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REVIEWS

AN OVERVIEW OF THE SIDE EFFECTS AND ADVERSE EVENTS IN PREHOSPITAL KETAMINE ANALGESIA FOR TRAUMA: A SYSTEMATIC REVIEW

Lee Barnes, BSc*[1]; Brad Gander, MSc, CCP[1]

Author Affiliations: 1. NHS South East Coast Ambulance Service, Crawley, UK.

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**Corresponding Author*: lee.barnes@secamb.nhs.uk

ABSTRACT

Introduction: In the United Kingdom, pain management is a frequent reason for ambulance use. The benefits of adequate pain management are well documented and have been shown to improve patient outcome and quality of life. Ketamine has been shown to be an effective analgesic in international prehospital settings, yet it does not feature in the scope of practice of all UK paramedics.

The aim of this literature review is to identify the type and incidence of adverse events and side effects when Ketamine analgesia is administered for traumatic pain in the prehospital setting.

Methods: A systematic electronic search was performed to identify literature documenting adverse events and side effects of analgesic ketamine in the prehospital setting. Additionally, manual reference screening and a snowballing technique were used to identify additional relevant material. A thematic analysis of their findings was undertaken to identify the range of side effects reported.

Results: Eight studies, containing a total of 1301 patients, met the inclusion criteria of this review. Four were randomised controlled trials and four were retrospective database reviews. Thematic analysis of reported side effects included cardiovascular, neuropsychological or gastrointestinal effects , and airway or respiratory compromise. Additional effects such as hypertonia, clonus and allergic reactions were reported in three studies.

Conclusion: A broad range of side effects were reported following analgesic ketamine for the treatment of traumatic pain. The incidence of serious adverse events was low. Variation in the dosing regimes, routes of administration, definitions of side effects, observation periods, and inclusion criteria was observed and may limit generalisability. This study provides an overview of the complications that may occur following administration and the requirement to carefully consider how Ketamine is utilized. When administered to appropriately selected and risk-assessed patients, Ketamine may be a useful tool in the paramedic's pain management armory.

INTRODUCTION

In England in 2019, 4.3 million patients were transported to the emergency department by ambulance, with up to 2.8 million of those patients presenting with pain (Whitley et al., 2023). The benefits of pain management are well documented and have been shown to improve patient outcome and quality of life

(Vysokovsky et al., 2021). Despite this, up to 45% of adults suffering from pain in the prehospital setting are inadequately treated (Siriwardena et al., 2019; Ferri et al., 2022). This could be attributed to a lack of available analgesic options, with little to no alternative between paracetamol for mild to moderate pain, or morphine for moderate to severe pain (Lord and Nicholls, 2014; Hodkinson, 2016).

Ketamine is a relatively new analgesic agent in the UK prehospital setting but has been used effectively for many years in international civilian and military arenas (Buckland et al., 2018). Analgesic Ketamine administration currently only features in the scope of practice of appropriately trained specialist paramedics in the UK (Association of Ambulance Chief Executives, 2019). Several comparative studies have reported that Ketamine is as effective, if not better, at relieving traumatic pain when compared to opioids (Kator et al., 2016; Sobieraj et al., 2020). Although the recent publication of the PACKMaN trial reported no significant difference in the analgesic efficacy of Ketamine compared to Morphine (Smyth et al., 2025). Nevertheless, Ketamine appeared to be faster acting and achieved a higher rate of significant improvements in pain after administration than Morphine. Despite this, its duration of action was shorter than Morphine and both groups of patients still experienced moderate or severe pain on arrival at hospital, thus indicating a need to continue to explore further analgesia strategies for prehospital clinicians.

Ketamine acts as an N-methyl-D aspirate (NMDA) antagonist. It decreases the frequency and mean opening time of ion channels by binding to the phencyclidine site on postsynaptic channels (Li and Vlisides, 2016). At lower concentrations ketamine prominently blocks closed channels giving an analgesic effect. At higher concentrations of ketamine, both open and closed ion channels are blocked giving anesthetic effects (Zorumski, Izumi, and Mennerick, 2016). NMDA receptors can be found in spinal, thalamic, limbic, and cortical regions of the brain. The drug is often referred to as a dissociative analgesic because it disrupts sensory input to higher centers of the central nervous system, impacting pain and emotional reactions along with memory (Best, Bodenschatz and Beran, 2014). Ketamine has a rapid transfer across the blood-brain barrier due to its water and lipid solubility but low protein binding ability. This allows the drug to be administered via various routes including intravenous (IV), intramuscular (IM) and intranasal (IN) (Gao, Rejaei, and Liu, 2016). The broad therapeutic range makes it versatile in both anesthesia and pain management (Rosenbaum et al., 2024).

