BMJ Open

Ketamine for the treatment of prehospital acute pain: a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038134
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2020
Complete List of Authors:	Sandberg, Mårten; Oslo University Hospital, Air Ambulance Department Hyldmo, Per Kristian; University of Stavanger Kongstad, Poul; Region of Skåne, Lund, Department of Prehospital Care and Disaster Medicine Dahl Friesgaard, Kristian; Prehospital Emergency Medical Service, Research Department, Central Denmark Region Raatiniemi, Lasse; Oulu University Hospital Larsen, Robert; Linköping University Magnusson, Vidar; Landspitalinn University Hospital Rognås, Leif; Aarhus University Hospital, Kurola, J; Kuopio University Hospital Rehn, Marius; Oslo University Hospital, Air Ambulance Department Vist, Gunn Elisabeth; Norwegian Institute of Public Health
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Adult intensive & critical care < ANAESTHETICS, Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Ketamine for the treatment of prehospital acute pain: a systematic review

Mårten Sandberg[1,2], Per Kristian Hyldmo[3,4,5], Poul Kongstad[6], Kristian Dahl Friesgaard[7,8], Lasse Raatiniemi[9,10], Robert Larsen[11], Vidar Magnusson[12], Leif Rognås[13,14,15], Jouni Kurola[16], Marius Rehn[2,3,4], Gunn Elisabeth Vist[17]

[1]Faculty of Medicine, University of Oslo, Oslo, Norway; [2]Division of Prehospital Services, Air Ambulance Department, Oslo University Hospital, Oslo, Norway; [3]Faculty of Health Sciences, University of Stavanger, Stavanger, Norway; [4]Department of Research, Norwegian Air Ambulance Foundation, Oslo, Norway; [5]Trauma Unit, Sørlandet Hospital, Kristiansand, Norway; [6]Department of Prehospital Care and Disaster Medicine, Region of Skåne, Lund, Sweden; [7]Research Department, Prehospital Emergency Medical Service, Central Denmark Region, Aarhus, Denmark; [8]Department of Anaesthesiology, Regional Hospital of Horsens, Denmark; [9]Centre for Prehospital Emergency Care, Oulu University Hospital, Oulu, Finland; [10]Anaesthesia Research group, MRC, Oulu University Hospital and University of Oulu, Finland; [11]Department of Clinical and Experimental Medicine, Division of Surgery, Orthopedics and Oncology, Faculty of Medicine and Health Sciences, University of Linköping, Sweden; [12]Landspitalinn University Hospital, Reykjavik, Iceland; [13]Danish Air Ambulance, Aarhus, Denmark; [14]Department of Anaesthesiology, Aarhus University Hospital, Aarhus, Denmark; [15]Department of Clinical Medicine, Aarhus University; [16]Centre for Prehospital Emergency Medicine, Kuopio University Hospital and University of Eastern Finland; [17]Division of Health Services, Norwegian Institute of Public Health, Oslo, Norway

Short title: Prehospital ketamine

Word count (excl. abstract and references): 4,077

Corresponding author:
Marius Rehn
Assoc. Professor/Consultant
Air Ambulance Department
Oslo University Hospital
Sykehusveien 19
1474 Nordbyhagen
Norway

Tel.: +47 90784044
E-mail: marius.rehn@norskluftambulanse.no

*

* The authors declare no conflicts of interest

Abstract

Background: Few publications have addressed the use of ketamine in analgesic doses (max 0.5 mg/kg ketamine i.v.) in the prehospital setting. We aimed to explore the effect and safety profile of ketamine compared to other analgesic drugs (or no drug) in adult prehospital patients with acute pain.

Methods: We conducted a systematic review of clinical trials assessing the prehospital administration of ketamine in analgesic doses compared to other analgesic drugs or no analgesic treatment in adults. We used the Cochrane and GRADE methodologies and exclusively assessed patient-centred outcomes. Two independent authors screened the trials for eligibility, extracted the data and assessed the risk of bias.

Results: We included eight studies (2,760 patients) in the review. Ketamine (administered i.v. with or without opioids) was compared with various opioids given alone, and intranasal ketamine given with nitrous oxide was compared to nitrous oxide given alone. Four RCTs and one cluster randomized trial included 699 patients. One prospective cohort study included 27 patients, and two retrospective cohort studies included 2,034 patients. Five of the eight studies had high risks of bias. Pain was statistically significant reduced when ketamine was administered, but the number of minor side effects was increased.

Conclusions: This systematic review of the current literature indicates that ketamine is a relatively safe and effective analgesic when administered by prehospital health providers with relevant training.

Strengths and limitations of the study

- A systematic review where main outcomes was assessed according to the GRADE method
- Studies were heterogeneous in terms of setting, patient population, outcomes and comparators
- Only English and Scandinavian language literature was included

Introduction

Prehospital acute pain is a frequent symptom and often inadequately managed[1-3]. Several analgesics are administered by prehospital emergency medical services throughout the world without solid evidence of their efficacy and safety. The heterogeneity in pain management strategies may reflect the varying competence levels of providers ranging from technicians with basic training to specially trained physicians. Opioids are most frequently used, but their cerebral, haemodynamic, and respiratory side effects remain a challenge in unstable and undifferentiated prehospital patients[4]. Ketamine is an alternative to opioids. The first report on ketamine was published in 1965[5], and the drug was approved for clinical use in humans five years later[6]. Ketamine exerts its effects mainly as an N-methyl-D-aspartate antagonist and, depending on the dose, can be considered as an analgesic, a sedative or an anaesthetic drug[7]. The analgesic properties of ketamine were recognized at introduction, but the main focus was its potential role as a sole anaesthetic or an induction agent[8]. The analgesic properties of low-dose ketamine were explored later[9]. Administered ketamine doses in some studies were large enough to cause a temporary loss of consciousness making it difficult to evaluate the clinical value of the purely analgesic effect as distinct from the anaesthetic effect[10]. Ketamine doses for acute pain in the subdissociative range (i.e., doses that are so low that the patient remains conscious) have not been established, but studies suggests that bolus doses of approximately 0.1-0.2 kg/mg i.v. are effective[11]. Relatively high doses, 0.2-0.5 mg/kg i.v., have also been advocated[12 13]. This is further complicated as dose required to cause dissociation varies between patients. In one experimental study, for instance, almost half of the subjects lost consciousness at a dose of 0.25 mg/kg[14]. Titrating the dose, starting at 0.1 mg/kg i.v. with a maximum limit of 0.5 mg/kg i.v., may be a pragmatic approach when the goal is to attain the analgesic effects of ketamine[15]. However, patient weight is often estimated, and the therapeutic range of analgesic drugs remains wide.

One attractive feature for prehospital use of ketamine is its ability to preserve upper airway reflexes. Respiratory rate may increase, as ketamine can cause bronchodilation, while rapid i.v. injection can cause transient apnea[16]. There is a risk of laryngospasm, which may require intubation in a very small number of cases[17]. Airway secretions are not unusual, and some recommend managing the secretions with a small dose of an antisialogogue, e.g., atropine (0.01 mg/kg)[18].

Ketamine can be administered intramuscularly, intranasally and intravenously. Although originally believed to cause an increase in intracranial pressure (ICP), recent work in critical care patients indicates that ketamine has little or no impact on ICP. In two studies comparing ketamine and sufentanil, the authors concluded that ketamine did not affect ICP and that it was safe to administer to patients with traumatic brain injury (TBI)[19 20]. In another study, ketamine in conjunction with propofol was administered to TBI patients, and a significant decrease in ICP was recorded[21]. In one study on children with TBI, a reduction in ICP by up to 30% was found, and cerebral perfusion was improved[22]. In these studies, ketamine was used in anaesthetic doses, and the results should be interpreted with caution.

Moderate or severe agitation occurs in 5-30% of adult patients; some providers administer boluses of midazolam to avoid this phenomenon[16]. A randomized controlled trial (RCT) showed that this practice significantly reduced agitation in adults; however, one trial found that it did not reduce agitation in children[16 23].

All patients managed prehospitally should have their analgesic needs assessed and addressed. Proper pain relief allows prehospital care providers to meet essential clinical endpoints, e.g., facilitating fracture manipulation. Although analgesia should be titrated for the desired effect, pain relief is frequently suboptimal, possibly due to concerns about adverse effects[24]. Ketamine may be a useful prehospital analgesic mainly due to its ability to provide excellent analgesic effects with a lower incidence of respiratory depression than that caused by opioids. These positive effects have been demonstrated in fracture management[25], burn treatment[26], and traumatic amputation[27].

The aim of this systematic literature review is to explore the effect and safety profile of ketamine compared to other analgesic drugs (or no drug) in prehospital patients with acute pain.

Methods

We conducted this systematic review according to the Cochrane Handbook for systematic reviews of interventions[28] and as described in our protocol (PROSPERO registration number CRD42018114399) as specified below.

Inclusion criteria

We used the following inclusion criteria:

Population	Adult patients with acute pain in the prehospital setting
Intervention	Ketamine
Comparison	Other analgesics, no analgesics or ketamine given in another dose or another route of administration or ketamine given in combination with other analgesics
Outcomes	Pain reduction, speed of onset, duration of effect, and relevant adverse effects such as mortality, morbidity, anaphylaxis, nausea and vomiting, hypotension, respiratory failure, loss of airway patency, emergence phenomena

We included all adult patients with acute pain, regardless of aetiology, managed in the prehospital setting. We also sought to identify groups of patients for whom the agents may be of particular benefit or harm. The following study designs were considered eligible for inclusion in the meta-analysis: systematic reviews, RCTs, non-randomized controlled studies, cohort studies with a control group, interrupted time series, and controlled before-and-after studies. Case series were also included for information relating to safety.

Exclusion criteria

Children and patients with chronic pain and/or patients who used ketamine as part of their regular treatments were not included in this review. We excluded all studies that were not conducted in the prehospital setting, as well as conference abstracts, letters and publications without full texts available.

Search strategy

An experienced research librarian in collaboration with the authors developed the search strategy based on the inclusion criteria. The following databases were searched from their inception: PubMed, EMBASE, Cochrane Library and Epistemonikos.

The most recent search was conducted on February 15, 2020, and the full search strategy is presented in Appendix 1. The search was limited to the following languages: Danish, English, Norwegian, and Swedish.

The reference lists of the included publications were checked in order to identify relevant articles not found in the original search.

Study selection

For each step in the review process, no assessor handled publications they had co-authored. MS and either PKH, MR or PK independently assessed all titles and abstracts identified from the search according to the inclusion criteria above. References that were considered potentially relevant were collected, and the full texts were assessed independently by two assessors using the same inclusion criteria. Any disagreement between the initial two assessors was discussed and resolved by all assessors. The process of study selection based on titles and abstracts, study selection based on full texts and risk of bias assessments were conducted using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org).

Assessment of risk of bias

MS and either PKH, MR or PK independently assessed the risk of bias for each of the included studies in accordance with the recommendations by the Cochrane Collaboration[28]. For RCTs, the following items were assessed for risk of bias: i) sequence generation; ii) concealment of allocation; iii) blinding of participants and personnel; iv) blinding of outcome assessor; v) incomplete outcome data; vi) selective outcome reporting; and vii) other risk of bias. For non-randomized controlled trials and other studies with a control group, the following items were also assessed for risk of bias: viii) similarity of baseline characteristics; ix) similarity of baseline outcome data; and x) contamination. All items were rated as either high, unclear or low risk of bias.

Data extraction and analysis

MS and either PKH or PK independently extracted data from each included study. We extracted data pertaining to full references; study design and country in which the study was conducted; characteristics of the population, e.g., number of patients; age; gender; cause of pain; setting and context; type and dose of analgesics given; cadre/competency of the health care personnel who administered the analgesic; comparison/control intervention; attrition; outcomes; and follow-up times.

Dichotomous outcomes are presented as risk ratios (RRs) with 95% confidence intervals (CIs). Continuous outcomes are presented as the mean difference between the groups with 95% CIs. If different scales were used to measure the same outcome, we would have calculated standardized mean difference with a 95% CI. We used Review Manager (RevMan 5.3) software to generate forest plots. Attrition was handled using intention-to-treat analysis. We evaluated statistical heterogeneity using the Q test and I^2 statistic.

Grading our confidence in the evidence

We assessed our confidence in the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[29]. Our confidence is presented as high, moderate, low or very low. The evidence across each outcome is assessed by eight criteria. Five criteria lowered our confidence in the evidence: i) risk of bias/ methodological limitations; ii) consistency between studies (statistical heterogeneity); iii) directness (similar study participants, intervention, comparator and outcome measures in the included studies to the population, and target interventions and measures); iv) precision of results; and v) reporting bias. Three criteria were used to consider upgrading evidence from observational studies that had not been downgraded: i) strong or very strong association between intervention and outcome; ii) large or very large dose response; and iii) situations where all plausible confounders would have reduced the effect. For questions about the effect of interventions, RCTs started at high confidence, and observational studies started at low confidence.

Breach of protocol

We have made a breach of the protocol; the largest study (Losvik and coworkers) we included also contained treatment data from a few children[34].

Results

The systematic literature search identified 1,197 references; we considered 60 to be potentially relevant and assessed those texts in full. We included seven of these studies in the final analysis. In addition, two unique references in the reference lists of the seven publications were assessed and one of the references were also included. Figure 1 shows the flow diagram of the identified references.

The 53 studies that were assessed in full text and excluded are presented in appendix 2 with their reason for exclusion.

Characterization of the trials

The eight included studies were conducted in Australia[30], Canada[31], France[32 33], Iraq[34], Sweden[35], the USA[36], and Vietnam[37]. A total of 2,760 prehospital patients with acute pain were included in these eight studies. Four RCTs[30-33] and one cluster randomized trial[37] included 699 patients. One prospective cohort study[35] included 27 patients. Two retrospective cohort studies[34 36] included 2,034 patients. The largest of these studies, with 1,876 patients, was conducted in the war zones and mine fields of northern and central Iraq[34]. Two authors state that their studies were conducted in rural areas, with one in Australia and one in Vietnam. The latter study included areas with mine fields, and three patients had been involved in mine accidents. This study also included children; however, the vast majority of included patients were likely adults because the mean ages of the groups were 35.5 years and 36.9 years. Therefore, this study was included.

Risk of bias assessment

Our assessments regarding each bias domain is provided in figure 2. Some trials had a high risk of bias, with the main reasons being lack of random sequence generation, lack of allocation concealment and lack of blinding of patients, personnel and outcome assessors.

Comparisons

The included studies covered five comparisons involving ketamine (table 1):

- Ketamine i.v. vs. opioids (morphine[37], fentanyl[36], pentazocine[34]) i.v.
- Ketamine i.v. and morphine i.v. vs. only morphine i.v.[30 33 35]
- Ketamine i.v. given as continuous administration vs. ketamine i.v. as single dose[32]

- Ketamine intranasally and nitrous oxide vs. only nitrous oxide[31]
- Ketamine i.v. vs. no analgesia/no medication[34]

We give a short description of the included studies in table 1, while the excluded studies are presented with their reason for exclusion in appendix 2. Note that one study contributed to two comparisons[34], meaning that 713 patients who received ketamine are compared twice, first with patients who received opioids and again with patients who did not receive analgesic treatment.

Ketamine vs. opioids

A change in pain score was reported in two studies. Bronsky and coworkers[36] used the numeric pain rating scale (NRS), where 1 represents no pain and 10 represents extreme pain, while Tran and coworkers[37] measured the change in pain using the visual analogue scale (VAS) but did not explicitly give a range. Figure 3 shows that both studies reported a greater reduction in pain scores with ketamine than with the opioids fentanyl and morphine.

The main outcome in the study by Losvik and coworkers[34] was the physiological severity score (PSS). The PSS was calculated from the blood pressure, respiratory rate and consciousness level[38]. They reported exactly the same change, at 1.5 (95% CI 1.4 to 1.6), in the PSS for both the ketamine and the pentazocine groups. Hence, no difference was found between the treatment groups.

Adverse events were reported in the Vietnamese study[37]; fewer patients with nausea and vomiting were found in the ketamine group than in the morphine group and fewer patients with agitation were found in the morphine group than in the ketamine group (figure 4).

In the study where ketamine and fentanyl were compared[36], four adverse events were reported: two patients experienced respiratory compromise, and two patients suffered haemodynamic instability. All four patients were in the fentanyl group.

The change in Glasgow coma scale (GCS) was measured by Bronsky[36] and coworkers and found to be similar for ketamine and fentanyl, MD -0.13 (95% CI -0.33 to 0.07).

