



Efficacy Evaluation of Nebulized Magnesium, as an Additional Complementary Treatment, in Clinical and Peak Flow Metric Improvements of Acute Asthma Attack: A Randomized Double-Blinded Clinical Trial

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Abstract

Background: Exacerbation of acute asthma attacks is a medical challenging problem that affects health systems all around the world. According to the reports, acute asthma has allocated about 1 to 12% of adults' referral to the emergency departments by itself. This study aimed to investigate the effect of additional nebulized magnesium sulfate, as an additional complementary treatment, on the management of acute asthma attack. Due to controversies and the fact that previous research has been unable to confirm the benefits of routine use of magnesium in the course of treatment of asthma acute phase, this trial was conducted.

Methods: Patients with a possible clinically suggested acute asthma attack, aged 18 to 65, were divided into two groups of intervention and control. An initial peak flow meter evaluation at arrival identified the severity of patients' asthma attack. 148 patients with moderate to severe attacks were included in the study in two groups. Patients of the control group received standard asthma treatment consisting of nebulized albuterol 2.5 mg and nebulized ipratropium bromide 0.5 mg, both in minutes 0, 20, and 40 after arrival and oral single-dose prednisolone 50 mg at arrival. Patients of the case group received additional doses of nebulized magnesium sulfate 0.3 g in minutes 0, 20, and 40 after arrival in addition to the standard treatment performed on the control group. The clinical setting of dyspnea Borg scale in both the case and control groups, as well as their PEFr and FEV₁ values, were recorded during the trial in minutes 0, 20, 40, and 60 after arrival. Chi-square, T-test, and Mann Whitney test were applied for data analysis.

Results: The study was conducted on 148 subjects who were divided into two groups of 75 and 73 as case and control groups, respectively. PEFr values in minutes 40 and 60 after arrival were 295.04 and 336.2 in the case group and 249.64 and 282.86 in the control group, and there was a significant difference in the PEFr improvements between the case and control groups ($P < 0.001$). In addition, FEV₁ in minutes 40 and 60 after arrival was respectively 2.26 and 2.66 in the case group and 1.88 and 2.23 in the control group. There were significant differences in FEV₁ improvements between the case and control groups ($P < 0.001$).

Conclusions: According to the results of this study, it can be concluded that administration of nebulized magnesium sulfate as an adjunctive medication to the standard treatment is beneficial in the management of moderate to severe acute asthma attacks and significantly leads to better control of acute attack in short term.

Keywords: Acute Asthma Attack, Nebulized Magnesium Sulfate, PEFr and FEV₁ Improvement, Treatment

1. Background

Exacerbation of acute asthma attacks is a medical challenging problem that affects health systems all around the world. According to the reports, acute asthma has allocated about 1 to 12% of adults' referral to the emergency departments by itself (1, 2). Standard treatment of an asthma attack includes short-acting bronchodilators, β_2 -agonists, inhaled anticholinergic drugs, and corticosteroids associated with health care (3). Besides, it has been shown that

the addition of several doses of nebulized ipratropium to beta-adrenergic drugs and steroids will reduce the rate of hospitalization and mortality in patients with acute asthma (4-6). Moderate to severe acute asthma attacks in patients that have received an inadequate response may lead to the hospitalization, high morbidity, and mortality. A number of studies have raised intravenous magnesium sulfate as an alternative therapy added to the treatment of patients resistant to the standard treatment (7).

Magnesium has a wide range of biological activities associated with airways (8). Bronchodilator effect of intravenous magnesium has been expressed by some descriptive studies (9,10), some clinical trials in patients with acute asthma (11-14), and a number of intervention reports (15-19). Recently, some reports have shown that adding intravenous magnesium to the standard therapy has not a significant effect on patients with acute asthma (20, 21); however, a clinical trial proved that it has beneficial effects in patients with severe asthma (22). It has also been shown that in patients with the severe chronic obstructive pulmonary disease, the use of parenteral magnesium sulfate leads to bronchodilation (23). In persistent asthma, the inhalational form of isotonic magnesium sulfate can be safely administered. Compared to normal saline, it can have an inhibitory effect on bronchoconstriction factors such as methacholine, histamine, and sodium metabisulfite (24-26). Moreover, persistent elevation of serum magnesium levels can increase albuterol bronchodilatory effects that are possibly mediated by the triggered tendency of B2 receptors. Magnesium also establishes T-cells, inhibits mast cell degranulation, and thus decreases inflammatory mediators.

