Use of ketamine in patients with refractory severe asthma exacerbations: systematic review of prospective studies.

Luigi La Via (luigilavia7@gmail.com)
Azienda Ospedaliero-Universitaria Policlinico - Vittorio Emanuele
Filippo Sanfilippo
Azienda Ospedaliero-Universitaria Policlinico - Vittorio Emanuele
Giuseppe Cuttone
University of Catania
Veronica Dezio
Azienda Ospedaliero-Universitaria Policlinico - Vittorio Emanuele
Monica Falcone
Magna Graecia University
Serena Brancati
University of Catania
Claudia Crimi
Azienda Ospedaliero-Universitaria Policlinico - Vittorio Emanuele
Marinella Astuto
Azienda Ospedaliero-Universitaria Policlinico - Vittorio Emanuele

Systematic Review

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Abstract

Background: Asthma is a heterogeneous disease with wide range of symptoms. Severe asthma exacerbations (SAEs) are characterized by worsening symptoms and bronchospasm requiring emergency department visits. In addition to conventional strategies for SAEs (inhaled β-agonists, anticholinergics, and systemic corticosteroids), another pharmacological option is represented by ketamine.

Objective: To explore the role of ketamine in refractory SAEs.

Methods: We performed a systematic search on PubMed and EMBASE up to August 12th, 2021. We selected prospective studies only, and outcomes of interest were: oxygenation/respiratory parameters, clinical status, need for invasive ventilation and effects on weaning.

Results: We included a total of seven studies, five being randomized controlled trials (RCTs, population range 44-92 patients). The two small prospective studies (n=10 and n=11) did not have a control group. Four studies focused on adults, and three enrolled a pediatric population. We found large heterogeneity regarding sample size, age and gender distribution, inclusion criteria (different severity scores, if any) and ketamine dosing (bolus and/or continuous infusion). Of the five RCTs, three compared ketamine to placebo, while one used fentanyl and the other aminophylline. The outcomes evaluated by the included studies were highly variable. Despite paucity of data and large heterogeneity, an overview of the included studies suggests absence of clear benefit produced by ketamine in patients with refractory SAE, and some signals towards side effects.

Conclusions: Our systematic review does not support the use of ketamine in refractory SAE. A limited number of prospective studies with large heterogeneity was found. Well-designed multicenter RCT are desirable.

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and remodeling, responsible for variable airflow obstruction, thickening of the airway wall and increased mucus production. These pathophysiological features determine a wide range of symptoms such as wheezing, dyspnea, chest tightness and cough, which may vary over time in onset, frequency and intensity[1]. Asthma prevalence ranges from 1–21%[2] in adults with a high health and economic burden[3], and it that has increased by nearly 30% in the last 20 years[4]. Moreover, despite the availability of effective and tailored pharmacological treatments[5–8] targeting patients' inflammatory and clinical phenotypes[9, 10], satisfactory control of asthma symptoms is still an unmet need[11] and a major challenge for clinicians[12], leading to exacerbations and admission to the emergency department for acute asthma attack. Indeed, severe asthma exacerbation (SAE) is characterized by a progressive increase of symptoms and severe bronchospasm requiring emergency room visits, adequate monitoring and possibly hospitalization. First-line management of SAEs includes inhaled short-acting β-agonists, anticholinergics, and systemic corticosteroids, with the goal of relieving airflow obstruction and hypoxemia as quickly as

possible and, in refractory cases, intravenous magnesium sulfate and aminophylline can also be considered[13]. The more SAE cases require also noninvasive ventilatory support[14] and nearly 10% of hospitalized SAE patients will need intensive care unit admission, with finally 2% of them requiring intubation and invasive mechanical ventilation[15] with possible continuous infusion of muscle relaxants.