Ketamine and morphine vs. only morphine

Changes in the pain scores were measured in the Australian study[30] using a scale from 0 to 10 and in the Swedish study[35] using a scale from 1 to 10. For both studies, 10 represented extreme pain. In the French study[33], a scale from 0 to 100 was used, and we have transferred this to a 0 to 10 scale in order to include this study in the meta-analysis. Figure 5 shows the change in the pain score when prehospital patients received both ketamine and morphine compared with patients who received only morphine. The RCT performed by Jennings and coworkers[30] found lower pain scores in patients receiving combined ketamine and morphine than in patients receiving only morphine. The RCT by Galinski and coworkers and the small prospective cohort[39] showed a trend in the same direction.

Adverse events were measured in both studies, and the results are illustrated in figure 6 It is important to note that the nausea and vomiting are included in the total adverse events in the RCTs. These results are characterized by few events but indicate that morphine alone may lead to fewer adverse events than the combination of ketamine and morphine.

The RCT by Jennings and coworkers[30] measured the GCS score and found that the median score was unchanged between initial assessment and the follow-up time, with a median score of 15 for both groups.

The French RCT reported use of fewer boluses of morphine when combined with ketamine (1 bolus (95%. CI 0 to 2) compared with 2.3 boluses (95% CI 1.8 to 3.8) when using morphine alone).

The Swedish, prospective cohort by Johansson and coworkers[39] reported a non-significant trend for shorter treatment time with morphine alone than with ketamine and morphine combined (10 min (95% CI -1.4 to 21.4).

Continuous ketamine administration vs. ketamine given as a bolus

One multicentre RCT conducted in France compared the continuous administration of ketamine with a bolus dose of ketamine, but both groups also received morphine[32]. Changes in pain were measured using a VAS from 0 to 10 (worst). and were similar in both groups (VAS -0.6 (95% CI -1.84 to 0.64)).

The main outcome of this study was the amount of additional morphine used (mg/kg) (p=0.18), indicating that there was no difference between the continuous group, at 0.048 (1st quartile, 3rd quartile 0.000, 0.150), and the bolus group, at 0.107 (1st quartile, 3rd quartile 0.052, 0.150). The duration of care for both groups was 35 minutes. Nausea and vomiting were not reported in patients in the continuous group but were reported in three patients in the bolus group.

Ketamine and nitrous oxide vs. only nitrous oxide

To measure the proportion of patients with a reduction in the pain score of 2 or more points, Andolfatto and coworkers used a verbal NRS pain score with a range from 0 (no pain at all) to 10 (extreme pain) and evaluated the scores after 15 minutes and 30 minutes[31]. More patients in the ketamine and nitrous oxide group had a reduction in pain of 2 or more points than those in the saline and nitrous oxide group at both time points (figure 7).

They reported no serious adverse effects in either group, but a considerable number of minor adverse events, such as feeling of unreality, dizziness, nausea, fatigue, general discomfort, mood change, hallucination, change in hearing and headache, occurred. Most of these side effects (52 of 66 events) were reported in the group of patients who received ketamine and nitrous oxide combined, as shown in figure 8.

Ketamine vs. no analgesic treatment

The retrospectively matched observational study of patients/causalities in the war zone in Iraq compared the use of ketamine with no analgesic treatment[34]. The main outcome in this study was the PSS, which was calculated from the blood pressure, respiratory rate and consciousness level. There was a non-significant trend for lower PSS with ketamine compared with no analgesics (MD -0.2 (95% CI -0.42 to 0.02)).

GRADE

The quality of the main outcomes for the comparisons involving the use of ketamine for the treatment of prehospital acute pain, was assessed according to the GRADE method[29]. The quality of evidence could be downgraded for various reasons (risk of bias, inconsistency, indirectness, imprecision and publication bias). Consequently, the quality of the evidence was classified as high, moderate, low or very low. As described in table 2, we have for many of these outcomes downgraded for study limitations/high risk of bias, or for imprecision because there were few events in many of these studies.

Discussion

In this systematic review addressing the effect and safety of prehospital administration of ketamine in analgesic doses, we included eight studies with 2,760 patients. The studies were heterogeneous in terms of setting, patient population and outcomes explored, as well as in their comparators, such as i.v. or intranasal ketamine with a variety of opioids or with nitrous oxide. In addition, a single dose of ketamine was compared with ketamine which was administered continuously. Although the evidence base includes five RCTs, five of the eight included studies have a high risk of bias. The RCTs were relatively small studies with 63, 65, 120, 135 and 308 patients included, respectively. The eight studies cover five different comparisons, so the amount of research evidence for each comparison is sparse. Only one of the outcomes in one of the comparisons has been measured in more than one study of similar design, and several of the outcomes has not been assessed in a prehospital study at all. When using GRADE to assess our confidence in the estimates, we more often than not, downgraded for high risk of bias or imprecision due to very few events or wide confidence intervals. Three of the eight included studies are observational studies. They have an initial high risk of bias compared to RCTs due to the lack of randomization. This is acknowledged in GRADE where observational studies start at low quality of evidence. Lack of blinding is a weakness in all of these studies. This becomes a challenge when the main outcome is subjective, pain, and we have downgraded for high risk of bias. However, there is moderate quality of the evidence for the main outcome, change in pain score, for one of the comparisons.

Two of the studies were conducted in Iraq and in Vietnam, respectively, where a number of patients were injured in mine accidents. These studies were the largest studies and included 1,909 patients. It is reasonable to assume that the results from studies conducted in war zones are not directly applicable in civilian settings since the victims tend to be male, relatively young and previously healthy and are not representative of trauma victims in general. The study from Iraq did not report on any of our predefined outcomes.

Clinical implications

Ketamine administered in analgesic doses (0.1-0.2 mg/kg) i.v. appears to be at least as effective as opioids administered alone considering pain reduction. In the study from Iraq, an initial dose of ketamine (0.2 mg/kg) was given in all cases of penetrating trauma and burns, but patients with TBI or blunt injury received only pentazocine[34]. The patients in the study conducted by Tran and coworkers received 0.2-0.3 mg/kg i.v. of ketamine[37]. Four[32 33 35 36] of the other five

studies included studies administered ketamine in 0.2-0.3 mg/kg i.v. doses, while in the last i.v. study[30], the patients received 10-20 mg i.v. of ketamine. In the study where ketamine was administered intranasally, the patients received an average of 0.75 mg/kg of ketamine[31]. Hence, the patients in all studies received appropriate analgesic doses of ketamine.

In general, very few adverse effects were reported in the included studies. Analgesic doses of ketamine resulted in more adverse events than those associated with opioids administered alone, with the exception of agitation, which was relatively more common in the ketamine group in the study performed by Tran and coworkers. Bronsky and coworkers reported that two patients experienced respiratory compromise and two suffered haemodynamic instability. All four patients were in the fentanyl group.

Given the safety profile of ketamine and the results reported in the included studies, it appears reasonable to suggest that low-dose ketamine for analgesic purposes can be administered safely during prehospital emergency care when proper indications and contraindications are identified. Prehospital healthcare providers with a level of training suitable to administer ketamine – that is personnel that are trained to handle potential adverse effects – must be identified. None of the included studies had enough power to detect differences in rare events (adverse events), and the quality of evidence was poor. One of the studies showed an increased number (pooled) of adverse events in the group receiving ketamine and morphine, indicating that an improved analgesic effect increases the risk for adverse events. It is unclear whether adverse events are more likely to occur with opioids than with ketamine. However, it is essential to note that our recommendations cover ketamine administered in analgesic doses and not in sedative and anaesthetic doses where advanced skills are required to be able to handle the patient in an adequate manner.

Studies from other settings

Ketamine is widely applied both prehospitally and in the hospital for rapid sequence induction of patients who are haemodynamically unstable[40]. In a recent systematic review and meta-analysis Yousefifard and coworkers included seven studies and pooled the effect estimates of observational and randomised interventional studies[41]. They concluded that ketamine is an effective and safe medication in prehospital pain management in trauma patients and can be considered as an acceptable alternative to opioids. The analgesic effect of low-dose ketamine is also employed in the hospital. In a recent systematic review and meta-analysis, Karlow and

coworkers studied ketamine as an alternative to opioids for acute pain in the emergency department (ED)[42]. The authors concluded that ketamine can be used an alternative to opioids in the ED, as they found that ketamine was noninferior to opioids. They also found that the rate of non-severe adverse effects was higher with ketamine. It is unclear to what extent results from ED studies can be extrapolated to the prehospital setting. However, when ketamine is administered by physicians with similar qualifications to patients with comparable pathophysiology in the two arenas, it seems reasonable to assume that the safety profile of the drug will be the same in both settings. This is the case for many prehospital services in Europe and Australia where anaesthesiologists and emergency physicians work in the emergency medical service. However, it is not obvious that the safety profile of ketamine in the prehospital setting is independent of the qualifications of the health care provider that administers the drug. Studies specifically addressing prehospital non-physician care providers administering ketamine should therefore be conducted. The body of evidence for benefit and possible harm is limited as few studies have been performed. Future studies need to address all relevant side effects, the optimal drug dose as well as all relevant outcome measures.

Conclusion:

This systematic review of the current literature indicates that ketamine is relatively safe and effective analgesic when administered by prehospital health providers with relevant training.

Acknowledgements

We thank research librarian Jane Kjemtrup Andersen (Viborg Regional Hospital, Denmark) for developing the search strategies.

Funding:

Scandinavian Society of Anaesthesiology and Intensive care medicine (SSAI) funded meetings and software costs. The Norwegian Air Ambulance Foundation funded publication costs. Otherwise this research received no further grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors contributions:

MS supervised the process of drafting this manuscript and coordinated all identification, data extraction and appraisal of included manuscripts. MS and either PKH, MR or PK independently assessed all potential eligible articles for inclusion. GEV coordinated all methodological

support. All authors are members of the SSAI task force on pre-hospital pain management and participated in design, manuscript drafting and revisions of the manuscript.

References

1. Jennings PA, Cameron P, Bernard S. Epidemiology of prehospital pain: an opportunity for improvement. *Emerg Med J* 2011;28(6):530-1.
2. Albrecht E, Taffe P, Yersin B, et al. Undertreatment of acute pain (oligoanalgesia) and medical practice variation in prehospital analgesia of adult trauma patients: a 10 yr retrospective study. *Br J Anaesth* 2013;110(1):96-106.
3. Galinski M, Ruscev M, Gonzalez G, et al. Prevalence and management of acute pain in prehospital emergency medicine. *Prehosp Emerg Care* 2010;14(3):334-9.
4. Bounes V, Barniol C, Minville V, et al. Predictors of pain relief and adverse events in patients receiving opioids in a prehospital setting. *Am J Emerg Med* 2011;29(5):512-7.
5. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther* 1965;6:279-91.
6. Aroni F, Iacovidou N, Dontas I, et al. Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. *J Clin Pharmacol* 2009;49(8):957-64.
7. Lodge D, Anis NA, Burton NR. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurones by amino acids and acetylcholine. *Neurosci Lett* 1982;29(3):281-6.
8. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg* 1966;45(1):29-40.
9. Sadove MS, Shulman M, Hatano S, et al. Analgesic effects of ketamine administered in subdissociative doses. *Anesth Analg* 1971;50(3):452-7.
10. Porter K. Ketamine in prehospital care. *Emerg Med J* 2004;21(3):351-4.
11. White PF, Way WL, Trevor AJ. Ketamine--its pharmacology and therapeutic uses. *Anesthesiology* 1982;56(2):119-36.
12. Svenson JE, Abernathy MK. Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med* 2007;25(8):977-80.
13. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. *Anesth Analg* 2003;96(3):789-95.
14. Kochs E, Scharein E, Mollenberg O, et al. Analgesic efficacy of low-dose ketamine. Somatosensory-evoked responses in relation to subjective pain ratings. *Anesthesiology* 1996;85(2):304-14.
15. Wedmore IS, Johnson T, Czarnik J, et al. Pain management in the wilderness and operational setting. *Emerg Med Clin North Am* 2005;23(2):585-601.
16. Craven R. Ketamine. *Anaesthesia* 2007;62 Suppl 1:48-53.
17. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: Part 2, Review and implications. *Ann Emerg Med* 1990;19(9):1033-46.
18. Kye YC, Rhee JE, Kim K, et al. Clinical effects of adjunctive atropine during ketamine sedation in pediatric emergency patients. *Am J Emerg Med* 2012;30(9):1981-5.
19. Bourgoin A, Albanese J, Leone M, et al. Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. *Crit Care Med* 2005;33(5):1109-13.

20. Bourgoin A, Albanese J, Wereszczynski N, et al. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Crit Care Med* 2003;31(3):711-7.
21. Albanese J, Arnaud S, Rey M, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology* 1997;87(6):1328-34.
22. Bar-Joseph G, Guilburd Y, Tamir A, et al. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr* 2009;4(1):40-6.
23. Sherwin TS, Green SM, Khan A, et al. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* 2000;35(3):229-38.
24. McManus JG, Jr., Sallee DR, Jr. Pain management in the prehospital environment. *Emerg Med Clin North Am* 2005;23(2):415-31.
25. Kennedy RM, Porter FL, Miller JP, et al. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics* 1998;102(4):956-63.
26. McGuinness SK, Wasiak J, Cleland H, et al. A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* 2011;12(10):1551-8.
27. Bonanno FG. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). *Injury* 2002;33(4):323-7.
28. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration. 2011.
29. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490-7.
30. Jennings PA, Cameron P, Bernard S, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. *Ann Emerg Med* 2012;59(6):497-503.
31. Andolfatto G, Innes K, Dick W, et al. Prehospital Analgesia With Intranasal Ketamine (PAIN-K): A Randomized Double-Blind Trial in Adults. *Ann Emerg Med* 2019; 74;241-50
32. Wiel E, Zitouni D, Assez N, et al. Continuous Infusion of Ketamine for Out-of-hospital Isolated Orthopedic Injuries Secondary to Trauma: A Randomized Controlled Trial. *Prehosp Emerg Care* 2015;19(1):10-16.
33. Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med* 2007;25(4):385-90.
34. Losvik OK, Murad MK, Skjerve E, et al. Ketamine for prehospital trauma analgesia in a low-resource rural trauma system: a retrospective comparative study of ketamine and opioid analgesia in a ten-year cohort in Iraq. *Scand J Trauma Resusc Emerg Med* 2015;23:94.
35. Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting. *Scand J Trauma Resusc Emerg Med* 2009;17:61.
36. Bronsky ES, Koola C, Orlando A, et al. Intravenous Low-Dose Ketamine Provides Greater Pain Control Compared to Fentanyl in a Civilian Prehospital Trauma System: A Propensity Matched Analysis. *Prehospital Emerg Care* 2018:1-8.
37. Tran KP, Nguyen Q, Truong XN, et al. A comparison of ketamine and morphine analgesia in prehospital trauma care: a cluster randomized clinical trial in rural Quang Tri province, Vietnam. *Prehosp Emerg Care* 2014;18(2):257-64.

38. Champion HR, Sacco WJ, Copes WS, et al. A revision of the Trauma Score. *J Trauma* 1989;29(5):623-9.
39. Johansson J, Sjoberg J, Nordgren M, et al. Prehospital analgesia using nasal administration of S-ketamine--a case series. *Scand J Trauma Resusc Emerg Med* 2013;21:38.
40. Kramer N, Lebowitz D, Walsh M, et al. Rapid Sequence Intubation in Traumatic Brain-injured Adults. *Cureus* 2018;10(4):e2530.
41. Yousefifard M, Askarian-Amiri S, Rafiei Alavi SN, et al. The Efficacy of Ketamine Administration in Prehospital Pain Management of Trauma Patients; a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med* 2020;8(1):e1.
42. Karlow N, Schlaepfer CH, Stoll CRT, et al. A Systematic Review and Meta-analysis of Ketamine as an Alternative to Opioids for Acute Pain in the Emergency Department. *Acad Emerg Med* 2018;25(10):1086-97.

