SYSTEMATIC REVIEW

Ketamine as a Prehospital Analgesic: A Systematic Review

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Abbreviations:
NMDA: N-methyl D-aspartate
RCT: randomized controlled trial

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Abstract

Objective: Analgesia in the prehospital setting is an extremely important, yet controversial topic. Ketamine, a N-methyl D-aspartate (NMDA) receptor antagonist, has been commonly used in the prehospital setting, including recommendations by the US Department of Defense and by the Royal Australian College of Pain Medicine, despite the paucity of high-level evidence.

Methods: Accordingly, a review of the literature was conducted using several electronic medical literature databases from the earliest available records to the time at which the search was conducted (October 2018).

Results: The search strategy yielded a total of 707 unique papers, of which 43 were short-listed for full review, and ultimately, ten papers were identified as meeting all the relevant inclusion criteria. The included studies varied significantly in the prehospital context and in the means of administering ketamine. There was only low-grade evidence that ketamine offered a safe and effective analgesia when used as the only analgesic, and only low-grade evidence that it was as effective as alternative opioid options. However, there was moderate evidence that co-administration of ketamine with morphine may improve analgesic efficacy and reduce morphine requirement.

Conclusions: Overall, ketamine as a prehospital analgesic may be best used in combination with opioids to reduce opioid requirement. It is suggested that future studies should use a standardized approach to measuring pain reduction. Future studies should also investigate short-term side effects and long-term complications or benefits of prehospital ketamine.

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Introduction

Background

For clinicians working in the prehospital setting, the analgesic management of moderate to severe pain can include opiates, such as morphine and fentanyl, or inhaled analgesics, such as nitrous oxide or methoioxyflurane.[1] More recently, however, various textbooks[2] and guidelines[3-5] have recommended the use of ketamine in prehospital analgesia. These recommendations have been incorporated into clinical practice. For example, paramedics in New South Wales and Australia Capital Territory have a protocol for its analgesic use,[6] and the US Department of Defense (Virginia USA) has recommended the use of ketamine for prehospital use in battlefield analgesia.[7] Ketamine acts primarily as an N-methyl D-aspartate (NMDA) receptor antagonist, although it may have other mechanisms of action.[8] The NMDA receptor is a ligand gated channel for the excitatory neurotransmitter glutamate, antagonism, of which produces its analgesic effect.

Ketamine has been posited to be an attractive choice in the prehospital setting for several reasons. Firstly, the drug has favorable pharmacokinetics – a rapid onset, short duration, titratable dose, and large therapeutic window, all of which make it an appealing option with a relatively low-risk profile.[9] This is particularly true in resource-limited settings,[7,10] where the large therapeutic window allows for management of greater numbers of patients where there may be limited access to full patient monitoring. Further, ketamine has favorable pharmacodynamic properties in the absence of shock. Although a direct cardiorespiratory depressant, by releasing endogenous catecholamines, there is maintenance of cardiovascular stability and respiration[11] and maintaining pharyngeal reflexes to ensure airway patency.[12] In addition to its analgesic benefits, other prehospital uses include sedation of violent or anxious patients,[12,13] procedural sedation,[3,14] and rapid sequence intubation.

	Intervention	Comparison	Outcome	Setting
Keywords	Ketamine Ketanest Ketalar	Analgesia	Pain Relief pain	prehospital, pre-hospital, prehospital, out of hospital, ambulance
MESH Terms	Ketamine	Analgesic Analgesics Pain	Pain Management	out-of-hospital emergency settings, Emergency Medical Services

Table 1. Keyword and Medical Subject Headings (MESH) Used for the Literature Search

Importance

While the safety of ketamine as an analgesic is well-established for use in the emergency department,[15-18] acute post-surgical,[8] and cancer pain,[19] the evidence is less clear in the prehospital setting.[1,20] A 2011 review[21] found a paucity of evidence on this issue with few well-designed clinical trials, and was unable to support or refute the use of ketamine within the prehospital context. However, since 2011, more studies have been published investigating the efficacy and safety of ketamine as a prehospital analgesic.

Goals of the Investigation

Therefore, the aim of this study was to review whether, in patients requiring prehospital analgesia, the use of ketamine results in satisfactory pain relief, and to compare this to other analgesic agents. The secondary aim was to quantify the incidence and types of adverse effects and complications from the use of ketamine.