This study aimed to investigate the effect of additional nebulized magnesium sulfate, as an additional complementary treatment, on the management of acute asthma attack. Due to the controversies in literature in answering the question, "weather Magnesium Sulfate Nebulizing is efficacious in the management of acute asthma attack or not?", this trial was designed. The fact that previous research has not been conclusive in the confirmation of definitive benefits of routine use of nebulized magnesium in the course of treatment of acute phase asthma was the hypothesis and the basis for this trial design.

2. Methods

Research population and design: This double-blind clinical trial was carried out on patients with symptoms of wheezing, coughing, and shortness of breath who had had a clinically and para-clinically confirmed history of asthma referring to acute emergency departments of our University Hospitals. The research project was registered in Iranian Clinical Trial Registry with the code IRCT2015111015446N8. The ethics committee granted an approval to accredit the ethical aspects of the project: ajums.REC.1392.345. Written consent was arranged for all patients included in the study.

Inclusion criteria: Patients clinically suspected of asthma with dyspnea attack referring to Emergency Department, aged 18 - 65 years old who were able to establish peak flow meter measurement, were included in the study.

Inclusion criteria: the patients with chronic obstructive pulmonary disease, congestive heart failure, pneumonia, kidney disease, and underlying lung disease were excluded from the study. Other exclusion criteria were fever, pregnancy, using beta 2-agonist during last 6 hours, and recent oral or parenteral corticosteroid consumption during last month.

Methods: The intervention and control groups were selected randomly using a block method and matched in terms of age, gender, and race. Patients with possible clinically suggested acute asthma attack, aged 18 to 65, were divided into two groups of intervention and control. An initial peak flow meter evaluation at arrival identified the severity of asthma attacks. 140 patients with moderate to severe attacks were included in the study in the two groups. Patients in the control group received standard asthma treatment and patients of the case group received additional doses of nebulized magnesium sulfate, added to the standard treatment.

The standard treatment consisted of oxygen and nebulized albuterol with a dose of 2.5 mg (Glaxo SmithKline, UK) and nebulized ipratropium bromide 0.5 mg (nephron pharmaceuticals corporation, USA) both administered in minutes 0, 20, and 40 after arrival. Prednisolone 50 mg oral single dose was prescribed as part of the standard treatment of moderate to severe asthma at arrival in both case and control groups.

Magnesium sulfate 0.3 g (Emergency Medical Products Inc., Chicago, USA) diluted in still water to reach the drug volume of 5 cc was nebulized in the intervention group as complementary medication to the standard treatment in frequent doses in minutes 0, 20, and 40 after arrival. Instead of magnesium sulfate in the control group, 5 cc of still water was added to the standard treatment per each nebulized administration in minutes 0, 20, and 40 after arrival for double blinding of the study. Peak flow meter evaluation was performed at the minutes 0, 20, 40, and 60 after arrival and the FEV1 and PEF values were recorded. 3 patients did not complete the trial because of their clinical deterioration and need for further aggressive medical management in the course of their asthma attack management (Figure 1). The process of the study was conducted by a qualified board certified emergency medicine specialist. Neither the patients nor the clinician operator knew which medication was administered to each patient. The volume of the nebulized drug was the same in both case and control groups. Type of intervention allocated to each patient at the time of block randomization was available in drug boxes with the special allocated numbers. These data were accessible for patients who discontinued the study because of deterioration of clinical states in the course of study and need for extra aggressive treatments.