Table 1. Summary of included studies

Reference Study design Country	Ketamine	Comparison	Outcomes
Ketamine i.v. versus opioids i.v.			
Bronsky 2018 Retrospective cohort USA	n=79, ketamine 0.3 mg/kg i.v. every 20 min as needed, maximum three doses	n=79, fentanyl 2 µg/kg bolus i.v. over 1 to 2 min with additional dose every 10 min as needed	Change in pain scores, serious adverse events, GCS
Losvik 2015 Retrospective cohort Iraq	n=713, ketamine 0.2 mg/kg i.v., in case of unrest, 5 mg diazepam i.v. During protracted evacuations with repeated ketamine doses, 1 mg atropine was administered. Repeat doses of ketamine allowed.	n=888, pentazocine 0.4 mg/kg i.v. for adults, repeat doses allowed	Change in physiological severity score
Tran 2014 Cluster- RCT Vietnam	n=169, ketamine 0.2 to 0.3 mg/kg was administered as slow intermittent i.v. injections	n=139, morphine administered in one single i.m. dose; 10 mg for adult patients, 5 mg for paediatric patients	Change in pain score, serious adverse events, adverse events, satisfaction, mean treatment time (head trauma)
Ketamine and morphine i.v. versus morphine i.v. alone			
Galinski 2007 RCT France	n=33, ketamine 0.2 mg/kg i.v. in 3 mg morphine every 5 min if necessary	n=32, morphine 3 mg i.v. every 5 min if necessary	Change in pain score, adverse events
Jennings 2012 RCT Australia	n=70, morphine 5 mg i.v. initial dose followed by a ketamine bolus of 10 or 20 mg according to body size, followed by 10 mg ketamine every 3 min thereafter until pain was relieved	n=65, morphine 5 mg i.v. initial dose followed by 5 mg i.v. every 5 min until pain was relieved	Change in pain score, adverse events, GCS
Johansson 2009 Prospective cohort	n=16, morphine 0.1 mg/kg i.v. followed by ketamine 0.2 mg/kg if pain score ≥4 after 5 min	n= 11, mg/kg morphine 0.1 mg/kg i.v. followed by	Change in pain score, adverse event, mean treatment time

Sweden		morphine 0.1 mg/kg if pain score ≥4 after 5 min	
Ketamine continuous i.v. administration versus ketamine i.v. one dose			
Wiel 2014 RCT France	n=30, all patients received ketamine 0.2 mg/kg i.v. bolus combined with morphine 0.1 mg/kg i.v. followed by ketamine 0.2 mg/kg/h. Additional morphine 0.05 mg/kg was allowed every 5 min if VAS > 3/10	n=33, all patients received a ketamine 0.2 mg/kg i.v. bolus combined with morphine 0.1 mg/kg i.v. followed by a saline infusion of the same volume. Additional morphine 0.05 mg/kg was allowed every 5 min if the VAS > 3/10	Change in pain score, adverse events, satisfaction
Intranasal ketamine and inhaled nitrous oxide versus only inhaled nitrous oxide			
Andolfatto 2019 RCT Canada	n=60, all patients received approx. 0.75 mg/kg intranasal ketamine (30 mg for patients < 50 kg, 50 mg for patients 50-100 kg, 75mg for patients > 100 kg) combined with inhaled nitrous oxide	n=60, all patients received inhaled nitrous oxide	Change in pain score, adverse events, satisfaction
Ketamine i.v. versus no analgesic treatment			
Losvik 2015 Retrospective cohort Iraq	n=713, ketamine 0.2 mg/kg i.v., in case of unrest, 5 mg diazepam i.v. During protracted evacuations with repeated ketamine doses, 1 mg atropine was administered. Repeat doses of ketamine allowed.	n=275, no analgesic treatment	Change in physiological severity score

Table 2. Summary of findings for the comparisons. ***The risk in the intervention group** (and its 95% CI) assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **GRADE Working Group grades of evidence: High certainty:** We are very confident that the true effect is similar to that of the estimated effect. **Moderate certainty:** We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimated effect. **Very low certainty:** We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimated effect.

Ketamine compared to opioids for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in the USA and Vietnam
Intervention: Ketamine
Comparison: Opioids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with opioids	Risk with ketamine				
Change in pain score assessed with VAS	The mean change in the pain score was 3.1	The mean change in the pain score in the intervention group was 0.4 less (0.8 less to 0)	-	308 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Change in pain score assessed with NRS scale from: 1 to 10	The mean change in the pain score was 2.5	The mean change in pain score in the intervention group was 3 less (3.86 less to 2.14 less)	-	158 (1 observational study)	⨁⨁◯◯ LOW	
Serious adverse events	51 per 1,000	0 per 1,000 (0 to 0)	Not estimable	158 (1 observational study)	⨁⨁◯◯ VERY LOW [b]	
Nausea and vomiting	194 per 1,000	47 per 1,000 (21 to 101)	RR 0.24 (0.11 to 0.52)	308 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Agitation	14 per 1,000	112 per 1,000 (27 to 474)	RR 7.81 (1.85 to 32.97)	308 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	

Explanations: a. High risk of bias, b: Only 4 events

Ketamine and morphine compared to only morphine for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in Sweden, France and Australia
Intervention: Ketamine and morphine
Comparison: Only morphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with only morphine	Risk with ketamine and morphine				
Change in pain scores Scale from: 1 to 10	The mean change in pain scores was 3.5	Mean 1.51 lower (3.36 lower to 0.33 higher)	-	135 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	

Ketamine and morphine compared to only morphine for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in Sweden, France and Australia
Intervention: Ketamine and morphine
Comparison: Only morphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with only morphine	**Risk with ketamine and morphine**				
Change in pain scores Scale from: 1 to 10	The mean change in pain score was 3.1	Mean 1.3 lower (2.95 lower to 0.35 higher)	-	27 (1 observational study)	⨁◯◯◯ VERY LOW [a]	
Serious adverse events	Not reported		Not estimable	-	-	None of the 2 studies reported any serious adverse events
Total number of adverse events	165 per 1 000	468 per 1 000 (289 to 764)	RR 2.84 (1.75 to 4.63)	200 (2 RCTs)	⨁⨁⨁◯ MODERATE [b]	

Explanations: a. This cohort only has 27 patients included b, Unclear randomization and open label

Continuous administration of ketamine compared to ketamine given as a bolus for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in France
Intervention: Continuous administration of ketamine
Comparison: Ketamine given as a bolus

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ketamine given as a bolus	**Risk with the continuous administration of ketamine**				
Change in pain scores. Scale from 0 to 10	The mean change in the pain score was 3.1	The mean change in pain score in the intervention group was 0.6 less (1.84 less to 0.64 more)	-	63 (1 RCT)	⨁⨁◯◯ LOW [a]	
Serious adverse events	-	-	not estimable	(1 study)	-	No serious events were reported
Nausea and vomiting	91 per 1,000	0 per 1,000 (0 to 0)	not estimable	63 (1 RCT)	⨁⨁◯◯ VERY LOW [a, b]	

Explanations: a. One study included only 63 patients, b. Only 3 events

Ketamine and nitrous oxide compared to only nitrous oxide for prehospital pain management

Patient or population: Prehospital pain management

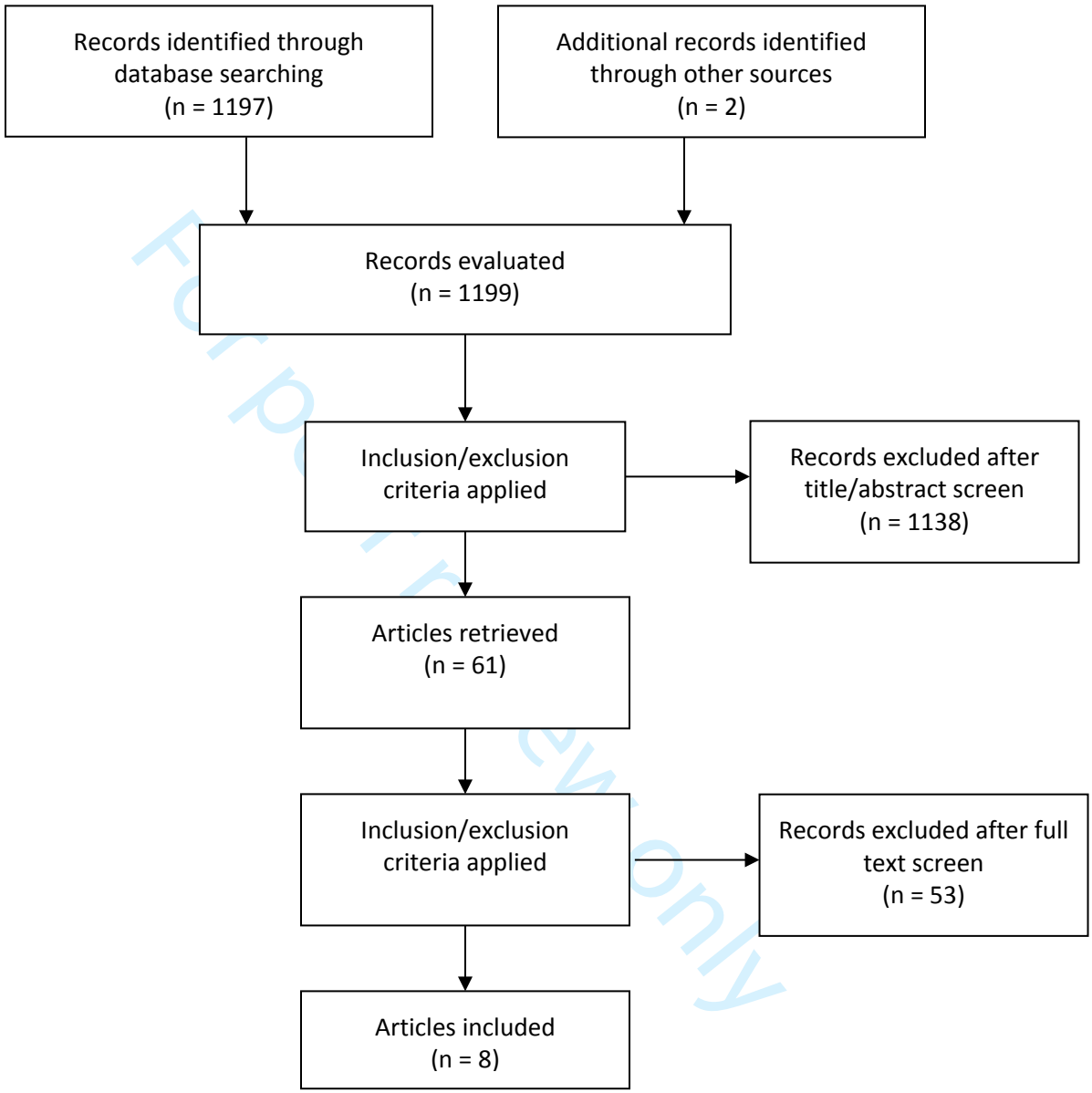
Setting: Prehospital setting in Canada

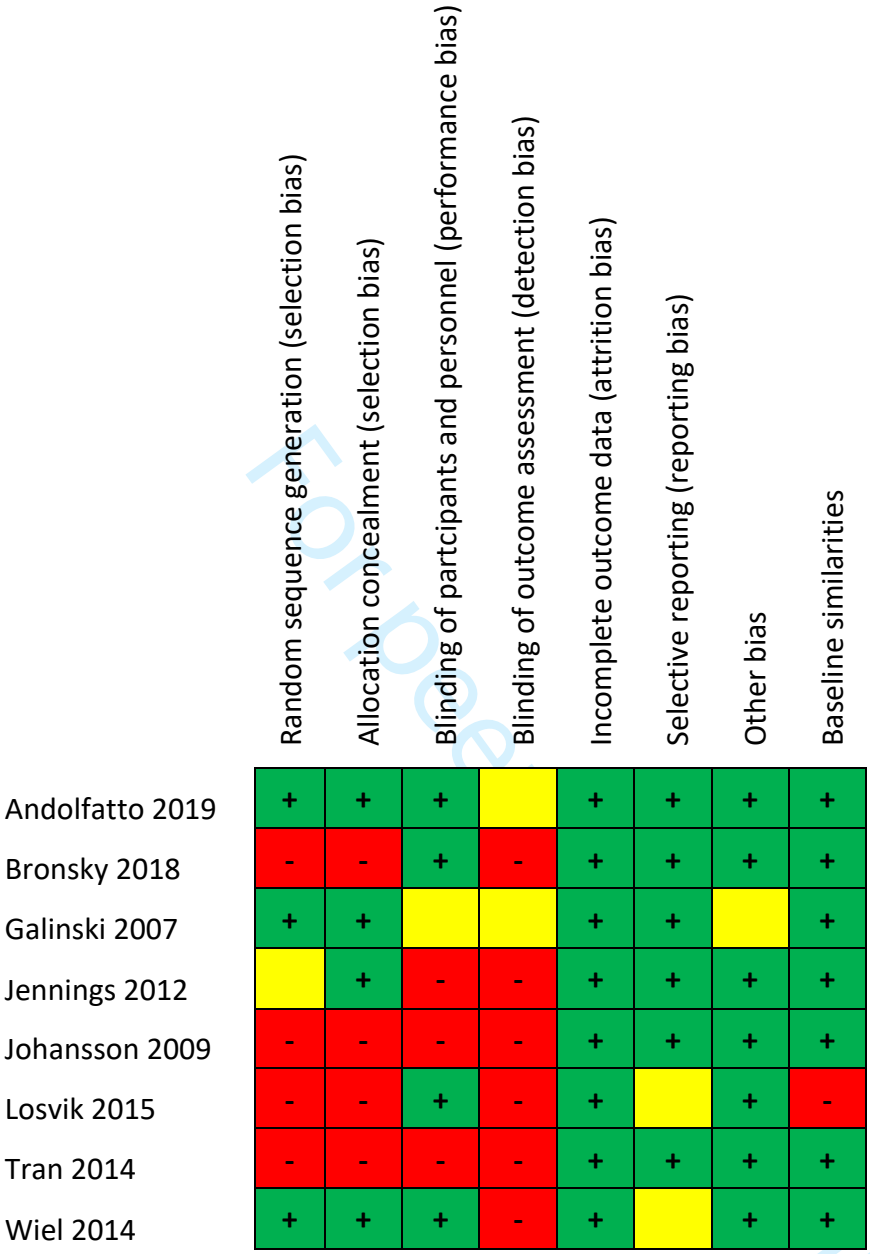
Intervention: Ketamine and nitrous oxide

Comparison: Only nitrous oxide

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with only nitrous oxide	Risk with ketamine and nitrous oxide				
≥2 point reduction in pain, 15 minutes	350 per 1 000	634 per 1 000 (427 to 931)	RR 1.81 (1.22 to 2.66)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
≥2 point reduction in pain, 30 minutes	407 per 1 000	758 per 1 000 (534 to 1 000)	RR 1.86 (1.31 to 2.66)	108 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
Serious adverse events	0 per 1 000	0 per 1 000 (0 to 0)	Not estimable	(1 RCT)	-	
Total number of adverse events	233 per 1 000	866 per 1 000 (541 to 1 000)	RR 3.71 (2.32 to 5.31)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
Number of patients with adverse events	200 per 1 000	616 per 1 000 (358 to 1 000)	RR 3.08 (1.79 to 5.31)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	

Explanations: a. Only one study with a total of 120 patients, large effect but unclear blinding





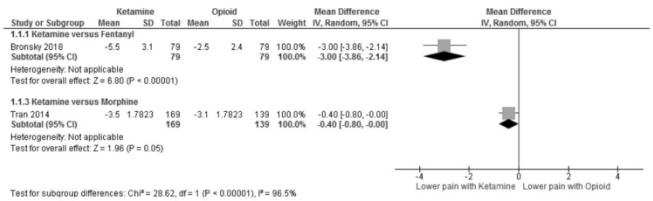


Fig. 3 - Ketamine versus opioids - change in pain score

583x825mm (72 x 72 DPI)

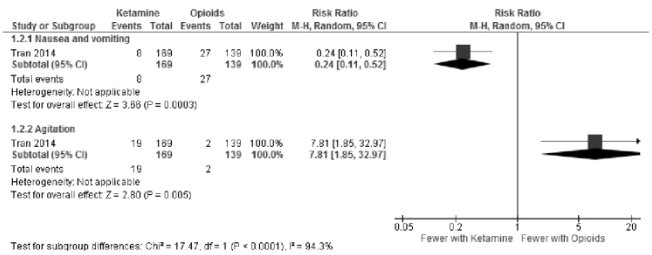


Fig. 4 - Ketamine versus opioids - adverse events

209x297mm (200 x 200 DPI)

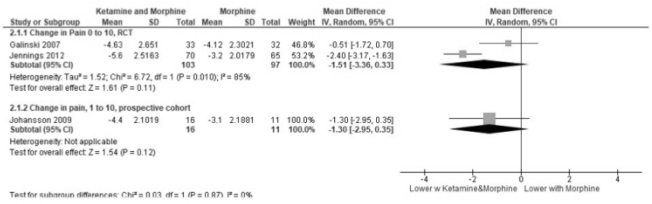


Fig. 5 - Combined ketamine and morphine compared with only morphine - change in pain score

209x296mm (150 x 150 DPI)

