Chapter

The Role of Ketamine in Trauma

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> *"I would especially commend the physician who, in acute diseases, by which the bulk of mankind are cutoff, conducts the treatment better than others."*
>
> *Hippocrates*

Abstract

Early and effective pain control in trauma patients improves outcomes and limits disability, but analgesia is often missed in the unstable patient, or hemodynamically depressing medications are avoided for fear of losing stability. This chapter outlines the role of ketamine in managing traumatic emergencies in both out-of-hospital and hospital environment, and beyond. Low-dose ketamine also called a sub-dissociative dose is safe, efficient and effective analgesic that can be considered for trauma patients, pediatric or adults, as an alternative to opioids or in combination with opioids for on additive or synergistic effect, with minimal impact on hemodynamic stability. Ketamine at higher doses is also an excellent drug for induction of anesthesia in rapid sequence induction (RSI), post-intubation sedation maintenance or procedural sedation in the trauma patient. Also, can be used for acute agitation and excited delirium. In this chapter, we are describing this drug focusing on a deeper understanding of the safety and efficacy of this agent and, if supported, to encourage physicians to consider ketamine for pain control in trauma and beyond. Also, we are presenting the current literature surrounding ketamine's evidences in the trauma condition to establish its utility and profile of safety for these patients.

Keywords: ketamine, analgesia, anesthesia, shock, trauma

1. Introduction

Trauma is one of the leading causes of death worldwide [1] with 5.8 million lives lost each year as a direct result of injury [2], and it is a major economic burden to society in both Europe and United States [1, 3]. Trauma management is demanding for clinicians, often a life-threatening and most of the time a painful condition. Early and effective pain control in trauma is essential not only for acute status control, but has also been associated with a lesser incidence of chronic pain, as well as a shorter period of recovery [1, 2]. Many factors influence the selection of analgesics, and we have available a generous options of pain killers, but in reality, an adequate pain control is often difficult to achieve. According to many reports, trauma patient analgesia is remaining an undermanaged condition [3–5]. Opioid analgesics are often appropriate first-line pain killers for acute pain but come with hemodynamic and respiratory depression, as well as concerns about the addiction risks. Ketamine

is a dissociative and analgesic drug that can be used alone or in combination with other analgesic medication. The terms low-dose, analgesic, pain control and sub-dissociative dose can be used interchangeably.

2. Pharmacologic properties

Ketamine is an agent with attractive pharmacological and pharmacokinetic characteristics. Ketamine is a potent dissociative agent with an evolving role in the management of both pediatric and adult trauma patients due to its sedative, analgesic and anesthetic properties, beside its sympathomimetic effect. Ketamine is a derivate of phenylcyclidine with a hallucinogenic property, beside its primarily antagonist activity on N-methyl-D-aspartate receptors although it also acts on opioid (μ), and muscarinic receptors, and sodium channels. Its action is targeting the central nervous system *via* the thalamo-cortical tracts. This drug inhibits presynaptic reuptake of catecholamines, with an onset time of 30 s. For being highly lipophilic, ketamine has a distribution half-life of 10 min, for a short duration of action after an initial bolus. Ketamine is the least protein bound from the i.v. anesthetics (25%) suffering a liver metabolization, generating active compounds (norketamine and hydroxynorketamine), and is eliminated mainly in the urine with an elimination half-life of 1.5–3 h.

The sedative and analgesic effects of this drug begin to wear off in 10–15 min.

For many years, ketamine was considered to be a harmful drug to use for airway management or in multiple trauma conditions, especially where a traumatic brain injury component was involved, due to fears of increasing intracranial pressure (ICP) [6]. But recent studies show which can be a real helpful drug, in certain conditions like the combative trauma patient who needs airway management or other situations like improving pain control or anesthesia induction in a hemodynamically unstable trauma patient [6]. Recent experiences show that do not raise intracranial pressure as was once assumed and does raise blood pressure improving cardiovascular stability, unlike most sedating drugs [6]. Also, a drug should be considered extremely helpful for acute invasive procedures that need to be performed under sedation [7, 8], offering a great advantage of analgesia and respiratory stability at the same time. Ketamine is known an optimal drug in various emergency settings. Also, away from the emergency room, studies have been performed to assess the safety and efficacy of ketamine for trauma patients, showing that ICU patients with a sub-dissociative ketamine infusion needed fewer opioid analgesics and had a better hemodynamic stability [9]. In this chapter, we present the current literature surrounding the safety and efficacy of ketamine in the trauma condition to establish its utility for these patients.

3. Systemic effects

Ketamine has minimal effects on the respiratory drive and protective reflexes of the protective airway reflexes are maintained, thus allowing to keep spontaneous ventilation. However, administering high doses that would be used for anesthetic effect there is a risk of respiratory depression [5, 9]. Ketamine is also responsible for bronchodilation, increased salivation, pulmonary vasodilation and increased cardiac output, through increasing mean arterial pressure and heart rate. Its profile on hemodynamics is favorable, making this agent a unique drug, a considerable option especially in approaching a shocked trauma patient. Also, its depressant effects on the gastrointestinal system are very minimal. Ketamine could have an antiplatelets

action by inhibiting phosphoinositide breakdown and mobilization of Ca^{2+} in those platelets stimulated by collagen [10].

4. Cerebral effects

The physiological mechanisms lead to neuroprotection, vasodilation and increased cerebral blood flow.

In particular, new clinical data and case studies support a therapeutic effect of ketamine in suppression of spreading depolarization (SD) following traumatic brain injury (TBI). This is fundamental as SD has been suggested as an important mechanism for secondary brain injury and delayed cerebral ischemia [10].

Ketamine has been recently discovered to be a "glutamate modulator." Its action is exerted at two levels: (a) presynaptic, inhibiting the release of glutamate and (b) post-synaptic, performing as a competitive blocker of NMDA receptors, also inhibiting calcium entrance into cells and the production of nitric oxide and oxygen-free radicals, modulating glucose metabolism and the generation of mitochondrial ATP, and also, inhibiting the apoptotic phenomenon. Furthermore, it inhibits the production and release of cytokines not only by the microglia but also by interleukin-8, tumor necrosis factor, Ca++, K+, oxygen-free radicals, adenosine triphosphate.

