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KETAMINE IN PREHOSPITAL MANAGEMENT OF TRAUMATIC BRAIN INJURIES: FROM CONTROVERSY TO ROUTINE USE. A SYSTEMATIC REVIEW OF CURRENT LITERATURE

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ABSTRACT

Research Objectives: To present the broadest available evidence regarding the safety and efficacy of ketamine in traumatic brain injury (TBI) and explain the evolution of clinical guidelines. This review aims to verify historical contraindications against current knowledge and demonstrate how ketamine's role has evolved from a contraindicated drug to a potentially beneficial therapeutic option in prehospital settings.
Methods: Systematic analysis of clinical studies and systematic reviews examining ketamine's effects on cerebral hemodynamics, intracranial pressure (ICP), and cerebral perfusion pressure (CPP). Evaluation of ketamine's utility as an analgesic-sedative drug in prehospital TBI care, including assessment of safety profiles and clinical outcomes across civilian and military settings.
Conclusions: Ketamine's effect on cerebral hemodynamics is at least neutral and often beneficial, contrary to historical concerns about increased ICP. The drug demonstrates high utility as a prehospital analgesic-sedative agent, providing effective pain control and sedation without compromising patient safety. Historical contraindications must be regularly re-verified in light of current evidence. Clinical guidelines have evolved significantly, reflecting growing recognition that proper ventilation control and hemodynamic monitoring eliminate previous safety concerns. Current evidence supports ketamine as a safe and potentially advantageous therapeutic option in prehospital TBI management, particularly for achieving rapid sequence intubation, maintaining hemodynamic stability, and preventing secondary brain injury in emergency settings.

KEYWORDS

Ketamine, Traumatic Brain Injury, Prehospital Treatment, Intracranial Pressure, Cerebral Perfusion Pressure, Analgesia, Sedation, Neuroprotection, Safety

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1. Introduction

Traumatic brain injury (TBI) represents one of the most significant public health challenges worldwide. It accounts for a substantial portion of morbidity, mortality, and long-term disability across various age groups and socioeconomic strata [1], [2]. Global estimates indicate tens of millions of TBI cases annually, making this type of injury one of the main causes of disability-adjusted life years lost, particularly in the working-age population [3], [4]. The magnitude of this problem extends beyond immediate mortality, as survivors often face prolonged rehabilitation, cognitive impairments, and reduced quality of life [5], [6].

In prehospital conditions, emergency rescue teams face critical time-sensitive decisions regarding rapid anesthesia induction, sedation to control agitation, and implementation of analgesia for severe pain [7], [8]. The choice of an induction and sedative drug is crucial for treatment outcomes, especially in the context of maintaining adequate cerebral perfusion pressure (CPP) [9], [10]. This decision becomes even more complex in the austere prehospital environment, where advanced monitoring capabilities may be limited and patient conditions can rapidly deteriorate [11], [12].

Ketamine, introduced into clinical practice in the 1960s, was for many years considered a contraindicated drug in TBI due to concerns about increased intracranial pressure (ICP) [13], [14]. Classic reports and observations among neurosurgical patients entrenched the belief that ketamine exacerbates cerebral edema and should therefore be avoided in patients with TBI [15], [16]. These historical concerns were primarily based on early studies conducted in spontaneously breathing patients without adequate sedation or controlled ventilation [17], [18].

At the same time, this drug possesses a number of highly desirable characteristics in prehospital practice that make it particularly attractive for emergency medical services. These include strong analgesic-dissociative action [19], [20], preservation of protective reflexes and airway patency [21], [22], hemodynamic stability with

an increase in arterial pressure and heart rate which can be beneficial for maintaining proper CPP [23], [24], various routes of administration including intravenous (IV), intramuscular (IM), and intranasal (IN) [25], [26], and a favorable safety profile in trauma populations compared to other sedative agents [27], [28]. These aspects have been widely analyzed in classic monographs and contemporary reviews [29], [30].

By the end of the 1990s and in subsequent decades, clinical studies and review papers began to emerge that challenged traditional views on ketamine's effect on ICP [31], [32]. It was demonstrated that with properly controlled ventilation and sedation, ketamine not only does not increase ICP but can actually decrease it while simultaneously improving CPP [33], [34]. In parallel, the number of studies from both civilian and military settings evaluating ketamine as an analgesic, sedative, and potentially neuroprotective modulator of phenomena such as spreading depolarizations has been steadily growing [35], [36], [37].

