5-2021

The Use of Ketamine in Asthma Exacerbations

Stephanie Frentzel
University of North Dakota, stephanie.frentzel@und.edu

The Use of Ketamine in Asthma Exacerbations

by

Stephanie Frentzel, PA-S

Bachelor of Science, Liberty University, 2018

Contributing Author:

Julie Solberg, MPAS

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2021

Table of Contents

Acknowledgments

I would like to thank my husband for all the unwavering support and steadfast love he has shown me. I would like to thank all my classmates that have stood by my side to encourage and cheer me along this process. My gratitude to Professor Julie Solberg for co-authoring this project, Brenda Thompson, for her support and contribution in this research's statistics, Nathan Leitheiser and Amanda Mueller, for their collaboration in the final edition of this paper.

Abstract

Asthma is a chronic, non-curable respiratory disease that has multi-factorial effects on the bronchial mucosa. Despite optimal prevention and standardized first-line asthma care, the symptoms can deteriorate, leading to an asthma exacerbation, which is a medical emergency. The purpose of this review was to determine the efficacy of ketamine use as an adjunctive medication for acute asthma exacerbations that had failed standard guideline-directed treatments. Relevant databases included searches looking for ketamine use in asthma. Ketamine can be used as an adjunctive medication and has been found to be beneficial in stopping the emergency's progression by alleviating bronchospasms, increasing oxygen availability, reducing respiratory failure leading to mechanical ventilation, and decreasing mortality. Preliminary results showed no positive outcomes of improvement in asthma symptoms with low dose ketamine. Several findings point to remarkable positive outcomes with an intravenous high dissociative dosing administration. Some experts feel strongly that the dose ranges and duration of treatment play a vital role in the efficacy of ketamine used as a pharmacological option. More research is needed with more extensive, high-quality, randomized studies that address and objectively measures varying dosage regimens to form a consensus on the efficacy of ketamine use in refractory asthma exacerbations.

Keywords: Asthma, acute asthma exacerbation, asthma standardized practice guidelines, ketamine, ketamine in asthma exacerbations, severe asthma, status asthmaticus.

Introduction

Asthma is a chronic inflammatory disorder of the respiratory system and requires strategic and aggressive management to combat this chronic illness. Comprehensive research in the treatment and management of asthma aims to lower the morbidity and mortality rates and improve people's quality of life. Understanding the importance of effective and timely treatment can improve the individuals experiencing an asthma attack. While many asthma patients receive appropriate care for their disease, some are refractory to the standard of care treatment and do not respond to the medications. Refractory asthma leads to dangerous respiratory complications such as hypoxia, respiratory failure, and even death. This study addresses the use of ketamine as an adjunctive therapy addition to the standardized treatment of care for asthma exacerbations and shows that its use can improve clinical outcomes.

Statement of the Problem

Despite having quality healthcare in America, the rate of death among people diagnosed with asthma is astounding. According to the Center for Disease Control and Prevention (CDC), in 2018, there were approximately 3,400 deaths attributed to asthma and more than 25 million American individuals fighting this non-curable chronic disease (CDC, 2018). Research has shown that despite optimal and timely care, a percentage of individuals do not respond well to the standardized treatment of care and continue to advance to a moderate to severe asthma exacerbation. This progression can lead to an increase in severity and even death.

Research Question

Does adding ketamine to the standard of care versus no ketamine improve outcomes in patients with an asthma exacerbation?

Methods

An extensive literature review was conducted to explore the use of ketamine as an adjunct to the standardized treatment of care, focusing on alleviating bronchospasms, increasing oxygen availability, reducing respiratory failure leading to mechanical ventilation, and decreasing mortality. Academic electronic databases were accessed to perform detailed reviews of available scholarly material. Databases that were searched included: Clinical Key, CINAHL, Cochrane, Embase, Scopus, and PubMed. The use of MeSH terms included: asthma, ketamine, and exacerbation. Keywords used were asthma exacerbation, practice guidelines, disease progression, emergency, hospital, and deaths. Each keyword was aligned with the mesh term and aided in the location of literature that discussed the use of ketamine in asthma. The literature review yielded a total of 183 articles. The inclusion material consists of pediatric and adult populations in available systematic reviews, randomized control trials, meta-analysis, pilot studies, case reports, and peer-reviewed journal articles.

Literature Review

In an overview, current research has shown marked advances in medical therapy for asthma. The goal of treatment is to correct and rapidly reverse the progression of asthma exacerbation. This research aims to determine if the addition of ketamine to the standard regimen for severe asthma exacerbations will show improvement of respiratory symptoms and can be considered as a useful addition for emergency treatment in moderate to severe exacerbations.

Prevalence and Pathophysiology of Asthma

There are more than 25 million Americans who have asthma each year. With 1 in 13 people having asthma, it is essential to manage and treat asthma attacks as promptly and efficaciously as possible. Each year, there are approximately 9.8 million office visits and over 1.8 million

emergency room visits attributed to an asthma diagnosis. The reality is that ten Americans die each day from asthma (Asthma and Allergy Foundation of America [AAFA], 2020). Unfortunately, there is no cure for asthma, and it is imperative to prevent asthma exacerbations.

The most recent national data shows that the current asthma prevalence for 2018 is astounding. Over 25 million people were diagnosed with asthma in 2018, which accounts for 7.7 percent of Americans suffering from this respiratory disease (Center for Disease Control and Prevention, [CDC], 2018). It is essential to note the importance of quick and early intervention for an asthma exacerbation and promote prevention to decrease the exacerbation severity. The national statistics point to 3,441 deaths in 2018 due to asthma (CDC, 2018). These high statistical values show the importance of provider education on the disease processes of asthma and new and upcoming treatments that may aid in treating this incurable disease.

Eder, Ege, and Mutius (2006) point out that a determination of asthma is made through clinical diagnosis and can be challenging to identify since no single instrument can say with absolute certainty that the patient has asthma. A determination of asthma is a step approach determined by a thorough medical history, a detailed physical exam, and determining if there is the reversibility of airway obstructions. Many risk factors account for the prevalence of asthma. Some are environmental exposures, obesity, allergens, and infections.

