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Ketamine and Pediatric PTSD: A Retrospective Analysis of Risk Following Anesthesia for Fractures

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Abstract

Introduction: Ketamine is widely used for pediatric procedural sedation, but its long-term psychological effects remain unclear. This study examines the incidence of post-traumatic stress disorder (PTSD) and depression in children receiving ketamine versus other anesthetics for fracture management.

Methods: A retrospective cohort study was conducted on 677,189 children aged 6–18 who received ketamine or another anesthetic. After 1:1 propensity score matching, the final cohort included 15,250 cases and 15,250 controls for PTSD and depression analyses. PTSD and depression incidence were assessed at 1 week, 1 month, 6 months, and 1 year post-exposure using survival analysis and risk estimation.

Results: Children in the ketamine group had a significantly higher risk of PTSD at 1 month (RR = 2.4, p = 0.016), 6 months (RR = 1.89, p = 0.026), and 1 year (RR = 1.70, p = 0.026). Kaplan-Meier analysis confirmed a lower probability of PTSD-free survival in the ketamine group. No significant difference in depression risk was observed at any time point (p > 0.05).

Conclusion: Ketamine exposure in children was associated with increased PTSD risk up to 1 year post-exposure, while no impact on depression was observed. These findings highlight the importance of long-term psychological monitoring following ketamine administration. Further research is needed to explore underlying mechanisms and potential mitigation strategies.

Keywords: Ketamine; Post-traumatic Stress Disorder (PTSD); Depression; Trauma

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Introduction

Ketamine, is a phencyclidine derivative and a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. It demonstrates greater anesthetic potency and fewer side effects [1]. Ketamine's pharmacological profile includes dissociative anesthesia, analgesia, amnesia, and sympathomimetic effects, making it useful for short procedures and trauma care. However, its use is associated with side effects such as emergence reactions, hallucinations, agitation, and potential for abuse and dependence [2].

In pediatrics, ketamine is widely used for procedural sedation due to its rapid onset and favorable safety profile, especially its ability to preserve airway reflexes and spontaneous respiration. A systematic review of pediatric dental sedation found that ketamine, alone or in combination with other agents, effectively reduced anxiety and improved cooperation in children undergoing procedures [3]. Additionally, its use in emergency and prehospital settings for children has been associated with significant pain reduction and low rates of adverse events [4]. Given these properties, ketamine continues to be a preferred agent for short procedural interventions and fracture management in pediatric patients.

More recently, ketamine has gained attention for its off-label use in adults with treatment-resistant depression (TRD). Intravenous ketamine has demonstrated rapid antidepressant effects, sometimes within hours, particularly in individuals unresponsive to conventional therapies [5]. This led to the FDA approval of intranasal esketamine (Spravato) for TRD in adults [6]. Despite its growing use, long-term safety concerns, risk of dissociation, and abuse potential remain areas

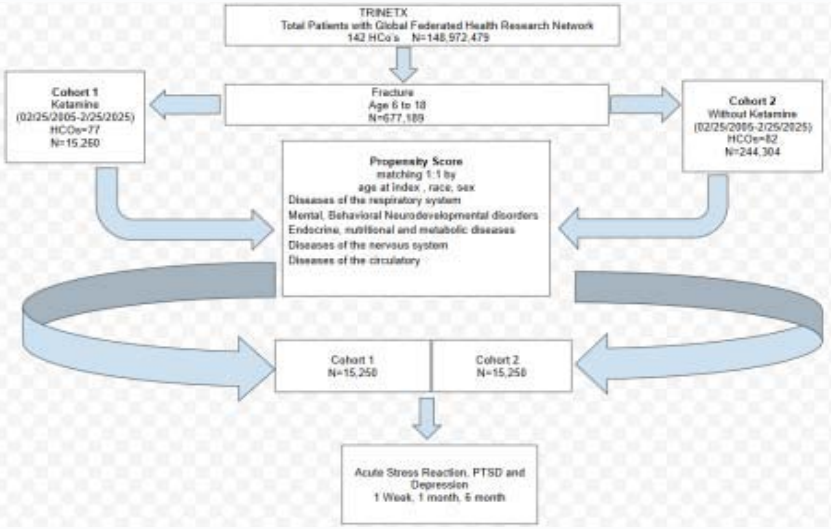

Figure 1: Flow Diagram showing Cohort Selection.

of active research and debate. This study investigates the long-term psychological effects of ketamine exposure in children undergoing fracture management.