This paradigm shift in understanding ketamine's role in TBI management reflects the broader evolution of evidence-based medicine, where historical dogmas must be continuously re-evaluated in light of new scientific evidence [38], [39]. The present systematic review aims to comprehensively examine this evolution and provide clinicians with current evidence-based guidance for ketamine use in prehospital TBI management [40].

2. Materials and Methods

A systematic review of the literature was conducted, encompassing both primary research studies and secondary sources including systematic reviews and meta-analyses. The comprehensive search strategy was designed to capture all relevant literature examining ketamine use in traumatic brain injury within prehospital and emergency care settings.

The databases MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, Epistemonikos, and ClinicalTrials.gov were systematically searched according to the Medical Subject Headings (MeSH) strategy. The search terms employed were: "ketamine" OR "S-ketamine" AND ("prehospital care" OR "emergency medical services") AND ("traumatic brain injury" OR "TBI" OR "head injury" OR "head trauma"). No language restrictions were applied initially, though only articles available in English were ultimately included in the final analysis.

Publications were included for analysis where patients with TBI of any severity (mild, moderate, or severe) were described, ketamine or S-ketamine was used in a prehospital or emergency department context, and data on safety, efficacy, intracranial pressure, cerebral perfusion pressure, clinical outcomes, or patient-reported outcomes were available. Studies were excluded if they involved only animal models, if they examined ketamine use exclusively in non-trauma settings, or if they lacked sufficient methodological detail to assess quality.

Two independent reviewers performed the initial selection of titles and abstracts, followed by full-text evaluation of studies meeting preliminary inclusion criteria. Any discrepancies between reviewers were resolved through consensus discussion, with the possibility of expert consultation when necessary. The inter-rater reliability was assessed using Cohen's kappa coefficient, demonstrating substantial agreement between reviewers.

Data extracted from included studies comprised: type of publication (original research, systematic review, meta-analysis, case series), study design (randomized controlled trial, cohort study, case-control study), country and setting (civilian versus military, ground versus air transport), population characteristics (age, sex, injury severity scores), ketamine dosing regimens and routes of administration, characteristics of control or comparison groups, primary and secondary endpoints analyzed, and the main conclusions of the study authors.

Given the heterogeneity of study designs, patient populations, and outcome measures across the included literature, a quantitative meta-analysis was not feasible. Therefore, the synthesis was narrative, critical, and qualitative in nature, focusing on identifying consistent patterns and themes across studies while acknowledging methodological limitations and potential sources of bias.

3. Results of Literature Review

3.1 Pharmacology of Ketamine in TBI Treatment

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that also acts on opioid receptors, monoaminergic receptors, and various ion channels [13], [28]. This unique multimodal mechanism of action distinguishes ketamine from other anesthetic agents and contributes to its distinctive pharmacological profile. In the context of traumatic brain injury, several key properties make ketamine particularly valuable for prehospital emergency care.

First, ketamine provides effective analgesia and dissociative sedation, enabling adequate pain control and agitation management, which are critical for limiting secondary increases in intracranial pressure [11], [19], [29]. The dissociative state produced by ketamine creates a trance-like condition characterized by profound analgesia, amnesia, and catalepsy, while maintaining protective airway reflexes [16], [20].

Second, unlike most other anesthetic agents, ketamine preserves protective reflexes and airway patency, reducing the immediate need for definitive airway management in some patients [21], [22], [29]. This characteristic is particularly advantageous in prehospital settings where advanced airway equipment or expertise may not be readily available.

Third, ketamine demonstrates remarkable hemodynamic stability, typically producing an increase in both arterial pressure and heart rate through stimulation of the sympathetic nervous system [11], [14], [23], [33]. This sympathomimetic effect can be beneficial for maintaining proper cerebral perfusion pressure in TBI patients, who are particularly vulnerable to secondary brain injury from hypotension [24], [39].

Fourth, ketamine's availability in multiple formulations allows for various routes of administration, including intravenous, intramuscular, and intranasal delivery [25], [26], [32]. This versatility is especially valuable in prehospital emergency care, where IV access may be difficult to obtain in critically injured patients.

Finally, ketamine exhibits a favorable safety profile with a lower risk of respiratory depression and circulatory instability compared to opioids or benzodiazepines [11], [27], [29]. This characteristic reduces the risk of iatrogenic harm during prehospital transport when continuous monitoring may be limited.

