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REVIEW ARTICLE

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Does the addition of fentanyl to ketamine improve haemodynamics, intubating conditions or mortality in emergency department intubation: A systematic review

Ian Ferguson[1,2,3] | James Bliss[1,2] | Anders Aneman[3,4]

[1]Emergency Department, Liverpool Hospital, Liverpool, New South Wales, Australia

[2]Greater Sydney Area HEMS, Ambulance NSW, Sydney, New South Wales, Australia

[3]South West Sydney Clinical School, University of New South Wales, Sydney, New South Wales, Australia

[4]Department of Intensive Care Medicine, Liverpool Hospital, Sydney, New South Wales, Australia

Correspondence
Ian Ferguson, Emergency Department, Liverpool Hospital, Liverpool, NSW, Australia.
Email: ianferguson@doctors.org.uk

Abstract

Background: Ketamine is an induction agent frequently used for general anaesthesia in emergency medicine. Generally regarded as haemodynamically stable, it can cause hypertension and tachycardia and may cause or worsen shock. The effects of ketamine may be improved by the addition of fentanyl to the induction regime. We conducted a systematic review to identify evidence with regard to the effect of adding fentanyl to an induction regime of ketamine and a paralysing agent on post-induction haemodynamics, intubating conditions and mortality.

Methods: We conducted a search of the Cochrane library, EMBASE, MEDLINE, PROQUEST, OpenGrey and clinical trial registries. Prominent authors were contacted in order to identify additional literature pertinent to the research question. Studies were included if they pertained to intubation of adult patients in the prehospital or emergency department environments and included an induction regime of ketamine and a paralysing agent, with at least one outcome measure of haemodynamics, intubating conditions or mortality. Search results were reviewed by two investigators independently, adjudicated by a third investigator where disagreement occurred.

Results: One observational study was identified that partially answered the research question.

Discussion: Only one observational study was identified that partially answered the research question. This paper demonstrated that the use of fentanyl as a pretreatment increases the incidence of post-induction hypotension, a phenomenon that was seen with propofol, midazolam and ketamine. The difference in hypotension between these agents was not statistically significant. The impact of this on patient-orientated outcomes is unclear.

1 | INTRODUCTION

Rapid sequence induction of anaesthesia (RSI) is a key step in the management of a subset of critically ill patients presenting to the emergency department (ED). While the absolute numbers of patients requiring this intervention is low, they represent an important cohort, due to high levels of morbidity and mortality.[1]

Rapid sequence induction involves a period of preoxygenation, followed by the administration of sedative medication(s) and a paralysing agent, in order to facilitate the passage of an endotracheal tube. This technique is not only employed for respiratory support but is also used for airway protection in the context of coma, and

Registration: PROSPERO www.crd.york.ac.uk/PROSPERO/index.php), registration number: 42017052746.

to facilitate further investigation and treatment.[2] By virtue of the transition of a patient who is self-ventilating at least to some degree, to complete apnoea, it is a critical intervention.

There is no ideal sedative agent for RSI, and wide variation in practice exists. The traditionally described technique utilizes thiopentone and suxamethonium,[3,4] although significant modifications have occurred over time, and sedatives such as propofol, midazolam, fentanyl, etomidate and ketamine[5-9] are all described in the literature. While suxamethonium has been the ubiquitous paralytic agent until recently, rocuronium is being used with increasing frequency.[10,11] The existence of a reversal agent[12] has also increased its appeal. Consequently, there are multiple possible combinations of sedatives and muscle relaxants that may be used, and while it can be argued that the combination should be tailored to individual patients, there is some evidence that use of a standardized protocol may improve processes[13] and potentially outcomes.

Where standardization has occurred, ketamine is a commonly used agent, either with or without an opioid.[7,14,15] This is a logical choice in an environment such as the ED or in prehospital care, where patients are undifferentiated, and may be overtly or cryptically shocked, due to the perceived haemodynamic stability of ketamine. However, the common understanding that ketamine is haemodynamically stable is flawed, given that it frequently causes tachycardia and hypertension, and in catecholamine-depleted patients, may cause hypotension.[16-18]

