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Ketamine in Refractory Asthma Exacerbations

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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 into an asthma exacerbation which is a medical emergency.

Purpose:

- To determine the efficacy of ketamine use as an adjunctive medication for acutes severe asthma exacerbations that had failed standard guideline directed treatments.

Methods:

- Relevant databases were searched looking for ketamine use in asthma exacerbations.
- 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.

Findings:

- Preliminary results showed no positive outcomes of improvement in asthma symptoms with low dose ketamine.
- Several findings point to noteworthy positive outcomes with an intravenous ketamine high dissociative dosing administration.
- In a small case report the use of nebulized ketamine showed promise at reversing the airway obstruction promptly.

Implications:

- Some experts feel strongly that the dose ranges and duration of treatment play a key role into the efficacy of ketamine used as a pharmacological option.
- More research is needed with larger, high quality, randomized studies that addresses 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 non-curable chronic inflammatory disorder of the respiratory system.

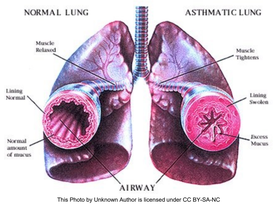
• Understanding the importance of effective and timely treatment can improve the outcomes of the individuals experiencing an asthma attack.

Comprehensive research in the treatment and management of asthma is aimed at:

- lowering the morbidity and mortality rates
- strategic and aggressive management to combat this chronic illness
- Improving the quality of life for people living with asthma
- Minimizing refractory asthma which can lead to respiratory complications such as hypoxia, respiratory failure, and even death.

Statement of the Problem

- More than 25 million Americans have asthma. (CDC, 2018)
- Refractory asthma is life threatening and can lead to a moderate to severe asthma exacerbation
- Over 3,400 deaths per year attributed to asthma (CDC, 2018)



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Research Question

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

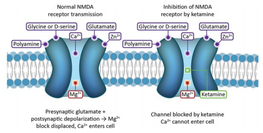
Literature Review

Standardized Care of Asthma Exacerbations

- Abrams et al, 2018 points out the need for a standard definition of asthma exacerbations recognized system wide.
- Treatment includes a robust history and physical exam, along with treating the exacerbation aggressively. (Al-Shamirani, Al-Harbi, Bagais, & Alenazi, 2019)
- First line standardized care includes oxygen, inhaled beta2 agonist, inhaled anticholinergics, and corticosteroids. (Bateman et al., 2008)

Ketamine Mechanism of Action

- Ketamine has hydrophilic and lipophilic properties with first-pass metabolism and hepatic clearance (Hendaus, Jomba & Alhammadi 2014)
- Noncompetitive N-methyl-D-aspartate receptor antagonist in the cortex and limbic system causing a dissociative state and is used for sedation and analgesic properties (Wong et al. 2014)



Reproduced with permission of Sage publishing, Frohlich, J. and Van Horn, J. Reviewing the ketamine model for schizophrenia. Journal of Psychopharmacology 2014 Apr; 28(4): 287–302. Published online 2013 Nov20. http://dx.doi.org/10.1177/0269881113512909

- Decreases influx of calcium into muscle by inhibiting L-type calcium channels (Goyal & Agrawal 2013) thus aiding relief of bronchospasms (Hendaus, Jomba & Alhammadi 2014)
- Reduces nitric oxide levels in the lungs by downregulating the nitric oxide synthetase enzyme (Goyal & Agrawal 2013)
- In significant concentration has shown to suppress macrophage function alleviating cytokine production and progression of an exacerbation (Goyal & Agrawal 2013)
- Adverse effects of ketamine can cause disorientation, vivid bad dreams, illusions (Goyal & Agrawal (2013) and hypersecretions, hypertension, tachycardia, and vomiting (Tiwari, Guglani, & Jat 2016)

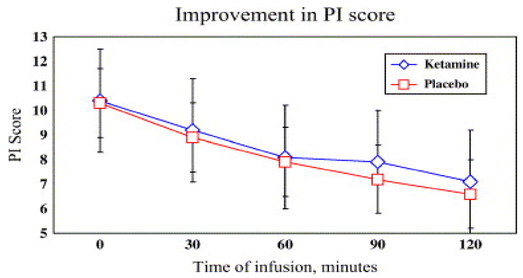
Adjunctive Ketamine in Asthma Exacerbations