Common side effects include anxiety, abnormal behavior, confusion, diplopia, nystagmus, nausea and vomiting, increased muscle tone, tonic clonic movements, and sleep disorders (Joint Formulary Committee, 2024a). Emergence phenomena - a term grouping anxiety, feeling of unease, hallucinations, floating sensation, vivid dreams, and delirium may also occur; however this is more common in higher doses of ketamine (Gales and Maxwell, 2018). Other uncommon side effects include arrythmias, hypotension and respiratory disorders (Joint Formulary Committee, 2024a). Several of these side effects have led to concerns over the routine use of Ketamine as an analgesic medication (Vadivelu et al., 2016; Gales and Maxwell, 2018).

To improve the understanding of how Ketamine analgesia may be considered for wider adoption within prehospital care, the safety profile should be explored. This literature

review aims to provide an overview of the range of side effects that arise from the prehospital administration of analgesic ketamine for the treatment of pain in trauma.

METHODS

Search Strategy

An electronic database search of the Cumulative Index to Nursing and Allied Health (CINAHL) Ultimate, PubMed, and Excerpta Medica (EMBASE) databases was performed. CINAHL Ultimate was accessed using the EBSCOhost platform and EMBASE searched via the Ovid platform. This review was structured using the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines (Page et al., 2021)

Search Terms

The search terms were established by identifying relevant keywords in the titles, abstracts, and full texts of articles already known to be eligible for inclusion. These terms were later enhanced by adding synonyms. Boolean operators and truncation were used to link search terms. An accuracy check was performed on the chosen databases to ensure that already known articles featured in the results. The full search strategy used can be seen in Table 1. The literature search was performed on the three documented databases between 23/04/2025 and 15/05/2025.

Search	Field	Search term
S1	Title / abstract	Ketamine AND Prehospital OR Pre-hospital OR out of hospital OR Paramedic* OR EMS OR emergency medical service* OR ambulance*
S2	Title / abstract	Analgesia OR acute pain OR pain management OR pain relief OR analgesic* OR traumatic pain AND Adverse event* OR side effect*
S3	S1 AND S2	

Table 1: Search strategy. (* truncation, OR AND Boolean operators)

When the literature search identified literature reviews, the original references were identified and assessed for inclusion. Additionally, a snowball sampling technique was used to identify other relevant material not obtained through the initial database searches. This process involved looking for further relevant literature from additional sources, such as suggested articles, similar authors, and manually reviewing identified article reference lists (Aveyard, 2019). The ProQuest (2023) platform was also used to search for PhD and MSc theses relevant to the research question.

Table 2 summarises the inclusion and exclusion criteria. Only studies using ketamine specifically for analgesia were included. Studies using only sedative or anesthetic doses were excluded to maintain relevance to the subject. Children were excluded due to differing pharmacodynamics and immature physiology. Non-English literature was excluded due to resource constraints. Grey literature was included to reduce publication and outcome bias and help identify adverse events not reported in commercially published stud-

Inclusion	Exclusion
• English language only • Prehospital setting • Civilian population • Analgesic Ketamine use • Adults • Published 01/01/2014 onwards	• No full text available • In-hospital studies • Military studies • Conference abstracts, letters • Ketamine used for another indication e.g. sedation or anaesthesia • Paediatrics

Table 2: Summary of inclusion and exclusion criteria.

ies. To ensure up to date evidence and reflect current practice, only studies published from 1st January 2014 onwards were included. Title and abstract screening, and full-text review was undertaken by both authors. Discrepancies were resolved via discussion, with a third reviewer available if a consensus on inclusion could not be reached.

Following the identification of articles eligible for final inclusion and data extraction, a thematic analysis of their respective findings was undertaken.

