Subanesthetic-Dose Ketamine to Decrease Emergence Delirium in the Surgical Patient With Posttraumatic Stress Disorder

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Recently, emergence delirium (ED) has been associated with patients with posttraumatic stress disorder (PTSD). Currently, no research exists to support best practice in this population. Identification of the pathophysiologic alterations that occur in ED and PTSD can guide pharmacotherapy. Emerging evidence suggests that glutaminergic dysfunction plays a role in ED and PTSD. A comprehensive understanding of the glutaminergic alterations that occur in ED and PTSD exposes a potential for pharmacologic intervention.

The anesthetic agent ketamine modulates glutamate neurotransmission via N-methyl-D-aspartate (NMDA) receptor antagonism. By appreciating the relationship that exists between ED, PTSD, and glutamate, one can extrapolate that a subanesthetic dose of ketamine may decrease ED in the surgical patient with PTSD.

Keywords: Emergence delirium, glutamate, ketamine, NMDA antagonist, posttraumatic stress disorder.

Emergence delirium (ED) is an acute alteration in neurologic psychomotor functioning that occurs in the immediate postoperative period. Emergence delirium transiently manifests as lethargy, confusion, combativeness, and/or severe disorientation. It is estimated to occur in 4.7% to 19% of adult patients emerging from general anesthesia. ED may result in major consequences due to incidental traumas such as self-extubation, removal of catheters, and injury to both the patient and staff. Management of ED may require pharmaceutical intervention, physical restraint, and additional staffing, potentially prolonging length of stay in the postanesthesia care unit. Recently a surge of research has associated ED with PTSD. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), PTSD is a debilitating disorder characterized by reexperiencing, avoidance, negative cognitions/mood, and arousal following exposure to actual or threatened death, serious injury, or sexual violation. The lifetime prevalence of PTSD has been estimated at 8.3% of the total population in the United States and is potentially as high as 31% in certain populations, such as military personnel and veterans. Patients with PTSD have reported higher rates of comorbid medical and psychological disorders, which may increase utilization of medical and surgical services.

Anesthesia providers caring for military service members have reported an increased incidence of ED compared with the general public. PTSD has been identified as an independent predictor of ED. Despite growing interest, there is no research supporting any pharmacologic intervention to decrease ED in patients with PTSD. Current research coupled with proposed pathophysiology suggest that in the surgical patient with PTSD undergoing general anesthesia subanesthetic dose ketamine will decrease ED.

Despite increasing concern among anesthesia providers correlating an increased incidence of ED in patients with PTSD there is no available literature, to the author’s knowledge, that supports any pharmacologic intervention, let alone endorsement of the use of subanesthetic-dose ketamine. In fact, many references available to the anesthesia provider explicitly name ED as an adverse effect of ketamine. Ketamine binds to N-methyl-D-aspartate (NMDA) receptors and inhibits their activation by the excitatory neurotransmitter, glutamate. Ketamine further decreases the presynaptic release of glutamate. Glutamate is the most abundant excitatory neurotransmitter in the central nervous system (CNS) and has gained increasing recognition for its pathophysiologic involvement in psychiatric disorders, including PTSD.

The rationale to use subanesthetic-dose ketamine evolved after looking at the proposed pathophysiologic alterations in PTSD and ED, noting that glutaminergic neurotransmission has been implicated in various pathways in both disorders. Both PTSD and ED are initially provoked by stress, and glutamate neurotransmission is increased during times of stress. Subsequently, the increased levels of glutamate result in various alterations in multiple areas of the brain that are responsible for fear, excitation, and stress behaviors. Therefore, by decreasing available glutamate binding sites on NMDA receptors and inhibiting further excessive release of glutamate, subanesthetic-dose ketamine should decrease ED in the surgical patient with PTSD.
This treatment intervention seems counterintuitive, because ketamine has been known to elicit ED. The incidence is increased in patients with psychological and personality disorders, and when administered in doses (> 2 mg/kg) used with induction of anesthesia.1,3,23 However, avoiding the use of ketamine in patients with mental illness has been proven unnecessary since the advent and popularity of treating PTSD with subanesthetic doses of ketamine.21,24,25 Recently, subanesthetic doses of ketamine have resulted in the reduction of symptoms in patients with chronic refractory PTSD.21,24,25 Additionally, in the pediatric population ketamine has yielded success in reducing the risk of ED in pediatric patients undergoing general anesthesia with sevoflurane.26 The suggested doses of ketamine to decrease postoperative pain, pediatric ED, PTSD, and depression have varied anywhere from 0.15 mg/kg to 0.5 mg/kg24,26-28 based on ideal body weight.

