ORIGINAL ARTICLE

Analgesia in Patients with Trauma in Emergency Medicine

A Systematic Review and Meta-analysis

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SUMMARY

Background: Suitable analgesic drugs and techniques are needed for the acute care of the approximately 18 200—18 400 seriously injured patients in Germany each year.

Methods: This systematic review and meta-analysis of analgesia in trauma patients was carried out on the basis of randomized, controlled trials and observational studies. A systematic search of the literature over the 10-year period ending in February 2016 was carried out in the PubMed, Google Scholar, and Springer Link Library databases. Some of the considered trials and studies were included in a meta-analysis. Mean differences (MD) of pain reduction or pain outcome as measured on the Numeric Rating Scale were taken as a summarizing measure of treatment efficacy.

Results: Out of 685 studies, 41 studies were considered and 10 studies were included in the meta-analysis. Among the drugs and drug combinations studied, none was clearly superior to another with respect to pain relief. Neither fentanyl versus morphine (MD –0.10 with a 95% confidence interval of [–0.58; 0.39], p = 0.70) nor ketamine versus morphine (MD –1.27 [–3.71; 1.16], p = 0.31), or the combination of ketamine and morphine versus morphine alone (MD –1.23 [–2.29; –0.18], p = 0.02) showed clear superiority regarding analgesia.

Conclusion: Ketamine, fentanyl, and morphine are suitable for analgesia in spontaneously breathing trauma patients. Fentanyl and ketamine have a rapid onset of action and a strong analgesic effect. Our quantitative meta-analysis revealed no evidence for the superiority of any of the three substances over the others. Suitable monitoring equipment, and expertise in emergency procedures are prerequisites for safe and effective analgesia by healthcare professionals..

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Each year 18 200–18 400 patients require treatment for severe injuries in Germany (1). In 2016, ca. 396 700 persons were injured in road traffic accidents (2). Adequate analgesia following trauma is a central aspect of emergency medical treatment before and after hospital admission (3–5). Although relief of pain is a fundamental human right (6), studies suggest that many trauma patients are undertreated in this respect (7). One of the tasks of the group convened to revise the German S3 guideline on treatment of multiple trauma and severe injuries in 2016 was to take steps towards the development of national recommendations on the treatment of pain in trauma patients (8).

The goals of this systematic analysis of the published literature were to compare the effects of various analgesics, alone and in combination, in (severely) injured but spontaneously breathing patients with no need for airway management; to review safety and adverse effects; and to formulate recommendations. To this end, we performed qualitative and quantitative analysis of the data from randomized controlled trials (RCTs) and observational studies.

Method

This study adhered to the principles of the PRISMA statement for systematic reviews and followed the PICO scheme (population, interventions, comparison, outcome). The protocol, search strategy, and search terms were entered in the PROSPERO registry of systematic reviews and have been published (www.crd.york.ac.uk/PROSPERO, ID: CRD42016046110). Details of the study's methods can be found in *eBox 1*. The endpoints of the meta-analysis were pain reduction (difference in pain rating before and after administration of analgesics) and the post-treatment score on the numeric rating scale (NRS).

Results

Selection of studies

The initial literature survey turned up 665 relevant publications. A further 20 items were identified by an additional hand search. Of these 685 publications, 624 were excluded after perusal of titles and abstracts. Full-text inspection eliminated a further 20 publications, leaving 41 for analysis *(Figure 1)*.

THE CLINICAL PERSPECTIVE

- The most familiar opioid or ketamine should be used for analgesia.
- Opioids and ketamine should be given intravenously. In exceptional cases the intranasal (atomizer) or intraosseous routes can be used instead.
- Monitoring of analgesia should comprise: three-channel ECG, breathing rate, heart rate, optional capnography, pulse oximetric oxygen saturation, and blood pressure. Emergency equipment for airway management, ventilation, suction, and resuscitation must be available.
- In the prehospital setting and after reaching the hospital, trauma patients should receive pain treatment comprising repositioning and pharmacotherapy adapted to the patients' pain.
- Together with assessment of vital signs and body language, the following questions should be asked:
  - "Are you in pain? If so, where is the pain?"
  - "Would you like a painkiller?"
  - "How strong is your pain (on a scale of 0 = no pain to 10 = worst imaginable pain)?"
- Nonpharmacological pain treatment should avoid further damage but not prolong the total rescue time in the case of life-threatening injuries.
- Severely displaced fractures and joint injuries should be repositioned, particularly in the presence of ischemic or neurovascular deficits and if a long delay before reaching the hospital is expected.

Study characteristics

Twenty-three of the 41 studies were of the emergency rescue services, covering a total of 67 269 patients (10, 16, 21, 22, 27–32, 37–40, e1–e9), and the remaining 18 studies, comprising 1899 patients, were carried out in hospital emergency departments (9, 11–15, 17– 20, 23–26, 33–36). Overall, the substances most commonly used for analgesia were the opiates fentanyl and morphine, the NMDA receptor antagonist ketamine, and combinations of ketamine with opiates, followed by methoxyflurane, nitrous oxide, paracetamol, pentazocine, and sufentanil or combinations thereof. An overview of the studies can be found in *eTable 1*. Ten studies were included in a meta-analysis of pain reduction but were highly heterogeneous.

Analgesics

Morphine

One RCT with 300 patients compared intravenous and inhaled morphine (10 or 20 mg). Inhalation of morphine was found to have efficacy comparable with that of intravenous administration, together with high safety (19). Observational studies showed that the intravenous administration of morphine can be safe and effective (30, 32).

