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Review

Parenteral opioids in emergency medicine – A systematic review of efficacy and safety

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ABSTRACT

Introduction and aim: Pain is a frequent symptom in emergency patients and opioids are commonly used to treat it at emergency departments and at pre-hospital settings. The aim of this systematic review is to examine the efficacy and safety of parenteral opioids used for acute pain in emergency medicine.
Method: Qualitative review of randomized controlled trials (RCTs) on parenteral opioids for acute pain in adult emergency patients. Main outcome measures were: type and dose of the opioid, analgesic efficacy as compared to either placebo or another opioid and adverse effects.
Results: Twenty double-blind RCTs with results on 2322 patients were included. Seven studies were placebo controlled. Majority of studies were performed in the emergency department. Only five studies were in prehospital setting.
Prehospital studies: Four studies were on mainly trauma-related pain, one ischemic chest pain. One study compared two different doses of morphine in mainly trauma pain showing faster analgesia with the larger dose but no difference at 30 min postdrug. Three other studies on the same pain model showed equal analgesic effects with morphine and other opioids. Alfentanil was more effective than morphine in ischemic chest pain.
Emergency department studies: Pain models used were acute abdominal pain seven, renal colic four, mixed (mainly abdominal pain) three and trauma pain one study. Five studies compared morphine to placebo in acute abdominal pain and in all studies morphine was more effective than placebo. In four out of five studies on acute abdominal pain morphine did not change diagnostic accuracy, clinical or radiological findings. Most commonly used morphine dose in the emergency department was 0.1 mg/kg (five studies). Other opioids showed analgesic effect comparable to morphine.
Adverse effects: Recording and reporting of adverse effects was very variable. Vital signs were recorded in 15 of the 20 studies (including all prehospital studies). Incidence of adverse effects in the opioid groups was 5–38% of the patients in the prehospital setting and 4–46% of the patients in the emergency department. Nausea or vomiting was reported in 11–25% of the patients given opioids. Study drug was discontinued because of adverse effects five patients (one placebo, two sufentanil, two morphine). Eight studies commented on administration of naloxone for reversal of opioid effects. One patient out of 1266 was given naloxone for drowsiness. Ventilatory depression defined by variable criteria occurred in occurred in 7 out of 756 emergency department patients.
Conclusion: Evidence for selection of optimal opioid and dose is scarce. Opioids, especially morphine, are effective in relieving acute pain also in emergency medicine patients. Studies so far are small and reporting of adverse effects is very variable. Therefore the safety of different opioids and doses remains to be studied. Also the optimal titration regimens need to be evaluated in future studies. The prevention and treatment of opioid-induced nausea and vomiting is an important clinical consideration that requires further clinical and scientific attention in this patient group.

Contents

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1. Introduction

Pain is a common symptom in emergency medicine causing over half of the visits in emergency departments [1,2]. However, there are several reports showing the inadequacy of treatment of acute pain in emergency departments [2–6]. This can be due to non-existent pain protocols [2,3,5] clinicians' attitudes toward opioid analgesics [1,2] or inappropriate concerns about the safety of opioids [2]. In pre-hospital care providing adequate pain relief is dependent on equipment and staffing of the ambulance service [6].

Opioids are commonly used as analgesics for acute patients at emergency departments and in pre-hospital settings. In our previous study, over third of respondents had received some kind of analgesic before arriving to the emergency department [1]. Parenteral administration of opioids is justified when pain is severe and rapid alleviation is needed, or the patient is unable to ingest oral medication. Although opioids are relatively safe, there are adverse effects like decrease of blood pressure, depression of consciousness and ventilation, vomiting and nausea that cause worry [1,2]. Managing these adverse effects can be challenging especially in the prehospital setting. This highlights the importance of the optimal dose. In two recent observational studies prescribed morphine doses showed great variation [6,7].

The aim of this qualitative systematic review is to examine the efficacy and safety of parenteral opioids used in the management of acute pain in acute and emergency medicine. This study was limited to adult patients, because both pain evaluation and pharmacokinetics of opioids in children is significantly different from adults [8,9]. Based on our previous knowledge in the literature we chose to perform a qualitative systematic review. We deemed that a quantitative review and meta-analysis was not possible due to large variability in methodology and reporting in the studies.