Asthma is a non-curable chronic disease that affects the respiratory system. This chronic condition affects the inflammatory process of the bronchial mucosa. During these responses, there is constriction of the airways, bronchial hyperresponsiveness, and variable airflow obstructions that are reversible (McCance & Huether, 2019). The most substantial identifiable risk factor for asthma is atopy. This genetic contributor points to a strong familial genetic link, and more than 100 genes have been identified that could play a part in the pathogenesis of this

disease. Other risk factors include exposure to environmental factors such as tobacco smoke, air pollutions, and airborne allergens. Co-morbidities play a role in asthma as well; some of these include obesity, gastroesophageal reflux disease, chronic respiratory infections, and vitamin D deficiency. McCance and Huether (2019) point out that asthma's pathophysiology has early and late responses from innate and adaptive immune systems. These processes are significant contributors to the persistent inflammation of the airways. In the initial acute phase, bronchoconstriction reaches its maximum at 30 minutes and resolves within the first three hours. During this phase, the antigen is exposed, and the immune mediators are activated, causing vascular permeability and increased edema along with bronchospasm of the smooth muscle within the bronchioles. The immune system promotes excessive mucous secretions from the goblet cells, and the airways become narrowed and obstructed to airflow (McCance & Huether, 2019). The major mediators are summonsed in the later asthmatic response at around four to eight hours after exposure. The lymphocytes, eosinophils, neutrophils, basophils, leukotrienes, and prostaglandin D all show up and begin their inflammatory response. Eosinophil mediators cause tissue injury with fibroblastic proliferation, which further leads to bronchial scaring along with substance P, neurokinin A, and calcitonin gene-related peptide that contributes to the hyperresponsiveness of the airways. Mucous plugs are formed, increasing airflow resistance, which causes impaired expiration and causes air-trapping and hyperinflation distal to the mucous plug obstructions. These immune processes decrease oxygenation and perfusion at the alveolar level. Hypoxemia sets in, causing a decrease in tidal volume, retention of carbon dioxide, respiratory acidosis, and, eventually, respiratory failure.

Standardized Care of Asthma Exacerbation

Abrams, Becker, and Szefler (2018) state that asthma exacerbations have a significant role in addressing asthma risks, therapies needed, and patient outcomes. It is imperative to have a uniform definition of an asthma exacerbation. A standard definition recognized system-wide will allow for a focused study of interventions and help implement ongoing future research to determine what therapies are best for asthma exacerbations. Abrams et al. (2018) point out it is difficult to distinguish between a poorly controlled patient in their asthma treatment versus an exacerbation. Defining an exacerbation varies amongst the medical societies, and the need to have a uniform definition is crucial in prompt, aggressive treatment to deter the patient from poor outcomes.

Additionally, an acute asthma exacerbation is a medical emergency that should be diagnosed and managed immediately. Symptoms include shortness of breath, coughing, wheezing, and reduction in lung function. In advanced stages of the exacerbation, the use of accessory muscles, along with the development of a silent chest, can lead to impending respiratory failure. The providers' role is to recognize the patient's severity based on clinical and objective findings and treat them aggressively (Al-Shamrani, Al-Harbi, Bagais, & Alenazi, 2019). The provider must continuously monitor the patient to tailor medication needs and respond accordingly. A full medical history and physical examination are a priority. It is crucial to rule out any underlying medical conditions that may look like an asthma exacerbation such as congestive heart failure, pneumonia, myocardial infarction, or a pneumothorax. The provider's goals must move from the assessment phase into the correction phase and treatment of hypoxemia, correcting the airflow obstruction and preventing further complications should be performed rapidly. One goal is to provide oxygen supplementation for patients with levels below

92% oxygen on room air. Hypoxia leads to death, and it is imperative to promptly treat the patient to sustain oxygen levels at 94% or higher. The drug of choice to reverse the airflow obstruction is an inhaled short-acting beta2-agonist.

The Global Initiative for Asthma (GINA) provides healthcare professionals with evidence-based asthma management and prevention guidelines. Bateman et al. (2008) point out that metered-dose inhalers are sufficient for mild to moderate exacerbations, and inhaled nebulized preparations should be reserved for moderate to severe exacerbations. Anticholinergics such as ipratropium bromide are commonly given to illicit bronchodilation and are recommended in the moderate to severe category. Oral or intravenous steroids are given to accelerate the resolution of the asthma exacerbation. It is vital to consider rehydration with fluids if dehydration is suspected and antibiotics are not generally prescribed due to most asthma exacerbations being viral in nature. Diagnostic labs are also beneficial, such as serum electrolytes, blood gas analysis, and a chest X-ray to rule out underlying complications. Some alternative adjunctive medications can also be considered, such as magnesium sulfate, salbutamol, aminophylline, inhaled heliox, and noninvasive positive-pressure ventilation (NIPPV). If the patient experiences progressive exhaustion, mental status changes, rising in the PaCO2 and progressive hypoxemia, or respiratory failure, endotracheal intubation will be necessary.

Another significant factor in an exacerbation is the potential of death. Bateman et al. (2008) point out that "exacerbations are episodic flare-ups of asthma that can be life-threatening and carry a significant burden to patients and the community" (p. 161). The challenges remain due to most studies having inconsistent terminology for an asthma exacerbation, which increases

the burden to develop an action plan that aids in prompt recognition to prevent worsening asthma conditions.

Indeed, there is an array of triggers that may lead to an asthma exacerbation. Castillo, Peters, and Busse (2017) state that several susceptibilities or risk factors are involved in determining an asthma exacerbation. The most common of the triggers are viral respiratory infections. Allergy sensitization also plays a role in the allergic inflammatory process along with bacterial infections. It is crucial to keep in mind that environmental airway pollutants may synergistically cause acute asthma exacerbation. Standardized care described for asthma is a stepwise approach and is strategically attempting to reduce and prevent asthma exacerbations. Prevention of exacerbations remains a primary unmet need in asthma management (Castillo et al., 2017). It is essential to understand asthma's pathogenesis to circumvent the inflammatory process and new strategies to treat these exacerbations. When exacerbations occur, standardized treatments should be followed, and despite optimal prevention and treatment, exacerbations still happen. It is imperative to stabilize asthma as soon as possible. There is a limited number of successful evidence-based therapies available to relieve the exacerbation with insufficient evidence to support their use.