Research Question

Participants—Studies of adult patients (aged over 21 years) who received ketamine for the primary purpose of pain reduction in the prehospital setting were included. Prehospital analgesia is defined as any analgesia that is given to a patient in an ambulance or retrieval team on-site or during transport to a hospital.

Intervention—The intervention consisted of the administration of ketamine. No restrictions were set for the route of administration, the administration of other medications concurrently, or the dosage. Studies in which ketamine was administered for indications other than analgesia were excluded.

Comparison—Any analgesic regimen for the reduction of prehospital pain without the concurrent administration of ketamine was used for comparison.

Outcomes—The primary outcome of interest in this study was quantitative measurements of reduction in severity of pain, OR a quantitative measurement on the degree of pain relief from ketamine. Studies which provided qualitative or expert opinions on adequate pain relief were not included. Secondary outcomes included the incidence of adverse events, its sedative effect, as well as the specifics of the administration of ketamine.

Study Design—Given the paucity of high-level, randomized controlled trials (RCTs) within this setting, it was decided a priori to include all study types. Overall, this gave a collection of randomized and non-randomized trials, cohort studies, case control studies, retrospective case studies, and case series in which ketamine was used as a prehospital analgesic.

Methods

Search Strategy

This systematic review was registered on PROSPERO (CRD42018094562), and subsequently, a review of the literature was conducted using several electronic medical literature databases. A search of AMED (Allied and Complementary Medicine Database; Health Care Information Service of the British Library; London UK; 1985 - September 2018); Medline (US National Library of Medicine, National Institutes of Health; Bethesda, Maryland USA); SCOPUS (Elsevier; Amsterdam, Netherlands); Web of Science (Thomson Reuters; New York, New York USA); Cochrane (The Cochrane Collaboration; London, United Kingdom); and EMBASE (Elsevier; Amsterdam, Netherlands) databases (1970-September 2018) was performed. Medical Subject Headings (MESH) were used to focus the search, and a range of keywords were used, as shown in Table 1, to ensure inclusion of all relevant articles, with only literature published in English, or those which could be translated to English, included. Back and forward referencing of the included studies were also hand searched to identify any further, relevant articles. A grey literature search of Bielefeld Academic Search Engine (Bielefeld University Library; Bielefeld, Germany), Open Grey (INIST-CNRS - Institut de l'Information Scientifique et Technique; Paris, France), and nongovernmental organization (NGO) search, as well as a review of relevant emergency, anesthetic, and prehospital conference papers and abstracts, was also conducted to identify further articles. No individual authors were contacted.

Inclusion and Exclusion Criteria

The titles and abstracts of identified articles were independently evaluated by two reviewers (AB and EW) for inclusion based on their relevance and adherence to the inclusion and exclusion criteria. Inclusion criteria included all articles relevant to the question that could be translated to English, that involved human subjects, and that were based in the prehospital setting. Populations of adults and all study types were allowed. Exclusion criteria were studies in which ketamine was used for another indication (ie, sedation of violent or anxious patient or rapid sequence intubation), if there was no quantitative measurement specifically for level of pain, or if ketamine was administered in the emergency setting rather than a prehospital one. Any disagreements in included studies after full-title and abstract review were discussed and negotiated between the two reviewers until a consensus was reached. Subsequent to this, a pilot data extraction of 20% of the papers included after full-text review was undertaken by two reviewers, which showed a strong kappa agreement ($k = 0.82$). Subsequently, the rest of the data extraction was undertaken by one reviewer (AB).

Evaluation of Articles

In order to assess the strength of the evidence in individual studies, two independent reviewers analyzed the bias using the validated

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Level	Description
1++	High-quality meta-analysis, systematic review of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case control or cohort studies; High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias, and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytical studies (eg, case report, case series)
4	Expert

Table 2. SIGN50 guidelines for evaluation of evidence grading of articles
Abbreviation: RCT, randomized controlled trial.