2. Methods

This review was performed according to the standards described in "Preferred reporting items for systematic reviews and meta-analyses: The Prisma statement" [10]. Search terms, inclusion and exclusion criteria, details on data extraction, registration of adverse effects and main outcomes were specified in a protocol.

2.1. Literature search

Relevant studies were retrieved from electronic databases including OVID Medline (1966–present), Pre-Medline and Cochrane Library. The search was last updated in September 2010. The following key words were included: [emergency medicine.mp or exp Emergency Medicine or exp Emergency Service; Hospital or exp Emergency Medical Services or emergency service.mp or emergency department or prehospital] and [exp pain or exp Analgesia or analgesia.mp] and [opioid.mp or exp analgesics; opioid]. Full search strategy for OVID SP Medline is presented in Fig. 1. The reference lists of retrieved trial reports were also searched for relevant studies. All titles and abstracts of studies indentified in the searches were independently reviewed by two authors (LNM; KH). Unpublished reports; letters and abstracts were not considered. Full reports of studies that could be described as randomized controlled trials comparing parenteral opioid to placebo; comparisons of two active opioids or opioid versus placebo arms of studies with several study arms were independently reviewed by all authors and inclusion of each study was decided by discussion. Fig. 2 presents the flow chart of identification of study reports.

2.2. Inclusion and exclusion criteria

Criteria for considering studies for this review:

- Randomized controlled trials (RCTs) of the analgesic effect of parenteral opioids for acute pain in emergency medicine.
- Adults (≥16 years of age). Mixed paediatric and adult populations were excluded.
- Pain outcome was reported.
- Studies were excluded if: there were less than ten patients per treatment group; they were on neurological complaints (e.g. migraine) or on procedural analgesia/sedation.

2.3. Data extraction

Data from original papers were extracted independently by all authors using a standard form. Collected data were checked and confirmed by all authors together. Following data were extracted: Study design: randomisation, blinding, allocation concealment; Participants: number and age, details of withdrawals and dropouts; Type of illness or trauma; Analgesic(s), dose, number of doses, route; Assessment of pain; Pain outcomes reported; Other than study analgesics administered; Duration of follow up; Data on rescue analgesia; Adverse effects reported. Oxford quality score (0–5) for each study report was recorded [11]. Authors of the original studies were not contacted for further information.

In order to assess the safety of opioid administration in emergency medicine, the registration and reporting of vital signs and adverse effects was examined. Reporting of vital signs, and the number and type of reported adverse effects was registered.

The main outcome measures were type and dose of the administered opioid, analgesic efficacy of studied opioid as compared to either placebo or another opioid and occurrence of adverse effects.

1	emergency medicine.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	12033
2	emergency service.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	34887
3	emergency medical services.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	27624
4	emergency department.mp (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	30678
5	prehospital.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	5948
6	1 or 2 or 3 or 4 or 5	85373
7	pain.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	417506
8	analgesia.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	61773
9	7 or 8	443469
10	opioid.mp (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	69230
11	opioid analgesics.mp. (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	1570
12	opioids.mp (mp=ti, ot, ab, nm, hw, kw, ui, an, sh)	16303
13	10 or 11 or 12	74209
14	6 and 9 and 13	453

Fig. 1. Full search strategy for OVID SP Medline.

3. Results

3.1. Trial methodology of the included studies

Forty possible titles were identified in the searches (Fig. 1). Twenty double-blind randomized controlled trials with results on 2322 patients were included (Tables 1 and 2). Seven studies were placebo controlled. Majority of studies were performed in the emergency department (Table 2). Only five studies investigated opioids in the prehospital environment (Table 1). The most frequently pain models were acute abdominal pain (seven studies), renal colic (four) and trauma (three). In five studies pain was of mixed type (including two studies where majority of patients had trauma-related pain). Oxford quality scores of the studies ranged from 2 to 5 (median 5). Pain was measured with visual analog scale (VAS) in 14, numerical rating scale (NRS) in five and verbal rating