Review of Literature

• **Physiology of Glutaminergic Neurotransmission.** Glutamate is the principle excitatory neurotransmitter in the CNS, and is highly concentrated in the brain.29 As an excitatory neurotransmitter, glutamate is secreted by the presynaptic terminal30 and depolarizes an ionotropic channel, which allows for the influx of cations through the cell membrane.1,3,23 The most common channel activated by glutamate is the NMDA receptor,31 which allows for the exchange of not only sodium and potassium but also calcium3 (Figure 1). Located throughout the brain and spinal cord, NMDA receptors are most heavily concentrated in the limbic system, particularly the amygdala and hippocampus, as well as the medial prefrontal cortex (mPFC).11,31 Activation of the NMDA receptor by glutamate initiates a series of chemical events that result in learning, memory, and the appreciation of pain.1,32

  • **The Stress Response.** The amygdala, hippocampus, and mPFC play an important role in the response to emotional and physical stressors. The amygdala receives such input and communicates feelings of fear and excitation to the hypothalamus, which has also been implicated in the response to auditory stimuli.11 The hypothalamus elicits the “fight or flight” response.11,30 The hippocampus is involved in the consolidation of memories, in addition to the ability to retrieve information, which allows a future response to similar situations.11,30,32 The hippocampus decreases fear and anxiety by inhibiting the amygdala,32 whereas the mPFC is responsible for carrying out thought processes such as cognitive behaviors, personality, decision making, and the planning of motor activities.30 Like the hippocampus, the mPFC has inhibitory control over the amygdala.32 Together, the amygdala, hippocampus, and mPFC relay information to other areas of the CNS and allow for a desired response to stress (Figure 2).

  • **Pathophysiology of Posttraumatic Stress Disorder.** A growing body of evidence supports the hypothesis that the hyperactive glutaminergic response associated with severe emotional and/or physical stress plays a major role in the pathophysiology of PTSD.11,22,32 Glutaminergic neurotransmission between the hippocampus, amygdala, and mPFC determine how the brain processes stressful stimuli and if these stimuli will reach conscious experience.4,11,22 During times of severe and uncontrollable stress, a massive release with impaired reuptake of glutamate occurs. Excessive extracellular glutamate increases stimulation of NMDA receptors, allowing a substantial influx of calcium ion into the neuron, which potentiates both short-term and long-term changes to neuronal tissue. Glutaminergic excess in exclusivity is associated with sufficient increases in intracellular calcium to cause irreversible changes to the cell, including cell death.22

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**Figure 1.** Synaptic Neurotransmission Pathway, Glutaminergic Excitation
Abbreviation: NMDA, N-methyl-D-aspartate.

**Figure 2.** Response to Stress
Abbreviation: mPFC, medial prefrontal cortex.
Additionally, increased glutaminergic tone causes dendritic remodeling of the mPFC and hippocampus, decreasing their overall volume and function. This decrease results in an impairment of the mPFC and hippocampal inhibitory control over the amygdala. The damaged hippocampus and mPFC allow an unopposed amygdala to transmit feelings of fear, hyperresponsiveness, excitation, and memory distortion to other areas of the CNS.11,22

- **Suggested Pathophysiology of Emergence Delirium in Posttraumatic Stress Disorder.** Commonly used anesthetic agents target receptors located on the amygdala and hippocampus, resulting in amnesia. Termination of anesthesia allows the agent to leave these areas of the brain, and emergence and awakening follow.4,11,23 Hearing is the first of the senses to return, and it is thought that unfamiliar auditory stimuli in the operating room trigger an exaggerated fear response driven by the already hyperresponsive amygdala.4,11 Additionally, the weakened hippocampus cannot accurately relay consolidated memory information to the hyperactive amygdala. The result is an altered perception of nonthreatening stimuli, causing an impairment in normal judgment.9,11 (Figure 3). These alterations manifest as the dissociative symptoms of ED that are unique to a patient with PTSD, such as flashbacks, re-creating battlefield experiences, shouting battle instructions, and violent behavior.9

