Section: Pediatrics

Original Research Article

EFFICACY OF COMBINED NEBULIZATION WITH FUROSEMIDE AND SALBUTAMOL COMPARED WITH SALBUTAMOL ALONE IN A WHEEZING CHILD: OPEN LABELLED RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: The significant burden of wheezing in growing children has led to exploration of many therapeutic approaches. Nebulized furosemide, a common loop diuretic, was tested as a treatment option for wheezing. **Objective**: To study the efficacy of combined nebulization with Furosemide and Salbutamol versus Salbutamol nebulization alone in wheezing children. **Study design:** Open Labelled Randomized Controlled Trial. **Study period:** Dec 2019 to Sept 2021. **Methods:** 100 Pediatric cases(1 to 12 yrs old) presenting with wheezing in Pediatric wards during. **Intervention:** All children 1 to 12 yrs, presenting to pediatric ward with wheeze, were randomized into two groups by sealed envelope allocation method (SNOSE) 50 in each group. Group A patients were given 10 mg/m2/24hr Furosemide and Salbutamol: 0.5 mg/kg/dose nebulization and group B patients received Salbutamol: 0.5 mg/kg/dose. **Outcomes:** After intervention, PASS score at the intervals of 10, 20, 30min was calculated. After 30min PEFR (children > 5 yrs) was also calculated. IEC approval and informed consent taken. Pharma/IEC-GMCA/568/2019. CTRI/2020/08/032890. **Result:** Baseline demographic details,duration of complaints,past history of similar episodes, and allergic disorders were similar in both groups. The mean PASS scores assessed at 10,20, 30min after nebulization, of group A was not significantly higher than group B. It was noted that over time,mean PASS score reduced significantly(p-value <0.01) in group A. In group A, there was significant rise in mean PEFR after nebulization (p-value <0.01). **Conclusion:** Furosemide along with Salbutamol nebulization is not significantly effective as compared to Salbutamol nebulization alone in treating wheezing children.

INTRODUCTION

Nebulized furosemide tested in adults as a treatment option for wheezing. The capacity to administer drug in a non-invasive method, with a low adverse effect profile, and in ambulatory care and home-based settings also is favorable.[1]

Asthma severity scores have been developed, validated, and used in pediatric care. The PASS (Paediatric Asthma Severity Score) was developed in the early 2000s. In one study, PASS was superior to spirometry at predicting the need for further treatment. Severity scores determine whether a patient requires admission or can be discharged. However, there are no published studies that examine the effectiveness of a pediatric asthma scoring system in triage to ICU vs ward treatment.[2]

The mechanism of action by which furosemide and drugs with diuretic properties improve lung mechanics is not clear. In adults nebulised furosemide is regarded as a potential therapy for the control of asthma. Inhaled furosemide greatly alleviates the sensation of dyspnoea induced experimentally by breath-holding and by a combination of resistive loading and hypercapnia.[3-6]

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In particular, inhaled furosemide causes a decrease in the activity of vagal irritant and C-fibre receptors, stimulation of which increases the intensity of dyspnoea and alters its quality while increasing the activity of pulmonary stretch receptors, activation of which relieves the sensation of respiratory distress.[7]
The beneficial effects of furosemide, in asthma challenge studies have raised the prospect that diuretics may have a role in the treatment of asthma in the future.
The characteristics of the fluid lining the airways affect bronchial reactivity causing bronchoconstriction induced by stimuli that affect the osmolality of the bronchial environment. The liquid and ion composition of the bronchial lining fluid is regulated by ion transport pathways in the epithelial cells of the airways. Loop diuretics inhibit the basolateral Na+/K+/Cl· co-transport in epithelial cells, this effect could change the bronchial response to osmole stimuli.[8,9]
To investigate whether inhaled furosemide would exhibit an additional therapeutic effect in children with wheeze a open-labelled randomized controlled trial performed in which patients with wheeze were randomized to receive either nebulized salbutamol (0.15 mg/kg) plus furosemide (10mg/m2) or nebulized salbutamol (0.15 mg/kg) In all patients, clinical asthma scores (CAS) were determined before and after drug administration, Peak expiratory flow rates (PEFR) were measured by a peak flow meter.[10]
We hypothesize that combined nebulization with furosemide and salbutamol is more effective than nebulization with salbutamol alone in wheezing child.

