

Prehospital Analgesia: Systematic Review of Evidence

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Abstract

The purpose of this systematic review is to investigate current evidence for analgesic use in the prehospital environment using expert military and civilian opinion to determine the important clinical questions. There was a high degree of agreement that pain should be no worse than mild, that pain relief be rapid (within 10 minutes), that patients should respond to verbal stimuli and not require ventilatory support, and that major adverse events should be avoided. Twenty-one studies provided information about 6,212 patients; the majority reported most of the outcomes of interest. With opioids 60-70% of patients still had pain levels above 30/100 mm on a Visual Analogue Scale after 10 minutes, falling to about 30% by 30-40 minutes. Fascia iliaca blocks demonstrated some efficacy for femoral fractures. No patient on opioids required ventilatory support; two required naloxone; sedation was rare. Cardiovascular instability was uncommon. Main adverse events were dizziness or giddiness, and pruritus with opioids. There was little evidence regarding the prehospital use of ketamine.

Introduction

That analgesia should be provided in the pre-hospital environment has not always been as widely agreed at it is today. As late as 1981 thinking about pre-hospital analgesia was different: 'Any agent that interferes with the patient's normal pain response may frustrate the physician attempting to make a diagnosis' and 'A suitable agent for use by paramedics in pre-hospital treatment should be quick-acting and short-lived in order to preserve the pain response for diagnostic purposes in the emergency department...' [1]. Many studies have shown inability to provide adequate pre-hospital analgesia [2-4]. Even as recently as 2000, only 1.8% of 1073 patients received any form of pre-hospital analgesia for extremity fractures [5].

Morphine has been used in the pre-hospital environment for many years. There are descriptions of its use in the mid-nineteenth century during the Crimean War [6], but the expansion in interest in pre-hospital analgesics came in the 1970s with the introduction of nitrous oxide and oxygen (Entonox), and then with nalbuphine in the 1980s. More opioid drugs have subsequently become available by more routes of administration. In the non-opioid category, ketamine is often suggested for use in the pre-hospital environment.

No systematic review of the available evidence has been published previously, although reviews have summarised options available for pre-hospital analgesia [7-9]. Most notable was a literature search for all available evidence using levels of evidence [9]. Studies found at that time were limited and mainly descriptive, and the review described options available from the various studies, rather than extracting data on efficacy and harm.

Providing pre-hospital analgesia is not a simple matter; there are a number of issues. These include the skills and knowledge of the analgesic provider; if the provider is well versed in pre-hospital care (including appropriate intravenous access and ventilatory

support) the options are very different from those where the provider has limited medical knowledge and skills. The location and type of other medical support may make a difference; if one is several days away from any medical help and specialised monitoring the options are different from those where these may be less than an hour away. The type of injury is important; an isolated closed limb injury will often require a different approach from multiple injuries associated with massive tissue disruption, hypovolaemia and hypothermia.

All of these issues, and others not detailed here, will affect choice of pre-hospital analgesic. Practical considerations are likely to outweigh academic ideals, but consideration of evidence of effectiveness or harm is important in either case. One of the drivers for this is the increasing number of buccal, sublingual and nasal opiates available, notably fentanyl, as well as increasing use of ketamine. While most of these are usually licensed for cancer breakthrough pain they may appear attractive to the pre-hospital care provider.

The purpose of this systematic review is to investigate current evidence for analgesics in the pre-hospital environment.

Methods

We searched Medline (PubMed) and EMBASE using free text terms of pre-hospital pain relief, pre-hospital analgesia, and wilderness analgesia, alone and with individual drug names (morphine, fentanyl, etc) and routes (intravenous, intramuscular, intranasal, lollipop, oral, transmucosal, regional techniques etc). Reference lists from reviews and papers retrieved were also examined for possible inclusion. No language exclusion applied and the date of last search was November 2009.

Any study, of any design, providing efficacy or adverse event results concerning pre-hospital analgesia was included if it reported results in adults. Studies were excluded if they contained no numerical results, were not original studies, or were actually performed only in hospital. We also excluded studies involving nalbuphine [10 - 14] which is not now available in the UK, but did include a study on methoxyflurane [15] because it is used extensively by the Australasian military and civilian emergency services.