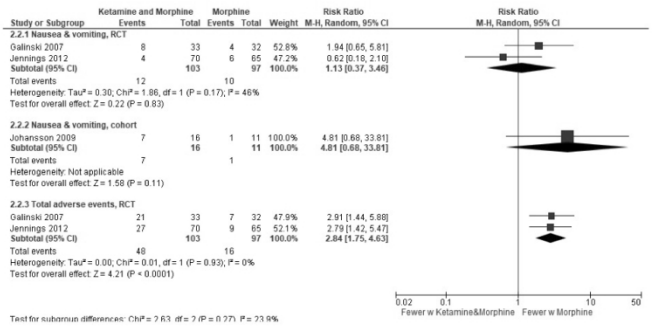


Fig. 6 - Combined ketamine and morphine compared with only morphine - adverse events

209x296mm (150 x 150 DPI)

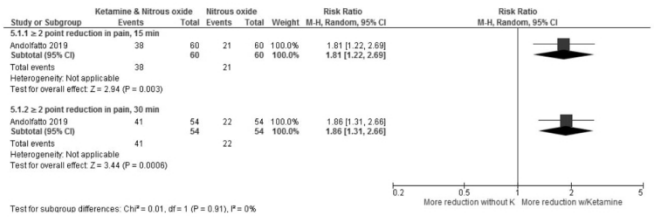


Fig. 7 - Ketamine and N2O vs only N2O - change in pain score

583x825mm (72 x 72 DPI)

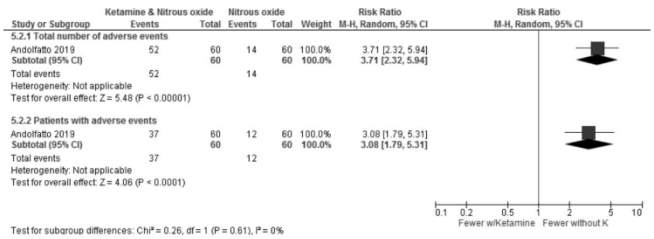


Fig. 8 - Ketamine and N2O vs only N2O - adverse events

583x825mm (72 x 72 DPI)

SEARCH STRATEGIES

PUBMED

#1,"Search ketamine[Text Word]"
#2,"Search analgesics, ketamine[Pharmacological Action]"
#3,"Search ketamine[MeSH Terms]"
#4,"Search (#1 OR #2 OR #3)"
#5,"Search emergency medical services[MeSH Terms]"
#6,"Search Ambulances[MeSH Terms]"
#7,"Search Ambulance*[Text Word]"
#8,"Search Prehospital[Text Word]"
#9,"Search Pre-hospital[Text Word]"
#10,"Search out of hospital[Text Word]"
#11,"Search Paramed*[Text Word]"
#12,"Search emergency medical technicians[MeSH Terms]"
#13,"Search (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)"
#14,"Search Danish[Language]"
#15,"Search Norwegian[Language]"
#16,"Search Swedish[Language]"
#17,"Search English[Language]"
#18,"Search (#14 OR #15 OR #16 OR #17)"
#19,"Search (#4 AND #13 AND #18)"
#20,"Search Animals[MeSH Terms]"
#21,"Search Humans[MeSH Terms]"
#22,"Search (#20 NOT #21)"
#23,"Search (#19 NOT #22)"
#24,"Search (""xxxx/xx/xx""[Date - Entrez]: ""xxxx/xx/xx""[Date - Entrez])"
#25,"Search (#23 AND #24)"

EMBASE

#1, analgesic agent/
#2, ketamine.m._titl.
#3, rescue personnel/
#4, ambulance/
#5, emergency health service/
#6, “emergency medical technician*”.ab,ti.
#7, “emergency responder*”.ab.ti.
#8, rescue service. ab.ti.
#9, “Paramed*”. ab.ti.
#10, “ambulance*”. ab.ti.
#11, pre-hospital. ab.ti.
#12, prehospital. ab.ti.
#13, out-of-hospital. ab.ti.
#14, or/3-13
#15, or/1-2
#16, and/14-15

Cochrane Library

#1 MeSH descriptor: [Ketamine] explode all trees
#2 MeSH descriptor: [Emergency Medical Technicians] explode all trees
#3 MeSH descriptor: [Ambulances] explode all trees
#4 paramed*
#5 out-of-hospital
#6, pre-hospital
#7, prehospital
#8, ambulance*
#9, #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10, #1 AND # 9

Epistemonikos

(title:((title:(prehospital OR pre-hospital OR out-of-hospital OR ambulance* OR "emergency medical technicians" OR "emergency medical service*") OR abstract:(prehospital OR pre-hospital OR out-of-hospital OR ambulance* OR "emergency medical technicians" OR "emergency medical service*")) AND (title:(ketamin*) OR abstract:(ketamin*)))

Appendix 2

Excluded reference	Reason for exclusion
Allison K, Porter K. Consensus on the pre-hospital approach to burns patient management. Injury 2004; 35: 734-8.	Ketamine not central in the text
Anonymous. Comments on the recommendations of the German Medical Society dated October 20, 2003 on the administration of analgesics by paramedics in emergency situations. Notarzt 2005; 21: 81-82.	Excluded due to language restrictions
Ansem RP, Hartman JA, Foudraine JF, van Loenen E, Rutten FL. [Analgetic ketamine feasible in ambulance emergency care]. Ned Tijdschr Geneeskd 1994; 138: 2301-4.	Excluded due to language restrictions
Ardeel E. Adverse effects following prehospital use of ketamine by paramedics. Acad Emerg Med 2012; 19: S269-S70.	Letter
Aries P, Montelescaut E, Pessey F, Danguy des Deserts M, Giacardi C. Pre-hospital emergency medicine: pain control. Lancet 2016; 387: 747.	Ketamine not central in the text
Arroyo-Novoa CM, Figueroa-Ramos MI, Miaskowski C, Padilla G, Paul SM, Rodriguez-Ortiz P, Stotts NA, Puntillo KA. Efficacy of small doses of ketamine with morphine to decrease procedural pain responses during open wound care. Clin J Pain 2011; 27: 561-6.	Patient population did not match the criteria
Barrett TW, Schriger DL. Move over morphine: Is ketamine an effective and safe alternative for treating acute pain? Answers to the September 2015 journal club. Ann Emerg Med 2016; 67: 289-94.	Setting did not match the criteria
Berg C. Out-of-hospital ketamine for pain, agitation, and airway intervention is safe and effective. Ann Emerg Med 2015; 66: S32.	Study design did not match the criteria
Bredmose PP, Grier G, Davies GE, Lockey DJ. Pre-hospital use of ketamine in paediatric trauma. Acta Anaesthesiol Scand 2009; 53: 543-5.	Patient population did not match the criteria

Bredmose PP, Lockey DJ, Grier G, Watts B, Davies G. Pre-hospital use of ketamine for analgesia and procedural sedation. EMJ 2009; 26: 62-4.	Study design did not match the criteria
Brokmann JC, Rossaint R, Hirsch F, Beckers SK, Czaplik M, Chowanetz M, Tamm M, Bergrath S. Analgesia by telemedically supported paramedics compared with physician-administered analgesia: A prospective, interventional, multicentre trial. Eur J Pain 2016; 20: 1176-84.	Ketamine not central in the text
Butler FK, Kotwal RS, Buckenmaier CC, 3rd, Edgar EP, O'Connor KC, Montgomery HR, Shackelford SA, Gandy JV, 3rd, Wedmore IS, Timby JW, Gross KR, Bailey JA. A triple-option analgesia plan for tactical combat casualty care: TCCC guidelines change 13-04. J Spec Oper Med 2014; 14: 13-25.	Study design did not match the criteria
Castle N, Naidoo R. Achieving prehospital analgesia. EMJ 2012; 29: 765-6.	Setting did not match the criteria
Castren M, Lindstrom V, Branzell JH, Niemi-Murola L. Prehospital personnel's attitudes to pain management. Scand J Pain 2015; 8: 17-22.	Study design did not match the criteria
Chesters A, Webb T. Ketamine for procedural sedation by a doctor-paramedic prehospital care team: a 4-year description of practice. Eur J Emerg Med 2015; 22: 401-6.	Patient population did not match the criteria
Corrigan M, Wilson SS, Hampton J. Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings. Am J Health Syst Pharm 2015; 72: 1544-54.	Study design did not match the criteria
Domonoske B, Gunter R, Love J. Ketamine may increase the risk of PE in selected trauma patients. Crit Care Med 2014; 42: A1610.	Setting did not match the criteria
Domonoske B, Love J. Ketamine reduces the incidence of VTE in selected trauma patients. Crit Care Med 2013; 41: A55.	Setting did not match the criteria
Eidenbenz D, Taffe P, Hugli O, Albrecht E, Pasquier M. A two-year retrospective review of the determinants of pre-hospital analgesia administration by alpine helicopter	Study design did not match the criteria

emergency medical physicians to patients with isolated limb injury. Anaesthesia 2016; 71: 779-87.	
Ellerton J, Paal P, Brugger H. Prehospital use of ketamine in mountain rescue. EMJ 2009; 26: 760-1.	Letter
Fisher AD, Rippee B, Shehan H, Conklin C, Mabry RL. Prehospital analgesia with ketamine for combat wounds: a case series. J Spec Oper Med 2014; 14: 11-7.	Study design did not match the criteria
Galinski M, Hoffman L, Bregeaud D, Kamboua M, Ageron FX, Rouanet C, Hubert JC, Istria J, Ruscev M, Tazarourte K, Pevirieri F, Lapostolle F, Adnet F. Procedural sedation and analgesia in trauma patients in an out-of-hospital emergency setting: A prospective multicenter observational study. Prehosp Emerg Care 2018; 22: 497-505.	Patient population did not match the criteria
Gausche-Hill M, Brown KM, Oliver ZJ, Sasson C, Dayan PS, Eschmann NM, Weik TS, Lawner BJ, Sahni R, Falck-Ytter Y, Wright JL, Todd K, Lang ES. An evidence-based guideline for prehospital analgesia in trauma. Prehosp Emerg Care; 18 25-34.	Study design did not match the criteria
Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, McKee M, Weiss M, Pitetti RD, Hostetler MA, Wathen JE, Treston G, Garcia Pena BM, Gerber AC, Losek JD. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. Ann Emerg Med 2009; 54: 171-80.	Patient population did not match the criteria
Guldner GT, Petinaux B, Clemens P, Foster S, Antoine S. Ketamine for procedural sedation and analgesia by nonanesthesiologists in the field: a review for military health care providers. Mil Med 2006; 171: 484-90.	Patient population did not match the criteria
Gurnani A, Sharma PK, Rautela RS, Bhattacharya A Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. Anaesth Intensive Care 1996; 24: 32-6	Patient population did not match the criteria
Henderson L. Special K for special situations. A review of ketamine for prehospital use. JEMS 2016; 41: 58-60.	Study design did not match the criteria

Hossfeld B, Holstrater S, Bernhard M, Lampl L, Helm M, Kulla M. Prehospital analgesia in adults. Anasthesiol Intensivmed Notfallmed Schmerzther 2016; 51: 84-96.	Excluded due to language restrictions
Iqbal M, Spaight PA, Siriwardena AN. Patients' and emergency clinicians' perceptions of improving pre-hospital pain management: A qualitative study. EMJ 2013; 30: e18.	Ketamine not central in the text
Jansen A, Boyle M. Prehospital pain relief, where are we now? A review of the literature. Australas J Paramed 2014; 11: 20.	Ketamine not central in the text
Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. Acta Anaesthesiol Scand 2011; 55: 638-43.	Study design did not match the criteria
Jennings PA, Cameron P, Bernard S. Determinants of clinically important pain severity reduction in the prehospital setting. EMJ 2012; 29: 333-34.	Ketamine not central in the text
Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, Masci K. Long-term pain prevalence and health-related quality of life outcomes for patients enrolled in a ketamine versus morphine for prehospital traumatic pain randomised controlled trial. EMJ 2014; 31: 840-43.	Setting did not match the criteria
Jennings PA, Cameron P, Bernard SA, Walker T, Fitzgerald M, Masci K. Ketamine is superior to morphine alone for the management of traumatic pain in the prehospital setting: A randomised controlled trial. Emerg Med Australas 2012; 24: 19.	Letter
Johansson J, Sjoberg J, Nordgren M, Sandstrom E, Sjoberg F, Zetterstrom H. Prehospital analgesia using nasal administration of S-ketamine--a case series. Scand J Trauma Resusc Emerg Med 2013; 21: 38.	Study design did not match the criteria
Kovar JL, Gleisberg GR, Ardeel ER, Basnawi A, Escott MEA. Hemodynamic changes in patients receiving ketamine sedation by emergency medical services. Acad Emerg Med 2012; 19: S87.	Study design did not match the criteria

Lovrincevic M, Kotob F, Santarosa J. Pain management in the trauma setting. Semin Anesth Perioper Med Pain 2005; 24: 34-40.	Setting did not match the criteria
Madeira F, Ferreira P, Lapa T, Tavares E. Prehospital pain management: Do we have to learn more about it? Eur J Anaesthesiol 2013; 30: 203-04.	Ketamine not central in the text
Marland S, Ellerton J, Andolfatto G, Strapazzon G, Thomassen O, Brandner B, Weatherall A, Paal P. Ketamine: Use in anesthesia. CNS Neurosci Ther 2013; 19: 381-89.	Setting did not match the criteria
McKay WP. Intravenous analgesia for out-of-hospital traumatic pain in adults: ketamine gives a greater reduction in pain than morphine but causes more adverse effects. Evid Based Nurs 2013; 16: 58-9.	Letter
McQueen C, Crombie N, Cormack S, Wheaton S. Prehospital use of ketamine for analgesia and procedural sedation by critical care paramedics in the UK: A note of caution? EMJ 2014; 31: 1029.	Letter
Moy R, Wright C. Ketamine for military prehospital analgesia and sedation in combat casualties. J R Army Med Corps 2018; 164: 436-37.	Study design did not match the criteria
Moy RJ, Le Clerc S. Ketamine in prehospital analgesia and anaesthesia. Trends Anaesth Crit Care 2011; 1: 243-45.	Study design did not match the criteria
Petz LN, Tyner S, Barnard E, Ervin A, Mora A, Clifford J, Fowler M, Bebarta VS. Prehospital and en route analgesic use in the combat setting: a prospectively designed, multicenter, observational study. Mil Med 2015; 180: 14-18.	Study design did not match the criteria
Porter K. Ketamine in prehospital care. EMJ 2004; 21: 351-4.	Study design did not match the criteria
Radvansky BM, Puri S, Sifonios AN, Eloy JD, Le V. Ketamine-a narrative review of its uses in medicine. Am J Ther 2016; 23: e1414-e26.	Study design did not match the criteria
Schauer SG, Mora AG, Maddry JK, Bebarta VS. Multicenter, prospective study of prehospital administration of analgesia in	Study design did not match the criteria

the U.S. combat theater of Afghanistan. Prehosp Emerg Care 2017; 21: 744-49.	
Schonenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. Psychopharmacology (Berl) 2005; 182: 420-5.	Study design did not match the criteria
Scott S, Paul B. UK and Victorian, Acute pain guidelines compared. Australas J Paramed 2013; 10: 32.	Letter
Steel A, Wharton R, Bates A, French J, Lewis S, Mackenzie R. Ketamine use in prehospital critical care. EMJ 2008; 25: 618-19.	Letter
Svenson JE, Abernathy MK. Ketamine for prehospital use: new look at an old drug. Am J Emerg Med 2007; 25: 977-80.	Patient population did not match the criteria
Wedmore IS, Butler FK. Battlefield analgesia in tactical combat casualty care. Wilderness Environ Med 2017; 28: S109-S16.	Study design did not match the criteria
Wood PR. Ketamine: Prehospital and in-hospital use. Trauma 2003; 5: 137-40.	Study design did not match the criteria
Zhang M, Cowan T, Smiles JP, Morgan M, Armstrong J, Goswami C, Sewell C. Prehospital analgesic choice in injured patients does not impact on rates of vomiting: Experience from a New South Wales primary retrieval service. Emerg Med Australas 2017; 30: 406-11.	Study design did not match the criteria

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	A I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7+8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10+11+12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 3-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 3-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Ketamine for the treatment of prehospital acute pain: a systematic review of benefit and harm

