Successful Use of Ketamine for Central Neurogenic Hyperventilation: A Case Report

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Abstract

This report describes the use of ketamine in a patient with central neurogenic hyperventilation following intracerebral hemorrhage. A 41-year-old man was admitted with right thalamic intracerebral hemorrhage with intraventricular extension requiring emergent external ventricular drain placement. After aggressive management of his neurologic status and other associated complications, the patient subacutely developed an altered respiratory pattern characterized by shallow, rapid breaths. After the use of multiple sedative agents to control respiratory drive had failed, a single 2 mg/kg bolus dose of intravenous ketamine was administered. In the 6 hours prior to ketamine dosing, respiratory rate ranged from 24 to 40 breaths per minute. Within minutes of ketamine administration, respiratory patterns improved and primarily ranged from 16 to 20. Twenty-four hours after ketamine administration, the patient was successfully extubated following 12 days of mechanical ventilation. Further research is needed to determine the widespread applicability of this strategy.

Keywords

hyperventilation, ketamine, intracerebral hemorrhage

Introduction

Central neurogenic hyperventilation (CNH) remains a diagnosis of exclusion with clinical criteria that include persistent hyperventilation during sleep and arterial blood gases characterized by a pure respiratory alkalosis.¹ This disease process has been associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia, diffusely infiltrating B-cell lymphoma, glioblastoma multiforme, anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, and chronic lacunar strokes.² Although largely associated with pathologies of the brain stem and cerebellum, the pathophysiology of CNH is unclear with no delineated structural pathway. Treatment options remain limited. In our center, we describe a patient who had characteristics of CNH after a large intracerebral hemorrhage (ICH) that proved refractory to conventional supportive treatments consisting of agitation and pain control. A single, bolus dose of ketamine was administered off-label and alleviated his refractory hyperventilation, resulting in successful extubation.

Case Report

A 41-year-old, African American male with medical history of end-stage renal disease on hemodialysis, seizure disorder,

hypertension, diabetes, asthma, chronic anemia, and previous right parietal hemorrhagic cerebral abscess presented with confusion and left-sided paresis. Initial Glasgow Coma Scale was 6, and the patient was emergently intubated. Computed tomography scan of the head revealed a hypertensive moderately large, right thalamic ICH (hematoma volume: 23 mL³; ICH score: 3) with intraventricular extension (IVH) into the lateral, third, and fourth ventricles. His treatment for ICH and IVH included the following: emergent placement of an external ventricular drain (EVD), aggressive blood pressure control,

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Table 1. Medication Treatments Aimed at Controlling Respiratory Rate.

Medication	Time Frame
Albuterol/ipratropium nebulization	ICU days 2-11
Broad-spectrum antibiotics for health-care-associated pneumonia	ICU days 4-12
Oxycodone 5 mg NGT every 4 hours	ICU days 6-10
Quetiapine 25 mg NGT twice daily	ICU days 6-7
Quetiapine 50 mg NGT twice daily	ICU days 7-8
Hydromorphone 1 mg IV every 1 hour as needed for pain	ICU days 9-11
Quetiapine 12.5 mg NGT twice daily	ICU days 9-10; ICU days 11-13
Oxycodone 10 mg NGT every 4 hours	ICU days 10-12
Ipratropium nebulization	ICU days 11-15
Ketamine 200 mg IV push	ICU day 11

Abbreviations: ICU, intensive care unit; IV, intravenous; mg, milligrams; NGT, nasogastric tube.

Figure 1. Patient respiratory patterns.

continuous renal replacement therapy, and a single dose of intraventricular alteplase for facilitation of IVH drainage.

The patient was stabilized; however, during his first week of hospitalization, he developed altered respiratory patterns, worsening oxygenation, and copious secretions. He underwent a bronchoscopy and bronchoalveolar lavage and received broad-spectrum antibiotics for pneumonia (Table 1). Following his pneumonia, he developed and maintained a hyperactive respiratory drive. Initially, he was sedated with continuous infusion propofol and then transitioned to dexmedetomidine to improve his mental status. During this time,

the dose of dexmedetomidine was titrated to a maximum infusion rate of 1.4 $\mu\text{g/kg/h}$ for approximately 24 hours; his respiratory rate improved to a range of 14 to 20 breaths per minute. Sedation was weaned after the initiation of scheduled quetiapine and oxycodone for agitation and pain control, respectively. However, despite optimization of the aforementioned interventions, the patient's altered respiratory drive returned on hospital day 10 with rates as high as 40 breaths per minute (Figure 1). Throughout this time period, Riker Sedation-Agitation Scale scores were consistently documented as 3 to 4 per the bedside nurse.

