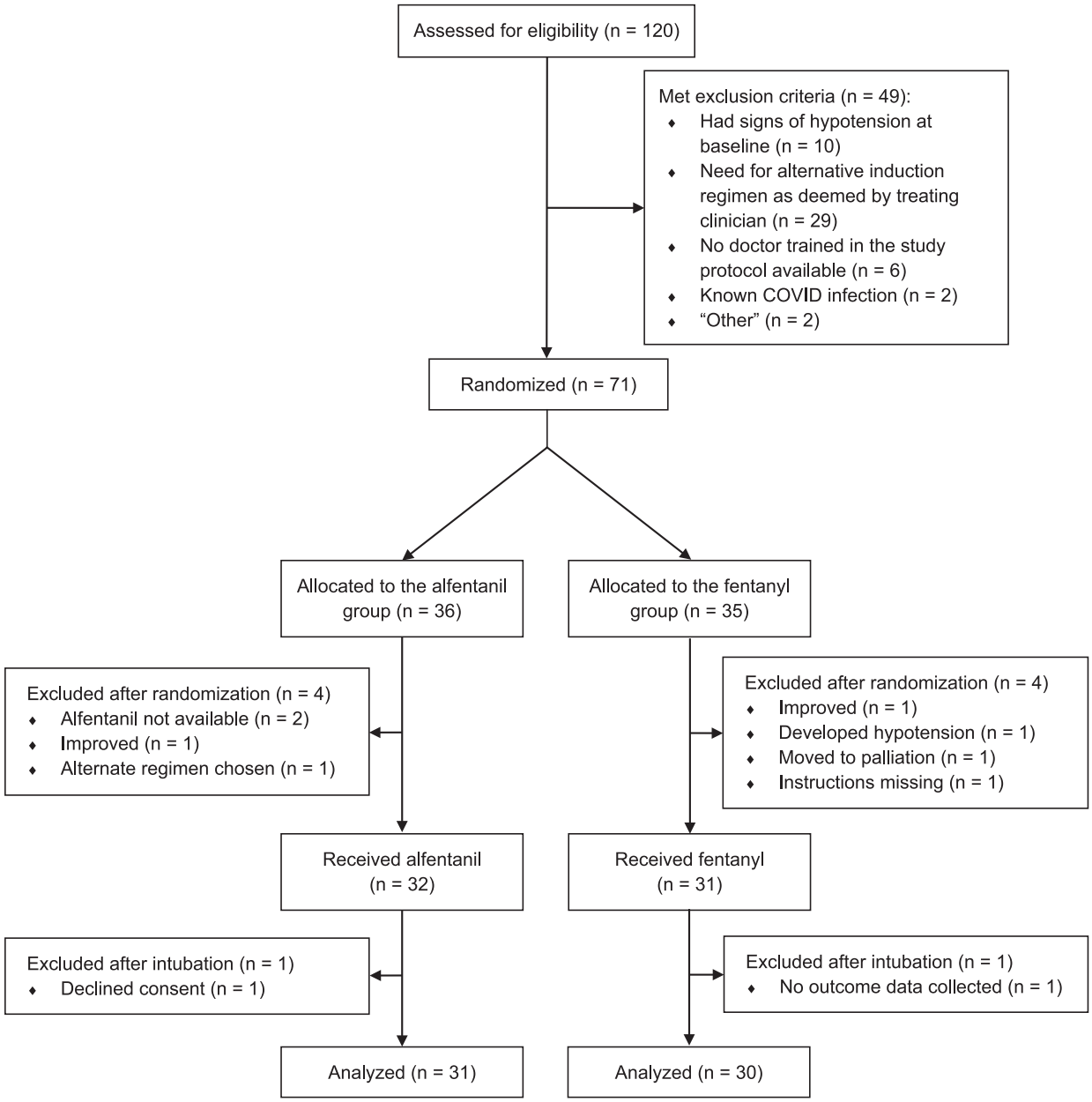

Fig. 1. Patient flow diagram for the trial.

similar hemodynamic parameters at each of the measured post-induction time-points.

