Ketamine as an analgesic in the pre-hospital setting: a systematic review

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Background: Pain is a common presenting complaint and there is considerable debate regarding the best practice for analgesia in the pre-hospital environment for trauma patients with severe pain.

Methods: A review of the literature was conducted using a number of electronic medical literature databases from their earliest record to the latest available at the time the search was conducted (May 2010). Medical Subject Headings, keywords and a pre-hospital search filter were used to yield relevant literature.

Results: The search strategy yielded a total of 837 references. Seven hundred and fifty of these references were excluded as they did not meet the inclusion criteria. Of the 87 articles short listed for abstract or full-text review, six reported on ketamine use as an analgesic agent in the pre-hospital setting. Two papers were prospective randomized-controlled trials, and the number of patients included in the studies ranged from 4 to 164. Three studies aimed to report on the effectiveness of ketamine for pain intensity reduction; two concluded that ketamine provided safe and effective pain relief and one reported that ketamine reduced the amount of morphine required but was not associated with a reduction in pain intensity. One study identified a significantly higher prevalence of adverse effects following ketamine administration. The other studies reported no significant side effects and concluded that ketamine was safe.

Conclusion: Ketamine is a safe and effective analgesic agent. The addition of ketamine as an analgesic agent may improve the management of patients presenting with acute traumatic pain in the pre-hospital setting.

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There is considerable debate regarding the best practice for analgesia in the pre-hospital environment for conscious trauma patients with severe pain. Current practice in the pre-hospital setting varies widely. Pain is one of the most common presentations for patients requiring emergency transport and yet an approach to pain relief that is effective and safe is not clear.

In many Australian and some international jurisdictions, ambulance practice involves the administration of a volatile anaesthetic agent, methoxyflurane (in analgesic doses); however, the analgesic effect is time limited due to the dosage and it has limited effectiveness in uncooperative, distressed patients. Furthermore, there is now widespread use of parenteral opioids (morphine and fentanyl) and more limited use of intranasal fentanyl for patients with severe pain. Over the last decade, most paramedics in developed and developing countries have been trained to insert an intravenous cannula1 and administer parenteral morphine or fentanyl.2 However, these agents have the associated problems of sedation, respiratory depression and nausea, which limit their effectiveness and utility in many patients.

Ketamine hydrochloride is an injectable anaesthesia drug with analgesic properties that has been used extensively in traumatology. Internationally, it is available as a racemic preparation or in its more active form, (S)-ketamine. When compared with opioids, ketamine has a low frequency of serious side effects in doses used for analgesia and has little negative effect on the blood pressure and heart rate but has been associated with tachycardia and hypertension. What makes ketamine even more desirable for use in the pre-hospital environment is that it allows patients to maintain their pharyngeal reflexes and maintain their own airway even when fully dissociated.3 A significant benefit of its use is that it is said to have an opioid-sparing
effect, and moderate-level evidence exists to indicate that it improves analgesia in patients with severe pain that is poorly responsive to opioids.

This systematic review aims to identify studies relevant to the use of ketamine as an analgesic agent in the pre-hospital environment.

**Methods**

**Research question**
The research questions for this systematic review were ‘Does the administration of ketamine effectively reduce pain intensity in patients suffering trauma in the pre-hospital setting?’ and ‘What side effects are associated with the administration of ketamine as an analgesic agent for patients suffering trauma in the pre-hospital setting?’

**Search strategy**
A review of the literature was conducted using several electronic medical literature databases, which are described in Table 1. This structured search included peer- and non-peer-reviewed (grey) literature and was combined with relevant Medical Subject Headings (MeSH) to focus the search to more relevant literature, including pain and analgesia. In addition, the keywords ketamine, ketanest, ketaset and ketalar were used to ensure that ketamine was included in the article. A pre-hospital search filter was used to further distil literature relating specifically to the pre-hospital population. The MeSH and keywords were combined and further limited to the full-text articles written in English and human studies. The reference lists of relevant peer-reviewed literature were also hand searched to identify any appropriate articles that may have been missed by the electronic search. The inclusion and exclusion criteria are listed in Table 2.

