

REVIEW ARTICLE

Review on pharmacological pain management in trauma patients in (pre-hospital) emergency medicine in the Netherlands

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Conflicts of interest

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Abstract

Pain is one of the main complaints of trauma patients in (pre-hospital) emergency medicine. Significant deficiencies in pain management in emergency medicine have been identified. No evidence-based protocols or guidelines have been developed so far, addressing effectiveness and safety issues, taking the specific circumstances of pain management of trauma patients in the chain of emergency care into account. The aim of this systematic review was to identify effective and safe initial pharmacological pain interventions, available in the Netherlands, for trauma patients with acute pain in the chain of emergency care. Up to December 2011, a systematic search strategy was performed with MeSH terms and free text words, using the bibliographic databases CINAHL, PubMed and Embase. Methodological quality of the articles was assessed using standardized evaluation forms. Of a total of 2328 studies, 25 relevant studies were identified. Paracetamol (both orally and intravenously) and intravenous opioids (morphine and fentanyl) proved to be effective. Non-steroidal anti-inflammatory drugs (NSAIDs) showed mixed results and are not recommended for use in pre-hospital ambulance or (helicopter) emergency medical services [(H)EMS]. These results could be used for the development of recommendations on evidence-based pharmacological pain management and an algorithm to support the provision of adequate (pre-hospital) pain management. Future studies should address analgesic effectiveness and safety of various drugs in (pre-hospital) emergency care. Furthermore, potential innovative routes of administration (e.g., intranasal opioids in adults) need further exploration.

1. Introduction

Emergency care and pain management in particular for trauma patients in the Netherlands is provided by various health-care providers. These are general practitioners (cooperatives) [GP(C)s], (helicopter) emergency medical services [(H)EMS] and emergency departments (EDs), which will be referred to as the

chain of emergency care. Professionals working in this chain of care have different backgrounds and are trained as general practitioners (GPs), paramedics, (emergency) nurses and (emergency) physicians, or medical specialists.

Pain is one of the main complaints of trauma patients in (pre-hospital) emergency medicine (Cordell et al., 2002) and its prevalence in pre-hospital

Databases

- CINAHL, PubMed and Embase.

What does this review add?

- Paracetamol appeared to be an effective analgesic in emergency care, both orally (p.o.) and intravenously (i.v.). No side effects were reported.
- Non-steroidal anti-inflammatory drugs (NSAIDs) showed mixed results regarding effectiveness; however, they are not recommended for use in pre-hospital emergency care for safety reasons.
- Intravenous titration of opioids, such as fentanyl and morphine, contributes to effective and safe pain management as emergency care professionals can closely monitor the quality of analgesia and the occurrence of side effects.

EMS is 70% (Berben et al., 2011a). Other studies in the ED report pain prevalence in these patients ranging from 52% to 90% (Cordell et al., 2002; Berben et al., 2008). Numbers on the prevalence of pain and pain management in trauma patients visiting GPs or treated by HEMS personnel are not available, although we can assume similar problems as in EMS and ED care.

From a humanitarian point of view, every patient is entitled to receive adequate pain management (Brennan et al., 2007). Inadequate relief of pain leads to delayed healing, reduced functional recovery and an impaired immune function (AHCPR, 1992). There is also increasing evidence that inadequate pain treatment may lead to chronic pain and disability, resulting in higher costs in health care (Carr and Goudas, 1999; Rivara et al., 2008; Macintyre et al., 2010).

Significant deficiencies in acute pain management in emergency medicine have been identified. Several studies reported an underestimation of pain by (emergency) physicians and nurses (Luger et al., 2003) and deficiencies in pre-hospital pain management (Abbuhl and Reed, 2003; Hennes et al., 2005; Berben et al., 2011a). Similar results are reported in the ED (Todd et al., 2007; Berben et al., 2008). This results in serious deficiencies and delays in pain management in the chain of emergency care (Berben et al., 2012).

At the same time, questions regarding the effectiveness of paracetamol for pain relief and the safety of non-steroidal anti-inflammatory drugs (NSAIDs) remain, specifically in the field of emergency care. Furthermore, it is unknown what opioids are considered most effective and to what extent intravenous (i.v.) administration of fentanyl or morphine does lead

to adverse events, such as respiratory or cardiovascular depression in pre-hospital or emergency circumstances. It is also unclear which routes of administration are possible, applicable and safe in emergency care.

To our knowledge, no evidence-based protocols or guidelines have been developed addressing the specific circumstances and safety issues of pain management of trauma patients in the chain of emergency care. To improve adequate pharmacological pain management in the chain of emergency care in the Netherlands, a systematic review on effectiveness and safety of pharmacological pain interventions is warranted.

The aim of this review was to identify effective and safe initial pharmacological pain interventions, available in the Netherlands, for trauma patients with acute pain in the chain of emergency care. These results can be used for the development of recommendations on evidence-based pharmacological pain management.

2. Literature search methods

2.1 Search

A systematic literature search was performed. We used the electronic databases of CINAHL, PubMed and Embase and included all articles until December 2011. The search terms pain, trauma and emergency medicine (and related terms) were combined with MeSH terms and free text (see Supporting Information Table S1). Furthermore, reference lists were searched for relevant articles. The search was restricted to articles written in English or Dutch and published as 'full paper'.

Articles were included when concerning emergency medicine, acute pain, adult trauma patients and pharmacological pain treatment. Furthermore, the trauma patients needed to be evaluable (Glasgow coma scale > 13), with a stable condition regarding vital signs (airway, breathing and circulation).

Abstracts of possible relevant studies were independently assessed by researchers, working in pairs (S.B., B.D., J.C., G.H.-d.W., H.K., L.S.). Studies were excluded for the following reasons: systematic review, medication was not available in the Netherlands, study populations consisted mostly or entirely of non-trauma patients, the timeline of the study exceeded the period of emergency care, pain relief was not used as an outcome measure, the effectiveness of the initial pharmacological pain treatment was not the aim of the study, or studies focused on procedural sedation and analgesia. In case of a systematic review, it was checked for relevant original studies. Other reasons for exclusion were as follows: the manuscripts concerned case studies or opinion articles or articles were of poor methodological quality.

2.2 Quality assessment

Methodological quality of the articles was assessed using standardized evaluation forms of the Dutch Institute of

Healthcare Improvement CBO. Following this assessment, the studies were classified by level of evidence (CBO, 2007), as used by the Australian National Health and Medical Research Council (2010) (http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf). A randomized double-blind clinical trial of good quality and adequate sample size received a level A2, while comparative studies not containing all characteristics of A2 (including cohort studies or case-control studies) were classified as level B. Studies of poor methodological quality and studies that did not meet the inclusion criteria were excluded. Studies were considered to be of poor methodological quality when relevance and aim were not clearly described; the research design, selection of participants or data collection were inadequate; and analysis of data, the description of results and conclusions were not accurate or clearly described.

2.3 Analysis

Literature on pharmacological pain treatment was categorized and analysed in three pharmacological groups: (1) non-opioids (paracetamol and NSAIDs); (2) (weak) opioids; and (3) (local) anaesthetics. We compared the studies regarding their general characteristics (study design, level of evidence, population, medication type and setting), the efficacy of the analgesics/anaesthetics and the reported safety aspects (adverse events). When single drugs were administered, the pain relief is described as a decrease of the pain assessment tool. A pain relief of 2 points on the numeric rating scale (NRS) or 20 mm on the visual analogue scale (VAS) or a relative decrease of 30% on the NRS/VAS was considered to be clinically significant (Farrar et al., 2003). NRS and VAS scores are presented as $\times/10$, unless described differently. When different routes of administration or different types of drugs were compared, the pain relief is described as 'equally effective, less effective or more effective'. In order to promote readability of this review, all studies will be described once, unless specific analgesics originate from different pharmacological groups.