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038134.R1
Article Type:	Original research
Date Submitted by the Author:	19-Sep-2020
Complete List of Authors:	Sandberg, Mårten; Oslo University Hospital, Air Ambulance Department Hyldmo, Per Kristian; University of Stavanger Kongstad, Poul; Region of Skåne, Lund, Department of Prehospital Care and Disaster Medicine Dahl Friesgaard, Kristian; Prehospital Emergency Medical Service, Research Department, Central Denmark Region Raatiniemi, Lasse; Oulu University Hospital Larsen, Robert; Linköping University Magnusson, Vidar; Landspitalinn University Hospital Rognås, Leif; Aarhus University Hospital, Kurola, J; Kuopio University Hospital Rehn, Marius; Oslo University Hospital, Air Ambulance Department Vist, Gunn Elisabeth; Norwegian Institute of Public Health
Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Anaesthesia, Evidence based practice
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Adult intensive & critical care < ANAESTHETICS, Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Ketamine for the treatment of prehospital acute pain: a systematic review of benefit and harm

Mårten Sandberg[1,2], Per Kristian Hyldmo[3,4,5], Poul Kongstad[6], Kristian Dahl Friesgaard[7,8], Lasse Raatiniemi[9,10], Robert Larsen[11,18], Vidar Magnusson[12], Leif Rognås[13,14,15], Jouni Kurola[16], Marius Rehn[2,3,4], Gunn Elisabeth Vist[17]

[1]Faculty of Medicine, University of Oslo, Oslo, Norway; [2]Division of Prehospital Services, Air Ambulance Department, Oslo University Hospital, Oslo, Norway; [3]Faculty of Health Sciences, University of Stavanger, Stavanger, Norway; [4]Department of Research, Norwegian Air Ambulance Foundation, Oslo, Norway; [5]Trauma Unit, Sørlandet Hospital, Kristiansand, Norway; [6]Department of Prehospital Care and Disaster Medicine, Region of Skåne, Lund, Sweden; [7]Research Department, Prehospital Emergency Medical Service, Central Denmark Region, Aarhus, Denmark; [8]Department of Anaesthesiology, Regional Hospital of Horsens, Denmark; [9]Centre for Prehospital Emergency Care, Oulu University Hospital, Oulu, Finland; [10]Anaesthesia Research group, MRC, Oulu University Hospital and University of Oulu, Finland; [11]Department of Anaesthesiology and Intensive Care in Linköping, and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden; [12]Landspitalinn University Hospital, Reykjavik, Iceland; [13]Danish Air Ambulance, Aarhus, Denmark; [14]Department of Anaesthesiology, Aarhus University Hospital, Aarhus, Denmark; [15]Department of Clinical Medicine, Aarhus University; [16]Centre for Prehospital Emergency Medicine, Kuopio University Hospital and University of Eastern Finland; [17]Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway; [18]Department of Biomedical and Clinical Sciences, Linköping University, Linköping Sweden

Short title: Prehospital ketamine

Word count (excl. abstract and references): 4,077

Corresponding author:
Marius Rehn
Assoc. Professor/Consultant
Air Ambulance Department
Oslo University Hospital
Sykehusveien 19
1474 Nordbyhagen
Norway

Tel.: +47 90784044
E-mail: rehmar@snla.no

*

* The authors declare no conflicts of interest

Abstract

Background: Few publications have addressed prehospital use of ketamine in analgesic doses. We aimed to assess the effect and safety profile of ketamine compared to other analgesic drugs (or no drug) in adult prehospital patients with acute pain.

Methods: A systematic review of clinical trials assessing prehospital administration of ketamine in analgesic doses compared to other analgesic drugs or no analgesic treatment in adults. We searched PubMed, EMBASE, Cochrane Library and Epistemonikos from inception until February 15th, 2020 including relevant articles in English- and Nordic languages. We used the Cochrane and GRADE methodologies and exclusively assessed patient-centred outcomes. Two independent authors screened trials for eligibility, extracted data and assessed risk of bias.

Results: We included eight studies (2,760 patients). Ketamine was compared with various opioids given alone, and intranasal ketamine given with nitrous oxide was compared to nitrous oxide given alone. Four RCTs and one cluster randomized trial included 699 patients. One prospective cohort included 27 patients, and two retrospective cohorts included 2,034 patients. Five of the eight studies had high risks of bias. Pain score with ketamine is probably lower than after opioids as demonstrated in a cluster-RCT (308 patients) and a retrospective cohort (158 patients) study, ΔVAS -0.4 (-0.8 to 0.0) and ΔNRS -3.0 (-3.86 to -2.14) respectively. Ketamine probably leads to less nausea and vomiting (RR 0.24 (0.11 to 0.52)) but more agitation (RR 7.81 (1.85 to 33)) than opioids.

Conclusions: This systematic literature review finds that ketamine probably reduces pain more than opioids and with less nausea and vomiting but higher risk of agitation. Risk of bias in included studies is high.

Other: SSAI funded meetings and software . The Norwegian Air Ambulance Foundation funded publication. Otherwise this research received no grant from any agency in the public, commercial or not-for-profit sectors. PROSPERO registration number CRD42018114399.

Strengths and limitations of the study

- A systematic review where main outcomes was assessed according to the GRADE method
- Studies were heterogeneous in terms of setting, patient population, outcomes and comparators
- Only English and Scandinavian language articles were included

Introduction

Prehospital acute pain is a frequent symptom and often inadequately managed[1-3]. Several analgesics are administered by prehospital emergency medical services throughout the world without solid evidence of their efficacy and safety. The heterogeneity in pain management strategies may reflect the varying competence levels of providers ranging from technicians with basic training to specially trained physicians. Opioids are most frequently used, but their cerebral, haemodynamic, and respiratory side effects remain a potential challenge in unstable and undifferentiated prehospital patients[4]. Ketamine is an alternative to opioids. Ketamine exerts its effects mainly as an N-methyl-D-aspartate antagonist and, depending on the dose, can be considered as an analgesic, a sedative or an anaesthetic drug[5]. One attractive feature for prehospital use of ketamine is its ability to preserve upper airway reflexes. Respiratory rate may increase, and ketamine can cause bronchodilation. While ketamine generally preserves respiratory function, ketamine can cause respiratory depression if given quickly[6]. There is a risk of laryngospasm, which may require intubation in a very small fraction of cases[7].

Ketamine can be administered in a variety of routes, most commonly intramuscularly, intranasally and intravenously, although per oral and per rectal doses are used in different settings. Although originally believed to cause an increase in intracranial pressure (ICP), recent work in critical care patients indicates that ketamine has little or no impact on ICP. In two studies comparing ketamine and sufentanil, the authors concluded that ketamine did not affect ICP and that it was safe to administer to patients with traumatic brain injury (TBI)[8 9]. In another study, ketamine in conjunction with propofol was administered to TBI patients, and a significant decrease in ICP was recorded[10]. In one study on children with TBI, a reduction in ICP by up to 30% was found, and cerebral perfusion was improved[11]. In these studies, ketamine was used in anaesthetic doses, and the results should be interpreted with caution.

Moderate or severe agitation occurs in 5-30% of adult patients; some clinicians administer boluses of midazolam to avoid this phenomenon[6]. A randomized controlled trial (RCT) showed that this practice significantly reduced agitation in adults; however, one trial found that it did not reduce agitation in children[6 12].

Proper pain relief allows prehospital care providers to meet essential clinical endpoints, e.g., facilitating fracture manipulation. Although analgesia should be titrated for the desired effect,

pain relief is frequently suboptimal, possibly due to concerns about adverse events[13]. Ketamine may be a useful prehospital analgesic mainly due to its ability to provide excellent analgesic effects with a lower incidence of respiratory depression than that caused by opioids. These positive effects have been demonstrated in fracture management[14], burn treatment[15], and traumatic amputation[16].

The aim of this systematic literature review is to explore the benefit and harm of ketamine compared to other analgesic drugs (or no drug) in prehospital patients with acute pain.

Methods

We conducted this systematic review according to the Cochrane Handbook for systematic reviews of interventions[17] and as described in our protocol (PROSPERO registration number CRD42018114399) as specified below.

Inclusion criteria

We used the following inclusion criteria:

Population	Adult patients (18 years of age or older) with acute pain in the prehospital setting
Intervention	Ketamine
Comparison	Other analgesics, no analgesics or ketamine given in another dose or another route of administration or ketamine given in combination with other analgesics
Outcomes	Pain reduction, speed of onset, duration of effect, and relevant adverse events such as mortality, morbidity, anaphylaxis, nausea and vomiting, hypotension, respiratory failure, loss of airway patency, emergence phenomena (as defined by study authors)

We included all adult patients (18 years of age or older) with acute pain, regardless of aetiology, managed in the prehospital setting. We also sought to identify adverse effects that are not previously reported. The following study designs were considered eligible for inclusion in the meta-analysis: Randomized Controlled Trials (RCTs), non-randomized controlled studies, cohort studies with a control group, interrupted time series, and controlled before-and-after studies. Case series were also included for information relating to safety. Systematic reviews of high quality answering to our inclusion criteria, were evaluated for eligible studies. Other systematic reviews would have been used to check for relevant references.

Exclusion criteria

Children (younger than 18 years of age) and patients with chronic pain and/or patients who used ketamine as part of their regular treatments were not included in this review. We excluded all studies that were not conducted in the prehospital setting, as well as conference abstracts, letters and publications without full texts available.

Search strategy

An experienced research librarian in collaboration with the authors developed the search strategy based on the inclusion criteria. The following databases were searched from their inception: PubMed, EMBASE, Cochrane Library and Epistemonikos.

The most recent search was conducted on February 15, 2020, and the full search strategy is presented in Appendix 1. The search was limited to the following languages: Danish, English, Finnish, Icelandic, Norwegian, and Swedish.

The reference lists of the included publications were checked in order to identify relevant articles not found in the original search.

Study selection

For each step in the review process, no assessor handled publications they had co-authored. MS and either PKH, MR or PK independently assessed all titles and abstracts identified from the search according to the inclusion criteria above. References that were considered potentially relevant were collected, and the full text articles were assessed independently by two assessors using the same inclusion criteria. Any disagreement between the initial two assessors was discussed and resolved by all assessors. The process of study selection based on titles and abstracts, study selection based on full text articles and risk of bias assessments were conducted using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org).

Assessment of risk of bias

MS and either PKH, MR or PK independently assessed the risk of bias for each of the included studies in accordance with the recommendations by the Cochrane Collaboration[17]. For RCTs, the following items were assessed for risk of bias: i) sequence generation; ii) concealment of allocation; iii) blinding of participants and personnel; iv) blinding of outcome assessor; v) incomplete outcome data; vi) selective outcome reporting; and vii) other risk of bias. For non-randomized controlled trials and other studies with a control group, the following items were also assessed for risk of bias: viii) similarity of baseline characteristics; ix) similarity of baseline

outcome data; and x) contamination. All items were rated as either high, unclear or low risk of bias.

Data extraction

MS and either PKH or PK independently extracted data from each included study. We extracted data pertaining to full references; study design and country in which the study was conducted; characteristics of the population, e.g., number of patients; age; gender; cause of pain; setting and context; type and dose of analgesics given; cadre/competency of the health care personnel who administered the analgesic; comparison/control intervention; attrition; outcomes; and follow-up times. We did not contact any study investigators to obtain information not described in the original articles.

The process of study selection based on titles and abstracts, study selection based on full text articles as well as risk of bias assessments were conducted using Covidence.

Statistical analysis

Dichotomous outcomes are presented as risk ratios (RRs) with 95% confidence intervals (CIs). Continuous outcomes are presented as the mean difference between the groups with 95% CIs. If different scales were used to measure the same outcome, we would have calculated standardized mean difference with a 95% CI. We used Review Manager (RevMan 5.3) software to generate forest plots. Attrition was handled using intention-to-treat analysis. We evaluated statistical heterogeneity using the Q test and I^2-statistic. Analysis was by inverse variance and random effects methods. Zero events were presented descriptively.

Grading our confidence in the evidence

We assessed our confidence in the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[18]. Our confidence is presented as high, moderate, low or very low. The evidence across each outcome is assessed by eight criteria. Five criteria lowered our confidence in the evidence: i) risk of bias/ methodological limitations; ii) consistency between studies (statistical heterogeneity); iii) directness (similar study participants, intervention, comparator and outcome measures in the included studies to the population, and target interventions and measures); iv) precision of results; and v) reporting bias. Three criteria were used to consider upgrading evidence from observational studies that had not been downgraded: i) strong or very strong association

between intervention and outcome; ii) large or very large dose response; and iii) situations where all plausible confounders would have reduced the effect. For questions about the effect of interventions, RCTs started at high confidence, and observational studies started at low confidence.

Breach of protocol

We did make a breach of protocol; the largest study (Losvik et al.) we included, also contained treatment data from a few children[19].

Patient and public involvement

The development of the research question and outcome measures were informed by studies indicating that prehospital acute pain is a frequent symptom and often inadequately managed[1-3]. No patients were directly involved in the design or conduct of this study. The results will be disseminated as a part of a Scandinavian society of anaesthesiology and intensive care medicine (SSAI) guideline on pre-hospital pain management.

Results

The systematic literature search identified 1,197 references; we considered 60 to be potentially relevant and assessed those publications in full. We included seven of these studies in the final analysis. In addition, two unique references in the reference lists of the seven publications were assessed and one of the references was also included. Figure 1 shows the flow diagram of the identified references. The 53 studies that were assessed in full text articles and excluded are presented in appendix 2 with the reason for their exclusion.

Characterization of the trials

The eight included studies were conducted in Australia[20], Canada[21], France[22 23], Iraq[19], Sweden[24], the USA[25], and Vietnam[26]. A total of 2,760 prehospital patients with acute pain were included in these eight studies. Four RCTs[20-23] and one cluster randomized trial[26] included 699 patients. One prospective cohort study[24] included 27 patients. Two retrospective cohort studies[19 25] included 2,034 patients. The largest of these studies, with 1,876 patients, was conducted in the war zones and mine fields of northern and central Iraq[19]. Two authors stated that their studies were conducted in rural areas, with one in Australia and one in Vietnam. The latter study included areas with mine fields, and three patients had been involved in mine accidents. This study also included children; however, the vast majority of included patients were probably adults because the mean ages of the groups were 35.5 years and 36.9 years. Therefore, this study was included. The reported time frame was similar in all studies; i.e. from drug administration to admission to hospital.

Table 1. Summary of included studies

Reference Study design Country	Ketamine	Comparison	Outcomes
Ketamine i.v. versus opioids i.v.			
Bronsky 2018 Retrospective cohort USA	n=79, ketamine 0.3 mg/kg i.v. every 20 min as needed, maximum three doses	n=79, fentanyl 2 µg/kg bolus i.v. over 1 to 2 min with additional dose every 10 min as needed	Change in pain scores, serious adverse events, GCS
Losvik 2015 Retrospective cohort Iraq	n=713, ketamine 0.2 mg/kg i.v., in case of unrest, 5 mg diazepam i.v. During protracted evacuations with repeated ketamine doses, 1 mg atropine was administered. Repeat doses of ketamine allowed.	n=888, pentazocine 0.4 mg/kg i.v. for adults, repeat doses allowed	Change in physiological severity score
Tran 2014 Cluster- RCT Vietnam	n=169, ketamine 0.2 to 0.3 mg/kg was administered as slow intermittent i.v. injections	n=139, morphine administered in one single i.m. dose; 10 mg for adult patients, 5 mg for paediatric patients	Change in pain score, serious adverse events, adverse events, satisfaction, mean treatment time (head trauma)
Ketamine and morphine i.v. versus morphine i.v. alone			
Galinski 2007 RCT France	n=33, ketamine 0.2 mg/kg i.v. in 3 mg morphine every 5 min if necessary	n=32, morphine 3 mg i.v. every 5 min if necessary	Change in pain score, adverse events

Jennings 2012 RCT Australia	n=70, morphine 5 mg i.v. initial dose followed by a ketamine bolus of 10 or 20 mg according to body size, followed by 10 mg ketamine every 3 min thereafter until pain was relieved	n=65, morphine 5 mg i.v. initial dose followed by 5 mg i.v. every 5 min until pain was relieved	Change in pain score, adverse events, GCS
Johansson 2009 Prospective cohort Sweden	n=16, morphine 0.1 mg/kg i.v. followed by ketamine 0.2 mg/kg if pain score ≥4 after 5 min	n= 11, mg/kg morphine 0.1 mg/kg i.v. followed by morphine 0.1 mg/kg if pain score ≥4 after 5 min	Change in pain score, adverse event, mean treatment time
Ketamine continuous i.v. administration versus ketamine i.v. one dose			
Wiel 2014 RCT France	n=30, all patients received ketamine 0.2 mg/kg i.v. bolus combined with morphine 0.1 mg/kg i.v. followed by ketamine 0.2 mg/kg/h. Additional morphine 0.05 mg/kg was allowed every 5 min if VAS > 3/10	n=33, all patients received a ketamine 0.2 mg/kg i.v. bolus combined with morphine 0.1 mg/kg i.v. followed by a saline infusion of the same volume. Additional morphine 0.05 mg/kg was allowed every 5 min if the VAS > 3/10	Change in pain score, adverse events, satisfaction
Intranasal ketamine and inhaled nitrous oxide versus only inhaled nitrous oxide			
Andolfatto 2019 RCT	n=60, all patients received approx. 0.75 mg/kg intranasal ketamine (30 mg	n=60, all patients received inhaled nitrous oxide	Change in pain score, adverse events, satisfaction

Canada	for patients < 50 kg, 50 mg for patients 50-100 kg, 75mg for patients > 100 kg) combined with inhaled nitrous oxide		
Ketamine i.v. versus no analgesic treatment			
Losvik 2015 Retrospective cohort Iraq	n=713, ketamine 0.2 mg/kg i.v., in case of unrest, 5 mg diazepam i.v. During protracted evacuations with repeated ketamine doses, 1 mg atropine was administered. Repeat doses of ketamine allowed.	n=275, no analgesic treatment	Change in physiological severity score

Risk of bias assessment

Our assessments regarding each bias domain is provided in figure 2. Three of the six RCTs had a high risk of bias, with the main reasons being lack of random sequence generation, lack of allocation concealment or lack of blinding of patients, personnel and outcome assessors.