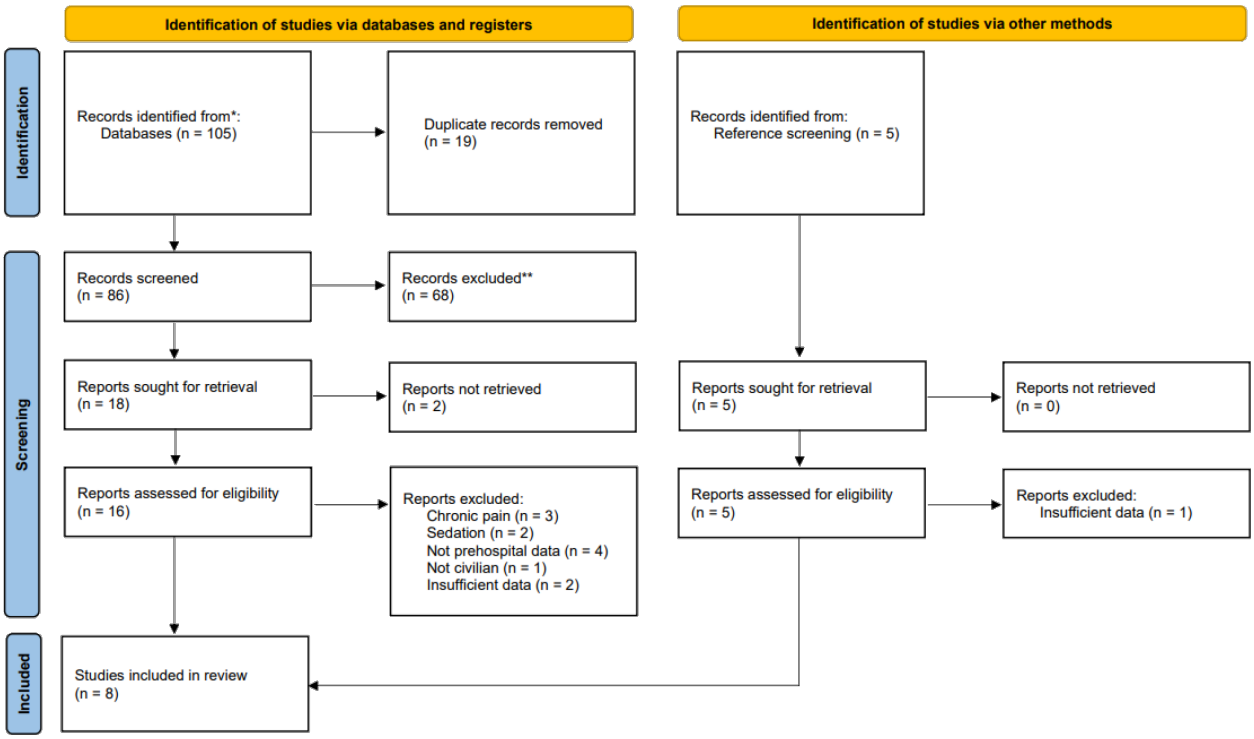

Figure 1: PRISMA diagram.

RESULTS

Gastrointestinal Effects

Nausea or vomiting was the most frequently documented side effect and featured in seven of the included papers (Tran et al., 2014; Cowley et al., 2018; Vanolli et al., 2020; Andolfatto et al., 2020; Le Cornec et al., 2023; Smyth et al., 2025). Some studies differentiated between the sensation of nausea and episodes of vomiting whilst others combined them when reporting side effects. The PACKMaN trial recorded 34 (16%) patients reporting nausea after receiving Ketamine and vomiting in 16 (7%) (Smyth et al., 2025). The multi-center KETAMORPH study of 251 patients Le Cornec et al. (2023) recorded events of nausea and vomiting separately. In the ketamine cohort of 120 patients, nausea was the third highest adverse event and vomiting the fourth, at 6.6 % and 5% respectively. Similarly, eight of the 169 (4.73%) patients who received Ketamine in a cluster RCT by Tran et al. (2014) experienced nausea and vomiting. Vanolli et al. (2020) reported nausea and vomiting as a combined side effect and found it to be present in 10% of their study population. Andolfatto et al. (2019) evaluated intranasal Ketamine administration and found 68% of patients were reported to experience at least one side effect or adverse

event, with nausea the third most frequent, contributing to 17% of all side effects. Vomiting was not present in any patients within this study.

