Review

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Status asthmaticus and the use of ketamine nebulization and magnesium sulfate: current strategies and outcomes

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Abstract

This narrative review aims to systematically explore and synthesize the current literature on the efficacy and safety of ketamine nebulization and magnesium sulfate as therapeutic interventions in the management of status asthmaticus. The review evaluates clinical outcomes, administration protocols, and potential adverse effects associated with these treatments. Ketamine has proven effective in managing asthma due to its bronchodilator properties, primarily by stimulating nitric oxide and catecholamine release. Magnesium sulfate has shown benefits by interfering with calcium influx, which alleviates bronchospasm and enhances bronchodilation. Both treatments have been associated with improvements in FEV1 and peak expiratory flow rates, which improve blood oxygenation and reduce bronchospasm. Despite the promising results, more research is needed to determine the optimal dosages and administration routes for these interventions. Furthermore, current studies often do not use these treatments as first-line options, which may introduce confounding variables. Future research should focus on establishing clear protocols for the use of ketamine and magnesium sulfate in refractory acute-severe asthma and status asthmaticus. This review highlights the potential for these treatments to improve clinical outcomes when standard corticosteroid therapies are insufficient, suggesting that with appropriate dosing and consideration, they could be valuable additions to the management strategies for severe asthma exacerbations.

Keywords: critical care, emergency medicine, pulmonology

Introduction

Asthma is well known for its global prevalence, array of phenotypes, and wide epidemiological profile. It is characteristically an obstructive lung disease of variable airflow limitation. Pathologically, this is due to bronchospasm, inflammation, remodeling, mucus production, and airway wall thickening from an antigen-mediated inflammatory cascade[1]. Symptom profiles are non-specific and include wheezing, shortness of breath, chest tightness, or cough, which may vary in frequency, onset, and intensity[2]. Asthma is a common global disease with substantial human and economic costs[3]. Prevalence is 5.4% across the ages surveyed (5–69). Prevalence was highest at 10.95% at the youngest ages (5–9) and lowest at 2.96% at the oldest (65–69). Across all ages, the prevalence of ever having asthma was one in ten[4]. The phenotypical profile is heterogeneous and a complex molecular and clinical topic under research for targeted therapies. It is based on age of onset, allergen sensitization, lung function, and comorbidities[5,6]. The exact phenotype profile is a result of both genetics and environmental exposure. Studies suggest that genetic risk factors are higher for childhood asthma and environmental exposures influence adult-onset asthma[5].

With a high prevalence, asthma is a familiar reason for both primary care and emergency department visits. The goal of treatment is symptom control and reduction in the loss of pulmonary function, i.e., forced expiratory volume in 1 second (FEV1)[7]. The pharmacological treatment is based on an iterative cycle of assessment and re-evaluation of control, risk factors, comorbidities, side effects, and patient satisfaction[2,3]. This is a treatment of incremental dosing of short-acting β2-agonist (inhaled), long-acting β2-agonist, long-acting muscarinic antagonist, or leukotriene receptor antagonist. Therapy is continually evaluated based on symptom control and adjusted accordingly[3].

In the emergency and ICU setting, asthma may become unresponsive to initial intensive therapy such as beta-2 agonists[8]. This is termed status asthmaticus and significant for a potential outcome in morbidity or death[9]. Quantification to the degree of unresponsiveness in time and intensity has limitations and is more

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commonly referred to as acute severe asthma[10,11]. Episodes of status asthmaticus are an immediate medical emergency. They require close observation and immediate aggressive administration of bronchodilators[12]. Though a majority of status asthmaticus patients' symptoms are steroid-sensitive, a subset (5%–10%) has a refractory response[1,13]. For these patients, decisions become increasingly complex requiring expertise and judicious evidence-based medicine decision making with consideration for the need to intubate[14]. The pathophysiology of the refractory response is not well understood and has been associated with increased production of IL-17A pulmonary secretions by $CD4^+$ TH17 cells that may correlate to the hyperresponsiveness and poor glucocorticoid response[15,16].