3. Results

In total, 2328 articles were identified and 25 articles were included in the review. The results of the systematic search are presented in a flowchart (Supporting Information Fig. S1). We excluded 110 articles after full-text assessment due to poor methodological quality ($n = 30$), the study population concerned non-trauma patients ($n = 12$), the study did not concern emergency medicine ($n = 4$), the pain medication under study was not available in the Netherlands ($n = 19$), the outcome measurements of the study did not primarily focus on the effect of pharmacological interventions for pain relief ($n = 26$) and other reasons (including language, procedural sedation and analgesia) ($n = 19$).

3.1 General characteristics

General characteristics of the studies are presented in Table 1. The NRS score or VAS score was used as an inclusion criterion in 12 studies (Tanabe et al., 2001; Evans et al., 2005; Cander et al., 2005; Galinski et al., 2007; Rickard et al., 2007; Viallon et al., 2007; Bounes et al., 2008; Johansson et al., 2009; Bounes et al., 2010; Garrick et al., 2011; Kariman et al., 2011; Craig et al., 2012).

Although all studies concerned trauma patients, six studies used a mixed patient group and their study population consisted of non-trauma patients as well (Baskett, 1970; Thal et al., 1979; Kanowitz et al., 2006; Rickard et al., 2007; Bounes et al., 2008; Garrick et al., 2011). In nine studies, the population consisted of both adults and children (Baskett, 1970; Thal et al., 1979; Ansem et al., 1994; Cander et al., 2005; Frakes et al., 2006; Kanowitz et al., 2006; Bounes et al., 2008; Garrick et al., 2011; Kariman et al., 2011).

Studies were carried out in the (H)EMS ($n = 12$) and ED ($n = 13$); one study was carried out in both settings (Kanowitz et al., 2006). No studies concerning the GP setting were found.

3.1.1 Analgesics and (local) anaesthetics

All groups of analgesics/local anaesthetics have been studied in emergency care, although opioids are the most frequently studied. Fourteen studies compared two or more types of drugs using various routes of administration (Ernst et al., 1994; Gurnani et al., 1996; Hoogewijs et al., 2000; Vergnion et al., 2001; Cander et al., 2005; Woo et al., 2005; Galinski et al., 2007; Rickard et al., 2007; Johansson et al., 2009; Shear et al., 2010; Bounes et al., 2010; Garrick et al., 2011; Kariman et al., 2011; Craig et al., 2012). Only one study compared different routes of administration of the same analgesic (Whitefield et al., 2002).

3.2 (In)effective pain medication

A summary of analgesics and reported pain relief is presented in Table 2. If available, pain relief is described as a decrease in VAS/NRS and associated p -value.

3.3 Non-opioids

3.3.1 Paracetamol

The studies of Hoogewijs et al. (2000), Woo et al. (2005), Viallon et al. (2007) and Craig et al. (2012) showed a pain reduction after the administration of

Table 1 Characteristics of the reviewed studies.

Author(s) (year) Country	Medication	Level of evidence	Design	N	Trauma (n)	Setting
Ansem et al. (1994) The Netherlands	S-ketamine 0.25 mg/kg i.v.	C	Prospective study	138	Musculoskeletal, soft tissue or skin trauma	EMS
Bartfield et al. (1995) United States	1% lidocaine 0.5 mL injection (1), followed by 2% lidocaine 5 mL topical application / Saline topical application, followed by 1% lidocaine injection (2)	B	RCT	54	Lacerations	ED
Baskett (1970) United Kingdom	50% nitrous oxide and 50% oxygen (Entonox) through inhalation	C	Pilot survey	66	Limb injuries (27), other injuries (11)	EMS
Bounes et al. (2008) France	Morphine 0.05 mg/kg i.v., followed by 0.025 mg/kg every 5 min / Morphine 0.1 mg/kg i.v., followed by 0.05 mg/kg every 5 min	A2	RCT	106	Fracture (42), dislocation (14), soft tissue injury (18)	EMS
Bounes et al. (2010) France	Sufentanil 0.15 µg/kg i.v., followed by 0.075 µg/kg every 3 min / Morphine 0.15 mg/kg i.v., followed by 0.075 mg/kg every 3 min	A2	RCT	108	Fracture (51), dislocation (25), soft tissue injury (13), other injuries (19)	EMS
Cander et al. (2005) Turkey	Metamizole sodium ^a 1 g i.v. / Diclofenac 75 mg i.m. / Tramadol 100 mg i.v.	C	Post-test design	100	Isolated traumatic injuries and fractures of extremities	ED
Craig et al. (2012) United Kingdom	Paracetamol 1 g i.v. over 15 min / Morphine 10 mg i.v. over 15 min	B	RCT pilot study	55	Isolated limb trauma	ED
Ernst et al. (1994) United States	0.5% diphenhydramine injection / 1% lidocaine injection	C	RCT	98	Lacerations	ED
Evans et al. (2005) United Kingdom	Morphine 5 mg i.v. through PCA, followed by dose of 1 mg / Morphine 1–10 mg i.v., titrated at a rate of 1–2 mg/min	A2	RCT	86	Fracture (55), other injuries (31)	ED
Frakes et al. (2006) United States	Fentanyl 5 µg/kg i.v. / Fentanyl 2 µg/kg i.v.	C	Descriptive retrospective study	100	Not specified	HEMS
Galinski et al. (2007) France	Ketamine 0.2 mg/kg i.v. over 10 min + morphine 0.1 mg/kg i.v., followed by 3 mg every 5 min / Placebo + morphine 0.1 mg/kg i.v., followed by 3 mg every 5 min	A2	RCT	73	Suspicion of bone fracture (43), burns (4), other (18)	EMS
Garrick et al. (2011) United States	Fentanyl 1 µg/kg i.v. or i.m., followed by 0.5 µg every 5 min to a max of 3 µg/kg (158 patients) / [Morphine 2–5 mg i.v. or 5–10 mg i.m., followed by 2–5 mg every 3–5 min (20 min i.m.) with a max of 15 mg; 66 patients]	C	Observational trial	318	Trauma (206)	EMS
Gurnani et al. (1996) India	S-ketamine 0.25 mg/kg i.v., followed by 0.1 mg/kg/h s.c. / Morphine 0.1 mg/kg i.v. every 4 h	B	Double-blind RCT	40	Acute musculoskeletal or soft tissue injury	ED
Hoogewijs et al. (2000) Belgium	Propacetamol 20 mg/kg i.v. / Piritramide 0.25 mg/kg i.m. / Tramadol 1 mg/kg i.v. / Diclofenac 1 mg/kg i.v.	C	Prospective, open, single blind randomized study	160	Single peripheral injury	ED
Johansson et al. (2009) Sweden	Ketamine 0.2 mg/kg i.v. + morphine 0.1 mg/kg / Morphine 0.2 mg/kg i.v.	B	Prospective clinical cohort study	27	Fracture	EMS

Table 1 (continued)