Airway or Respiratory Compromise

A range of airway or respiratory sequelae were reported. Vanolli et al. (2020) reported the development of bradypnea, respiratory depression, apnea or desaturation in 26% (n = 10), 13% (n = 5), 10 (n = 4) and 26% (n = 10) of patients respectively. Additionally, one patient developed airway obstruction, and one developed laryngospasm. Cowley et al. (2018) and Zietlow et al. (2019) also reported respiratory depression within their cohorts, in three (0.6%) and eight (5%) patients. Smyth et al. (2025) found 15 (7%) of patients desaturated, however just one required ventilatory support. Excess salivation was documented in two studies (Tran et al., 2014; Vanolli et al., 2020) with a wide variation in incidence. Vanolli et al. (2020) reported 41% (n = 16) of patients experienced hypersalivation following ketamine administration whereas Tran et al. (2014) found just three (1.7%) of 169 subjects receiving ketamine experienced excess salivation.

Cardiovascular Effects

An increase in systolic blood pressure was reported in six studies (Tran et al., 2014; Cowley et al., 2018; Zietlow et al., 2019; Vanolli et al., 2020; Le Cornec et al., 2023; Smyth et al., 2025). Zietlow et al. (2019) found seven (4.4%) hypotensive patients became normotensive following ketamine administration and both Le Cornec et al. (2023), and Tran et al. (2014), reported a slight increase in mean systolic blood pressure when compared to pre-administration recordings. Cowley et al. (2018) also observed 6 cases (1.37%) of patients having a transient blood pressure increase. Smyth et al. (2025) recorded 17 (8%) cases of hypertension and 6 (3%) of hypotension following Ketamine administration. Conversely, Bronsky et al. (2018) recorded a mean systolic blood pressure decrease of 4.2mmHg following analgesic ketamine administration. Both Vanolli et al. (2020) and Smyth et al. (2025) reported occurrences of tachycardia or arrhythmia in 15 (38%) and 3 (1%) patients within their study populations.

Neuropsychological Effects

Neuropsychological effects were reported in six studies (Tran et al., 2014; Cowley et al., 2018; Andolfatto et al., 2020; Vanolli et al., 2020; Le Cornec et al., 2023; Smyth et al., 2025). The definition varies between studies within this review with some not documenting their defining symptoms of EP, whilst others recorded the symptoms individually. Tran et al. (2014) reported 19 of 169 patients as becoming agitated following Ketamine administration. Le Cornec et al. (2023) recorded EP as a group of symptoms including dysphoria, agitation or hallucinations. EP was the most common adverse event in the ketamine group, with 19% of patients experiencing symptoms. Visual disturbance was recorded as a separate adverse event. Cowley et al. (2018) reported mild EP in two (0.45%) of the 449 patients in their study, however there was no indication of what symptoms were considered mild EP. Vanolli et al. (2020) defined EP as vivid visual hallucinations or dreaming during the recovery phase and found hallucinations (72%) and agitation (49%) were the two most common side effects recorded. Interestingly, whilst hallucinations were frequently encountered, it was reported these were mostly a positive patient experience. Andolfatto et al. (2019) recorded individual symptoms which are considered EP. Of the 37 subjects reporting adverse events, 2% were recorded as experiencing hallucinations

whilst another 2% reported a change in hearing. 27% of patients experienced the feeling of unreality and a further 20% reported dizziness. 5% recorded a mood change. This was the only study in present literature review which administered ketamine intranasally. Finally, Smyth et al. (2025) documented sedation 23 (11%), excitatory movements 2 (1%), and adverse behavioral reactions 22 (10%). Adverse behavioral reactions, which were not specifically defined, were the most common occurring adverse event in the ketamine cohort.

Other

Other uncategorised side effects or adverse events included hypertonia (13%), clonus (5%) and hiccups (5%), and all featured within the study by Vanolli et al (2020). Both Vanolli et al. (2020) and Smyth et al. (2025) reported allergic reactions to Ketamine administration in 2 (5%) and 1 (<1%) patients.