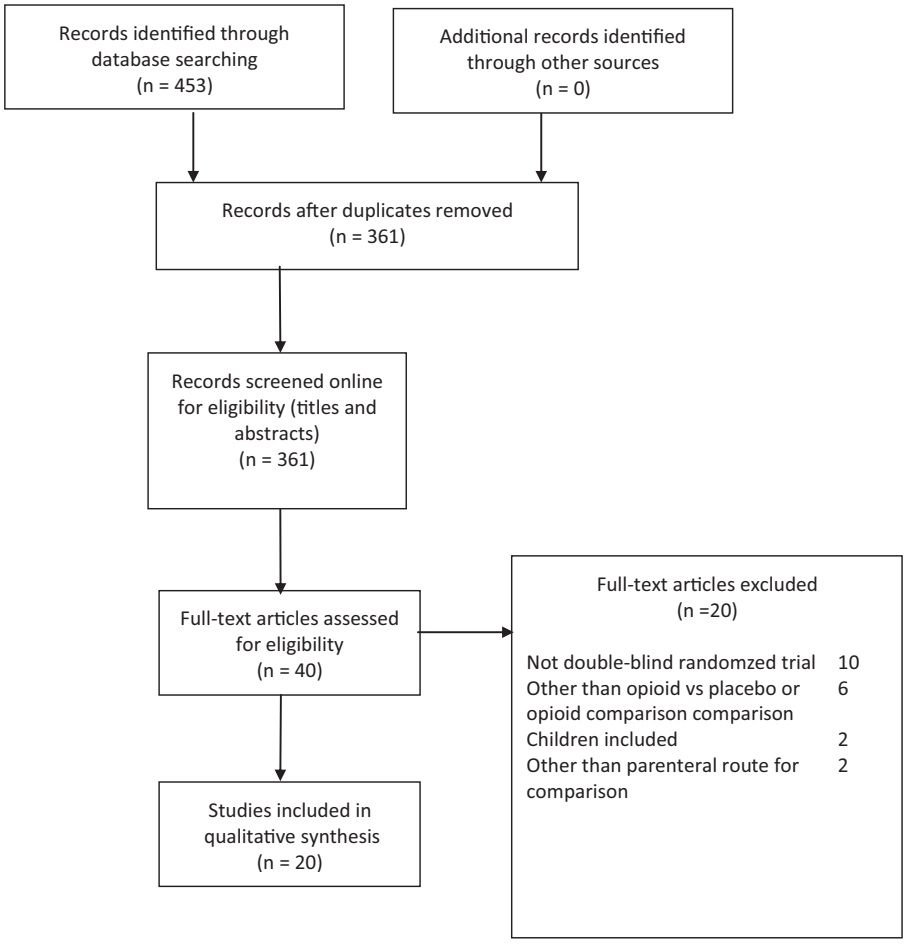

Fig. 2. Flow chart of identification of study reports.

Table 1
Randomized controlled studies on efficacy of parenteral opioids for acute pain in the prehospital setting.

