Efficacy of nebulized furosemide in children with moderate attack of asthma

*M. Alshehri, T. Almegamesi** and A. Alfrayh***
*Department of Pediatrics, College of Medicine, King Khalid University,
P. O. Box 641, Abha, Kingdom of Saudi Arabia.
E-mail: fariss2000@yahoo.com
**King Faisal Specialist Hospital, Jeddah,
***College of Medicine, King Saud University.

Summary

Background: Bronchodilators are the most commonly used drugs for asthma. However, alternative treatment is necessary for those patients who experience adverse effects from bronchodilators.

Objective: To investigate the efficacy of nebulized furosemide in children with moderate asthma exacerbations.

Method and materials: A double-blind randomized, controlled trial involving three groups of children with moderate attack of asthma. Twenty children were enrolled in group A and received nebulized albuterol, 20 children in group B received nebulized furosemide and 19 children in group C received both albuterol and furosemide. Pulmonary function parameters, peak flow rates, respiratory rate, oxygen saturation and clinical scores were obtained before and after treatment.

Results: The maximum increases in FEV_1 achieved were 21.1± 4.6 %, 20.8± 3.2 and 21.7±4.9 in groups A, B and C respectively. The differences between the groups were not significant. Maximum increase in FVC was 20.3±1.6, 22.5±5.8% and 24.5±4.9% in groups B and C respectively. The difference between the three groups was not statistically significant. With regards to peak expiratory flow rate (PEFR), the mean increase after treatment was 23.5±8.6% and 21.8±6.3% in groups A and B respectively. There was significant increase in PEFR in group C children (26.0± 9.1%; p = 0.01). There was no statistical significant difference among the three groups regarding the improvement in respiratory rate, SaO_2 and clinical scores.

Conclusion: Combination of both furosemide and albuterol led to significant increase in peak flow rate but it did not significantly affect FEV_1, FVC, FEF 25-75, respiratory rate, SaO_2 or clinical scores as compared to other groups. There were no significant adverse effects from the three drugs used.

Key-words: *Nebulized furosemide, Nebulized albuterol, Children, Asthma.*

Résumé

Introduction: Des bronchodilatateurs sont des drogues les plus orinairement consommées au cours de l'asthme. Toutefois, médecine douce et nécessaire pour des patients qui étaient victimes de l'effect des bronchodilateurs.

Objectif: Étudier l'efficacité de la nébulisation du furosemide chez des enfants atteints des exacabations modérées de l'asthme.

Méthodes et matériels: Randomisé test a double insu, épreuve controllée impliquant trois groupes des enfants atteints de la crise d'asthme modéré. Vingt enfants ont été inscrits dans le groupe A et ils ont récu la nébulisation d'albuterol, 20 enfants dans le groupe B ont récu la nébulisation du furosemide et 19 enfants dans le groupe C avaient récu l'abuterol et furosemide les deux. Fonction paramètre pulmonaire, taux élevé d'écoulement, taux respiratoire, scores cliniques et la saturation d'oxygène ont été obtenus avant et après le traitement.

Résultats: Augmentations maximales en FEV, réalisée étaient 21, 1 ± 4, 6%, 20,8 ± 3, 2 et 21, 7 ± 4, 9 dans les groupes A, B et C respectivement. Les écarts entre les groupes n'étaient pas importants. Augmentation maximales dans le FVC était 20,3 ± 1,6, 22,5 ± 5,8% et 24,5 ± 4,9% dans les groupes B et C respectivement. La différence entre les trois groupes n'était pas statisquemet importante. Par rapport au taux élevé d'écoulement expiratoire (TEEE) augmentation moyenne après traitement était 23,5 ± 8,6% et 21,8 ± 6, 3% dans les groupes A et B respectivement. Il y avait une augmentation importante dans le (TEEE) chez les enfants dans le groupe C (26,0 ± 9,1%; P = 0,01). Il n'y avait aucune différence statistiqument importante parmi les trois groupes en ce qui concerne une amélioration dans le taux respiratoire. Sa02 et scores cliniques.

Conclusion: Combination de furosemide et albuterol les deux a provoque une augmentation importante dans le taux élevé écoulement mais ceci n'a pas sériousement influencé FEV, FVC, FEF 25 - 75, taux respiratoire, Sa02 ou scores cliniques par rapport aux autres groupes. Il n'y avait aucun effet grave a la suite de l'utilisation des trois drogues.