Comparisons

The included studies covered five comparisons involving ketamine (table 1):

- Ketamine i.v. vs. opioids (morphine[26], fentanyl[25], pentazocine[19]) i.v.
- Ketamine i.v. and morphine i.v. vs. only morphine i.v.[20 23 24]
- Ketamine i.v. given as continuous administration vs. ketamine i.v. as single dose[22]
- Ketamine intranasally and nitrous oxide vs. only nitrous oxide[21]
- Ketamine i.v. vs. no analgesia/no medication[19]

In table 1, we give a short description of the included studies and the doses used, while the excluded studies are presented with the reason for their exclusion in appendix 2. One study contributed to two comparisons[19], meaning that 713 patients who received ketamine are compared twice, first with patients who received opioids and again with patients who did not receive analgesic treatment.

Ketamine vs. opioids

A change in pain score was reported in two studies. Bronsky et al.[25] used the numeric pain rating scale (NRS), where 1 represents no pain and 10 represents extreme pain, while Tran et al.[26] measured the change in pain using the visual analogue scale (VAS) but did not explicitly give a range. Figure 3 shows that both studies reported a greater reduction in pain scores with ketamine than with the opioids fentanyl (MD -3.0 (95% CI -3.86 to 2.14)) and morphine (MD -0.4 (95% CI -0.08 to 0.0)).

The main outcome in the study by Losvik et al.[19] was the physiological severity score (PSS). The PSS was calculated from the blood pressure, respiratory rate and consciousness level[27]. They reported exactly the same change, at 1.5 (95% CI 1.4 to 1.6), in the PSS for both the ketamine and the pentazocine groups. Hence, no difference was found between the treatment groups.

Adverse events were reported in the Vietnamese study[26]; fewer patients with nausea and vomiting were found in the ketamine group than in the morphine group and fewer patients with agitation were found in the morphine group than in the ketamine group (figure 4).

In the study where ketamine and fentanyl were compared[25], four adverse events were reported: two patients experienced respiratory compromise, and two patients suffered haemodynamic instability. All four patients were in the fentanyl group.

The change in Glasgow coma scale (GCS) was measured by Bronsky et al.[25] and found to be similar for ketamine and fentanyl, MD -0.13 (95% CI -0.33 to 0.07).

Ketamine and morphine vs. only morphine

Changes in the pain scores were measured in both the Australian [20] and in the Swedish study[24] using a scale from 1 to 10 where 10 represented extreme pain. In the French study[23], a scale from 0 to 100 was used, and we have transferred this to a 0 to 10 scale in order to include this study in the meta-analysis. Figure 5 shows the change in the pain score when prehospital patients received both ketamine and morphine compared with patients who received only morphine. Although the RCT performed by Jennings et al.[20] found lower pain scores in patients receiving combined ketamine and morphine than in patients receiving only morphine. When combined with the RCT by Galinski et al.[23], the meta-analysis shows a non-significant reduction (MD -1.51 (95% CI -3.36 to 0.33)) in pain score. The small prospective cohort[28] also found a non-significant reduction (MD -1.30 (95% CI -2.95 to 0.35)) in pain score.

Adverse events were measured in both studies, and the results are illustrated in figure 6. It is important to note that the nausea and vomiting are included in the total adverse events in the RCTs. These results are characterized by few events but indicate that morphine alone may lead to fewer adverse events than the combination of ketamine and morphine.

The RCT by Jennings et al.[20] measured the GCS score and found that the median score was unchanged between initial assessment and the follow-up time, with a median score of 15 for both groups.

The French RCT reported use of fewer boluses of morphine when combined with ketamine (1 bolus (95%. CI 0 to 2) compared with 2.3 boluses (95% CI 1.8 to 3.8) when using morphine alone)[22].

The Swedish, prospective cohort by Johansson et al.[28] reported a non-significant trend for shorter treatment time with morphine alone than with ketamine and morphine combined (10 min (95% CI -1.4 to 21.4). Ketamine was administered nasally thereby avoiding the need for i.v. access.

Continuous ketamine administration vs. ketamine given as a bolus

One multicentre RCT conducted in France compared the continuous administration of ketamine with a bolus dose of ketamine, but both groups also received morphine[22]. Changes in pain were measured using a VAS from 0 to 10 (worst). and were similar in both groups (VAS -0.6 (95% CI -1.84 to 0.64)).

The main outcome of this study was the amount of additional morphine used (mg/kg) (p=0.18), indicating that there was no difference between the continuous group, at 0.048 (1st quartile, 3rd quartile 0.000, 0.150), and the bolus group, at 0.107 (1st quartile, 3rd quartile 0.052, 0.150). The duration of care for both groups was 35 minutes. Nausea and vomiting were not reported in patients in the continuous group but were reported in three patients in the bolus group.

Ketamine and nitrous oxide vs. only nitrous oxide

Andolfatto et al. used a verbal NRS pain score and evaluated the scores after 15 minutes and 30 minutes[21]. More patients in the ketamine and nitrous oxide group had a reduction in pain of 2 or more points than those in the saline and nitrous oxide group at both time points (figure 7).

They reported no serious adverse effects in either group, but a considerable number of minor adverse events, such as feeling of unreality, dizziness, nausea, fatigue, general discomfort, mood change, hallucination, change in hearing and headache, occurred. Most of these side effects (52 of 66 events) were reported in the group of patients who received ketamine and nitrous oxide combined, as shown in figure 8.

Ketamine vs. no analgesic treatment

The retrospectively matched observational study of patients/causalities in the war zone in Iraq compared the use of ketamine with no analgesic treatment[19]. The main outcome in this study was the PSS, which was calculated from the blood pressure, respiratory rate and consciousness level. There was a non-significant trend for lower PSS with ketamine compared with no analgesics (MD -0.2 (95% CI -0.42 to 0.02)).

Adverse events from ketamine across the five comparisons

Seven of the eight studies reported on adverse events and/or side effects from use of ketamine. Five studies reported on nausea and vomiting from ketamine alone (8/169)[26], from ketamine continuous administration (0/30)[22], from ketamine bolus administration (3/33)[22], and from combined ketamine and morphine (8/33)[23], (4/70)[20], (7/16)[24]. Time for administering each bolus were not reported. Only one study reported on agitation, from ketamine alone (19/169)[26]. Four studies reported adverse events, and two stated that nausea and vomiting were included as adverse events, from ketamine and morphine (21/33)[23], (27/70)[20]. One study reported adverse events from ketamine and nitrous oxide (52/60)[21], and one study reported no adverse events from ketamine alone (0/79)[25].

GRADE

The quality of the main outcomes for the comparisons involving the use of ketamine for the treatment of prehospital acute pain, was assessed according to the GRADE method[18]. The quality of evidence could be downgraded for various reasons (risk of bias, inconsistency, indirectness, imprecision and publication bias). Consequently, the quality of the evidence was classified as high, moderate, low or very low. As described in table 2, we have for many of these outcomes downgraded for study limitations/high risk of bias, or for imprecision because there were few events in many of these studies.

Table 2. Summary of findings for the comparisons. ***The risk in the intervention group** (and its 95% CI) assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **GRADE Working Group grades of evidence: High certainty:** We are very confident that the true effect is similar to that of the estimated effect. **Moderate certainty:** We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimated effect. **Very low certainty:** We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimated effect.

Ketamine compared to opioids for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in the USA and Vietnam
Intervention: Ketamine
Comparison: Opioids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with opioids	Risk with ketamine				
Change in pain score assessed with VAS	The mean change in the pain score was 3.1	The mean change in the pain score in the intervention group was 0.4 less (0.8 less to 0)	-	308 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Change in pain score assessed with NRS scale from: 1 to 10	The mean change in the pain score was 2.5	The mean change in pain score in the intervention group was 3 less (3.86 less to 2.14 less)	-	158 (1 observational study)	⨁⨁◯◯ LOW	
Serious adverse events	51 per 1,000	0 per 1,000 (0 to 0)	Not estimable	158 (1 observational study)	⨁⨁◯◯ VERY LOW [b]	
Nausea and vomiting	194 per 1,000	47 per 1,000 (21 to 101)	RR 0.24 (0.11 to 0.52)	308 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Agitation	14 per 1,000	112 per 1,000 (27 to 474)	RR 7.81 (1.85 to 32.97)	308 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	

Explanations: a. Downgraded one level for high risk of bias, b: Downgraded one level for imprecision, only 4 events and all four of them in the same group. There were no events in the other group and therefore RR cannot be estimated

Ketamine and morphine compared to only morphine for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in Sweden, France and Australia
Intervention: Ketamine and morphine
Comparison: Only morphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with only morphine	Risk with ketamine and morphine				
Change in pain scores Scale from: 1 to 10	The mean change in pain scores was 3.5	Mean 1.51 lower (3.36 lower to 0.33 higher)	-	135 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	

Ketamine and morphine compared to only morphine for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in Sweden, France and Australia
Intervention: Ketamine and morphine
Comparison: Only morphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with only morphine	Risk with ketamine and morphine				
Change in pain scores Scale from: 1 to 10	The mean change in pain score was 3.1	Mean 1.3 lower (2.95 lower to 0.35 higher)	-	27 (1 observational study)	⨁◯◯◯ VERY LOW[a]	
Serious adverse events	Not reported		Not estimable	-	-	None of the 2 studies reported any serious adverse events
Total number of adverse events	165 per 1 000	468 per 1 000 (289 to 764)	RR 2.84 (1.75 to 4.63)	200 (2 RCTs)	⨁⨁⨁◯ MODERATE[b]	

Explanations: a. Downgraded one level for imprecision, this cohort only has 27 patients included b, Downgraded one level for risk of bias due to unclear randomization and open label design

Continuous administration of ketamine compared to ketamine given as a bolus for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in France
Intervention: Continuous administration of ketamine
Comparison: Ketamine given as a bolus

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ketamine given as a bolus	Risk with the continuous administration of ketamine				
Change in pain scores. Scale from 0 to 10	The mean change in the pain score was 3.1	The mean change in pain score in the intervention group was 0.6 less (1.84 less to 0.64 more)	-	63 (1 RCT)	⨁⨁◯◯ LOW[a]	
Serious adverse events	-	-	not estimable	(1 study)	-	No serious events were reported
Nausea and vomiting	91 per 1,000	0 per 1,000 (0 to 0)	not estimable	63 (1 RCT)	⨁⨁◯◯ VERY LOW[a, b]	

Explanations: a. Downgraded one level for imprecision, one study included with 63 patients, b. Downgraded one level for imprecision, only 3 events

Ketamine and nitrous oxide compared to only nitrous oxide for prehospital pain management

Patient or population: Prehospital pain management
Setting: Prehospital setting in Canada
Intervention: Ketamine and nitrous oxide
Comparison: Only nitrous oxide

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with only nitrous oxide	**Risk with ketamine and nitrous oxide**				
≥2 point reduction in pain, 15 minutes	350 per 1 000	634 per 1 000 (427 to 931)	RR 1.81 (1.22 to 2.66)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
≥2 point reduction in pain, 30 minutes	407 per 1 000	758 per 1 000 (534 to 1 000)	RR 1.86 (1.31 to 2.66)	108 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
Serious adverse events	0 per 1 000	0 per 1 000 (0 to 0)	Not estimable	(1 RCT)	-	
Total number of adverse events	233 per 1 000	866 per 1 000 (541 to 1 000)	RR 3.71 (2.32 to 5.31)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
Number of patients with adverse events	200 per 1 000	616 per 1 000 (358 to 1 000)	RR 3.08 (1.79 to 5.31)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	

Explanations: a. Downgraded one level for imprecision, only one study with a total of 120 patients. There are also large effects, but with unclear blinding we do not upgrade

Discussion

In this systematic review addressing the effect and safety of prehospital administration of ketamine in analgesic doses, we included eight studies with 2,760 patients in total.

Strengths and limitations of this systematic review

The included studies were heterogeneous in terms of setting, patient population and outcomes explored, as well as in their comparators, such as i.v. or intranasal ketamine with a variety of opioids or with nitrous oxide. In addition, a single dose of ketamine was compared with ketamine which was administered continuously.

Although the evidence base includes five RCTs, five of the eight included studies have a high risk of bias. The RCTs were relatively small studies with 63, 65, 120, 135 and 308 patients included, respectively. None of the studies were designed or powered to truly test the safety of ketamine. Adverse events and the severity thereof were inconsistently reported.

The eight studies cover five different comparisons, so the amount of research evidence for each comparison is sparse. Only one of the outcomes in one of the comparisons has been measured in more than one study of similar design, and several of the outcomes has not been assessed in a prehospital study at all. When using GRADE to assess our confidence in the estimates, we more often than not, downgraded for high risk of bias or imprecision due to very few events or wide confidence intervals. Three of the eight included studies are observational studies. They have an initial high risk of bias compared to RCTs due to the lack of randomization. This is acknowledged in GRADE where observational studies start at low quality of evidence. Lack of blinding is a weakness in all of these studies. This becomes a challenge when the main outcome is subjective, pain, and we have downgraded for high risk of bias. However, there is moderate quality of the evidence for the main outcome, change in pain score, for one of the comparisons.

This systematic review has the benefit of systematic and transparent pre-planned methodology (PROSPERO registration number CRD42018114399): Decisions and judgements were conducted by two authors independently of each other, hence, reducing the risk of bias in the conduct of the review. We conducted a wide literature search in several databases, but it is still possible that there exist relevant studies that we did not identify, both in other databases and in other languages. As always with systematic reviews, there is the possibility that relevant studies may have been published after our search was conducted. Our deviation from the protocol to

include a large study even though it included some children may be interpreted as a limitation. However, we would argue that the inclusion of extra patients (1876 patients added to the 884 patients from the other seven studies) where the large majority were adults adds greatly to the available information regarding side effects/adverse events.

Two of the studies were conducted in Iraq and in Vietnam, respectively, where a number of patients were injured in mine accidents. These studies were the largest studies and included 1,909 patients. It is reasonable to assume that the results from studies conducted in war zones are not directly applicable in civilian settings since the victims tend to be male, relatively young and previously healthy and are not representative of trauma victims in general. The study from Iraq did not report on any of our predefined outcomes.

Clinical implications

Ketamine administered in analgesic doses (0.1-0.2 mg/kg) i.v. appears to be at least as effective as opioids administered alone considering pain reduction. In the study from Iraq, an initial dose of ketamine (0.2 mg/kg) was given in all cases of penetrating trauma and burns, but patients with TBI or blunt injury received only pentazocine[19]. The patients in the study conducted by Tran et al. received 0.2-0.3 mg/kg i.v. of ketamine[26]. Four[22-25] of the other five studies included studies administered ketamine in 0.2-0.3 mg/kg i.v. doses, while in the last i.v. study[20], the patients received 10-20 mg i.v. of ketamine. In the study where ketamine was administered intranasally, the patients received an average of 0.75 mg/kg of ketamine[21]. Hence, the patients in all studies received appropriate analgesic doses of ketamine.

Adverse events

In general, very few adverse events were reported in the included studies. Most of the events were related to nausea and vomiting. Agitation was more common in the ketamine group in the study performed by Tran et al.[26] Bronsky et al. reported that two patients experienced respiratory compromise and two suffered haemodynamic instability[25]. All four patients were in the fentanyl group.