Our findings are consistent with two previous studies of emergent intubation where etomidate was used as the primary sedative agent. Pouraghaei et al. [20] studied the use of alfentanil, fentanyl, and sufentanil in ED trauma patients sedated with etomidate and found no significant differences in mean SBP or HR at three, five, or ten minutes after intubation. Rout and Rocke [19] found comparable mean SBPs and HRs between groups post-induction and post-intubation when they investigated the use of alfentanil and fentanyl in hypertensive women who required emergency Cesarean sections. The elective anesthesia literature has also reported similar congruity when comparing the two opioids as adjuncts to propofol or thiopentone [14-16,18,21]. One exception is the study by Salihoglu et al. [17], where higher SBPs were observed in the fentanyl group at two-minutes post-induction but not at any other time-points. However, this may be explained by deviations from typical opioid pharmacokinetics in their study population of morbidly obese adults. To the best of our knowledge, our study is the first to investigate the hemodynamic effects of alfentanil and fentanyl as adjuncts to ketamine in a hemodynamically stable ED population requiring intubation for trauma or medical indications.

The potential severity of hypertension (the highest of the maximum post-induction SBPs) appeared to be lower with alfentanil than with fentanyl and our post-hoc assessment suggested that alfentanil is associated with less variation in peri-intubation hemodynamics. However, this may have arisen from sampling variability and seems to have limited clinical significance given that there were no differences between the groups in 30-day mortality or ventilator-free days during the 30 days following intubation. Indeed, while hypertension has been associated with adverse outcomes in certain conditions such as subarachnoid and intracerebral hemorrhage [30], the clinical significance of an

Table 1
Baseline characteristics of study participants and peri-intubation interventions administered.

Characteristic	Alfentanil group (n = 31)	Fentanyl group (n = 30)
Age, years, median [IQR]	50 [39 to 63]	58 [33 to 70]
Sex, number (%)*		
Male	19 (61)	18 (60)
Female	12 (39)	11 (37)
Other	0 (0)	1 (3)
Estimated body weight, kg, median [IQR]	80 [70 to 90]	80 [70 to 90]
Co-morbidities, number (%)		
Hypertension	8 (26)	12 (40)
Diabetes	5 (16)	8 (27)
COPD / asthma	5 (16)	7 (23)
Epilepsy	2 (6)	1 (3)
Ischemic heart disease	5 (16)	5 (17)
Cerebrovascular disease	6 (19)	0 (0)
Active cancer	0 (0)	3 (10)
Other	16 (52)	17 (57)
None	7 (23)	4 (13)
Co-morbidities unknown	1 (3)	0 (0)
Indication for intubation, number (%)*		
Overdose	12 (39)	10 (33)
Reduced consciousness (other medical cause)	6 (19)	5 (17)
Stroke / intracranial hemorrhage	3 (10)	6 (20)
Acute respiratory failure (medical)	2 (6)	3 (10)
Seizure	2 (6)	2 (7)
Other medical indication	4 (13)	2 (7)
Trauma	2 (6)	2 (7)
Pre-intubation vasopressor and IV fluid use		
Vasopressor running at time of induction, number (%)	3 (10)	1 (3)
Received IV fluid before induction, number (%)	18 (58)	23 (77)
Volume of IV fluid administered before induction, mL, median [IQR]	250 [0 to 500]	250 [100 to 500]
Doses of medications administered		
Volume of opioid, mL/kg, median [IQR]	0.10 [0.10 to 0.15]	0.10 [0.10 to 0.10]
Ketamine dose, mg/kg, mean (SD)	1.12 (0.39)	1.24 (0.37)
Rocuronium dose, mg/kg, median [IQR]	2.00 [1.67 to 2.14]	1.77 [1.50 to 2.00]
Baseline physiology		
SBP, mmHg, mean (SD)	140 (24)	142 (26)
DBP, mmHg, mean (SD)	89 (23)	85 (16)
Heart rate, beats per minute, mean (SD)	99 (25)	93 (25)
SpO_2 (%), median [IQR]	100 [98 to 100]	100 [99 to 100]
Glasgow Coma Scale, median [IQR]	6 [3 to 7]	7 [4 to 9]
Respiratory rate (breaths per minute), mean (SD)	20 (8)	20 (8)
Intubation characteristics for first attempt, number (%)		
Intubation predicted to be difficult	10 (32)	5 (17)
Intubator performed >100 prior intubations	12 (39)	17 (57)
Intubator performed 10–100 prior intubations	19 (61)	11 (37)
Intubator performed <10 prior intubations	0 (0)	2 (7)
Intubator was a specialist emergency physician	2 (6)	9 (30)
Intubator was an emergency resident	29 (94)	21 (70)
Treating clinician was an emergency specialist	24 (77)	29 (97)
Treating clinician was an emergency resident	7 (23)	1 (3)
Bougie used	26 (84)	30 (100)
Stylet used	2 (6)	0 (0)
Cricoid pressure applied	1 (3)	1 (3)
External laryngeal manipulation used	6 (19)	12 (40)
Manual in-line stabilization used	1 (3)	1 (3)
Video laryngoscopy used, standard geometry	31 (100)	29 (97)
Direct laryngoscopy used, Miller blade	0 (0)	1 (3)

