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Effect of Nebulized 3% Hypertonic Saline with Salbutamol on Management of Acute Asthma in Outpatient Adults: A Double-blind, Randomized Clinical Trial in Emergency Department

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ABSTRACT

Asthma is one of the most common disorders of respiratory tract, management of which still remains as a serious health problem. This study aimed to compare the efficacy of 3% hypertonic saline (HS) plus salbutamol with solely salbutamol on management of acute adults' asthma based on peak flow meter findings.

In this double-blind randomized clinical trial, 340 adult patients with acute asthma attacks admitted to emergency department of Ahvaz Golestan and Emam hospitals were enrolled during 2014-2015. The patients were allocated randomly to intervention group (nebulized 2.5 mg of salbutamol and 2.5 mL of 3% HS solution for three consecutive 20-min periods) and control group (nebulized only salbutamol in the same dose and time of the intervention group). The principal outcome measures were forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEFR), which were assessed at baseline, and 20, 40 and 60 minutes after treatment in both groups.

HS plus salbutamol resulted in a significant increase compared with solely salbutamol in both PEFR and FEV1 in 40th min (0.11±1.36; p=0.036 and 0.05±1.16; p=0.033, respectively) and 60th min (0.15±1.12; p<0.001 and 0.11±1.22; p=0.011, respectively), while no significant difference was observed in baseline and 20th min. Also, PEFR and FEV1 in both groups significantly increased as the treatment processed and the time passed.

The results showed the beneficial effects of 3% HS in management of adults with acute asthma in the short term.

Keywords: Acute asthma; Emergency department; Hypertonic saline; Salbutamol

INTRODUCTION

Asthma is one of the most common causes of disability and death in human societies which its management is still a serious health problem.[1,2] Currently, 8.4% of individuals in the United States and 4.3% of the population worldwide suffer from asthma, and average annual prevalence of asthma in adults reported9.5%.[3]

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In Iran as a developing country, the overall prevalence of asthma in a recent systematic review and meta-analysis was reported 4.56% among men and 4.17% among women, which was higher than some other Asian countries such as Oman, Pakistan, South Korea, India, China, Taiwan, and Indonesia.[4] The main risk factors of adults' asthma are considered genetics, urbanization, air pollution, exposure to tobacco smoke and consumption of fast food.[5]

The goals of asthma management are prevention of illness, maintenance of lung function, keeping normal activity, prevention of relapses, providing optimal drug with minimal side effects and patients' satisfaction.[6] Administration of nebulizer, spray and spacer of inhaled short-acting agonist (salbutamol) is the most effective treatment of acute exacerbation of asthma.[7] In patients with persistent asthma whose symptoms are not controlled by receiving a short-acting antagonist, inhaled corticosteroid (ICS) is the first-line treatment.[8]

Recently, the efficacy of nebulized drugs in the management of respiratory diseases has attracted a great interest.[9] One of these drugs is hypertonic saline (HS) which has been studied for controlling symptoms of some respiratory diseases such as chronic obstructive pulmonary disease (COPD),[10] cystic fibrosis (CF),[11,12] and bronchiolitis[13-15], and contradictory results are reported in these regards. This solution is safe, affordable, accessible and usable in emergency patients who have contraindication for medical treatments and pregnant women.[15,16] To the best our knowledge, most previous relevant studies were conducted on hospitalized children and infants and no study assessed the efficacy of HS on management of adults' asthma in emergency department (ED). Therefore, we decided to delineate the effect of 3% HS with salbutamol on management of adult patients with acute asthma in the ED.

MATERIALS AND METHODS

Study Design

This study was a double-blind controlled randomized clinical trial with investigator (first research assistant), patients, clinician (second research assistant) who delivered the drug being blinded to the therapeutic option. Trial was registered in Iranian Registry of Clinical Trials (IRCT, http://www.irct.ir/) with code No. IRCT2016060526630N2.

Ethical Consideration

Study followed principles of declaration of Helsinki and was approved by Ethic Review Board of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (No. ajums.rec.1393.120). All patients were informed about the study details and a written consent was obtained from all patients. We also informed patients that they had the right to go out of the study at any time, and identified all of them only by number, not name or initials.