As far as intubation and the need for sedation, a study by Papiris, Kotanidou, Malagari, and Roussos (2002) addresses that no standard sedation protocol for an asthmatic patient exists. Ketamine was mentioned for its bronchodilation properties and can show promise in the asthmatic patient. It appears useful in the emergency intubation that requires ventilatory assistance. Pointing out that ketamine is an option as a general anesthetic with a sedative analgesic. Intubation via intravenous administration of 1-2 mg ketamine/kg at a rate of 0.5 mg/kg/min results in 10-15 minutes of anesthesia without respiratory depression. It was noted

that bronchodilation appears within minutes via the intravenous treatment and usually lasts 20-30 minutes. With its bronchodilation effect, it is an excellent sedating agent and may alleviate the need for intubation. There were limitations, as well. Ketamine has sympathomimetic effects and is contraindicated in patients with hypertension, cardiovascular disease, high intracranial pressure, and preeclampsia. The liver metabolizes ketamine to norketamine, which has anesthetic properties and a long half-life of about 120 minutes. This process may lead to drug accumulation and prolonged side effects and limits ketamine use for sedation prior to intubation for some patient populations.

Furthermore, Pollart, Compton, and Elward (2011) point out that treatment goals are correction of severe hypoxemia, rapid reversal of the obstruction, and initiating therapy rapidly while monitoring for response to the medications. The mainstay for treatment of moderate to severe asthma exacerbations are oxygen and inhaled short-acting beta2 agonist. Early use of corticosteroids has been found to reduce the risk of reoccurring exacerbations, and inhaled anticholinergics can be added to improve lung function. Intravenous magnesium sulfate added to standard therapy has shown a slight improvement in lung function in adults.

Together, Saadeh and Oppenheimer (2018) state that ipratropium bromide is a quaternary amine and does not cross the blood-brain barrier. The ammonium compound is structurally similar to atropine and can be synergistic with beta2 agonists and aid in bronchodilator effects. Corticosteroids help decrease mucus production, and its actions require approximately 4-6 hours to occur because protein synthesis is needed to start the anti-inflammatory effects. Ketamine is a short-acting pentachlorophenol derivative that promotes bronchodilation outcomes by increasing the endogenous catecholamine levels. This increase causes binding to the beta receptors and

causes smooth muscle relaxation, which leads to bronchodilation (Saadeh & Oppenheimer, 2018).

Ketamine in Asthma Exacerbations

A review of a double-blinded, randomized, placebo-controlled trial on pediatric patients from the age of 2 to 18 years of age who experienced acute asthma exacerbation was done. In this study by Allen & Macias (2005), they measured the effects of an intravenous bolus of ketamine at 0.2mg/kg, followed by a two-hour ketamine infusion of 0.5 mg/kg/h. The placebo received equal volumes with a normal saline placebo. They tried to determine if the ketamine would improve the pulmonary index scoring scale's severity by 2 points. There were sixty-eight patients ($N = 68$) enrolled. The ketamine group was randomized at 33 patients ($n = 33$) receiving the ketamine infusions and 35 patients ($n = 35$) receiving the randomized placebo. At the beginning of the trial, the mean pulmonary index score in the placebo group was 10.3 ±1.1 versus the ketamine group having 3.2 ±2.0. The mean difference of 0.2; and a 95 % CI [-0.5, 0.8] (Allen & Macias, 2005, p. 46). The study found no significant improvement in the pulmonary index score between the two groups. Allen and Macias (2005) suggest that one reason it lacked improvement was that the dose given was insufficient. They felt that the dose was too low to cause measurable bronchodilation.

One limitation is that it is virtually impossible to study the effects of bronchodilation alone with ketamine. In this study, ketamine was given concomitant with a beta-agonist. It is difficult to surmise that the impact of bronchodilation was from ketamine alone versus the standard therapy of beta-agonists for asthma exacerbations. If a beta-agonist were withheld, that would not be an ethical practice.

Elkoundi, Bentalha, Koraichi, and El Kettani (2018), states that nebulized ketamine can be an effective medication to use in avoiding the use of mechanical ventilation in a severe asthma exacerbation that is refractory to standardized treatments. The case presents with a 26-month-old female patient ($N = 1$) with a history of asthma that presents to the emergency department with respiratory distress, wheezing, and with the use of standardized home treatments of an albuterol inhaler. The patient was documented as having labored breathing, accessory muscle use, tachypneic, tachycardiac, and oxygen saturation of 90% on room air. The patient received three doses of albuterol 2mg, ipratropium bromide 250 µg via nebulization device for an hour duration, and intravenous (IV) methylprednisolone 2mg/kg/24h. The patient status continued to deteriorate, and a bolus of magnesium sulfate 50mg/kg was administered, along with two additional IV doses of albuterol 15 µg/kg. Arterial blood gases revealed pH 7.29, pCO2 68, pO2 96, HCO3 26, and oxygen saturation of 91% (Elkoundi et al., 2018). The staff determined that they would attempt to use ketamine nebulization in hopes of a rapid improvement to prevent intubation. Ketamine 1 mg/kg via nebulization was started, and after twenty minutes, the patient's respiratory status showed remarkable improvement. Findings noted improved air entry and minimal audible wheezing. Second blood gas was obtained, showing pH 7.33, pCO2 of 37, pO2 of 250, and HCO3 of 22 (Elkoundi et al., 2018). With the notable improvement, a second dose of ketamine via nebulization was administered. The patient's symptoms further improved by decreased respiratory distress, wheezing improvement, and increased oxygen saturation to 98%. This patient was admitted and later discharged from the hospital following a 48-hour observation for worsening asthma exacerbations. This case report's strengths are the rapid improvement of the severe symptoms and diagnostic lab values, pointing to a promising option in these extreme asthma circumstances. The route of nebulization allows

for the prompt delivery of the medication and quick absorption within the lung. The bronchodilation benefits of ketamine delivered quickly has shown rapid response and marked improvement within this study.