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Data extraction was guided by a Delphi process, in which UK military emergency medicine and anaesthetic consultants were asked about criteria for an ideal pre-hospital analgesic, as well as civilian doctors involved with helicopter emergency services in southern England. Their comments were used to determine which patient outcomes would be sought from included studies, for both efficacy and adverse events. They were asked whether they agreed or disagreed with the following statements regarding adequacy of outcomes:

1. Pain score of <30/100 mm on visual analogue scale (VAS).
2. Rapid onset of action. Pain relief achieved within:
 - a. 5 minutes
 - b. 10 minutes
 - c. 15 minutes
 - d. 20 minutes
3. Patients should remain responsive to verbal stimuli.
4. Patient should not require any airway manoeuvres or ventilatory support to be performed following administration.
5. Absence of any harmful adverse events following administration.

We looked specifically for analgesic failure, here defined as pain intensity of more than 30/100 mm on VAS, or its equivalent, at any time, but particularly within 10-20 minutes; more than

30/100 mm is equivalent to pain of at least moderate intensity [16]. Information was also sought on need for ventilatory support, sedation sufficient to make patient unresponsive to verbal stimulus, and general comments about adverse events.

Results

Available evidence

Electronic and bibliographic searches provided 85 references of possible pre-hospital analgesic studies. After excluding 64 studies for various reasons (Figure 1), 21 studies with numerical results concerning pre-hospital analgesia in adults remained (Table 1).

Three studies specifically examined military injuries, predominantly battle injuries [17-19]. The other studies reported on various acute medical patients and traumatic injuries in civilians. Treatments used included intravenous morphine, fentanyl, alfentanil, tramadol, pentazocine, ketamine, transmucosal and intranasal fentanyl, fascia iliaca blocks, inhalational nitrous oxide and oxygen (Entonox), and methoxyflurane. Doses and dosing schedules were variable.

Of the 21 studies, four were randomised double blind trials [20-23], one a randomised open trial [24], 11 were prospective observational studies [15,18,19, 25-32], and five retrospective reviews [17,33-36]. The total number of patients studied was 6,212, most of whom were in three large studies, one prospective study of Entonox (1,243 patients [30]), and two retrospective

Study [reference]	Analgesia	Timing	Ventilation	Sedation	Adverse events
Morphine					
Beecher 1946 [17]	+	—	—	—	—
Bruns et al., 1992 [25]	—	—	+	+	+
Bounes et al, 2008 [20]	+	+	+	+	+
Ricard-Hibon et al, 2008 [26]	+	—	+	+	+
Fentanyl, and fenatanyl vs morphine					
Kanowitz et al, 2006 [33]	+	—	+	+	+
Thomas et al, 2005 [34]	—	—	+	+	+
Kotwal et al, 2004 [19]	+	+	+	+	+
Rickard et al, 2007 [24]	+	—	+	+	+
Galinski et al, 2005 [21]	+	+	+	+	+
Alfentanil vs morphine					
Silfvast & Saarnivaara, 2001 [22]	+	+	+	+	+
Tramadol, and tramadol vs morphine					
Ward et al, 1997 [27]	+	—	+	+	+
Vergnion et al, 2001 [23]	+	+	+	+	+
Ketamine					
Svenson & Abernathy, 2007 [35]	—	—	+	+	+
Bredmose et al, 2009 [36]	—	+	+	+	+
Bion, 1984 [18]	+	+	+	+	+
Fascia iliaca block					
Lopez et al, 2003 [28]	+	+	+	+	+
Gozlan et all, 2005 [29]	+	+	+	+	+
Inhalational					
McKinnon, 1981 [30]	—	—	+	+	+
Stewart et al, 1983 [31]	—	—	+	+	+
Donen et al, 1982 [32]	—	—	+	+	+
Buntine et al, 2007 [15]	+	+	+	+	+

Table 1: Outcomes available in each of the 21 included studies

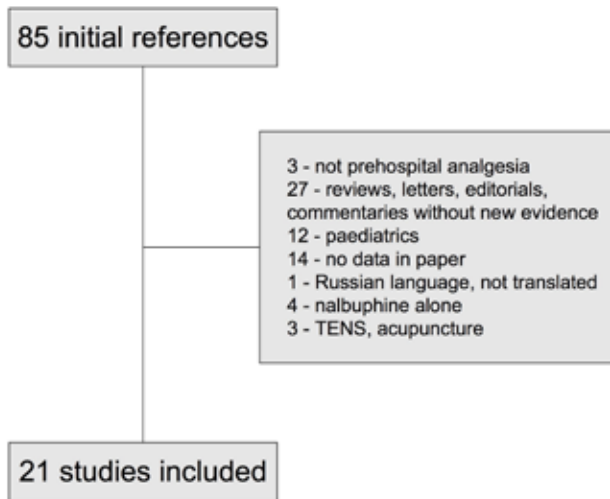


Figure 1: Flow of references identified for the systematic review

reviews (1,030 patients [36] and 2,129 patients [33]) both looking mainly at adverse events rather than pain scores and effectiveness.