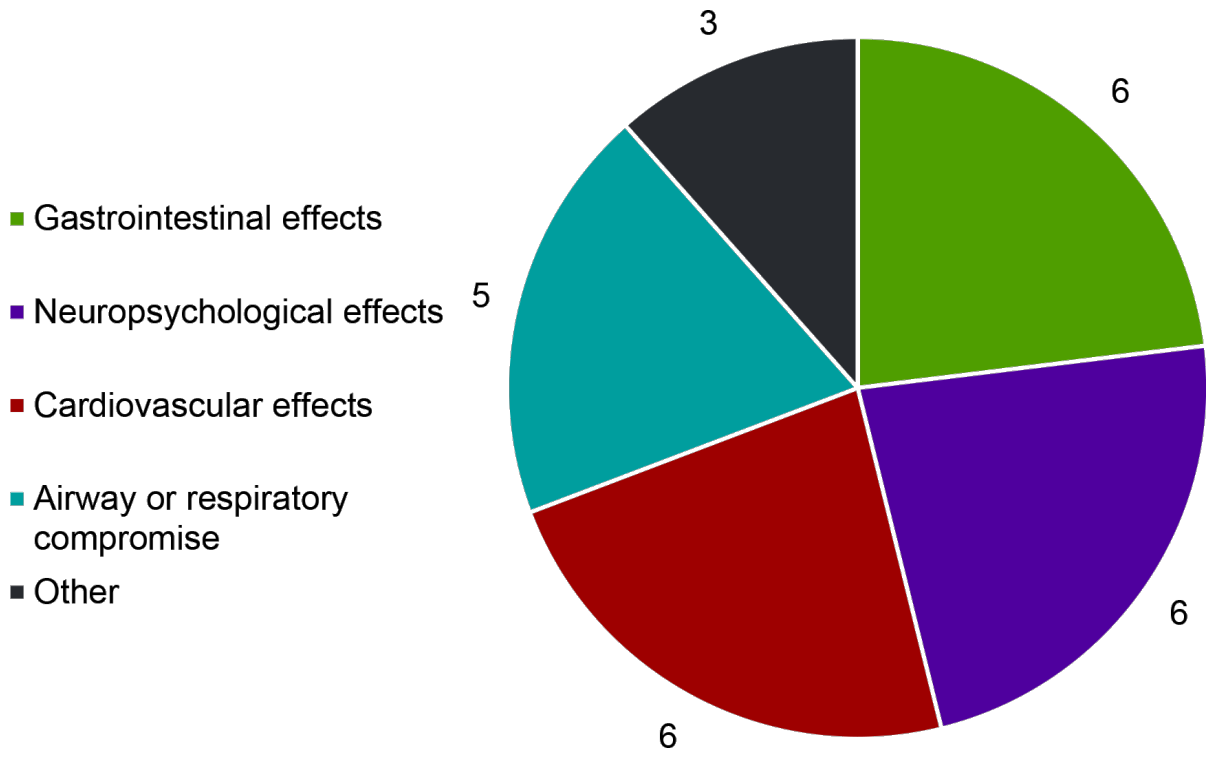

Figure 2: Number of studies reporting side effects.

Theme	Gastrointestinal effects	Airway or respiratory compromise	Cardiovascular effects	Neuropsychological effects	Other
Side effects reported	• Nausea • Vomiting • Nausea and vomiting (combined)	• Bradypnea • Desaturation • Respiratory depression • Apnea • Airway obstruction • Laryngospasm • Need for advanced airway management or ventilation • Hypersalivation	• Tachycardia • Hypertension • Transient increase in blood pressure • Hypotension • Arrhythmia	• Hallucinations • Agitation • Anxiety • Emergence reaction • Stereotypy • Visual disturbance • Mood change • Hearing disturbance • Fatigue • Distress • Excitatory movements • Sedation	• Hypertonia • Clonus • Hiccups • Dizziness • Anaphylaxis • Allergic reaction

Table 3: Thematic Analysis.

DISCUSSION

The aim of this literature review was to identify the frequency and nature of side effects and adverse events reported when Ketamine is administered as an analgesic for traumatic pain treatment in prehospital settings. Neuropsychological, cardiovascular and gastrointestinal effects were all frequently reported. Additionally, instances of airway or respiratory compromise was also described in four of the eight included studies. Whilst some of these effects can be life threatening, the frequency of serious adverse events reported across all studies was low. When combining the populations of all studies within this review, side effects following Ketamine administration were recorded in 19% of the population, with most described as clinically insignificant and not requiring intervention.

The difference in analgesic duration seen between Ketamine and other medications has often necessitated treatment with multi-modal analgesia. However, coadministration of ketamine with other analgesics was associated with increased adverse events across several studies (Bronsky et al., 2018; Tran et al., 2014). A systematic review by Yousefifard et al. (2020) found a 33.4% increase in adverse effects when ketamine was combined with morphine. Similarly, Sandberg et al. (2020) reported more adverse events with ketamine-opioid combinations than with ketamine alone. Bansal et al. (2020) observed heightened neuropsychological effects with ketamine-morphine coadministration. Despite the increased side effect profile, Ketamine may have an opioid-sparing effect (Cohen et al., 2022; Guo et al., 2023), and thus analgesic strategies involving co-administration of other medications may be cautiously considered.