The cerebral metabolic rate of oxygen is increased, although in a heterogeneous action, more in insula and the frontal lobes, while decreasing in the temporal lobes, pons and cerebellum. Cerebral blood flow does not follow the same pattern. Probably, a dose-dependent uncoupling mechanism is implied. Intracranial pressure remains unaffected or even sometime decreased, being associated with increases in cerebral perfusion pressure.

Cerebral oxygenation remains unchanged. Moreover, ketamine does not compromise the autoregulatory mechanisms or the carbon dioxide (CO_2) reactivity of the cerebral vasculature [10, 11].

It is important to promote recent findings that NMDA receptors have different protein subpopulations in their composition, capable of triggering various pathways that stimulate proliferation, synaptogenesis or neuronal regeneration, depending on which protein is activated [12].

Extensive studies have shown that after stroke or traumatic brain injury, NMDA receptors remain hypofunctional, which could be responsible for cognitive impairments. Activating and stimulating these receptors by alternative pathways (glycine/serine) is a promising strategy [12].

5. Summary of evidence

5.1 What is the efficacy of ketamine for analgesia?

There are convincing evidences demonstrating the efficacy and safety of ketamine as an analgesic for trauma patients.

In a very recent meta-analysis published in 2020, where controlled human studies were included, Mahmoud Yousefifard performed extensive search conducted in electronic databases gathering data to the end of 2018. The efficacy and side effects of ketamine administration in prehospital pain management were compared with those of opioid analgesics. Data from seven articles were included in the present meta-analysis. Ketamine administration was not much more effective than administrating morphine or fentanyl in prehospital pain management of trauma patients.

However, co-administration of ketamine + morphine was considerably more effective than ketamine alone, in alleviating pain in prehospital settings. Finally, it was concluded that ketamine alone had less side effects than morphine alone. However, co-administration of ketamine + morphine increases the risk of side effects compared with when morphine is prescribed alone [13].

In 2020, Gaël de Rocquigny published a systemic review in regarding the use of ketamine for prehospital pain control on the battlefield [14]. This included a database searching for studies on ketamine use in combating prehospital settings, at the point of injury or during evacuation. Eight studies were included with 2029 casualties receiving ketamine. Ketamine use increased from 3.9% during the period preceding its addition to the Tactical Combat Casualty Care guidelines in 2012 to 19.8% after this guidelines release. It was the analgesic of choice (up to 52% of casualties) in one of the studies. Ketamine has been preferred to be given during tactical medical evacuation when no analgesic was administered at the point of injury. Pain score decreased from moderate or severe to mild or none, often after only one dose. In one study, ketamine administration during tactical evacuation was associated with increased systolic blood pressure as opposed to those situations when morphine was given. Incoherent speech, hallucinations and extremity movements were the most seen adverse events reported. However, all studies tend to strengthen the belief in the efficacy and safety of ketamine when given at 50-mg to 100-mg intravenous for prehospital analgesia in combat casualties. So, from these army studies, we can easily extrapolate these findings and apply to the civil medicine.

In 2018, Mary K. Walters published a study on the ketamine as an analgesic adjuvant in a trauma patient with rib fractures. This was a retrospective study, based on case-control chart review assessing ICU adult patients with a diagnosis of ≥1 rib fracture and an Injury Severity Score > 15. Patients received standard-of-care analgesia with the physician's choice medication with or without ketamine as a continuous, fixed, intravenous infusion at 0.1 mg/kg/h. The authors pointed out that low-dose ketamine appears to be a safe and effective adjuvant option to reduce pain and decrease opioid use in rib fracture [15].

In 2019, Thomas Carver published a prospective, randomized, double-blind placebo-controlled trial on ketamine infusion for pain control in multiple rib fractures. This level II of evidence study included adult patients with three or more rib fractures admitted to a Level I Trauma Center. Other exclusion criteria were Glasgow Coma Scale score less than 13 and chronic opiate use. The experimental arm received low-dose ketamine (LDK) at 2.5 μg/kg/min, while the placebo cohort received an equivalent rate of 0.9% normal saline. The primary outcome was reduction in numeric pain score (NPS) during the first 24 h. From the secondary outcomes studied, oral morphine equivalent (OME) utilization was included. The average Injury Severity Score (ISS) was 14. Low-dose ketamine failed to decrease NPS or OME within the overall cohort, but a decrease in OME was observed among patients with an ISS greater than 15. This study authors also conclude that confirmatory studies are necessary to determine whether LDK is a useful adjunct among severely injured patients [16].

In 2017, Babak Mahshidfar conducted a randomized double-blinded clinical trial to compare low-dose ketamine (LDK) with morphine for pain relief in trauma patients. He enrolled 300 trauma patients from the emergency room of two university hospitals. The patients were randomly divided into two groups. The first group was administered i.v. 0.2 mg/kg of ketamine, while the second group received 0.1 mg/kg of i.v. morphine. The results of this study suggest that LDK, at a dose of 0.2 mg/kg, in the earlier minutes leads to significant reduction of pain when compared with that of intravenous morphine. It also created fewer complications than morphine [17].

In 2014, Joshua P Miller performed an institutional review board-approved, randomized, prospective, double-blinded trial at a tertiary, Level 1 Trauma Center. The

study was focused on low-dose ketamine vs. morphine for acute pain control in the ED. They enrolled adult patients with acute abdominal, flank, low back or extremity pain. Subjects were consented and randomized to intravenous LDK (0.3 mg/kg) or intravenous MOR (0.1 mg/kg). The primary outcome was the maximum change in NRS scores. Low-dose ketamine compared with MOR for acute pain did not produce a greater reduction in NRS pain. But it is assumed that LDK induced a significant analgesic effect within 5 min and provided a moderate reduction in pain for 2 h. The time to achieve maximum reduction in NRS pain scores was at 5 min for LDK and 100 min for MOR. Vital signs, adverse events, clinician and nurse satisfaction scores were similar between groups [18].