MATERIALS AND METHODS

Study Design: Open Labelled Randomized controlled trial
Study population: Source: Patients of age group 1 to 12 yrs. presenting with wheeze
Sample Size: A total of 100 patients(50 in each group) between 1 to 12 years of age with wheeze. The sample size after calculating the basis of Mean difference and Standard deviation values from a similar trial conducted in Istanbul, Turkey[3] with 80% power and Type I error of 10%. With help of SPSS software, over a period of 21 months from the time of getting ethical committee approval.
After taking informed consent, history taking and clinical examination done, investigations sent. All children aged 1 year to 12 years presenting with wheezing in wards Paediatric Department at tertiary care hospital were included. Age less than 1 year, those already on salbutamol and furosemide therapy, cystic fibrosis, bronchopneumonia, tuberculosis, chronic kidney disease, severely ill child, congenital heart disease were excluded.

At 10, 20, 30 min after nebulization, mean PASS score of group A was lower as compared to group B but not statistically significant.
It was found that over time, mean PASS score reduced significantly (both p values <0.01).
In both the groups, there was significant rise in mean PEFR after nebulization, but the difference between the two groups is not significant

RESULTS

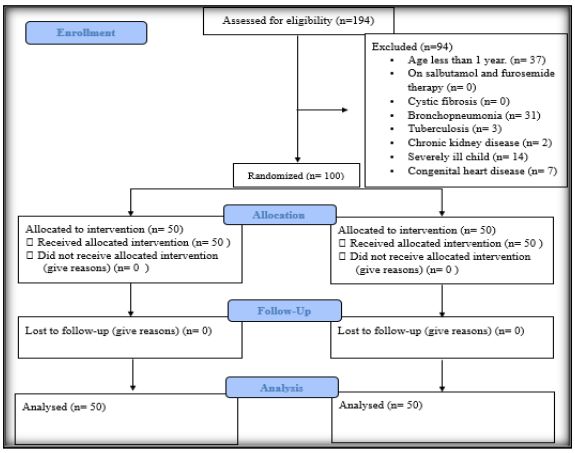

Figure 1: consort flow diagram

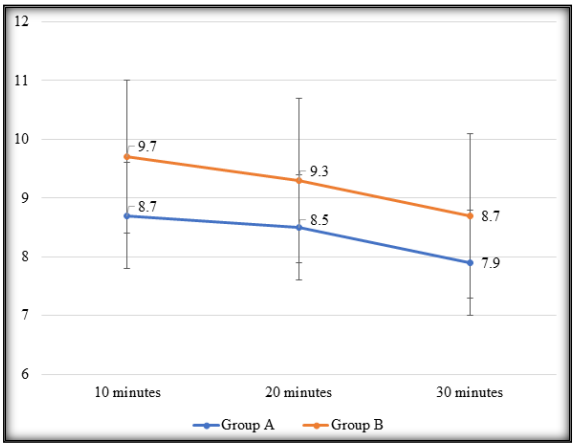

Figure 2: Graph:Mean PASS Score at 10min, 20 min and 30 min:

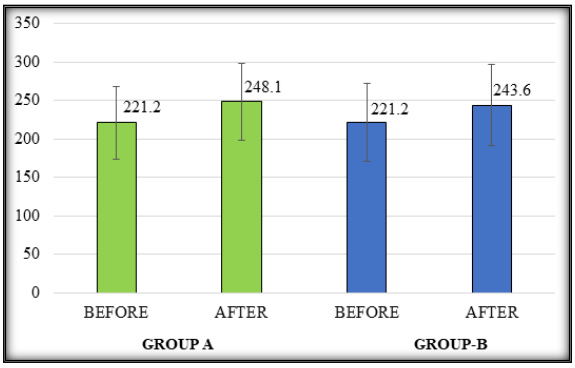

Figure 3: Mean PEFR Before and after Nebulization in GROUP A and GROUP B (Lit/min)

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Table 1: Demographic details