Participants

This study was conducted on adult patients with acute asthma attack who admitted to the ED of Ahvaz Golestan and Emam Hospitals, Ahvaz, Iran, from May 2014 through March 2015. Inclusion criteria were as follow: 1) aged over 15 years, 2) having acute asthma and history of asthma symptoms (wheezing and shortness of breath and cough) approved based on clinical and para-clinical British guideline on the management of asthma by an emergency medicine specialist (first research assistant),[17] 3) lack of using bronchodilators 6 hours before admitting to the ED, and 4) having ability to perform peak flow meter. Patients with pulmonary diseases (such as lung cancer or laryngeal edema), left ventricular dysfunction, eosinophilic pneumonia, systemic vasculitis (such as polyarteritis nodosa and COPD), interstitial lung disease, and lung mass, and also critically ill patients who required cardiopulmonary resuscitation, were excluded from the study. Furthermore, patients determined to be in life threatening conditions were immediately managed and were not further considered for the study.

Due to lack of the similar study, we performed a pilot study on 10 patients (not included for the main sample) to estimate sample size. Based on the results and using the sample size formula of clinical trial with confidence level of 90%, the number of needed samples was calculated as 164 subjects. For getting more confident results with a 20% dropout rate, we considered 170 subjects in each group.

Randomization

Patients were randomly allocated to two groups of intervention which received nebulized 3% HS plus nebulized salbutamol (n=170) and control which received solely nebulized salbutamol (n=170) based on age and sex using a computer-generated list of random

numbers by an individual outside the study.

Outcome Measures

For collecting demoghraphic and clinical chaeactristics of patients a researcher-made questionnaire was used including age, sex, occupation and symptoms. Forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEFR) were measured as the main outcomes using a digital peak flow meter after calibration (Cegla GmbH & Co. KG. Germany/Nabz Hayat, Tehran, Iran; HRC-test asthma) in the recruitment center by the first research assistant who was unaware of groups' assignment.

Intervention

In the intervention group, 2.5 mg of salbutamol (Cipla Ltd. India/ Kimiara Heram, Tehran, Iran, 2.5 mg/2 cc) and 2.5 mL of 3% HS solution (Shahid Ghazi Pharmaceutical Co. Tabriz, Iran) were nebulized for three consecutive 20-min periods. Patients in the control group received only salbutamol with the same dose and time of the intervention group. Study drugs were identical in appearance and odor and were labeled with codes and wrapped in an envelope bearing the respective codes. The study drugs were administered in both groups before treatment (baseline) and at the 20, 40, and 60 minutes after treatment by an ultrasonic nebulizer (ɱ SUCHATZKI, Germany/Medika, Tehran, Iran; Micro 800 XX series), and the investigator assessed PEER and FEV1 about 2 min before above mention times in both groups. The study drugs were prepared by a pharmacist (not involved in the study), administered by a clinician (second research assistant) and compliance with medication administration was assured by the investigator's direct observation of each nebulization.

Data Analysis

For doing statistical analysis, the Statistical Package for the Social Sciences (SPSS) software version 21 (SPSS, Inc. Chicago, IL, USA) was used. Descriptive statistical tests (mean, standard deviation, frequency and percentage) were used for demographic and clinical characteristics. Independent sample t-test and paired sample t-test were used to compare quantitative variables in between groups and within groups, respectively. Also, Chi-square test was performed for comparing qualitative variables. Repeated-measures analysis of variance (ANOVA) was used to test significance of changes in variables over times in course of the study. p <0.05 was considered to indicate statistical significance.

RESULTS

Follow up

Out of 355 patients were eligible in this study, 10 patients did not met inclusion criteria and 5 declined to participate. Of the remaining 340 patients (170 in each group), 10 patients in intervention group and 1 in the control group were excluded due to intervention discontinue. So, final analysis was done for 160 patients in the intervention group and 169 patients in the control group (Figure 1).

Demographical and Clinical Data

The mean age of patients in the control and the intervention groups was 46.90±14.60 and 46.10±11.90 years, respectively. Results show no statistically significant difference between two groups pertaining to demographical and clinical characteristics suggesting a high level of homogeneity of variables between the two groups in this study (Table 1).