Introduction

Bronchial asthma is the most common chronic paediatric illness.[1] It is now becoming increasingly recognized that asthma is a response to certain stimuli that results in the production and secretion of various chemical mediators, leading to bronchospasm, mucous productions, and bronchial edema. The development of the latter has received considerable attention since one of the signs of inflammation is vascular leakage of fluids and macromolcules.[2] Numerous mediators such as histamine, prostaglandin (PGE2 and PGD2), leukotienes (LTB4, LTC4 and LTD4) have been identified as playing a role. Platelets activating factor (PAF), serotonin, bradykinin, and neurohormones (such as substance P) have all been shown to be capable of causing increased microvascular permeablitiy and subsequent broncahial oedema.[3]

Furosemide has been observed to have both diuretic as well as local pulmonary effects.[4] Diuretic action of furosemide may lead to a reduction in interstitial and peri-brochiolar pulmonary edema, resulting in improved pulmonary mechanics and gas exchange.[5] The positive effect of inhaled furosemide in adult asthmatic patients has been previously reported.[6] The easy availability of furosemide its low cost, and the high number of asthmatic children attending our chest

*Correspondence

clinics were all factors that lead us to investigate the efficacy of furosemide in the treatment of children with moderate attacks of asthma in our environment.

Materials and methods

Study design

A questionnaire was completed detailing demographics, details of the present episode and medications being taken before inclusion in the study (Table 1). After assessment of clinical severity by a clinical score[7] (Table 2), base line measurement of pulmonary function, peak expiratory flow rate (PEFR), respiratory rate, heart rate, and room air oxygen saturation (SaO_2) by pulse oximetry were performed.

All children (Age <12 yrs) seen at the Abha Medical Consultative Institute from December 2001 to December 2002 who met the criteria of moderate attacks of asthma set by the American Thoracic Society[8] were included in the study. Inclusion criteria also included to perform pulmonary function testing; and baseline forced expiratory volume in 1 second FEV_1 between 50% and 80% of the predicted value. Exclusion criteria included a) an FEV_1 of less than 50%, (because we thought it was unethical to include patients this sick in our trial); b) Patients with their first wheezing episode; c) Children who had used albuterol within four hours of the current visit; d) Those with concurrent cardiopulmonary disease; and e) Children with known or suspected hypersensitivity to albuterol or furosemide.

The randomization code for the study groups was generated from a standard table of random numbers in blocks. The drugs were indistinguishable. For the assigned treatment groups, the physician and nurse and the patients receiving the nebulized solutions were blinded as to which medications were administered during the study.

The furosemide used was a sterile solution of 10mg/ml sodium furosemide and it was given at 1.0 mg/kg with 2 ml of normal saline. Albuterol was (Ventolin 0.5% Nebulized Solution, Glaxo) was administered at a dose of 0.15 mg/kg with 2 ml of normal saline. The inhalations were given by nebulizer at an oxygen flow of 8l/min over a 10 minute period. A tight-fitting plastic face mask fitted over the nose and mouth was used until the nebulizer chamber was dry. To avoid any potential confounding effects, neither corticosteroids nor other bronchodilators were administered during the study.

Pulmonary function was assessed by the measurements of FVC, FEV_1, and FEF_{25-75} on a computerized wedge spirometer with correction for age, height, weight, race and sex.[9]

After initial demonstration and teaching, pulmonary function test was performed and the highest value in each set was used for analysis according to the recommendation of American Thoracic Society.[9] Flow rates were measured by Mini-Wright flow meter (Airmed Ltd. Harlow, England). The subjects were seated upright and the nose occluded and three successive readings of the peak flow rate (PFR) were then recorded and the maximum PFR was used for all calculations. Encouragement and small prizes particularly in younger children were used to ensure enthusiasm and competition.

The primary outcome measures for the study was the percentage changes in respiratory parameters from baseline (±SE) after each treatment. Secondary outcome variables including FVC, FEF_{25-75}, peak flow rate, respiratory rate, heart rate, room air SaO_2, use of accessory muscle, wheezing scores were measured before treatment (at zero time) and after experimental therapy (at 30 minutes). Side effects reported by patients, parents or observed by attending physicians were recorded. It is of note informed consent was obtained for each eligible child and the study was approved by local ethic board.

Statistical analysis

The initial status of the three groups was assessed to confirm their comparability after randomization. Pulmonary function parameters and flow rates at base line and after drug administration were compared by using Student's paired *t*-test.