For the steroid-resistant status asthmaticus phenotypes, last-line non-standard modalities are considered. Non-standard modalities listed in the literature include anesthetic agents, intravenous magnesium sulfate, helium/oxygen gas mixtures, and ECMO[17]. In the scope of this literature review, two of the published pharmacological interventions were surveyed: nebulized ketamine and intravenous magnesium sulfate. Ketamine is a well-known rapid onset anesthetic known for its sedative, analgesic, and antiemetic effects. It causes bronchodilation and stimulation of the sympathetic nervous system. With its bronchodilator profile, it has been previously advocated as a treatment of patients with acute asthma attack[18]. Inhaled magnesium sulfate was previously approved for use by the Global Initiative in National Asthma with some studies confirming bronchodilation effects; however, the effects remain controversial[19].

Methods

This narrative review was conducted to synthesize the current literature on the use of ketamine nebulization and magnesium sulfate in the treatment of status asthmaticus. A comprehensive search of electronic databases including PubMed and Google Scholar was performed to identify relevant studies published from 2020 to June 2024. Keywords used in the search included "status asthmaticus," "ketamine nebulization," "magnesium sulfate," "acute severe asthma," and "bronchodilation."

Inclusion criteria for the review were clinical trials, observational studies, case reports, and review articles that evaluated the efficacy, safety, administration protocols, and outcomes of ketamine nebulization and magnesium sulfate in patients with status asthmaticus.

Exclusion criteria were studies not published in English, studies without full text available, and those not specifically addressing the therapeutic use of ketamine and magnesium sulfate in asthma management.

Two reviewers independently performed data extraction, with discrepancies resolved through discussion and consensus. The primary outcomes evaluated included improvement in pulmonary function tests such as FEV1 and peak expiratory flow rates, reduction in hospital admissions, and adverse effects associated with the treatments. Secondary outcomes included dosage optimization and administration routes.

Findings were synthesized narratively due to the heterogeneity of the included studies in terms of design, patient populations, and outcome measures. The review aimed to highlight current strategies, clinical outcomes, and areas requiring further research. Ethical approval and informed consent were not applicable as this study did not involve any human participants.

Ketamine nebulization in status asthmaticus

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that has effects on monoamine transporters and opioid receptors. It is a phencyclidine derivative that is made up of two isomers metabolized through first pass by liver isozymes[20,21]. Its metabolites norketamine and dehydronorketamine have a rapid onset and a short duration of action, making it suitable for the treatment of medical emergencies such as status asthmaticus[20]. Its effectiveness in the treatment of asthma comes from its ability to act as a bronchodilator and airway relaxant while improving respiratory parameters like respiratory rates and peak expiratory flow rates (PEFR)[22]. It does this by interrupting the inflammatory cascade, which is a hallmark of status asthmaticus. The mechanisms of action that culminate in its bronchodilator effects include the inhibition of voltage-sensitive calcium channels, postsynaptic muscarinic and nicotinic receptors, as well as downregulating nitric oxide synthase activity to reduce nitric oxide production[23]. Furthermore, it prevents the reuptake of catecholamines like epinephrine, thereby potentiating beta-2 activation which favors bronchodilation[20,21,24,25]. Lastly, ketamine is involved in the suppression of immune cell function, including cytokine production and their oxidative ability, to dampen the symptoms of asthma caused by immune cell response[20,22,24]. These effects reduce airway resistance and increase lung compliance, in addition to relieving bronchospasm and ensuring effective blood oxygenation.

The recommended dose of ketamine for the treatment of asthma has changed over the years as titration of dosage is important for optimization of therapeutic effects while minimizing adverse side effects. The initial 1971 study conducted by Betts and Parkin utilized this medication by administering a 75 mg/kg dose via intramuscular injection followed by an intravenous dose of 10 mg/kg every 15 minutes until a total dose of 115 mg was reached[20]. There have been numerous studies conducted since that have investigated the dose-dependent effects of the medication and according to the 2021 North American and international guidelines, the recommended dose for patients experiencing severe acute asthmatic symptoms is an intravenous bolus of 1–2 mg/kg, followed by a 20–60 μg/kg/min infusion. This dosage was adopted because it minimizes major adverse effects like respiratory depression, hypertension, emergence agitation, and laryngospasm while relieving acute asthmatic symptoms[20,26].