Supporting Literature

- Shalmovitz & Hawhtorne (2008) reviewed 14 case reports with dose ranges of 0.6mg/kg/h to 4.8 mg/kg/h and suggest the dissociating effect aids in the respiratory work of breathing along with an anxiolytic effect.
- In a case report Kiureghian & Kowalski (2015) found that using Noninvasive positive pressure ventilation and ketamine over 40 minutes with a total dose of 300 mg provided time for the standard medications to be efficacious.
- Wong et al. (2014) comments that most studies with ketamine have been done on intubated patients, noting improvement in wheezing, respiratory rates, peak inspiratory pressures, and tidal volumes.
- Goyal and Agrawal (2013) reviewed 3 studies (131 patients) with ketamine use in refractory asthma that failed treatment of first line medications showing favorable responses by decreasing wheezing and improving oxygen saturations.
- Lam et al., (2019) noted ketamine's efficacious dosage for bronchodilation ranged from 0.75 mg to 3 mg/kg/hour, suggesting that its efficacy is dose dependent.
- Esmailian et al. (2018) 0.4 mg/kg and 0.5 mg/kg of ketamine had peak expiratory flow improvements.

Non-supporting Literature

- Maddox & Seupaul (2014) found no measurable improved outcomes in a single randomized control trial (N=68) using 0.2mg/kg followed by a continuous infusion of 0.5mg/kg/h
- A Cochrane review conducted by Jat & Chawla (2012) found there is a lack of evidence for the use of ketamine in asthma and expressed the need for additional trials to substantiate its use.
- Esmailian et al. (2018) 0.3 mg/kg showed no significant difference than placebo.
- Allen & Macias (2005) reviewed a double-blinded, randomized, placebo-controlled trial (N=68) and found no significant improvement with 0.2mg/kg followed by a two-hour infusion of ketamine of 0.5mg/kg/h.



Reprinted fromMedicine 46(1), Allen, J., Macias, C. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma, 4 Annuals of Emergency 3-50, ©2005, with permission from Elsevier

- Hendaus, Jomha & Alhammadi (2019) reviewed 10 small clinical studies and found it hard to determine the efficacy of ketamine use in asthma exacerbations due to the different dosages and small participant numbers.

Discussion

- Global Initiative for Asthma (GINA) acknowledges the language of an asthma exacerbations as a true emergency and standardized first line treatment should be performed rapidly (Bateman et al. 2008).
- Adjunctive medications are an option for refractory asthma not responding to first line medications.
- Ketamine low dosage of 0.2 mg/kg showed no improvement
- Small clinical study showed higher dose of ketamine at 0.4mg/kg and 0.5mg/kg improved expiratory flow rates.

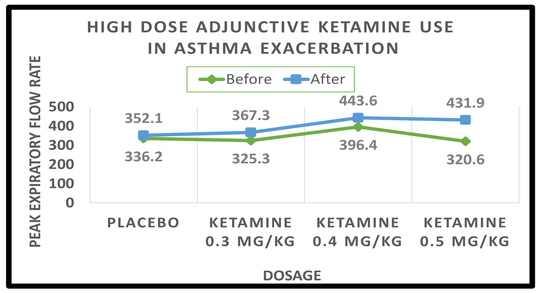


Figure 1. By Stephanie Frentzel, data from Esmailian, M, Esfahani, M, and Heydari, F (2018).

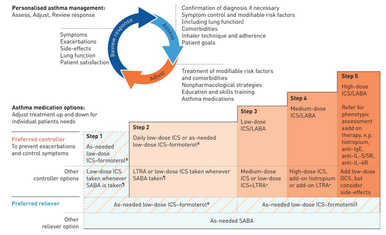
Conclusion

Consensus of the literature review and the use of ketamine as an adjunctive option was not met, and the limitations include:

- It is hard to prove efficacy with concomitant standardized treatments
- Unethical to withhold first line treatment to test ketamine efficacy alone
- Small participant numbers in studies
- Lack of larger randomized, placebo-controlled studies
- Nebulized ketamine shows promise, but only murine models exist
- Further research is required to determine the dosage, safety, and efficacy of ketamine in acute severe asthma exacerbations.

Applicability to Clinical Practice

- Due to the severity of asthma exacerbations it is important to address the use of ketamine as an adjunct to the standardized treatment of care in emergency settings.
- 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.
- The key is to provide efficacious and prompt delivery of life-saving treatments for a patient experiencing an asthma exacerbation.



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