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Use of ketamine for severe asthma exacerbation in a pregnant patient with persistent bronchospasm: a case report

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Abstract

Background: Estimated 4%–8% of pregnancies are complicated by asthma. Adequate management in this population is critical to minimize complications. Patients presenting with asthma exacerbation are typically managed with standard bronchodilators and systemic corticosteroids. However, additional agents may be used in patients with refractory asthma exacerbation. Ketamine has been used in refractory bronchospasm, although its efficacy in published literature is heterogeneous.

Case Presentation: We present a case of a pregnant patient with severe asthma exacerbation refractory to standard and salvage treatment who achieved termination of bronchospasm with ketamine infusion.

Conclusion: After receiving ketamine infusion for several days, the patient had improved air flow and achieved successful extubation, without experiencing rebound bronchospasm. Although this individual clinical case alone cannot change guidelines or directives to use in refractory asthma exacerbations, it offers a possible treatment option to patients and providers in unusually severe cases with extenuating risk factors.

Keywords: Asthma, Bronchospasms, Case Report, Ketamine, Pregnancy

Introduction

Estimated 4%–8% of pregnancies are complicated by asthma, with approximately 23% of pregnant patients with asthma requiring an emergency department (ED) visit or hospitalization.[1,2] Expedient and effective asthma exacerbation management is critical in this population to minimize episodes of hypoxia and mitigate risks such as "lower birth weights, caesarian delivery, antepartum hemorrhage, preterm labor, membrane-related disorders, and hypertensive disorders of pregnancy."[2] Guideline-recommended management of acute exacerbations does not differ between pregnant and nonpregnant patients. Despite this, a cohort study revealed that pregnant women with asthma were significantly less likely to receive appropriate treatment in the ED compared with nonpregnant women, perhaps because of perceived risk of harm to the fetus.[3] In addition, according to the American College of Obstetrics and Gynecology, it is safer to treat pregnant women with appropriate medications than permit persistent asthma exacerbation symptoms.[4]

Patients presenting with asthma exacerbation are typically managed with standard bronchodilators and systemic corticosteroids.[1] However, severe exacerbations causing progressive hypoxia require supportive oxygen therapy and additional adjunctive therapies such as intravenous (IV) magnesium and parenteral beta-2 agonists.[1] Methylxanthines (aminophylline and theophylline) were previously used as adjunctive therapy but have not demonstrated benefit when added to beta-2 agonists and are currently not recommended in guidelines.[1,5] The efficacy of ketamine in refractory bronchospasm is inconsistent in published literature, and therefore, ketamine is not considered standard treatment. Furthermore, the use of ketamine in pregnancy for the treatment of refractory bronchospasm has not been well studied. We present a case of a pregnant patient with severe asthma exacerbation refractory to standard treatment who achieved termination of bronchospasm with ketamine.

Case presentation

A 24-year-old, 60-kg woman, 14-week gestation, with a history of asthma exacerbations without intubation presented to the ED with worsening shortness of breath, possibly precipitated by exposure to respiratory syncytial virus. Medications administered by emergency medical service included methylprednisolone 125 mg IV, epinephrine 0.3 mg intramuscularly (IM), and albuterol 7.5 mg via a nebulizer.

Upon hospital arrival, the patient exhibited tachycardia, wheezing, and accessory muscle use. She was placed on noninvasive positive-pressure ventilation (NIPPV). Magnesium 2 g IV, a second epinephrine 0.3 mg IM, terbutaline 0.25 mg subcutaneously, and continuous albuterol with scheduled ipratropium-albuterol were administered. Despite these salvage therapies and NIPPV, her respiratory status continued to deteriorate, necessitating intubation and mechanical ventilation. Ketamine 1.8 mg/kg IV push and rocuronium 0.6 mg/kg IV push were administered for rapid sequence intubation (RSI). Titratable fentanyl (25–300 μg/h), propofol (10–50 μg/kg/min), and ketamine (0.05–0.4 mg/kg/h) infusions were initiated for pain and agitation management and to facilitate ventilator synchrony.

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Ketamine infusion was initiated at 0.05 mg/kg/h and increased according to institution guidelines up by 0.05 mg/kg/h every 10 minutes to achieve a Richmond Agitation-Sedation Scale goal of 0. The infusion was increased to 0.2 mg/kg/h before discontinuation within an hour of initiation.