In 2012, Paul A. Jennings proved that intravenous morphine plus ketamine provides analgesia superior to that of intravenous morphine alone. This is a prehospital study, randomized, prospective and controlled study. Patients with traumatic condition and a verbal pain score of greater than 5 after 5 mg of i.v. morphine were eligible for enrollment. Patients included in the ketamine group were administered a bolus of 10 or 20 mg, followed by 10 mg every 3 min. The second group patients received just morphine 5 mg i.v. every 5 min until pain free. Pain scores were regularly assessed until hospital arrival. The study conclusion was intravenous morphine plus ketamine for out-of-hospital adult trauma patients providing analgesia superior to that of intravenous morphine alone but was associated with an increase in the rate of minor adverse effects [19].

In 2017, Benov and colleagues published a review of data cases from 17 years of time frame from the military prehospital trauma registry of the Israeli Defense Forces. This included data from 141 solders patients, victims of explosion, who had received ketamine for analgesia. This review made a relatively conclusive statement: "Ketamine in subanesthetic doses is almost an ideal analgesic exhibited through its profound pain relief, its margin of safety, and its role in potentiation of opioids and prevention of opioid hyperalgesia" [20].

In 2007, Michel Galinski investigated the morphine consumption associated with ketamine for severe acute pain in emergency setting, where patients with a visual analog scale (VAS) score of minimum 60/100 were included. The K group patients received 0.2 mg/kg of i.v. ketamine over 10 min, while the P group patients received sodium chloride, as the control group. The patients from both groups were given an initial intravenous morphine dose of 0.1 mg/kg, plus as required doses were supplemented with 3 mg every 5 min. Efficient analgesia was defined as a VAS score not exceeding 30/100. The goals of this study were to assess morphine consumption and VAS at 30 min. They concluded that morphine consumption was much less in the K group vs. the P group. The VAS score at T30 did not differ significantly between the two groups [21]. We could assume the fact that the VAS score at T30 was similar for the two groups due to the fact that the time action for the ketamine dose is roughly around 10–15 min, and the K group received just an initial dose. So probably I would have been better also to have a VAS score at T15, for example, for more realistic and objective findings.

In 2019, Sheila C. Takieddine investigated whether ketamine administered *via* patient-controlled analgesia (PCA) provides adequate analgesia while reducing opioid consumption in the traumatically injured patient. Non-intubated trauma patients in intensive care, who were receiving PCA, were randomized to ketamine or hydromorphone PCA plus opioid analgesics for breakthrough pain. They concluded that ketamine PCA led to lower cumulative opioid consumption and lower oxygen supplementation requirements, though hallucinations occurred more frequently with the use of ketamine. They also concluded that additional studies are needed to investigate the tolerability of ketamine as an alternative to traditional opioid-based PCA [22].

In 2017, Kaitlin A. Pruskowski conducted a study to investigate the efficiency of the initiation of a ketamine continuous infusion in critically ill trauma patients for sedation and analgesic purposes. The secondary goals were to find out the patient population in which ketamine was administered, assess the time patients reached their goal level of sedation and find out the dosing required as adjunctive sedative agents. This retrospective chart review was investigated for 19-month period. This study was focused on the critically ill mechanically ventilated trauma patients. The study concluded that the use of ketamine in critically ill mechanically ventilated adult trauma patients was associated with decreased opioid use but it was also associated with the increased use of dexmedetomidine and ziprasidone to achieve and maintain sedation [23].

In 2014, Kim Phung Tran published a prospective study aiming to compare the analgesic effects and side effects of ketamine and morphine in out-of-hospital environment. The conclusion of this research was that ketamine had a pain control effect similar to morphine, and also accompanied by a lower risk of airway patency issues. The side effects as agitation and hallucinations were higher in incidence in the ketamine group. These conclusions are to be well appreciated as utility and application, particularly in rough and low-resource environments [24].

Bredmose PP conducted in 2009 another prospective study in the field of prehospital care investigating ketamine for analgesia and procedural sedation. This study evaluated the role of ketamine for analgesia and sedation in 1030 trauma patients in a prehospital trauma service led by physicians. Ketamine administration was the first choice in awake non-trapped victims with blunt trauma for analgesia and procedural sedation. This study data interpretation did not point out concerns for loss of airway, oxygen desaturation or clinically significant emergence reactions associated with ketamine use. Ketamine could be considered relatively safe when administered by physicians in out-of-hospital trauma care [25].

Still remaining in the prehospital field, it is advocated that there are many features of ketamine that seem to make it an ideal drug for prehospital use, including disaster surgery where extra personnel and advanced monitoring are not available.

In light of these premises, James E. Svenson performed a retrospective study of all patients transported by a regional aeromedical program. Data were collected from 40 patients, where ketamine was used. The study included pediatric and adult patients with age between 2 months and 75 years old. The indications for administration varied, from trauma to medical conditions. Shock status with need for analgesia, combativeness or agitation, intact airway concerns, or pain unresponsive to opioid drugs were the most common indications for use. Ketamine was administered either intravenously or intramuscularly (when no intravenous access was available). Minimal or no adverse effects [26] were reported.

In 2019, Kugler, Nathan published a level I of evidence study, randomized, double-blind placebo-controlled prospective trial enrolling elderly patients (age, ≥65 years) with three or more rib fractures presented to a Level I trauma center. The exclusion criteria were Glasgow Coma Scale score less than 14 and/or chronic opiate medication. Patients were randomized in two groups, either low-dose ketamine (LDK) at 2 μg/kg/min or an equivalent rate of 0.9% natrium chloride. This study conclusion is that low-dose ketamine failed to affect NPS or OME within the overall cohort, but a decrease in OME was observed in those with an Injury Severity Score greater than 15. Also, in this view, it is recommended that additional studies are necessary to confirm whether LDK benefits severely injured elderly patients [27].