Author(s) (year) Country	Medication	Level of evidence	Design	N	Trauma (n)	Setting
Kanowitz et al. (2006) United States	Fentanyl 1–2 µg/kg i.v., followed by titration at a rate of 1 µg/kg	C	Retrospective chart review	2,219	Musculoskeletal (1672), multi-system (43), miscellaneous trauma (56)	EMS and ED
Kariman et al. (2011) Iran	50% nitrous oxide and 50% oxygen through inhalation up to a max of 15 min / Fentanyl 2 mg/kg i.v.	B	Randomized trial	100	Isolated long bone fracture or main joint dislocation	ED
Rickard et al. (2007) Australia	Fentanyl 180 µg ± 2 doses of 60 µg i.n. in ≥5-min intervals / Morphine 2.5–5 mg ± 2 doses of 2.5–5 mg i.v. in ≥5-min intervals	B	RCT	258	Non-cardiac pain: fracture/ dislocation (79), other injuries (16)	EMS
Shear et al. (2010) United States	Fentanyl 100 µg transbuccal + placebo p.o. / Oxycodone/paracetamol 5/325 mg p.o. + placebo transbuccal	B	Double-blind trial	60	Extremity injury with need for X-ray to rule out fracture	ED
Tanabe et al. (2001) United States	Ibuprofen 800 mg p.o.	B	Randomized trial	77	Minor musculoskeletal trauma	ED
Thal et al. (1979) United States	50% nitrous oxide and 50% oxygen (Nitronox) through inhalation	C	Post-test design	47	Musculoskeletal pain (31), burns (5)	EMS
Vergnion et al. (2001) Belgium	Tramadol 100 mg i.v., followed by 50 mg every 10 min; max 200 mg / Morphine 5–10 mg i.v., followed by 5 mg every 5 min; max 15–20 mg	B	RCT	105	Musculoskeletal trauma	EMS
Viallon et al. (2007) France	Paracetamol 1 g p.o.	C	Uncontrolled before and after design	571	Osteoarticular injury	ED
Whitefield et al. (2002) United Kingdom	Ibuprofen 5% gel topical application/ Ibuprofen 400 mg p.o.	C	Double-blind, double-dummy trial	100	Acute soft tissue injuries	ED
Woo et al. (2005) China	Paracetamol 1 g p.o. / Indomethacin 25 mg p.o. / Diclofenac 25 mg p.o. / Paracetamol 1 g + diclofenac 25 mg p.o.	B	RCT	300	Isolated musculoskeletal injury	ED

ED, emergency department; HEMS, helicopter emergency medical service; i.m., intramuscular; i.n., intranasal; i.v., intravenous; PCA, patient-controlled analgesia; p.o., oral; RCT, randomized controlled trial; s.c., subcutaneous.

*Metamizole sodium is not available in the Netherlands.

Levels of evidence

A1 Systematic review of at least two independently performed studies of A2 level.

A2 Randomized double-blind clinical trial of good quality and adequate sample size.

B Comparative study, but not with all characteristics of A2 (this includes case–control study, cohort study).

C Uncontrolled design.

D Expert opinion.

paracetamol. However, only Craig et al. (2012) and Viallon et al. (2007) reported an effective pain relief of more than 20 mm/2 points of the VAS/NRS after i.v. and oral (p.o.) administration of paracetamol, respectively.

3.3.2 NSAIDs

Whitefield et al. (2002) compared different routes of administration for ibuprofen (gel application and p.o.

route). They found no statistically significant differences in pain relief between patients that received application of ibuprofen gel or oral ibuprofen. Pain relief in both groups was less than 20 mm on the VAS score. Tanabe et al. (2001) showed that ibuprofen or distraction by music did not have an added value in pain relief compared with standard care. The reported pain relief was less than 2 points on the NRS score. Oral and topical application of ibuprofen were both ineffective.

Table 2 Characteristics of the reviewed studies: pain relief.

Author(s) (year)	Medication	Pain score outcome measure	Pain relief results
Ansem et al. (1994)	S-ketamine 0.25 mg/kg i.v.	5-point VRS at baseline and every 5 min	VRS scores shown in a figure; exact results are not specified. 125 patients (90.5%) reported pain relief on arrival in the hospital. Patients needed one dose ($n = 74$), two doses ($n = 26$), or two doses and 50% nitrous oxide and 50% oxygen ($n = 26$), and a second dose of 50% nitrous oxide and 50% oxygen ($n = 9$).
Bartfield et al. (1995)	1% lidocaine 0.5 mL injection (1), followed by 2% lidocaine 5 mL topical application / Saline topical application followed by 1% lidocaine injection (2)	VAS immediately after injections	VAS scores for the second injection (after topical application) were statistically significantly lower in both study groups, $7.7/100 \pm 11.2$ for lidocaine ($p < 0.0002$) and $12.1/100 \pm 20.5$ for saline ($p < 0.001$)
Baskett (1970)	50% nitrous oxide and 50% oxygen (Entonox) through inhalation	Pain during follow-up and after admission to hospital ($n = 50$)	50 patients reported much relief in pain; results are not specified.
Bounes et al. (2008)	Morphine 0.05 mg/kg i.v. followed by 0.025 mg/kg every 5 min / Morphine 0.1 mg/kg i.v., followed by 0.05 mg/kg every 5 min	NRS at baseline, every 5 min for half an hour	At 30 min, 66% of the patients in the first group had an NRS of 30 or lower versus 76% of those in the second group ($p = 0.25$). At 10 min, 17% of the patients in the first group had an NRS score of 30 or lower versus 40% of those in the second group (OR: 3.4; 95% CI: 1.3–8.8; $p < 0.01$).
Bounes et al. (2010)	Sufentanil 0.15 μ g/kg i.v., followed by 0.075 μ g/kg / Morphine 0.15 mg/kg i.v., followed by 0.075 mg/kg	NRS at baseline, baseline, after 3, 6, 9, 12, 15 and 30 min	At 15 min, 74% of the sufentanil group had an NRS ≤ 3 versus 70% in the morphine group ($\Delta 4\%$; 95% CI: 13–21%). At 9 min, 65% of the sufentanil group experienced pain relief versus 46% of those in the morphine group ($\Delta 18\%$; 95% CI: 0.1–35%).
Cander et al. (2005)	Metamizole sodium ^a 1 g i.v. / Diclofenac 75 mg i.m. / Tramadol 100 mg i.v.	VAS after 15, 30 and 45 min	Metamizole: 72% experienced pain relief after 30 min Diclofenac: 65% experienced pain relief after 45 min Tramadol: 92% experienced pain relief after 15 min VAS scores not presented; pain relief was not specified.
Craig et al. (2012)	Paracetamol 1 g i.v. / Morphine 10 mg i.v.	VAS at baseline, after 5, 15, 30 and 60 min	No significant difference in analgesic effect between the paracetamol and morphine groups at any time interval. In the paracetamol group, VAS decreased from 76.4 (SD 15.0) to 59.7 (SD 23.5) after 45 min and 52.9 (SD 27.4) after 60 min; in the morphine group, VAS decreased from 70.1 (9.9) to 55.0 (SD 29.7) after 30 min and 44.0 (SD 22.6) after 60 min.
Ernst et al. (1994)	0.5% diphenhydramine injection / 1% lidocaine injection	VAS by patient and physician for pain of injection and pain of suturing.	Lidocaine was significantly more effective than diphenhydramine according to patients ($p < 0.002$) and physicians ($p < 0.004$) for suturing facial lacerations. Exact VAS scores, specified for location, are not presented. No statistically significant differences were found for pain on injection and suturing for all other locations.
Evans et al. (2005)	Morphine 5 mg i.v. through PCA, followed by dose of 1 mg / Morphine 1–10 mg i.v., titrated at a rate of 1–2 mg/min	VAS at baseline and after 15, 30, 45, 60, 90, and 120 min	No statistically significant differences were found between groups. VAS scores are shown in a figure, exact numbers are not presented; based on the figure, both types of analgesia appeared effective.
Frakes et al. (2006)	Fentanyl 5 μ g/kg i.v. / Fentanyl 2 μ g/kg i.v.	NRS at baseline and on arrival in receiving hospital	NRS decreased from 7.6 (SD 2.2) to 3.7 (SD 2.8) with a fentanyl dose of 1.6 (SD 0.8) μ g/kg ($p < 0.001$). Poor correlation between dose and the analgesic effect ($r = 0.22$). Dose > 2 μ g/kg provided better pain relief than a lower dose, 5.1 (SD 2.1) versus 3.6 (SD 2.4; $p < 0.02$).