In addition to proper dosing, nebulization can be used as a route of delivery to minimize life-threatening side effects like respiratory depression. A 2021 study conducted by Farshadfar *et al* found that besides the improvement of peak expiratory flow rates, bronchospasm, and blood oxygen saturation, nebulized ketamine displayed little to no side effects of respiratory depression after administration for 30 and 60 minutes. This makes it a safer option when compared to intravenous, intramuscular, oral, sublingual, or even subcutaneous routes of administration[25,27]. Route of administration also has an effect on duration of onset and peak plasma volumes as maximum concentrations can be measured after 1 minute when given intravenously versus 5 minute when given through intramuscular injection and within 15 minute of intranasal administration[28]. Hence, different routes of admission should be considered in order to tailor duration of peak concentration and onset.

Regardless of route of admission, ketamine should be used cautiously and tailored to each patient to avoid side effects. Some patient demographics that should be monitored closely are patients with seizure disorder as ketamine could reduce the seizure threshold and precipitate breakthrough seizures, patients with increased ocular and intracranial pressure (ICP) should also be considered as ketamine causes an increase in cerebral blood flow and thereby could worsen pre-existing ICP symptoms. While most of the side effects of ketamine are well documented in the adult population, teens and children have been found to experience minimal adverse effects from the medication. The disposition of the medication also differs in children versus adults as children have been shown to exhibit higher measurable concentrations of the metabolite norketamine after intramuscular injection administration when compared to oral or rectal routes. This is thought to be as a result of increased first pass effect when the latter routes are used as opposed to the former[23].

Mechanical ventilation can be used as a treatment method for severe asthma in patients who are refractory to other treatment methods. Although it presents the benefit of supporting the respiratory system while working on resolving bronchoconstriction from status asthmaticus, it is an invasive option that requires appropriate pharmacological constructive collaboration to be effective[29]. Because traditional intubation techniques are often complicated by hyperinflation, pneumothorax, and systemic hypertension, it is beneficial to avoid intubation by using less invasive treatment options if available. This highlights another use for ketamine as there are studies that point to the effectiveness of the medication in the avoidance of mechanical ventilation and therefore the avoidance of further complications in the setting of status asthmaticus[29,30] (Table 1).

Magnesium sulphate in status asthmaticus

Magnesium sulfate has shown to be effective as adjunctive therapy, surpassing the efficacy of standard therapy alone in patients experiencing acute severe asthma. The effectiveness of treatment outcomes, as well as the prevention of hospitalization and expedited discharge from the emergency department, hinges on the appropriate medication route, dosage, and timely intervention[31]. The mechanisms underlying the action of magnesium sulfate in acute asthma are multifaceted. Researchers have identified its involvement in cellular homeostasis, acetylcholine, and histamine release modulation. Additionally, it acts as a calcium antagonist, impeding bronchial smooth muscle contraction and fostering bronchodilation[32]. Patients receiving magnesium sulfate at established doses exhibit no serious adverse effects. Furthermore, serum magnesium levels and ionized magnesium levels remain within acceptable ranges, facilitating the relaxation of smooth muscles during treatment[33]. In a retrospective cohort study conducted by Mittal *et al*, involving 878 188 children under 18 years hospitalized for acute asthma exacerbations between 2010 and 2017, it was found that intravenous magnesium sulfate was more frequently administered to children over 5 years old, non-Hispanic black children, those with a history of ED visits in the previous year, and those with increased inpatient lengths of stay and ICU admission rates. The use of magnesium sulfate increased in high and moderate-volume hospitals (3.4% and 2.9% per year respectively, *P* value of 0.04) compared to low-volume hospitals (1.2% per year), with a corresponding decrease in length of stay noted over the study period (1.6 days in 2010 versus 1.4 days in 2017; *P* value of less than 0.001). However, there was no statistically significant association between IV magnesium sulfate use and changes in inpatient admission, ICU admission, or 7-day readmission rates[34]. Dosage recommendations for magnesium sulfate in children with status asthmaticus typically range from 25 to 75 mg/kg/dose to achieve a magnesium concentration within the therapeutic range (2.5–4 mg/dL)[35]. A Cochrane review analyzed studies indicated that a single IV dose of 1.2 or 2 g over 15–30 minutes decreased hospital admission and improved lung function in adults with acute severe asthma as compared to placebo (odds ratio of 0.75, 95% confidence interval of 0.60–0.92; *P* value of 0.18, number = 972)[36]. However, prolonged magnesium infusions are increasingly being used by clinicians, which is a safe alternative as demonstrated by the retrospective study of 447 children performed by Johnson *et al*: with adverse effects occurring with magnesium infusions >24 hours[37]. There is