Main Outcomes

Comparison of PEFR between the intervention and the control groups during different times is presented in Table 2 and Figure 2. The results of independent samples t-test showed no significant difference between mean changes of PEFR of two groups at baseline (p=0.826) and 20^{th} min (p=0.754), while a significant difference was found in 40^{th} min (0.11±1.36; p=0.036) and 60^{th} min (0.15±1.12; p<0.001). Repeated measures ANOVA indicated that PEFR significantly differed between the two groups (F= 7.3, p=0.010) and over time (F=25.6, p=0.001), and there was an interaction effect between group and time (F=24.1, p=0.001).

Compared to baseline, the results of independent samples t-test showed no significant difference between mean changes of PEFR of intervention and control groups at 20^{th} min (0.12±1.80 vs 0.11±1.91 respectively, p=0.354), while a significant difference was found between groups in 40^{th} min (0.24±1.23 vs 0.15±2.31 respectively, p = 0.04) and 60^{th} min (0.34±6.10 vs 0.23±7.11 respectively, p<0.001).

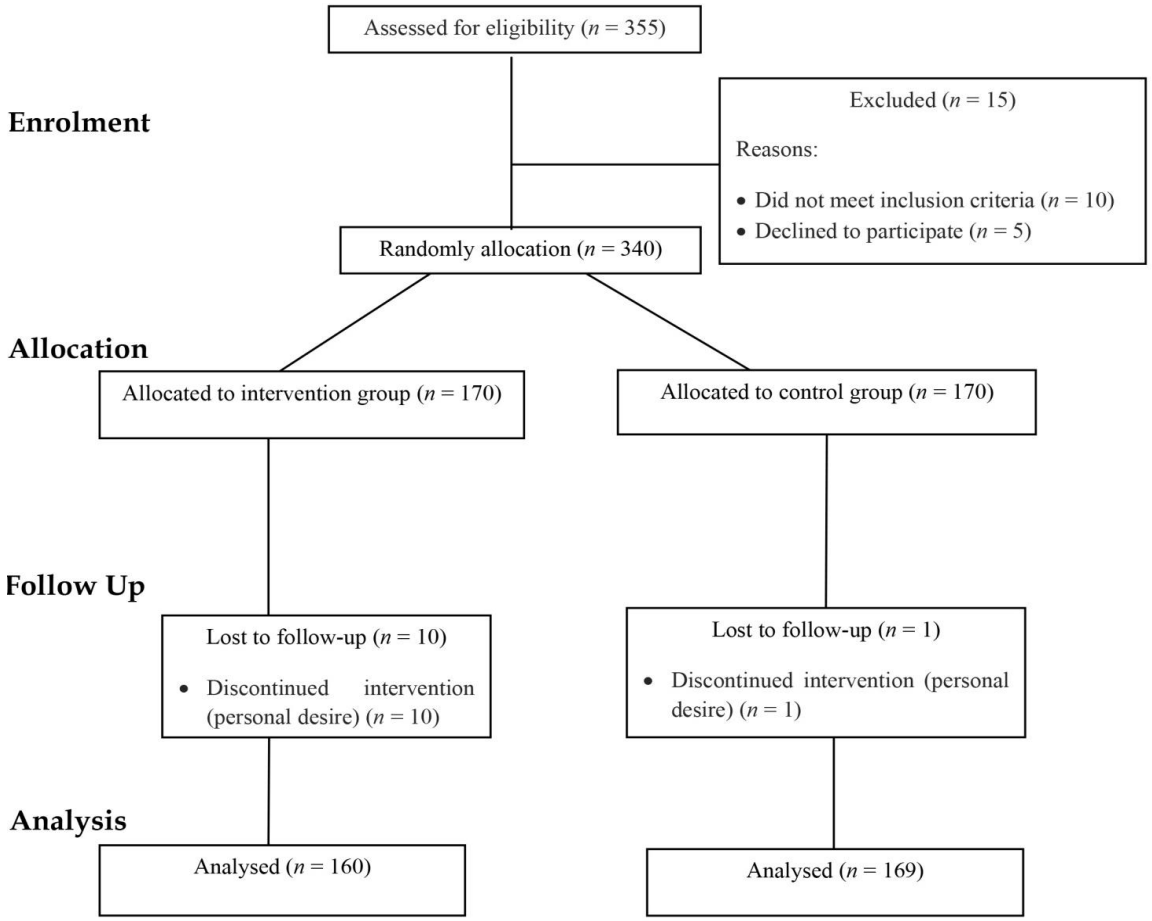

Figure 1. Flowchart showing the phases of randomized trial including enrollment, allocation, follow up, and analysis in a study onthe effect of nebulized 3% hypertonic saline with salbutamol on management of acute asthma in outpatient adults.