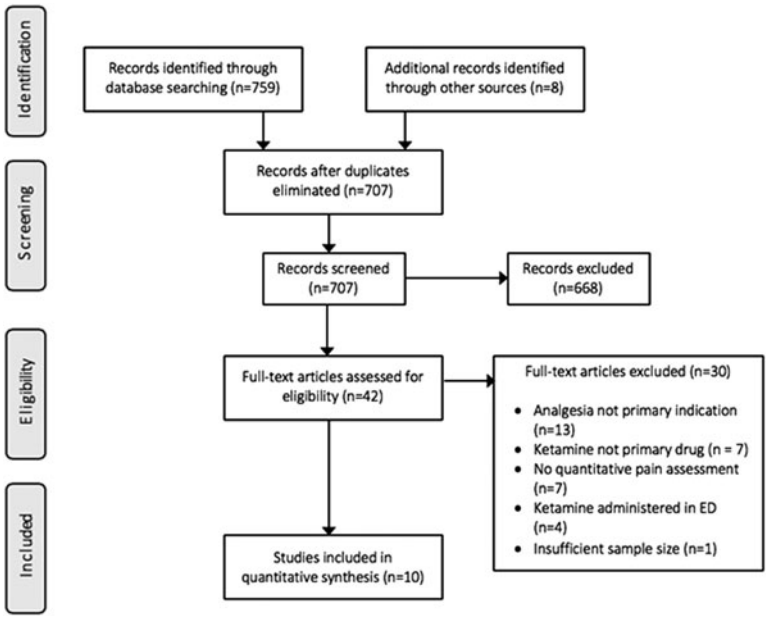

Figure 1. PRISMA Flow Diagram of Publication Assessment for Study Inclusion.
Abbreviation: ED, emergency department.

SIGN 50 methodological assessment tool,[22] which utilizes a checklist of criteria that have a significant effect on bias to assess and score the bias as either high-quality (++), acceptable (+), or low-quality (-), as well as grading the evidence based on study type: RCTs being Grade I, case control or cohort studies being Grade II, and non-analytical opinions such as case reports and case studies being Grade III (Table 2). Expert opinions are Grade IV, but were excluded from the systematic review due to its inclusion-exclusion criteria. Any disagreements on strength of evidence ratings were discussed and negotiated between the two reviewers until a consensus was reached.

The significant heterogeneity in study design, analgesic regimens, and pain assessment meant that a meta-analysis could not be appropriately performed, and a qualitative synthesis of the papers in each subgroup was made using the GRADE hierarchy of recommendations,[23] in which grades evidence on a scale from A-D from high to very low level of evidence.

Results

Overall, the search identified 767 references, with 707 unique papers. Of these references, 668 were excluded as they did not meet the inclusion criteria. Of the 42 articles that were short listed for full-text review, a total of 10 were identified as meeting all the criteria, as shown in Figure 1.

Studies fell into one of three groups based on their study design:

1. One-arm studies evaluating only ketamine in the prehospital setting, without comparator group;
2. Multi-arm studies comparing ketamine to other analgesics, or no analgesic, in the prehospital setting; or
3. Multi-arm studies comparing the analgesic efficacy of the co-administration of ketamine and morphine with morphine alone in the prehospital setting.

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Characteristics of Included Studies			Details of Ketamine Administration			Outcomes		
Study	**Study Design and Sample Size**	**Setting and Patient**	**Route and Dosage**	**Concurrent Medications**	**How was Pain Assessed**	**Reported Outcome**	**Comment on Adverse Effect/ Complication**	**Study Quality**
Bion 1984[11]	Prospective cohort study comparing ketamine (n = 8) with pentazocine (n = 9)	Prehospital military - Cambodia and Thailand	1mg/kg IV, 2-3mg/kg IM	Titrated dose up to 30mg, mean of 20.5 mg, IV route	Four-point numerical scale	Ketamine was less effective than pentazocine due to its sedative effects, although the difference was not statistically significant.	Increase in SBP and RR following ketamine, with dizziness in one-third of patients. No other side effects noted.	2+
Lovsik et al 2015[33]	Retrospective cohort study comparing ketamine (n = 731) with both no analgesia (n = 88) and pentazocine (n = 235)	Prehospital - Iraq	0.2mg/kg loading dose, with repeated doses (total not reported), IV route	5mg diazepam in case of unrest and agitation, 1mg atropine for excess salivation	Physiological severity score	Ketamine analgesia was more effective than no analgesia or pentazocine.	Adverse events not reported on. Ketamine associated with significantly better effect on SBP than opioids.	2+
Tran et al 2014[34]	Prospective cluster randomized design comparing ketamine (n = 169) with morphine analgesia (n = 139)	Prehospital - Vietnam	Slow intermittent IV infusion 0.2-0.3mg.kg, mean dose 15 mg	Unspecified	Visual analogue scale	Ketamine yielded an analgesic effect similar to morphine.	Events of agitation and hallucinations are higher, nausea and vomiting are lower; less risk of airway problems.	2++