Study Type of pain PI inclusion criteria	Analgesics	Main analgesia results
Bounes 2008 [12] (a) 72% trauma (b) 66% trauma NRS ≥ 60/100	(a) Morphine 0.05 mg/kg + 0.025 mg iv ever 5 min until NRS ≤ 30/100 (*) (N = 53) (b) Morphine 0.1 mg/kg + 0.05 mg iv every 5 min until NRS ≤ 30/100 (*) (N = 53) *All patients given paracetamol 1 g iv at T0	No difference between groups in the primary outcome, percentage of patients with NRS ≤ 30 at T30. At T10 17% of patients in group a had NRS ≤ 30 compared to 40% of patients in groups b (p < 0.01). NRS score of 100 was the sole independent predictive factor for failure of analgesia. Median dose of morphine injected was greater in group b (0.2 mg/kg) compared to group a (0.1 mg/kg) (p < 0.0001) while there was no difference between groups in number of additional doses. Patient satisfaction with analgesia better in group b (excellent or good in 97% of patients) compared to group a (85%) (p < 0.05). No difference between groups in physician satisfaction with analgesia
Bounes 2010 [13] Trauma NRS ≥ 60/100	(a) Morphine 0.15 mg/kg + 0.075 mg/kg iv every 3 min until NRS ≤ 3 (*) (N = 54) (b) Sufentanil 0.15 μg/kg + 0.075 μg/kg iv every 3 min until NRS ≤ 3 (*) (N = 54) *All patients were given paracetamol 1 g iv + ketoprofen 100 mg iv at T0	Primary outcome: proportion of patients with NRS ≤ 30 at T15 70% of patients given morphine and 74% of patients given sufentanil (Δ 4%, 95%CI −13 to 21%). No difference in median NRS scores at 15 or 30 min. Median (IQR) number of reinjections morphine group 1 (1–3), sufentanil group 2 (1–4). Patient satisfaction 98% in both groups with excellent or good analgesia, physician satisfaction 98% excellent–good analgesia in sufentanil group, 89% in morphine group. Duration of analgesia was in favour of morphine (data in figure, statistics?). During 6 h postdrug 32% of patients given morphine and 51% of patients given sufentanil needed rescue analgesia (Δ 19%, 95%CI −0.4 to 38%)
Galinski 2005 [14] >50% trauma VAS ≥ 60/100	(a) Morphine 0.1 mg/kg + 3 mg iv as needed until VAS ≤ 30/100 (N = 26) (b) Fentanyl 1 μg/kg + 30 μg as needed until VAS ≤ 30/100 (N = 28)	There was no difference in pain intensity, patient satisfaction, number of patients achieving the goal VAS ≤ 30/100 (morphine 65%, fentanyl 57% of patients) or incidence of adverse effects between the study groups. At T30 mean VAS (95%CI) change was 45 (34–56) an 42 (32–52) in morphine and fentanyl groups, respectively (ns). Non-opioid analgesics given to 10 and 13 patients in morphine and fentanyl groups respectively
Silfvast 2001 [15] Ischemic chest pain	(a) Alfentanil 0.5 mg iv + same again after 2 min if needed max 1 mg (N = 16) (b) Morphine 5 mg iv + same again after 2 min if needed max 10 mg (N = 20)	Analgesia was faster and more effective with alfentanil compared to morphine (p < 0.05) (not defined exactly). All patients in morphine group and half of the patients in alfentanil group received both doses of study drugs (p < 0.0003)
Vergnion 2001 [16] Traumatic musculoskeletal pain	(a) Tramadol 100 mg + after 10 min 50 mg iv if needed every 5 min upto 200 mg iv (N = 53) (b) Morphine 5 (≤70 kg) − 10 mg (>70 kg) iv + after 10 min 5 mg iv if needed every 5 min upto 15 (≤70 kg) − 10 mg (>70 kg) iv (N = 48)	There was no difference in mean decrease of pain intensity between the groups at 40 min postdrug. Pain intensity decreased in both groups (no statistics reported). Global assessment of efficacy and tolerance: number of patients satisfied or very satisfied 40 (76%) and 32 (67%) in tramadol and morphine groups, respectively (ns). Antiemetic was administered to 6 and 3 patients in tramadol and morphine groups, respectively

scale (VRS) in one study. Four studies reported a predefined pain intensity level for inclusion; in three studies pain intensity had to be at least 60 on scale 0–100 and in one study mild on 4-point verbal scale or at least 20 on scale 0–100. Measured median/mean baseline pain intensity was 70–100 (scale 0–100) in 16 studies.

Analgesia related outcome measures used in the studies were: pain intensity (18 studies), pain relief (5), patient or investigator satisfaction with analgesia (6), use of rescue analgesia (7), change in physical examination or diagnostics (6) and adverse effects or safety (13). Duration of the study 15–60 min in 14 studies, 2 h in four, 6 h in one and not reported in one study.

Most frequently used opioid was morphine (16 studies). Other opioid analgesics studied included fentanyl (2 studies), pethidine (3), hydromorphone (3) and tramadol (2). Alfentanil, sufentanil and papaveretum were studied in single trials. Multiple dosing was used in 11 and a single dose in nine studies. Details on study analgesics and main results are presented in Tables 1 and 2.

3.2. Analgesic efficacy

3.2.1. Prehospital setting

In four out of five prehospital studies majority of patients suffered from acute pain related to trauma (Table 1). Bounes et al. compared [12] two different morphine titration regimens: first morphine 0.05 mg/kg followed by 0.025 mg/kg repeatedly until pain was NRS 30/100 or less or in similar manner 0.1 mg/kg + 0.05 mg/kg iv. Larger dose provided more rapid analgesia. At 10 min postdrug pain was 30/100 or less in 40% of patients given the larger dose compared to 17% given the smaller dose. At 30 min postdrug there was no difference in proportion of patients with pain 30/100 or less. Patients given the lager morphine dose experienced almost twice more adverse effects, especially vomiting. However, the difference in adverse effects was not statistically significant. In other studies with trauma pain sufentanil, fentanyl or tramadol was not superior to morphine in terms of analgesia or patient satisfaction with pain relief. Only one small trial studied acute chest pain. Alfentanil 0.5 mg was more effective than morphine 5 mg in relieving acute ischemic chest pain [15].