5.2 What is the clinical evidence of ketamine in RSI and sedation?

One of other benefits of using ketamine in trauma is that could be an option for rapid sequence intubation (RSI) induction and maintaining sedation. Ketamine

has emerged as an alternative for RSI induction, because the conventional propofol makes hemodynamics vulnerable and induction doses of etomidate during rapid sequence intubation cause transient adrenal dysfunction, where clinical significance on trauma patients is uncertain.

Cameron P. Upchurch in 2017 published the four-year retrospective study comparing etomidate and ketamine for induction during rapid sequence intubation of adult trauma patients. In this analysis spanning an institutional protocol switch from etomidate to ketamine as the standard rapid sequence intubation induction agent for adult trauma patients, patient-centered outcomes were similar for patients who received etomidate and ketamine [28].

In 2019, Josefine Baekgaard investigated whether ketamine should be preferred over other induction agents for RSI in trauma patients. Library was systematically searched for studies reporting RSI of adult trauma patients with ketamine compared with another induction agent (etomidate, propofol, thiopental or midazolam). Extremely few studies have compared induction agents for RSI in trauma patients. Only four studies were included. The review conclusion was that no significant differences have been found in mortality, length of hospital stay or a number of blood transfusions after induction with ketamine compared with other induction agents, but a clinically relevant benefit or harm cannot be excluded [29].

In 2021, Lucy Stanke aiming to bring more evidences in the prehospital field of RSI drug comparison published a retrospective study to evaluated adult patients undergoing prehospital RSI over 13 months within a regional emergency transport medicine service. The purpose of this study was to evaluate hemodynamic changes after the administration of ketamine versus etomidate in prehospital RSI. The analysis emphasized that no cardiovascular differences were reported between patients who received ketamine versus etomidate for out-of-hospital RSI. None of these two drugs was associated with an increased requirement for additional hypnotics, and neither drug was associated with an increased first-attempt tracheal intubation success rate. This study also concluded that more studies, on larger cohorts and prospective designs, are needed to identify patients who may benefit from either ketamine or etomidate [30].

During emergency situations where RSI of anesthesia is required like in shocked or hypotensive patients (e.g., massive hemorrhage due to ruptured major vessels, pelvic fracture or other polytrauma conditions), prior resuscitation is often suboptimal and comorbidities (particularly cardiovascular) may be extensive, making challenges even worst. The induction drugs with the most favorable pharmacological properties offering a hemodynamic stability appear to be etomidate and ketamine. However, etomidate has been withdrawn from use in some countries and is known to impair steroidogenesis. Ketamine has been traditionally contra-indicated in the presence of head trauma, but we argue in this article that any adverse effects of the drug on intracranial pressure or cerebral blood flow are in fact attenuated or reversed by a better cardiovascular stability, sedation and controlled ventilation conferred by the drug. Ketamine represents a very rational option for RSI in hemodynamically compromised patients [31].

5.3 What is the clinical evidence of ketamine in traumatic brain injury?

For many years, the use of ketamine was restricted in TBI patients based on evidence from the 70s that suggested its detrimental effect on intracranial pressure. New research in healthy volunteers or in patients without neurological comorbidities scheduled for general surgery demonstrated that intracranial pressure, cerebral blood flow and cerebral perfusion pressure increase during anesthesia with variable doses of ketamine and no neurological side effects or sequels were noticed [32, 33]. Other series of studies with small numbers of patients with different central nervous

system pathologies that had in common abnormal cerebral spinal fluid circulation reported similar findings, emphasizing the absence of side effects [34–39]. Other recent systematic studies with various degrees and types of limitations reported that in heterogeneous acute brain populations (subarachnoid hemorrhage, tumors, TBI), ketamine induces only temporary variations in intracranial pressure without modifying cerebral perfusion pressure and has no detrimental effect on outcome, intensive care unit stay or mortality [36–38]. When assessing populations of severe acute bran injury, ketamine was not associated with an increase of intracranial pressure in sedated and normocapnic mechanically ventilated patients; furthermore, ketamine may decrease intracranial pressure in some individualized situations [39]. Other recent updates of ketamine administration in TBI led to similar findings [40].

As regards the ketamine use in acute phase of severe traumatic brain injury (TBI), in 2021, Daniel Agustin Godoy stated that ketamine is "an old drug for new uses," having more and more evidences of its benefits even in this condition. In the acute phase of severe acute brain injury, it is paramount to prevent and avoid secondary insults that can further complicate a primary brain injury [41]. Managing a goal-driven sedation and optimal pain control is a cornerstone of improving patient survival, satisfaction and minimizing distress. Without an optimal sedation, there are rising consequences including delayed recovery, difficult weaning from mechanical ventilation, higher complication rate and prolonged hospital staying [42].

Several different classes of hypnotic drugs are used in the management of patients with TBI [43–45]. These drugs are used at induction of anesthesia, to provide and keep sedation, to reduce elevated intracranial pressure, to control seizures and facilitate mechanical ventilation [46, 47]. To date, it is unclear which agent or combination of drugs is the most effective in achieving these goals. Ketamine is a versatile agent with attractive pharmacological and pharmacokinetic properties.

Controversies concerning the optimal sedation management persist, especially in critically TBI, who were systematically excluded from large randomized studies [44]. Different from other agents, ketamine does not depress respiratory activity or airway reflexes (except at very high doses) and may have potential neuroprotective effects, as well as a potential in decreasing seizures and non-convulsive epileptic activity [48, 49]. These properties make from ketamine a realistic choice when profound analgesia and sedation are required.

But there are still some restrictions in severe traumatic brain injury, and certain conditions would contraindicate ketamine administration, such as loss of cerebral autoregulation, hydrocephalus or the concomitant presence of untreated brain aneurysms [40, 50, 51].

5.4 What is the ketamine evidence in eye pathology?

Ketamine induces intraocular pressure (IOP) changes bur, which are mild and without clinical significance [52, 53]. The current guidelines do not limit the use of ketamine in known or suspected open globe injuries [54].

Ketamine is not recommended to be used for procedural sedation in eye examination as one of the known side effects of this drug is nystagmus.