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; IV, intravenous; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, oxygen saturation.
* Percentages may not add to 100% due to rounding.

Table 2
Primary and secondary outcomes, number (%).

Variable	Alfentanil group (n = 31)	Fentanyl group (n = 30)	Absolute risk difference (%, 95% CI)
Primary outcome*	18 (58)	15 (50)	8 (−17 to 33)
Hypoxia†	7 (23)	3 (10)	13 (−6 to 31)
Hypotension‡	9 (29)	7 (23)	6 (−16 to 28)
Hypertension§	13 (42)	12 (40)	2 (−23 to 27)
First-pass success	25 (81)	28 (93)	−13 (−29 to 4)
Good laryngoscopic view on first attempt¶	26 (84)	29 (97)	−13 (−27 to 2)

Abbreviations: CI, confidence interval.
* The primary outcome was met in patients with a baseline SBP ≤160 mmHg if they had any recorded systolic blood pressure (SBP) outside the range of 100-160 mmHg within six minutes of induction, and in patients with a baseline SBP >160 mmHg if they had any recorded SBP <100 mmHg or any recorded SBP that represented a > 20% increase from baseline within six minutes of induction.
† Hypoxia refers to any recorded oxygen saturation ≤ 93% within six minutes of induction.
‡ Hypotension refers to any recorded SBP <100 mmHg within six minutes of induction, regardless of baseline SBP.
§ Hypertension refers to any recorded SBP >160 mmHg within six minutes of induction, regardless of baseline SBP.
¶ Good laryngoscopic view refers to a Cormack-Lehane grade I/II view.

elevated SBP at a single isolated time-point is uncertain so our findings should only be treated as hypothesis-generating.

Although the inclusion of an opioid in the RSI regimen increases the cognitive load on clinicians and the risk of complications such as respiratory depression if given too early, the practice appears to reduce the rate and severity of peri-intubation hypertension. In the randomized trial by Ferguson et al. [4], 69% of patients who received standardized weight-based doses of ketamine and rocuronium without an opioid for ED RSI had a recorded SBP >150 mmHg during the ten minutes following induction, compared to 55% of patients in the group where fentanyl was added to the regimen. This is consistent with the anesthetic literature, where alfentanil and fentanyl have been shown to attenuate immediate post-intubation hypertension when either is added to the classic combination of a sedative and a neuromuscular blocking agent [14,17].