It is recognized that hypotension and hypoxia are undesirable in patients undergoing RSI, particularly those with a brain injury, as this has a measurable impact on patient outcomes,[19] but there is also evidence that hypertension may be associated with worse outcomes.[20] Whether this is due to worsening intracranial hypertension, the exacerbation of bleeding or other factors is unclear, but it is apparent that, for critically ill patients undergoing RSI, there is likely to be a "goldilocks phenomenon" associated with blood pressure, with the best outcomes being seen in those who maintain a blood pressure within a "normal" range. While this almost certainly applies to some patient groups more than others (particularly the group with potential for secondary brain injury), prospectively distinguishing which patients are in these groups in the prehospital setting or emergency department may be difficult, and so, physicians working in these environments must treat patients undergoing RSI as if they have potential brain injury unless there is compelling evidence to the contrary. While the goalposts of the "goldilocks zone" are not well defined, there is some limited literature advocating aiming for changes <20% from baseline.[21]

In addition to haemodynamic management, there are also additional considerations when choosing an agent for RSI, including the adequacy of intubating conditions,[22] as if these are poor and reduce first-pass success, there is an increasing tendency to hypoxia, as well as other complications. There is some evidence suggesting that, in this regard, ketamine maybe less favourable than agents such as propofol or thiopentone.[23,24]

For these reasons, while recognizing that it remains a logical choice, ketamine cannot be regarded as an *ideal* agent for RSI; it is, however, possible that the modulation of its effect by use of an auxiliary agent may improve its performance, both in terms of haemodynamic profile and intubating conditions.

Editorial Comment

In emergency conditions, prehospital or emergency department, use of ketamine is common in order to avoid negative circulatory side effects. This systematic review addresses evidence concerning whether or not fentanyl added to ketamine in this context is beneficial.

The opioid, fentanyl, is used as a co-induction agent for general anaesthesia, as it has the potential to blunt the pressor response to intubation[25]; there is also speculation that it may improve intubating conditions, either through its own intrinsic action or simply by deepening the plane of anaesthesia.[7,26] If this is the case, in theory, the protocolized addition of fentanyl to ketamine when used for RSI may result in more stable peri-induction haemodynamics and better intubating conditions. It is plausible that this would improve patient-orientated outcomes such as mortality. However, it is also possible that the introduction of an additional medication may actually be harmful, as a result of increasing complexity, causing more hypotension or due to other currently unknown factors.

This systematic review aims to identify, appraise and present the available evidence with regard to whether the addition of fentanyl to a rapid sequence intubation regime consisting of ketamine and a paralysing agent improves intubating conditions, post-induction haemodynamic parameters or mortality.

2 | METHODS

This protocol for this review was registered on PROSPERO, the International Prospective Register of Systematic Reviews www.crd.york.ac.uk/PROSPERO/index.php), registration number: 42017052746.

We searched for studies investigating the effect of adding fentanyl to an induction regime of ketamine and a paralytic agent. We prospectively decided to include both randomized and observational studies, and inclusion was determined using the following criteria:

- Population: Adult patients undergoing rapid sequence intubation with ketamine and a paralytic drug in the emergency department or prehospital setting.
- Intervention: The administration of fentanyl as a co-induction agent.
- Comparator: No co-induction agent or a placebo.
- Outcome: Post-induction haemodynamics, intubating conditions and/or mortality.

2.1 | Study setting

We aimed to evaluate the impact of adding fentanyl to an induction regime in the emergency department or prehospital setting, as we felt that the characteristics of these patients would be different to those in other settings such as operating theatres or intensive care units, where diagnosis would be likely to be clearer, and physiology corrected to a greater extent. Consequently, we excluded studies with populations from outside the emergency department and prehospital settings.

2.2 | Literature search

After completing an initial literature search as per our protocol, no studies were identified that answered the research question. As such, we elected to liberalize our search strategy, as detailed (Table 1). A search for prior systematic reviews was conducted and included interrogation of the Cochrane Database for Systematic Reviews, Database of Abstracts of Reviews of Effect (DARE), the Health Technology Assessment Database and PROSPERO.

Subsequently the Medline, EMBASE and ProQuest databases were searched for primary studies, and the grey literature was searched using OpenGrey and by contacting prominent authors to identify unpublished work. The International Clinical Trials Registry Platform was searched for relevant registered clinical trials. References of any retrieved papers were hand searched. No date or language restrictions were imposed on the search (which is detailed in Figure 1). Following completion of the search, two authors (IF and JB) independently reviewed the titles and abstracts according to the inclusion and exclusion criteria (Table 2) to determine which papers needed retrieval for full text review. Any disagreement at this stage was resolved by retrieval of the paper in question for full text review.The same authors then reviewed the full-text articles against the same criteria to decide on inclusion in the systematic review. Disagreement was resolved by consensus, and where necessary adjudication by a third author (AA).