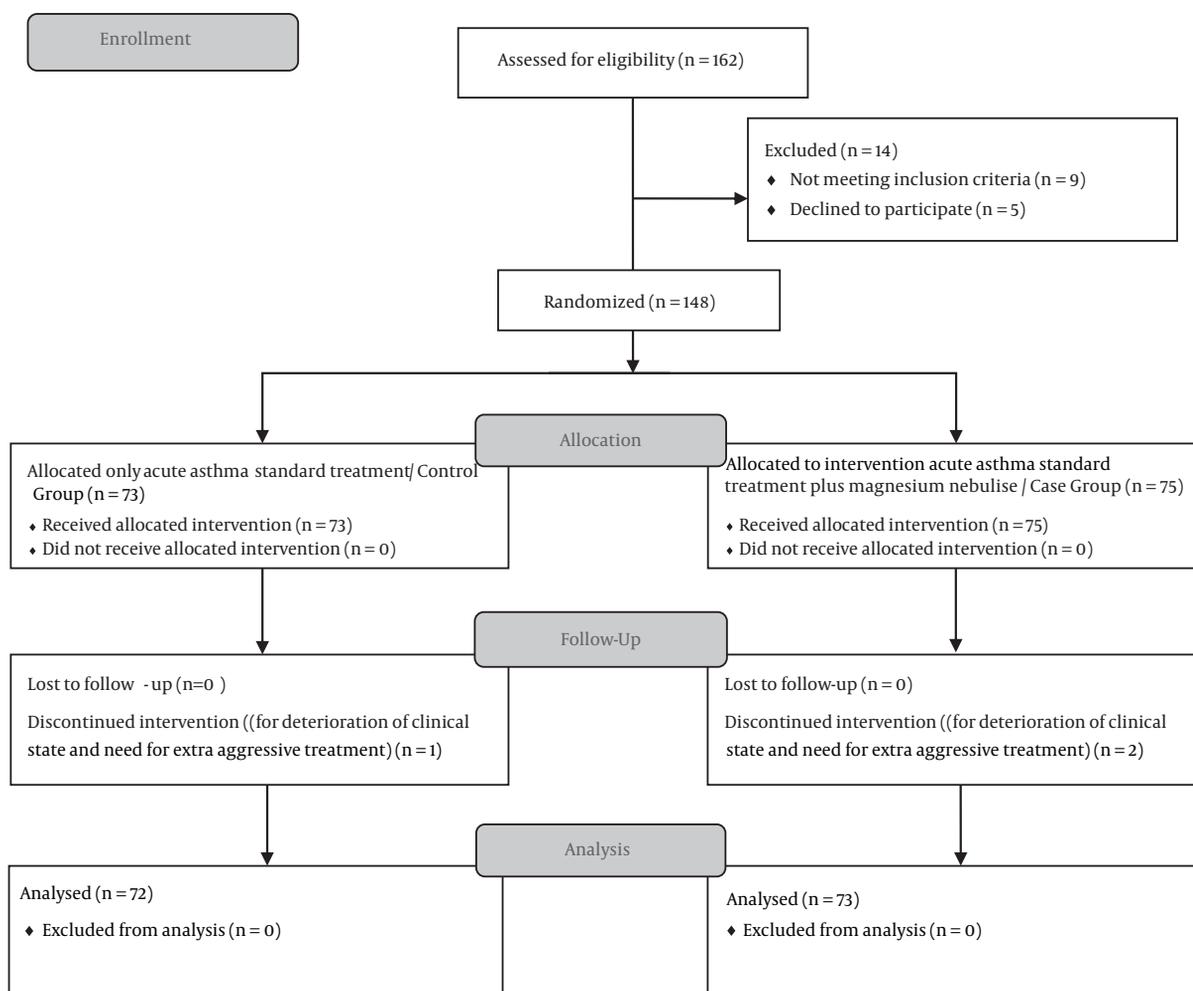


Figure 1. CONSORT Flow Diagram

Finally, the results of the study included the severity of clinical asthma attacks (Borg Dyspnea Scale) and the values of FEV1 and PEFr that were compared in each group and between the two groups. With regard to the same volume of the nebulized drug in both groups, the study was conducted as a double-blind and those involved in the study were unaware of the content of the prescribed medication. The patient's temperature and O₂ saturation and hemodynamic variables such as pulse rate, respiratory rate, and blood pressure were examined and recorded at 0, 20, 40, and 60 minutes. Later, the diagnosis of asthma was confirmed in all patients, applying spirometry test, as confirming the diagnostic test.

Statistical analysis: In order to analyze the data, descriptive data analysis method was used including tables of frequency and diagrams and the research variables were

described. Chi-square was used in data analysis, t-test in case of being normal, and Mann-Whitney non-parametric test otherwise.

3. Results

The study was conducted on possible acute asthma patients who were admitted for acute asthma based on their initial clinical findings. 14 patients were excluded from the study because they did not meet the inclusion criteria or refused to take part in the study. 148 patients were divided randomly into two groups of 75 and 73 as case and control groups, respectively. This study showed that the mean age of the subjects in the control group was 34.97 ± 10.59 and in the intervention group was 36.36 ± 10.7 years.