Unlike many other anesthetic agents that can cause significant arterial pressure reduction, ketamine does not substantially lower mean arterial pressure and does not cause cerebral perfusion pressure reduction [6], [7], [12], [14], [23], [24], [33], [39]. This maintenance of hemodynamic stability is particularly crucial in TBI patients, where even brief episodes of hypotension can lead to worsened neurological outcomes.

3.2 Safety Profile of Ketamine: Effect on Intracranial Pressure

Historical concerns about ketamine's use in traumatic brain injury primarily stemmed from the seminal work of Shapiro et al., who demonstrated increases in intracranial pressure in selected patients with severe intracranial pathology [35]. This 1972 study examined ketamine administration in neurosurgical patients and reported ICP elevations, leading to decades of widespread avoidance of ketamine in head-injured patients. Similar observations were subsequently made by Belopavlovic and Buchthal, who analyzed ICP modification with and without midazolam premedication, finding that ketamine alone could increase ICP in certain patient populations [5].

Additional early studies in neurosurgical patient populations further reinforced this belief, creating a strong clinical dogma against ketamine use in TBI [8], [9], [15], [16]. These historical data became deeply embedded in clinical practice guidelines and medical education, persisting for several decades despite emerging contradictory evidence.

methodological limitations that called their conclusions into question [17], [18], [31]. Most notably, these studies were conducted in spontaneously breathing patients without adequate sedation or controlled ventilation. The ICP elevations observed may have resulted from increased cerebral blood flow secondary to hypercapnia from respiratory depression, rather than from direct ketamine effects on cerebral vasculature [1], [7], [15].

Contemporary research with more rigorous methodology has systematically challenged and refuted these historical concerns. Albanèse and colleagues demonstrated that ketamine actually decreases intracranial pressure and electroencephalographic activity in TBI patients during propofol sedation [1]. This landmark study was among the first to show that with proper ventilation control and concurrent sedation, ketamine's effects on ICP are benign or even beneficial.

Multiple subsequent studies have confirmed these findings. Dengler et al. reported that ketamine boluses were associated with reductions in intracranial pressure and increases in cerebral perfusion pressure in patients with severe TBI [12]. Their retrospective observational study of mechanically ventilated patients demonstrated

that ketamine administration was followed by significant decreases in ICP and increases in CPP, contradicting the historical contraindication.

Recent systematic reviews and meta-analyses have provided comprehensive evidence supporting ketamine's safety in TBI patients. Gregers et al. conducted a systematic review specifically examining ketamine as an anesthetic for patients with acute brain injury, concluding that current evidence does not support the historical contraindication when ketamine is used with controlled ventilation and adequate sedation [17]. Similarly, Sciorilli et al. performed a systematic review and meta-analysis specifically addressing whether ketamine is safe for traumatic brain injury, finding no evidence of increased ICP or adverse neurological outcomes with ketamine use [34].

Green and colleagues have been particularly vocal in advocating for re-evaluation of ketamine's contraindication status, arguing that with the exception of patients with hydrocephalus, there is no evidence-based contraindication to ketamine use in patients with elevated ICP [15]. Their analysis emphasized that the key factor is not ketamine itself, but rather the clinical context in which it is administered, particularly the adequacy of ventilation and the use of concurrent sedating agents.

Pediatric studies have extended these safety findings to younger patient populations. Laws et al. examined acute effects of ketamine on intracranial pressure in children with severe TBI [24], finding no clinically significant ICP elevations following ketamine administration in appropriately managed patients. Mazandi et al. similarly reported safe co-administration of ketamine in pediatric patients with neurologic conditions at risk for intracranial hypertension [26], and Loi et al. found favorable outcomes with ketamine use in the intubation of critically ill children with neurologic indications [25].

Some studies have even suggested potential neuroprotective effects of ketamine beyond simple ICP stability. Hertle and colleagues demonstrated that ketamine affects the occurrence of spreading depolarizations, which are increasingly recognized as important contributors to secondary brain injury [19], [20]. Their research suggests that ketamine's NMDA receptor antagonism may reduce these harmful electrophysiological events, potentially offering protection against secondary brain damage.

3.3 Clinical Application in Prehospital Emergency Settings

The practical application of ketamine in prehospital and emergency settings has been extensively studied in both civilian and military contexts. These real-world studies provide crucial evidence regarding ketamine's effectiveness, safety, and operational feasibility outside of controlled clinical environments.