Demographic Data	Group A	Group B
1) Mean age (years)	8.57±2.68	7.56±2.31
2) M: F	35(70%): 15 (30%)	33(66%): 17(34%)
3) Month of Admission	Sept(20%)	August(14%)
4) Presenting complaints		
Cough	50(100%)	50(100%)
Difficulty in breathing	45(90%)	47(94%)
Fever	49(98%)	44(88%)
Noisy breathing	28(56%)	25(30%)
Chest pain	3(6%)	2(4%)
5) Days of complaints	2 or 3 days (36%each)	2 or 3 days (32% and 28%)
6) Past history		
History of similar episode	48(96%)	49(98%)
Allergic disorders	47(94%)	49(98%)
Hospitalization for similar complaints	42(84%)	36(72%)
History of worm infestation	23(46%)	22(44%)
Pallor	27(54%)	35(70%)

DISCUSSION

Inhaled furosemide is protective against bronchoconstriction in asthma induced by exercise, hyperventilation, and other stimuli. These studies have shown that when furosemide is administered as an aerosol, it can prevent or ameliorate asthma exacerbations. The purpose of this study was to investigate whether inhaled furosemide has a therapeutic effect in children with wheeze.[11-13]

Although inhaled furosemide has been shown to have a protective effect against many Broncho constrictive agents and exercise,[7-10] its effectiveness in acute settings is still debated. Our study compared inhaled salbutamol alone with a combination of inhaled salbutamol and inhaled furosemide in children with wheeze.

We conducted this trial because very few studies in pediatrics are conducted with combination of furosemide with salbutamol. Furosemide decreases the edema caused by alveolar fluid in wheezing which occurs a decrease in the activity of vagal nerves and c-fiber receptors, increases the intensity of dyspnea, alters its quality and impairs the activity of pulmonary stretch receptors, activation of which relieves the sensation of respiratory distress.[15]

All children aged 1 to 12 years, presenting with wheeze, fulfilling the inclusion and exclusion criteria, enrolled and randomized into two groups by sealed envelope allocation method (SNOSE) (Group A & Group B) after informed written consent. The time of enrolment was taken as 0 minutes. Details regarding the patient's, age, sex, MRD No., family history, clinical history, physical examination, and investigations were recorded. In clinical examination Respiratory rate, PASS score, SPO2, and PEFR were recorded at 0 minutes & again after nebulization at the interval of 10, 20, and 30 minutes.

A total 100 patients enrolled in our study, divided into two groups group A (salbutamol & furosemide) and group B (salbutamol only). In group A patients were given 10 mg/m2/24 hr. furosemide and salbutamol: 0.5 mg/kg/dose nebulization. Similarly, group B patients received Salbutamol: 0.5 mg/kg/dose. We calculated PASS scores at 10 ,20 and 30 min. After 30 minutes PEFR(>5years) was also calculated.

Mean age of Group A (8.57±2.68 years) was comparatively higher as compared to Group B (7.56±2.31) (p-value <0.01). A. Krishna Prasad et al. study suggest mean age of 6.42 years17. Balaji MD et al. study suggests mean age as 7.66 (SD = 2.72) years.

Most of the admissions were during September and August (13% and 11% respectively). Among Group A, most of them were admitted in September (20%), and among (Group B), majority admitted in month of August (14%), not significant. (P value 0.295). A. Krishna Prasad et al study suggests cases reported from August to November 17, similar to AK Singh et al36., due to high levels of pollen in the environment, dry weather, and decrease in humidity.

Proportion of males was slightly high among Group A, not statistically significant (p-value 0.668). Shivakumar R et al majority of the patients were males and Balaji et al slight male preponderance was observed, not statistically significant.

Most common presenting symptom was cough, followed by difficulty breathing (98% and 94%) in Groups A and B. Fever, noisy breathing and chest pain were slightly more in Group A. Occurrence of symptoms was similar in both groups (all p values >0.05). A. Krishna Prasad et al. found that Cough was the most common symptom, seen in 95%, followed by wheezing (90%) and difficulty in breathing (83%), similar to AK Singh et al. (98.7%) and Olufemi et al. This shows that nocturnal cough/cough without wheezing may be the only presenting symptom.