Ketamine

Retrospective studies showed safe analgesia with ketamine (alone or in combination with midazolam) (33, e1, e2, e4, e9). Only in one of the included studies was S-ketamine used (e10). Administration of ketamine in a dosage <2 mg/kg was followed by a decrease in pulse-oximetric oxygen saturation (SpO_2) in 0.7% of cases, but no ventilation was required (e9); assisted ventilation was needed, however, in 6% of cases after high-dose ketamine (2 mg/kg) (34). The adverse effects reported as being associated with ketamine included dysphoria (4%), hypersalivation (1%), and vomiting (5%) (e9). In one single case, laryngospasm lasting for 1 min was reported (34). Intranasal ketamine seems to be safe and effective in children (36).

Fentanyl

Intravenous administration of fentanyl by paramedics and emergency physicians was safe and effective with no significant adverse effects (31, 37, 38, e3, e5). Two observational studies showed that intranasal fentanyl in a dose of 50 to 100 µg or 2 µg/kg was safe, effective, and associated with no or only few adverse effects in adults and children (31, 35).

Fentanyl versus morphine

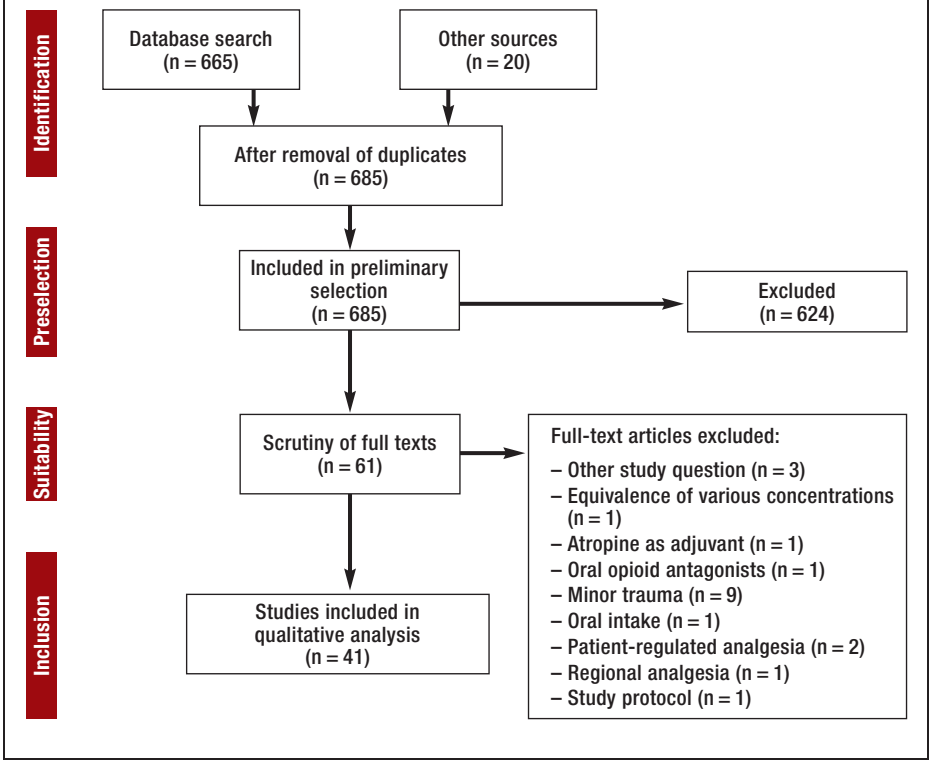
Data from four RCTs (9, 15, 16, 27) and one cohort study (28) permitted comparison of analgesia with fentanyl and with morphine in terms of post-treatment NRS score and pain reduction (RCTs: fentanyl pre-NRS 6.8 to 8.4/post-NRS 3.5 to 6.6, morphine pre-NRS 7.0 to 8.3/post-NRS 4.0 to 6.2; cohort study: fentanyl pre-NRS 8.0/post-NRS 5.5, morphine pre-NRS 8.0/post-NRS 5.8). The post-treatment NRS score showed no clear-cut advantage of fentanyl over morphine (mean difference: −0.10, 95% confidence interval [−0.58; 0.39], p = 0.70) *(Figure 2)*, but all medications investigated brought about a marked reduction in pain.

One cohort study that was not included in the meta-analysis showed greater pain reduction with fentanyl i.v. than with morphine i.v. (fentanyl pre-NRS 8.5/post-NRS 4.4, morphine pre-NRS 8.2/post-NRS 5.9) (38). Both RCTs and retrospective studies compared intranasal/inhaled fentanyl with morphine i.v. The RCTs found that intranasal/inhaled fentanyl was equivalent to morphine i.v. for pain reduction (fentanyl pre-NRS 6.8 to 8.4/post-NRS 3.0 to 6.6, morphine pre-NRS 7.0 to 8.7/post-NRS 3.0 to 6.2) (9, 13, 15, 27, 40). Retrospective analysis also showed that morphine i.v. was comparable in efficacy with intranasal fentanyl (pre-NRS: fentanyl 8.4, morphine 8.3; pain difference: fentanyl −4.5, morphine −4.5) (e8).

Ketamine versus morphine

Analgesia with ketamine or ketamine/morphine and analgesia with morphine could be compared in terms of post-treatment NRS score and pain reduction using the data from four RCTs (ketamine: pre-NRS 7.1 to 8.6/post-NRS 3.2 to 3.4, pain reduction 4.9 to 5.6; morphine: pre-NRS 7.0 to 8.5/post-NRS 3.9 to 4.2, pain reduction 3.2 to 5.0) (17, 21, 24, 25) and one cohort study (39). Ketamine and ketamine combinations were more effective analgesics than morphine alone (post-NRS: mean difference −1.23 [−2.29; −0.18], p = 0.02 *[Figure 3]*; pain reduction: mean difference −1.27 [−3.71; 1.16], p = 0.31 *[Figure 4]*). Analgesia with morphine and ketamine took

FIGURE 1



PRISMA flow chart of literature survey and study selection

effect significantly more rapidly than morphine alone (17, 21, 39). However, two of the RCTs showed that pain reduction was comparable after 30 min (24, 25).