Airway or respiratory compromise, including apnea and the requirement for ventilatory support, were reported in four studies. Reassuringly, the overall incidence within these was low, however, this provides an important reminder of the need for pre-administration preparation and risk assessment. Excessive salivation, which may increase the risk of airway compromise, was also reported as a complication within two studies. Ketamine-induced laryngospasm is a known rare complication following administration and has been well described in pediatric populations (Green et al., 2010). This complication may be managed with prompt airway management, positioning and positive pressure ventilation (Butler, 2015). Moreover, gastrointestinal effects, including the onset of vomiting, were also frequently reported. These factors reinforce the requirement for clinicians to ensure airway management equipment is readily available and patients can be accessed and positioned for airway management if required.

When compared to opioid analgesia, multiple studies found that patients receiving ketamine experienced fewer instances of nausea and vomiting (Tran et al., 2014; Le Cornec et al., 2023; Smyth et al., 2025). The significance of these findings is particularly relevant in trauma care. Vomiting can lead to airway compromise in immobilised or unconscious trauma patients, or those positioned supine for spinal precautions (Purvis, Carlin, and Driscoll, 2017). Additionally, vomiting is known to increase intracranial pressure (ICP), potentially posing risks for patients with head injuries (Zamani et al., 2015).

Ketamine may hold an advantage over opiate medications in patients with hemodynamic instability. This review found multiple studies reporting small increases in systolic blood pressure following administration. The RCT of Ketamine and Morphine in trauma

patients by Tran et al. (2014) found Ketamine beneficial in a subgroup of patients with systolic BP below 80 mmHg. This result aligns with an experimental study by Watso et al. (2023), where low-dose Ketamine increased BP and provided superior analgesia compared to Morphine in simulated hypovolemic conditions. These findings continue to support the role of Ketamine as an analgesic option for hemodynamically unstable patients, or where avoiding hypotension is important, such as in the setting of traumatic brain injury.

A frequent concern over the use of ketamine often relates to the incidence and management of associated EP, including hallucinations and agitation (Martinez et al., 2015; Gales and Maxwell, 2018). These may present challenges in treatment in the presence of prolonged or complex extrications (Tran et al. 2014), such as those carried out from remote locations by Hazardous Area Response Teams [HART] in the UK. An audit of ketamine administered by HART Paramedics by Metcalf et al. (2018) identified no incidents of severe negative psychological symptoms. Anxiety was observed following administration on a few occasions and was managed non-pharmacologically to good effect. Reducing stimuli and creating a calm environment prior to administration can decrease the likelihood of such reactions (Green and Li, 2000). This can be difficult to achieve in the prehospital setting, and efforts should be made to ensure the surrounding environment is controlled wherever possible. Simulation should involve all clinicians and agencies expected to be in attendance at such cases to maintain a shared awareness. Furthermore, the development and use of pre-administration checklists, incorporating scene and logistical factors, should be considered as an additional means of enhancing safety.

The co-administration of Ketamine with benzodiazepines has been shown to mitigate neuropsychological side effects (Perumal et al., 2015; Gonsalvez et al., 2018; Vanolli et al., 2020). Services adopting Ketamine into their drugs formulary should consider the availability and use of benzodiazepines, such as Midazolam, in these circumstances. It is recognized that this approach carries a risk of iatrogenic over-sedation and therefore should be reserved for use by clinicians with experience and capability in managing sedated patients.

LIMITATIONS

This systematic review has several limitations. Firstly, there was heterogeneity in the drug dosing regime, route of administration and definition of adverse events in the evaluated literature. Secondly, there was variability in how adverse events and side effects were recorded, with many being documented as a secondary outcome or having no formal method for recording them within the study design. This may have resulted in detection bias or misrepresentation of the data where some findings have been unreported. Thirdly, inclusion criteria varied throughout individual studies with some studies excluding certain injury groups, such as head injuries and dislocations. Fourth, although no studies with a primary focus on pediatric analgesia were included, a small number of articles contained a small amount of pediatric data within their findings. Finally, adverse events and side effects were largely recorded until arrival at hospital, therefore could have missed adverse events occurring after this timepoint.