There are some limitations to this case study. First, it had a small sample size with no confidence intervals or p values. Secondly, the use of nebulized ketamine in treating a severe asthma exacerbation has never been investigated and done on a human at the time of publication (Elkoundi et al., 2018). Only murine models have shown rising favor in using nebulized ketamine and how it attenuates the airway inflammatory processes and improves the respiratory outcomes by its bronchodilation mechanisms. These animal studies will help direct future human studies on the efficacy of nebulized ketamine.

Next, a single-blind, randomized clinical trial with a placebo control done at Al-Zahra teaching hospital in Isfahan, Iran, aimed to study the effects of intravenous low dose ketamine in treating asthmatic patients admitted into the emergency department for an asthma exacerbation. In this study, there were 92 patients ($N = 92$) enrolled. The age of the patients was not at a significant difference $p = .09$. 15 patients ($n = 15$) (16.3%) were administered 0.3 mg/kg ketamine, 14 ($n = 14$) (15.2%) of the patients were given 0.4 mg/kg, and 16 ($n = 16$) (17.4%) patients were given 0.5 mg/kg of ketamine (Esmailian, Esfahani, & Heydari, 2018). A placebo of normal saline was given in the same doses for the remaining patients. In measuring the efficacy of ketamine at differing doses, a one-way analysis of variance (ANOVA) was used, and in all the tests, $p < .05$ was considered significant. All the groups received continuous monitoring, oxygen therapy, arterial oxygenation monitoring, and standardized treatment of care with standard dosing. Ketamine was used as an adjunct in addition to the standard treatment. The mean peak expiratory flow rate (PEFR) was measured before treatment and then one hour after the treatment

in each group along with the placebo. The mean PEFR reflected 336.2 ± 101.5 liters in the placebo group and 345.8 ± 84.7 liters in the ketamine group before initiating treatment (Esmailian et al., 2018). The $p = .6$ At the one-hour mark of intervention, they were 352.1 ± 101.2 and 415.8 ± 76.2 liters. $p = .001$. In the study Esmailian et al. (2018) note, the larger dose of ketamine at 0.4 mg/kg $p = .02$ and 0.5 mg/kg $p < .001$ showed an increased improvement in the PEFR compared to the placebo group. The 0.3 mg/kg dose showed no significant difference in the placebo df:3, 88; F=23.8; $p = .17$. The evidence seems to allude that the dose of 0.4 mg/kg and 0.5 mg/kg of ketamine has marked improvements in the PEFR and was found to be beneficial in treating asthma symptoms.

This study also has a few limitations. Small participant numbers make it difficult to conclude the study is showing measurable outcomes. Additional studies with a significantly larger group of participants would make for a more measurable study and less generalization of the findings. Additionally, Goyal and Agrawal (2013) completed a systematic review, and twenty-two articles were reviewed in the use of ketamine as a bronchodilator. These patients were administered ketamine in addition to standardized therapies due to inadequate responses to the first line agents that were delivered. In total, 244 patients ($N = 244$) had received ketamine. Goyal and Agrawal (2013) state that ketamine was used in 13 articles for 53 patients ($n = 53$) for respiratory failure with intubation and mechanical ventilation. Anesthetic agents in asthma patients had three reports, with a total of 58 patients ($n = 58$). In three studies, 131 patients ($n = 131$) were treated with intravenous ketamine for status asthmaticus. One study had two ($n = 2$) patients that used intravenous ketamine for analgesia and sedation measures in patients with asthma. The information pointed out that ketamine showed favorable responses by decreasing wheezing and the improvement of oxygen saturations. The use of ketamine can cause an

anticholinergic effect on the smooth muscles of the airways. Ketamine decreases the influx of calcium into muscles by inhibiting the L-type calcium channels causing a decrease in the intracellular calcium. This leads to relaxation of the smooth muscles in the airway. Ketamine also reduces nitric oxide levels in the lung by downregulation of the nitric oxide synthetase enzyme. Blocking this enzyme reduces nitric oxide production in the lung, leading to bronchoconstriction (Goyal & Agrawal, 2013). It is also important to point out that ketamine may also improve the release of immune mediators. A significant concentration of ketamine is known to suppress macrophages' function and can interfere in the immune system's recruitment phase. This may help alleviate cytokine production and the progression of an exacerbation (Goyal & Agrawal, 2013).

One limitation of the use of ketamine is that it increases airway secretions, which would lead to the use of additional medication to combat the hypersecretions. Also, patients may experience disorientation, vivid, bad dreams, and some state they have seen illusions. Another limitation is that most studies have a small sample size. Some prospective observations studies had no control groups to compare to, and the dosage and duration have not been well established. Goyal & Agrawal (2013) state that ketamine has a use for refractory patients to standardized therapies and can be used as a rescue agent due to the bronchodilator effects but additional studies are needed.

An additional review of ketamine use as a life-saving adjunct in severe childhood asthma was done. In this review, the authors defined ketamine as an induction agent, pain killer, anti-depressant, and relief of bronchospasms (Hendaus, Jomha, & Alhammadi, 2019). They point out that ketamine is a dissociative agent that has various administration capabilities. It is absorbed intravenously, intramuscularly, and topically. It has both hydrophilic and lipophilic properties

and undergoes first-pass metabolism, and is metabolized by the liver. Another point made was that choosing to use ketamine for rapid sequence intubation would be the right medication choice with its bronchodilation effects. A strength is that it would be an excellent choice to use in the pediatric population with its good safety profile. The study's limitations point out that after reviewing ten small clinical studies, it was hard to decide if ketamine was useful in treating severe asthma based on variations in dosing and small participant numbers. More extensive randomized controlled trials are needed to study the efficacy of ketamine in severe asthma management.

Equally important is understanding the mechanism of action of ketamine. According to Wong, Lee, and Rehder (2014), ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist in the cortex and limbic system, causing dissociative states and used for analgesic and sedative properties. Wong et al. (2014) state that most of the studies that have been done with ketamine and severe asthma exacerbations were done on intubated patients that showed clinical improvements in wheezing, respiratory rates, peak inspiratory pressures, and tidal volume. With the limitations of small prospective observational studies and multiple case reports, it once again points to the need for more research in this area.