In addition to the conventional strategies for the treatment of SAE, another pharmacological option may be represented by ketamine. Ketamine is a rapid onset drug with well-known sedative, analgesic and antiemetic effects. The use of ketamine in severe asthma has been advocated for its sympathetic stimulation and the consequent relaxation of smooth muscles and bronchodilation. Therefore, ketamine may improve lung compliance and reduce airways resistances when administered in continuous infusion. Moreover, it may increase bronchial secretions which may relieve mucus plugs. Suggested dosages have been in the range of 0.5 to 2 mg/kg/h. Nonetheless, ketamine has several dose-dependent side effects, such as hypertension, tachycardia, increase in intracranial pressure and sedative effects. Moreover, it can cause drooling, myoclonia, nystagmus, hallucinations and psychomotor agitation crises. There are conflicting clinical reports on the value of using ketamine in patients with SAE. Therefore, we performed a systematic search of the literature to explore the role of ketamine in acute severe asthma unresponsive to conventional treatment.

Materials And Methods

Search strategy and registration

We undertook a systematic web-based advanced literature search through the *NHS Library Evidence* tool on the effects of Ketamine in unresponsive asthma.

The protocol of our systematic review was regularly registered on PROSPERO (identified record number CRD42021273466). We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta-analyses[16] and a PRISMA checklist is provided separately (Supplementary material 1).

Our core search was structured by combining the two main terms of the topic: "*ketamine*" AND "*asthma*". An initial computerized search of PubMed was conducted from inception until August 12th, 2021 to identify the relevant articles. We also performed a search on EMBASE limited to the findings from 2016 in order to retrieve the newest conference abstracts not yet published to allow a reasonable time for the peer-review process. Two further searches were performed manually and independently by three authors, also exploring the list of references of the findings of the systematic search. Inclusion criteria were pre-specified according to the PICOS approach (Table 1).

Table 1
PICOS Criteria

PICOS	
Participants	Adult and pediatric patients with severe asthma refractory to conventional therapy
Intervention	Ketamine
Comparison	Placebo or other pharmacological strategies
Outcome	Improvement in oxygenation parameters; amelioration of clinical conditions; reduction of escalation to invasive ventilation; facilitation in weaning from mechanical ventilation; decrease in peak inspiratory pressures and increase in lung compliance; evaluation of side effects.
Studies included	Randomized controlled trials; prospective studies for sensitivity analysis only.

After an initial decision to include all type of studies regardless of their methodological design, preferred to select only prospective studies (randomized or not) in order to focus on higher quality and level of evidence. Regarding the population, we accepted studies focusing on both adults and pediatric patients where ketamine was used to treat refractory asthma and patients in the control group received placebo or other second-tier drugs for severe asthma. We excluded retrospective studies, case series and case reports; we also discarded experimental animal studies, book chapters, reviews, editorials and letters to the editor. Language restrictions were applied: we read the full manuscript only for articles published in English. For studies published in other languages, we read the abstract and contacted the authors for further information, if necessary. Study selection for determining the eligibility for inclusion in the systematic review and data extraction were performed independently by four reviewers. Discordances were resolved involving two senior authors. Data were inserted in a password-protected Excel database.

Outcomes analysis

We primarily compared the effects of ketamine as adjunctive therapy for severe and refractory asthma on oxygenation and respiratory parameters (i.e. peak inspiratory pressures, airways resistance, lung compliance), and clinical status, need for invasive ventilation and effects on weaning from mechanical ventilation. As a secondary focus of our analysis, we evaluated the reported side effects in the patients treated with ketamine compared to the control group. We considered the possibility to perform a quantitative assessment (meta-analysis) if at least three studies consistently reported the same outcome.

GRADE of evidence

Grade of evidence performed according to the recommendations of the Grading of Recommendations Assessment, Development and Evaluation working group was preliminarily considered only if meta-analysis was feasible.

Results

From our systematic search, 105 items were found on Pubmed and 71 on EMBASE. We selected the potentially relevant articles and subsequently reviewed their full-text against our PICOS criteria. We initially included 9 studies, but one was subsequently excluded because it was a national survey conducted in Chile reporting the use of pharmacological and non-pharmacological approaches, outcomes and costs of the management of the asthma exacerbations in the pediatric population. Another study was excluded as after evaluation of full text it was not focused on asthma but included a heterogeneous population of mechanically ventilated patients admitted to intensive care and subsequently developing bronchospasm (defined as a thoracic compliance below 35 mL/cmH_2O)[17].