6. When not to use ketamine?

An absolute contraindication is hypersensitivity to this drug [40]. Due to hepatic metabolism and mainly kidney elimination, it should not be administrated in the context of liver failure and/or renal failure [40, 50, 51]. Other relative contraindications are those conditions where high blood pressure triggers potentially dangerous

complications such as diastolic cardiac dysfunction, coronary ischemia or aortic dissection [40, 55]. In severe alcoholism, toxicity of ketamine has been described [40]. Use of ketamine in pediatrics is restricted to children younger than 3 months of age. There was reported higher incidence of airway complications like laryngospasm in very young patients [52].

Concerning the TBI, there are only a few contraindications nowadays. These were presented in a previous section.

Nevertheless, ketamine attributes to psychotomimetic effects, which could be the main reserve for not being a first choice when sedation is required [48, 49].

7. When to use ketamine?

In this section, indications for ketamine use will be divided in four general situations: analgesia, procedural sedation, induction of anesthesia/RSI and acute agitation/excited delirium [56].

Analgesia

- Ketamine's analgesic effect is comparable to opioids but with a lesser impact on hemodynamics or respiratory system.
- Ketamine could be an optimal analgesic in a trauma condition with moderate to severe pain, in or at risk for developing hemorrhagic shock or respiratory failure [57].
- Ketamine potentiates the analgesic effect of opioids and could be given to trauma patients with insufficient pain control after receiving opioids or when a top-up of opioids may be risky or harmful.
- Ketamine may be given to the trauma condition, as an alternative to opioids or other non-opioids medication.
- Ketamine could be an adequate option for the trauma patient receiving buprenorphine/naloxone for opioid misuse.

Procedural sedation

- Ketamine is optimal choice as a procedural sedation agent in patients with or at risk for respiratory failure or hemorrhagic shock.
- For short sedation procedures as in burns debridement or musculoskeletal injuries maneuvers.

Induction of anesthesia/rapid sequence intubation

- Is an optimal choice in shocked trauma patients for RSI due to its analgesic and sedative features and also for its cardiovascular stability?

Acute agitation/excited delirium

- Ketamine may be used in trauma conditions when fast control of agitation is required such as in patients with delirium or when rapid control is essential to diminish the risk of injury to staff, family or the patients themselves.

8. Dosing

The dose considerations of ketamine in adults can be either body weight-based or non-weight-based. For a better accuracy in dose calculations in pediatrics, the dose should always be weight or length based using a standardized measuring tape.

There are no standard recommendations for the ketamine dose. What follows are dose recommendations based on literature review and expert opinion.

Analgesia dosing recommendations

Intermittent dose:

- 0.1–0.3 mg/kg (maximum 30 mg) i.v. every 20 min as required for a maximum of three doses.
- This can be given by slow i.v. push or as an i.v. bag over 10–15 min (associated with side effects such as feelings of unreality and oversedation with no difference in analgesic efficacy) [58].
- 0.5–1.0 mg/kg intranasal (i.n.)

Adult continuous infusion dose:

- 0.1–0.4 mg/kg/hour i.v.

Adult non-weight-based analgesic dosing:

50 mg i.m., repeat as required every 30–60 min for pain control or until nystagmus develops indicating approach of the dissociative state.

20 mg slow i.v./i.o. push over 1 min, repeat as required every 20 min for desired analgesia or until nystagmus appears indicating reaching the dissociative state.

Procedural sedation

- 1 mg/kg i.v. (maximum 100 mg per dose)

Induction of anesthesia/RSI

- 2 mg/kg i.v. (maximum 200 mg)

Acute agitation/excited delirium

- 3–5 mg/kg i.m.
- 1–2 mg/kg i.v.

Other observations

- i.v. access in the acutely agitated patient or the patient with excited delirium might be too risky and difficult; so, it is not advisable due to the increased risk to the practitioner of occupational needle stick injury.
- High-dose (5 mg/kg) prehospital i.m. ketamine administration is associated with an increased intubation rate upon arrival to the hospital [59–61]. Clinicians giving high-dose ketamine should be prepared to control the airway.

- In some expert's opinion doses between 0.5 and 0.9 mg/kg i.v. are not efficacious for sedation and could trigger a sense of unreality that can lead to issues in patient management.

9. Safety profile

Ketamine can induce a transient apnea in high doses or with fast administration. These conditions are associated with higher intubation rate. Patients given ketamine should be kept under observation for the risk of respiratory failure, and clinicians using ketamine, especially in high doses, should be ready to take over airway control.

There is a lack of safety data to support recommendations in what concerning the use of ketamine in pregnancy and during breast feeding [62].

Another previous controversy, but recently cleared, ketamine use can be considered in trauma patients with schizophrenia as there does not seems to be a higher incidence of psychosis in these kinds of conditions [63, 64].

10. Complications and side effects

Fast IV administration can trigger transient apnea. Ketamine should be given in a slow bolus, over 1 min or more unless being used in RSI where it is followed shortly by a muscle relaxing drug and intubation. Transient apnea following i.m. administration appears to be extremely rare [43].

Reported side effects are laryngospasm, hypersalivation, nausea, dizziness, nystagmus, dysphoria and emergence agitation. Most of the time, these side effects are transient and self-limited and do not require any intervention or rescue. If laryngospasm occurs, it can be managed with repositioning or jaw thrust and positive pressure ventilation. In rare instances, intubation may be necessary.

Emergence reactions are notable to be rare. When appears, these can be safely managed with benzodiazepine use. Pre-medicating with benzodiazepines is not recommended.

11. Co-administration with other drugs

When used in concomitantly, ketamine increases the pain control effects of opioids. The administration of ketamine and opioids in combination improves analgesia with lesser doses of opioids thus decreasing the chance of opioid-induced adverse effects on cardiovascular and respiratory system [65].

Combining ketamine with opioid medication has been reported to block opioid-induced hyperalgesia and acute opioid tolerance.

When used in concomitantly, ketamine increases the sedative effects of benzodiazepines with its risk for respiratory depression. Extra caution should be sought, and airway monitoring should be considered.