One cluster-randomized study that was not included in the meta-analysis showed comparable pain reduction with morphine i.v. (3.1) and with ketamine i.v. (3.5); however, airway problems and vomiting were reported more frequently in the morphine group (29).

Fentanyl versus ketamine

Two RCTs compared ketamine/midazolam i. v. with fentanyl/midazolam i. v. In one study the results were comparable (20), while the other found swifter pain reduction with a lower risk of hypoxia in the ketamine group (11) (fentanyl: pre-NRS 7 to 8/post-NRS 1 to 2; ketamine: pre-NRS 7 to 9/post-NRS 1 to 3). Owing to high heterogeneity, however, no meta-analysis could be performed. One RCT compared ketamine/propofol i.v. with fentanyl/midazolam i. v. for short anesthesia in the emergency department (post-NRS: median = 0, interquartile ratio [IQR] 0 to 1 versus median = 3, IQR 1 to 6; $p < 0.001$). In the course of treatment, better pain reduction was described in the ketamine group and a higher incidence of SpO_2 decrease in the fentanyl group (26). One RCT in children compared intranasal fentanyl with intranasal ketamine and found comparable pain reduction (fentanyl: pre-NRS 8, post-NRS 3; ketamine: pre-NRS 8, post-NRS 3) (18).

Sufentanil versus morphine

One RCT compared sufentanil i.v. with morphine i.v. in trauma-related pain (10). Sufentanil acted more rapidly than morphine, but was not superior with regard to pain reduction after 15 min (sufentanil: pre-NRS ≥ 6, post-NRS 3.0; morphine pre-NRS ≥ 6, post-NRS 4.0).

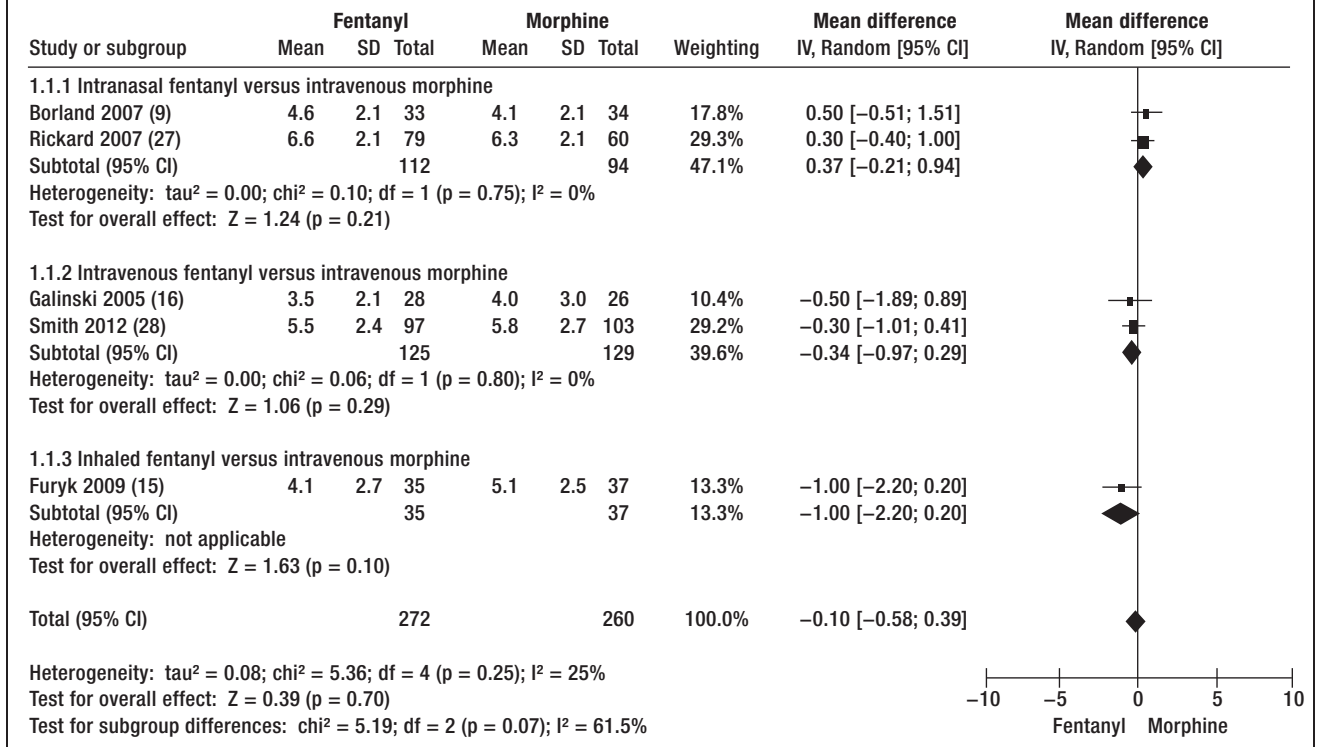
Onset and course of pain reduction by fentanyl, ketamine, and morphine

One cohort study reported that fentanyl and morphine were equally effective (28), but it seems that analgesia can usually be achieved more quickly with fentanyl than with morphine (16, 38). With regard to the onset of pain reduction, inhaled fentanyl and morphine i.v. were described as equivalent (9, 27, 40), but sometimes fentanyl was faster acting (13, 15). One RCT reported that morphine and ketamine were equally effective, while in other studies ketamine, alone or in combination with other substances, was more effective or quicker-acting than morphine alone (17, 21, 24, 25). Compared with fentanyl, ketamine was faster (11) or equally fast (18, 20) to take effect. The duration of effect that can be expected was given as 10 to 15 min for ketamine, 20 to 40 min for fentanyl, and up to 4 h for morphine (4, e11).