TABLE 1 Search strategy

Medline 1946-October Week 2, 2018 Ketamine.mp OR exp Ketamine/ AND Fentanyl.mp OR exp Fentanyl/ 1125 hits
EMBASE 1980-2018 Week 43 Ketamine.mp OR exp Ketamine/ AND Fentanyl.mp OR exp Fentanyl/ AND Exp Endotracheal intubation/OR intubation.mp OR exp intubation/ 679 hits
Proquest (accessed 23/10/18) ketamine AND fentanyl AND (intubation OR rapid sequence intubation OR rapid sequence induction) 964 hits
OpenGrey (accessed 23/10/18) Ketamine 134 hits Fentanyl 69 hits
Cochrane Central Register of Controlled Trials (accessed 23/10/18) Ketamine AND fentanyl 552 trials 4 reviews No Cochrane protocols.

2.3 | Risk of bias assessment

Two authors independently assessed the risk of bias using Cochrane's "Suggested risk of bias criteria for EPOC reviews," a system which assigns a "high", "low" or "unclear" risk of bias across nine domains, according to prespecified criteria.

2.4 | Grading of evidence

A level of evidence was then allocated according to the GRADE criteria. These criteria automatically allocate a level of "high" to randomized controlled trials and "low" to observational studies, with the final level of evidence potentially being modified with respect to factors such as sample size, precision and potential for bias.

2.5 | Reasons for exclusion

We excluded 2848 of the 2849 studies that were initially screened after the removal of duplicates. Forty-four of these were retrieved for full-text review, with the exclusion of 11 review articles, 14 manuscripts pertaining to excluded settings and 18 manuscripts with interventions, comparators or outcomes that were not relevant to the research question.

2.6 | Statistical analysis

We intended to calculate risk ratios for dichotomous variables, with 95% confidence intervals. For continuous outcomes, we aimed to report relative risk, with 95% confidence intervals. No subgroup analyses were planned. In the event of identifying several manuscripts suitable for combination in a meta-analysis, we intended to use trial sequence analysis to avoid reaching a false-positive result as a consequence of cumulative random error.[27]

3 | RESULTS

The initial literature search identified a total of 3523 studies, of which 674 were duplicates, leaving a total of 2849. Following initial screening, 34 underwent full-text review. One manuscript provided data relevant to the review question. One randomized controlled trial is registered that will address the study questions, but is in the early phase of recruitment.[28]