Several secondary analyses were also carried out when appropriate. These included independent-samples t test to compare furosemide group (B) with albuterol group (A) and also to compare albuterol and furosemide group (C) with albuterol group (A) and one way ANOVA to compare the three drug regimes. In addition, the changes in the various scores were analyzed by repeated measures ANOVA. The level of statistical significance was set at $p < 0.05$.

Results

Between December 2001 and December 2002, 64 children met the inclusion criteria for this study. Parents of five of the children refused consent for their children to participate in the study. Thus, of the 59 children who were enrolled in the study. Randomization produced equivalent groups with respect to contributory variables such as demographics, duration of present illness, baseline severity measures, and medications before the study. Twenty children were randomly assigned to Nebulized albuterol (Group A) and twenty children to Nebulized furosemide (Group B) and nineteen children received both Nebulized furosemide and albuterol (Group C). There was no significant demographic or clinical difference between the three groups (Table 1).

Pulmonary function parameters were calculated according to the degree of change in those particular parameters before and after the treatment as percentage of the predicted value.

Primary and secondary outcome variables at baseline and after 30 minutes of drugs administration in all three groups are detailed in Table 3.

There was a significant increase in FEV_1 following treatment in groups A 21.1± 4.6% ($p < 0.001$) and B 20.8± 3.2% ($p < 0.001$) respectively. However, the difference between the two groups was not statistically significant ($p = 0.056$). FEV_1 improvement was more in group C children treated with a combination of furosemide and albuterol (21.7±4.9 and $p < 0.001$) in comparison to the children in group A or group B (Figure 1) but this increase was not statistically significant ($p = 0.45$). FVC achieved a maximum increase of 20.3±1.6 ($p < 0.001$) and 22.5±5.8 ($p < 0.001$) in groups A and B respectively. The difference between the two groups was not statistically significant. The increase in FVC in group C patients treated with a combination of furosemide and albuterol was significant

Table 1 Base-line clinical characteristics of the study groups

Characteristics	Abuterol (Group A)	Furosemide (Group B)	Abuterol and furosemide (Group C)
Age (years)			
Mean ± SD	8.5± 3.4	8.3 ± 3.2	8.4± 2.9
(Range)	(5 - 12)	(5 - 12)	(5 - 12)
Sex			
Male	9	10	11
Female	11	10	8
Mean duration of asthmatic attacks (hr)	38.8 ± 4.9	40.6 ± 6.7	42.3 ± 8.5
Mean hospitalization for asthma in previous years (no)	0.36	0.25	0.34
History of atopy (%)			
patients	48.6	43.7	50.2
Family	56.7	63.7	58.4
Currently using inhaled steroids			
Beclomethasone	12	14	11
Dipropionate budesonide	3	4	7
Fluticasone propionate	4	2	1
Lung function test results (% of predicted value at zero time)			
FEV_1	56.0 ± 16.3	56.7 ± 17.3	58.5 ± 14.5
FVC	58.7± 17.9	57.5 ± 16.3	58.9 ± 13.7
PEFR	57.2 ± 25.4	58.0 ± 24.0	59.0 ± 22.0
Body weight (kg) (mean ± SD)	26.2 ± 11.5	25.3± 12.4	27.1 ± 13.2
Fever (within 48 hours)	9	11	10
Respiratory rate/min	40.2 ± 6.6	41.0 ±7.4	39.7 ± 8.2
Heart rate/min	80.5 ± 8.9	83.8 ± 10.4	86.2 ± 9.5
Use of accessory muscle use	2.5 ± 0.7	2.6 ± 0.8	2.4 ± 0.6
Wheeze score	2.1 ± 0.5	2.3 ± 0.7	2.1 ± 0.4

Table 2 Clinical scores in children with asthma[7]

Severity	Accessory muscle score	Wheeze score
0	No retractions	No wheeze and well
1	Intercostals retractions	End-expiratory wheeze
2	Intercostals and suprasternal retractions	Pan-expiratory ± inspiratory wheeze
3	Nasal flaring	Wheeze audible without stethoscope

(24.5±4.9 %; p< 0.001. The maximum levels of $FEF_{25-75\%}$ were 21.6±3.7 % (p < 0.01) and 22.6±2.8 % (p< 0.01) for groups A and B respectively but there was no statistically significant difference between the two groups. The improvement in $FEF_{25-75\%}$ observed in children in group C was 24.6 (p value < 0.001). This was not significant when compared with groups A or B (p >0.05) (Fig. 1).