Therefore, we included a total of 7 studies, including 5 RCTs [18–22] with a population ranging from 44 to 92 enrolled patients, and 2 prospective studies of 10 and 11 patients respectively (without the control group)[23, 24]. Of the seven included studies, four enrolled adults only[19, 21, 22, 24] and three focused on the pediatric population[18, 20, 23].

Table 2 describes the characteristics of the included studies and the main results reported by the authors. With regard to the study populations, a large heterogeneity was found regarding the number of patients included and their distribution by gender and age. Regarding the inclusion criteria of the single studies, three of them[19, 22, 24] did not clearly specify the use of scores/criteria for patients' selection. Of the remaining four studies, one used criteria defined by the authors[21], while the remaining three used known scores for lung diseases:

Table 2

Summary of the included studies. RCT: Randomized Controlled Trial; K: Ketamine; MV: Mechanical Ventilation; PEEPi: Positive End Expiratory Pressure Intrinsic; Cdyn: Dynamic Compliance; Rsmax: Airway Resistance; PEFR: Peak Expiratory Flow Rate; Ppeak: Pressure Peak; FEV1:Forced Expiratory Volume in 1 second; PRAM: Pediatric Respiratory Assessment Measure; PIS: Pulmonary Index Score; CAS: Clinical Asthma Score.

First author, year, Design	N of patients Age (Range)	Inclusion Criteria	Ketamine dose(s) Comparison dose	Outcomes reported by the authors Side effects reported
Esmailian M, 2018; RCT	92 48 years (34–62)	-	- K: bolus 0.3 mg/kg (16.3%), 0.4 mg/kg (15.2%), and 0.5 mg/kg (17.4%) - Placebo	PEFR before and 1 h after treatment. No side effects reported.
Allen JY, 2005; RCT	68 6 years (2–10)	PIS > 8	- K: bolus 0.2 mg/kg + infusion 0.5 mg/kg/h (2 h) - Placebo	PIS score at 0, 30, 60, 90, and 120 minutes. No side effects reported.
Tiwari A, 2016; RCT	48 48 months (16–144)	PRAM ≥ 5 after 2 h of standard therapy	- K: bolus 0.5 mg/kg (20 min) + infusion 0.6 mg/kg/h (3 h) - Aminophylline: 5 mg/kg bolus (20 min) + infusion 0.9 mg/kg/h (3 h)	ΔPRAM in the first 24 h, Hypertension, Tachycardia. No side effects reported.
Nedel W, 2020; RCT	45 65 (51–79)	- Adults intubated for acute bronchospasm. -Rs_{max}≥12 $cmH_2O/L/s$	- K: bolus 2 mg/kg + infusion 2 mg/kg/h - Fentanyl: bolus 1 mcg/kg + infusion of 1 mcg/kg/h	Rsmax, Cdyn, PEEPi, Duration of MV at baseline, 3h and 24h. No side effects reported.
Howton JC, 1996; RCT	44 33 (26–40)	-	- K: bolus 0.1 mg/kg + infusion at 0.5 mg/kg/h - Placebo	Respiratory rate, hemodynamic parameters, Borg Score, P/F ratio, FEV_1 before and after treatment. Side effects reported.
Petrillo TM, 2001; Prospective	10 8 (5–16)	CAS > 12	- K: bolus 1 mg/kg + infusion 0.75 mg/kg/h (1 h)	CAS, vital signs, PEFR before K administration, within 10 min after K administration, and 1 h after infusion. Side effects reported.

First author, year, Design	N of patients Age (Range)	Inclusion Criteria	Ketamine dose(s) Comparison dose	Outcomes reported by the authors Side effects reported
Heshmati F, 2003; Prospective	11 30 (15–40)	-	- K: bolus 1 mg/kg + infusion 1 mg/kg/h (2 h)	Ppeak, $PaCO_2$, PaO_2 before K administration, 15 min after administration and 2 h after infusion. No side effects reported.