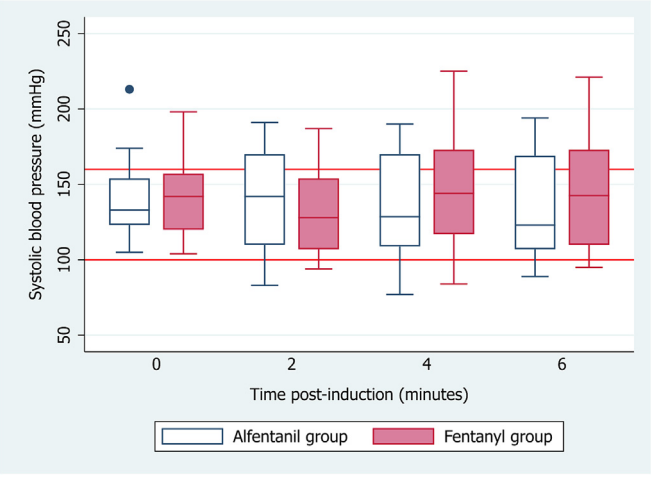

Fig. 2. Box plot of systolic blood pressure at induction and at two-minute intervals thereafter until six minutes, by group. Data obtained from 31 patients in the alfentanil group (median dose = 5 μg/kg) and 30 patients in the fentanyl group (median dose = 1 μg/kg).

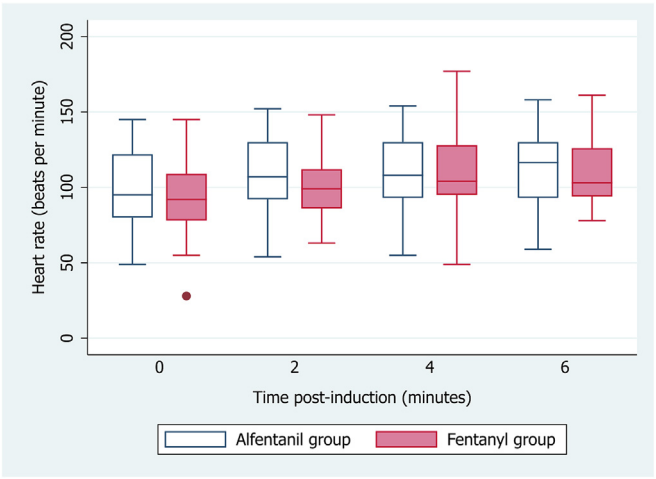

Fig. 3. Box plot of heart rate at induction and at two-minute intervals thereafter until six minutes, by group. Data obtained from 31 patients in the alfentanil group (median dose = 5 μg/kg) and 30 patients in the fentanyl group (median dose = 1 μg/kg).

We equated fentanyl and alfentanil in a 1:5 dose ratio based on expert consensus amongst anesthesiologists that this represents equianalgesic doses, a claim substantiated by anesthetic textbooks [31], but this might not have produced equipotent hemodynamic effects. Previous studies comparing alfentanil and fentanyl in doses larger than those used in this study have proposed that such equipotency may instead occur at ratios between 1:6 and 1:9 [14,15], albeit with limited generalizability because the dose-response curves of fentanyl and alfentanil seem to be non-parallel which implies that the true ratio may vary with dosage [32]. However, it remains possible that alfentanil was underdosed relative to fentanyl in this study and consequently, that its sympatholytic effects were understated.