Methods

Study Design

This study utilized a nationwide retrospective cohort study. The study examined the rates of PTSD for children with fractures using ketamine *vs*. other anesthetics using TriNetX Research Network. De-identifed data from the TriNetx Health Network for 677,189 children ages 6 to 18 who received either ketamine or another anesthetic for fracture management was used. Acute stress reaction, PTSD and depression were identified using pre-established ICD10 codes within the TriNetX database. The ICD10 codes corresponding to the measured outcomes were used to formulate the case definition. The time window for the analysis began 1 day after the exposure to the index event. The study excluded patients with the event of interest before this time window.

Data Analysis

Statistical analysis was done using the TriNetX platform. A 1:1 propensity score matching was conducted to control for confounding variables between cohorts based on age at index, race, sex, and respiratory, mental, behavioral and neurodevelopmental, endocrine, nutritional, metabolic, nervous system and circulatory diseases. This subsequently refined the cohort to 15,250 cases and 15,250 controls (Figure 1).

The incidence, risk ratio (RR), odds ratio (OR), and hazard ratio (HR) were calculated for each outcome. For PTSD and Depression, incidence, RR and OR were calculated at 1-week, 6-month and 1-year follow-up intervals. However, ASR was only evaluated at the 1-week and 1-month interval. The Kaplan-Meier survival analysis was used in calculating hazard ratios for each clinical outcome. Significance for this study was set at $p<0.05$.

Ethical Considerations

This study involved secondary analysis of de-identified data and was conducted in compliance with the standards outlined in the HIPAA Privacy Rule. As no direct interaction or intervention with human subjects occurred, the study was exempt from informed consent requirements.

Results and Discussion

At one week post-exposure, statistical analysis revealed no significant difference in the risk of acute stress reaction (ASR) between children who received ketamine and those who received other anesthetics. The odds of developing ASR were not significantly elevated in the ketamine group compared to the control group. Similarly, there was no significant difference in the incidence of depression between the two groups at this time point. Overall, the analysis demonstrated no association between ketamine exposure and an increased risk of depression in the immediate post-injury period.

At one month post-exposure, children who received ketamine exhibited a significantly higher risk of developing acute stress reaction (ASR) compared to those in the control group, with a 2.4-fold increased risk ($p = 0.016$). This finding was further supported by Kaplan-Meier survival analysis, which demonstrated a significantly elevated hazard ratio (HR = 5.903, p = 0.000), indicating a substantially greater likelihood of developing ASR over time in the ketamine group. However, among those who developed ASR, there was no significant difference in the number of episodes between the two groups. In contrast, the analysis of depression outcomes revealed no significant difference in incidence between children treated with ketamine and those in the control group ($p = 1.000$). The risk ratio, odds ratio, and hazard ratio for depression were all non-significant, suggesting that ketamine exposure in the context of fracture management does not increase the short-term risk of depression. Additionally, the number of depression episodes did not differ significantly between groups ($p = 0.369$).

At six months post-exposure, children who received ketamine demonstrated a significantly higher risk of developing post-traumatic stress disorder (PTSD) compared to those who received other anesthetics. The risk of PTSD was nearly twice as high in the ketamine group ($p = 0.026$). This finding was reinforced by Kaplan-Meier analysis, which revealed a significantly elevated hazard ratio (HR = 1.837, p = 0.000), indicating an increased likelihood of developing

Table 1: Comparison of PTSD Incidence Between Ketamine and Control Groups at 1 Week, 1 Month, 6 Months, and 1 Year Post-Anesthetic Exposure.

TIME POINT	KETAMINE INCIDENCE	CONTROL RISK RATIO P-VALUE INCIDENCE
1 week	0.001	0.001 1.9 0.095
1 month	0.002	0.001 2.4 0.016
6 months	0.002	0.001 1.889 0.026
1 year	0.003	0.002 1.704 0.026

Table 2: Comparison of Depression Incidence Between Ketamine and Control Groups at 1 Week, 1 Month, 6 Months, and 1 Year Post-Anesthetic Exposure Depression Results.