Duration of complaints was similar in both groups (p-value 0.497).

Most common past history was the history of similar episodes in the past (96% and 98% respectively) followed by history of allergic disorders (94% and 98% respectively). Past history was similar in both groups (all p values >0.05). Shivakumar R et al exposure to smoke (Chulha/Chimneys) precipitated the symptoms in 39.02%, exposure to pollens in 35.36%, Exposure to passive smoking through the smoking habit of close relative associated with 24.39%.

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Balaji et al suggest that 67% children found to have a positive history of triggering factors for an acute exacerbation. 21% had exposure to dust as a triggering factor compared to cold, 5%,27% of children have both cold and dust exposure as triggering factor,11% children had pets as triggering factors. Asthmatic children had a higher prevalence of other allergies and of allergen skin test reactivity and most asthmatics had their first asthmatic episode before their third birthday.

Most common family history was history of allergy (80% vs 66%), exposure to indoor air pollution (stove/coal) was second most common family history seen in 42% group A and 48%group B. H/o skin disease was seen in 18% group A and 28% group B. Lesser common family history was H/o contact with tuberculosis in 14% cases and 16% controls and any smoker in close contact with child in 6% group A and 4% group B. Family history was similar in both groups (all p values >0.05). Family history of atopic disorders in 40%, which is similar to AK Singh et al.36(35%) and Farzana et al. (39.2%). Balaji et al reported family history of atopic disorders in 54% of cases35 and Hinchager et al. in 60.8% of cases, whereas Sadhanaraut et al in only 5% of cases, Kinchoka VM et al. 77.8% of children.

In both groups, PASS scores assessed at 10, 20 and 30 minutes after nebulization.

At 10 minutes, most of Group A and Group B had moderate PASS scores (86% and 96%) respectively). 4(8%) of Group A and none of Group B had mild scores, not significant (p-value 0.107).

At 20 minutes, most of Group A as well as Group B had moderate PASS scores (84% and 94%) respectively). 7(14%) Group A and only one Group B had mild scores. A severe score was assessed in one Group A and in 2 Group B showing better effect of regimen used in Group A, not significant (p-value 0.078).

At 30 minutes, most of the Group A as well as Group B had moderate PASS scores (78% and 86%) respectively). 11(22%) Group A and 7(14%) Group B had mild scores. None of the patients from both groups had severe scores. This also shows effect of regimen used in Group A, not significant (p-value 0.298).

At interval of 10, 20 and 30 minutes after nebulization, mean PASS score of Group A was not significantly higher as compared to Group B (8.7±1.3 Vs 9.7±0.9, 8.5±1.4 Vs 9.3± 0.9 and 7.9±1.4vs 8.7±0.9 respectively)

Mean PASS score at 20 and 30 minutes was compared with the score at 10 minutes, it was found that over the time, mean PASS score reduced significantly (both p values <0.01).

In Group A, mean PEFR before nebulization was similar to Group B (221.2±47.2 and 221.2±51.0 respectively) (p-value 0.997). Mean PEFR increased in both groups but rise was more in Group A. In both groups, mean PEFR after nebulization was similar and the difference was not significant. (P value 0.0674).

So, our results indicate there is no improvement in PASS score and PEFR with addition of nebulized furosemide.

Nuhoglu Ç et al.— addition of nebulized furosemide to salbutamol in pediatric patients with an acute asthma attack does not produce improvement in clinical and spirometric parameters than nebulized salbutamol alone.

Gonzalez-Sanchez et al conducted to investigate the effectiveness of the combination of nebulized albuterol plus furosemide compared with placebo and found no significant differences in spirometric values (FEV1), results similar to our study.

Alshehri et concluded that Combination of both furosemide and albuterol led to significant increase in peak flow rate but it did not significantly affect FEV1, FVC, FEF 25-75, respiratory rate, SaO2 or clinical scores. There were no significant adverse effects from the three drugs used.

CONCLUSION

Addition of furosemide to salbutamol nebulization has no effect on Pediatric assessment severity score(PASS) and Peak expiratory flow rate (PEFR).

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