Table 2 (continued)

Author(s) (year)	Medication	Pain score outcome measure	Pain relief results
Galinski et al. (2007)	Ketamine 0.2 mg/kg i.v. over 10 min + morphine 0.1 mg/kg i.v., followed by 3 mg every 5 min / Placebo + morphine 0.1 mg/kg i.v., followed by 3 mg every 5 min	VAS at baseline and every 5 min until arrival at hospital	After 30 min, morphine consumption was significantly lower in the ketamine group compared to the placebo group, with 0.149 mg/kg (0.132–0.165) and 0.202 mg/kg (0.181–0.223), respectively ($p < 0.001$). VAS after 30 min did not differ significantly between the two groups, with 34.1 (25.6–42.6) in the ketamine group and 39.5 (32.4–46.6) in the placebo group. Ketamine was more effective and had a faster onset than placebo, as shown in a figure, although exact Δ VAS scores are not presented.
Garrick et al. (2011)	Fentanyl 1 μ g/kg i.v. or i.m., followed by 0.5 μ g / [Morphine 2–5 mg i.v. or 5–10 mg i.m. followed by 2–5 mg (20 min. i.m.)]	VAS at baseline and on arrival in ED	VAS decrease on arrival was 3.82 points for fentanyl and 2 for morphine; fentanyl had a faster onset with a decrease of 2.74 points after the first dose and 1.07 points in the morphine group.
Gurnani et al. (1996)	S-ketamine 0.25 mg/kg i.v., followed by 0.1 mg/kg/h s.c. / Morphine 0.1 mg/kg i.v. every 4 h	VAS at baseline, after 15 min, 1, 2, 4, 8, 12 and 24 hours.	VAS scores are presented in a figure; exact numbers not specified. S-ketamine was more effective and had a faster onset than morphine (after 15 min: $p < 0.05$; after 1 and 2 h: $p < 0.01$). The demand for additional analgesia (3 mg morphine) was significantly higher in the morphine group ($p < 0.001$).
Hoogewijs et al. (2000)	Propacetamol 20 mg/kg i.v. / Piritramide 0.25 mg/kg i.m. / Tramadol 1 mg/kg i.v. / Diclofenac 1 mg/kg i.v.	VAS by patients and VRS by observer at baseline and after 10, 30 and 60 min	Propacetamol, diclofenac and tramadol: 1.9-point decrease in VAS after 30 min ($p \leq 0.02$). Piritramide: decrease in VAS after 60 min ($p \leq 0.01$). VRS scores showed a similar trend. VAS and VRS scores presented in figures, no exact numbers were not specified.
Johansson et al. (2009)	Ketamine 0.2 mg/kg i.v. + morphine 0.1 mg/kg / Morphine 0.2 mg/kg i.v.	NRS at baseline and at arrival at hospital	NRS scores differed statistically significantly between the morphine group and the ketamine + morphine group at arrival (5.4 ± 1.9 vs. 3.1 ± 1.4) ($p < 0.05$). NRS decrease in the morphine group was 3.1 and 4.4 points in the ketamine + morphine group.
Kanowitz et al. (2006)	Fentanyl 1–2 μ g/kg i.v., followed by titration at a rate of 1 μ g/kg	NRS, VRS or PFS and effect on vital signs during transport and during stay in the ED (611 patients)	An NRS was available for 92% and showed a significant decrease from 8.4 to 3.7 ($p < 0.000$), the average administration was 118 μ g fentanyl (SD 67; range 5–400).
Kariman et al. (2011)	50% nitrous oxide and 50% oxygen through inhalation up to a max of 15 min / Fentanyl 2 mg/kg i.v.	VAS at baseline and after 3, 6 and 9 min	No statistically significant difference in VAS score was detected, except at 9 min with 2.2 for the nitrous oxide/ oxygen group and 3.1 for the fentanyl group [$\Delta -0.9$ (95% CI: $-1.7 - -0.1$)] ($p = 0.006$). VAS decrease after 3 min was 3.3 ± 2.2 in the nitrous oxide/ oxygen group and 2.8 ± 1.6 in the fentanyl group.
Rickard et al. (2007)	Fentanyl 180 μ g \pm 2 doses of 60 μ g i.n. in ≥ 5 -min intervals / Morphine 2,5-5 mg \pm 2 doses of 2–5 mg i.v. in ≥ 5 -min intervals	NRS at baseline, before analgesia (after ≥ 5 min, ≥ 5 min, ≥ 5 min) and at destination	NRS decreased after 30 min, for the fentanyl group 4.22 (95% CI: 3.74–4.71), for the morphine group 3.57 (95% CI: 3.10– 4.03; $p = 0.08$)
Shear et al. (2010)	Fentanyl 100 μ g transbuccal and placebo p.o. / Oxycodone/paracetamol 5/325 mg p.o. + placebo transbuccal	NRS at baseline, every 5 min for an hour	Transbuccal fentanyl had a faster pain relief onset, with a decrease in NRS of 2 points (median, 10 min vs. 35 min; $p < 0.0001$). The maximal reduction in NRS in the fentanyl group was 6 points (median; IQR, 4–7), in the oxycodone/ paracetamol group 3 points (median; 2–5), a statistically significant difference ($p = 0.0004$).

Table 2 (continued)

Author(s) (year)	Medication	Pain score outcome measure	Pain relief results
Tanabe et al. (2001)	Ibuprofen 800 mg p.o.	NRS at baseline, after 30 and 60 min	Statistically significant decrease in NRS after 30 min, varying from 0.71 (ibuprofen, 5.79–5.0), 0.71 (music, 6.46–5.75) and 0.96 points (control, 6.57–5.61) ($F = 16.18$; $p < 0.01$).
Thal et al. (1979)	50% nitrous oxide and 50% oxygen (Nitronox) through inhalation	Pain during treatment in ambulance	44 patients (93.6%) experienced partial or complete relief of pain; results are not specified.
Vergnion et al. (2001)	Tramadol 100 mg i.v., followed by 50 mg every 10 min; max 200 mg / Morphine 5–10 mg i.v., followed by 5 mg every 5 min; max 15–20 mg	4-point VRS at baseline and after 40 min [none (0), mild (1), moderate (2), severe (3)]	The average decrease in the tramadol group was $1.21/4 \pm 0.70$ and $1.19/4 \pm 0.71$ in the morphine group after 40 min. Both drugs were equally effective ($p < 0.001$).
Viallon et al. (2007)	Paracetamol 1 g p.o.	VAS at baseline, 30 and 60 min and discharge	Median VAS after 60 min changed from 57 ± 18 (baseline) to 30 ± 18 , $p < 0.0001$, and at discharge changed to 26 ± 18 , $p < 0.0001$. 81% had pain relief at discharge.
Whitefield et al. (2002)	Ibuprofen 5% gel topical application / Ibuprofen 400 mg p.o.	Secondary endpoints: VAS at baseline, after 30 min and up to 7/14 days	No statistically significant differences were found after 30 min
Woo et al. (2005)	Paracetamol 1 g p.o. / Indomethacin 25 mg p.o. / Diclofenac 25 mg p.o. / Paracetamol 1 g + diclofenac 25 mg p.o.	VAS at baseline, after 30, 60, 90 and 120 min at rest and with limb movement	The mean change in VAS at rest and with activity was less than 13 mm in all groups (60 min). The paracetamol-diclofenac group had VAS relief >13 mm at 90 min and after 120 min. This group had the greatest pain relief.

BP, blood pressure; DBP, diastolic blood pressure; GCS, Glasgow coma scale; HR, heart rate; i.m., intramuscular; i.n., intranasal; i.v., intravenous; MAP, mean arterial blood pressure; max, maximum; min, minutes; NRS, numeric rating scale; PCA, patient-controlled analgesia; PFS, paediatric faces scale; p.o., oral; RR, respiratory rate; SBP, systolic blood pressure; s.c., subcutaneous; SpO₂, oxygen saturation; VAS, visual analogue scale; VRS, verbal rating scale.

*Metamizole sodium is not available in the Netherlands.

3.3.3 Comparison of NSAIDs and other drugs

Hoogewijs et al. (2000), Cander et al. (2005) and Woo et al. (2005) compared NSAIDs with other types of drugs. The studies used either the p.o. (Woo et al., 2005), intramuscular (i.m.) (Cander et al., 2005) or the i.v. route of administration (Hoogewijs et al., 2000).