The doses of fentanyl and alfentanil used in this study were relatively low (equivalent median dose to fentanyl 1 μg/kg), possibly due to the treating physicians' concerns regarding potential hypotension. In the literature, this dose is typically reserved for elderly patients or patients with hemodynamic compromise [13,33], as doses up to 5 μg/kg may be required to abolish the sympathetic response in healthy young adults [34]. Previous studies of pre-hospital RSI have demonstrated favorable hemodynamic outcomes with an induction regimen of fentanyl 3 μg/kg and ketamine 2 mg/kg in non-shocked trauma patients [13,33], although the use of complete-case analysis may have resulted in under-reporting of hypotension due to differential information bias. With regard to alfentanil, doses between 20 and 40 μg/kg have been shown to attenuate the sympathetic response when used with ketamine 1 mg/kg in patients undergoing elective operations [35]. While these studies were in different patient populations, future studies of hemodynamically stable ED patients should consider protocolizing the use of these larger opioid doses given that the majority of patients who met the primary outcome in this study did so via hypertension.

No difference was seen in the adequacy of intubating conditions, conflicting with a randomized controlled trial conducted by Jabbour-Khoury et al. [16], in which alfentanil produced better intubating conditions than fentanyl when used with propofol for induction. However, their induction regimen did not include neuromuscular blockade, whereas high-dose rocuronium (>1.5 mg/kg), which has been shown to minimize the risk of inadequate or slow paralysis [36,37], was used in our cohort and is the likely reason for this discrepancy. Additionally, the lower rates of bougie use and specialist emergency physician supervision, and more first attempts by an inexperienced laryngoscopist may have negatively affected first-pass success in the alfentanil group [38].

The first-pass intubation success rate was consistent with those found in large registry studies. Alkhouri et al. [39] reported a rate of 84.3% in a study of 3710 intubations performed across 43 EDs in Australia and New Zealand, and Brown et al. [40] reported a rate of 85% for RSI in their international study of 17,583 ED intubations.