Benzodiazepines should not be used prophylactically to prevent emergence reactions and should only be considered to manage an emergence reaction if the patient is a danger to themselves or staff. Suboptimal sedation requesting additional ketamine versus a true emergence reaction should be taken into consideration before the benzodiazepine administration.

12. Considerations with non-prescribed drugs

Ketamine increases the sedative effects of alcohol, and it is essential to anticipate the risks of respiratory decompensation when ketamine is administered to an acutely intoxicated patient [57].

Ketamine should be excluded if cocaine use is suspected as ketamine's sympathomimetic effects could superimpose over the cardiovascular toxicity of cocaine [18].

13. Geriatrics

In the literature, there are not sufficient data in what concerning the use of ketamine in the geriatrics. It is advisable to decrease the dose when using ketamine in the elderly since NMDA receptor binding is slowed with age.

14. Pediatrics

Ketamine is an alternative option to opioids and benzodiazepines for analgesia and sedation in the pediatric trauma patient over the age of 3 months.

Because of possible negative consequences on the developing brain in kids who have received repeated or prolonged exposure to drugs that block NMDA receptors, the use of ketamine in infants less than 3 years of age should be assessed within the context of the benefits and risks of the procedure [19].

Before ketamine use, it is first to take into account the adjunct measures for analgesia such as fractures immobilization or dislocations reductions.

Precautions should be taken when using ketamine out of hospital in the head-injured child. Adverse effects of ketamine in the children with head injuries have not been reported in the literature, though evidence on this topic is limited [66].

15. Conclusion

Analgesia and sedation are dynamic processes that must meet specific goals, be controlled and be easily modified according to the progress of patient's condition. Knowledge of drug pharmacology and its safety margin and profile are paramount to limit their side effects. Setting a goal-directed strategy, establishing local protocols of administration and monitoring treatment are the cornerstone of an efficient analgesia and sedation strategy. These qualities contribute to fulfilling an optimal and safe level of sedation, looking to balance the deleterious effects of under or over sedation [12].

Further studies on the use of ketamine in the adult and pediatric trauma patient population are required.

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References

[1] Finkelstein EA, Corso PS, Miller TR. The Incidence and Economic Burden of Injuries in the United States. New York, NY: Oxford University Press; 2006. Available from: http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195179484.001.0001/acprof-9780195179484

[2] GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;**385**:117-171

[3] Scholten AC, Haagsma JA, Panneman MJM, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: Incidence, costs and disability-adjusted life years. PLoS One. 2014;**9**:e110905

[4] McGreevy K, Bottros M, Raja S. Preventing chronic pain following acute pain: Risk factors, preventive strategies, and their efficacy. European Journal of Pain Supplements. 2011;**5**(2):365-372. DOI: 10.1016/j.eujps.2011.08.013

[5] Peters M, Sommer M, et al. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Annals of Surgery. 2007;**245**(3):487-494. DOI: 10.1097/01.sla.0000245495.79781.65

[6] Epps C, Ware L, Packard A. Ethnic wait time differences in analgesic administration in the emergency department. Pain Management Nursing. 2008;**9**(1):26-32. DOI: 10.1016/j.pmn.2007.07.005

[7] Anantha R, Stewart T, Rajagopalan A, Walsh J, Merritt N. Analgesia in the management of paediatric and adolescent trauma during the resuscitative phase: The role of the pediatric trauma centre. Injury. 2014;**45**(5):845-849. DOI: 10.1016/j.injury.2013.10.048

[8] Aminiahidashti H, Shafiee S, Hosseininejad S, et al. Propofol-fentanyl versus propofol-ketamine for procedural sedation and analgesia in patients with trauma. The American Journal of Emergency Medicine. 2018;**36**(10):1766-1770. DOI: 10.1016/j.ajem.2018.01.080

[9] Silka P, Roth M, Geiderman J. Patterns of analgesic use in trauma patients in the ED. The American Journal of Emergency Medicine. 2002;**20**(4):298-302. DOI: 10.1053/ajem.2002.34195

[10] Hartings JA et al. Prognostic value of spreading depolarizations in patients with severe traumatic brain injury. JAMA Neurology. 2020;**77**:489-499. DOI: 10.1001/jamaneurol.2019.4476

[11] Slupe AM, Kirsch JR. Effects of anesthesia on cerebral blood flow, metabolism, and neuroprotection. Journal of Cerebral Blood Flow and Metabolism. 2018;**38**:2192-2208

[12] Godoy DA, Badenes R, Pelosi P, et al. Ketamine in acute phase of severe traumatic brain injury "an old drug for new uses?". Critical Care. 2021;**25**:19. DOI: 10.1186/s13054-020-03452-x

[13] Yousefifard M, Askarian-Amiri S, Alavi SNR, Sadeghi M, Saberian P, Baratloo A, et al. The efficacy of ketamine administration in prehospital pain management of trauma patients; a systematic review and meta-analysis. Archives of Academic Emergency Medicine. 2020;**8**(1):e1

[14] Bakes KM, Buchanan JA, Moreira ME, Byyny R, Pons PT. Emergency Medicine Secrets. 5th ed. Maryland Heights, Missouri, United States: Elsevier Mosby; 2011. p. 563

[15] Walters M, Farhat J, Bischoff J, Foss M, Evans C. Ketamine as an

analgesic adjuvant in adult trauma intensive care unit patients with rib fracture. The Annals of Pharmacotherapy. 2018;**52**(9):849-854. DOI: 10.1177/1060028018768451

[16] Carver TW, Kugler NW, Juul J, Peppard WJ, Drescher KM, Somberg LB, et al. Ketamine infusion for pain control in adult patients with multiple rib fractures: Results of a randomized control trial. Journal of Trauma and Acute Care Surgery 2019. 2019;**86**(2):181-188. DOI: 10.1097/TA.0000000000002103

[17] Mahshidfar B, Mofidi M, Fattahi M. Acute pain management in emergency department, low dose ketamine versus morphine, a randomized clinical trial. Anesthesiology and Pain Medicine. 2017;**7**(6):e60561. DOI: 10.5812/aapm.60561