Additionally, a review of the Cochrane database was done. The review's findings point out that there is a lack of evidence of the usefulness of ketamine in acute exacerbations. In the study by Jat and Chawla (2012), more trials are needed regarding ketamine. One study lacked evidence of the benefits of the use and did not support ketamine in a severe asthma patient. At the same time, observational reports showed benefits with intubated and non-intubated patients. They expressed the need for additional randomized controlled trials that use a high level of methodology, and different dosing regimens should be reviewed and investigated.

In a case report by Kiureghian and Kowalski (2015), their report discusses ketamine administration and the utilization of noninvasive positive pressure ventilation (NIPPV) to circumvent the use of mechanical ventilation. The goals of a provider are to avoid intubation and mechanical ventilation. The reversal of bronchoconstriction with proper medications and management must be aggressive and rapid. In this case report, an adult patient ($N = 1$) presented to the emergency room unable to speak, sitting in a tripod position, and in severe respiratory distress with severe dyspnea. Standardized treatment of oxygen, nebulized beta2 agonist and ipratropium, 125 mg of methylprednisolone, 2 grams of magnesium sulfate, and an isotonic fluid bolus was started. Point of care venous blood gasses was obtained, showing a pH of 7.08, CO of 67, and a lactic acid of 79.0 mg/dl (Kiureghian & Kowalski, 2015). Due to the patient's altered mental status, the choice to start the patient on a bilevel positive airway pressure ventilation (BIPAP) was made. The patient became agitated and did not tolerate the use of the device.

A bolus was given 50 mg of ketamine, which caused dissociation, and then the BIPAP was applied and tolerated by the patient. This also allowed for continuous albuterol to be given during the next ten minutes. The patient continued to improve, and several repeat doses of 50 mg of ketamine were given at approximately 5 to 10-minute intervals during the treatment with BIPAP. Over 40 minutes, a total dose of ketamine was 300 mg. The blood gasses were redrawn, showing marked improvement of pH of 7.21, CO of 59, and a lactic acid level of 24.0 mg/dl (Kiureghian & Kowalski, 2015). The patient was moved to the intensive care unit and later switched to a nasal canal and discharged home approximately 48 hours after his arrival to the emergency room. Kiureghian and Kowalski (2015) believed that the use of ketamine provided the ability for the NIPPV to be used and provided time for the standard medications to be efficacious, along with reversing bronchoconstriction and avoiding intubation.

Additional studies are needed to prove the benefits of ketamine use and NIPPV to circumvent mechanical ventilation. The small sample size, no p values, or confidence intervals would be a limitation to the findings. Nevertheless, the findings of this case report would warrant additional future studies.

Similarly, this case report outlines the treatment of a 44-year-old man (N = 1) who presented with a severe asthma exacerbation and was admitted to the intensive care unit (ICU) for refractory hypercapnic respiratory failure that required intubation with mechanical support. He was later placed on a veno-venous extracorporeal membrane oxygenation (ECMO) device. This therapy is usually done as a salvage measure when mechanical ventilation cannot be maintained. This 44-year-old male had a history of uncontrolled, moderate, persistent asthma that had presented to the emergency room with difficulty breathing after being unresponsive to the standardized medication treatment for a severe asthma exacerbation. His status quickly deteriorated and required intubation with positive pressure mechanical ventilation support. In this study, ketamine was initially used at 0.5 mg/kg/h with a continuous infusion for pain control. On day four of the ICU stay, ketamine was titrated to 2 mg/kg/h for bronchodilation measures (Lam et al., 2019). It was noted that the infusion dose associated with the efficacy of bronchodilation ranged from 0.75 to 3 mg/kg/h (Lam et al., 2019). It was further suggested that the use of ketamine for a severe asthma exacerbation is dose-dependent. The bronchodilation response may be dependent on initiating high dose ketamine. Key findings outlined that the patients' wheezing had stopped entirely by the fifth day and had a complete resolution by day 10 in the ICU.

This study's limitations are that many medication regimens were administered, and the observations should be viewed with caution and discretion. The standardized use of traditional interventions had a considerable part in the positive outcomes of this case report and the use of

ECMO, which could have also improved this patient's disposition. Further studies are required to ensure the optimal dose needed to improve respiratory functions and controlled clinical studies to determine the appropriate doses for the efficacy and use of ketamine.

Moreover, another single randomized controlled trial was reviewed on the benefits of ketamine compared to placebo with an asthma exacerbation that failed standardized therapy. In this trial by Maddox and Seupaul (2014), the purpose was to determine the difference in asthma severity using the pulmonary index scoring system. This system is based on physical findings and ranges from 0 to 15 points. Ratings of < 7 were considered mild exacerbations, and ratings of > 14 were deemed severe. The mean pulmonary index score had a mean difference of 0.40 and a 95% CI [-0.4, 1.3] (Maddox & Seupaul, 2014). Patients ($N = 68$) were randomized to receive a ketamine or placebo dose. The initial dose of ketamine was 0.2mg/kg, followed by a continuous infusion of 0.5mg/kg per hour. This study's target was to verify if ketamine would be beneficial in severe asthma exacerbation because it provides analgesia and decreases airway resistance. It has been known to sustain cardiac and respiratory functions while mitigating the need for intubation. The use of ketamine as an adjunct showed promise but unfortunately did not measure improved outcomes in this study. According to Maddox and Seupaul (2014), the trial points out that the dose may be suboptimal, and a need for further studies with a higher dose range may show improvements. Maddox and Seupaul found some reports showing a higher dose of 2-3mg/kg bolus with a 2-3 mg/h continuous infusion might offer better outcomes. They stated the need for high-quality randomized trials with varying doses is needed to prove the efficacy of ketamine use as an adjunct medication.

As we see in a case report by Shalmovitz and Hawthorne (2008), the authors suggest that intravenous ketamine at a dissociative dose may be beneficial in severe asthma exacerbations.