Military medical services have accumulated substantial experience with ketamine use in combat casualty care, where austere environments and resource limitations necessitate versatile and robust therapeutic options [14], [37]. Grathwohl et al. compared total intravenous anesthesia including ketamine versus volatile gas anesthesia for combat field anesthesia, demonstrating that ketamine-based protocols were feasible and safe in these challenging conditions [14]. Torres and colleagues reported a comprehensive 10-year analysis of ketamine administration in prehospital combat-injured patients with TBI, finding no adverse effects on survival rates [37]. Their study, which included a large cohort of severely injured combat casualties, provided strong evidence supporting ketamine's safety profile in real-world military applications.

Kane et al. specifically examined the association between traumatic brain injuries and ketamine infusion side effects following combat injury. Their analysis found that TBI patients receiving ketamine infusions did not experience higher rates of adverse effects compared to non-TBI trauma patients, further supporting the safety of ketamine in this population [22]. Additionally, Melcer and colleagues investigated whether prehospital ketamine administration was associated with changes in post-traumatic stress disorder (PTSD) prognosis, exploring potential psychological benefits beyond the acute trauma management phase [27].

Civilian emergency medical services have similarly incorporated ketamine into prehospital protocols with favorable results. Jabre et al. conducted a multicenter randomized controlled trial comparing etomidate versus ketamine for rapid sequence intubation in acutely ill patients. This large trial demonstrated that ketamine was non-inferior to etomidate for emergency intubation while avoiding the adrenal suppression concerns associated with etomidate use. The study provided high-quality evidence supporting ketamine as a first-line induction agent for prehospital rapid sequence intubation [21].

For pain management specifically, Sandberg and colleagues performed a systematic review examining ketamine for the treatment of prehospital acute pain. Their analysis revealed significant pain reduction with ketamine administration without serious adverse events, supporting its use as an analgesic agent in prehospital trauma care [32]. Yousefifard et al. conducted a systematic review and meta-analysis specifically addressing the efficacy of ketamine administration in prehospital pain management of trauma patients, confirming substantial analgesic efficacy with an acceptable safety profile [38].

Mo and colleagues examined ketamine safety and use in the emergency department for pain and agitation management, analyzing a large health system's experience. Their review of ketamine use across diverse patient populations and indications demonstrated consistent safety and effectiveness, with few serious adverse events. This real-world evidence from routine clinical practice complemented findings from controlled trials [29].

Smischney et al. evaluated ketamine/propofol admixture (commonly known as "ketofol") as an induction agent for endotracheal intubation in the emergency department. This combination approach, which leverages the complementary properties of both agents, has gained popularity as a strategy to optimize hemodynamic stability while ensuring adequate sedation depth [36].

Reede and colleagues provided comprehensive guidelines for ketamine administration in trauma settings, synthesizing current evidence into practical recommendations for emergency medical services personnel. Their review emphasized the importance of proper training, appropriate patient selection, and adherence to established protocols to maximize safety and effectiveness [30].

Groth et al. surveyed current practices and safety of medication use during rapid sequence intubation, finding that ketamine has become increasingly accepted as a preferred induction agent in many emergency medical systems. This shift in practice patterns reflects the accumulating evidence supporting ketamine's favorable risk-benefit profile in emergency airway management [18].

3.4 Comparative Studies and Current Evidence Synthesis

Several systematic reviews and meta-analyses have synthesized the growing body of evidence regarding ketamine use in TBI. Sameer and Al Abbas conducted a systematic review and meta-analysis examining clinical outcomes of ketamine in patients with traumatic brain injury. Their analysis, which included multiple studies across diverse patient populations, concluded that ketamine was associated with favorable or neutral outcomes regarding mortality, neurological recovery, and hospital length of stay [31].

Zeiler and colleagues specifically examined the ketamine effect on ICP in traumatic brain injury, conducting a comprehensive systematic review of all available evidence. Their analysis concluded that in mechanically ventilated patients with controlled sedation, ketamine does not increase ICP and may actually reduce it in some circumstances. This review was instrumental in shifting clinical opinion regarding ketamine's role in neurocritical care [39].

Zanza et al. reviewed ketamine in acute brain injury from the perspective of cerebral circulation and electrical activity, examining both hemodynamic and neurophysiological effects. Their analysis emphasized that ketamine's effects on cerebral metabolism and blood flow are complex and context-dependent, but generally neutral or beneficial when used appropriately [40].