Orally administered diclofenac was as ineffective as paracetamol, indomethacin and paracetamol + diclofenac p.o. combined. Pain reduction for the four treatment groups was less than 20 mm on the VAS score in all groups (Woo et al., 2005).

Diclofenac (i.m.) had a slower onset compared with tramadol i.v. (Cander et al., 2005). VAS scores were not presented in this study and pain relief was not specified.

Hoogewijs et al. (2000) found that diclofenac i.v., propacetamol i.v. and tramadol i.v. resulted in an equally, statistically significant reduction of pain of less than 2 points on the VAS score, meaning all drugs were ineffective.

3.4 Opioids

Studies regarding opioids examined the effect of fentanyl or morphine, or compared the effectiveness of different opioids: fentanyl and morphine, fentanyl and oxycodone/paracetamol, piritramide and tramadol, sufentanil and morphine, and tramadol and morphine.

Frakes et al. (2006) and Kanowitz et al. (2006) found that fentanyl i.v. was clinically effective in pain relief during pre-hospital 'critical care' air transport, and in EMS and the ED (Kanowitz et al., 2006).

Evans et al. (2005) compared morphine i.v. via patient-controlled analgesia (PCA) and morphine i.v. titrated according to a protocol in the ED. There were no statistically significant differences between groups regarding pain relief. Both routes of administration appeared to be clinically effective (based on curve analysis of the VAS score). Bounes et al. (2008) found that morphine was effective in reducing pain in pre-hospital EMS.

Fentanyl and morphine appeared to be equally effective after i.v. administration (Vergnion et al., 2001; Evans et al., 2005), based on the figures presented in this article. Effective pain relief was seen after i.v. administration of fentanyl and morphine (Frakes et al., 2006; Kanowitz et al., 2006; Rickard et al., 2007; Garrick et al., 2011) and intranasal (i.n.) administration of fentanyl (Rickard et al., 2007). Fentanyl had a faster onset compared with morphine (Garrick et al., 2011). Fentanyl (transbuccal) compared to a tablet of oxycodone with paracetamol were both effective, although fentanyl had a faster onset (Shear et al., 2010). Morphine (i.v.) compared with tramadol (i.v.) appeared to be equally effective (Vergnion et al., 2001). Based on the study of Cander et al. (2005), tramadol i.v. appeared effective; according to Hoogewijs et al. (2000), tramadol i.v. was nearly effective. Piritramide i.m. appeared to have a slower onset compared to patient groups that received other opioids i.v. (Hoogewijs et al., 2000).

Bounes et al. (2010) compared sufentanil i.v. with morphine i.v. regarding pain relief. They found that sufentanil and morphine in EMS trauma patients appeared to be effective, although sufentanil had a faster onset.

Vergnion et al. (2001) compared tramadol i.v. and morphine i.v. in the pre-hospital setting; both drugs appeared to be effective regarding pain relief for trauma patients (based on a 4-point verbal rating scale).

3.4.1 Comparison of paracetamol and opioids

Craig et al. (2012) found an effective pain relief after the administration of morphine i.v., with morphine being equally effective as paracetamol i.v., although with a faster onset.

Shear et al. (2010) found that transbuccal fentanyl was more effective and had a faster onset than oxycodone/paracetamol p.o. The maximal reduction in NRS score in the fentanyl group was higher.

3.5 (Local) anaesthetics

3.5.1 Lidocaine

Bartfield et al. (1995) found that topical application of lidocaine on the skin combined with infiltration with lidocaine compared to infiltration with lidocaine alone was not clinically more effective in reducing pain after injection.

Ernst et al. (1994) found that infiltration with lidocaine was not an effective local anaesthetic for suturing facial lacerations in emergency care.

3.5.2 Nitrous oxide/oxygen mixture

Although nitrous oxide can be considered as a general anaesthetic, it is frequently used as an analgesic under circumstances dealing with acute pain. Baskett (1970) and Thal et al. (1979) studied the effect of a mixture of 50% nitrous oxide and 50% oxygen on pain in adult trauma patients. In both studies, patients reported pain relief; however, results were not specified by VAS/NRS scores. Based on these results, the effectiveness of a mixture of 50% nitrous oxide and 50% oxygen could not be ascertained.

Kariman et al. (2011) compared 50% nitrous oxide and 50% oxygen through inhalation with fentanyl i.v. and found no statistically significant difference in VAS scores. Both drugs appeared equally effective in pain relief.

3.5.3 S-ketamine

Ansem et al. (1994) studied the effect of S-ketamine in EMS. Although 90.5% of the patients reported pain relief on arrival in the hospital, exact decreases in VRS scores were not presented. As a result, the effectiveness of S-ketamine in this study could not be assessed.

Gurnani et al. (1996) compared the effect of S-ketamine i.v., followed by subcutaneous (s.c.) administration and morphine i.v. VAS scores were shown in a figure; S-ketamine appeared to be more effective and had a faster onset than morphine. The superior analgesic effect of S-ketamine in this study was attributed to its loading dose and route of administration.

Galinski et al. (2007) compared the morphine consumption between administration of S-ketamine i.v. and placebo. Morphine consumption was significantly lower in the S-ketamine group compared with the placebo group. VAS scores did not differ significantly between groups. The combination of S-ketamine and morphine i.v. was more effective and had a faster onset than placebo and morphine i.v. Results were presented in a figure.

Johansson et al. (2009) compared morphine i.v. with a combination of S-ketamine and morphine i.v. Due to differences in baseline pain scores of patients in both groups, no conclusions can be drawn based on the differences in pain relief (outcome) presented in this study.

3.6 Safety aspects of drugs

A summary of safety aspects related to administration of pain medication in the emergency care setting is

presented in Table 3. Most included studies formulated outcome measures related to safety aspects; seven studies (Thal et al., 1979; Bartfield et al., 1995; Tanabe et al., 2001; Cander et al., 2005; Frakes et al., 2006; Rickard et al., 2007; Viallon et al., 2007) did not primarily focus on adverse events of drug administration.

Adverse effects or side effects related to paracetamol were not found. Hoogewijs et al. (2000) described side effects of propacetamol i.v., e.g., pain on injection, vagal reaction and SpO₂ decrease.

Patients at risk for known adverse events of NSAIDs were usually excluded from the studies examining safety aspect of NSAIDs in emergency care. Reported side/adverse effects of NSAIDs were pain on injection, vagal reaction, dizziness and indigestion, nausea/vomiting and allergy.

Likewise, patients with known contraindications to the opioids under study were excluded on forehand. This concerned patients with hypotension, risk for respiratory depression and hypoxia. Described side/adverse effects for opioids were nausea and vomiting, drowsiness, confusion, hypotension, itching, sedation, decreased heart rate and low respiratory rate/SpO₂. None of the reported adverse effects required antagonization or rescue medication regarding maintenance of breathing or circulation.

Reported side effects of the anaesthetic agents 50% nitrous oxide and 50% oxygen mixture were nausea, drowsiness and a delirium like state. Administration of S-ketamine caused the following side effects: agitation or dysphoria, altered consciousness, diplopia, disorientation, dizziness and hallucinations/dreams. For lidocaine, no side effects were reported.

