

ORIGINAL RESEARCH

The Effect of Low-Dose Ketamine in Treating Acute Asthma Attack; a Randomized Clinical Trial

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Abstract: **Introduction:** Efficient treatment of asthma can play an important role in controlling asthma attacks, rapid recovery and decrease of patient mortality. Therefore, in the present study the therapeutic effect of low-dose ketamine is evaluated in patients with acute asthma attack. **Methods:** In the present single-blind, randomized clinical trial with placebo control, the effect of low-dose intravenous ketamine in treating 18 to 85 year-old asthmatic patients who presented to the emergency department was evaluated. Peak expiratory flow rate (PEFR) and the patients' response to treatment were measured before and 1 hour after treatment. Additionally, using SPSS 22.0, effectiveness of ketamine with 0.3, 0.4, and 0.5 mg/kg doses followed by infusion of the same dose during 30 minutes were compared with placebo. **Results:** 92 patients were enrolled (59.8% female, mean age 48.5 ± 13.9 years). 15 (16.3%) patients were treated with 0.3 mg/kg ketamine, 14 (15.2%) with 0.4 mg/kg, and 16 (17.4%) with 0.5 mg/kg doses. Mean PEFR was 336.2 ± 101.5 liters in the placebo group and 345.8 ± 84.7 liters in the ketamine group before intervention ($p = 0.6$), while after intervention, they were 352.1 ± 101.2 and 415.8 ± 76.2 liters, respectively ($p = 0.001$). Ketamine treatment with 0.4 and 0.5 mg/kg doses led to a higher increase in PEFR compared to 0.3mg/kg dose (df: 3, 88; $F = 23.8$; $p < 0.001$). **Conclusion:** It seems that administration of 0.4 - 0.5 mg/kg doses of intravenous ketamine followed by infusion of the same dose during 30 minutes can be effective for rapid recovery of PEFR in patients with mild to moderate asthma.

Keywords: Ketamine; asthma; efficiency; peak expiratory flow rate; emergency service, hospital

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1. Introduction

Asthma is a diffused obstruction of airways that may present as shortness of breath, wheezing, and coughing. It is one of the most common chronic illnesses, which presently affects 300 million people all over the world and this number is predicted to rise to 100 million in 2025 (1). In Iran, the average prevalence of this disease in the under 18-year-old population is estimated to be 13.4% (2). Clinical symptoms of asthma are relieved spontaneously or using drugs. Comprehensive research has been done on control and treatment of asthma and standard treatments have been developed. Yet, a high percentage of patients do not respond well to the treatments and might experience severe attacks and dangerous complications such as hypoxia, respira-

tory arrest, and mortality. A bunch of controlling or preventive drugs such as steroids, inhaled beta agonists and anticholinergics, and short-acting theophylline are suggested for management of the patients (3). Ketamine is a well-known drug with safe and predictable sedative, analgesic, and antiemetic effects. The half-life of this drug is 2-4 hours and it is rapidly absorbed, crosses blood-brain barrier, and exerts its effect on central nervous system (CNS) (5). It is also a bronchodilator, and using a 1-2 mg/kg dose of it has been approved as an inductive agent in rapid sequence intubation (RSI) of asthma patients (4). It protects airways and respiratory reflexes without any disturbances to the cardiovascular system. Therefore, it may be prescribed in emergency departments with limited monitoring devices. The important thing about this drug is that in doses lower than 1mg/kg it does not have sedative effects, while in higher doses it can cause side effects such as apnea and laryngospasm. These side effects can be severe in 1-2% of patients and are very dose-dependent and more probable in higher doses and in-

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travenous (IV) prescription (6). Using 1-2 mg/kg IV doses followed by 2-3 mg/kg IV infusion has been able to delay the need for intubation in pediatric asthma attack (7). Introducing new ways for controlling asthma attack with the aim of rapid recovery, decreasing cost, and discharging patients from emergency department seems necessary from therapeutic and logistic viewpoints. Therefore, the present study aims to evaluate the effect of low-dose ketamine in treatment of patients with acute asthma attack.

2. Methods

2.1. Study design and setting

The present study is a single blind, randomized clinical trial with placebo control that evaluates the effect of low-dose ketamine in treating asthmatic patients who presented to the emergency department of Al-Zahra teaching Hospital, Isfahan, Iran, during January to August 2016. Informed written consent was obtained from all patients included in the study. In addition, the present study was approved by the Ethics Committee of Isfahan University of Medical Sciences. The researchers adhered to the principles of Helsinki Declaration and patient data confidentiality. This study has been registered on Iranian Registry of Clinical Trials (IRCT) under the number IRCT2015102912072N9.