Prior to his aberrantly high respiratory drive, the patient had been oxygenating adequately with plans for extubation. However, this spontaneous elevation in respiratory rate coupled with his marginal neurological examination compromised his extubation. Underlying pathologies that may have resulted in a reactive tachypnea (ie, infection or sepsis, pulmonary embolism, pain, agitation) were ruled out. Finally, as a diagnosis of exclusion, the patient was diagnosed with CNH. At day 11, only continuous infusion of sedation had proved effective in controlling his respiratory rate. At this point, the treating team administered a single bolus dose of ketamine (2 mg/kg) as an alternative to control his respiratory drive. Within 1 hour of ketamine administration, his respiratory rate returned to less than 20 breaths per minute with few outliers (Figure 1). The patient was successfully extubated on intensive care unit (ICU) day 12, with all scheduled medications for agitation and pain control weaned within 48 hours of ketamine administration. After several days of close monitoring, the patient's respiratory rate remained controlled and he was transferred to a lower level of care on day 16. Verbal informed consent to write this report was obtained from the next of kin during the patient's hospitalization. After treatment in a lower level of care for 5 days, the patient was transferred back to the ICU for possible pneumonia. Family made the decision to transition care to comfort measures only and the patient died.

Discussion

Management of CNH in patients with severe neurologic injury presents a challenging clinical scenario for clinicians because of its limited treatment options with opioids typically used to decrease respiratory rate and decrease oxygen consumption.³ We describe a patient whose high respiratory rate proved refractory to opioids, continuous infusion sedatives, and antipsychotic agents. We administered a single, bolus dose of ketamine that resulted in reduced respiratory rate and successful extubation.

We considered ketamine as a potential treatment option for several reasons. First discovered in 1962, ketamine has been widely used for induction of general anesthesia, procedural sedation, spinal anesthesia, rapid sequence intubation, and postoperative pain management.⁴ Ketamine is a strong bronchodilator that results in intact upper respiratory reflexes. It also stimulates central nervous system outflow and decreases catecholamine reuptake, demonstrating favorable effects on hemodynamic status.⁴ Additionally, ketamine exerts its pharmacologic effects not only by acting at multiple opioid receptors (μ and κ) but also serving as an antagonist to NMDA receptors.⁵ Our patient had been treated with conventional therapies without stabilization of respiratory drive, making the dual mechanism of ketamine an attractive treatment approach.

The NMDA neurotransmitter system has been previously shown to aid in controlling respiration in adults, as the absence of a functioning NMDA receptor pathway may lead to acute respiratory failure and death.⁶ Animal models have shown that

hypoxia is associated with increased levels of circulating glutamine and leads to potential NMDA receptor hyperactivity.⁷ A report of CNH in a patient with anti-NMDA receptor encephalitis further demonstrates the potential role of NMDA in controlling respiratory drive.⁸ We suggest that a functional neurotransmitter imbalance characterized by the presence of low inhibitory tone and hyperactivity of NMDA receptors may lead to hyperactive respiratory patterns.⁸ Antagonism of NMDA receptors by ketamine may blunt the excitability caused by glutamine excess and may facilitate stabilization of respiratory drive.

Second, NMDA receptor antagonism with ketamine has been shown to prevent the development of central sensitization, also known as the "windup phenomenon." This unique effect has been shown to reduce the development of chronic pain and opioid tolerance, as well as improve the efficacy of administered opioid doses.⁹ On the day of treatment with ketamine, the patient had received his scheduled dose of oxycodone both 7 hours and 1 hour prior to ketamine administration. Since our patient had received prolonged treatment with opioids, we believed the administration of ketamine would facilitate an enhanced response to continued treatment with opioids and further aid in controlling respiratory drive. There is evidence to suggest that ketamine may minimize hypoventilation and actually stimulate respiratory drive in patients undergoing deep sedation for procedures. In a study of 54 women undergoing breast surgery, severe hypoventilation was found to be significantly lower (0% vs 28%) in patients who received ketamine in addition to propofol and midazolam for procedural sedation.¹⁰ This evidence may suggest that, in our patient, the beneficial effects observed may be due to ketamine administration enhancing the effects of opioids. However, it is difficult to apply data from noncritically ill women undergoing elective surgery to our patient, as ketamine may have varying effects based upon numerous factors including gender, critical illness, and use of concurrent medications.

Other beneficial effects of ketamine may also aid in treating CNH. One potential pathophysiologic mechanism is an increase in inflammatory cytokines that directly stimulate the respiratory control centers in the pons and medulla leading to excessive hyperventilation.¹¹ Ketamine has been shown to have indirect immunomodulatory effects with perioperative administration, resulting in lower interleukin 6 levels and reflecting a reduced inflammatory state.¹² A second review also demonstrated that ketamine serves as a "homeostatic regulator" of the acute inflammatory response and reduces stress-induced immune disturbances.¹³ Based upon these downstream effects, ketamine may potentially possess another mechanism that makes it an attractive option at managing excessive hyperventilation following neurologic injury.