4. Discussion

In this review, we identified pharmacological pain interventions for trauma patients with acute pain in the chain of emergency care. Due to the (extreme) heterogeneity of the included studies, a meta-analysis was not performed. Paracetamol appeared to be an effective analgesic, both p.o. and i.v. Only side effects for propacetamol i.v. were reported. The NSAIDs diclofenac and ibuprofen (p.o., i.m., i.v. and topically applied) showed mixed results regarding effectiveness. Administration of diclofenac i.v., i.m. and the combination of paracetamol and diclofenac p.o. resulted in effective pain relief. Topical application of NSAIDs and ibuprofen p.o. was shown not to be clinically effective. Reported side effects of NSAIDs were pain on injection, vagal reaction, dizziness and indigestion, nausea/vomiting and allergy. Fentanyl and morphine demonstrated to be equally effective analgesics after

i.v. and i.n. administration, as was also the case for tramadol i.v. However, piritramide i.m. appeared to be less effective. Reported side effects for opioids were nausea and vomiting, drowsiness, confusion, hypotension, sedation, decreased heart rates and low respiratory rates/SpO₂. The anaesthetic 50% nitrous oxide and 50% oxygen is effective in pain relief; however, this could only be ascertained in one study. Reported side effects of the 50% nitrous oxide and 50% oxygen mixture were nausea, drowsiness and a delirium-like state. The effectiveness of S-ketamine in emergency care could not be determined based on the included studies. Side effects of S-ketamine were agitation or dysphoria, altered consciousness, diplopia, disorientation, dizziness and hallucinations/dreams.

Finally, injections with 1% lidocaine appeared to be an effective local anaesthetic for suturing. Side effects were not reported.

This review was conducted using a thorough search strategy and showed a new overview of effectiveness and safety aspects of pharmacological pain management in emergency care; however, some aspects need to be discussed.

4.1 Effectiveness, simplicity and safety

Pain management in trauma patients in the chain of emergency care needs systematic improvement (Berben et al., 2008, 2011b). However, the context of (pre-hospital) emergency care requires an optimal balance between patient safety and adequate pain relief, as pharmacological pain treatment can lead to serious adverse effects such as respiratory or cardiovascular depression, which can be life threatening to the patient. Furthermore, medical specialists like anaesthesiologists are not (permanently) available to assist the GP, paramedics, (emergency) nurses and (emergency) physicians in pain management. Moreover, the time frame for risk assessment and pain treatment under emergency conditions is relatively short. Although many analgesic techniques, which are effective in hospital environments, have been adopted in the pre-hospital environment, these do not always comply with the ideal of simplicity, safety and effectiveness when used in the field (Macintyre et al., 2010). In order to provide effective analgesic treatment in trauma patients in the chain of emergency care, these issues should be taken into account.

Paracetamol is widely used in clinical practice and is a simple, safe and effective analgesic with few contraindications (Institute for Clinical Systems Improvement, 2008; Macintyre et al., 2010). Since the

Table 3 Characteristics of the reviewed studies: safety aspects.

Author(s) (year)	Medication	Safety aspects outcome measure	Safety aspects reported	Exclusion criteria safety
Ansem et al. (1994)	S-ketamine 0.25 mg/kg i.v.	Documentation of side effects	Side effects: agitation (9%), altered consciousness (27%), disorientation (17%) and hallucinations (5%)	GCS < 12 and cardiovascular disease
Bartfield et al. (1995)	1% lidocaine 0.5 mL injection (1), followed by 2% lidocaine 5 mL topical application / Saline topical application, followed by 1% lidocaine injection (2)	–	–	Allergy to lidocaine, altered pain perception through intoxication or injury to the sensory nerves
Baskett (1970)	50% nitrous oxide and 50% oxygen (Entonox) through inhalation	Patient report in ED and 2/3 days after admission to hospital	23 patients felt drowsy, but did not fall asleep. No unpleasant side effects reported.	Impaired consciousness, drunkenness, or oral or maxillofacial injuries
Bounes et al. (2008)	Morphine 0.05 mg/kg i.v., followed by 0.025 mg/kg every 5 min / Morphine 0.1 mg/kg i.v., followed by 0.05 mg/kg every 5 min	Monitoring of HR, BP, RR, SpO ₂ , sedation level with 5-point sedation scale and adverse effects	There were no severe adverse effects; incidence was comparable in both groups. Nausea occurred in two patients in both groups (<i>n</i> = 2), and dizziness as well (<i>n</i> = 2). One patient in the second group needed oxygen because of a moderate decrease in SpO ₂ (92%).	Respiratory, renal or hepatic insufficiency, allergy to medication, incapacity to use NRS, hypotension (SBP < 90), bradypnea (RR < 12), SpO ₂ < 90%, seizures or GCS < 14, pregnancy, or drug addiction
Bounes et al. (2010)	Sufentanil 0.15 µg/kg i.v., followed by 0.075 µg/kg / Morphine 0.15 mg/kg i.v., followed by 0.075 mg/kg	Monitoring of HR, BP, RR, SpO ₂ , sedation level with 5-point sedation scale and adverse events	Adverse events were mild to moderate; none required antagonization. Medication stopped due to moderate adverse effects (<i>n</i> = 2) in both groups. More patients in the sufentanil group (<i>n</i> = 5) reported sedation levels ≥2, compared to the morphine group (<i>n</i> = 2). Three patients (sufentanil, <i>n</i> = 1; morphine, <i>n</i> = 2) needed oxygen because of a decrease in SpO ₂ (89%).	Allergy to morphine, sufentanil, acetaminophen or ketoprofen; respiratory, renal, or hepatic failure; communication difficulties; altered consciousness because of alcohol or drugs; life-threatening situations; epilepsy; treatment with MAO inhibitor; pregnancy lactation, drug addiction
Cander et al. (2005)	Metamizole sodium ^a 1 g i.v. / Diclofenac 75 mg i.m. / Tramadol 100 mg i.v.	–	–	–
Craig et al. (2012)	Paracetamol 1 g i.v. / Morphine 10 mg i.v.	Requirement for rescue analgesia, frequency of adverse reactions and monitoring vital signs	Eight patients in both groups required rescue analgesia; not significantly different (<i>p</i> = 0.95). Significantly more adverse reactions in the morphine group (<i>n</i> = 8) compared to the paracetamol group (<i>n</i> = 2; <i>p</i> = 0.03).	Allergy to morphine or paracetamol, chest pain, GCS < 15, liver disease, jaundice, major trauma, pregnancy, lactation, immediate limb-saving procedure, extreme distress, communication difficulties
Ernst et al. (1994)	0.5% diphenhydramine injection / 1% lidocaine injection	Wound dehiscence or infection, healing problems and severe pain at the injection site	No complications during suturing reported. Two wound infections reported, one in both groups.	Allergy to amides or diphenhydramine, alcohol or drug use, altered mental status, pregnancy, glaucoma, or prostate problems

Table 3 (continued)