They also state that the dissociating effect may also decrease the respiratory work of breathing and cause an anxiolytic effect. The authors reviewed 14 case reports of patients that had been treated with ketamine to thwart mechanical ventilation. There were significant range variations from 0.6mg/h to 4.8 mg/h. An interesting fact is that all the patients showed marked improvements, and none of them required intubation. In this review of this case report, a 28-year-old woman ($N = 1$) presented to the emergency room complaining of 8 hours of progressively worsening wheezing and shortness of breath. She had an environmental exposure that led to an asthma exacerbation. Upon presentation, she was extremely short of breath and able to speak one-word sentences. Her respiratory rate was 35 breaths/min, oxygen saturation via pulse oximetry was 75% on room air, and upon lung auscultation showed bilateral audible wheezing. Standardized medical treatment was initiated with oxygen, nebulized albuterol and ipratropium over ten minutes, followed by a normal saline bolus of 1000 mL, dexamethasone, and magnesium sulfate (Shlamovitz & Hawthorne, 2008). Progressively, the patient began to worsen, showing a decreased respiratory rate, extreme fatigue, and no audible wheezing on auscultation. An administration of ketamine at 0.75 mg/kg intravenous push was given, and the patient entered a dissociative state showing improvement within one minute of administration. The patient's respiratory rate decreased to 20 breaths/min and showed improved air movement with audible wheezing, and oxygen saturation increased to 100%. Thirty minutes after the initial bolus of ketamine, the patient’s status worsened. A second ketamine bolus of 0.75 mg/kg was given along with a continuous drip of 0.15 mg/kg/h. The patient again went into a dissociative state for approximately 10 minutes. Upon awakening, she was able to speak five to six-word sentences along with noteworthy improvement in respiratory distress. The provider decided to keep the patient on a ketamine drip with continuous nebulized albuterol for approximately 2

hours (Shlamovitz & Hawthorne, 2008). The patient was then admitted to the intensive care unit and later discharged with no further asthma exacerbations. The success of ketamine during a severe asthma exacerbation was attributed to the dissociative medication dosing allowing for the standardized medications to take effect. The small case report of one patient is a limitation of these findings but shows promising prospects for further more extensive population-based research.

In a trial by Tiwari, Guglani, and Jat (2016), a randomized, open-label, one-year controlled trial was conducted in a tertiary care center located in North India. The trial was comparing ketamine use to aminophylline use in acute asthma in children. The trial included 48 patients ($N = 48$). Each group consisted of 24 patients ($n = 24$). This study's objective was to determine the efficacy and safety of the use of ketamine compared to aminophylline in children as a second-line adjunct. The trial hoped to see marked improvement in the pediatric respiratory assessment measure (PRAM) score who had responded poorly to the standardized medical therapies (Tiwari et al., 2016). The trial was to detect a two-point difference in the PRAM scoring system. In the trial, each group had a significance level of 0.05, a power of 80% ($\beta = .20$), and a standard deviation of 2.46 (Tiwari et al., 2016). The PRAM scores were measured at enrollment and then at 30 min, 60 min, 90 min, 120 min, 180 min, and 24 hours. Tiwari et al. (2016) were looking at the primary outcomes, and it appears that the PRAM scores at the three-hour intervention were similar. The ketamine group ($n = 24$) was 3.79 ± 1.84 versus the aminophylline group ($n = 24$) of 3.88 ± 1.92, with a mean difference of 0.08; and a 95% CI [-1.18, 1.01], and

P = .879 respectively. Interestingly, the secondary findings showed that ketamine had reported adverse effects of hypertension *P* =.489 in two patients, 23 patients with tachycardia *P* =.489, and one ketamine patient had experienced vomiting.

Tiwari et al. (2016) addressed that the baseline and primary outcomes appear to be similar to a change in the PRAM score of 4.00 ± 1.25 and 4.17 ± 1.68, *P* =.699. The results showed no difference between the groups, and it appeared that ketamine use is equally effective as an adjunctive choice in moderate to severe asthma exacerbations (Tiwari et al., 2016).

Significant limitations were present in this trial. First, this was a single-center study. Secondly, ketamine should have been compared to a placebo. The ethics committee agreed that it would be unethical to use a placebo during this trial with a patient experiencing failed standardized treatment in a moderate to severe asthma exacerbation. Thirdly, the treating medical teams and the patient and family members were not blinded to the intervention. According to Tiwari et al. (2016), further studies should be performed on appropriate dosing ranges that would cause bronchodilation without causing undue harm to the patients due to adverse side effects.

Discussion

Asthma is a chronic, non-curable respiratory disease that affects millions in America. With the current national prevalence of asthma rising yearly, health care providers need to be educated on the pathogenesis of asthma and promote prevention and awareness of the disease progression. On average, 10 people die each day from this disease, and it is of the utmost importance to treat asthma aggressively (Asthma and Allergy Foundation of America [AAFA], 2020). Interestingly, McCance and Huether (2019) point out that asthma is affected by an inflammatory process that affects the mucosa of the lung's bronchial structures. With the inflammatory response, there is the constriction of the airways, airway hyperresponsiveness, and

obstruction. The goal of the provider is to respond rapidly with appropriate interventions. In the article by Eder, Ege, and Mutius (2006), stated that no one instrument could say with absolute certainty that a patient has asthma. Therefore, providers must use a stepwise approach in determining if a patient has asthma and promote evidence-based treatments that promote prevention along with early, quick interventions.