**Critical appraisal of included articles**
All included articles were critically appraised and assessed for quality. The quality of the articles was assessed using a structured tool developed by the Scottish Intercollegiate Guidelines Network (SIGN). Each checklist includes an assessment of the methodological quality; summary of the key points of the study; the strengths and weaknesses; and the study’s applicability to the patient groups targeted by the review. Study quality was rated as ++ (well conducted, high quality); + (moderate quality); or – (low quality).

The level of evidence (LOE) was categorized according to the study design as defined by the International Liaison Committee on Resuscitation.

**Types of studies**
Given the paucity of high-level, randomized-controlled trials in this area, it was decided *a priori* to allow the inclusion of all study types. High-level studies (LOE 1 and 2) were given priority; however, other types of studies would be considered, including non-randomized trials, cohort studies, case–control studies, retrospective case series and case studies. Abstracts of relevant studies where full-text articles were not available would be excluded.

**Types of participants**
This systematic review considered all English-language publications that reported on patients presenting with pain and managed in the pre-hospital environment. It is well understood that the compo-

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**Table 1**

<table>
<thead>
<tr>
<th>Databases searched.</th>
<th>AMED (1985–April 2010)</th>
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<tbody>
<tr>
<td><strong>Peer-reviewed databases</strong></td>
<td>Cinahl (1989–2010)</td>
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<tr>
<td></td>
<td>Ovid MEDLINE (1996–5 March 2010)</td>
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<tr>
<td></td>
<td>Cochrane Central Register of Controlled Trials</td>
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<td>Cochrane Database of Systematic Reviews</td>
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<td></td>
<td>DARE (Database of Abstracts of Reviews of Effects)</td>
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<td></td>
<td>Embase (All years)</td>
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<td></td>
<td>Meditext (Commencement–2010)</td>
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<td></td>
<td>PsycINFO (1987–April week 2 2010)</td>
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<td></td>
<td>Scopus (Commencement to 5 March 2010)</td>
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| **Non-peer-reviewed databases** | Google (Google Scholar) |

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**Table 2**

<table>
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<th>Systematic review inclusion and exclusion criteria.</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>Relevant to the research question</td>
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<tr>
<td>Written in English</td>
</tr>
<tr>
<td>Study involving human subjects</td>
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<tr>
<td>Population of any age</td>
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<tr>
<td>Based in the pre-hospital setting</td>
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<td>All study types</td>
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sition of emergency medical systems (EMS) varies internationally. The professional qualification, skill sets and experience of EMS providers vary considerably, and may comprise medical specialists (anaesthetist, emergency physician, trauma surgeon), nursing personnel or paramedics. Many EMSs use models of mixed skill sets. For this reason, the qualification of the care provider was not limited, and all types of EMS crewing were included. There was no age limit applied to participants or the aetiology of pain.

**Types of outcome measures**
The outcome measures that were considered for inclusion were:

- Pain intensity reduction.
- Effective pain relief.
- Clinically significant side effects.
- Adverse events.
- Prevalence of ‘emergence phenomenon’.

The outcomes identified were evaluated in a number of ways, including the use of validated metrics, information from medical records or audit databases or patient descriptions.

**Results**
The search strategy yielded a total of 837 references. Seven hundred and fifty of these references were excluded as they did not meet the inclusion criteria (Fig. 1).

Of the 87 articles short listed for abstract or full-text review, six were identified as meeting the inclusion criteria: Bredmose et al., Cottingham and Thomson, Galinski et al., Svenson and Abernathy, Johansson et al. and Porter.

**Study design**
The study design and population characteristics of the included studies are summarized in Table 3. Most studies focused on patients in pain following trauma, with one including patients with pain of a medical aetiology. Johansson et al. limited the population to patients with isolated bone fractures.

**Intervention**
The common intervention in these studies was the administration of ketamine for the purpose of relieving pain. All studies reported ketamine being administered in combination with another agent (opioid or benzodiazepine), which is a common practice internationally. Two randomized-controlled trials compared the effectiveness of morphine, followed by ketamine or morphine combined with ketamine to morphine alone.