Table 1

Review of outcomes and adverse effects of ketamine nebulization and infusion on status asthmaticus

Study author	Intervention	Population	Outcomes	Adverse effects
Farshadfar *et al*, 2021[1]	Nebulized ketamine vs. intravenous magnesium sulfate	70 adult patients with corticosteroid-resistant asthma	PEFR increased by 29.4% in the ketamine group and by 15.2% in the $MgSO_4$ group. However, there was no statistically significant difference between the groups.	No significant adverse effects were reported.
Goyal *et al*, 2013[22]	Nebulized ketamine	244 patients (age 5 month–70 yr) with severe asthma or status asthmaticus	Improved clinical outcomes, reduction in oxygen requirements and need for mechanical ventilation.	Minor dysphoria or hallucinations and increased secretions
Heshmati *et al*, 2003[23]	Ketamine infusion	11 patients aged 15–40 yr with severe status asthmaticus unresponsive to conventional therapy/ventilation	Statistically significant increase in PaO_2 and decrease in peak airway pressure and $PaCO_2$	Increased airway secretions
Hendaus *et al*, 2016[20]	Ketamine for severe childhood asthma exacerbation	Systematic review (control trials, case reports, retrospective studies)	Studies showed reduced bronchospasm and need for intubation while others reported no significant benefit over conventional therapy	Increased blood pressure, hallucinations, and respiratory depression in some cases

different dosing regimens used by different clinicians. Irazuzta *et al* studied 38 children in the emergency department of a hospital in Paraguay and concluded that the administration of a prolonged high-dose magnesium infusion early on (50 mg/kg/h over 4 hours) for noninfectious asthma is linked to a quicker discharge from ED (47% children discharged at 24 hours in high-dose magnesium infusion group versus 10% in the bolus group; *P* value of 0.032) with an absolute risk reduction (ARR) of 37% (95% CI, 10–63) and a number needed to treat (NNT) of 2.7 (95% CI, 1.6–9.5)[38]. However, a recent retrospective cohort study on 210 children by Kapuscinski *et al* revealed an increased requirement for mechanical ventilation (invasive or noninvasive) or a need for added therapies (terbutaline, epinephrine, aminophylline, ketamine, Heliox, or more doses of magnesium sulfate) with the use of higher doses of magnesium sulfate >27 mg/kg/dose[39]. A prospective randomized controlled pilot study demonstrated equal efficacy and safety of nebulized magnesium sulfate and intravenous magnesium sulfate in 28 Thai children with severe asthma exacerbations.[40]. As far as the efficacy of nebulized magnesium sulfate in adults is concerned, Mohamed *et al* concluded an increase in PEFR and SaO_2 with minimal side effects, decreased ICU and ward admission with inhaled magnesium sulfate as an add-on to standard treatment (beta agonist and hydrocortisone) as compared to traditional treatment (nebulized salbutamol and ipratropium bromide) in a randomized single-blind controlled trial of 82 adults more than 18 years old[41]. A double-blinded randomized controlled study of 30 patients showed that nebulized magnesium sulfate alone (PEFR improvement of 54 ± 35.6 L/min, *P* value of 0.001) is equally effective (*P* value of 0.389) as inhaled salbutamol (PEFR improvement 67.0 ± 41.9 L/min, *P* value of 0.001); however, the efficacy of inhaled magnesium sulfate is less (*P* value of 0.014) than the combination of nebulized magnesium and salbutamol (PEFR improvement 92.0 ± 26.9 L/min, *P* value of 0.000)[19] (Table 2).