Due to the complexity of asthma, several scoring systems classify the severity of an exacerbation. Most systems classify exacerbations as mild, moderate, and severe. Abrams, Becker, and Szefler (2018) stated that the definition of an exacerbation varies, and almost no two studies view an exacerbation as the same. To help this problem, the 2018 Global Initiative for Asthma (GINA) added the language of clinical symptoms of an exacerbation. Exacerbations are a real medical emergency, and GINA points out symptoms of an acute asthma exacerbation are shortness of breath, coughing, wheezing, and decreased lung functions. Bateman et al. (2008) make the additional point that a patient can experience respiratory failure and even death in an advanced exacerbation. The need for a uniform definition with an accompanying list of clinical symptoms might aid the provider in prompt treatment along with thwarting the progression of the exacerbation and prevention of severe outcomes. GINA outlines a strategic approach to treating asthma with a stepwise approach. Bateman et al. (2008) establish this approach with standardized treatments of oxygen therapy, metered or inhaled beta2 agonist, ipratropium bromide, along with oral or intravenous steroids. Pollart, Compton, and Elward (2011) find it essential to correct hypoxia as soon as possible by reversing the airway obstruction with a bronchodilation medication. Sometimes further adjunctive medications are administered to stop the exacerbation progression, but there are limitations to overcome. There are insufficient evidence-based studies that clearly outline which adjunct is best to be used. Additionally, there is

also a need for further studies on which sedation protocol would be best practice if there is a need for mechanical ventilation.

In efforts of stabilizing the patient as quickly as possible adjunctive medications should be considered in a patient that appears to be refractory to first-line treatments. Lam et al. (2019) point out ketamine has several pharmacokinetic and pharmacodynamic advantages in asthma exacerbation treatment. For severe asthma exacerbations, it has sedative and analgesic properties and has the sympathomimetic activity of bronchial smooth muscles causing bronchodilation of the airways. Many providers choose to use ketamine as an induction agent during intubation. Ketamine has a rapid onset and short duration and is beneficial while performing rapid sequence intubation. Providers have found positive outcomes with ketamine for analgesia and sedation and have decreased anxiety and agitation of the patient's respiratory distress. Kiureghian and Kowalski (2015) documented the use of ketamine and noninvasive positive pressure ventilation (NIPPV) to circumvent mechanical ventilation. They believed that using a dissociative dose of ketamine during respiratory distress abetted the patient's anxiety, which allowed time for the standardized medications to be efficacious. The use of ketamine does come with some risks. Lam et al. (2019) state that ketamine at a dissociate dose has known adverse reactions and may be a consideration that would need to be examined before choosing to administer ketamine. Another study revealed ketamine could be considered as a second-line adjunct. Tiwari et al. (2016) agreed that ketamine use as adjunctive measures is as efficacious as aminophylline for second-line therapies.

On the contrary, a small double-blinded, randomized, placebo-controlled trial done by Allen and Macias (2005) revealed a lower dose of ketamine of 0.2 mg/kg followed by a two-hour continuous infusion of 0.5 mg/kg revealed no measurable respiratory improvement. Maddox

and Seupaul (2014) found similar results with their single randomized control trial. While reviewing 10 small clinical studies, Hendaus et al. (2016) found it much the same. They found it difficult to determine if ketamine was an efficacious adjunct to the standardized care due to the varying dosing regimens and small participant numbers.

In contrast, Esmailian et al. (2018) found marked improvements with a higher dose of ketamine. Clinical evidence alluded that a dose of 0.4mg/kg ketamine and 0.5 mg/kg ketamine had marked improvements in the peak expiratory flow rates compared to the lower dose of 0.3 mg/kg of ketamine, which had no measurable improvement. Favorable responses were found in the use of ketamine for the treatment of acute asthma exacerbations, and Goyal and Agrawal (2013) noted the effect of decreased wheezing and improvement in oxygen saturation. Additionally, Hendaus et al. (2019) agreed that ketamine has beneficial bronchodilation effects along with a good safety profile. A case report by Elkoundi et al. (2018) reported positive outcomes of the use of nebulized ketamine as an adjunctive treatment. With the rapid absorption within the lung, its bronchodilation effects were markedly rapid. Although nebulized ketamine was used in this case report, no documented clinical trials have been done on humans. All trials to date have been done on murine models but show great promise for further studies. The need for more extensive randomized, placebo-controlled studies would strengthen the evidence that nebulized ketamine could be considered an adjunct for use in moderate to severe asthma exacerbations.

There has been no clear consensus on the use of ketamine as an adjunctive medication in a moderate to severe asthma exacerbation. Relevant considerations have been suggested pointing to further research that is needed for the use of ketamine as an adjunct. It is essential to point out that more extensive randomized control trials are needed to determine the appropriate dosage

needed to promote bronchodilation and positive medical emergency outcomes. Finding an efficacious dosage should be emphasized in these research studies. It appears that a large dissociative dose might be an alternative explanation of positive outcomes in an asthmatic patient and warrants new high-quality research to prove its strength in standard treatment guidelines. Furthermore, the need for more extensive randomized, placebo-controlled studies would help to strengthen the evidence that nebulized ketamine was an excellent adjunct to use in moderate to severe asthma exacerbations.

Conclusion

Given the large number of individuals combating asthma annually, it is of the utmost importance to improve asthma outcomes and is always the primary goal of a healthcare provider. During this literature review, it is clear that asthma pathogenesis is extraordinarily complex, and prompt treatment is needed to deter asthma progression. Based on the literature review, the use of ketamine as an adjunct to standardized care does not have a consensus. What is interesting is that most of the data retrieved are a low dose regimen of ketamine. Some research points to a high dissociative dose of ketamine having more efficacy. It did have some positive outcomes in increasing the peak expiratory flow due to its bronchodilation abilities. This higher dose is thought to be useful in avoiding intubation and is an excellent choice for sedation medication.

The use of ketamine is debatable, and further studies are warranted. It is unethical to withhold standardized treatments, and this makes it challenging in the testing process. Additional clinical trials should address dosing regimens that promote bronchodilation and its efficacy in a moderate to severe asthma patient. Lastly, high-quality human studies need to be performed to determine the use of nebulized ketamine in acute asthma exacerbations. With the nebulization of ketamine, it could promote direct lung tissue absorption and forego systemic adverse reactions.

With the prevalence of this disease and its growing population, new and exciting research is always on the horizon. Evidence-based research will establish and provide possible new treatments for asthma, along with limitations as well.

Applicability to Clinical Practice

Due to the severity of asthma exacerbations, it is essential to address the use of ketamine as an adjunct to the standardized treatment of care in emergency settings. The key is to provide efficacious and prompt delivery of life-saving treatments for a patient experiencing an asthma exacerbation. Implementation of this adjunctive medication will possibly lower mortality rates and show a marked improvement on the standardized treatment plan of a moderate to severe asthma exacerbation.