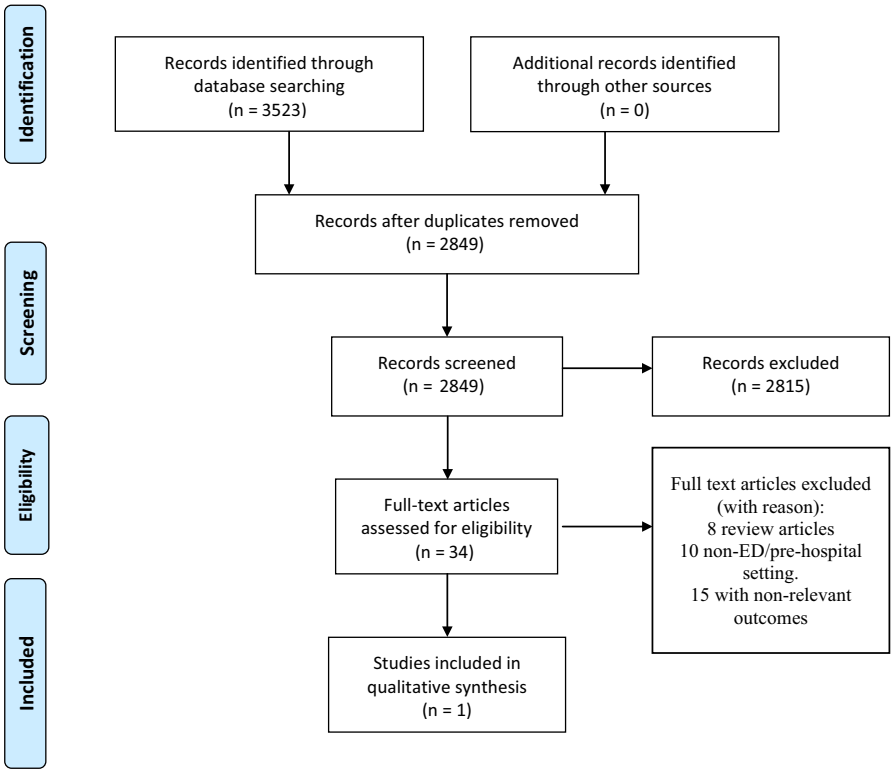

FIGURE 1 PRISMA flow diagram

TABLE 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adults (18 y and only, requiring rapid sequence intubation in the emergency department or pre-hospital environments • Induction regime consisting of ketamine and a muscle relaxant • Comparators: Any (including placebo or no comparator) • Outcome measures including at least one of haemodynamics, intubating conditions or mortality	• Paediatric patients (17 y and under) • Those intubated in a hospital environment outside the emergency department (eg operating theatres, intensive care unit) • Intubation by means other than RSI (eg fibre-optic intubation, delayed sequence intubation, etc) • Review articles/editorials

3.1 | Study design, setting and participants

The included study was a secondary analysis of a prospectively collected airway registry from 14 emergency departments in Japan.[29] The registry included 7570 of 7804 patients undergoing intubation in participating EDs between February 2012 and November 2016 (97% capture rate). Following exclusion of patients in cardiac arrest, those undergoing a sedative-only intubation, trauma and paediatric patients, those with pre-intubation hypotension (systolic blood pressure <90 mm Hg) and those in whom other pretreatments than fentanyl, sedatives other than ketamine, midazolam and fentanyl or paralytics other than suxamethonium, rocuronium or vecuronium were used, 1263 patients were included in the cohort studied.

3.2 | Intervention and primary outcome

The cohort was dichotomized according to whether fentanyl was used for pretreatment or not, with a primary outcome measure of post-induction hypotension (at least one measurement of a systolic blood pressure <90 mm Hg within 30 minutes of the induction of anaesthesia).

3.3 | Trial results

The baseline characteristics in both groups demonstrated significant differences. The fentanyl group was more likely to be intubated by emergency medicine residents or attending physicians (rather than more junior "transitional year" residents) and to undergo video, rather than direct laryngoscopy. The fentanyl group had a lower median systolic blood pressure at baseline, of 132 mm Hg (interquartile range: 111-156 mm Hg) vs 140 mm Hg in the non-fentanyl group (interquartile range: 119-170 mm Hg). However, the choice of sedatives was similar between the two groups, with midazolam, propofol and ketamine being chosen in 61%, 23% and 17% of the fentanyl group, respectively, vs 62%, 24% and 14%, respectively, in the non-fentanyl group. Rocuronium was used in 93% of the fentanyl group vs 85% of the

non-fentanyl group, a finding that was statistically, but not clinically significant.

There was a difference in the primary outcome of post-intubation hypotension of 17% in the fentanyl group vs 6% in the non-fentanyl group (a relative risk of 2.81, 95% confidence interval 2.00-3.92). In an adjusted model, fentanyl remained associated with post-intubation hypotension. While there was a trend towards less hypotension when ketamine was the sedative agent of choice, with midazolam and then propofol being associated with more frequent episodes, the difference in odds ratio between these agents was non-significant. As the numbers of patients treated with ketamine in each group was small, there is a risk of type II error.

Intubation was achieved on first pass more frequently in the fentanyl rather than the non-fentanyl group, with a relative risk of needing more than one attempt at intubation of 0.74 (95% CI 0.60-0.93) in the fentanyl group. However, this was not stratified according to sedative agent, and significant confounders were present that may have affected intubation difficulty (particularly intubator experience and the use of videolaryngoscopy), and so it is not possible to conclude that the combination of fentanyl and ketamine is more likely than ketamine alone to be associated with increased first-pass success.

3.4 | Risk of bias assessment

Risk of bias was assessed using the "Suggested risk of bias criteria for EPOC reviews" which consists of nine domains. We assessed the included study as being at high risk of bias in the domains of random sequence generation, allocation concealment, baseline outcome measure similarity, baseline characteristics similarity and "other" risk of bias. The risk of bias was assessed as low in the domains of protection against contamination and selective outcome reporting. The risk of bias was unclear in the domains of incomplete outcome data and knowledge of allocated interventions.