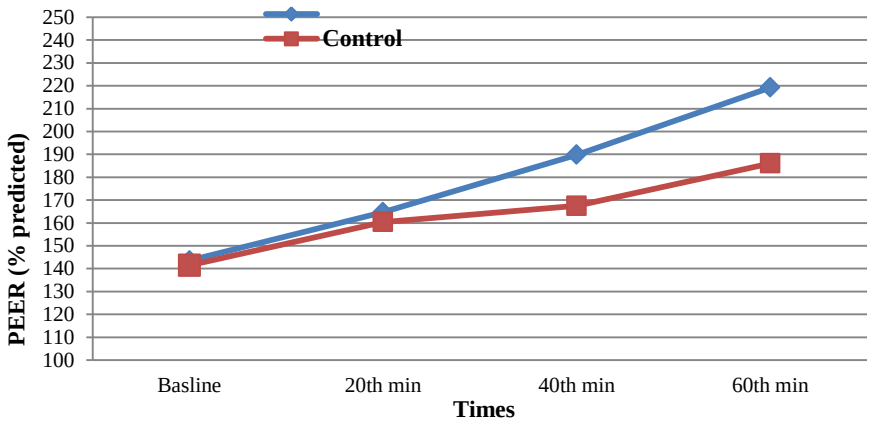

Figure 2. Comparison of peak expiratory flow rate (PEFR) in adult patients with acute asthma attack, who nebulized either 2.5 mg of salbutamol and 2.5 mL of 3% hypertonic saline solution for three consecutive 20-min periods or 2.5 mg of salbutamol for three consecutive 20-min periods to evaluate the effect of nebulized 3% hypertonic saline with salbutamol on management of acute asthma in outpatient adults. PEFR (% predicted) was assessed in baseline (before treatment) and 20, 40 and 60 minutes after treatment. Data are presented as mean.

Table 1. Comparison of demographical and clinical variables in the intervention and control groups[*] of the study evaluating effect of nebulized 3% hypertonic saline with salbutamol on management of acute asthma in outpatient adults

Groups Variables		Intervention[**] (n= 160)	Control[***] (n= 169)	Test result	*p*-value
Age (year)		46.10 ± 11.90	46.90 ± 14.60	t = - 1.80[†]	0.390
Sex	Male	80 (50.0)	83 (49.1)	$\chi^2 = 1.34$[††]	0.510
	Female	80 (50.0)	86 (50.9)		
Occupation	Unemployed	10 (6.2)	9 (5.2)	$\chi^2 = 0.57$[††]	0.971
	Staff	25 (15.7)	28 (16.4)		
	Worker	17 (10.6)	20 (11.7)		
	Farmer	7 (4.3)	8 (4.5)		
	Housewife	73 (45.6)	74 (43.7)		
	Free job	25 (15.7)	25 (15.7)		
	Student	3 (1.9)	5 (2.8)		
Symptoms	Cough	26 (16.2)	31 (18.5)	$\chi^2 = 1.74$[††]	0.620
	Shortness of breath	85 (53.1)	84 (49.9)		
	Chest pain	10 (6.2)	9 (5.2)		
	Cough with chest pain	18 (11.3)	20 (11.7)		
	Shortness of breath with chest pain	21 (13.2)	25 (15.7)		

[*] All values are expressed as mean ± standard deviation (SD) and number (percent)

[**] Nebulized 2.5 mg of salbutamol and 2.5 mL of 3% hypertonic saline solution for three consecutive 20-min periods

[***] Nebulized 2.5 mg of salbutamol for three consecutive 20-min periods

[†] Independent samples t-test

[††] Chi-square test

Table 2. Comparison of peak expiratory flow rate (PEFR) (% predicted) at different times in intervention and control groups[*] to evaluate the effect of nebulized 3% hypertonic saline with salbutamol on management of acute asthma in outpatient adults

Groups Times	Intervention[**]	Control[***]	Test result	*p*-value[†]
Baseline	143.51 ± 71.00	141.52 ± 55.51	t = 0.22	0.826
20th min	164.65 ± 71.33	160.43 ± 54.38	t = 0.30	0.754
40th min	189.82 ± 72.89	167.50 ± 55.91	t = 2.70	0.036
60th min	219.20 ± 78.33	186.02 ± 69.71	t = - 7.40	< 0.001
P-value[††]	Group (F = 7.3) = 0.010 Time (F = 25.6) = 0.001 Group × time (F = 24.1) = 0.001			