Author(s) (year)	Medication	Safety aspects outcome measure	Safety aspects reported	Exclusion criteria safety
Evans et al. (2005)	Morphine 5 mg i.v. through PCA, followed by dose of 1 mg / Morphine 1–10 mg i.v., titrated at a rate of 1–2 mg/min	Monitoring of vital signs (HR, BP, SpO ₂ , RR and GCS) and documentation of any adverse events	No severe adverse events were observed, 20.7% (<i>n</i> = 9) in PCA group and 7% (<i>n</i> = 3) in control group experienced mild sedation. Other: nausea (<i>n</i> = 3), vomiting (<i>n</i> = 2), confusion (<i>n</i> = 2), allergy (<i>n</i> = 1), dizziness (<i>n</i> = 3), low BP (<i>n</i> = 1), other (<i>n</i> = 1).	Allergy to morphine
Frakes et al. (2006)	Fentanyl 5 µg/kg i.v. / Fentanyl 2 µg/kg i.v.	–	Advantages and lower risks of fentanyl use are described in the Introduction	–
Galinski et al. (2007)	Ketamine 0.2 mg/kg i.v. over 10 min + morphine 0.1 mg/kg i.v., followed by 3 mg every 5 min / Placebo + morphine 0.1 mg/kg i.v., followed by 3 mg every 5 min	Monitoring of HR, BP, RR, SpO ₂ and sedation level. Documentation of hallucination, dysphoria, weakness sensation, diplopia, nausea, vomiting, dizziness, itching and bradypnea	No statistically significant differences in vital signs were found. Incidence of neuropsychological adverse effects was significantly greater in the ketamine group: hallucinations (<i>n</i> = 4), dizziness (<i>n</i> = 6), diplopia (<i>n</i> = 2), dysphoria (<i>n</i> = 6), placebo group: dysphoria (<i>n</i> = 1). Level of sedation, nausea, vomiting, and itching did not differ, with <i>n</i> = 7, <i>n</i> = 8 and <i>n</i> = 1 respectively in the ketamine group, and <i>n</i> = 2, <i>n</i> = 4 and <i>n</i> = 1 in the placebo group.	Acute respiratory, haemodynamic or neurologic compromise; GCS < 15, psychiatric history, chronic respiratory, renal, or hepatic failure, ketamine sensitivity, opioid allergy, chronic pain, incapacity to understand VAS, pregnancy, or indication for local or regional analgesia
Garrick et al. (2011)	Fentanyl 1 µg/kg i.v. or i.m., followed by 0.5 µg / [Morphine 2–5 mg i.v. or 5–10 mg i.m., followed by 2–5 mg (20 min i.m.)]	Documentation of adverse events and side effects	Three adverse reactions, dizziness (<i>n</i> = 2) and nausea (<i>n</i> = 1). No vital sign abnormalities noted; none required antagonization.	Opioid allergy, renal or hepatic insufficiency, haemodynamic, respiratory or neurological compromise, head trauma
Gurnani et al. (1996)	S-ketamine 0.25 mg/kg i.v., followed by 0.1 mg/kg/h s.c. / Morphine 0.1 mg/kg i.v. every 4 h	Monitoring of HR, MAP, RR, tidal volume, SpO ₂ and sedation score. Reported dreams and hallucinations.	Patients in S-ketamine group had dreams (<i>n</i> = 2). Incidence of nausea in morphine group was statistically significantly higher (<i>p</i> < 0.01).	Severe shock, hypertension, hepatic, cardiac, renal and debilitating diseases
Hoogewijs et al. (2000)	Propacetamol 20 mg/kg i.v. / Piritramide 0.25 mg/kg i.m. / Tramadol 1 mg/kg i.v. / Diclofenac 1 mg/kg i.v.	Monitoring of HR, SBP, DBP, RR and SpO ₂ . Documentation of side effects, time of onset and duration.	No significant differences in vital signs. Dizziness (<i>n</i> = 10), pain on injection (<i>n</i> = 7), nausea (<i>n</i> = 3) and SpO ₂ decrease (<i>n</i> = 6) reported. The piritramide group reported significantly more side effects.	Allergy to study drug, pregnancy, lactation or Group I: hepatocellular insufficiency Group II: risk for respiratory depression Group III: use of MAO inhibitory agents, hypnotics or other central-acting medication, alcohol abuse Group IV: specific gastrointestinal problems

Table 3 (continued)

Author(s) (year)	Medication	Safety aspects outcome measure	Safety aspects reported	Exclusion criteria safety
Johansson et al. (2009)	Ketamine 0.2 mg/kg i.v. + morphine 0.1 mg/kg/ Morphine 0.2 mg/kg i.v.	Scores for nausea, sedation (AVPU), hallucinations, frequencies of nausea and vomiting and monitoring of HR, SBP, RR and SpO ₂ .	BP differed statistically significantly between morphine group and ketamine + morphine group (134 ± 21 mmHg vs. 167 ± 32 mmHg) (<i>p</i> < 0.05). All patients were alert or responded to voice. Nausea (<i>n</i> = 4) and vomiting (<i>n</i> = 3) occurred more often in ketamine + morphine group, morphine group: nausea (<i>n</i> = 1).	Inability to use NRS, chronic pain, acute myocardial infarction and unconsciousness
Kanowitz et al. (2006)	Fentanyl 1–2 µg/kg i.v., followed by titration at a rate of 1 µg/kg	Vital signs: HR, BP, SpO ₂ , RR, GCS, use of reversal medication and use of recovery methods	HR, BP and RR all decreased significantly; however, within normal limits, only 12 patients showed vital sign abnormalities (decrease in SBP or GCS), of which only one needed recovery intervention.	Contraindications: hypersensitivity, hypotension, respiratory depression, myasthenia gravis
Kariman et al. (2011)	50% nitrous oxide and 50% oxygen through inhalation up to a max of 15 min / Fentanyl 2 mg/kg i.v.	Monitoring of HR, BP, RR, SpO ₂ , documentation of adverse effects.	No statistically significant differences in vital signs were found and incidence of side effects. Side effects of nitrous oxide/oxygen were dizziness (<i>n</i> = 4), delirium-like state (<i>n</i> = 2) and for fentanyl delirium-like state (<i>n</i> = 3), dizziness (<i>n</i> = 2) and sweating (<i>n</i> = 2).	Head and trunk trauma, non-orthopaedic limb injuries, GCS < 15, abdominal distension, lung disease, pneumothorax, haemothorax or a recent dive
Rickard et al. (2007)	Fentanyl 180 µg ± 2 doses of 60 µg i.n. in ≥5-min intervals / Morphine 2.5-5 mg ± 2 doses of 2.5–5 mg i.v. in ≥ 5-min intervals	–	62 adverse events reported in 51 patients, 27% (<i>n</i> = 36) in the fentanyl group and 15% (<i>n</i> = 15) in the morphine group. Adverse events: low respiratory rate/SpO ₂ (<i>n</i> = 10), hypotension (<i>n</i> = 13), sleepy/dizzy (<i>n</i> = 5), nausea (<i>n</i> = 15).	Allergy to morphine, fentanyl or other opiates, hypoxia (SpO ₂ < 85%), hypotension (SBP < 110 mmHg), HR < 50 or > 150, altered conscious state (GCS < 15), vomiting
Shear et al. (2010)	Fentanyl 100 µg transbuccal and placebo p.o./ Oxycodone/paracetamol 5/325-mg p.o. + placebo transbuccal	Rescue medication rate. Monitoring of HR, BP, RR and SpO ₂ .	Rescue medication (<i>n</i> = 22), more frequently required in the oxycodone/ paracetamol group (57% vs. 17%). No vital sign abnormalities or significant side effects. Nausea occurred more frequently (<i>p</i> = 0.005) in the oxycodone group (27%) [fentanyl group (0%)]. Dizziness occurred equally frequent in oxycodone/paracetamol and fentanyl subjects (20% vs. 13%; <i>p</i> = 0.71).	Allergy to study drugs or concurrent therapy with medications (phenothiazines, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors) or pregnancy, lactation, opioid abuse
Tanabe et al. (2001)	Ibuprofen 800 mg p.o.	–	–	Contra-indication to ibuprofen not specified

Table 3 (continued)

Author(s) (year)	Medication	Safety aspects outcome measure	Safety aspects reported	Exclusion criteria safety
Thal et al. (1979)	50% nitrous oxide and 50% oxygen (Nitronox) through inhalation	–	Nausea ($n = 1$), drowsiness ($n = 8$).	Head, chest or maxillofacial injury, drunkenness, COPD
Vergnion et al. (2001)	Tramadol 100 mg i.v., followed by 50 mg every 10 min; max 200 mg / Morphine 5–10 mg i.v., followed by 5 mg every 5 min; max 15–20 mg	4-point sedation scale and monitoring of HR, BP, RR, SpO ₂ , GCS, recording of adverse events	Side effects: drowsiness occurred in tramadol group (T) ($n = 8$) and in morphine group (M) ($n = 7$). Nausea and vomiting: T ($n = 9$, 17%), M ($n = 7$, 15%). No serious adverse events reported.	Contraindications to study medication, severe head injury, multiple trauma, GCS < 2, pregnancy.
Viallon et al. (2007)	Paracetamol 1 g p.o.	–	–	Allergy to paracetamol
Whitefield et al. (2002)	Ibuprofen 5% gel topical application / Ibuprofen 400 mg p.o.	Patients asked to report adverse events	Six adverse events reported; none related to study treatment	Hypersensitivity to ibuprofen, aspirin or other NSAID, asthma, renal disease, peptic ulcer, pregnancy or lactation
Woo et al. (2005)	Paracetamol 1 g p.o. / Indomethacin 25 mg p.o. / Diclofenac 25 mg p.o. / Paracetamol 1 g + diclofenac 25 mg p.o.	Number and type of adverse events	Adverse effects occurred in <7% and were not severe: nausea/vomiting (paracetamol + diclofenac; $n = 1$), drowsiness (paracetamol; $n = 1$), allergy (paracetamol and paracetamol + diclofenac; $n = 2$), and no cases of gastrointestinal haemorrhage or renal damage	Predetermined exclusion criteria not specified