TIME POINT	KETAMINE INCIDENCE	CONTROL RISK RATIO P-VALUE INCIDENCE
1 week	0.001	0.001 1.0 0.095
1 month	0.001	0.001 1.0 0.016
6 months	0.001	0.002 0.808 0.026
1 year	0.003	0.003 0.769 0.026

PTSD over time among ketamine recipients. Despite this elevated risk, the number of PTSD episodes did not differ significantly between the groups. In contrast, analysis of depression outcomes showed no significant difference in risk between the ketamine and control groups. The risk ratio, odds ratio, and hazard ratio for depression were all non-significant, suggesting that ketamine exposure does not increase the likelihood of developing depression at six months post-treatment. Additionally, there was no significant difference in the number of depression episodes between groups ($p = 0.097$).

At one year post-exposure, children who received ketamine demonstrated a significantly higher risk of developing post-traumatic stress disorder (PTSD) compared to those who received other anesthetics, with a 70% increased risk in the ketamine group ($p = 0.026$). Kaplan-Meier analysis revealed a significant difference in survival curves between the groups ($p = 0.028$); however, the corresponding hazard ratio (HR = 1.694) did not reach statistical significance ($p = 0.116$), suggesting some uncertainty regarding the long-term trajectory of PTSD development. Interestingly, while the ketamine group was more likely to develop PTSD, the control group experienced significantly more PTSD episodes ($p = 0.027$), indicating that although ketamine may elevate the risk of PTSD, the severity or recurrence of symptoms may be lower. In terms of depression, no significant differences were found between the ketamine and control groups at the one-year mark. The risk ratio, odds ratio, and hazard ratio for depression were all non-significant, suggesting that ketamine exposure does not increase the long-term risk of depression. Although the control group exhibited a higher number of depression episodes, this difference did not reach statistical significance ($p = 0.082$).

The findings suggest that children who received ketamine had a significantly higher risk of developing PTSD at one month, six months, and one year post-exposure compared to those who received an alternative anesthetic (Table 1). The risk was nearly twice as high at six months (RR = 1.889, p = 0.026) and remained elevated at one year (RR = 1.704, p = 0.026). Kaplan-Meier survival analysis further confirmed that children in the ketamine group had a significantly lower probability of remaining PTSD-free. However, while the incidence of PTSD was higher in the ketamine group, the number of PTSD episodes was generally lower than in the control group, suggesting that while ketamine may increase PTSD susceptibility, its severity might be milder than in non-ketamine-exposed children.

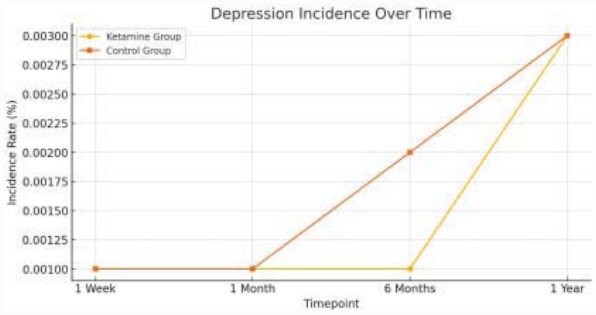

Figure 2: Graph showing incidence of depression in children treated with ketamine *vs*. other anesthetics following fracture management in the following one year.

Our study's findings align with emerging evidence from recent literature highlighting the potential psychological risks of ketamine exposure in pediatric populations. Similar to our results, a systematic review and meta-analysis reported that while ketamine did not consistently prevent PTSD, it may worsen symptoms in patients already vulnerable to trauma-related disorders, likely through overstimulation of stress-related neurobiological pathways and memory fragmentation [7]. Furthermore, a large-scale retrospective study examining psychiatric outcomes following ketamine use in orthopedic surgeries found that pediatric patients exhibited a higher risk of developing psychiatric conditions, including PTSD, compared to other age groups [8]. These parallels reinforce our findings that ketamine use in children undergoing fracture management is associated with a significantly higher risk of developing PTSD at multiple follow-up intervals. These studies underscore the importance of long-term psychological monitoring and cautious use of ketamine in pediatric trauma care.