[*] All values are expressed as mean ± SD

[**] Nebulized 2.5 mg of salbutamol and 2.5 mL of 3% hypertonic saline solution for three consecutive 20-min periods

[***] Nebulized 2.5 mg of salbutamol for three consecutive 20-min periods

[†] Independent samples t-test

[††] Repeated measures ANOVA

Table 3. Comparison of forced expiratory volume in 1 second (FEV1) (% predicted) at different times in intervention and control groups[*] to evaluate the effect of nebulized 3% hypertonic saline with salbutamol on management of acute asthma in outpatient adults

Groups Times	Intervention[**]	Control[***]	Test results	*p*-value[†]
Baseline	1.37 ± 0.55	1.32 ± 0.71	t= - 0.60	0.540
20th min	1.56 ± 0.49	1.51 ± 0.73	t= - 1.80	0.383
40th min	1.65 ± 0.78	1.56 ± 0.79	t= 2.7	0.033
60th min	1.83 ± 0.81	1.62 ± 0.83	t= 2.5	0.011
P-value[††]	Group (F = 6.4) = 0.011 Time (F = 3.5) = 0.021 Group × time (F = 6.8) = 0.001			

[*] All values are expressed as mean ± SD

[**] Nebulized 2.5 mg of salbutamol and 2.5 mL of 3% hypertonic saline solution for three consecutive 20-min periods

[***] Nebulized 2.5 mg of salbutamol for three consecutive 20-min periods

[†] Independent samples t-test [††] Repeated measures ANOVA

Comparison of FEV1 between the intervention and the control groups during different times is presented in Table 3 and Figure 3.

The results of independent samples t-test showed a significant difference between mean changes of FEV1 of two groups in 40th min (0.05±1.16; *p*=0.033) and 60th min (0.11±1.22; *p*=0.011), while no significant difference was observed in baseline (*p*=0.540) and 20th min (*p*=0.383). Repeated measures ANOVA showed that FEV1 significantly differed between the two groups (F=6.4, *p*=0.011) and over time (F=3.5, *p*=0.021), and an interaction of time and group was observed (F=6.8, *p*=0.001). Compared to baseline, the results of independent samples t-test showed no significant difference between mean changes of FEV1 of intervention and control groups at 20th min (0.12±0.14 vs 0.12±0.20 respectively, P=0.954) and 40th min (0.16±0.28 vs 0.15±0.90 respectively, *p*=0.441), and a significant difference was seen only at 60th min (0.25±1.80 vs 0.18±1.21 respectively, *p*<0.001).

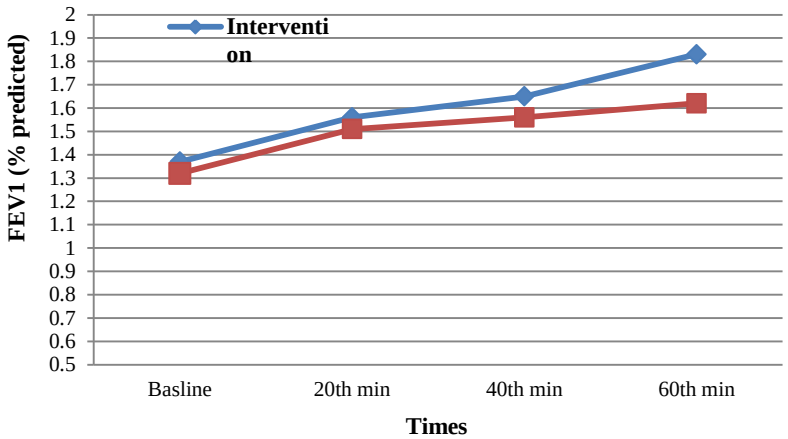

Figure 3. Comparison of forced expiratory volume in 1 second (FEV1) in adult patients with acute asthma attack, who nebulized either 2.5 mg of salbutamol and 2.5 mL of 3% hypertonic saline solution for three consecutive 20-min periods or 2.5 mg of salbutamol for three consecutive 20-min periods to evaluate the effect of nebulized 3% hypertonic saline with salbutamol on management of acute asthma in outpatient adults. FEV1 (% predicted) was assessed in baseline (before treatment) and 20, 40, and 60 minutes after treatment. Data are presented as mean.