Delphi responses

Forty of the military anaesthetic and emergency medicine consultants responded to the Delphi exercise, as well as 16 civilian air ambulance doctors; there was good agreement (Table 2). There was a high degree of agreement that analgesia pain should be no worse than mild [16], that pain relief should be rapid (within 10 minutes), that patients should respond to verbal stimuli, not require ventilation, and that major adverse events should be avoided.

They were also given an opportunity to make additional comments about what they would find important in pre-hospital analgesia. These were concerned mainly with issues of adverse events, typically the severity of events like nausea and vomiting, and whether cardiovascular stability should also be a criterion for choosing pre-hospital analgesia. Civilian physicians were more accepting of possible adverse events in order to obtain high quality analgesia.

Analgesic failure and timing

The majority of included studies reported most of the outcomes of interest. Least often reported were the timing of analgesia (within 10-20 minutes; 10/21 studies) and the extent of analgesia (14/21). Need for ventilatory support, sedation, and adverse events were reported in 20/21 studies (Table 1).

Many studies provided average pain scores, usually with a standard deviation. Initial average pain scores were above 60/100 mm or equivalent, and typically 80/100 mm. After treatment, pain scores were usually lower, typically averaging 30-40/100 mm, but with standard deviations almost as large as the average, indicating large disparity between individuals. These data were unhelpful in determining failure rate, but did indicate that analgesic failure was occurring.

Some studies on opioids [17, 19–21, 23–27, 33–34] provided information on the proportion of patients achieving analgesic success and failure. Figure 2 shows the failure rates (pain \geq 30/100 mm) between 10 and 40 minutes after treatment with intravenous morphine, fentanyl, and tramadol, and transmucosal fentanyl. After 10 minutes, about 60-70% of patients still had pain levels above 30/100 mm, but by 30-40 minutes this had fallen to about 30%. There was no obvious difference between opioid chosen in

Number	Question	Military (n=40)	Civilian (n=16)
		Agree (%)	Agree (%)
1	Pain score of < 30/100 mm on VAS (or equivalent) achieved	68	56
2	Rapid onset of action. Pain relief achieved within:		
	5 minutes	72	100
	10 minutes	23	
	15 minutes	3	
	20 minutes	3	
3	Patients should remain responsive to verbal stimuli	100	75
4	Patient should not require any airway manoeuvres or ventilatory support to be performed following administration	97	88
5	Absence of any harmful adverse events following administration	92	88

Table 2: Results of the Delphi exercise – replies from 40 military anaesthetic and emergency medicine consultants and 16 civilian helicopter emergency service doctors

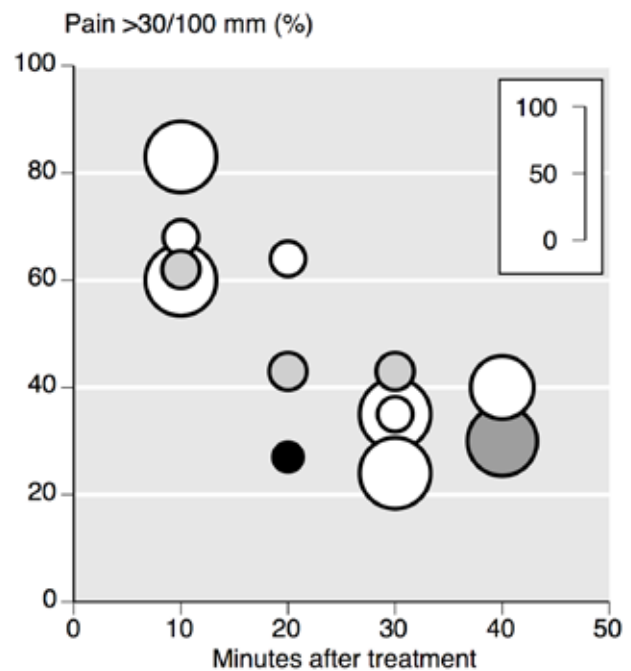


Figure 2: Failure rates (pain greater than 30mm) between 10 and 40 minutes after treatment with intravenous morphine (white), fentanyl (light gray), and tramadol (dark gray), and transmucosal fentanyl (black); the larger the circle's diameter the larger the number in the study.

this limited data set (Figure 2), and each study used different dose levels and dosing schedules. Failure rates on arrival at hospital were reported as 43% [17] and 17% [19], both involving battle injuries.