Salbutamol versus magnesium sulfate: a comparison

In a randomized clinical trial involving pediatric patients with status asthmaticus, the Pediatric Rapid Assessment Measure (PRAM) score was utilized as the assessment tool to monitor patient progress. Eligible patients with a PRAM score exceeding 4 were randomly assigned to receive either three consecutive nebulization of salbutamol solution or various doses of magnesium nebulization (250, 500, and 750 mg) administered every 20 minutes for 1 hour. Significant reductions in PRAM scores were observed in both the salbutamol and magnesium nebulization groups. Moreover, greater improvements were noted when the treatments were combined over 24 hours. Additionally, a linear correlation was observed between clinical improvement and escalating doses of magnesium in conjunction with salbutamol[42].

Assessing treatment outcomes and adverse effects

A randomized controlled trial in patients aged 18 or younger showed improved pulmonary function (CI [0.80–3.08], *P* = 0.0008) and reduced hospital admissions (CI [0.31–0.95], *P* = 0.03) with IV magnesium sulfate, but inconsistent results with nebulized magnesium sulfate[32]. A study in children aged 2–16 found that 47% of those receiving high-dose prolonged magnesium sulfate infusion therapy were discharged within 24 hours, compared to 10% with bolus therapy, with lower healthcare costs for the infusion group ($P < 0.016$)[38]. Another study showed no significant reduction in hospital stay duration with magnesium and albuterol (*P* = 0.037), though albuterol treatment duration increased ($P = 0.001$)[46]. Cochrane reviews confirmed IV magnesium sulfate reduced hospital admissions (OR 0.32, CI 0.54–0.74)[43], and Ozdemir *et al* reported improved pulmonary function with systemic magnesium sulfate in children[44]. However, no correlation was found between magnesium use and hospital outcomes, ventilation duration, or mortality in a cohort of 25 882 children[45,47]. Continuous magnesium infusion resulted in fewer severe adverse effects, mainly mild hypotension, with no magnesium toxicity[48]. It is also beneficial in pregnant patients with status asthmaticus, though it may cause neonatal toxicity, such as neuromuscular or respiratory depression[49]. One study found no mortality benefit with IV magnesium sulfate (1.3% vs. 1.8%, *P* = 0.488)[50].

Standard of care and additional management

The main objective of the treatment of asthma is to control the disease, improve symptoms, and prevent exacerbations. The primary classes of medication for asthma management include short-acting β adrenergic agonists, which are the first-line therapy, along with short-acting muscarinic antagonists and inhaled and systemic steroids. Additional medications such as methylxanthines (e.g., theophylline and aminophylline), magnesium sulfate, helium-oxygen therapy, leukotriene modifiers, and ketamine may also be used as secondary measures[51,52].

Management for severe cases of asthma typically includes inhaled β agonists (2.5 mg) given every 1–4 hours by nebulization, with dosing intervals depending on the clinical situation, dyspnea, and PEF/FEV1 ratio. The use of anticholinergics in admitted patients is controversial and not recommended. Systemic corticosteroids should be administered in a daily dose of 50 mg of prednisolone or prednisone as a morning dose or 200 mg of hydrocortisone in divided doses. Some patients may improve with intravenous aminophylline, with a typical loading dose of 5 mg/kg intravenously over 20 minutes, followed by an infusion at a rate of 0.5–0.7 mg/kg/hour. Oral leukotrienes can also be administered and have been shown to increase FEV1[52].

Ketamine versus magnesium sulphate

A randomized double-blinded study by Farshadfar *et al* compared intravenous magnesium sulfate to nebulized ketamine in steroid-resistant severe asthma patients. Both groups, receiving standard treatments like corticosteroids and beta-2 agonists, showed improved peak expiratory flow rate (PEFR), with ketamine slightly outperforming magnesium sulfate[1]. Acute asthma exacerbations can be steroid-responsive or resistant, and combining standard therapy with ketamine or magnesium sulfate improves clinical outcomes[1,51,53,54].