The Bredmose study reported the use of ketamine to facilitate the insertion of a chest tube in three patients. There were no occasions where ketamine was administered to induce anaesthesia. Ketamine was used as a procedural sedative in five patients in the Svenson study.

**Effects of interventions**
It was not possible to undertake a quantitative meta-analysis due to the small number of papers meeting the inclusion criteria, and the heterogeneity between studies. A description of the reported effectiveness of the six included studies is provided below.
Effectiveness

Only three studies aimed to report on the effectiveness of ketamine for pain reduction,\textsuperscript{10,11,13} and only two of these used a pain rating score as their endpoint.\textsuperscript{11,13} The remaining studies sought to describe the indications for use, the side effects encountered, the mechanisms of injury requiring ketamine administration and the total dose of ketamine administered.

Of the three studies that reported on the effectiveness of ketamine in reducing traumatic pain, two concluded that ketamine provided effective pain relief\textsuperscript{10,13} and one reported that ketamine reduced the amount of morphine required but was not associated with a reduction in pain intensity.\textsuperscript{11} Galinski et al.\textsuperscript{11} found that the visual analogue scale pain measure (measured in millimetres from 0 to 100, 0 indicating no pain and 100 indicating ‘worst pain ever’) was not statistically different between the morphine and ketamine intervention group and the morphine alone control group (34.1 vs. 39.5 mm; \(P = \text{NS}\)). At the 30-min time period, a larger proportion of the ketamine group had their pain reduced to below 30 mm than the morphine group; however, this difference did not reach statistical significance (61\% vs. 41\%; \(P = 0.2\)).

Johansson et al.\textsuperscript{13} used a numerical rating scale pain measure (measured by a patient providing a score between 0 and 10, 0 indicating no pain and 10 indicating ‘worst pain ever’) and found that the pain scores were significantly different on admission to hospital: 5.4 ± 1.9 in the morphine-only group and 3.1 ± 1.4 in the morphine, followed by the ketamine group (\(P < 0.05\)).

The other studies\textsuperscript{9,10,12} did not measure effectiveness using an accepted pain measure, but did report effective pain relief.

Adverse effects

Five of the six studies\textsuperscript{9–13}, investigated the prevalence of side effects associated with the analgesic agents used in each of the studies.

Galinski et al.\textsuperscript{11} reported that neuropsychological adverse effects were significantly greater in the ketamine group. These side effects included hallucinations, dizziness, diplopia and dysphoria. Despite these side effects, the authors stated that these were weak and brief, none needed treatment and the patients’ satisfaction between the two groups was not found to be different. The level of sedation, nausea, vomiting and itching did not differ between the two groups. The other studies reported no significant side effects and concluded that ketamine was safe.

The Bredmose study\textsuperscript{9} stated that there were no documented cases where basic airway manoeuvres had to be implemented following the administration of ketamine in their cohort of 164 children. They did identify four cases where the oxygen saturations were reported to decline; however, none of these children desaturated > 4\% from their pre-ketamine saturations. The Johansson study\textsuperscript{13} reported no other side effects apart from nausea and vomiting experienced in both groups. They did report a mean increase in systolic blood pressure in the ketamine group on admission to hospital (mean [SD]; 141 [33] mmHg vs. 167 [32] mmHg; \(P < 0.05\)).

Methodological quality

Methodological quality was assessed using a structured tool developed by the SIGN.\textsuperscript{7} One study was rated as well constructed and of high quality,\textsuperscript{11} two studies were rated as moderate quality,\textsuperscript{9,13} and three studies were rated as low quality.\textsuperscript{9,12,14}
Discussion

There are few studies based in the pre-hospital environment examining the effectiveness of ketamine as an analgesic agent. The majority of the studies that have been published provide low levels of evidence, with only two randomized-controlled trials published. Unfortunately, even the randomized-controlled studies contained very small numbers.