3.2.2. Emergency department

Studies investigating opioids for acute pain in emergency department are shown in Table 2. Five studies compared morphine to placebo in acute abdominal pain and one in acute renal colic. In all studies morphine was more effective than placebo. Four of the five studies on acute abdominal pain reported that morphine did not change diagnostic accuracy, clinical or radiological findings. One study [26] reported a change in findings of physical examination in half of the patients after 5 or 10 mg of morphine. The most commonly used dose of morphine was 0.1 mg/kg iv (five studies). Equal analgesic efficacy was reported in studies comparing morphine to other opioids (Table 2). However, the doses, follow up times and outcome measures used in these studies were variable precluding further conclusions.

3.3. Safety

3.3.1. Prehospital setting

All five studies performed in the prehospital setting recorded vital signs. Recording and reporting of the adverse effects was variable between studies. The number of adverse effects recorded according to study protocols varied between 0 and 8. The number of reported adverse effects varied between 2 and 9. The incidence of

Table 2
Randomized controlled studies on efficacy of parenteral opioids for acute pain in the emergency department.

Study Type of pain PI inclusion criteria	Analgesics	Main analgesia results
Attard 1992 [17] Acute abdominal pain	a) papaveretum upto 20 mg im ($N = 50$) b) placebo im ($N = 50$)	Pain and tenderness at 60 min after study drugs was significantly lower in papaveretum group compared to placebo ($p < 0.001$). Pain and tenderness were better (20% change) in 47 and 35 patients given papaveretum compared to 7 and 8 patients given placebo. Assessed by phycisian 48 patients given papaveretum were comfortable compared to 9 given placebo ($p < 0.0001$). Phycician correctly identified 44/50 patients given papaveretum and 41/50 given placebo.
Bartfield 2003 [18] Acute abdominal pain	a) fentanyl 1.5 μg/kg iv + nebulized saline ($N = 24$) b) saline iv + nebulized fentanyl 1,5 μg/kg ($N = 26$)	There was no difference in the primary outcome of change in pain intensity at 30 min postdrug between groups. At 15 min postdrug mean change in pain score was greater in patients given iv fentanyl (25) compared to nebulised fentanyl (10) ($p = 0.005$). There was no difference in number of patients given rescue medication (12/24 and 18/26 patients given iv and nebulised fentanyl, respectively).
Bektas 2009 [19] Suspected renal colic Mild pain on 4-point VRS or 20/100 on VAS	a) paracetamol 1 g iv ($N = 55$) b) morphine 0.1 mg/kg iv ($N = 55$) c) placebo iv ($N = 55$)	Only morphine and placebo data analysed for this review. Significantly greater decrease in pain intensity at 15 and 30 min postdrug in morphine group compared to placebo ($p = 0.045$). No difference in need of rescue analgesia (24/49 patients in morphine and 34/51 placebo groups). No difference in number of patients experiencing at least one adverse effect (16/49 patients in morphine and 8/51 placebo groups).
Birnbaum 2007 [20] Various: abdominal or pelvic pain in 2/3 of patients	a) morphine 0.1 mg/kg iv (max 10 mg) + placebo iv after 30 min ($N = 138$) b) morphine 0.1 (max 10 mg) + 0.05 mg/kg (max 15 mg) after 30 min iv ($N = 142$)	Primary outcome change in pain intensity baseline −60 min postdrug: pain decreased in both groups, minor statistical difference favoring morphine 0.15 mg/kg not reaching the limit of preset value of 1.3 unit on numerical rating scale for clinical significance. No difference between groups in pain relief scores or adverse effects. Four patients in group a and 2 in group b recived non-opioid analgesic before study drugs.