In the intensive care unit (ICU), the initial arterial blood gases demonstrated a pH of 7.20, pCO_2 55 mmHg, pO_2 117 mmHg, HCO_3 20 mmol/L. The patient received methylprednisolone 80 mg IV every 6 hours, and scheduled ipratropium-albuterol with albuterol as needed. On Day 3, nebulized medications were changed to budesonide 0.5 mg every 12 hours, formoterol fumarate 20 µg every 12 hours, ipratropium 500 µg every 4 hours, and levalbuterol 2.5 mg every 4 hours. On Day 4, midazolam (1–10 mg/h) infusion was added to improve ventilator synchrony and sedation. All sedation infusions were titrated to maximum institutional rates, except midazolam, which had a peak dose of 7.5 mg/h.

Treatment

Despite treatment with bronchodilators and systemic plus inhaled corticosteroids, the bronchospasm persisted at Day 5, which prompted a trial of ketamine. The patient received a bolus of 30 mg IV, followed by a fixed-dose ketamine infusion of 1 mg/kg/h. In addition, magnesium 4 g per 100 mL was administered intravenously. The following morning, the patient continued to exhibit breath stacking, wheezing, and increased work of breathing on physical examination. After 15 hours of starting the infusion, the ketamine dose was increased to 1.5 mg/kg/h. On Day 7, approximately 24 hours after the dose adjustment, pulmonary auscultation revealed improved air flow and decreased expiratory wheezing. A 2-hour pressure support ventilation trial was tolerated before switching back to assist-controlled, volume-cycled ventilator mode.

On Day 9, fentanyl and propofol were discontinued, and a dexmedetomidine infusion was initiated to facilitate extubation. The patient was successfully extubated within 2 hours of the sedation change, and all infusions were subsequently discontinued, with ketamine as the last agent to be removed to avoid rebound bronchospasm. The patient received ketamine for approximately 51 hours in total, with 36 hours at 1.5 mg/kg/h. No recurrence of bronchospasm was observed despite abruptly stopping the ketamine infusion. Systemic methylprednisolone was continued with a dose taper for several days.

Patient outcome

The patient improved to room air the following day and was discharged successfully with outpatient follow-up at a high-risk pregnancy clinic. There were no documented subsequent hospitalizations for asthma exacerbation or any other complications.

Throughout the admission and postadmission periods, the fetal heart tones remained within the normal range of 140 to 160 s. Subsequent follow-up ultrasound revealed congenital anomalies of asymmetrical mild left-sided ventriculomegaly. However, no definitive abnormalities were observed at the level of the mesencephalon, and the development of the brainstem and cerebellum appeared normal. The postnatal plan involved scheduling a neonatal head ultrasound for further assessment, along with pediatric neurological examinations.

Discussion

Asthma is a common illness with symptoms that vary from occasional wheezing to severe hypersensitivity and inflammation, leading to airway obstruction, as observed in our patient. Studies have demonstrated the benefits of ketamine as an induction agent, including its ability to stabilize bronchial airways and potentially induce bronchodilatory effects.[6] Among several proposed mechanisms of action, ketamine inhibits the *N*-methyl-D-aspartate receptor-mediated bronchoconstriction and inhibits L-type calcium channels to reduce intracellular calcium in airway smooth muscle and facilitate muscle relaxation.[7–9] Neither human nor animal studies have demonstrated teratogenicity associated with ketamine.[10] However, in rodents and Macaque monkeys, high doses of perinatal ketamine resulted in neurotoxicity and neuroapoptosis, respectively.[10–13] Of note, these studies may have limited clinical significance, as the ketamine doses used were higher (10 mg/kg) than the ranges used in practice. Data regarding dose-dependent ketamine-induced uterine contractions are controversial.[10,14–18] Nonetheless, the American College of Obstetricians and Gynecologists recommends prioritizing the treatment of asthma to alleviate the mother's bronchospasm using all necessary means when the patient's life is at risk. The ultimate goal is to ensure sufficient oxygenation of the fetus by avoiding hypoxic episodes in the mother.[4]