Mechanism and efficacy

Ketamine, acting as an NMDA receptor antagonist, reduces inflammation and induces bronchodilation when nebulized,

Table 2

Review of outcomes and adverse effects of magnesium sulfate infusion on status asthmaticus

Study author	Intervention	Population	Outcomes	Adverse effects
Irazuzta *et al*, 2017[38]	$MgSO_4$ infusion	Pediatric patients with acute severe asthma (patient count not provided)	High-dose continuous magnesium sulfate infusion (HDMI) showed a 47% discharge rate compared to 10% with standard bolus. Reduced hospital admissions by approximately 20%.	Epigastric warmth, tingling, and pain at the injection site. No significant adverse effects reported.
Egelund *et al*, 2012[33]	High-dose $MgSO_4$ infusion (50–75 mg/kg bolus followed by 40 mg/kg/h for 4 hours)	19 pediatric patients with status asthmaticus (compared to 38 controls)	Continuous $MgSO_4$ infusion lowered heart and respiratory rates without adverse hemodynamic effects. Serum Mg levels associated with smooth muscle relaxation.	Mild infusion-related reactions in 3 patients (nausea, vomiting, pain at injection site, flushing).
Mittal *et al*, 2020[34]	IV $MgSO_4$ use in pediatric asthma exacerbations from 2010 to 2017	878,188 pediatric acute asthma exacerbations in 35 US children's hospitals	No significant association with reduced hospital or ICU admission rates. Length of stay decreased from 1.6 to 1.4 days. IV magnesium use doubled from 17% to 36%.	No specific adverse effects were reported in the study.
Kapuscinski *et al*, 2020[39]	Association of IV $MgSO_4$ doses and escalation in therapy	210 pediatric patients with asthma exacerbations	Patients <40 kg receiving >27 mg/kg had a higher rate of therapy escalation (18.3%) compared to those receiving ≤27 mg/kg (4.5%)	Decrease SBP or DBP >20% observed in some patients.
Daengsuwan *et al*, 2017[40]	Nebulized $MgSO_4$ vs. IV $MgSO_4$	28 children with severe acute asthma (15 nebulized, 13 intravenous)	No statistically significant differences in clinical outcomes for length of stay. Both forms were effective, with clinical improvement noted at 60 minutes and continuing over 24 hours.	No adverse effects reported in either group.
Mohamed *et al*, 2018[41]	Nebulized $MgSO_4$	82 adult asthmatics with acute exacerbation (41 in each group)	The $MgSO_4$ group showed a 31% improvement in PEFR compared to 7.2% in the control group. SaO_2 improved by 2.7% versus 0.71%. 43% reduction in ICU admission and 76% reduction in ward admission in the $MgSO_4$ group.	No significant side effects were reported in the study
Asif *et al*, 2024[42]	$MgSO_4$ (250 mg, 500 mg, 750 mg) doses with salbutamol	104 children with status asthmaticus (2–12 years old)	Significant improvement in PRAM scores at 24 hours, with the highest improvement in the 750 mg $MgSO_4$ group. The 750 mg $MgSO_4$ group also had the shortest hospitalization duration.	Nausea and respiratory depression were reported in the higher $MgSO_4$ dose groups.
Griffiths *et al*, 2016[43]	IV $MgSO_4$	182 children with acute asthma	$MgSO_4$ reduced hospital admissions by 68% (OR 0.32) in children with moderate to severe exacerbations.	Few adverse events reported. Mild symptoms such as epigastric warmth and tingling at the infusion site.
Ali Özdemir *et al*, 2020[44]	IV $MgSO_4$	115 children aged 6–17 years with acute asthma	Significant improvement in FEV1, PEF, and FEF25–75 post-$MgSO_4$ infusion. Group with moderate asthma showed greater improvement compared to mild asthma group.	Minor side effects reported included nausea, vomiting, and slight decreases in SpO_2 during infusion
Taher *et al*, 2022[45]	Prolonged IV $MgSO_4$ infusions	135 pediatric patients (27 treatment, 108 control) with refractory status asthmaticus	No significant difference in mechanical ventilation requirement (25.9% vs. 18.5%). Treatment group had longer PICU length of stay (3.63 vs. 1.09 days) and higher ECMO requirement (11.1% vs. 0%). No difference in mortality.	51.9% experienced adverse events, primarily hypotension (48.1%).

while magnesium sulfate relaxes muscles by regulating calcium, typically administered intravenously[1]. Both treatments, when added to standard therapy, improve PEFR and overall efficacy in managing status asthmaticus or corticosteroid-resistant asthma, reducing hospital mortality[1,53].