Table 4. Studies Comparing Ketamine to Other Analgesics, or No Analgesics, in the Prehospital Setting
Abbreviations: IM, intramuscular; IN, intranasal; IV, intravenous; RR, respiratory rate; SBP, systolic blood pressure.

Group 1: Studies Evaluating Only Ketamine in the Prehospital Setting without a Comparison Group

A total of nine studies either retrospectively or prospectively observed the analgesic efficacy and safety of ketamine in the prehospital setting, the majority of which were case series. The metric for assessing analgesia was unspecified in five of these studies,[24-28] and not a specific scale of analgesia in another,[29] and so were excluded. Three studies used the numerical rating scale, and all stated that ketamine provided safe and adequate analgesia, with very few observed or recorded side effects listed within the studies (Table 3[30-32]). There was, however, marked heterogeneity in both the sample sizes (from nine[30] to 585[29]) and populations investigated, from tertiary center prehospital retrivals[24] to soldiers in military settings.[29]

Overall Recommendation: There is low (Grade C) evidence supporting the analgesic efficacy and safety of ketamine in the prehospital setting.

Group 2: Studies Comparing Ketamine to Other Analgesics, or No Analgesics, in the Prehospital Setting

No RCTs were found. Three prospective observational studies were identified that made a comparison between ketamine and other prehospital analgesic options (all opioids), as shown in Table 4.[11,33,34] Two compared ketamine with pentazocine (an opioid), one with morphine, and one with no analgesia. Two of these studies had three arms to include a no analgesia option. One of these was a prospective clutter randomized study. All studies used either a numerical rating scale or visual analogue scale to measure effectiveness. Two of the three reported ketamine to be equally or more effective than opioid analgesia (morphine, pentazocine, or fentanyl), with one paper from 1984 finding it to be less effective. Again, there was marked heterogeneity between the studies with small study sizes, and the dosage of ketamine ranging from a median of 15mg to 77mg.

Overall recommendation: There is low (Grade C) evidence that ketamine was at least as effective as opioids as a prehospital analgesic agent.

Group 3: Studies Comparing the Analgesic Efficacy of the Co-Administration of Ketamine and Morphine with Morphine Alone in the Prehospital Setting

An overall of four studies evaluated the pain relief offered by morphine alone compared with morphine and ketamine, as shown in Table 5.[35-38] Three studies were RCTs. One RCTs reported no difference in pain relief, but a reduction in morphine requirements; one RCT reported a reduction in pain alone; and one RCT compared a ketamine infusion with placebo after both study arms had received a morphine bolus, and reported no difference in pain relief. One study investigated the impact of co-administration on morphine requirement, finding that it was lower when ketamine was given.

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Overall Recommendation: There is moderate (Grade B) evidence that co-administration of ketamine with morphine lead to equal or greater pain reduction, as well as reducing morphine requirement.

Discussion

This systematic review set out to update the evidence of ketamine as a prehospital analgesia, given the appearance of more publications on this topic since the most recent systematic review. Overall, the main findings of this paper are that, in comparing the effectiveness of using ketamine or opioids as the sole prehospital analgesic, there is low-grade evidence that ketamine is equivalent with, or slightly superior to, opioid analgesia. Further, there is moderate evidence that the co-administration of ketamine with morphine in the prehospital setting may improve analgesic effectiveness and reduce of morphine requirement. Finally, the studies support a low incidence of a cardio-respiratory depressant effects of ketamine, although the small sample sizes in most of the studies mean they may have been under-powered to detect effects.