[18] Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: A randomized controlled trial. The American Journal of Emergency Medicine. 2015;**33**(3):402-408. DOI: 10.1016/j.ajem.2014.12.058

[19] Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: A randomized controlled trial. Annals of Emergency Medicine. 2012;**59**(6):497-503. DOI: 10.1016/j.annemergmed.2011.11.012

[20] Benov A, Salas M, Nakar H, et al. Battlefield pain management: A view of 17 years in Israel Defense Forces. Journal of Trauma and Acute Care Surgery. 2017;**83**(1 Suppl 1):S150-S155. DOI: 10.1097/TA.0000000000001481

[21] Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: Ketamine reduces morphine consumption. The American Journal of Emergency Medicine. 2007;**25**(4):385-390. DOI: 10.1016/j.ajem.2006.11.016

[22] Takieddine SC, Droege CA, Ernst N, Droege ME, Webb M, Branson RD, et al. Ketamine versus hydromorphone patient-controlled analgesia for acute pain in trauma patients. Journal of Surgical Research. 2018;**225**:6-14. DOI: 10.1016/j.jss.2017.12.019

[23] Pruskowski KA, Harbourt K, Pajoumand M, Chui SHJ, Reynolds HN. Impact of ketamine use on adjunctive analgesic and sedative medications in critically ill trauma patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2017;**37**(12):1537-1544. DOI: 10.1002/phar.2042

[24] Tran KP, Nguyen Q, Truong XN, Le V, Le VP, Mai N, et al. A comparison of ketamine and morphine analgesia in prehospital trauma care: A cluster randomized clinical trial in rural Quang Tri Province, Vietnam. Prehospital Emergency Care. 2014;**18**(2):257-264. DOI: 10.3109/10903127.2013.851307

[25] Bredmose PP, Lockey DJ, Grier G, et al. Pre-hospital use of ketamine for analgesia and procedural sedation. Emergency Medicine Journal. 2009;**26**:62-64

[26] Svenson JE, Abernathy MK. Ketamine for prehospital use: New look at an old drug. The American Journal of Emergency Medicine. 2007;**25**(8):977-980. DOI: 10.1016/j.ajem.2007.02.040

[27] Kugler NW, Carver TW, Juul J, Peppard WJ, Boyle K, Drescher KM, et al. Ketamine infusion for pain control in elderly patients with multiple rib fractures: Results of a randomized controlled trial. Journal of Trauma and Acute Care Surgery. 2019;**87**(5):1181-1188. DOI: 10.1097/TA.0000000000002479

[28] Upchurch CP, Grijalva CG, Russ S, Collins SP, Semler MW, Rice TW, et al. Comparison of etomidate and ketamine for induction during rapid sequence intubation of adult trauma patients. Annals of Emergency Medicine. 2017;**69**(1):24-33. DOI: 10.1016/j.annemergmed.2016.08.009. ISSN 0196-0644

[29] Baekgaard JS, Eskesen TG, Sillesen M, Rasmussen LS, Steinmetz J. Ketamine as a rapid sequence induction agent in the trauma population: A systematic review. Anesthesia & Analgesia. 2019;**128**(3):504-510. DOI: 10.1213/ANE.0000000000003568

[30] Stanke L, Nakajima S, Zimmerman LH, Collopy K, Fales C, Powers W IV. Hemodynamic effects of ketamine versus etomidate for prehospital rapid sequence intubation. Air Medical Journal. 2021;**40**(5):312-316. DOI: 10.1016/j.amj.2021.05.009

[31] Morris C, Perris A, Klein J, Mahoney P. Anaesthesia in haemodynamically compromised emergency patients: Does ketamine represent the best choice of induction agent? Anaesthesia. 2009;**64**(5):532-539. DOI: 10.1111/j.1365-2044.2008.05835

[32] Sari A, Okuda Y, Takeshita H. The effect of ketamine on cerebrospinal fluid pressure. Anesthesia and Analgesia. 1972;**51**:560-565

[33] Gardner AE, Olson BE, Lichtiger M. Cerebrospinal-fluid pressure during dissociative anesthesia with ketamine. Anesthesiology. 1971;**35**:226-228

[34] Tjaden RJ, Ethier R, Gilbert RG, et al. The use of CI-581 (Ketalar) for pediatric pneumoencephalography. Journal of the Canadian Association of Radiologists. 1969;**20**:155-156

[35] Evans J, Rosen M, Weeks RD, et al. Ketamine in neurosurgical procedures [letter]. Lancet. 1971;**1**:40

[36] Gibbs JM. The effect of intravenous ketamine on cerebrospinal fluid pressure. British Journal of Anaesthesia. 1972;**44**:1298-1302

[37] List WF, Crumrine RS, Cascorbi HF, et al. Increased cerebrospinal fluid pressure after ketamine. Anesthesiology. 1972;**36**:98-99

[38] Lockhart CH, Jenkins JJ. Ketamine induced apnea in patients with increased intracranial pressure. Anesthesiology. 1972;**37**:92-93

[39] Shapiro HM, Wyte SR, Harris AB. Ketamine anaesthesia in patients with intracranial pathology. British Journal of Anaesthesia. 1972;**44**:1200-1204

[40] Gregers MCT, Mikkelsen S, Lindvig KP, Brøchner AC. Ketamine as an anesthetic for patients with acute brain injury: A systematic review [published online ahead of print, 2020 Apr 23]. Neurocritical Care. 2020. DOI: 10.1007/s12028-020-00975-7

[41] Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurology. 2008;**7**:728-741

[42] Petrica A, Ionac M, Brinzeu C, Brinzeu A. Surgical site infections surveillance in neurosurgery patients. Timisoara Medical Journal. 2009;**59**(3):339-343

[43] Godoy DA, Lubillo S, Rabinstein AA. Pathophysiology and management of intracranial hypertension and tissular brain hypoxia after severe traumatic brain injury: An integrative approach. Neurosurgery Clinics of North America. 2018;**29**:195-212