AVPU, 1 Alert, 2 respond to Voice, 3 respond to Pain, 4 Unresponsive; BP, blood pressure; DBP, diastolic blood pressure; GCS, Glasgow coma scale; HR, heart rate; i.m., intramuscular; i.n., intranasal; i.v., intravenous; MAP, mean arterial blood pressure; max, maximum; min, minutes; NRS, numeric rating scale; PCA, patient-controlled analgesia; PFS, paediatric faces scale; p.o., oral; RR, respiratory rate; SBP, systolic blood pressure; s.c., subcutaneous; SpO₂, oxygen saturation; VAS, visual analogue scale; VRS, verbal rating scale.

^aMetamizole sodium is not available in the Netherlands.

drug may be administered intravenously, it can also be provided to patients when the p.o. route is contraindicated. Intravenous administration of paracetamol in the ED seemed to have a faster onset (Hoogewijs et al., 2000; Viallon et al., 2007), whereas paracetamol administered p.o. does not require an i.v. catheter insertion and is therefore easier and less time-consuming for emergency care professionals. Rectal administration of paracetamol has a variable bioavailability (Feldman, 1975), and it may not be simply applicable under pre-hospital emergency conditions; therefore, this route of administration is not recommended in emergency care.

NSAIDs are potential agents for pain relief in patients with moderate to severe pain; however, they have many contraindications and can cause serious side effects (Macintyre et al., 2010). The studies on the safety of NSAIDs in the chain of emergency care (Hoogewijs et al., 2000; Whitefield et al., 2002; Woo

et al., 2005) showed that no serious adverse effects occurred, although patients with known contraindications were excluded. Due to the limited time frame and restricted possibilities for adequate risk assessment on potential contraindications and side effects in the pre-hospital setting, (parenteral) NSAIDs are not recommended for use in (H)EMS. Especially in trauma patients with (presumed) hypovolaemia, the administration of NSAIDs does not seem to be safe. In the ED, where more time for risk assessment is available, NSAIDs p.o. can be used safely.

Various studies investigated the effectiveness and safety of morphine and fentanyl i.v. Despite the risk for respiratory or cardiovascular depression, both opioids showed to be safe and effective analgesics during transportation with (H)EMS. Frequent titration of opioids leads to rapid and effective pain relief in the ED (Macintyre et al., 2010). Intravenous titration contributes to safety in pain management as emergency

care professionals can closely monitor the dose for effect and the occurrence of side effects. Furthermore, it enables them to respond quickly to inadequate dosing or ceasing and, if necessary, antagonising the medication when serious side effects occur. At all times, frequent monitoring of respiratory (and haemodynamic) parameters of the patient is required. Side effects such as respiratory depression can usually be avoided by careful titration of the dose for effect. When a fast onset and relatively short duration is desired, fentanyl seems appropriate in the chain of emergency care (Frakes et al., 2006; Kanowitz et al., 2006), whereas morphine may be administered when a longer duration of pain relief is desired. Sufentanil is a powerful drug, approximately 10 times more potent as its analogue, fentanyl (Pharmacotherapeutic compass / *Farmacotherapeutisch Kompas*, 2012). Therefore, it seems less safe for initial analgesia purposes as it also possesses sedative properties. Morphine i.v. through PCA showed to be effective in the ED (Evans et al., 2005); however, as it requires more organizational and logistical input from the ED staff, it does not seem to be of additional value to the previously discussed i.v. routes of administration.

For safety reasons, emergency care organizations should consider the use of two types of opioids: one with a relatively short duration and one with a longer duration. This leads to professionals being well acquainted with these two analgesics and, consequently, to safer practice. Unfortunately, we found only one study on the effectiveness and safety of i.n. fentanyl (Rickard et al., 2007), and none on inhalational or sublingual administration of opioids in emergency medicine, although studies on fentanyl i.n. administration in children with moderate to severe pain have shown that the i.n. route is effective, safe and easier than the i.v. route of administration (Borland et al., 2007, 2008; Finn and Harris, 2010). These potential innovative routes of administration for emergency care need to be studied further.

The effectiveness of S-ketamine in emergency care could not be ascertained in this review, although the use of S-ketamine seems to grow in popularity in practice. However, the combination of S-ketamine and morphine showed to be effective in pain relief, and it reduced the morphine consumption (Galinski et al., 2007). Furthermore, as S-ketamine does not have a cardiodepressant effect; it is potentially suitable for pain relief in trauma patients with hypovolaemia. Further study on the applicability, effectiveness and safety of S-ketamine for pain relief in trauma patients in emergency medicine is recommended.

4.2 Implications for pain guideline or pain protocol development

Studies on effectiveness and safety of analgesics in the chain of emergency care were scarce; only one study performed in the chain of care was found (EMS and ED; Kanowitz et al., 2006). This might also explain the lack of evidence-based guidelines addressing this particular topic. In this review, a summary of effective and safe analgesics in (pre)hospital-based emergency care is presented. Although the studies compared different types of drugs or routes of administration, this review can provide building blocks for the development of pain protocols and pain guidelines for trauma patients in the chain of emergency care in different countries.

4.3 Limitations in literature search and analysis

The systematic review was carefully conducted; however, only a limited number of studies could be included based on the inclusion and exclusion criteria. As these studies focused on different analgesics or studied different routes of administration, comparability between studies was rather limited.

Furthermore, adequate pharmacological pain management is influenced by many factors such as education, competences and knowledge of professionals in emergency medicine, key opinion leaders in the field and the influence of pharmaceutical companies. In this review, we critically appraised the findings of previous analgesic studies in emergency care in order to overcome these limitations. However, we limited our report to effective and safe analgesics that were available in the Netherlands because we aimed to develop a national guideline for adequate pain management in the chain of emergency care.

The excluded analgesics were NSAIDs [ketorolac (Wright et al., 1994; Turturro et al., 1995; Neighbor and Puntillo, 1998; Rainer et al., 2000), mefenamic acid (Stableforth, 1977; Sleet and Khan, 1980), diflunisal (Aghababian, 1986) and piroxicam (Morán, 1990)], opioids [nalbuphine (Stene et al., 1988; Chambers and Guly, 1994; Hyland-McGuire and Guly, 1998; Woollard et al., 2002, 2004), hydrocodone (Marco et al., 2005) and butorphanol (Scott et al., 1994)] and a type of paracetamol [hydrocodone-acetaminophen (Turturro et al., 1998)]. This may have led to the loss of relevant information for emergency care settings in other countries. However, various analgesic drugs in all classes of analgesics have been described, resulting in a review of analgesics of potential interest for other European countries.

5. Conclusions

This review provides an overview of the effectiveness and safety of pharmacological pain management in trauma patients in the chain of (pre-hospital) emergency care.

Paracetamol (both p.o. and i.v.) and opioids (morphine i.v. and fentanyl i.v.) proved to be safe and effective analgesics for trauma patients in the chain of emergency care. NSAIDs showed mixed results regarding effectiveness and safety and are not recommended for use in pre-hospital emergency care, provided by ambulance EMS or HEMS. Effectiveness of S-ketamine could not be ascertained. Potentially innovative routes of administration, such as the use of i.n. fentanyl in adults, need to be explored further.

Author contributions

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All authors discussed the results and commented on the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Results of systematic literature search.

Table S1. Search strategies.