Given the pharmacokinetics of ketamine, we felt that a single, bolus dose would allow us to assess its efficacy in correcting hyperventilation. The onset of action following an intravenous dose of ketamine is 30 to 60 seconds, with maximal effect seen soon after. Moreover, evidence suggests

that while the immediate sedative effects of ketamine resolve rapidly as the medication redistributes into peripheral compartments, other effects may remain for up to 4 to 7 days. Berman and colleagues demonstrated that administration of a single dose of ketamine produced antidepressant effects from those suffering major depression,¹⁴ an effect that was later replicated in a second study with a larger patient sample.¹⁵ The antidepressant effects are also postulated to result from NMDA receptor antagonism.

Although there is limited evidence, studies have shown that single-dosage ketamine usage in the critically ill may demonstrate supplemental effects outside of direct sedation with prolonged analgesia. In our patient, a single dose of ketamine resolved hyperventilation shortly after administration. The effects persisted for the remainder of his ICU stay and ultimately allowed for avoidance of a prolonged ventilator wean and transfer to a lower level of care.

Primary concern with administering ketamine to our patient involved the potential for increased intracranial pressure (ICP). Based upon data from the 1970s in those with nontraumatic intracranial lesions, ketamine was once thought to result in increased ICP.¹⁶ However, several recently published studies have demonstrated no ICP issues following ketamine administration.¹⁶ Our patient's EVD was successfully removed on hospital day 7 before ketamine administration. However, the patient was monitored closely and did not neurologically deteriorate following ketamine administration.

Conclusion

This report describes the use of ketamine in a patient with CNH following ICH. No adverse effects were noted from our bolus ketamine administration, and our patient demonstrated a rapid clinical improvement in respiratory rate. However, this represents 1 case and further investigation is needed regarding the role of ketamine for CNH.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Plum F, Swanson AG. Central neurogenic hyperventilation in man. *AMA Arch Neurol Psychiatry*. 1959;81(5):535-549.

2. Johnston SC, Singh V, Ralston HJ III, Gold WM. Chronic dyspnea and hyperventilation in an awake patient with small subcortical infarcts. *Neurology*. 2001;57(11):2131-2133.
3. Adachi YU, Sano H, Doi M, Sato S. Central neurogenic hyperventilation treated with intravenous fentanyl followed by transdermal application. *J Anesth*. 2007;21(3):417-419.
4. Mohrien KM, Jones GM, MacDermott JR, Murphy CV. Remifentanyl, ketamine, and fentanyl: a review of alternative continuous infusion agents for sedation in the critically ill. *Crit Care Nurs Q*. 2014;37(2):137-151.
5. Mion G, Villeveille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther*. 2013;19(6):370-380.
6. Poon CS, Zhou Z, Champagnat J. NMDA receptor activity in utero averts respiratory depression and anomalous long-term depression in newborn mice. *J Neurosci*. 2000;20(9):RC73.
7. Waters KA, Machaalani R. Role of NMDA receptors in development of respiratory control. *Respir Physiol Neurobiol*. 2005;149(1-3):123-130.
8. Vural A, Arsava EM, Dericioglu N, Topcuoglu MA. Central neurogenic hyperventilation in anti-NMDA receptor encephalitis. *Intern Med*. 2012;51(19):2789-2792.
9. De Pinto M, Jelacic J, Edwards WT. Very-low-dose ketamine for the management of pain and sedation in the ICU. *J Opioid Manag*. 2008;4(1):54-56.
10. De Oliveira GS Jr, Fitzgerald PC, Hansen N, Ahmad S, McCarthy RJ. The effect of ketamine on hypoventilation during deep sedation with midazolam and propofol: a randomised, double-blind, placebo-controlled trial. *Eur J Anaesthesiol*. 2014;31(12):654-662.
11. Tarulli AW, Lim C, Bui JD, Saper CB, Alexander MP. Central neurogenic hyperventilation: a case report and discussion of pathophysiology. *Arch Neurol*. 2005;62(10):1632-1634.
12. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg*. 2012;115(4):934-943.
13. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. *CNS Neurosci Ther*. 2013;19(6):403-410.
14. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351-354.
15. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63(8):856-864.
16. Bourgoin A, Albanese J, Wereszczynski N, Charbit M, Vialet R, Martin C. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Crit Care Med*. 2003;31(3):711-717.