Chang 2006 [21] Various, >50% abdominal pain	a) hydromorphone 0.015 mg/kg iv max 1.5 mg ($N = 99$) b) morphine 0.1 mg/kg iv max 10 mg ($N = 99$)	Primary outcome, decrease in pain intensity NRS at 30 min, hydromorphone −5.4, morphine −4.5 (Δ −1.3 95%CI −2.2–−0.5). No difference in median pain scores between groups at 5,30,120 min postdrug. The incidence of adverse effects at 30 min similar in groups except for pruritus (0 in hydromorphone and 6 in morphine group). There was no difference in number of patients given rescue analgesia, 22 and 31 patients in hydromorphone and morphine groups, respectively.
Chang 2009 [22] Various, approx 50% abdominal pain	a) hydromorphone 0.0075 mg/kg iv max 0.75 mg ($N = 97$) b) morphine 0.05 mg/kg iv max 5mg ($N = 97$)	No difference in pain intensity at 30 min (primary outcome) or any time during the 2 h follow-up. Satisfaction with pain medication good–excellent in 63.4% and 62.2% of patients in hydromorphone and morphine groups, respectively. Pain relief at 30 min none-slight 34.4% and 41.1%, and moderate-complete in 65.6 and 58.9% of patients in hydromorphone and morphine groups, respectively. Majority of patients failed to achieve ≥50% pain relief within 30 min postdrug. Number of patients given rescue analgesia during 2 h: hydromorphone 14, morphine 22 (ns).
Eray 2002 [23] Renal colic	a) tramadol 50 mg iv ($N = 24$) b) pethidine 50 mg iv ($N = 23$)	No differences in VAS scores by ANOVA; Both drugs decreased pain intensity at 15 and 30 min compared to baseline ($p = 0.000$). Pethidine was more effective than tramadol in reducing pain at 15 and 30 min postdrug ($p = 0.008$). Rescue medication was given to 11 patients (48%) in pethidine and 16 patients (67%) in tramadol group (ns). Rescue analgesia given to 48 and 67% of patients at 30 min in tramadol and pethidine groups, respectively.
Gallagher 2006 [24] Acute abdominal pain	a) morphine 0.1 mg/kg iv max 10 mg ($N = 80$) b) placebo iv ($N = 80$)	Median (IQR) reduction in pain intensity was 33 (−8–−73) after morphine and −2 (1–−16) after placebo (statistical significance?). Morphine did not change clinically significant diagnostic accuracy.
Jasani 1994 [25] Renal colic	a) hydromorphone 1 mg iv max 2 mg ($N = 36$) b) pethidine 50 mg iv max 100 mg ($N = 37$)	Pain intensity at 15, 30, 60, 120 min postdrug significantly less with hydromorphone compared to pethidine ($p < 0.05$). More nonresponders (significant pain after second dose necessating additional treatment) in pethidine group compared to hydromorphone (25 vs 11, respectively) ($p < 0.001$). Time to remedication similar in both groups (hydromorphone 21.3, pethidine 22.5 min). Unclear reporting of number of patients receiving second dose of study drugs or rescue analgesia.
Lovecchio 1997 [26] Acute abdominal pain	a) morphine 10mg iv max 10 mg ($N = 19$) b) Morphine 5mg iv max 5 mg ($N = 13$)c) placebo ($N = 16$)	Both morphine doses decreased pain intensity assessed by patient and examiner-perceived comfort level significantly compared to baseline ($p < 0.005$–0.0005). No change in pre-post values in the placebo group. No statistics on differences between groups provided. Morphine (both low and high dose) changed physical examination with regard to tenderness and localization in 9/19 and 7/13 patients given morphine 10 and 5 mg, respectively. No statistics reported.

Table 2 (*Continued*)