Given the safety profile of ketamine and the results reported in the included studies, it appears reasonable to suggest that low-dose ketamine for analgesic purposes can be administered safely during prehospital emergency care when proper indications and contraindications are identified. Prehospital healthcare providers with a level of training suitable to administer

ketamine – that is personnel that are trained to handle potential adverse events – must be identified. None of the included studies had enough power to detect differences in rare events, and the quality of evidence was poor. One of the studies showed an increased number (pooled) of adverse events in the group receiving ketamine and morphine, indicating that an improved analgesic effect increases the risk for adverse events. It is unclear whether adverse events are more likely to occur with opioids than with ketamine. However, it is essential to note that this review describes ketamine administered in analgesic doses and not in sedative and anaesthetic doses where advanced skills are required to be able to handle the patient in an adequate manner.

Studies from other settings

In a recent systematic review and meta-analysis Yousefifard et al. included seven studies and pooled the effect estimates of observational and randomised interventional studies[29]. They concluded that ketamine is an effective and safe medication in prehospital pain management in trauma patients and can be considered as an acceptable alternative to opioids. The analgesic effect of low-dose ketamine is also employed in the hospital. In a recent systematic review and meta-analysis, Karlow et al. studied ketamine as an alternative to opioids for acute pain in the emergency department (ED)[30]. The authors concluded that ketamine can be used as an alternative to opioids in the ED, as they found that ketamine was noninferior to opioids. They also found that the rate of non-severe adverse effects was higher with ketamine. It is unclear to what extent results from ED studies can be extrapolated to the prehospital setting. However, it is not obvious that the safety profile of ketamine in the prehospital setting is independent of the qualifications of the health care provider that administers the drug. Studies specifically addressing competence of prehospital providers administering ketamine should therefore be conducted. The body of evidence for benefit and possible harm is limited as few studies have been performed. Future studies need to address all relevant side effects, the optimal drug dose as well as all relevant outcome measures.

Conclusion:

This systematic review of the current literature indicates that ketamine is an effective analgesic to be administered prehospitally.

Acknowledgements

We thank research librarian Jane Kjemtrup Andersen (Viborg Regional Hospital, Denmark) for developing the search strategies.

Authors contributions:

MS supervised the process of drafting this manuscript and coordinated all identification, data extraction and appraisal of included manuscripts. MS and either PKH, MR or PK independently assessed all potential eligible articles for inclusion. GEV coordinated all methodological support. MS, PKH, PK, KDF, LR, RL, VM, LR, JK, MR, GEV are members of the SSAI task force on pre-hospital pain management and participated in planning, design, interpretation of results, manuscript drafting and revisions of the manuscript.

Competing interest:

The authors declare no conflicts of interest

Funding:

SSAI funded meetings and software costs. The Norwegian Air Ambulance Foundation funded publication costs. Otherwise this research received no further grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement:

No additional data available

Figure legends:

Figure 1: Flow diagram of evaluated records

Figure 2: Risk of bias

Figure 3: Ketamine versus opioids - change in pain score

Figure 4: Ketamine versus opioids - adverse events

Figure 5: Combined ketamine and morphine compared with only morphine - change in pain score

Figure 6: Combined ketamine and morphine compared with only morphine - adverse events

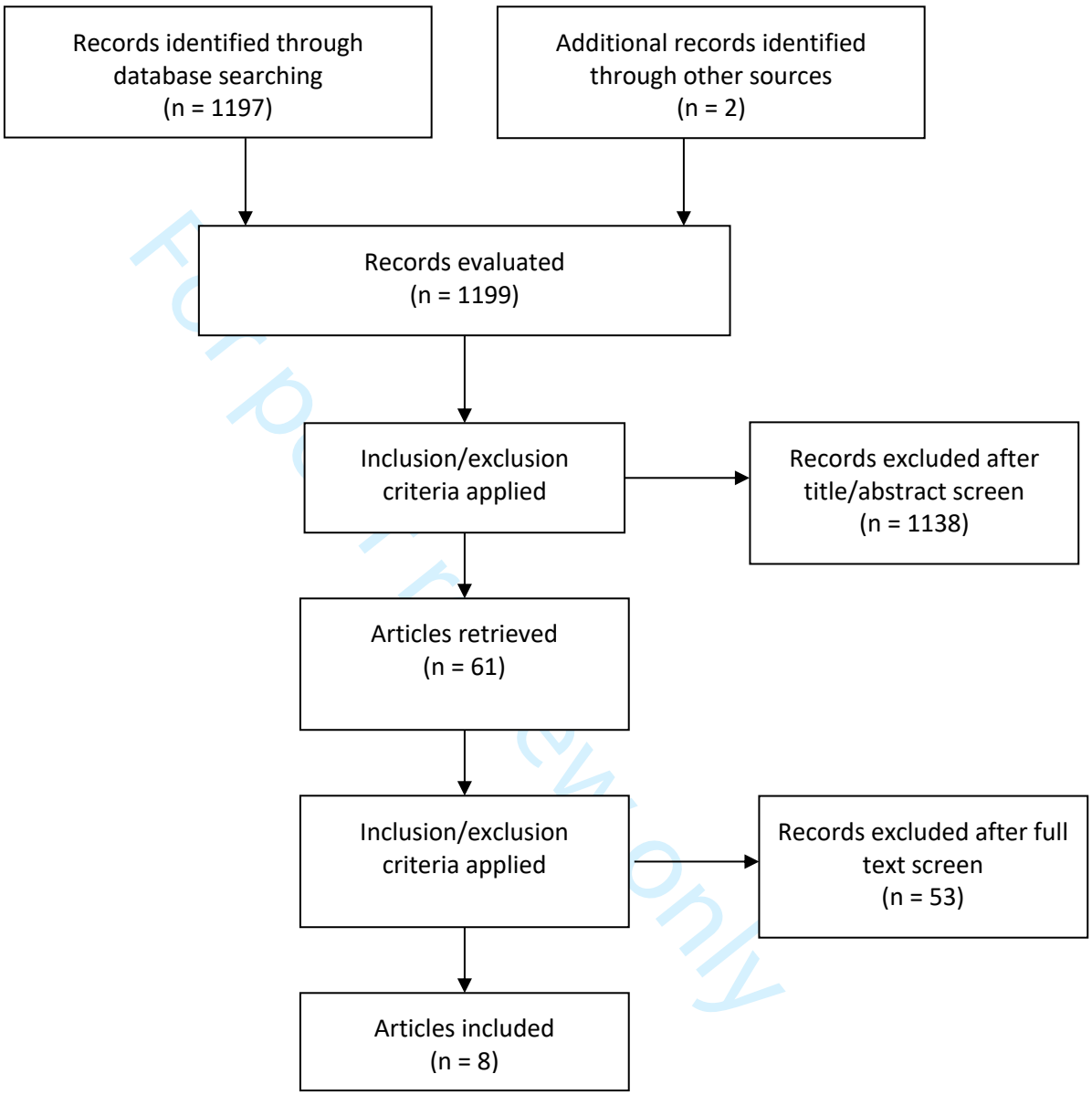
Figure 7: Ketamine and N2O vs only N2O - change in pain score

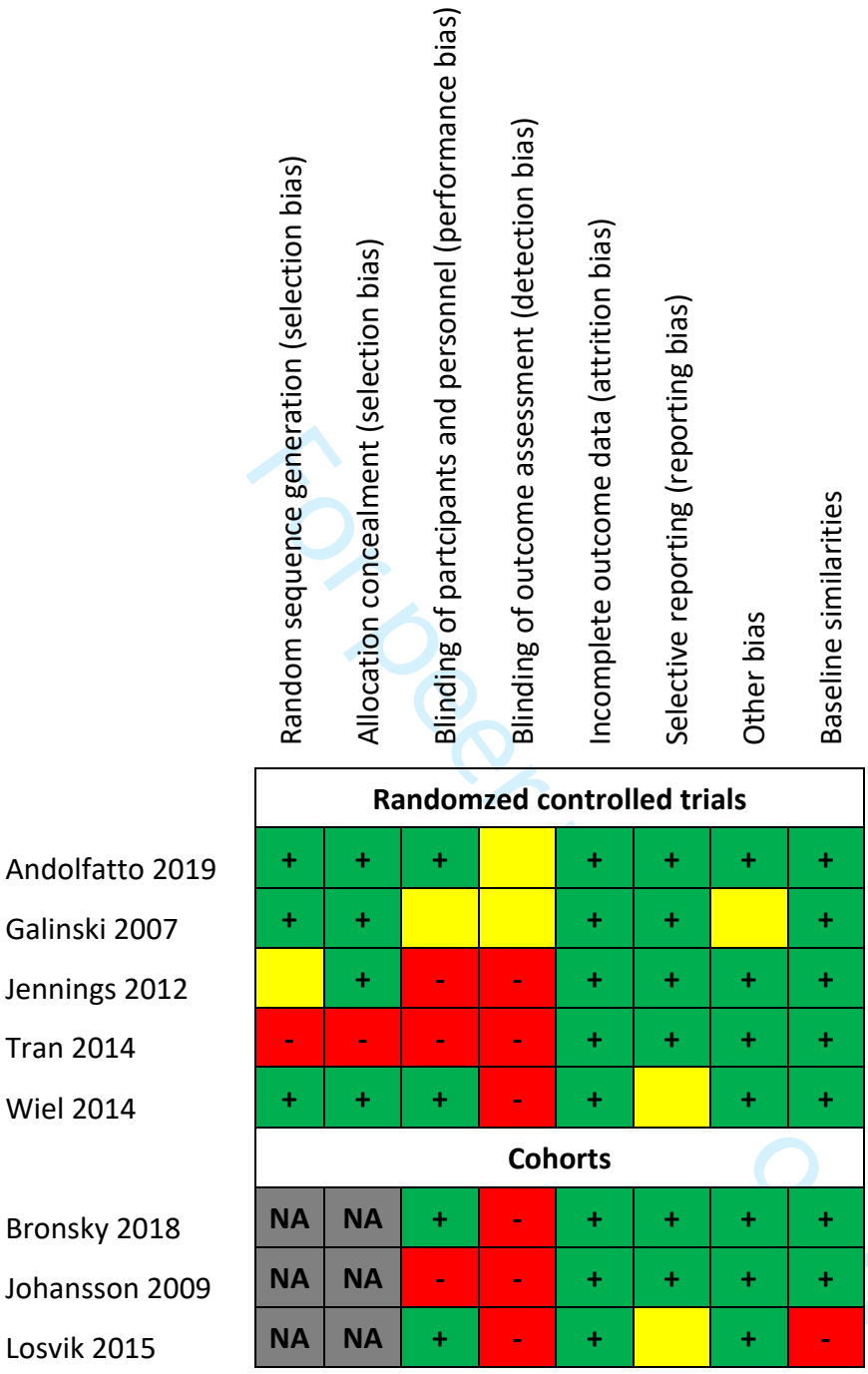
Figure 8: Ketamine and N2O vs only N2O - adverse events

References

1. Jennings PA, Cameron P, Bernard S. Epidemiology of prehospital pain: an opportunity for improvement. *Emerg Med J* 2011;28(6):530-1.
2. Albrecht E, Taffe P, Yersin B, et al. Undertreatment of acute pain (oligoanalgesia) and medical practice variation in prehospital analgesia of adult trauma patients: a 10 yr retrospective study. *Br J Anaesth* 2013;110(1):96-106.
3. Galinski M, Ruscev M, Gonzalez G, et al. Prevalence and management of acute pain in prehospital emergency medicine. *Prehosp Emerg Care* 2010;14(3):334-9.
4. Bounes V, Barniol C, Minville V, et al. Predictors of pain relief and adverse events in patients receiving opioids in a prehospital setting. *Am J Emerg Med* 2011;29(5):512-7.
5. Lodge D, Anis NA, Burton NR. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurones by amino acids and acetylcholine. *Neurosci Lett* 1982;29(3):281-6.
6. Craven R. Ketamine. *Anaesthesia* 2007;62 Suppl 1:48-53.
7. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: Part 2, Review and implications. *Ann Emerg Med* 1990;19(9):1033-46.
8. Bourgoin A, Albanese J, Leone M, et al. Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. *Crit Care Med* 2005;33(5):1109-13.
9. Bourgoin A, Albanese J, Wereszczynski N, et al. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Crit Care Med* 2003;31(3):711-7.
10. Albanese J, Arnaud S, Rey M, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology* 1997;87(6):1328-34.
11. Bar-Joseph G, Guilburd Y, Tamir A, et al. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr* 2009;4(1):40-6.
12. Sherwin TS, Green SM, Khan A, et al. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* 2000;35(3):229-38.
13. McManus JG, Jr., Sallee DR, Jr. Pain management in the prehospital environment. *Emerg Med Clin North Am* 2005;23(2):415-31.
14. Kennedy RM, Porter FL, Miller JP, et al. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics* 1998;102(4):956-63.
15. McGuinness SK, Wasiak J, Cleland H, et al. A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* 2011;12(10):1551-8.
16. Bonanno FG. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). *Injury* 2002;33(4):323-7.
17. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration. 2011.
18. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490-7.
19. Losvik OK, Murad MK, Skjerve E, et al. Ketamine for prehospital trauma analgesia in a low-resource rural trauma system: a retrospective comparative study of ketamine and opioid analgesia in a ten-year cohort in Iraq. *Scand J Trauma Resusc Emerg Med* 2015;23:94.

20. Jennings PA, Cameron P, Bernard S, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. *Ann Emerg Med* 2012;59(6):497-503.
21. Andolfatto G, Innes K, Dick W, et al. Prehospital analgesia with intranasal ketamine (PAIN-K): a randomized double-blind trial in adults. *Ann Emerg Med* 2019;74;241-50
22. Wiel E, Zitouni D, Assez N, et al. Continuous infusion of ketamine for out-of-hospital isolated orthopedic injuries secondary to trauma: a randomized controlled trial. *Prehosp Emerg Care* 2015;19(1):10-16.
23. Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med* 2007;25(4):385-90.
24. Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting. *Scand J Trauma Resusc Emerg Med* 2009;17:61.
25. Bronsky ES, Koola C, Orlando A, et al. Intravenous low-dose ketamine provides greater pain control compared to fentanyl in a civilian prehospital trauma system: a propensity matched analysis. *Prehosp Emerg Care* 2018:1-8.
26. Tran KP, Nguyen Q, Truong XN, et al. A comparison of ketamine and morphine analgesia in prehospital trauma care: a cluster randomized clinical trial in rural Quang Tri province, Vietnam. *Prehosp Emerg Care* 2014;18(2):257-64.
27. Champion HR, Sacco WJ, Copes WS, et al. A revision of the Trauma Score. *J Trauma* 1989;29(5):623-9.
28. Johansson J, Sjoberg J, Nordgren M, et al. Prehospital analgesia using nasal administration of S-ketamine--a case series. *Scand J Trauma Resusc Emerg Med* 2013;21:38.
29. Yousefifard M, Askarian-Amiri S, Rafiei Alavi SN, et al. The efficacy of ketamine administration in prehospital pain management of trauma patients; a systematic review and meta-analysis. *Arch Acad Emerg Med* 2020;8(1):e1.
30. Karlow N, Schlaepfer CH, Stoll CRT, et al. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the emergency department. *Acad Emerg Med* 2018;25(10):1086-97.