Reference	Setting	Methodology	# Patients	Results	Limitations
Tran, K., P. et al (2014).	Vietnam	• Cluster RCT-regional sector, divided into 2 sectors with alternating treatment monthly. • Adverse events registered throughout evacuation until arrival at ED. • Ketamine dose: 0.2-0.3mg/kg slow IV. • Blood pressure, respiratory rate was recorded prior to analgesic administration and on arrival at hospital	• 169 • Sub analysis of haemorrhage cases with systolic blood pressure less that 90mmHg: 32 in ketamine group • Sub analysis of 28 ketamine patients with traumatic head injury	• Nausea and vomiting: 5% • Agitation: 11% • Excessive salivation: 1.8% • No significant impact on respiratory rate. • All patients maintained airway responsiveness and O2 sats. • Mean blood pressure was 9.3mm higher post Ketamine in the haemorrhage subgroup. • 27/ 28 ketamine patients had the same conscious level on arrival at ED in the head trauma subgroup.	• No blinding, possible observer bias • Small subset analyses • Study based in a previous war zone with a large number of trauma injuries from undetected land mines. • Study included 24 children • Some patients in very rural, low- resource locations with initial evacuation by bicycle or motorbike. Could affect adverse events.

Table 4: Characteristics of included studies.

CONCLUSION

This literature review has identified a broad range of side effects reported following analgesic ketamine for the treatment of traumatic pain. The frequency of adverse events and side effects was low whilst ranging from short-lasting and clinically insignificant neuropsychological effects to airway compromise. The relative cardiovascular stability of this medication was frequently reported, with multiple studies reporting moderate increases in blood pressure following administration. This study provides an important overview of the complications that may occur following administration, and the requirement to carefully consider how Ketamine is utilized within an analgesic strategy. When administered to appropriately selected and risk-assessed patients, Ketamine may be a useful tool in the paramedic's pain management armory.

The majority of studies identified compared Ketamine with Morphine. Whilst this provides a direct comparison to a medication currently widely used in prehospital care, newer analgesic options are now becoming available, such as inhaled Methoxyflurane. Further evaluation and comparison of the side effects of alternative medications may help to evaluate options and guide wider implementation. Further research should also explore the pre-administration characteristics of patients who experience complications to identify those at risk. Additionally, the long-term effects of adverse events following Ketamine administration should be studied.

Reference	Setting	Methodology	# Patients	Results	Limitations
Bronsky et al (2018)	United States	• 2-year retrospective review • Ketamine: 0.3mg/kg administered IV every 20 minutes. Max 3 doses. • Adverse events recorded from scene arrival through to emergency department discharge.	• 79	• Slight reduction in BP following administration • No significant AE recorded in patients receiving Ketamine	• Retrospective • Increased BP, intracranial pressure excluded from study at discretion of paramedic. • Adverse events are a secondary outcome. • Only 'significant' adverse events were recorded. • Dysphoria or altered mental state not recorded.
Cowley, A. et al. (2018).	United Kingdom	• 4-year retrospective review • Dosing IV: 0.1mg/kg titrated. Max 0.5mg/kg over 30 minutes intervals. • (40-70kg: 5mg aliquots, <70kg: 10mg aliquots) • All adverse events recorded whilst patient in care of critical care paramedic.	• 449	• 16 AE recorded 3.6%. • BP increase: 6 • Respiratory depression: 3 • Vomiting: 3 • Mild emergence phenomena: 2 • Distressed: 1 • Accidental overdose: 1 • All recorded AE caused no harm to patients.	• Retrospective • Study included some Ketamine use for sedation and did not separate AE, although mean dosing was the same for both groups. • Study included some children over 12 years old • Antiemetic use or co-administration with other analgesics not recorded in study. • AE were not recorded by clinicians in a formal way. Free text box used. Therefore, open to reporting bias. • Some AE may have been unreported due to lack of recall by clinician.
Andolfatto et al (2019)	Canada	• Single-centre RCT • Ketamine (0.75mg/kg) administered intranasal. Half dose to each nostril alongside the usual use of nitrous oxide. • Patients were assessed every 15 minutes for AE until hospital arrival. • AE considered serious if intervention was required or higher-level clinicians were called to scene.	• 60 receiving Ketamine	• 37 (62%) of patients in the Ketamine group experienced AE. • Some patients experienced more than 1 AE. Total of 52 recorded. • Feeling of unreality: 27%, • Dizziness: 20% • Nausea: 7% • Fatigue: 10% • General discomfort: 5% • Mood change: 5 % • Hallucinations: 2% • Hearing change: 2% • No significant change in vital signs • All AE considered minor, with no intervention	• Single centre research • Small sample size may not allow incidence of rare AE. • Component of unblinding. 63% of paramedics correctly identified Ketamine. • Co administration alongside Nitrous oxide. Difficult to differentiate between AE
Zietlow et al (2019)	United States	• 2-year retrospective review • Dosing IV or IO: 0.5-2mg/kg over 1-2 minutes followed by 0.25mg/kg • every 5-10 minutes. • IM dosing: 2-5mg/kg repeated as needed.	• 158 patients	• No significant difference in HR, BP, RR, or SpO2 pre or post administration of Ketamine • No emergence episodes encountered. • 5% (n=3) had either decreased RR or Sp02 requiring ventilation. • All recovered in less than 30 seconds	• Single centre study • Retrospective • 3.2% (n=5) of patients were <18years of age • Study included Ketamine administration for sedation as well as analgesia all recorded in the same group.