The evolution of ketamine's role is also reflected in historical analyses. Domino provided a comprehensive overview of "taming the ketamine tiger", discussing how this once-controversial agent has been rehabilitated through rigorous scientific investigation [13]. Mion examined the history of anaesthesia focusing on the ketamine story from past to present and future, placing current evidence in historical context and highlighting lessons learned about the importance of evidence-based medicine [28].

Studies examining ketamine's effects on spreading depolarizations have opened new avenues of research regarding potential neuroprotective mechanisms. These phenomena, which represent waves of neuronal and glial depolarization spreading through brain tissue, are increasingly recognized as important contributors to secondary brain injury. Ketamine's ability to modulate these events suggests mechanisms of benefit beyond simple maintenance of hemodynamic parameters [19], [20].

Research examining ketamine's effects on cerebral perfusion and hemodynamics has been particularly informative. Armstead and Vavilala discussed the role of adenosine and ATP in cerebral hemodynamic regulation, providing mechanistic insights into how ketamine's effects on these systems may contribute to maintained or improved cerebral perfusion[2]. Schmittner et al. examined effects of fentanyl and S(+)-ketamine on cerebral hemodynamics in patients with intracranial pathologies, demonstrating that the S-enantiomer of ketamine maintains the favorable hemodynamic profile of the racemic mixture [33].

Kolenda and colleagues studied ketamine for analgosedative therapy in intensive care treatment of head-injured patients, providing early evidence of safety in neurocritical care settings. Their work helped establish that ketamine could be safely used for ongoing sedation in mechanically ventilated TBI patients, not just for induction or single-dose administration [23].

The pediatric literature has paralleled adult studies in supporting ketamine's safety and efficacy. Cohen et al. provided a comprehensive review of pain management in trauma patients, emphasizing ketamine's unique advantages in pediatric populations where minimizing respiratory depression is particularly critical [11]. Green and Johnson's classic review of ketamine sedation for pediatric procedures established foundational knowledge regarding safe ketamine use in children that has been extended to emergency trauma care [16].

4. Discussion

This systematic review demonstrates a remarkable paradigm shift in our understanding of ketamine's role in traumatic brain injury management. The journey from absolute contraindication to routine use represents not only an evolution in medical knowledge but also exemplifies the critical importance of evidence-based medicine and the necessity of periodically re-evaluating long-held clinical dogmas.

The historical contraindication of ketamine in TBI was based primarily on early studies that, while methodologically sound for their era, failed to account for critical confounding variables. The landmark work by Shapiro et al. [35], conducted in 1972, examined ketamine in spontaneously breathing neurosurgical patients without controlled ventilation or concurrent sedation. Under these conditions, the observed ICP elevations likely resulted from increased cerebral blood flow secondary to hypercapnia and inadequate sedation, rather than from direct ketamine effects on cerebral vasculature [1], [15], [17].

Contemporary research has definitively demonstrated that when ketamine is administered to mechanically ventilated patients with controlled sedation and normocapnia, ICP either remains stable or decreases while cerebral perfusion pressure is maintained or improved [1], [12], [34], [39]. This finding has profound implications for prehospital emergency care, where ketamine's unique pharmacological profile offers distinct advantages over alternative agents.

The hemodynamic stability provided by ketamine is particularly valuable in TBI management. Unlike propofol, which commonly causes hypotension and may compromise cerebral perfusion, ketamine typically maintains or increases mean arterial pressure through sympathetic nervous system stimulation [23], [24], [33]. This characteristic is crucial because even brief episodes of hypotension in TBI patients are associated with significantly worse neurological outcomes and increased mortality [6], [10], [39].

The prehospital environment presents unique challenges that make ketamine's properties especially advantageous. Limited monitoring capabilities, unpredictable patient conditions, difficult working environments, and variable transport times necessitate agents with robust safety profiles and operational flexibility [14], [30], [32]. Ketamine's preservation of protective airway reflexes reduces the immediate need for definitive airway management in some patients, while its multiple routes of administration provide options when intravenous access is difficult to obtain [21], [25], [26].

The military medical experience has been particularly instructive in demonstrating ketamine's utility under austere conditions. Studies from combat casualty care show that ketamine can be safely and effectively used in severely injured patients with TBI, even in environments with minimal resources and monitoring [14], [22], [37]. These findings translate directly to civilian prehospital care, supporting broader adoption of ketamine in emergency medical services protocols.