On the contrary, ketamine exposure was not associated with an increased risk of depression at any time point. The risk ratios, odds ratios, and hazard ratios for depression remained non-significant across all follow-ups, indicating that ketamine did not contribute to long-term depressive symptoms. Interestingly, the control group reported slightly more episodes of depression than the ketamine group, though this difference did not reach statistical significance. These results align with prior research suggesting that ketamine has rapid-acting antidepressant properties, potentially mitigating the risk of post-operative depression [9]. However, the persistent elevation in PTSD risk raises concerns about ketamine's potential effects on stress-related psychiatric disorders, warranting further investigation into the underlying neurobiological mechanisms.

In contrast to our findings, a study has demonstrated a potential protective effect of ketamine-exposure in adults with prior diagnosis of trauma-related psychiatric outcomes. The study involved a cohort of U.S service members, who had suffered severe combat injuries and found the odds of developing PTSD in one year post injury was reduced when given ketamine prior to hospitalization. However, these results were only significant among patients who had not suffered a traumatic brain injury prior to ketamine-exposure. Mechanistically, the study proposes that ketamine may offer a long-term protective effect by potentially modulating the stress response, reducing acute pain or altering the consolidation of traumatic memories [10]. The discrepancy of the findings from our study may suggest that patient age, psychiatric history, and time of ketamine exposure is significant in determining the analgesics effect.

The proposed mechanism by which ketamine exposure may increase the risk of PTSD in children undergoing fracture management involves its dual action on neurochemical pathways. As a non-competitive NMDA receptor antagonist, ketamine blocks glutamate release in the brain, potentially disrupting normal traumatic memory consolidation. This disruption may lead to heightened dissociative symptoms and fragmented traumatic memories, which are hallmark features of chronic PTSD [11]. Additionally, ketamine's strong sympathomimetic effects may paradoxically enhance the consolidation of traumatic experiences, especially when administered immediately after the traumatic event.This combined interference with and reinforcement of trauma-related memory processing could contribute to the increased incidence of PTSD observed in pediatric patients receiving ketamine for fracture management [11, 12].

Overall, these findings indicate that ketamine use in children is associated with an increased risk of developing PTSD within one year of exposure, although the clinical severity may be attenuated. No association was found between ketamine and long-term depression. These results underscore the importance of ongoing psychological monitoring in pediatric patients receiving ketamine, particularly in trauma-related settings. Future research should aim to further elucidate the neurobiological mechanisms underlying ketamine's role in traumatic memory processing and PTSD development in children. Longitudinal studies with extended follow-up periods are needed to determine whether the observed psychological effects persist beyond one year or resolve over time. It is also crucial to explore whether specific dosing strategies, timing of administration, or co-administration with other agents might reduce the risk of adverse psychological outcomes. Comparative trials evaluating ketamine against other anesthetic agents in pediatric trauma populations could inform safer sedation protocols.

Limitations

This study has several limitations. First, as a retrospective cohort study, it is subject to potential confounding variables despite rigorous propensity score matching. While we controlled for key demographic and clinical factors, other unmeasured variables, such as pre-existing trauma history or environmental stressors, could influence PTSD and depression risk. Second, the study relies on diagnostic coding from medical records, which may not fully capture subclinical psychiatric symptoms or misclassified diagnoses. Third, the follow-up period was limited to one year, and it is unclear whether PTSD risk persists or resolves over a longer duration. Future research should incorporate longitudinal prospective studies with validated psychiatric assessments to further elucidate ketamine's long-term psychological effects in pediatric populations.

Conclusion

This retrospective cohort study provides evidence that ketamine exposure in children undergoing fracture management is associated with an increased risk of PTSD up to one-year post-exposure. At the same time, no significant relationship was found with depression. These findings highlight the need for long-term psychological monitoring in pediatric patients receiving ketamine for procedural sedation. While ketamine's potential role as an antidepressant is supported by its neutral effect on depression incidence, its impact on stress-related disorders warrants further investigation. Clinicians should carefully consider these risks when selecting anesthetic agents for pediatric populations, particularly in children with a history of trauma or psychiatric vulnerability. Future research should explore alternative anesthetic options, long-term psychiatric trajectories, and potential interventions to mitigate PTSD risk following ketamine exposure.

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Submission Declaration

The authors declare that this manuscript is original, has not been published elsewhere, is not under consideration for publication elsewhere, and has been approved by all authors and relevant authorities. If accepted, it will not be published elsewhere in the same form, in any language, without the consent of the copyright holder.

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