References

Abrams, E., Becker, A., & Szefler, S. (2018). Where does worsening asthma end and an asthma exacerbation begin? *American College of Allergy, Asthma & Immunology,* 123, 320-330. http://dx.doi.org/10.1016/j.anai.2018.11.017

Allen, J., & Macias C. (2005). The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. *Annals of Emergency Medicine, An International Journal*, 46(1), 43– 50. http://dx.doi.org/10.1016/j.annemergmed.2005.02.024

Al-Shamrani, A., Al-Harbi, A., Bagais, K., Alenazi, A., & Alqwaiee, M. (2019). Management of asthma exacerbation in the emergency departments. *International Journal of Pediatrics and Adolescent Medicine,* 6(2), 61-67. http://dx.doi.org/10.1016/j.ijpam.2019.02.001

Asthma and Allergy Foundation of America. (2020). *Asthma facts and figures* [PDF]. Retrieved from www.aafa.org/asthma-facts

Bateman, E., Hurd, S., Barnes, P., Bousquet, J., Drazen, J., FitzGerald, J., …. Zar, H. (2008). Global strategy for asthma management and prevention: GINA executive summary. *The European Respiratory Journal*, *31*(1), 143–178. https://dx.doi.org/10.1183/09031936.00138707

Castillo, J., Peters, S., & Busse, W. (2017). Asthma exacerbations: Pathogenesis, prevention, and treatment. *The American Academy of Allergy, Asthma, and Immunology,* 5(4), 918-927. http://dx.doi.org/10.1016/j.jaip.2017.05.001

Center for Disease Control and Prevention. (2018). *Current asthma prevalence 2018.* [PDF]. Retrieved from www.cdc.gov/asthma

Center for Disease Control and Prevention. (2018). *Asthma mortality 2018.* [PDF]. Retrieved from www.cdc.gov/asthma

Eder, W., Ege, M., & Von Mutius, E. (2006). The asthma epidemic. *New England Journal of Medicine*, *355*(21), 2226-2235. http://dx.doi.org/10.1056/NEJMra054308

Elkoundi, A., Bentalha, A., Koraichi, A., & El Kettani, S. (2018). Nebulized ketamine to avoid mechanical ventilation in a pediatric patient with severe asthma exacerbation. *American Journal of Emergency Medicine,* 36, 734.e3-734.e4. http://dx.doi.org/10.1016/j.ajem.2018.01.027

Esmailian, M., Esfahani, M., & Heydari, F. (2018). The effect of low-dose ketamine in treating acute asthma attack; A randomized clinical trial. *Emergency, 6*(1), e21. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6036522

Goyal, S., & Agrawal, A. (2013). Ketamine in status asthmaticus: A review. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine*, 17(3), 154–161. http://dx.doi.org/10.4103/0972-5229.117048

Hendaus, M., Jomha, F., & Alhammadi, A. (2016). Is ketamine a life-saving agent in childhood acute severe asthma? *Therapeutics and Clinical Risk Management,* 12, 273-279. http://dx.doi.org/10.2147/TCRM.S100389

Jat, K., & Chawla, D (2012). Ketamine for management of acute exacerbations of asthma in children. *Cochrane Database of Systematic Reviews,* 11, 1-17. http://dx.doi.org/10.1002/14651858.CD009293.pub2

Kiureghian, E., & Kowalski, J. (2015). Intravenous ketamine to facilitate noninvasive ventilation in a patient with a severe asthma exacerbation. *American Journal of Emergency Medicine,* 33, 1720e1-1720e2. http://dx.doi.org/10.1016/j.ajem.2015.03.066

Lam, E., Rochani, A., Kaushal, G., Thoma, B., Tanjuakio, J., West, F., & Hirose, H. (2019). Pharmacokinetics of ketamine at dissociative doses in an adult patient with refractory status asthmaticus receiving extracorporeal membrane oxygenation therapy. *Clinical Therapeutics,* 41(5), 994-999. http://dx.doi.org/10.1016/j.clinthera.2019.03.005

Maddox, R., & Seupaul, R. (2014). Is ketamine effective for the management of acute asthma exacerbations in children? *Annals of Emergency Medicine,* 63(3), 309-310. http://dx.doi.org/10.1016/j.annemergmed.2013.08.017

McCance, K., & Huether, S. (2019). The pulmonary system. In V. Brashers & N. Rote (Eds), *Pathophysiology the basics for disease in adults and children* (pp. 1177-1220). St Louis, MI: Elsevier.

Papiris, S., Kotanidou, A., Malagari, K., & Roussos, C. (2002). Clinical review: Severe asthma. *Critical Care* 6(1) 30-44. https://dx.doi.org/10.1186/cc1451

Pollart, S., Compton, R., & Elward, K. (2011). Management of acute asthma exacerbations. *American Academy of Family Physicians,* 84(1), 40-47. Retrieved from https://www.aafp.org/afp/2011/0701/p40.html

Saadeh, C., & Oppenheimer, J. (2018). Status Asthmaticus. *Medscape,* 1-34. Retrieved from https://emedicine.medscpe.com/article/2129484-print

Shlamovitz, G., & Hawthorne, T. (2011). Intravenous ketamine in a dissociating dose as a temporizing measure to avoid mechanical ventilation in adult patient with severe asthma exacerbation. *The* Journal of Emergency Medicine, 41(5), 492-494. http://dx.doi.org/10.1016/j.jemermed.2008.03.035

Tiwari, A., Guglani, V., & Jat, K. (2016). Ketamine versus aminophylline for acute asthma in children: A randomized, controlled trial. *Annals of Thoracic Medicine,* 11(4), 283-288. http://dx.doi.org/10.4103/1817-1737.191874

Wong, J., Lee, J., Turner, D., & Rehder, K. (2014). A review of the use of adjunctive therapies in severe acute asthma exacerbation in critically ill children. *Journal Expert Review of Respiratory Medicine*, 8(4), 423-441. http://dx.doi.org/10.1586/17476348.2014.915752