Drug and route	Number of patients	Ventilatory support	Sedation	Nausea (N) & vomiting (V)	Cardiovascular instability	Other
IV morphine	815	Hypoventilation (3); only 1 treated with naloxone	3	Nausea (20), Vomiting (8), N & V (16)	↓ BP (9), no support given	Pruritus (4), dizziness (5), dysphoria (1), fatigue (1), rash (1)
IV fentanyl	2224	Reduced respiratory rate or saturation (3), 1 given naloxone but no ventilatory support	4	Nausea (6), vomiting (3)	↓ BP (9), no support given	Dysphoria (1)
Transmucosal fentanyl	22	Hypoventilation (1) given naloxone	0	Nausea (3), vomiting (2)	None	Pruritus (5), light headed (2)
Intranasal fentanyl	127	Reduced respiratory rate or saturations (7), none needed ventilatory support	0	Nausea (9)	↓ BP (8), no support given	Sleepy/dizzy (5), bad taste (5), irritated throat (2), watery eyes (2), congestion (2), chest tightness (1), dysphoria (1)
IV alfentanil	16	0	0	Nausea (1)	0	Dizzy (4)
IV tramadol	154	0	0	Nausea (40), vomiting (6)	0	Dizzy (8)
IV ketamine	870	0	0	0	0	Dizzy (3)
IV pentazocine	9	0	9	0	0	0
Fascia iliaca	79	0	0	0	0	Rapid absorption of local anaesthetic leading to headache, tachycardia, and increased BP (1)
Inhalational Entonox	1555	0	3	Nausea (15), N&V (69)	0	Dizzy/light headed (177), drowsy (123), excitement (44), giddy (16), amnesia, numbness and headache (16)
Inhalational methoxyflurane	83	0	Increased sedation score (29)	Nausea (7)	0	Euphoria (3), dizzy (2), headache (1), hallucinations (1), sore throat and lip paraesthesia (1)

Table 3: Adverse events recorded according to treatment used. The numbers quoted are the number of patients with each adverse event.

Fascia iliaca blocks demonstrated some efficacy for femoral fractures. Though some pain relief was noted after 10 minutes, low levels of analgesic failure were noted at later times, with 26/27 with mild pain on arrival at hospital [28], and 30-minute pain scores averaging below 30/100 mm [29]. For inhalational analgesia, three studies with 1550 patients using Entonox reported 30% marked or complete pain relief on arrival at emergency department, with 53% partial, and 8% with mild or no relief [30-32]. Pain returned when gas was stopped. Inhalational methoxyflurane produced mean scores of 35/100 mm after 20 minutes in 83 patients [15].

Table 3 shows the number of cases of need for ventilatory support, sedation, nausea and vomiting, and cardiovascular instability reported, as well as other adverse events recorded. Among opioids, the pattern of reporting was quite similar, though it was notable that no patient required ventilatory support and only two patients required naloxone. Sedation was rarely a problem

with any opioid treatment at the doses used. Nausea and vomiting were more frequent with intravenous tramadol and inhalational Entonox, but the severity was not mentioned. Cardiovascular instability again was uncommon, with a few instances of reduced blood pressure without necessity of intervention. Other adverse events were mainly dizziness or giddiness, with the expected pruritus with opioids. Excitement experienced with Entonox was unexplained [30].

Discussion

The absence of evidence was the clearest outcome of this review, despite a broad search strategy and inclusion criteria, with 21 studies and over 6,000 patients included. At least 11 different interventions were tested and outcomes used limited how much could usefully be adduced for any one of them. There were no clear winners between the opioids, although fentanyl tended to

give the impression of being a good agent albeit with only a small sample, and a relatively large oral/transmucosal dose of 1,600 µg which is not without adverse effects [19].

Despite early onset of analgesia being a desired outcome of military and civilian physicians, the clear tendency was for up to 30 minutes to be required for the proportion of patients with good analgesia to reach a maximum. It is also of interest to note the absence of efficacy data for the use of ketamine in the pre-hospital environment, despite its widely accepted use in this environment by both military and civilian practitioners. Fascia iliaca blocks showed great promise but are probably of limited use beyond analgesia for fractured femurs [28-29]. Finally, Entonox was characterised with a relatively high proportion of complete or partial failures while using the gas (53% partial, and 8% with mild or no relief) and with pain recurring within minutes of stopping the gas [30-32].