Study Type of pain PI inclusion criteria	Analgesics	Main analgesia results
Miller 2004 [27] Trauma	a) butorphanol 0.5–1.0 mg iv ($N = 46$) b) morphine 2.5–5 mg iv ($N = 48$)	There were no differences between study groups in VAS scores 30, 60, 120 min postdrug. Treatment failure (=need for further analgesia during 120 min study period) in 3/49 and 4/45 patients given butorphanol and morphine, respectively. No difference in satisfaction between groups on 10-point scale. Results reported also by gender. Females had low pain intensity with butorphanol compared to morphine at 60 min ($p < 0.046$), no difference at other times. Initial dose mean a) 0.87 mg, repeated dose 0.8 mg b) initial 4.2 mg, repeated 4.15 mg.
O'Connor 2000 [28] Renal colic	a) pethidine intial dose 20 mg + repeated doses 10 mg upto 100 mg iv ($N = 54$) b) morphine initial dose 2 mg + reapeted doses 1 mg upto 10 mg iv ($N = 40$)	There was no difference between study groups in pain intensity at 30 min, patient satisfaction median 9.1 and 8.55 in morphine and pethidine groups, respectively) or incidence of adverse effects. All patients were given 10 mg metoclopramide iv as antiemetic prophylaxis.
Pace 1996 [29] Acute abdominal pain	a) morphine initial dose 0.1 + 0.05 mg/kg iv every 5–10 min until adequate analgesia or upto 20 mg ($N = 35$) b) placebo in similar manner ($N = 36$)	Morphine decreased pain intensity significantly at 15 min postdrug compared to placebo ($p < 0.01$). There was no statistical difference between groups in the accuracy of diagnosis.
Thomas 2003 [30] Severe abdominal pain	a) morphine 1 mg/ml in dose and frequence decided by the physician upto 15 mg iv ($N = 38$) b) placebo in similar manner ($N = 36$)	Median change in VAS was significantly greater with morphine compared to placebo ($p = 0.008$). Proportion of patients with VAS drop ≥ 13 (baseline −60 min postdrug) was 73.7% and 41.7% of patients in morphine and placebo groups ($p = 0.005$), respectively. There were no differences between study groups in changes in physical or diagnostic accuracy.
Vermeulen 1999 [31] Acute abdominal pain	a) morphine 0.1 mg/kg iv max 10 mg ($N = 175$) b) placebo ($N = 165$)	Pain intensity decreased significantly in both groups ($p = 0.001$) after study drugs. Pain relief was greater in morphine group compared to placebo (no statistics reported). Morphine did not influence the appropriateness of decision to operate.

adverse effects varied from 5 to 38% of the patients. Most frequently reported adverse effects in the prehospital setting were nausea, vomiting and sedation. Nausea or vomiting was reported in 11% of patients given morphine and in 16% given other opioids. Sedation occurred in 10% of patients given morphine and in 4% given other opioids. Two studies reported on administration of naloxone for reversal of opioid effects. No patient required naloxone. Oxygen saturation $\leq$90% was reported in three patients [13] and $\leq$95% in one patient [12]. In the trial comparing sufentanil and morphine [13] study drug was discontinued because of unspecified adverse effects the in two patients in each group. There were no study discontinuations because of adverse effects in the study comparing two morphine dosing regimens [12]. Other studies did not provide data on this.

3.3.2. Emergency department

Vital sign were recorded in 10 studies while five studies made no comment on vital signs. Also in the emergency department setting the recording and reporting of the adverse effects was variable between studies. The number of adverse effects registered varied between 0 and 10 and the number of reported between 0 and 8. Three studies reported that no adverse effects occurred and one that no serous adverse effects occurred. The reported incidence of adverse effects varied between 0 and 16% of the patients in the placebo groups (four studies) and 4–46% in the opioid groups.

Most frequently reported adverse effects were nausea or vomiting. The incidence of nausea or vomiting in patients given morphine was 16% while it was 14% in patients given placebo in the same studies. Nausea or vomiting occurred in 25% of the patients given other opioids. One study was excluded from analysis on nausea and vomiting because all patients were given prophylactic antiemetic [28]. Study drug was discontinued because of nausea in one patient given placebo [29]. Data on sedation were reported only in two studies [27,29]. In these studies no patient experienced moderate or severe sedation.

Data on incidence of ventilatory depression were reported in seven studies. Ventilatory depression defined by variable criteria (no criteria, ventilatory rate $\leq$12/min or oxygen saturation $\leq$90%) occurred in 7 out of 756 patients. Administration of naloxone for reversal of opioid effects was commented in six studies. Naloxone was administered because of drowsiness to one patient (out of 1266 patients) given hydromorphone 0.0075 mg/kg.