DISCUSSION

In this clinical trial, we compared the effects of 3% HS plus salbutamol with salbutamol alone based on peak flow meter findings in adult patients with acute asthma. In line with our research hypothesis, 3% HS plus salbutamol led to a significant increase in PEFR and FEV1 in 40th min (11% and 5% respectively) and 60th min (15% and 11% respectively) in the intervention group compared to the control group that only nebulized salbutamol. The results also showed that PEFR and FEV1 in both groups were significantly increased as the treatment processed and the time passed, however this increase were more noticeable in the intervention group. The percent changes in PEFR compared to the baseline valued showed a significant difference between two groups in 40th min (24% and 15% respectively) and 60th min (34% and 23% respectively), while regarding to FEV1 only in 60th min (25% and 18% respectively) significant difference was observed between groups.

To the best of our knowledge, present study is the first investigation which evaluate the immediate impact of 3% HS in adult patients with acute asthma. Most previous studies were conducted on either children and infants with other respiratory conditions such as CF[11,12] and bronchiolitis[13-15] or hospitalized adults with other respiratory diseases.[10,18] In a recent study Koskela et al demonstrated that inhalation of HS solution (with osmolalities of 600, 900, 1200, 1500, 1800, and 2100 mOsm/kg) for 2 min period improves percentage increase in FEV1 (6.1 ± 5.5 vs 2.8 ± 3.5; p = 0.02) and variation of PEFR (14.9 ± 9.0 vs 9.29 ± 4.74; p = 0.01) after nebulization of 0.4 mg of salbutamol in asthmatic patients with chronic cough compared to non-asthmatic patients with chronic cough during the incremental saline challenge with salbutamol pretreatment.[18] Also, Purokivi et al reported that nebulization of HS solution for 2 min (with osmolalities of 600, 900, 1200, 1500, 1800, and 2100 mOsm/kg) lead to improvement of FEV1 after 4 inhalations of 100 mcg salbutamol in adult patients with stable asthma during the provocation tests.[19] In another study, Daviskas et al showed the effectiveness of 15-20 mL inhalation of HS over a period of 10–15 min in treatment of stable asthma in adult patients. They found that mucociliary clearance (MCC) of the whole right lung in 1 h was significantly higher in asthmatic patients compared to healthy subjects with 14.4% HS (68±10% vs 53±12%), 0.9% HS (44±14% vs 41±15%) and control (39±13% vs 36±13%).[20] However foresaid studies are in line with our findings and showed the effectiveness of HS in management of adults asthma, in our study design and setting, dosage of both HS and salbutamol and patients conditions were different. In most mention studies, HS was used as an inhalational challenge for cough provocation tests among stable asthmatic patients in outpatient respiratory clinics, while in present study we evaluated therapeutic efficacy of 3% HS with higher inhalation time (20 min) and salbutamol with higher dosage (2.5 mg) among adult patients with acute asthma in the ED. Also we considered both PEFR and FEV1 as outcomes while mentioned studies evaluated only one of these variables or another items.

In our study, adherence to the therapeutic intervention was high and no serious adverse events were recorded. These findings suggest that the inhalation of 3% HS as part of the management of acute asthma is both well tolerated and feasible in clinical practice. The postulated mechanisms of benefit of 3% HS in asthmatic patients are as follows: 1) HS induces an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid and improving mucus clearance,[20,21] 2) HS breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion,[21] 3) HS stimulates cilial beat via the release of prostaglandin E2,[22] 4) HS can theoretically reduce edema of the airway wall by absorbing water from the mucosa and submucosa,[23] 5) HS inhalation can also cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction.[19,20]

In this study we used adequate sample size and double blinded design to minimize the common bias and limitations associated with research. Most founded studies regarding to our subject were performed on other conditions, which limit comparison of our results to other researches. Since our study only conducted on adult patients with acute asthma, results may need caution while extrapolating to adults with other diseases.Our results showed the short term efficacy of 3% HS in acute asthma attacks. Therefore, it may be used as a supplemental drug along with salbutamol in patients with acute asthma attacks admitted to the emergency department.

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