The findings of this review may have implications for advice to clinical practice. For example, the Australian College of Pain Medicine (Melbourne, VIC, Australia) places ketamine as a prehospital analgesic as Level 2 evidence according to National Health and Medical Research Council (NHMRC; Canberra, Australia) guidelines,[39,40] based on their analysis of Jennings, et al's 2011 review.[21] Given the presence of new randomized trials[34,36,38] and more cohort studies and case series[30-33,41] since 2011, consideration could be given to reconsider this. For example, this review reports low-grade evidence that ketamine is a safe and effective analgesic option on its own, and only low-grade evidence that it is at least as effective as opioids or fentanyl. However, with regard to the co-administration of ketamine with morphine, there is moderate evidence that it may lead to equal or greater pain reduction, as well as lower morphine requirement.

This paper has identified three areas that have implications for future research. First, several studies were excluded as they did not offer clear methodology on how ketamine's analgesic effectiveness was evaluated. Resource limitation in prehospital medicine, as well as the fact that ketamine is often the preferred option in the hemodynamically unstable patient,[42] may account for the lack of documented pain intensity and adverse event monitoring. The lack of standardized measurement of outcomes does mean that a meta-analysis could not be appropriately performed. It would be beneficial if future studies incorporated standardized measures of pain assessment, such as a numerical scale or visual analogue scale.

Second, due to the small sample size of a number of these studies, it is possible that they are under-powered to detect rare adverse events. The variability in sample sizes of included studies were such that adverse events occurring with an upper 95% confidence interval rate from 1%-38% (estimated using the rule of threes[43]). However, any study with a sample size less than 50 (six of the 10 included studies) could only detect adverse events occurring in over five percent of the sample. While there do exist reports of frequent adverse events following prehospital administration, for example a case series of 13 patients that reported three cases of hypoxia, one of laryngospasm, and five episodes of emergence phenomenon,[44] these patients were given a high ketamine for chemical restraint. Analgesic doses of ketamine should produce less frequent, but no less important, adverse events. A common hesitation with the use of ketamine in the prehospital setting is a concern about its side effects –emergence phenomenon, dissociation, transient apnea, and increased salivary secretions leading to laryngospasm.[16] Measuring and reporting of undesirable effects of ketamine analgesia is therefore important, not only to quantifying the range and frequency of potential side effects, but also to allow them to be managed and mitigated. For example, awareness of the presence of emergence phenomenon after ketamine administration means that it is often co-administered with midazolam (as it was in seven of the 10 included studies), which can reduce the rate of emergence phenomena by two-thirds.[45]

Finally, it may be useful to investigate the long-term benefits, side effects, and complications of ketamine. This review was only able to identify two papers that looked at the emergency department admission or long-term (six-month follow-up) effects of prehospital ketamine administration. Jennings, et al[46] investigated the long-term effects of ketamine versus morphine use in a prehospital setting, finding that in the long term, there was no difference in prevalence or persistent pain or health-related quality of life six months after injury.

Limitations

This review was limited by a relatively small number of studies included, few of which were randomized controlled studies. In addition, there were few studies where ketamine was used either as the primary analgesic (which would have allowed a direct measurement of its analgesic efficiency) or where is was compared head-to-head with another analgesic agent, in particular an opioid. The review was also limited to studies published in English.

Conclusion

The administration of safe, effective analgesia in the prehospital environment is imperative.[41,47] Ketamine, with its favorable pharmacokinetic and pharmacodynamic properties, is an extremely attractive option in a wide variety of settings. This study, by reviewing the current literature on ketamine as a prehospital analgesic, found only low-quality evidence to support the use of ketamine as a single- or first-line analgesic. There is, however, moderate evidence for the co-administration of ketamine with morphine as a safe and effective prehospital analgesic option that may also reduce opioid requirement. There is insufficient power in the included studies to adequately address the short- and long-term safety of ketamine, which should be further studied.

Author Contributions

AB conducted the literature search, extraction, and constructed the results and discussion section. MM, IF, and BB all refined the research question, discussion, and reviewed the paper.