Other analgesics

Two RCTs compared the effect of N_2O with that of ketamine or fentanyl (22, 23) and described equivalent

FIGURE 2



Post-therapeutic pain status according to Numeric Rating Scale (NRS) score after analgesia with fentanyl or morphine. The data showed no clear-cut advantage of fentanyl over morphine.

IV, Inverse variance; Random, random effect; SD, standard deviation; 95% CI, 95% confidence interval

analgesia. Similar results were reported for pentazocine (e6). A prehospital observational study in which paracetamol i.v. was administered to patients who predominantly had trauma of the extremities found pain reduction of NRS <5 in 50% of cases. The analgesia was described as mostly insufficient to manage severe pain (e7). One RCT compared paracetamol i.v. and morphine i.v.: the pain reduction was comparable, but morphine was quicker to take effect than paracetamol (12). Another RCT comparing paracetamol with ibuprofen described similar pain reduction in the two groups (14).

Adverse effects of the most commonly used analgesics

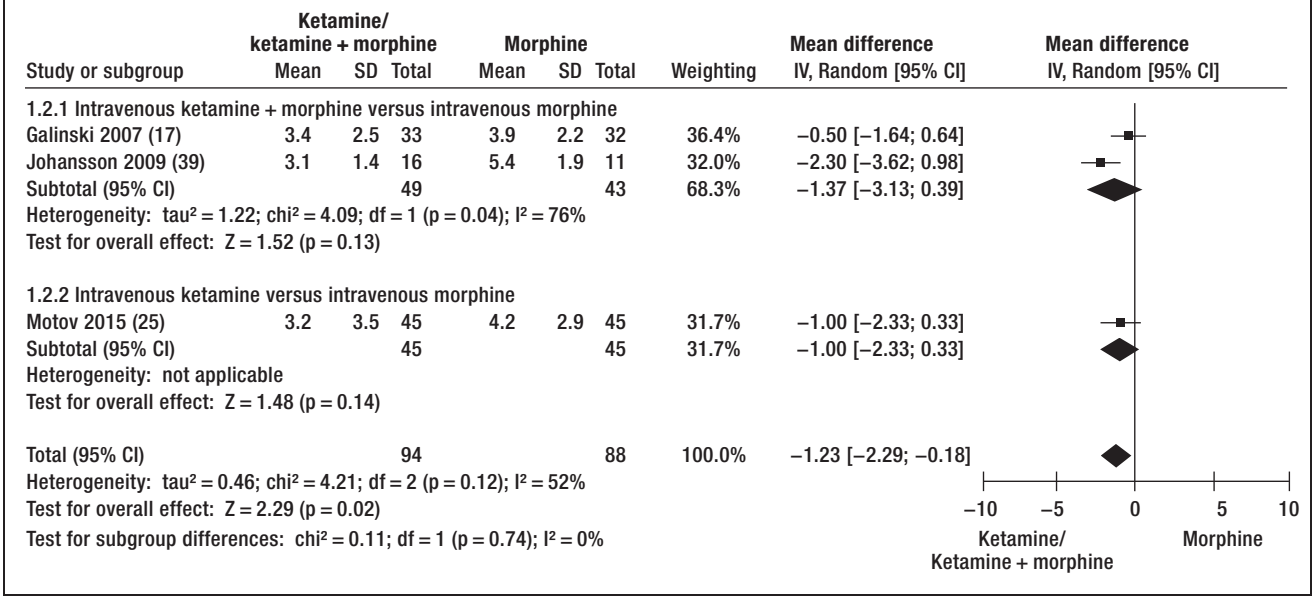
The documented adverse effects of fentanyl, ketamine, and morphine, the most commonly used analgesics, are summarized in *eTable 2*. Ketamine or combinations including ketamine led to (desired) reduced vigilance in 1.5 to 18% of cases (17, 18, 21, 36). Agitation may occur with ketamine. Decreases in SpO_2 were found in all studies for fentanyl (mean 0.6%, maximum 16.1% [26]), ketamine (mean 0.4%, maximum 11.5% [33]), and morphine (mean 0.6%, maximum 4.8% [24]). Overall, assisted ventilation was necessary for 0.05% of patients with ketamine, 0.02% with fentanyl, and 0% with morphine *(eTable 2)*. Hypersalivation was reported in 0.5 to 3% of cases, predominantly in children, but was clinically irrelevant and required no intervention (e9, 29, 33). Nausea and vomiting were the principal adverse effects of morphine (4.8%), fentanyl (1.5%), and ketamine (0.5%). Hypotension was described in 1.6% of cases for fentanyl and in 0.5% of cases for morphine *(eTable 2)*.

Discussion

Analgesics

Despite the variously defined endpoints, all the analgesics used in the identified studies and the meta-analyses seem to be similar in efficacy; nevertheless, fentanyl, ketamine, and combinations of fentanyl or ketamine with other substances take effect more rapidly than morphine (1 to 3 min versus 5 to 15 min after i.v. administration). Morphine is the oldest of the analgesics investigated in this systematic review. It has a very wide field of application, and its adverse effects are nausea, vomiting, decreased SpO_2, and reduced vigilance (e12). Fentanyl is described as very effective with a swift onset of action (e12) and a low risk of adverse effects (e.g., hypotension and hypoxemia) (e13). International guidelines recommend morphine, fentanyl, and ketamine, administered by trained personnel, for pre-hospital analgesia (e14, e15). There are no data on the pre-hospital use of piritramide.