4. Discussion

Effectiveness of opioids in various types of acute pain is well established [32]. For various reasons pain is inadequately managed in the emergency departments [1–3,6]. Parenteral opioids are needed for alleviation of severe acute pain in the prehospital setting and emergency departments. There is no general consensus or evidence based data for the choice and dose of optimal opioid analgesic for this particular setting. Concerns related to safety of opioids in emergency patients are common [3]. Reliable data on opioid efficacy and safety in the emergency patients are needed to improve the situation. However, the number of randomized controlled trials in this area is surprisingly low, only 20 trials fulfilling inclusion criteria were identified in the present study. A recent review suggested that future studies should evaluate higher doses of opioids than for treatment of severe or acute pain [33].

Morphine in variable doses was the most commonly studied opioid in this set of studies. The most commonly used dose was 0.1 mg/kg iv. Morphine was clearly used as gold standard in studies comparing two different opioids. Morphine is hydrophilic and relatively slow acting when compared to more lipophilic fentanyl and alfentanil. On the other hand, it may provide more longstanding analgesia than the more short acting opioids.

There is considerable variation in opioid requirements between individuals. Factors affecting opioid response include type and intensity of pain stimulus, concurrent medications and illnesses, gender, age and genetic variability in opioid metabolism and opioid receptors [27,34,35]. Titration of opioid dose to clinical effect will therefore provide best analgesia for each individual. The optimal dose and opioid is still unclear. Larger dose will enhance the possibility of faster analgesia [12,20] but also increase the risk of adverse effects [12,18]. Optimal titration regimens need to be evaluated in future studies.

Age is a risk factor for inadequate analgesia in a number of clinical settings, also in the emergency department [34,36]. Increasing age changes the pharmacokinetics and dynamics of opioids and decreases the need of opioids [34,37,38]. We found only one study focused on elderly subjects [22]. A single dose of morphine 0.05 mg/kg and hydromorphone 0.0075 mg/kg iv failed to achieve ≥50% reduction in pain within 30 minutes of administration.

Acute abdominal pain, renal colic and trauma-related pain were the most commonly studies pain models. Only one trial studied acute chest pain. Only few studies were performed in the prehospital setting. Four out of five prehospital studies were on trauma pain. The challenges of study design and execution are more demanding in the prehospital setting than in the emergency department. In the prehospital environment with little time and limited possibilities for safety monitoring need of easy, reliable, fast and safe analgesia is more pronounced than in the emergency department. Morphine, the relatively slow acting drug, was the most frequently used opioid in these studies, too. Bounes and co-workers [13] suggest, that intravenous morphine titration using a loading dose followed by strictly administered lower doses at regular intervals should remain the criterion standard.

Safety is important consideration in opioid administration. Common adverse effects like nausea and vomiting may delay patient flow in the emergency department while rare but serious adverse effects like ventilatory depression may cause significant morbidity and even mortality [39]. Background incidence of symptoms like nausea will depend on the clinical condition and affect the results. Transfer of data from one medical condition to other may not be justified. One of the aims of the present study was to assess safety of various opioids and doses in the setting of emergency medicine. However, small studies with variable materials and methods precluded reliable evaluation of adverse effects. In future, safety of opioids in this patient group needs to be studied in larger studies for true incidence. The incidence of opioid induced ventilatory depression in emergency medicine patients seemed low in the present study but could not be reliable estimated due variation in methodology and reporting.

Nausea and vomiting are common in patients treated within the field of emergency medicine. The exact incidence of these symptoms depends on the patient characteristics and acute clinical condition of the patient. Administration of opioids for pain relief increases the risk of nausea and vomiting. Various anti-emetics have been tried for prevention and management of opioid-induced nausea and vomiting in this patient group. The results have been inconclusive. However, prevention and treatment of opioid-induced nausea and vomiting is an important clinical consideration and it requires further clinical and scientific attention both in the prehospital and emergency department environment.

The main limitation of this review is the strict inclusion criteria. Studies were excluded because they were not blinded, randomised or controlled or there were children included as participants. Second limitation comes from considerable heterogeneity of included studies precluding quantitative analysis including meta-analysis and further conclusions on efficacy and safety.

5. Conclusion

In conclusion, evidence for selection of optimal opioid and dose for emergency medicine in hospital and in the prehospital setting is scarce. Placebo controlled studies show that opioids, especially morphine are effective in relieving acute pain also in emergency medicine patients.

6. Implications

Optimal titration regimens need to be evaluated in future studies. Safety of different opioids and dosing regimens remains to be studied since present studies are small and reporting of adverse effects variable.

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