- - the Pediatric Respiratory Assessment Measure (PRAM) score, which includes 5 parameters: suprasternal retraction, contraction of the inspiratory scalene muscles, thoracic excursion, wheezing, SpO2[20];
- - the Pulmonary Index Score (PIS), which includes respiratory rates, wheezing, inspiratory/expiratory ratio, use of accessory muscles, SpO2[18];
- - the Clinical Asthma Score (CAS), which analyzes SpO2, wheezing, inspiratory breath sounds, use of accessory muscles and neurological status[23].

Regarding ketamine dosing, the included studies used different dosages of ketamine. In particular, most of the studies used an intravenous bolus dose of ketamine followed by continuous infusion[20, 21, 23–25]. In these studies, the bolus ranged from 0.1 to 2.0 mg/kg, while the infusion was used with a variable range from 0.5 to 2.0 mg/kg/h. Only one study[19] used the ketamine bolus exclusively with dosage ranging from 0.3 mg/kg to 0.5 mg/kg. Of the five randomized studies with a control group, three compared ketamine to placebo [18, 19, 22], while the remaining two used fentanyl[21] (bolus 1 mcg/kg, followed by continuous infusion at 1 mcg/kg/h) or aminophylline[20] (slow bolus of 5 mg/kg over 20 minutes, followed by infusion 0.9 mg/kg/h for 3 hours).

The outcomes were variable in the different studies, gas exchange (PaO_2 and $PaCO_2$) and respiratory mechanics indices (Ppeak, PEFR, FEV_1) were mainly evaluated.

Only three studies included complications as secondary outcomes[20, 22, 23]. Tiwari et al.[20] observed hypertension in n = 2/24 patients in the ketamine group vs no one in the aminophylline group, and tachycardia was noted in n = 23/24 and n = 21/24 in the ketamine and aminophylline groups, respectively.

Discussion

The purpose of our systematic review was to summarize the clinical evidence regarding the use of ketamine in patients with severe asthma refractory to conventional medical treatment, selecting higher-quality studies (randomized and prospective only). We found a paucity of data on the possible benefits and complications related to the use of ketamine in this patient population. Together with the reduced

quality and quantity of data, we also noted a profound heterogeneity in the control group, where the treatment ranged from placebo to other drugs such as fentanyl and aminophylline. The ketamine dosages used were also largely different between studies. Furthermore, the outcomes evaluated by the included studies, were profoundly variable. Therefore, we could not conduct a quantitative analysis (meta-analysis) and the evaluation remains quite subjective.

Before discussing the results of our systematic review, it may be worth to briefly discuss the pharmacological properties of ketamine that may contribute to its use in patients with asthma. Ketamine is a phencyclidine derivative with non-competitive antagonist effects on N-methyl-D-aspartate (NMDA) receptors. However, it may clinically have numerous other effect sites, both ion channels and receptors (i.e. L-type voltage-gated Ca2 + channels, nicotinic and muscarinic acetylcholine receptors, voltage-sensitive Na + channels, μ and δ opioid receptors, etc). This large number of target sites for ketamine may contribute to the wide range of effects of the drug[26]. Regarding the role of ketamine in asthma, bronchodilation is supposed to be a combination of several targets: direct blockade of NMDA receptor-induced airway constriction, reduction of nitric oxide levels in pulmonary tissues (down-regulation of inducible nitric oxide synthetase activity), increase in synaptic catecholamine levels (blockade of presynaptic re-uptake), inhibition of vagal outflow, direct smooth muscle relaxation by reduction of calcium influx (L-type calcium channels), reduction of inflammation with blunted macrophage recruitment and cytokine production [27–30].

Despite this background, the results obtained from the administration of ketamine in patients with severe refractory asthma seem predominantly neutral or eventually negative. Indeed, from the qualitative analysis of the included studies it would appear that ketamine did not offer particular clinical benefits. Therefore, our systematic review does not offer significant support for the clinical use of ketamine with this indication.