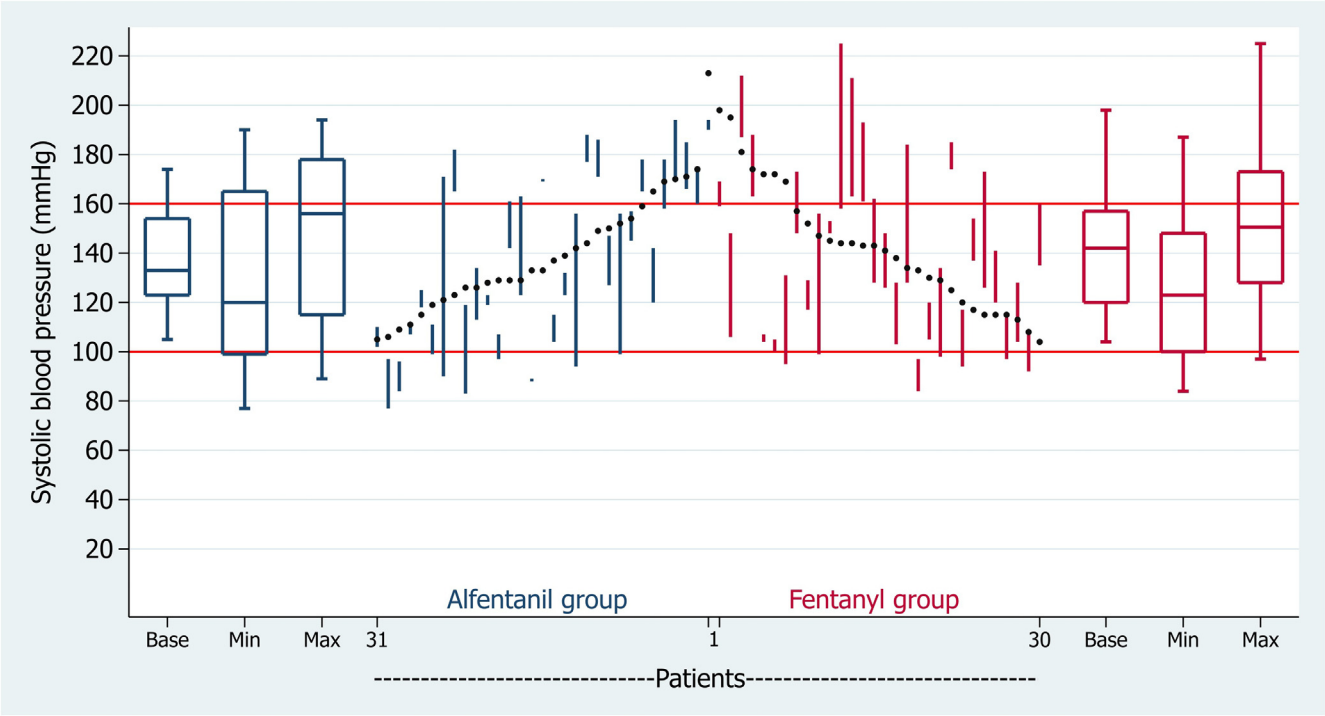

Fig. 4. Changes in systolic blood pressure of individual patients. Parallel line plot of the maximum and minimum systolic blood pressure recorded in each individual patient during the first six minutes after induction (extremes of the vertical lines) with their corresponding baseline systolic blood pressure (solid black dots). Box plots flanking the main plot show the baseline (Base), minimum (Min), and maximum (Max) systolic blood pressure in each group during this period.

Hypoxia occurred more frequently in our study cohort than in larger studies of emergent intubation [41,42]. Apart from the varying definitions of hypoxia, this discrepancy may have also arisen from sampling variability compounded by our small sample size, hypoxia being uncommon, and our patients receiving an opioid during induction. Although the rapid sequential administration of boluses during induction should limit the degree of opioid-induced hypoventilation that occurs before the onset of other medications, this possibility cannot be excluded.

4.1. Limitations

Our study has several important limitations. Firstly, our results should only be viewed as hypothesis-generating rather than conclusive given a small sample size befitting a pilot study. Secondly, the local preparation of study opioids could have resulted in unintentional unblinding. Thirdly, hemodynamic data was only collected until six minutes post-induction so subsequent differences may have been missed. Fourthly, measurement error may have arisen from the use of NIBP, but this aligns with standard clinical practice and should have limited impact on between-group comparisons. Fifthly, non-consecutive recruitment may have led to selection bias, which limits the generalizability of our findings. Sixthly, the non-standardized ketamine dosing is a potential confounder, as not all patients received doses >1 mg/kg. Finally, our primary outcome is not patient-centered, although it is arguably clinically relevant.

5. Conclusions

This study suggested that the adjunctive use of alfentanil compared to fentanyl with ketamine and rocuronium in ED RSI resulted in similar early post-induction hemodynamic changes. The two opioids produced comparable intubating conditions and resulted in similar 30-day mortality. Future studies should consider protocolizing the use of larger opioid doses.

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Prior presentations

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Author contributions

IF conceived the study. IF & MM designed the trial. IF obtained ethical approval and trial registration. IF, AB, BB, KL & JG undertook recruitment at participating centers. IF, YZ, AB, BB, KL & JG managed the data, including quality control. YZ and MM provided statistical analysis. YZ drafted the manuscript and all authors contributed to revision and approval of the final version. IF takes responsibility for the paper as a whole.

CRediT authorship contribution statement

Yichen Zhang: Visualization, Investigation, Formal analysis, Data curation, Writing – review & editing, Writing – original draft. **Matthew Miller:** Supervision, Methodology, Formal analysis, Writing – review & editing. **Alexander Buttfield:** Resources, Project administration, Investigation, Data curation, Writing – review & editing. **Brian Burns:** Resources, Project administration, Investigation, Data curation, Writing – review & editing. **Kimberley Lawrie:** Investigation, Data curation, Writing – review & editing. **James Gaston:** Investigation, Data curation, Writing – review & editing. **Ian Ferguson:** Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization, Writing – review & editing.

Declaration of competing 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2024.07.027.

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