FIGURE 3



Post-therapeutic pain status after administration of ketamine or ketamine/morphine versus analgesia with morphine alone.
Scores on the Numeric Rating Scale (NRS) show advantages for the ketamine combinations.
IV, Inverse variance; Random, random effect; SD, standard deviation; 95% CI, 95% confidence interval

Numerous studies in Germany and other countries have shown that ketamine, alone or in combination with an opioid, is safe and effective when used not just by physicians but also by appropriately trained paramedics and nurses (20, 21, 24, 25, 29, 33, 36, 39, e1, e2, e4, e9, e16, e17). Analgosedation with ketamine can lead to dysphoria and vivid hallucinations or even to agitation (e18). For this reason, accompanying administration of a low-dose benzodiazepine is recommended (e19). Ketamine has the advantage that the patient is sufficiently protected from pain and shielded from external stimuli during the rescue process or invasive procedures (e.g., repositioning or splinting). Moreover, ketamine is particularly well-suited for analgesia of hemodynamically unstable patients (e20–e22). Several reviews have shown that ketamine does not differ from other substances in respect of intracranial pressure (ICP), cerebral perfusion pressure (CPP), neurological outcome, mortality, or length of stay in the intensive care unit (e23, e24); in fact, it is especially suitable for use in patients with head injuries (e25). In ventilated patients with elevated ICP, ketamine is effective in lowering the ICP and prevents undesired increases in ICP with stable blood pressure and CPP (e26). Steps must be taken to avoid hypercapnia. Nonpharmacological pain treatment and the embryotoxological aspects of the analgesics reviewed here are discussed in *eBoxes 2 and 3*.

Alternative routes of administration

Analgesics should be administered intravenously in the context of emergency medicine (5). All analgesics approved for i.v. administration can also be given by the intraosseous (i.o.) route (e27). Intranasal administration is an alternative in both children and adults. Most analgesics have not been approved for intranasal use, but clinical experience with ketamine and fentanyl has been reported (18, 31, e10, e28, e29).

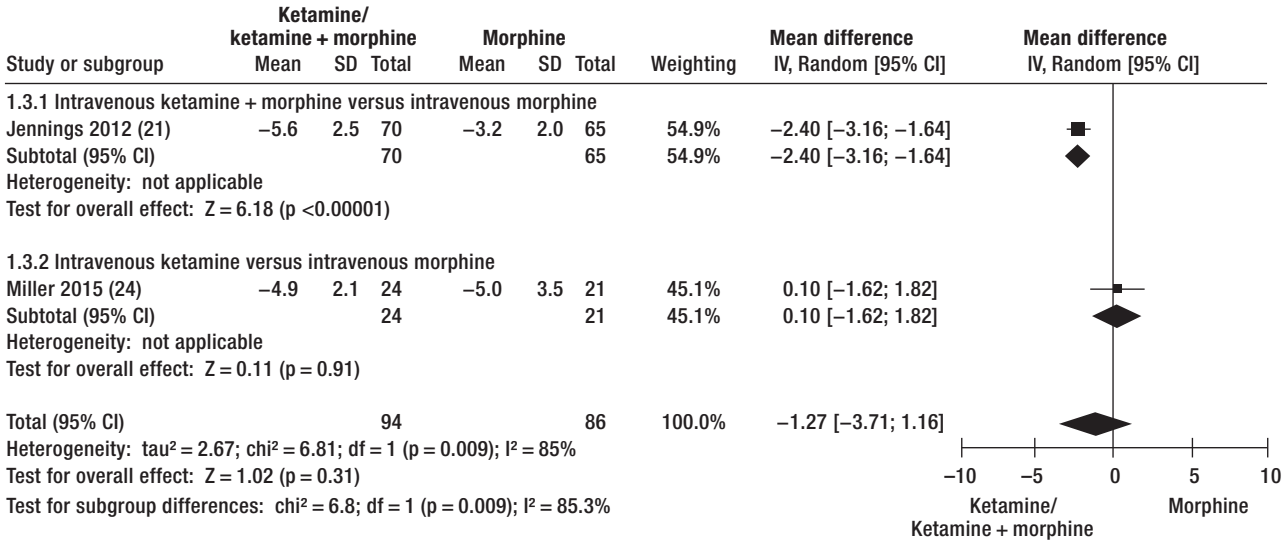
Safety and monitoring

The prerequisites for safe analgesia are knowledge of the pharmacological characteristics of the substances involved, training in their administration, and presence of emergency equipment for treatment of any complications, independent of the user (e.g., nurse, paramedic, or emergency physician) or the situation (prehospital or in the hospital). The monitoring measures and the emergency equipment needed at hand depend on the expected complications and adverse effects. Monitoring of a spontaneously breathing patient under analgesia comprises ECG, blood pressure, breathing rate, heart rate, and SpO_2, together with capnography if required (e30–e32). Patients under analgesia should regularly receive oxygen. The equipment for mask ventilation and suction must be available, and every user must be in the position to keep the airway free and perform ventilation. An intravenous access is recommended for treatment of hypotension or administration of naloxone as an opioid antagonist (e22, e23). Titrated administration is advised to avoid respiratory depression.