Table 1 shows that age and BMI were higher in the case

group than in the control group. Age was 36.36 years in the case group and 34.97 years in the control group. The difference was not statistically significant ($P = 0.217$). BMI was respectively 27.65 and 26.47 and the difference was not statistically significant ($P = 0.755$). The frequency of gender was quite the same in both groups and the difference was not statistically significant ($P = 0.581$).

PEFR was higher in the case group than in the control group in all the study intervals. There were higher improvements for PEFR and FEV1 in minutes 20, 40, and 60 in the case group than in the control group, and the differences were statistically significant ($P < 0.001$) (Figures 2 and 3). For clinical Borg Dyspnea scale, there was a significant difference between improvement of the case group and that of the control group as well as lower admission rates ($P < 0.001$).

4. Discussion

This study aimed to evaluate the clinical and peak flow metric effect of the addition of nebulized magnesium sulfide as a complementary medication to the standard treatment of acute asthma attack. The study was conducted on 148 participants who met the inclusion criteria admitted for acute asthma. The study results revealed marked improvements in PEFR and FEV1 in the trial group after adding complementary nebulized magnesium treatment compared to the control group that used the standard medication in the minutes 20, 40, and 60 after arrival; the improvements were statistically significant ($P < 0.001$).

In the Skobeloff et al. study, evaluation of 38 treated patients suffering moderate to severe asthma attack with a parenteral infusion of 1.2 g of magnesium sulfate showed beneficial influences on the improvement of the maximum expiratory flow and the reduction of the need for hospitalization (13). On the contrary, in the Green et al. study, administration of 2 g of magnesium sulfate in 120 patients with varying degrees of severity of asthma attacks did not show significant improvements in the rate of hospitalization or maximum expiratory flow (20). According to the study results of Tiffany et al. 48 patients with moderate to severe acute asthma exacerbation did not significantly benefit from the administration of 2 g intravenously infused magnesium sulfate in terms of their clinical states; however, patients with severe asthma attack, after administration of magnesium sulfate, had better recovery than the control group (21).

Nannini et al. (2000) during a clinical trial on 35 known asthmatic patients with bronchoconstriction induced by methacholine examined the effect of inhaled magnesium sulfate with salbutamol on the treatment of the patients. There were 2 groups; the case group

that received nebulized isotonic magnesium plus salbutamol and the control group that received nebulized normal saline plus salbutamol. Finally, in patients who received magnesium sulfate, the maximum expiratory flow response increased significantly compared to the control group (27).

In the Porter et al. study, 42 patients aged 18 - 55 years with a PEF less than 25% of the acceptable limits were randomly divided into two groups of control (placebo) and case (2 g of intravenous magnesium sulfate). The PEF improved in the case group less than in the control group although the patients' asthma status and the period of hospitalization were not different (28). In order to demonstrate the beneficial effects of magnesium sulfate on the severity of the attack of the disease, Bloch et al. selected 145 patients with different intensities of asthma attacks. After the administration of 2 g of intravenous magnesium sulfate or a placebo, they pursued the response to the treatment. The researchers reported that when maximum FEV1 current is more than the predictable 25%, magnesium sulfate does not result in greater improvements in lung function or in the period of hospitalization; however, patients with FEV1 less than 25% who were randomly examined, after administration of magnesium sulfate, had a better lung function and fewer hospital admissions than the control group (22).

In a study conducted by Agarwal et al. (2005), the trial goal was to compare nebulized magnesium plus albuterol versus nebulized albuterol alone. In the course of the adult acute asthma attack management, the study results showed that in the group receiving magnesium sulfate and salbutamol, PEFR values in minutes 15, 60, and 75 were 142.8, 172.4, and 204, respectively, while in the group receiving nebulized salbutamol they were 133.2, 168.2, and 202.4, respectively, indicating that the rates were higher in the group of nebulized magnesium sulfate plus salbutamol than in the other group at all the checked times during the study; however, the differences were not statistically significant. Their findings were not consistent with the findings of the present study (29).

Steve Goodacre et al. (2013) examined intravenous or nebulized magnesium sulfate in comparison with placebo in the treatment of acute asthma in adults and showed that the differences in the mean changes of PEFR between the group receiving nebulized magnesium sulfate and the group receiving placebo were not clinically significant (30).