Synergistic effects

The combination of ketamine or magnesium sulfate with standard asthma therapies enhances treatment efficacy, especially for corticosteroid-resistant cases. These therapies offer unique mechanisms that complement standard treatments, improving outcomes in acute asthma exacerbations[1,51,54].

Discussion

This study evaluated the efficacy and safety of ketamine nebulization and magnesium sulfate for managing status asthmaticus. Ketamine, historically used for anesthesia due to its ability to preserve heart function, breathing, and airway reflexes, was

designated an essential medication by WHO in 1962 and approved by the FDA in 1970[20]. Its use in asthma treatment was first demonstrated in 1971 by Betts and Parkin, who highlighted its effectiveness in resolving wheezing[21]. Extensive studies since then have confirmed ketamine's efficacy at various doses and routes, including intramuscular, intravenous, and nebulization, though dosing should be tailored for specific populations[20,22,23].

Magnesium sulfate became popular as an adjunctive medication for the treatment of asthma in the early 2000s. Magnesium disrupts smooth muscle contraction by competitively antagonizing calcium, thereby eliciting improvement of acute asthmatic symptoms, making it an effective adjunctive medication. Its effectiveness has been moderately documented, with some studies highlighting a 25% increase in FEV1 after 10 and 20 minutes of administration of nebulized magnesium sulfate as adjunct therapy[21]. A major limitation in the quality of the current literature is that in numerous studies, the efficacy of medications like ketamine and magnesium sulfate is evaluated in the context of acute asthmatic episodes that are refractory to first-line agents, and never as first-line treatment or as part of it[1].

When treating patients who do not respond to initial treatments like anticholinergics (ipratropium) and Beta 2 agonists (terbutaline or salbutamol) with systemic corticosteroids, supplementary drugs are considered in the effort to stabilize patients. These drugs are administered after trials of anticholinergics and systemic corticosteroids[21,26]. This may have introduced confounding variables because the extent to which the first-line agents modulate the efficacy of ketamine and magnesium sulfate was not considered. Furthermore, some studies differ in initial therapy due to different standards of treatment, making them non-uniform and reducing their comparability. There are also limited studies that evaluate the efficacy of these medications, which may reduce the power of the study due to the smaller sample size[55,56].

Several emerging therapies for acute asthma, including nebulized recombinant human DNAse and heliox-driven nebulizers, have been investigated, but none have shown clear benefits over the current, cost-effective standard treatment[26,57]. Recent research has focused on preventing status asthmaticus through personalized IgG antibodies to interleukins and TNF alpha, but standard therapy remains the most affordable and safest option[26,57].

This narrative review systematically synthesizes current evidence on the efficacy and safety of ketamine nebulization and magnesium sulfate in treating status asthmaticus. It provides valuable insights into their potential role as adjunctive therapies, with a focus on comparing nebulized and intravenous administration routes.

Future directions

Future studies should establish optimal magnesium sulfate doses and infusion protocols to reduce admissions and clarify its role in refractory acute-severe asthma[58,59]. While ketamine shows promise in dissociative dosing and as an adjunct to NIPPV, more research is needed to confirm its efficacy and safety, especially in status asthmaticus and status epilepticus[60,61]. Key areas for exploration include dosing, advanced pharmacotherapy, and outcomes, particularly in minorities and low-income groups[58,59]. Studies from 2013 to 2016 highlighted the need for larger controlled trials to confirm ketamine's effectiveness in severe asthma[20,60]. Ketamine's potential, shown in ARDS-COVID patients, suggests broader applications in managing critical conditions[61].

Conclusion

Both ketamine nebulization and magnesium sulfate offer significant bronchodilation benefits in managing steroid-resistant asthma. Ketamine works by stimulating nitric oxide production and catecholamines, while magnesium sulfate inhibits histamine and acetylcholine release and calcium influx. These interventions improve FEV1, peak expiratory flow rates, and blood oxygenation. Adding them to current treatments can enhance outcomes and reduce mortality when corticosteroids are ineffective, provided they are used with appropriate dosing.

Ethical approval

Ethics approval was not required for this review.

Consent

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