Undertreatment

Pain has direct physiological effects (blood pressure, breathing rate, heart rate, oxygen consumption, inflammatory reaction) and is a risk factor for post-traumatic stress disorder (e34). From the patient's point of view, adequate analgesia is an important goal of emergency

FIGURE 4



Pain reduction expressed as difference in scores on the Numeric Rating Scale (NRS) before and after analgesia with ketamine/morphine or ketamine alone and with morphine

IV, Inverse variance; Random, random effect; SD, standard deviation; 95% CI, 95% confidence interval

medical care (5, e35). However, only half of trauma patients receive analgesics at all, and in most of those cases the analgesia achieved is insufficient (4, 7, e36–e40); this is independent of the professional role of the person administering the analgesic (e41– e44). The principal reasons for inadequate analgesia are concern about adverse effects and uncertainty regarding dosage. Proper training in analgesia is therefore essential and the corresponding steps must be taken (5).

Pain assessment

The perception of pain is subjective, and pain is rated differently by patients and professionals (e45). Not all patients want analgesia, so every patient should be asked (e46). The NRS cannot be used in all patients; an alternative is to ask patients whether they are suffering severe or unbearable pain (e47).

In most cases, however, the NRS is useful in assessing the success of analgesia. The aim is to achieve an NRS score ≤ 4 (e19, e48, e49). The vital signs (e.g., breathing rate) may also serve to indicate whether adults are in pain (e50), and for children one can use pain evaluation scales adapted to the pediatric age group (e51–e53). Geriatric patients often have more and worse comorbidities, are frequently accustomed to pain, and are less liable to complain of pain; they must therefore be questioned in greater depth (e19).

Limitations

This review and meta-analysis focuses on the analgesics most commonly used in Germany. The selected study design, with several endpoints (e.g., safety, efficacy, and adverse effects), led to a wide-ranging survey of the literature. However, the high degree of heterogeneity among the studies with regard to endpoints, study quality, and study characteristics represents a crucial limitation. For example, not all controlled studies recorded the time of onset of pain reduction. Many of the studies included did not report adverse effects uniformly. These limitations have to be borne in mind when interpreting the results. Only a small number of studies assessed the trauma by means of the Injury Severity Score (ISS), and very few of them investigated analgesia in seriously injured patients (ISS >15).

Conclusion

Healthcare professionals must be in the position to carry out safe and effective analgesia. The basis is formed by physical measures for pain relief. The preferred means of administration of analgesic drugs is the intravenous route; however, other routes are possible. The recommended analgesics are fentanyl, ketamine, and morphine, with comparable efficacy. Our quantitative meta-analysis shows that there are very few comparable studies of acceptable quality. The current state of knowledge permits no evidence-based statement of superiority of any one of these substances over the others for analgesia in trauma patients in emergency medicine. Analgesia must be carried out only by properly trained persons, the patient must be monitored without interruption, and emergency equipment for treatment of complications must be at hand.

KEY MESSAGES

- The analgesics fentanyl, ketamine and morphine possess comparably efficacy.
- The quality of the studies included was mostly low and the heterogeneity (I^2) high. The lack of consistent reporting limits the comparability of the studies. For this reason, no one substance can be stated as superior to the others.
- Many studies point out that only half of trauma patients receive analgesics at all, and in most of those cases the analgesia achieved is insufficient. The principal reasons are concern about adverse effects and uncertainty regarding dosage.
- Analgesia is safe when administered by trained personnel.

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Conflict of interest statement
Prof. Böttiger has received lecture fees and/or reimbursement of travel costs from medupdate, Baxalta Deutschland, Bayer Vital, Boehringer Ingelheim Pharma, ZOLL Medical Deutschland, C.R. Bard, and Forum für medizinische Fortbildung.

The remaining authors declare that no conflict of interest exists.

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Supplementary material
eReferences:
www.aerzteblatt-international.de/ref4617

eTables, eFigure, eBoxes:
www.aerzteblatt-international.de/17m0785

CLINICAL SNAPSHOT

Persistent Retrosternal Pain in a 72-Year-Old Woman

A 72-year-old woman presented to the emergency department with chest pain, bilateral pedal edema, weight loss of 4 kg in the past 4 months, reflux symptoms, anorexia, a normal heart rate (70/min), and a low arterial blood pressure. Her laboratory values on admission were notable for elevated levels of BNP, troponin, D-dimers (3.6 µg/mL), and creatinine (1.4 mg/dL), as well as hypoproteinemia (6 g/dL), hypoalbuminemia (2.6 g/dL), and marked proteinuria (7 g/d). A chest x-ray revealed nonspecific degenerative bone changes. The retrosternal pain and the very high troponin-T value (0.195 ng/mL [<0.014]) suggested an acute coronary syndrome, prompting coronary angiography; this, however, ruled out coronary artery disease. She developed a contrast-induced nephrotic syndrome and myocardial hypertrophy. Serum and urinary electrophoresis studies and mucosal biopsies of the stomach and rectum were obtained. Bence-Jones proteins and a monoclonal gammopathy of the IgG light chain kappa type were found and a secondary amyloidosis of type AL was diagnosed. Bone marrow biopsy revealed multiple myeloma as the cause. The patient died shortly after the diagnosis was made because of progressive left-heart failure and renal failure necessitating dialysis.