Mahajan et al. (2004) during a clinical trial in the United States examined the effect of adding inhaled magnesium sulfate to albuterol in children with mild to moderate asthma. The difference in the rate of FEV1 in minutes 10 and 20 and after a single dose of compound treatment

Table 1. Standard Division and Mean Value of BMI and Age in Studied Group

Group	Variable	Number	Minimum	Maximum	Mean ± Standard Division
Control group	Age	75	19	60	34.97 ± 10.59
	BMI	75	21.38	33.20	26.47 ± 2.39
Case group	Age	73	21	63	36.36 ± 11.7
	BMI	73	21.22	43.25	27.65 ± 4.16

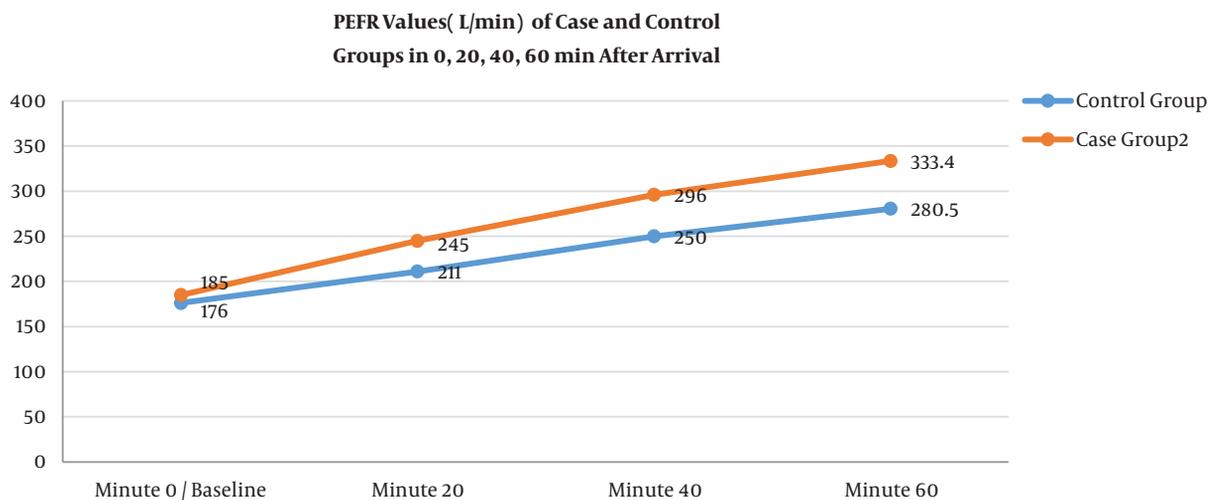


Figure 2. PEFR

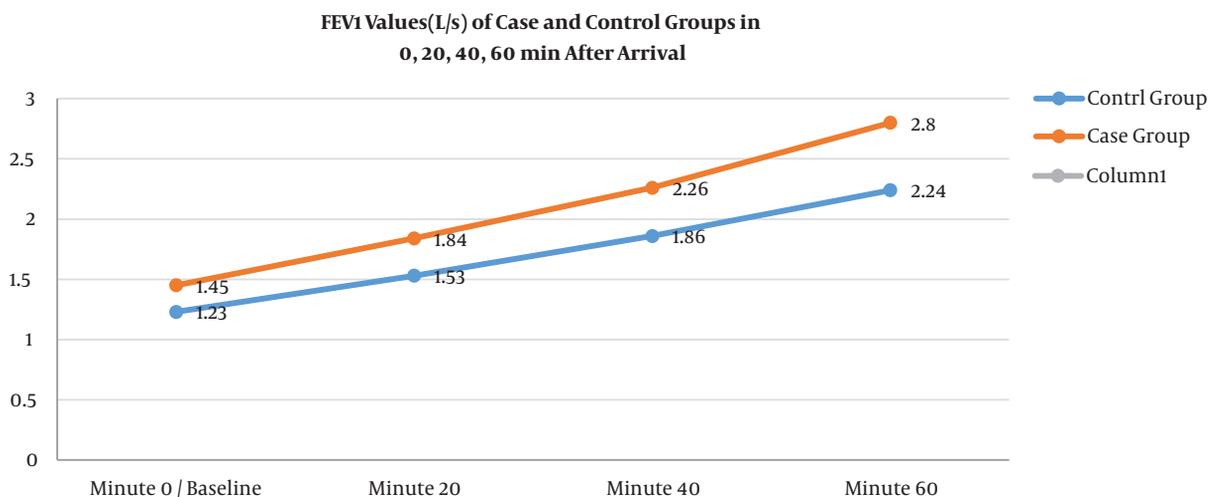


Figure 3. PEFR

with magnesium sulfate and albuterol was significant in comparison with the control group (albuterol and saline). As a result, it seems that adding magnesium to albuterol can be useful for a short time in children with exacerbation

of mild to moderate acute asthma (31).