2.2. Participants

Patients with mild to moderate asthma (table 1), aged between 18 to 85 years old, without any prohibition for using IV ketamine and history of allergic reaction, were included. If the patient's clinical condition worsened during the study, or needed ventilator support for respiration or showed ketamine side effects, he/she would be excluded. Non-randomized, convenience sampling was done and patients were randomly allocated to intervention (IV ketamine) and control (placebo) groups using block randomization.

2.3. Intervention:

All patients underwent pulse oximetry and constant monitoring of arterial oxygen saturation, as well as oxygen therapy if needed. Both groups received basic treatments of asthma attack with standard doses including inhaled beta agonists and anticholinergics, and IV corticosteroids. The intervention group received IV ketamine with 0.3, 0.4, or 0.5 mg/kg doses in addition to the standard treatment. Since ketamine is colorless and odorless and its appearance is like water, distilled water was used as placebo for the control group. IV ketamine vials were 10 cc in volume with 50 mg/cc concentration (made by ROTEXMEDICA Company, Germany). At the time of use, drug was drawn in a syringe based on the patient's weight and the volume was then set to 5 cc using distilled water. Its injection was done during 1-2 minutes

in a peripheral vein. Subsequently, the same dose was infused during 30 minutes. Peak expiratory flow rate (PEFR) was measured and recorded before and 1 hour after treatment for all patients. The method for determining PEFR was as follows: first, the device was set at 0, then it was held in a horizontal state and the patient was asked to hold the device's pipe, which was washed and disinfected before, with their lips in a manner that air could only pass through the pipe. They were then asked to forcefully blow their expiratory flow into the peak flow meter (SIBEL, Spain) after a deep inhalation. Finally, the indicator would show a number representing the peak expiratory flow. The peak expiratory flow for each patient was then compared to their expected natural flow based on their sex, age, and height, and if it was lower than 70% of the normal rate, the case was considered as acute asthma attack. The peak flow meter number was read and reported by one person, for all patients. Response to treatment was determined based on PEFR an hour after treatment initiation and was rated as good (PEFR > 70%), partial (40% < PEFR < 69%), and poor (PEFR < 40%) (table1).

2.4. Data gathering

A senior emergency medicine resident was responsible for data gathering using a check list that consisted of demographic data (sex, age), possible side effects of ketamine, and PEFR of patients before and 1 hour after intervention.

2.5. Statistical Analysis

The sample size calculated for this study was 60 cases considering $Z_{\alpha} = 1.96$, $Z_{\beta} = 0.84$, $S = 59$, $d = 30$. Data were entered to SPSS 22.0. After making sure data distribution was normal using Kolmogorov-Smirnov test ($p = 0.62$), they were presented as mean and standard deviation for quantitative data and frequency and percentage for qualitative data. Independent t-test was used for comparison of PEFR between the ketamine and placebo groups. In addition, to evaluate the efficiency of various ketamine doses (0.3, 0.4, 0.5 mg/kg) one-way ANOVA was used. In all tests, $p < 0.05$ was considered significant.

3. Results

92 patients were enrolled (59.8% female, mean age 48.5 ± 13.9 years). 47 (51.1%) of the patients were in the placebo group and 45 (48.9%) in the ketamine group. 15 (16.3%) patients were treated with 0.3 mg/kg ketamine, 14 (15.2%) with 0.4 mg/kg, and 16 (17.4%) with 0.5 mg/kg doses. Age distribution between the studied groups was not significantly different ($p = 0.09$) but sex distribution significantly differed ($p = 0.01$). Since patient's sex is entered in the formula for calculation of PEFR, this difference in distribution is adjusted for the analyses. Mean PEFR was 336.2 ± 101.5 liters in the



Table 1: Definitions and measurement

PEFR *	PEFR was measured using a peak flow meter and the normal rate varies a little based on sex, age, and height of the patient
Asthma attack	Acute attack: PEFR < 70% Mild to moderate attack: 40% < PEFR < 69% Severe attack: PEFR < 40%
Response to treatment	Good response: PEFR > 70% Partial response: 40% < PEFR < 69% Poor response: PEFR < 40%
Apnea	Oxygen saturation dropping to < 85% for at least 3 seconds or decrease in respiratory rate to < 8 /minute

*: Peak expiratory flow rate.