[44] Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in

adult patients in the ICU. Critical Care Medicine. 2018;**46**:e825-e873

[45] Ciobanu D, Banicioiu-Covei M, Rotaru LT, Nica S, Petrica A, Puticiu M. Theoretical docking studies of anesthetic drugs interactions used in emergency departments. Journal of Science and Arts. 2020;**20**(2):419-424

[46] Dejeu IL, Vicaș LG, Jurca T, Fritea L, Svera P, Gabor GA, et al. Liposomes with caffeic acid: Morphological and structural characterisation, their properties and stability in time. PRO. 2021;**9**:912. DOI: 10.3390/pr9060912

[47] Huniadi A, Sorian A, Iuhas C, Bodog A, Sandor MI. The effect of cannabis in the treatment of Hodgkin's lymphoma in a pregnant patient—Extensive case report and literature review. Journal of BUON. 2021;**26**(1): 11-16

[48] Takeshita H, Okuda Y, Sari A. The effects of ketamine on cerebral circulation and metabolism in man. Anesthesiology. 1972;**36**:69-75

[49] Kolenda H, Gremmelt A, Rading S, Braun U, Markakis E. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. Acta Neurochirurgica (Wien). 1996;**138**:1193-1199

[50] Himmelseher S, Durieux ME. Revising a dogma: Ketamine for patients with neurological injury? Anesthesia and Analgesia. 2005;**101**:524-534

[51] Hurth KP, Jaworski A, Thomas KB, Kirsch WB, Rudoni MA, Wohlfarth KM. The reemergence of ketamine for treatment in critically ill adults. Critical Care Medicine. 2020;**48**:899-911

[52] Halstead SM, Deakyne SJ, Bajaj L, Enzenauer R, Roosevelt GE. The effect of ketamine on intraocular pressure in pediatric patients during procedural sedation. Academic Emergency Medicine. 2012;**19**(10):1145-1150. DOI: 10.1111/j.1553-2712.2012.01450.x

[53] Drayna PC, Estrada C, Wang W, Saville BR, Arnold DH. Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. The American Journal of Emergency Medicine. 2012;**30**(7):1215-1218. DOI: 10.1016/j.ajem.2011.06.001

[54] Tactical Combat Casualty Care. TCCC Guidelines for Medical Personnel; 2019. Available from: https://www.naemt.org/docs/default-source/education-documents/tccc/tccc-mp-updates-190801/tccc-guidelines-for-medical-personnel-190801.pdf?sfvrsn=cc99d692_2 [Accessed: July 16, 2020]

[55] Green SM, Andolfatto G, Krauss BS. Ketamine and intracranial pressure: No contraindication except hydrocephalus. Annals of Emergency Medicine. 2015;**65**:52-54

[56] Morgan MM, Perina DG, Acquisto NM, Fallat ME, Gallagher JM, Brown KM, et al. Ketamine use in prehospital and hospital treatment of the acute trauma patient: A joint position statement. Prehospital Emergency Care. 2021;**25**(4):588-592. DOI: 10.1080/10903127.2020.1801920

[57] Butler FK, Kotwal RS, Buckenmaier CC, Edgar EP, O'Connor KC, Montgomery HR, et al. A triple-option analgesia plan for tactical combat casualty care: TCCC Guidelines Change 13-04. Journal of Special Operations Medicine. 2014;**14**(1):13-25

[58] Motov S, Mai M, Pushkar I, Likourezos A, Drapkin J, Yasavolian M, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. The American Journal of Emergency Medicine. 2017;**35**(8):1095-1100. DOI: 10.1016/j.ajem.2017.03.004

[59] Burnett AM, Peterson BK, Stellpflug SJ, Engebretsen KM, Glasrud KJ, Marks J, et al. The association between ketamine given for prehospital chemical restraint with intubation and hospital admission. The American Journal of Emergency Medicine. 2015;**33**(1):76-79. DOI: 10.1016/j.ajem.2014.10.016

[60] Hollis GJ, Keene TM, Ardlie RM, Caldicott DG, Stapleton SG. Prehospital ketamine use by paramedics in the Australian Capital Territory: A 12 month retrospective analysis. Emergency Medicine Australasia. 2017;**29**(1):89-95. DOI: 10.1111/1742-6723.12685

[61] Guldner GT, Petinaux B, Clemens P, Foster S, Antoine S. Ketamine for procedural sedation and analgesia by nonanesthesiologists in the field: A review for military health care providers. Military Medicine. 2006;**171**(6):484-490. DOI: 10.7205/milmed.171.6.484

[62] Bumbu A, Nacer K, Bratu O, Berechet M, Bumbu G, Bumbu B. Ureteral lesions in gynecological pathology. In: Proceedings of the 14th National Congress of Urogynecology and the National Conference of the Romanian Association for the Study of Pain, Bucharest, Romania. 2017. pp. 26-27

[63] Lebin JA, Akhavan AR, Hippe DS, Gittinger MH, Pasic J, McCoy AM, et al. Psychiatric outcomes of patients with severe agitation following administration of prehospital ketamine. Academic Emergency Medicine. 2019;**26**(8):889-896

[64] Kudoh A, Katagai H, Takazawa T. Anesthesia with ketamine, propofol, and fentanyl decreases the frequency of postoperative psychosis emergence and confusion in schizophrenic patients. Journal of Clinical Anesthesia. 2002;**14**(2):107-110. DOI: 10.1016/S0952-8180(01)00363-4

[65] Botea M. In: Waisundara VY, Banjari I, Balkić J, editors. Analgesics, Pain Management—Practices, Novel Therapies and Bioactives. London: IntechOpen; 2020. DOI: 10.5772/intechopen.94319. Available from: https://www.intechopen.com/chapters/73965

[66] De Rocquigny G, Dubecq C, Martinez T, Peffer J, Cauet A, Travers S, et al. Use of ketamine for prehospital pain control on the battlefield: A systematic review. Journal of Trauma and Acute Care Surgery. 2020;**88**(1):180-185. DOI: 10.1097/TA.0000000000002522