With regards to PEFR, the mean increase after treatment was 23.5±8.6% (p<0.001) and 21.8±6.3% (p<0.001) for groups A and B respectively. There was no significant difference between the two groups (p >0.0.05). The increase in PEFR in children treated with both furosemide and albuterol (Group C) was 26.0± 9.1% (p<0.0001) and this was statistically significant when compared with groups A and B (p<0.01) (Fig. 1). Respiratory rate decreased by13.7±2.1 and 10.8± 3.9 breaths/minute in groups A and B respectively, but the difference was not significant (p = 0.53) with P value 0.53. The maximum decrease in respiratory rate in group C children treated with both medicines was 14.2±2.6 breaths/minute (p =0.001).

The maximum increase in SaO_2 was 3.4±0.9 % and 4.6±1.1 % in groups A and B respectively. The maximum increase in SaO_2 in group C children was 4.5±1.2% but this was not statistically significant when compared to groups A and B.

Adjustment for covariates such as age, sex, FEV_1 at base line, previous hospitalizations, or use of inhaled corticosteroids before study did not significantly alter these findings.

Side effects such as mild tremor and tachycardia were encountered mainly in children treated with albuterol alone and in children treated with both albuterol and furosemide. There were no adverse effects in children treated with nebulized furosemide. None of the side effects caused termination of or a significant delay in the study. All the side effect resolved within two hours of the drug administrations.

At termination of the study the patients were treated by

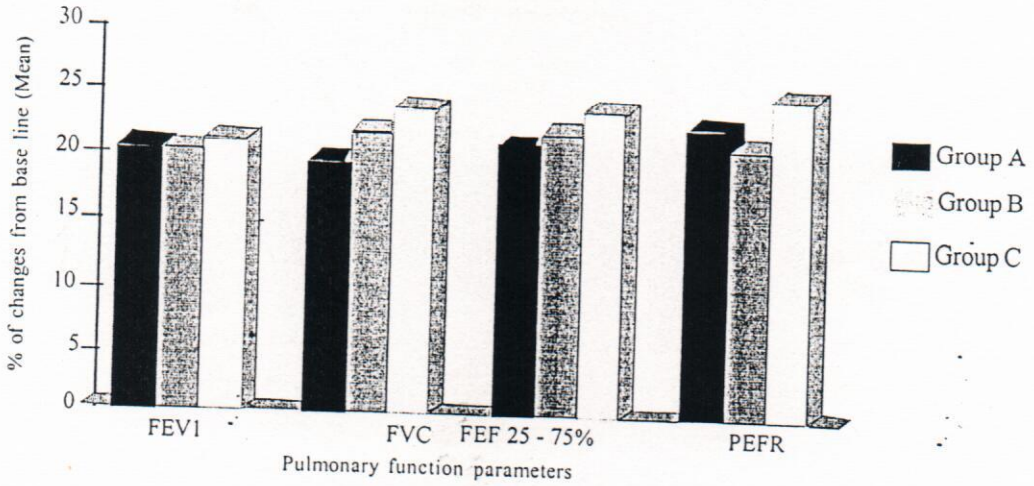

Fig. 1 *Comparison between effects of aerosolized albuterol (group A) with erosolized furosemide (group B) and combination of both drugs (group C) with regards to spirometer and peak flow meter parameters.*

the standard treatment (including albuterol 2 puff every 6 hour for 5 days, prednisolone 1 mg/kg/day for 5 days and to be assessed again at 5 days from time of discharge) and discharged home. None of the children needed hospitalization.

Discussion

Our study showed improvement in the primary outcome FEV_1 after drug administration in all three groups of patients. The percentage changes in the predicted value of FEV_1 for children treated with nebulized albuterol (Group A) and nebulized furosemide (Group B) were similar. Other pulmonary function parameters such as FVC and FEF25-75%, increased in children treated with nebulized abuterol or nebulized furosemide after treatment and the degree of change in the percentage of predicted value was significant .There was no significant difference in the degree of change in the percentage of predicted value between children treated with nebulized albuterol and those treated with nebulized furosemide.

In addition group C children treated with both nebulized furosemide and albuterol showed significant increase in FEV_1, FVC and FEF25-75 as compared to the base line measurements. Compared to the percentage increase in these parameters after treatment in groups A and B, there was no statistically significant difference ($p>0.05$) between groups A, B, or C.

With regard to PEFR there was significant immediate improvement in groups A and B. Similarly, there was also significant improvement in the peak flow rate in children treated with both drugs (Group C). There was significant difference in the percentage change when group C was compared with either group A or group B ($p<0.01$). Other outcome variable such as respiratory rate and SaO_2 showed significant improvement after treatment in the three groups but there was no significant difference established among all treatment groups.