Table 2: Comparing mean change in peak expiratory flow rate (PEFR) in different groups

Group	PEFR		Change	P*
	Before	After		
Placebo	336.2 ± 101.5	352.1 ± 101.2	16.0 ± 30.5	Ref
0.3 mg/kg ketamine	325.3 ± 48.1	367.3 ± 56.9	42.0 ± 23.0	0.17
0.4 mg/kg ketamine	396.4 ± 89.4	443.6 ± 67.9	52.9 ± 45.0	0.02
0.5 mg/kg ketamine	320.6 ± 91.9	431.9 ± 80.2	111.3 ± 62.8	< 0.001

*, significance level has been reported based on comparison with the placebo group. Data were presented as mean ± standard deviation.

placebo group and 345.8 ± 84.7 liters in the ketamine group before intervention (p = 0.6), while after intervention, they were 352.1 ± 101.2 and 415.8 ± 76.2 liters, respectively (p = 0.001). Treatment with low-dose ketamine has significantly increased PEFR compared to placebo (p < 0.0001). PEFR before intervention was not significantly different between the placebo group and different ketamine dose groups (df: 3, 88; F = 2.2; p = 0.1). However, ketamine treatment with 0.4 mg/kg (p = 0.02) and 0.5 mg/kg (p < 0.001) doses led to a significant increase in PEFR compared to placebo. PEFR changes in the 0.3 mg/kg dose group did not differ from the placebo group (df: 3, 88; F = 23.8; p = 0.17) (table 2). Side effects of ketamine were not observed in any of the patients.

4. Discussion

The findings of the present study reveal that treatment of asthma with low-dose ketamine increases PEFR. This rise is significant in 0.4 and 0.5 mg/kg doses. 0.5 mg/kg dose had higher efficiency compared to the 0.4 mg/kg dose. As we have mentioned before, asthma is one of the most common chronic illnesses all over the world. Based on the involvement of the area, symptoms vary between a wheezing sound to airway obstruction. Severe asthma can lead to respiratory deficiency and need for ventilator. Inhaled corticosteroids are among the drugs suggested for asthma treatment in children and adults (8-11). To open the bronchial airways in asthmatic patients, ketamine may also be help-

ful. The first effective use of this drug in relieving pediatric asthma has been reported about 30 years ago (12). In various studies, ketamine has been suggested as an inductive agent for endotracheal intubation in asthma patients due to its benefits for bronchial airway stabilization. Its serial injection will provide better results (4, 13-17). Ketamine increases respiratory rate and subsequently, oxygen pressure, and decreases CO₂ pressure, which leads to asthma symptom relief (18). Its most important probable side effects include hallucination, agitation, apnea, and laryngospasm (6). In a study by Huber et al., after ketamine prescription a two third increase in airway stability was reported (19). In a study to evaluate the effectiveness of ketamine in symptom relief and pediatric asthma indices, 1 mg/kg dose of ketamine on admission and 0.75 mg/kg dose during the first hour were intravenously administered and the patients' vital signs, PEFR, and clinical asthma score were evaluated. The results showed that in all the afore-mentioned indices, after IV ketamine administration, asthma symptoms were relieved (17). In a clinical trial by Howton et al. IV administration of low-dose ketamine with 0.2 mg/kg dose and repeated injection of 0.5 mg/kg dose 3 times per hour in patients over 18 years old, had a significant effect on respiratory rate, respiratory flow, and Berg's score of asthmatic patients compared to the placebo group. While in a similar study with the same initial dose and twice a day injection with 0.5 mg/kg dose, asthmatic children's condition did not significantly improve (20). The effect of low-dose ketamine in adults who were not ventilator-dependent showed



that this drug is generally effective for relieving bronchial airway spasms and increasing blood oxygen saturation, although in some cases it will be accompanied by side effects such as hallucination, agitation and increase in pulmonary secretions (16). Some have reported ketamine to be the drug that makes asthmatic children independent of mechanical ventilators (7). Based on the findings of this study, it seems that administration of 0.4 and 0.5 mg/kg doses of ketamine can have beneficial effects in asthma symptom relief compared to the placebo group.

5. Limitation

The present study had some limitations such as small number of patients in each group of ketamine doses, which makes interpretation and generalization of the results difficult. Further study on the subject with a larger number of participants and more accurate methodology is suggested to make the findings more generalizable.

6. Conclusion

It seems that administration of 0.4 - 0.5 mg/kg doses of IV ketamine followed by infusion of the same dose during 30 minutes can be effective for rapid recovery of PEFR in mild to moderate asthma patients.

7. Appendix

7.1. Acknowledgements

None.

7.2. Author contribution

All the authors meet the standard authorship criteria according to the recommendations of international committee of medical journal editors.

7.3. Funding/Support

None.

7.4. Conflict of interest

The authors declare that there is no conflict.

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