- **Pharmacodynamic Theory to Support Ketamine Use.** Much of the pathophysiology of ED and PTSD is not yet fully understood. However, research has indicated that contributions of excessive glutamate to the acute and chronic sequelae of stress yield a potential for therapeutic and neuroprotective effects. Inhibition of excessive activation of NMDA receptors is thought to achieve a level of glutaminergic homeostasis. Currently there are no known studies that have evaluated the NMDA-antagonist ketamine as a treatment of ED in patients with PTSD. Predictions of the clinical effects may be made based on an understanding of the pathophysiologic alterations proposed in both PTSD and ED. Although many neurobiological pathways play a role in the failure of the stress response to be appropriately expressed during emergence of anesthesia in patients with PTSD, the dysregulation of the glutaminergic pathway appears to augment these stress responses at critical sites.

Glutamate has been implicated in a variety of short-term and long-term alterations that occur to the neurons and the tissues of the amygdala, hippocampus, and mPFC. Because of the excitotoxic nature of excessive glutamate from prolonged stimulation, ketamine may decrease any further structural damage from the acute stresses of surgery and anesthesia. Ketamine may also suppress conditioned fear responses during emergence by reducing stimulation of the overdriven amygdala. This may potentially enable some of the advantageous intrinsic functions of the hippocampus and mPFC by further abating the amygdala’s contribution to the stress response.

**Clinical Recommendations**

This article identifies a gap in knowledge that exists in anesthesia practice. Currently, no evidence-based intervention exists for decreasing ED in patients with PTSD. Initial research is needed to support or refute the use of subanesthetic doses of ketamine to decrease ED in patients with PTSD. Furthermore, various unknowns exist in the pharmacokinetics and pharmacodynamics of subanesthetic-dose ketamine. With the dosage used for induction of anesthesia, ketamine has an onset of 3 to 5 minutes and is eliminated within 2 to 3 hours.1 However, research using single-dose subanesthetic ketamine for treatment of PTSD illustrates rapid beneficial clinical effects that extend far beyond total elimination from the body, lasting 7 to 14 days.21,24,25 The exact mechanisms of the long-term signaling cascade that occurs after a single subanesthetic dose of ketamine remain undiscovered. Regardless, promising results are evident when
subanesthetic-dose ketamine is used in patients with PTSD.\textsuperscript{21,24,25}

Current guidelines for the management of ED in patients with PTSD suggest a perioperative approach, beginning with the identification of PTSD and other mental health disorders preoperatively.\textsuperscript{8,10} To anticipate ED on emergence and in the postoperative period, Lovestrand et al\textsuperscript{10} recommend that providers promote trust and alleviate anxiety by acknowledging the patient’s concerns and identifying known triggers of PTSD.\textsuperscript{10} The provider also should include a family member or friend who may provide emotional support into the postoperative period.\textsuperscript{10} Intraoperative and postoperative staff should be involved in the plan for stimulation reduction by dimming the lights and speaking in quiet voices during awakening.\textsuperscript{10}

**Conclusion**

Unfortunately, experiencing a trauma is a common occurrence; 89.7% of the general population have met DSM-V criteria for traumatic event exposure.\textsuperscript{17} Subsequently, 8.3% will receive a diagnosis of PTSD in their lifetime.\textsuperscript{17} It is estimated that 4.7% of adults have a clinical diagnosis of PTSD during any given year.\textsuperscript{17} Only 49.9% of individuals given this diagnosis will go on to receive treatment; the remainder go untreated or untreated.\textsuperscript{33} Recently, evidence and clinical practice have identified an association between ED in those with PTSD\textsuperscript{7-9,11-15} and identifying known triggers of PTSD.\textsuperscript{10} The provider also should include a family member or friend who may provide emotional support into the postoperative period.\textsuperscript{10} Intraoperative and postoperative staff should be involved in the plan for stimulation reduction by dimming the lights and speaking in quiet voices during awakening.\textsuperscript{10}

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**DISCLOSURES**

The author has declared no financial relationships with any commercial entity related to the content of this article. The author did not discuss off-label use within the article.