Previous studies had concluded that furosemide prevents broncho-costriction induced by exercise,[11] cold air,[12] early or late phase allergens,[13,14] distilled water administration by ultrasonic nebulizer.[15-16] The airway of asthmatic patients adapt poorly to local osmotic changes and it has been proposed that this may be due to an essential defect on the bronchial epithelium which is related to the inability to control osmolality and ionic concentration of fluid covering the airway. Furosemide may interfere with transport of ions such as Na^+, Cl^-, and K^+ via the mucous epithelium, thus changing the osmolality of secretions and simultaneously modifying brochial reactivity.[17] Furosemide has been shown to have a bronchodilator effect similar to salbutamol.[18,19] Thus furosemide may have a relaxing effect on smooth muscles.

Another explanation advanced is that furosemide may improve pulmonary distensibility and reduce airway resistance, resulting in an increase in the exchange of gases by blocking the release of secondary constrictor mediators such as histamine or leukotreins from mediators such as histamine or leuktireine from mediators cells.[20] Furosemide also has been shown to prevent the release of the acetylcholine from cholinergic nerves and the release of the brochconstrictor tachykinin.[20]

There were several reports describing the protective effect of inhaled furosemide in asthmatic patients by itself and in combination with other drugs. Ono et al[6], showed that inhaled furosemide (20mg) had a bronchodilator effect on mild to moderate asthma when used with intravenous aminophylline (250mg), concluding that inhaled furosemide could benefit some acute asthma patients, especially those having adverse effects from â2-agonists. Another report[21] concluded that furosemide, at dose of 100mg, had the same bronchodilator effect as albuterol (1%), on FEV and $FEF_{25-75\%}$. The reports on furosemide's effect in children have been carried out in patients with mild, stable asthma with broncho-constriction induced by exercise, cold air and ultrasonically nebulized water. Seidenberg et al.[22] did not observe bronchodilatation after furosemide (28mg) in cold air-induced broncho-construction. However, Chin et al.[23] concluded that aerosolized furosemide (1mg/kg) had a bronchodilator effect in children with mild stable asthma. November et al.[24] showed that 30mg of furosemide was effective for treatment of children

with exercise – induced asthma in terms of duration. Melo et al.,[25] reported that furosemide (20mg.m) had provided comparable efficacy to disodium cromoglycate in preventing exercise-induced asthma in children.

Pendino et al.[26] showed that PEFR improved significantly in furosemide treated group when patients with an exacerbations of relatively short duration (8 hours). Pendino et al.,[26] concluded that furosemide could offer additive bronchodilator benefit in acute asthma of relatively short duration.

In contradistinction to our findings, other studies, report on this aspect showed that inhaled furosemide was an ineffective treatment for asthma exacerbation when authors compared inhaled furosemide (40mg) with inhaled metaproternol (15mg) and then with the combination of both drugs.[27] Karpel et al.,[27] showed that the effect of furosemide alone was less than that of albuterol and no sustained effects were observed beyond 15 minutes. In addition, Van Bever et al.[28] reported that aerosolized furosemide had no effect in wheezy infants and Ravel et al.[29] also found that furosemide inhalation had no effect on pulmonary function in infants with respiratory diseases.

A possible reason why some studies showed improvement in patients with respiratory diseases and other studies did not may be that due to the wide variation of utilizing different nebulization systems,[30] furosemide doses used, treatment duration and clinical conditions of patients, play a role in these different results.

This study and other previous studies have raised many questions such as the optimum aerosolization technique. The duration of time the pulmonary function would be sustained after administration of nebulized furosemide; adequacy of a dose of 2 mg/kg of furosemide versus 1mg/kg/dose; frequency and duration of administration of inhaled furosemide; safety of prolonged administration.

There are few side effects encountered in this study such as, tremor and increased heart rate in patients treated with albuterol alone or patients treated with both albuterol and furosemide. It is of note there was no adverse effect encountered in patients treated with furosemide group and there was no diuresis effect noticed in these children. Some authors had reported that there were no significant adverse effects with nebulized furosemide.[25,29,31,32] This agrees with the findings in this study of the side effects causing termination of or a significantly delay in the study and all the side effects resolved within two hours of the study.

The limitations of this study include the short observation time of the children (maximum of 24 hours) as the clinic provides only day care. Apart from monitoring clinical parameters, laboratory investigations and long term follow up need to be carried out so as to assess the long-term safety of nebulized furosemide in children with asthma. Further research in this area is recommended.

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