While the propensity of NSAIDs to increase bleeding and possible renal complications were an obvious reason why this class of drug has not been tested, it was less clear why cyclooxygenase-2-inhibitors have been omitted. These drugs can provide high levels of pain relief and long duration of action by virtue of a high acute pain dose without increasing bleeding [37-38]. There is also obvious scope for use of paracetamol and/or analgesic combinations, none of which was tested; only single analgesics were tested alone, and no test of multimodal analgesia was made.

This review used several methodological techniques to maximise its relevance. These involved systematic searching and broad acceptance of study design, a consensus approach to desirable outcomes of efficacy and harm, and the definition of analgesic failure as a universal outcome. Moreover, in addition to electronic searches, retrieved articles were read for any other sources of data, as were general review articles and book chapters, because observational studies can be poorly elicited by electronic searching [39,40].

Although a number of reviews have been undertaken previously, this is, we believe, the first attempt at a systematic review of pre-hospital analgesia. As is so often the case, we found limited evidence without any clear-cut answer. It is likely that considerable valuable information exists as audits and surveys, but is not published because such methods are generally considered inferior to randomised trials. While that may be the case for explanatory studies about *whether* an analgesic works, it may be less so for pragmatic issues of how to use analgesics of proven efficacy to obtain the best results in particular clinical circumstances [41].

This reasoning underpinned the broad entry criteria used to maximise the amount of available data; restriction to randomised, double blind trials would have meant excluding 95% of the patients. We balanced the broader inclusion criteria, with many more patients, against the increased possibility of bias.

The Delphi study provided outcomes that experienced senior clinicians considered of pragmatic importance. Despite the relatively small sample sizes it is still interesting to note that the two populations of physicians rated analgesic onset and verbal response somewhat differently. The military tended to recognise that the onset could be slightly delayed if side effects were to be minimised; civilian physicians were less tolerant of delay in analgesic effect. This difference may be due to experiences of treating multiple simultaneous casualties in a hostile environment rather than single casualties in a relatively benign environment.

This dichotomy is important, since the only way of achieving rapid onset of analgesia, certainly with opiates, is by using relatively high doses with increased risks of adverse effects. Even the use of inhalational agents, which may provide a suitably rapid onset, may be expected to be associated with troublesome side effects such as the excitement of Entonox or the sedation with methoxyflurane.

Most, but not all, physicians agreed that a pain score of below 30/100 mm (mild pain, 1/3 numeric rating scale) was a desirable analgesic outcome. We chose this because it has been shown to be a consistent border between verbal and VAS scales [16], and because anything more than mild pain could reasonably be described as uncontrolled or unacceptable. Many studies reported average pain scores, but the wide standard deviations demonstrated how differently individuals had recorded their pain, indicating that the average response was perhaps experienced only by a few. Future studies should consider reporting information on individuals, particularly after defining what constitutes analgesic or other failure. The failure rate then becomes the primary outcome of any study of any design.

The large number of options available for scoring pain, from 100 mm visual analogue scale to 0-3 numerical rating scale, with their many variants, is a potential confusing factor. Teasing apart the effects of variation in dose levels and dosing schedules will always be difficult, but a simple scoring system may enable a clearer recognition of clinically significant differences between techniques. That should be the goal, rather than being lost in statistical differences of dubious clinical relevance. The military rule since 2008, has been to use the simpler 0-3 scale equating to no pain, mild, moderate, and severe pain [42].

There is no obvious guidance from the evidence available. More, better, and better thought out research is needed, and this review suggests some ways in which that could be achieved; publication of surveys and audits of appropriate quality would help. Given the paucity of information and the extreme variation in patients, providers, and environments, the pragmatic advice would be to take heed of the title of Ella Fitzgerald's 1939 song: "T'aint what you do (It's the way that you do it)", and then find ways of doing it better.

Disclaimer

The views expressed in this work are those of the authors and are not necessarily those of the Defence Medical Services nor the Ministry of Defence.

Conflict of interest statement

DJ Aldington and R A Moore have been consultants for various pharmaceutical companies and members of scientific and clinical advisory boards, they have received speakers' fees, participated in meetings supported by unrestricted grants from industry, and have received sponsored research funding from several companies. RAM is funded by NIHR Biomedical Research Centre Programme. All authors state that none of these declarations presents a conflict of interest in relation to the content of this review.

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