In our case, ketamine was chosen for RSI because of its theoretical ability to induce bronchodilation by releasing catecholamines.[9,19] The standard dosing of ketamine for RSI is typically within the range of 1 to 2 mg/kg administered intravenously.[20–22] The likelihood of failed intubation is approximately 8 to 10 times higher in pregnant patients compared with the general population.[23,24] Therefore, to achieve optimal dissociation during RSI, we administered ketamine at the upper range of the recommended dosage, specifically 1.8 mg/kg. It is important to note that this dose, although higher, remains within the safe range and is associated with few adverse effects. Historically, ketamine was used for obstetric (OB) cases and as labor analgesia before the popularity of epidural techniques. Clinical observations have supported the safety of ketamine for both the fetus and neonate in OB anesthesia. Although ketamine crosses the placenta, administering IV ketamine at a dosage of less than 2 mg/kg to parturient women has consistently shown no detrimental effects on neonatal well-being, as assessed by using Apgar scores. Lower doses of ketamine are generally not linked to significant neonatal depression.[25] Ketamine is considered an optimal choice for induction in patients with hypotension and asthma. However, caution should be exercised when administering it to patients with pregnancy-induced hypertension, such as preeclampsia or eclampsia.

Postintubation, our patient experienced persistent, refractory bronchospasm despite multiple first-line and salvage therapies. Therefore, a fixed-dose ketamine infusion was initiated with a goal to target bronchospasm. Ketamine was selected for its additional sedative effect to avoid the risks introduced by the use of neuromuscular blockers in pregnant patients.[26] Furthermore, ketamine is an opioid and sedative/hypnotic-sparing agent, enabling dose reductions of other infusions once the bronchospasm subsided in our patient.[27]

The literature supporting the use of ketamine in severe bronchospasm primarily originates in the pediatric population, with varying doses reported. In one retrospective chart review, 17 mechanically ventilated and paralyzed pediatric patients received ketamine infusions for refractory bronchospasm, with a duration of 40 hours (±31 hours). Gas exchange, as indicated by the ratio of PaO_2/FIO_2, began to improve as early as 1 hour after initiation.[28] This study contributed to establishing expectations for dosing and effective treatment duration.[29,30] Moreover, early use of ketamine for bronchospasm is generally not well supported.[31] In the one available randomized control trial specific to acute asthma exacerbation in adults, treatment with a 3-hour ketamine infusion of 0.1 mg/kg bolus followed by 0.5 mg/kg/h in the ED demonstrated no difference in bronchodilator effect compared with standard of care.[29] Similarly, in our patient, a short initial infusion of low-dose ketamine after intubation did not alleviate the bronchospasm.

Much of the evidence associated with ketamine use in adults is equivocal about its efficacy but is often driven by the chronic obstructive pulmonary disease population, which may have limited expected benefits considering the underlying disease etiology. In one randomized controlled trial comparing IV ketamine to IV fentanyl for the management of bronchospasm in the ICU, only 13 of 45 enrolled patients were diagnosed with asthma exacerbation, and the subgroup analysis found no difference in airway resistance between the treatment groups.[32] Although ketamine did not demonstrate effectiveness in this study, it further established safe maximal dosing in our patient. A recent systematic review found no clear benefit of using ketamine in asthma exacerbations because of the heterogeneity of existing studies.[33] However, considering our patient's pregnancy status, a trial ketamine infusion was deemed the preferred next treatment option over other agents used in refractory asthma.

After multiple days of ketamine infusion, the bronchospasm was terminated. Our patient did not experience any major adverse drug reactions, except for a mild increase in heart rate, despite literature reports of emergence phenomena, hypertension, and excessive secretions associated with ketamine.[28,31,32] In our case, ketamine was used as a salvage therapy, chosen over aminophylline to mitigate the risk of potential fetal harm associated with the latter, given the patient's pregnancy. Unfortunately, because of loss to follow-up and a lack of documentation for the birth and postpartum periods, we are unable to provide an update on the neonatal outcomes.

Conclusion

In conclusion, our pregnant patient with refractory bronchospasm experienced improved airflow and successful extubation without rebound bronchospasm after several days of ketamine infusion. Although this individual clinical case cannot alter guidelines or directives for refractory asthma exacerbations, it presents a potential treatment option for patients and providers in exceptionally severe cases with extenuating risk factors. Randomized studies investigating ketamine infusion in adults and pregnant patients with refractory bronchospasm could be valuable in establishing more definitive clinical guidance.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Johnson M, Abbas M, and Jones J participated in the design and literature review of the case report. All authors participated in writing and reviewing the article.

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Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. The International Review Board (IRB) Ethics Committee of Beaumont Hospital states that the publication of single patient case report is exempt from IRB approval. Written informed consent was obtained from the patient. This manuscript has the consent of the patient for the use of her data and for the publication of the data that appear in the article.

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