4 | DISCUSSION

We performed a thorough review of the literature and were able to find only one observational paper that provided any evidence to answer the review question of whether the addition of fentanyl to an induction regime of ketamine and a paralysing agent improves haemodynamics, intubating conditions or mortality. This study was not focused specifically on ketamine and included patients who underwent rapid sequence induction with any of ketamine, midazolam or propofol, in combination with any of suxamethonium, rocuronium or vecuronium. While hypotension was more frequent in the group pretreated with fentanyl, and there was no proof that ketamine mitigated this risk (with the odds ratio for the difference in hypotension between the agents not reaching statistical significance), the overall number of patients treated with ketamine was low, raising the possibility of type II error.

Additionally, the primary outcome of post-induction hypotension was reached if there was a single systolic blood pressure reading <90 mm Hg within 30 minutes of induction. As the sedative agents used have half-lives of a shorter duration than this, it is highly likely that other sedative infusions were commenced within this time frame. However, this is not reported, and so it is impossible to conclude with any certainty that the occurrence of hypotension was related to the intervention, rather than other unmeasured confounders such subsequent sedative regime.

With respect to the difference in intubating conditions, there were significant differences between the two groups (particularly the seniority of intubators and use of videolaryngoscopy) that are likely to bias the results making it difficult to conclude that there was any true difference between the groups attributable to the use of fentanyl as a pretreatment agent.

However, the results of this study do nonetheless suggest that fentanyl may be associated with post-intubation hypotension when used for rapid sequence intubation. Given the pressor effect associated with ketamine, whether the impact of this on patient-orientated outcomes such as mortality is offset by less hypertension is unclear.

Jabre et al[30] reported a well-conducted randomized controlled trial comparing induction with ketamine and etomidate. They showed equivalence in most outcomes, including demonstrating a similar pressor effect with both agents, which was marked enough to be clinically significant in a large minority of participants.

Price et al[31] took advantage of a national shortage of etomidate to report on the effect of ketamine in a number of prehospital services in the United States. They compared a cohort undergoing RSI with ketamine and etomidate, with fentanyl as a co-induction agent in 80% of cases. They reported no difference in systolic blood pressure pre- and post-induction, suggesting that fentanyl may be an effective choice in ameliorating the pressor effect.

Lyon et al[7] reported on a retrospective before and after cohort study of trauma patients undergoing RSI in the setting of a physician/paramedic staffed helicopter emergency medicine service (HEMS). They compared the post-induction haemodynamics of a group induced with etomidate and suxamethonium with a group induced with fentanyl, ketamine and rocuronium following a change in their standard operating procedure.

A lower mean increase in systolic blood pressure post-induction was reported in the fentanyl and ketamine group, as compared with the etomidate group, with a significant pressor effect being seen with the latter.

So, while post-induction hypotension is undesirable, it is unclear whether reducing the hypertensive response to intubation is also desirable and where the ideal balance lies.

While all of these studies commented on intubation difficulty, there was heterogeneity in these outcomes, and due to this, as well as to methodological limitations of the studies, it is difficult to reach firm conclusions, but there was no evidence that the addition of fentanyl to an induction regime obviously has a large impact on intubating conditions. The study included in this systematic review does not

add further information to this aspect of the clinical question, due to the previously discussed confounding.

5 | CONCLUSIONS

The current evidence regarding the effect of fentanyl in combination with ketamine and a muscle relaxant with regard to post-intubation haemodynamics suggests that it is likely to increase the incidence of hypotension, although the level of evidence in this regard would be classified as "low" according to the GRADE criteria.

With regard to intubating conditions, no firm conclusion can be drawn as to whether fentanyl has any impact, and the evidence for this outcome would be classified as "very low" according to GRADE.

There are also no data to show the impact on mortality as a result of adding fentanyl to a ketamine and paralysis induction regime.

Given the importance that is placed upon peri-induction haemodynamics and first-pass intubation success in order to avoid secondary injury, the lack of clarity with regard to an optimized induction regime is a critical knowledge gap. There is a need for well-conducted, prospective randomized controlled trials to address these questions more definitively.

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AUTHOR'S CONTRIBUTIONS

I. F. conceptualized the study, wrote the review protocol, conducted the literature search and wrote the first draft of the manuscript. J. B. reviewed the results of the search, edited the manuscript and approved the final draft. A. A. provided methodological guidance, edited the manuscript and approved the final draft.

ORCID

Ian Ferguson https://orcid.org/0000-0001-5915-6315

Anders Aneman https://orcid.org/0000-0003-2096-5304

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SUPPORTING INFORMATION

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

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