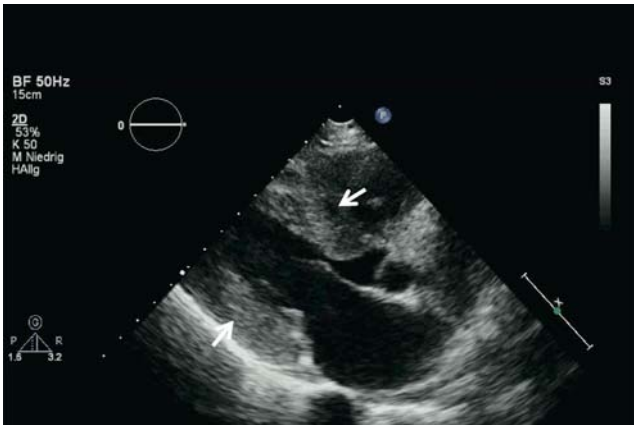

Figure 1: Echocardiography, parasternal longitudinal axis, moderately severe left ventricular myocardial hypertrophy (arrows)

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Supplementary material to:

Analgesia in Patients with Trauma in Emergency Medicine

A Systematic Review and Meta-analysis

by David Häske, Bernd W. Böttiger, Bertil Bouillon, Matthias Fischer, Gernot Gaier, Bernhard Gliwitzky, Matthias Helm, Peter Hilbert-Carius, Björn Hossfeld, Christoph Meisner, Benjamin Schempf, Arasch Wafaisade, and Michael Bernhard

Dtsch Arztebl Int 2017; 114: 785–92. DOI: 10.3238/arztebl.2017.0785

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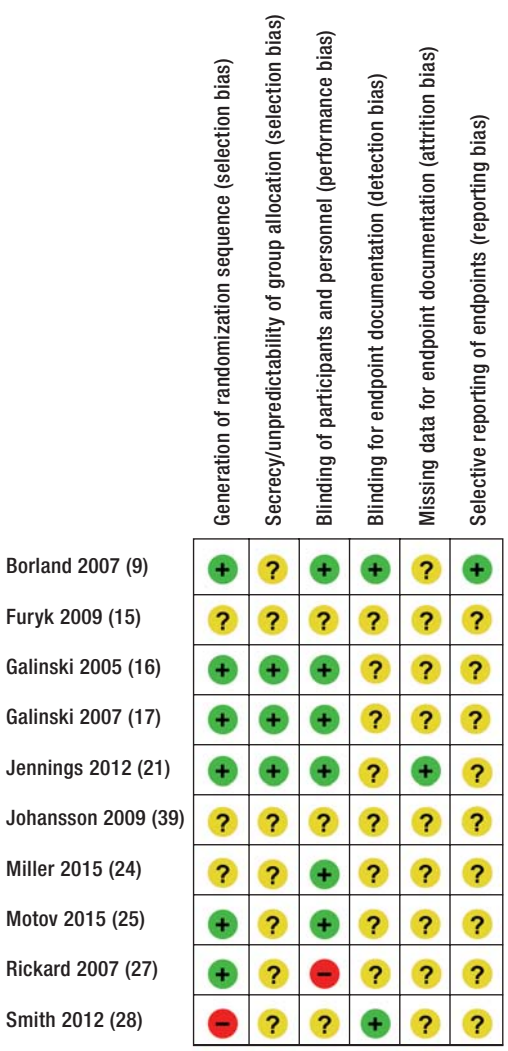
eTABLE 2

Adverse effects

	Fentanyl		Ketamine		Morphine		Ketamine + morphine	
	n	% [95% CI]	n	% [95% CI]	n	% [95% CI]	n	% [95% CI]
Total number of patients in all studies that reported adverse effects	**6373**		**2105**		**1098**		**119**	
Loss of vigilance	31	0.49 [0.33–0.69]	58	2.76 [2.10–3.55]	36	3.28 [2.31–4.51]	3	2.52 [0.52–7.19]
Dysphoria	6	0.09 [0.03–0.20]	41	1.95 [1.40–2.63]	3	0.27 [0.06–0.80]	13	10.08 [5.95–17.96]
Pruritus	0	0.00 [0.00–0.05]	0	0.00 [0.00–0.14]	3	0.27 [0.06–0.80]	0	0.00 [0.00–2.49]
Decrease in pulse oximetric oxygen saturation	37	0.58 [0.41–0.80]	8	0.58 [0.16–0.75]	6	0.55 [0.20–1.19]	0	0.00 [0.00–2.49]
Ventilation required	1	0.02 [0.00–0.09]	1	0.05 [0.00–0.26]	0	0.00 [0.00–0.27]	0	0.00 [0.00–2.49]
Salivation	0	0.00 [0.00–0.05]	4	0.19 [0.05–0.49]	0	0.00 [0.00–0.27]	0	0.00 [0.00–2.49]
Nausea	23	0.36 [0.23–0.54]	21	1.00 [0.62–1.52]	26	2.37 [1.55–3.45]	15	12.61 [7.23–19.94]
Vomiting	97	1.52 [1.24–1.85]	13	0.62 [0.33–1.05]	53	4.83 [3.64–6.27]	4	3.36 [0.92–8.32]
Hypotension	100	1.57 [1.28–1.91]	0	0.00 [0.00–0.14]	5	0.46 [0.15–1.06]	0	0.00 [0.00–2.49]

The table lists the adverse effects for fentanyl, ketamine, and morphine (9, 10, 13, 15–33, 35, 36, 38, 39, e1–e5, e9). Studies that reported no adverse effects or undesired outcomes (37, 40, e6, e8) were excluded, as were studies that (according to the manufacturer's information) used a dosage designed to produce anesthesia (1 to 2 mg/kg bodyweight) and not analgesia (0.25 to 0.5 mg/kg bodyweight) (11, 33, 34).
For all studies that reported adverse effects, the number of patients, the reported events (n,%), and the 95% confidence interval (95% CI) are given.

eFIGURE



Risk of bias table according to the Cochrane Collaboration's risk of bias tool.
+, Low risk; ?, unclear risk; –, high risk.

eBOX 1

Material and methods

- **Search**

A systematic survey of the literature in the PubMed database was carried out with the following search terms: (prehospital OR pre-hospital OR out-of-hospital OR emergenc*) AND (injury OR injuries OR trauma) AND (analgesia OR analgesic* OR pain management) AND (controlled clinical trial OR randomized controlled trial OR clinical trial OR meta-analysis OR systematic review). Publications over a 10-year period up to February 2016 were searched in order to make the survey as up-to-date as possible. The search was extended by scrutinizing the reference lists of the identified reviews and original articles. Furthermore, Google Scholar und the SpringerLink Library were searched.