Emerging evidence regarding ketamine's potential neuroprotective mechanisms adds another dimension to its therapeutic profile. The drug's NMDA receptor antagonism may reduce excitotoxicity and modulate spreading depolarizations, phenomena increasingly recognized as important contributors to secondary brain injury [19], [20], [40]. While these neuroprotective effects require further investigation in prospective clinical trials, they suggest that ketamine may offer benefits beyond simple maintenance of hemodynamic parameters.

The evolution of clinical guidelines reflects this accumulating evidence. Major trauma systems and military medical protocols have increasingly incorporated ketamine into standard treatment algorithms for severe TBI management [18], [30]. Emergency medicine and neurocritical care societies have revised their recommendations to recognize ketamine as an acceptable and often preferred agent for TBI patients requiring rapid sequence intubation or procedural sedation [9], [17], [31].

However, several important considerations warrant emphasis. Proper training in ketamine administration remains essential, as does appropriate patient selection and clinical judgment. Guidelines consistently emphasize that ketamine should be used as part of comprehensive TBI management protocols rather than in isolation [30], [34]. Adequate ventilation support and hemodynamic monitoring are critical components of safe ketamine use, and providers must be prepared to manage potential adverse effects including emergence phenomena and transient hypertension [13], [28], [29].

The pediatric literature has extended these safety findings across age groups, demonstrating that ketamine can be safely used in children with TBI when appropriate precautions are taken [11], [16], [24], [25], [26]. This is particularly important given the unique challenges of pediatric trauma care and the relative contraindications of some alternative agents in young children.

Future research should focus on several key areas. Optimal dosing strategies for different clinical scenarios require further definition through prospective studies. Long-term neurological outcomes following ketamine use in TBI need comprehensive evaluation through large-scale cohort studies with extended follow-

up. The potential neuroprotective mechanisms warrant investigation through basic science and translational research. Comparative effectiveness studies examining ketamine versus alternative agents across diverse patient populations would further inform evidence-based protocol development.

Cost-effectiveness analyses would also be valuable, particularly for resource-limited settings where medication costs and availability significantly influence protocol decisions. Implementation science research examining barriers and facilitators to ketamine adoption in prehospital systems could accelerate evidence-based practice changes. Quality improvement studies evaluating outcomes before and after ketamine protocol implementation would provide real-world effectiveness data.

5. Conclusions

This systematic review demonstrates that current evidence overwhelmingly supports ketamine as a safe and effective agent for prehospital traumatic brain injury management. Historical contraindications have been definitively refuted by methodologically rigorous studies showing neutral to beneficial effects on cerebral hemodynamics when ketamine is used with appropriate ventilation control and concurrent sedation.

Ketamine's unique pharmacological profile, combining effective analgesia and sedation with hemodynamic stability and preserved protective reflexes, makes it particularly well-suited for prehospital emergency care. The drug's versatility in administration routes and favorable safety profile compared to alternatives further enhance its utility in resource-limited and austere environments.

Clinical guidelines should continue evolving based on accumulating evidence, and healthcare systems should update protocols to reflect current knowledge. Regular re-evaluation of historical contraindications remains essential for evidence-based medicine, and the ketamine story serves as an important reminder of this principle.

Healthcare providers should receive appropriate training in ketamine use for TBI patients, with emphasis on the critical importance of ventilation control, hemodynamic monitoring, and integration into comprehensive trauma management protocols. Emergency medical services systems should consider incorporating ketamine into standard operating procedures for prehospital TBI management, with appropriate medical oversight and quality assurance mechanisms.

Future research should address remaining knowledge gaps including optimal dosing strategies, long-term neurological outcomes, potential neuroprotective mechanisms, and comparative effectiveness across diverse patient populations and clinical scenarios. Implementation science studies would facilitate evidence-based protocol adoption across emergency medical services systems.

In conclusion, ketamine has successfully transitioned from a contraindicated drug to a valuable and often preferred therapeutic option in prehospital traumatic brain injury management. This remarkable evolution exemplifies how rigorous scientific investigation can overturn longstanding clinical dogmas, ultimately improving patient care through evidence-based practice. The lessons learned from this journey should inform how we approach other controversial interventions and remind us of the necessity for continuous re-evaluation of clinical practices in light of emerging evidence.

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