The effect of magnesium on improving lung function is not exactly clear. Significant improvements in lung function a short time after the administration within the inter-

vals of 20 minutes in this study and in other studies points to its bronchodilatory effects on the airways. The relaxant effect of magnesium sulfate on the smooth muscles of the airway can be displayed in the laboratory (32, 33). In several clinical studies, its bronchial dilatory effects on airways have been reported (11, 13, 15, 16).

Blitz et al. (2005) during a systematic review investigated the effect of magnesium inhalation on acute asthma attack management. In this review study, six clinical trials involving 296 patients were ultimately evaluated. The use of inhaled magnesium sulfate, especially when accompanied by a β 2-agonist, had a significant impact on the treatment of acute asthma, pulmonary function, and the hospitalization of these patients (34). Aggrawal et al. (2006), in a clinical trial conducted on 100 patients with acute asthma in India, investigated the effect of inhaled magnesium sulfate with salbutamol on the treatment of the patients. The patients were randomly divided into two groups. One group received salbutamol and isotonic magnesium sulfate and the other group received salbutamol and normal saline. This study showed that adding inhaled magnesium sulfate to salbutamol had no significant effect on the treatment of patients with life-threatening and severe attacks of acute asthma (29).

It is not clear whether magnesium sulfate is effective in treating asthma attack via providing this element or it has a direct medicinal effect on the airways. In this regard, some researchers have examined the effect of inhaled magnesium sulfate and reported that the use of inhaled magnesium sulfate and inhaled beta-agonist is effective in the improvement of lung function and lower need for hospitalization in patients with severe asthma attacks (34). Perhaps the beneficial effect of inhaled magnesium sulfate on the improvement of lung function in patients with severe attacks can be attributed, to some extent, to the direct effects of the drug on the smooth muscles of the airways. It should be noted that like potassium, magnesium is mainly an intravenous ion and thus measuring its serum level cannot accurately reflect its intracellular level or its total rate in the body and in spite of natural serum level, a number of patients might be remarkably in a shortage of magnesium (35). On the other hand, it should not be forgotten that the effect of beta-agonists is on the acute reduction of magnesium serum level and it is not clear whether it has any effect on the achievement of biological magnesium or not (36).

In general, given the possible usefulness of inhaled magnesium sulfate and regarding that both inhaled and intravenous magnesium sulfate are more effective in patients with severe asthma attacks, and due to the fact that serum level of magnesium sulfate is not reduced in these patients, the direct effects of magnesium on smooth muscles are more likely to occur and perhaps, magnesium can

be used in combination with other bronchodilators in future. However, magnesium is easy to use and because of availability and low cost, it is potentially a valuable drug for the treatment of asthma attacks. Side effects and complications of this drug are also very limited (37).

Magnesium possibly has bronchodilatory effects mediated by increasing the affinity of Beta 2 receptors to Beta 2 agonists or up-regulating the receptors. The other possible influences may be facilitated by inhibition of bronchoconstriction because of diminishing uptake of calcium and its release in smooth muscles of airways. Another impact is mediated by decreasing choline acetyl release and relaxation of smooth muscle of airways, as its consequences. Prostacyclin and nitrous oxide synthesis and histamine release restriction are other etiologies for magnesium bronchodilatory potential (29).

There is not adequate clinical research in the literature on evaluating possible effects of nebulized magnesium sulfate on improving the clinical and paraclinical setting of patients with an acute asthma attack. The current study revealed the positive influences of nebulized magnesium as beneficial a treatment for the acute phase.

4.1. Conclusions

Our clinical trial study demonstrated that nebulized magnesium, as an adjunctive treatment to moderate to severe acute asthma attacks, is beneficial and influential. There were no additional side effects. It can significantly lead to better control of asthma attacks in short term. Therefore, nebulized magnesium probably can be used as a supplemental medication for patients with moderate to severe asthma attacks in Emergency Departments. More investigations should be conducted to confirm the definite efficacy.

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