- **Inclusion criteria**

Published studies on analgesia without invasive airway management in trauma patients were included. Various analgesics were assessed, alone and in combination, with regard to safe pain reduction. The endpoints were pain reduction or post-treatment Numeric Rating Scale (NRS) score for emergency medical treatment, onset of action, and adverse effects profile, if reported, Only publications in German or English were included. Two authors independently decided on inclusion or exclusion. If they did not agree, they could consult an additional author.

- **Study selection and evaluation**

After exclusion of duplicates, all titles and abstracts were checked by two authors and it was decided whether to access the full text. The numbers of indexed titles and abstracts were documented. Full texts were checked for relevance and included or excluded accordingly. In the case of disagreement, a further author could be consulted. Two reviewers working independently estimated the risk of bias of each study using Cochrane's Revman 5. The risk of bias was rated as low, unclear, or high *(eFigure)*.

- **Data analysis**

Because our review was not limited to the meta-analysis of medications, we included not only randomized controlled trials (RCTs) and cohort studies, but also, for example, observational studies, particularly for research questions concerning routes of administration, safety and monitoring, undertreatment with analgesics, pain assessment, nonpharmacological pain treatment, and undesired events. The corresponding findings were described qualitatively.

- **Statistical method**

The meta-analysis compared the analgesia achieved by two different analgesics, with post-treatment NRS score and pain reduction as endpoints. The results for continuous data were expressed as mean difference with 95% confidence interval. Heterogeneity was tested by means of the chi-square test. Because the power of the test was expected to be low (given the small number of studies with predominantly low case numbers), the level of significance for heterogeneity was set at 0.2. The meta-analysis was performed on pooled endpoints using Review Manager (RevMan, version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Conversions of measures of dispersion or effect size were carried out according to the recommendations of the Cochrane Handbook (http://handbook.cochrane.org). Some controlled studies could not be included in the meta-analysis because the endpoint parameters were not comparable or relevant data were missing (11, 18, 20, 26, 29, 38, 40, e8). Details of the study populations can be found in *eTable 1*.

eBOX 2

Nonpharmacological pain treatment

The management of injuries of the extremities (e.g., repositioning or splinting) should prevent further damage without prolonging the time before the patient reaches the hospital (e54). Repositioning and splinting go a long way towards relieving pain and are intended to prevent soft tissue necrosis, neurovascular damage, and compartment syndrome, as well as maintaining perfusion. In the case of musculoskeletal trauma, the injured limb should be positioned flat and immobilized above and below the site of injury. Regular reassessment of the neurovascular status before and after manipulations is mandatory (e55–e57). However, repositioning should be performed only by properly trained personnel with the patient under adequate analgesia. The principal goal is restoration and maintenance of local perfusion by continuous longitudinal tension and manual correction in a position as close as possible to neutral (e58–e61). If the neurovascular status is unaffected and the user has no experience of repositioning, the injured extremity can be fixed in the position as found and the patient swiftly transported to an appropriate hospital, particularly in life-threatening situations (e55, e60).

eBOX 3

Embryotoxicological evaluation

In pregnant women, not only does the appropriate drug have to be chosen with care but the altered physiological circumstances have to be taken into account. Particular attention should be paid to nausea and vomiting, aspiration, and vena cava compression syndrome in advanced pregnancy. Also during pregnancy, the analgetic potency of paracetamol is often inadequate for severe injuries. The Pharmacovigilance and Information Center for Embryonal Toxicology, Charité—Universitätsmedizin Berlin has stated that opioids do not always constitute a teratogenic risk factor. Single doses in the context of initial emergency care are unproblematic. In the case of extended treatment or repeated doses before delivery, the newborn may present with respiratory depression, withdrawal symptoms, and adjustment disorders.

Neither morphine nor fentanyl has been systematically investigated, but there are no indications that either substance presents a serious risk when used in pregnancy. There are no data on short-term use, particularly in the initial emergency care scenario. Morphine has a half-life of 1.7 to 4.5 h, in newborns up to 13.9 h. The relative dose (child's dose via breast milk per kg divided by mother's dose per kg) ranges from 9.09 to 35% (e62, e63, e64), depending on the route of administration. To date, no abnormal findings have been reported in breast-fed infants. The half-life of fentanyl is ca. 2 to 12 h, depending on how it is given, and up to 17 h in neonates. The relative dose is 2.9 to 5%, depending on the route of administration. Again, no abnormalities have been reported in breast-fed infants. After a single intravenous dose (short half-life) the amount of drug transferred to the child will generally be low, because the swift distribution means that the serum concentration decreases rapidly (e65, e66, e67).

The use of ketamine in breast-feeding women has not been systematically investigated, and there are no data on crossover into breast milk. Because of the fast distribution, no great amount of drug can be expected to be transferred to the infant, particularly with low oral bioavailability (20 to 30%). In pregnancy, ketamine exerts a dose-dependent stimulatory action on the tone and contraction frequency of the uterus (e68, e69), which may lead to undersupply of the fetus. For this reason, in severely injured pregnant women it should be decided case by case whether the risk of hypotension is higher or lower than that of elevated uterine activity. In the initial emergency care scenario, the mother's life takes precedence. Thus ketamine can be used in the initial treatment of severely injured pregnant women, but should if possible be avoided in monotrauma due to the danger of increased uterine activity. Further information can be found (in German) at: www.embryotox.de.