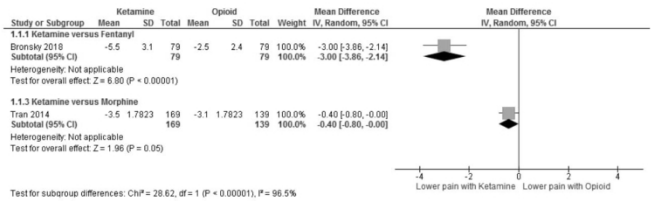


Fig. 3 - Ketamine versus opioids - change in pain score

583x825mm (72 x 72 DPI)

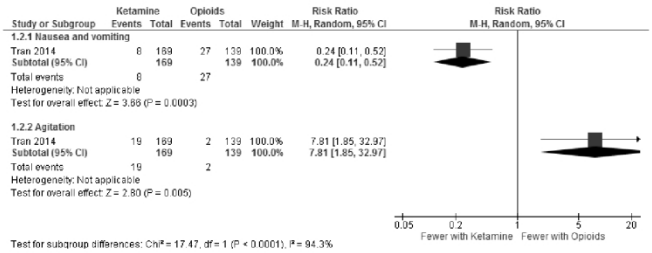


Fig. 4 - Ketamine versus opioids - adverse events

209x297mm (200 x 200 DPI)

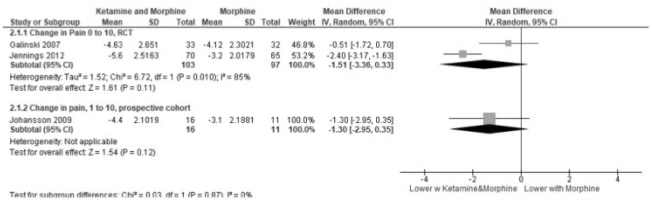


Fig. 5 - Combined ketamine and morphine compared with only morphine - change in pain score

209x296mm (150 x 150 DPI)

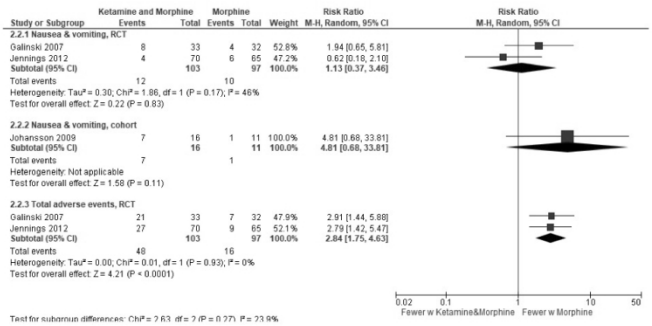


Fig. 6 - Combined ketamine and morphine compared with only morphine - adverse events

209x296mm (150 x 150 DPI)

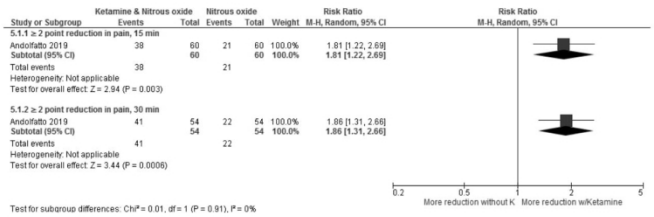


Fig. 7 - Ketamine and N2O vs only N2O - change in pain score

583x825mm (72 x 72 DPI)

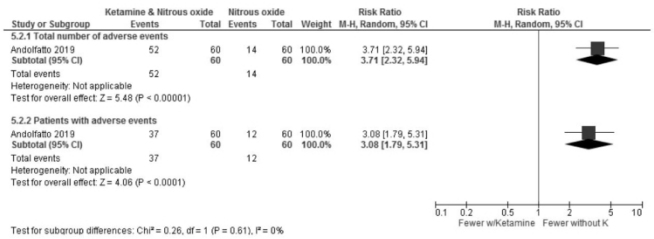


Fig. 8 - Ketamine and N2O vs only N2O - adverse events

583x825mm (72 x 72 DPI)

SEARCH STRATEGIES

PUBMED

#1,"Search ketamine[Text Word]"
#2,"Search analgesics, ketamine[Pharmacological Action]"
#3,"Search ketamine[MeSH Terms]"
#4,"Search (#1 OR #2 OR #3)"
#5,"Search emergency medical services[MeSH Terms]"
#6,"Search Ambulances[MeSH Terms]"
#7,"Search Ambulance*[Text Word]"
#8,"Search Prehospital[Text Word]"
#9,"Search Pre-hospital[Text Word]"
#10,"Search out of hospital[Text Word]"
#11,"Search Paramed*[Text Word]"
#12,"Search emergency medical technicians[MeSH Terms]"
#13,"Search (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)"
#14,"Search Danish[Language]"
#15,"Search Norwegian[Language]"
#16,"Search Swedish[Language]"
#17,"Search English[Language]"
#18,"Search (#14 OR #15 OR #16 OR #17)"
#19,"Search (#4 AND #13 AND #18)"
#20,"Search Animals[MeSH Terms]"
#21,"Search Humans[MeSH Terms]"
#22,"Search (#20 NOT #21)"
#23,"Search (#19 NOT #22)"
#24,"Search (""xxxx/xx/xx""[Date - Entrez]: ""xxxx/xx/xx""[Date - Entrez])"
#25,"Search (#23 AND #24)"

EMBASE

#1, analgesic agent/
#2, ketamine.m._titl.
#3, rescue personnel/
#4, ambulance/
#5, emergency health service/
#6, “emergency medical technician*”.ab,ti.
#7, “emergency responder*”.ab.ti.
#8, rescue service. ab.ti.
#9, “Paramed*”. ab.ti.
#10, “ambulance*”. ab.ti.
#11, pre-hospital. ab.ti.
#12, prehospital. ab.ti.
#13, out-of-hospital. ab.ti.
#14, or/3-13
#15, or/1-2
#16, and/14-15

Cochrane Library

#1 MeSH descriptor: [Ketamine] explode all trees
#2 MeSH descriptor: [Emergency Medical Technicians] explode all trees
#3 MeSH descriptor: [Ambulances] explode all trees
#4 paramed*
#5 out-of-hospital
#6, pre-hospital
#7, prehospital
#8, ambulance*
#9, #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10, #1 AND # 9

Epistemonikos

(title:((title:(prehospital OR pre-hospital OR out-of-hospital OR ambulance* OR “emergency medical technicians” OR “emergency medical service*”) OR abstract:(prehospital OR pre-hospital OR out-of-hospital OR ambulance* OR “emergency medical technicians” OR “emergency medical service*”)) AND (title:(ketamin*) OR abstract:(ketamin*)))

Appendix 2

Excluded reference	Reason for exclusion
Allison K, Porter K. Consensus on the pre-hospital approach to burns patient management. Injury 2004; 35: 734-8.	Ketamine not central in the text
Anonymous. Comments on the recommendations of the German Medical Society dated October 20, 2003 on the administration of analgesics by paramedics in emergency situations. Notarzt 2005; 21: 81-82.	Excluded due to language restrictions
Ansem RP, Hartman JA, Foudraine JF, van Loenen E, Rutten FL. [Analgetic ketamine feasible in ambulance emergency care]. Ned Tijdschr Geneeskd 1994; 138: 2301-4.	Excluded due to language restrictions
Ardeel E. Adverse effects following prehospital use of ketamine by paramedics. Acad Emerg Med 2012; 19: S269-S70.	Letter
Aries P, Montelescaut E, Pessey F, Danguy des Deserts M, Giacardi C. Pre-hospital emergency medicine: pain control. Lancet 2016; 387: 747.	Ketamine not central in the text
Arroyo-Novoa CM, Figueroa-Ramos MI, Miaskowski C, Padilla G, Paul SM, Rodriguez-Ortiz P, Stotts NA, Puntillo KA. Efficacy of small doses of ketamine with morphine to decrease procedural pain responses during open wound care. Clin J Pain 2011; 27: 561-6.	Patient population did not match the criteria
Barrett TW, Schriger DL. Move over morphine: Is ketamine an effective and safe alternative for treating acute pain? Answers to the September 2015 journal club. Ann Emerg Med 2016; 67: 289-94.	Setting did not match the criteria
Berg C. Out-of-hospital ketamine for pain, agitation, and airway intervention is safe and effective. Ann Emerg Med 2015; 66: S32.	Study design did not match the criteria
Bredmose PP, Grier G, Davies GE, Lockey DJ. Pre-hospital use of ketamine in paediatric trauma. Acta Anaesthesiol Scand 2009; 53: 543-5.	Patient population did not match the criteria

Bredmose PP, Lockey DJ, Grier G, Watts B, Davies G. Pre-hospital use of ketamine for analgesia and procedural sedation. EMJ 2009; 26: 62-4.	Study design did not match the criteria
Brokmann JC, Rossaint R, Hirsch F, Beckers SK, Czaplik M, Chowanetz M, Tamm M, Bergrath S. Analgesia by telemedically supported paramedics compared with physician-administered analgesia: A prospective, interventional, multicentre trial. Eur J Pain 2016; 20: 1176-84.	Ketamine not central in the text
Butler FK, Kotwal RS, Buckenmaier CC, 3rd, Edgar EP, O'Connor KC, Montgomery HR, Shackelford SA, Gandy JV, 3rd, Wedmore IS, Timby JW, Gross KR, Bailey JA. A triple-option analgesia plan for tactical combat casualty care: TCCC guidelines change 13-04. J Spec Oper Med 2014; 14: 13-25.	Study design did not match the criteria
Castle N, Naidoo R. Achieving prehospital analgesia. EMJ 2012; 29: 765-6.	Setting did not match the criteria
Castren M, Lindstrom V, Branzell JH, Niemi-Murola L. Prehospital personnel's attitudes to pain management. Scand J Pain 2015; 8: 17-22.	Study design did not match the criteria
Chesters A, Webb T. Ketamine for procedural sedation by a doctor-paramedic prehospital care team: a 4-year description of practice. Eur J Emerg Med 2015; 22: 401-6.	Patient population did not match the criteria
Corrigan M, Wilson SS, Hampton J. Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings. Am J Health Syst Pharm 2015; 72: 1544-54.	Study design did not match the criteria
Domonoske B, Gunter R, Love J. Ketamine may increase the risk of PE in selected trauma patients. Crit Care Med 2014; 42: A1610.	Setting did not match the criteria
Domonoske B, Love J. Ketamine reduces the incidence of VTE in selected trauma patients. Crit Care Med 2013; 41: A55.	Setting did not match the criteria
Eidenbenz D, Taffe P, Hugli O, Albrecht E, Pasquier M. A two-year retrospective review of the determinants of pre-hospital analgesia administration by alpine helicopter	Study design did not match the criteria

emergency medical physicians to patients with isolated limb injury. Anaesthesia 2016; 71: 779-87.	
Ellerton J, Paal P, Brugger H. Prehospital use of ketamine in mountain rescue. EMJ 2009; 26: 760-1.	Letter
Fisher AD, Rippee B, Shehan H, Conklin C, Mabry RL. Prehospital analgesia with ketamine for combat wounds: a case series. J Spec Oper Med 2014; 14: 11-7.	Study design did not match the criteria
Galinski M, Hoffman L, Bregeaud D, Kamboua M, Ageron FX, Rouanet C, Hubert JC, Istria J, Ruscev M, Tazarourte K, Pevirieri F, Lapostolle F, Adnet F. Procedural sedation and analgesia in trauma patients in an out-of-hospital emergency setting: A prospective multicenter observational study. Prehosp Emerg Care 2018; 22: 497-505.	Patient population did not match the criteria
Gausche-Hill M, Brown KM, Oliver ZJ, Sasson C, Dayan PS, Eschmann NM, Weik TS, Lawner BJ, Sahni R, Falck-Ytter Y, Wright JL, Todd K, Lang ES. An evidence-based guideline for prehospital analgesia in trauma. Prehosp Emerg Care; 18 25-34.	Study design did not match the criteria
Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, McKee M, Weiss M, Pitetti RD, Hostetler MA, Wathen JE, Treston G, Garcia Pena BM, Gerber AC, Losek JD. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. Ann Emerg Med 2009; 54: 171-80.	Patient population did not match the criteria
Guldner GT, Petinaux B, Clemens P, Foster S, Antoine S. Ketamine for procedural sedation and analgesia by nonanesthesiologists in the field: a review for military health care providers. Mil Med 2006; 171: 484-90.	Patient population did not match the criteria
Gurnani A, Sharma PK, Rautela RS, Bhattacharya A Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. Anaesth Intensive Care 1996; 24: 32-6	Patient population did not match the criteria
Henderson L. Special K for special situations. A review of ketamine for prehospital use. JEMS 2016; 41: 58-60.	Study design did not match the criteria

Hossfeld B, Holstrater S, Bernhard M, Lampl L, Helm M, Kulla M. Prehospital analgesia in adults. Anasthesiol Intensivmed Notfallmed Schmerzther 2016; 51: 84-96.	Excluded due to language restrictions
Iqbal M, Spaight PA, Siriwardena AN. Patients' and emergency clinicians' perceptions of improving pre-hospital pain management: A qualitative study. EMJ 2013; 30: e18.	Ketamine not central in the text
Jansen A, Boyle M. Prehospital pain relief, where are we now? A review of the literature. Australas J Paramed 2014; 11: 20.	Ketamine not central in the text
Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. Acta Anaesthesiol Scand 2011; 55: 638-43.	Study design did not match the criteria
Jennings PA, Cameron P, Bernard S. Determinants of clinically important pain severity reduction in the prehospital setting. EMJ 2012; 29: 333-34.	Ketamine not central in the text
Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, Masci K. Long-term pain prevalence and health-related quality of life outcomes for patients enrolled in a ketamine versus morphine for prehospital traumatic pain randomised controlled trial. EMJ 2014; 31: 840-43.	Setting did not match the criteria
Jennings PA, Cameron P, Bernard SA, Walker T, Fitzgerald M, Masci K. Ketamine is superior to morphine alone for the management of traumatic pain in the prehospital setting: A randomised controlled trial. Emerg Med Australas 2012; 24: 19.	Letter
Johansson J, Sjoberg J, Nordgren M, Sandstrom E, Sjoberg F, Zetterstrom H. Prehospital analgesia using nasal administration of S-ketamine--a case series. Scand J Trauma Resusc Emerg Med 2013; 21: 38.	Study design did not match the criteria
Kovar JL, Gleisberg GR, Ardeel ER, Basnawi A, Escott MEA. Hemodynamic changes in patients receiving ketamine sedation by emergency medical services. Acad Emerg Med 2012; 19: S87.	Study design did not match the criteria

Lovrincevic M, Kotob F, Santarosa J. Pain management in the trauma setting. Semin Anesth Perioper Med Pain 2005; 24: 34-40.	Setting did not match the criteria
Madeira F, Ferreira P, Lapa T, Tavares E. Prehospital pain management: Do we have to learn more about it? Eur J Anaesthesiol 2013; 30: 203-04.	Ketamine not central in the text
Marland S, Ellerton J, Andolfatto G, Strapazzon G, Thomassen O, Brandner B, Weatherall A, Paal P. Ketamine: Use in anesthesia. CNS Neurosci Ther 2013; 19: 381-89.	Setting did not match the criteria
McKay WP. Intravenous analgesia for out-of-hospital traumatic pain in adults: ketamine gives a greater reduction in pain than morphine but causes more adverse effects. Evid Based Nurs 2013; 16: 58-9.	Letter
McQueen C, Crombie N, Cormack S, Wheaton S. Prehospital use of ketamine for analgesia and procedural sedation by critical care paramedics in the UK: A note of caution? EMJ 2014; 31: 1029.	Letter
Moy R, Wright C. Ketamine for military prehospital analgesia and sedation in combat casualties. J R Army Med Corps 2018; 164: 436-37.	Study design did not match the criteria
Moy RJ, Le Clerc S. Ketamine in prehospital analgesia and anaesthesia. Trends Anaesth Crit Care 2011; 1: 243-45.	Study design did not match the criteria
Petz LN, Tyner S, Barnard E, Ervin A, Mora A, Clifford J, Fowler M, Bebarta VS. Prehospital and en route analgesic use in the combat setting: a prospectively designed, multicenter, observational study. Mil Med 2015; 180: 14-18.	Study design did not match the criteria
Porter K. Ketamine in prehospital care. EMJ 2004; 21: 351-4.	Study design did not match the criteria
Radvansky BM, Puri S, Sifonios AN, Eloy JD, Le V. Ketamine-a narrative review of its uses in medicine. Am J Ther 2016; 23: e1414-e26.	Study design did not match the criteria
Schauer SG, Mora AG, Maddry JK, Bebarta VS. Multicenter, prospective study of prehospital administration of analgesia in	Study design did not match the criteria

the U.S. combat theater of Afghanistan. Prehosp Emerg Care 2017; 21: 744-49.	
Schonenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. Psychopharmacology (Berl) 2005; 182: 420-5.	Study design did not match the criteria
Scott S, Paul B. UK and Victorian, Acute pain guidelines compared. Australas J Paramed 2013; 10: 32.	Letter
Steel A, Wharton R, Bates A, French J, Lewis S, Mackenzie R. Ketamine use in prehospital critical care. EMJ 2008; 25: 618-19.	Letter
Svenson JE, Abernathy MK. Ketamine for prehospital use: new look at an old drug. Am J Emerg Med 2007; 25: 977-80.	Patient population did not match the criteria
Wedmore IS, Butler FK. Battlefield analgesia in tactical combat casualty care. Wilderness Environ Med 2017; 28: S109-S16.	Study design did not match the criteria
Wood PR. Ketamine: Prehospital and in-hospital use. Trauma 2003; 5: 137-40.	Study design did not match the criteria
Zhang M, Cowan T, Smiles JP, Morgan M, Armstrong J, Goswami C, Sewell C. Prehospital analgesic choice in injured patients does not impact on rates of vomiting: Experience from a New South Wales primary retrieval service. Emerg Med Australas 2017; 30: 406-11.	Study design did not match the criteria

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	A I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7+8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10+11+12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 3-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 3-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 3-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.