The only study showing some significant benefit from ketamine was conducted by Esmailian et al.[19] on 92 adults. This study was the largest one retrieved by our systematic review and measured the Peak Expiratory Flow Rate (PEFR), evaluating the effects of increasing doses of Ketamine (0.3, 0.4 or 0.5 mg/kg as a bolus only, without continuous infusion) as compared to placebo. In this study, a significant improvement in PEFR occurred for the 0.4 and 0.5 mg/kg bolus doses; however, the authors did not perform any further measurements of respiratory function and mechanics. Furthermore, the authors excluded patients reporting side effects from ketamine treatment[19]. In another study, Nedel et al.[21] compared the effects of ketamine (2 mg/kg bolus and subsequent infusion at 2 mg/kg/h) and fentanyl administration (bolus of 1 mcg/kg and continuous infusion of 1 mcg/kg/h). Main outcomes were changes in respiratory mechanics (Airway Resistances – Rsmax; intrinsic Positive End Expiratory Pressure – PEEPi; and dynamic compliance - Cdyn) at different time-points (pre-treatment, at 3 and 24 hours). In both groups, there was a decrease in Rsmax and a stability of Cdyn (albeit at severely compromised values). In this sense, the decrease in respiratory resistance over the course of 24 hours in these patients was almost identical between groups (ketamine and fentanyl), thus possibly attributable to other treatment strategies (b2-agonist and steroid therapy) or eventually to similar effects of ketamine

and fentanyl. Interestingly, there was a progressive increase in PEEPi in both groups at 24 hours. In this sense, it is possible that in the presence of low values of Cdyn, a reduction in Rsmax with an increase in minute-volume ventilation favored air trapping and lung hyperinflation. In one pediatric study, Tiwari et al. [20] compared ketamine to aminophylline and showed similar improvements in the PRAM score and gas exchange in both groups. Furthermore, the evaluation of side effects showed a similar (and high) incidence of tachycardia, while only two patients, both in the ketamine group, had developed hypertension.

Of note, during the screening and the systematic research, among the studies analyzed we also found a national multicenter survey conducted in Chile on a pediatric patient's population with exacerbation of asthma[31]. In this survey, all patients received salbutamol and 98% received systemic steroid administration. Regarding the additional rescue drug therapies to improve respiratory function, the most used medication was magnesium sulfate (6%) followed by aminophylline (0.8%) and finally by an anecdotic use of ketamine (0.5%, n = 2/396). Although conducted in a single country and limited to the pediatric population, this survey confirms that ketamine remains a drug rarely used in this setting. Notably, ketamine use is banned in some countries and undergoes special legislation for its use in many others.

In summary, from this overview of the included studies we noted an absence of any clear and relevant benefit produced by the administration of ketamine in patients with refractory asthma, and some signals towards side effects related to its use.

However, we also found a randomized study published almost 30 years ago suggesting beneficial effects of ketamine bolus (1 mg/kg) as compared to placebo in mechanically ventilated adult patients admitted to intensive care and developing bronchospasm. In particular, the authors found improvement of gas exchange with increase in oxygenation and stable values of $PaCO_2$ in the ketamine group whilst the oxygenation worsened and the $PaCO_2$ increased in the placebo group[17]. Nonetheless, the benefits of ketamine in patients with refractory asthma seem not clear and its use should be probably reserved for well-structured experimental research setting with clear objectives and outcomes. On the other hand, performing a large randomized study may be challenging as the number of patients presenting with acute refractory asthma is not very large.

Limitations

Our study presents several limitations. Firstly, the number of included studies was low with a paucity of patients enrolled. Secondly, the design of the papers was not homogeneous, as we considered both randomized and non-randomized prospective clinical trials. Thirdly, the results presented by the included studies were clinically heterogeneous, and therefore a meta-analysis was not feasible. Lastly, we analyzed data from pediatric and adult patients together, possibly facing a risk of bias.

Conclusions

Our systematic review highlights that the use of ketamine currently lacks of robust data and future studies require improved design to determine its role in severe or refractory asthma. Current evidence does not convincingly support its use in patients with severe asthma exacerbation refractory to conventional therapy. Well-designed multicenter randomized studies are probably needed to understand the role of ketamine in this patient's population, although recruitment may be slow.

Abbreviations

Severe asthma exacerbations (SAEs), randomized controlled trial (RCT), Pediatric Respiratory Assessment Measure (PRAM), Pulmonary Index Score (PIS), Clinical Asthma Score (CAS), N-methyl-D-aspartate (NMDA), Peak Expiratory Flow Rate (PEFR), Airway Resistances (Rsmax), intrinsic Positive End Expiratory Pressure (PEEPi), dynamic compliance (Cdyn).