EMS and emergency departments are faced with the challenge of providing effective pain management for both humanitarian reasons and to reduce the likelihood of chronic pain syndromes and pain-related anxiety and disability following the acute phase. The presence of moderate to severe pain and poor analgesia is also associated with tachycardia, sleep disturbances, hypertension, increased stress response and immunosuppression. Furthermore, the benefit of effective pre-hospital analgesia continues beyond the pre-hospital setting. Effective pre-hospital analgesia facilitates the in-hospital diagnostic and therapeutic process and has been shown to increase the likelihood of timely ED analgesia.

This review aimed to evaluate the effectiveness and safety of the addition of ketamine to commonly used pre-hospital analgesic agents (generally opioids) for patients presenting with acute pain. The results of the search for evidence resulted in a range of quantitative and qualitative studies of varying quality and utility. There was significant heterogeneity in the interventions and populations and reflects the diverse EMS used internationally.

The papers included addressed issues such as dosing, combination of agents with analgesic adjuvants, effectiveness of analgesia and incidence of adverse events. Unfortunately, not all studies used a valid, reproducible measure of acute pain, which made ‘quantifying’ the magnitude of efficacy of the addition of ketamine to alternative analgesic therapies difficult.

A number of side effects have been reported following the administration of ketamine, and include transient tachycardia and an increase in blood pressure, arrhythmia, respiratory depression and apnoea, enhanced skeletal tone and purposeless movement, diplopia and nystagmus, laryngospasm and emergence reactions. Generally, these have been observed in anaesthetic doses or following procedural sedation, rather than in the lower doses commonly used for analgesia. There is a risk, albeit low, of airway compromise in patients following ketamine administration, highlighting the importance of any personnel administering the agent to be competent in managing an airway.

The studies included in this review did not report any serious adverse events associated with either ketamine or alternate analgesic agents. Galinski et al. reported that the frequencies of hallucinations, dizziness, diplopia and dysphoria were greater in the ketamine group; however, the authors stated that these were weak and brief and did not require intervention.

Cottingham and Thomson stated that none of the four patients they described had any recollection of their prolonged entrapment or serious accident, which may be a beneficial property of that agent if recollection of severe pain and distressing events at the time of the incident are associated with the likelihood of persistent pain and post-traumatic stress disorders.

While the studies included in this review utilized randomized-controlled or observational designs, their findings were in most cases limited by small sample sizes, potential for the introduction of significant bias and lack of validated metrics. The review suggests that ketamine is an analgesic option in the pre-hospital and emergency care setting that should be considered seriously, particularly for severe pain or in mass casualty incidents.

Implications for practice

From the overall results of this systematic review, several recommendations can be made for practice. Firstly, ketamine when administered in analgesic (sub-anaesthetic) doses [0.1 (11)–0.5 (12) mg/kg intravenously] appears at least as effective as or more effective than an opioid alone at reducing pain intensity in the pre-hospital setting. Secondly, analgesic doses of ketamine appear not to cause a greater frequency or severity of side effects compared with other analgesics. And finally, the studies to date generally involve EMS with physician crewing, critical care nurse crewing or combinations of the two. Given the safety profile of the drug and the lack of serious side effects identified in the literature, it appears that the drug could be administered safely by appropriately trained and supported paramedics.

Implications for research

This review has identified several future priorities for research. A well-designed randomized-controlled trial with sufficient sample size and power should be developed to compare the analgesic efficacy of...
ketamine to opioids administered in the pre-hospital setting. Furthermore, research should compare the prevalence and magnitude of side effects, alterations in haemodynamic parameters and variables reflecting oxygen balance (oxygen saturation and blood gas analysis where available) between ketamine and other analgesic agents. Future research should be focused on the efficacy of intravenous ketamine as an analgesic and should be rigorously compared with other routes such as intramuscular, intranasal and oral routes.

Conclusion

Undertaking high-level, randomized-controlled trials in the pre-hospital setting presents many logistical and ethical challenges. However, such trials are integral to identifying clinical improvements and validating current practice. The results of this systematic review show that ketamine is a safe and effective analgesic agent. Several recommendations for practice and future research exploring the use of ketamine are provided, and the addition of ketamine as an analgesic agent may improve the management of people presenting with acute pain in the pre-hospital setting.

References


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