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Characteristics of Included Studies			Details of Ketamine Administration			Outcomes		
Study	**Study Design and Sample Size**	**Setting and Patient**	**Route and Dosage**	**Concurrent Medications**	**How was Pain Assessed**	**Reported Outcome**	**Comment on Adverse Effects/ Complications**	**Study Quality**
Fisher et al 2014[30]	Retrospective case series, n = 9	Military Setting- American Army	1mg/kg IV, 2-3mg/kg IM	hydromorphone and/or midazolam	Numerical rating scale	Pain reduced to 4/ 10 or below in all patients.	Overall, few side effects. Some patients reported hallucinations, vivid dreams, limb movements, and no recollection of events.	3
Haske et al 2014[31]	Retrospective case series, n = 528	EMS- Germany	Mean of 27mg +/- 12mg, IV route	midazolam	Numerical rating scale	Significant pain relief. Mean initial pain was 8, reduced to 3 on transfer to ED.	2.8% had side effects, all other vitals were virtually unchanged.	2+
Johansson et al 2013[32]	Retrospective case series, n = 9	Prehospital- Sweden	0.5mg/kg bolus, with additional up to 1.0mg/kg in adults and 1.5mg/kg in children, IN route	unspecified	Numerical rating scale	Significant reduction in pain.	Minor - no hypersecretion or psychotomimetic effects, with 3 patients experiencing vertigo.	3

Table 3. Studies Evaluating Only Ketamine in the Prehospital Setting without a Comparison Group
Abbreviations: ED, emergency department; EMS, Emergency Medical Services; IM, intramuscular; IN, intranasal; IV, intravenous.

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Characteristics of Included Studies			Details of Ketamine Administration			Outcomes		
Study	**Methods**	**Setting**	**Dosage**	**Concurrent Medication**	**How was Pain Assessed**	**Findings**	**Comment on Adverse Effects/ Complications**	**Study Quality**
Gallinski et al 2007[35]	Prospective, multi-centered double blinded RCT comparing morphine with ketamine (n = 38) and morphine alone (n = 35)	Mobile intensive care service-France	0.2mg/kg loading and 3mg every 5 min until visual analogue scale < 30/100mm, IV route	0.1mg/kg morphine IV with loading dose	Visual analogue scale	Low dose ketamine reduced morphine requirement, did not lead to greater pain reduction than morphine alone.	No difference between ketamine and placebo group with regard to BP, HR, RR, or oxygen saturation. The incidence of neuropsychological adverse effects was significantly greater in the ketamine group.	1+
Jennings et al 2012[36]	Prospective, multi-centered RCT comparing morphine with ketamine (n = 70) and morphine alone (n = 65)	Prehospital-Australia	Morphine 5mg IV, followed by ketamine bolus of 10-20mg, followed by 10mg every 3 minutes thereafter	Unspecified	Numeric rating scale	Pain control was superior with co-admin. of ketamine with morphine by clinically significant margin (reduction of NRS > 1.3).	Adverse effects were minor. 27/70 patients on ketamine experienced adverse effects, including emergence phenomenon in 4.	1+
Johansson et al 2009[37]	Prospective clinical cohort study comparing analgesia with morphine (n = 16) and ketamine to morphine alone (n = 11)	Prehospital-Sweden	Morphine only: 0.3 mg/kg morphine Ketamine: 0.1mg/ kg morphine, 0.2mg/kg ketamine, IV route	Unspecified	Numeric rating scale	Co-admin. of morphine and ketamine lead to more significant reduction in pain than morphine alone.	Four patients experienced nausea, and three experienced vomiting in the ketamine group. BP significantly higher on admission for ketamine group.	2++
Wiel et al 2015[38]	Single blinded, RCT comparing morphine requirement between a group receiving morphine and a continuous infusion ketamine (n = 32) and morphine and a continuous infusion of saline (n = 32)	Prehospital-France	Both groups: ketamine bolus 0.2mg/kg, morphine 0.1mg/kg Group 1: continuous ketamine infusion Group 2: saline infusion Morphine 0.05mg/ kg every 5 minutes, IV route	Midazolam	Visual analogue scale and morphine consumption	No difference in pain reduction or morphine requirement between the two groups.	No adverse events recorded.	1+

Table 5. Studies Comparing the Analgesic Efficacy of the Co-Administration of Ketamine and Morphine with Morphine Alone in the Prehospital Setting.
Abbreviations: BP, blood pressure; HR, heart rate; IM, intramuscular; IN, intranasal; IV, intravenous; RCT, randomized controlled trial; RR, respiratory rate.