Declarations

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Figures

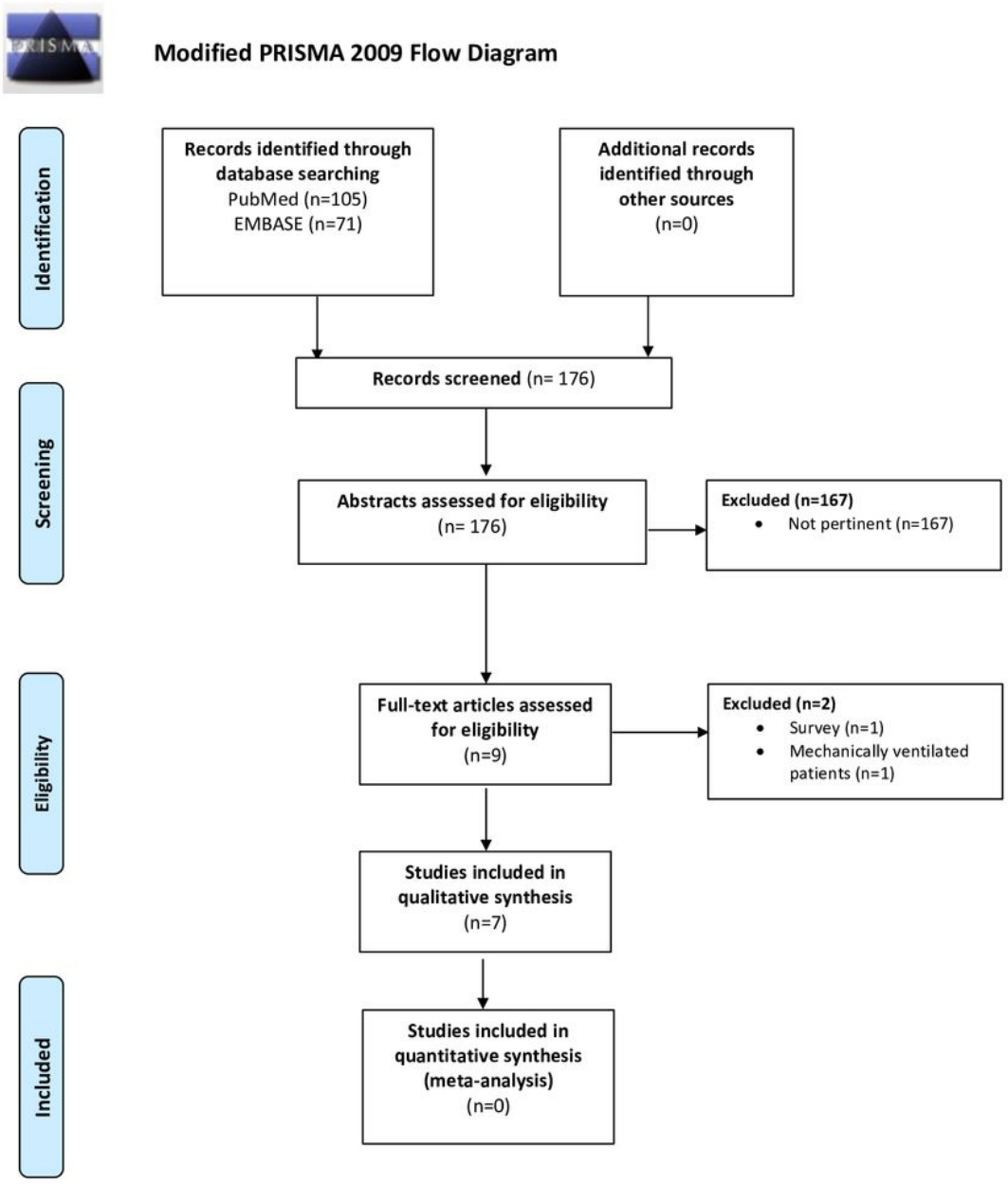

Figure 1

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