Table 4 (continued): Characteristics of included studies.

Reference	Setting	Methodology	# Patients	Results	Limitations
Vanolli K., et al (2020)	Switzerland	• Retrospective survey of physician's experience in the use of Ketamine.	• 39	• Most common AE witnessed was visual hallucinations. • Hallucinations: 78% • Agitation: 49% • Hypersalivation: 41% • Tachycardia: 38% • Bradypnea: 26% • Desaturation:26% • Emergence: 23% • Respiratory depression: 13% • Nausea & vomiting: 10% • Airway obstruction: 3% • Concluded that AE was seldom reported, and all participating physicians considered Ketamine safe.	• Retrospective • Single centre, small sample size. • Survey self-reported. Results subjective to individual physician with no way of verifying answers to study • Unable to establish Ketamine dose administered. • Survey did not ask if AE occurred with Ketamine alone or when co administered. • Midazolam administered by 36% of those surveyed to avoid hallucination.
Le Cornec et al (2023)	France	• Multi-centre RCT • Ketamine dose: 20mg over 2 minutes followed by 10mg every 5 minutes. • Adverse events documented at 30-minute intervals until arrival at ED.	• 128 receiving Ketamine	• After 30 minutes of administration the ketamine (K) group reported 49/120 (40.8%) patients had adverse events. • Nausea: 6.7%, • Vomiting: 6%, • Decreased consciousness: 8%, • Visual disturbance: 17.5% • Emergence phenomenon: 20% • Hypertension: 4.2% • No patients experienced severe adverse events or required intervention to manage adverse events.	• Single blinded, crew not blind to medication. • Non-Anglo-American EMS system. • Hypotension not reported. • Follow up period only prehospital so may miss later complications. • Head injuries, unstable patients, fractures needing relocation excluded from study. • Potential for publication bias in not reporting hypotension. • Some conflict of interest recorded for 2 authors. • No mention of other medications such as antiemetics or haemodynamics.
Smyth et al., (2025)	United Kingdom	• Multi-centre RCT across two regional ambulance services • Ketamine dose: 15mg over 5 mins, with second 15mg if pain continued 5 mins post initial dose	• 219	• Serious AE: 4 (2%) • Experienced AE: 106 (48%) • Vomiting: 16 (7%) Advanced airway management: 1 (<1%) • Desaturation: 15 (7%) • Need for ventilatory support: 1 (<1%) • Arrhythmia: 3 (1%) • Hypotension: 6 (3%) • Hypertension: 17 (8%) • Sedation: 23 (11%) • Excitatory movements: 2 (1%) • Adverse behavioural reactions: 22 (10%) • Allergic reaction: 1 (<1%) • Nausea: 34 (16%) • Naloxone administered: 2 (1%) • Midazolam administered: 7 (3%)	• Potential for unblinding due to predictable side effects of Ketamine
AE- adverse events, BP- blood pressure, ED – emergency department, HR- heart rate, IV- intravenous, IO- intraosseous, RCT – randomised controlled trial, RR-respiratory rate					

Table 4 (continued): Characteristics of included studies.

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