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Comparative Efficacy of Nebulized L-adrenaline versus Salbutamol in Infants with Acute Bronchiolitis

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Abstract

Background: Bronchiolitis is one of the most prevalent diseases of infancy for which large number of infants need hospitalization, particularly during winter period. RSV (Respiratory syncitial virus) is the principal causative pathogenic organism. Reliving symptoms are the main aim of management though none of the treatment modalities is specific. Bronchodilators like salbutamol, adrenaline, anti-cholinergic drugs, ipratropium bromide and saline nebulization have been used with varying results.

Methods: This prospective study included 52 infants (2-12 months, male:female ratio 2:1) with bronchiolitis (with 1st episode of wheeze, previously healthy baby, physical findings with cough, running nose, fever, coryza and inflation of lungs) to understand comparative efficacy of nebulized salbutamol with adrenaline in bronchiolitis. The cases were randomized into nebulized salbutamol group (n=25) and nebulized adrenaline group (n=27). After randomization three nebulization were given at the interval of 20 minutes. Outcome of therapy was evaluated by respiratory rate, MRDAI (Modified Respiratory Distress Assessment Instrument) score and O_2 saturation before and after therapy.

Results: Study cases in both the groups presented with cough (100%), respiratory distress (100%), feeding difficulty (90.3%), running nose (98%) and wheeze (100%). Majority of the cases live in urban area and mostly from non-smoker family. In salbutamol group respiratory rate, MRDAI score and O_2 saturation (before nebulization RR-67.5±6.1, MRDAI score-14.6±1.3, SaO_2 93.9±1.6 and after nebulization RR-52.5±4.9, MRDAI score-6.4±1.7, SaO_2-97.1±1.5) significantly improved after 3 nebulizations. In adrenaline group respiratory rate, MRDAI score and O_2 saturation (before nebulization RR-64.9±5.9, MRDAI score-15.0±0.8, SaO_2-94.1±1.4 and after nebulization RR-50.0±2.9, MRDAI score-7.7±1.0, SaO_2-97.9±1.5) also significantly improved after 3 nebulizations. Improvement was more significant in adrenaline group. Heart rate in both groups were increased (salbutmol group-151.8±10.6 and in adrenaline group-160.2±10.1) but more in adrenaline group. When comparative efficacy evaluated, it was observed that nebulized adrenaline therapy was significantly superior to nebulized salbutamol therapy in reliving symptoms (p=.004).

Conclusion: The study concluded that both nebulized salbutamol and l-adrenaline are effective and nebulized l- adrenaline is significantly superior to nebulized salbutamol in infant with bronchiolitis in reliving symptom.

Key words: *Nebulized l-adrenaline, nebulized salbutamol, acute bronchiolitis.*

Introduction

Bronchiolitis is an acute viral inflammatory lesion of small airways. More than 70% cases are due to respiratory syncytial virus (RSV), other pathogens are Parainfluenza virus, Adenovirus, Rhinovirus, Influenza virus and Mycoplasma pneumonae. The occurrence is highest in mid winter to late spring. The peak incidence of bronchiolitis is 2-6 months of age and virtually all children become infected during first 3 year of life[1]. Bronchiolitis occurs most commonly in male infants who have not been breastfed and live in crowded condition. The source of viral infection is usually a family member with minor respiratory illness. Infants whose mothers smoke cigarette are more likely to acquire bronchiolitis than infants of non-smoking mother. The occurrence is more observed where a heavy smoker stays with children[2]. In USA >90,000 hospital admissions yearly are due to bronchiolitis, the majority of infants younger than 90 days[3].

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Variation in the management of bronchiolitis has been documented. Hospitalized patients receive a variety of treatment modalities with uncertain efficacy such as bronchodilator, ribavirin, steroids and antibiotics. These variant modalities of treatment significantly impact the cost and adverse events associated with hospitalization[4].

Bronchodilators are often used in the treatment of bronchiolitis but data on efficacy are conflicting. Most studies have shown no beneficial effect on lung mechanics. JD Kellner et al done an evidence based study where they commented that bronchodilator produce modest short term improvement in clinical scores[5].

In an article, Arivolli Verappan and Ashir Kumar described that any form of steroid is effective in bronchiolitis, specially nebulized budesonide 1000 micro-gram/dose. They also comment that L-epinephrine was effective as well as less costly in treatment of bronchiolitis[6]. Ribavirine a broad spectrum anti viral agent is the only specific therapy for RSV infection in infant[1]. Ray and Singh concluded in a recent study that both nebulized epinephrine and salbutamol caused significant improvement in mean symptom score and oxygenation. However the epinephrine group showed a significantly better improvement in study parameters than salbutamol group. They concluded by saying "Adrenaline is more effective than salbutamol and is thus a better, inexpensive and relatively safe alternative"[7].

Bertrand P et al had been done a prospective study on efficacy of nebulized epinephrine versus salbutamol in hospitalized infants with bronchiolitis. They commented that nebulized epinephrine decreased the baseline clinical score of bronchiolitis faster than salbutamol. They also concluded that nebulized epinephrine is more effective agent than salbutamol in the initial treatment of bronchiolitis and is equally safe[8].

The study was conducted to understand the comperative efficacy of nebulized salbutamol versus nebulized l-adrenaline in reliving in acute bronchiolitis.

Materials and Methods

The study was a prospective, randomized, interventional study conducted at Dhaka Shishu (Children) Hospital from July 2002 to December 2003.

Previously healthy infants (2-12 months) having first episode of wheeze accompanying physical findings of viral infection i.e., coryza, cough, fever, etc and evidence of hyperinflation of the lungs clinically and radiologically were included in this study. The patients with evidence of similar previous attack, asthma, previous use of corticosteroid and history of atopy or allergy and presence of congenital heart disease and tuberculosis were excluded.

After selecting the cases relevant history and physical examination finding were recorded in a pretested questionnaire. Heart rate, respiratory rate and the severity of illness were assessed by using a combination of MRDAI score (Modified Respiratory Distress Assessment Instrument) (Table-1) and O_2 saturation. Oxygen saturation was measured non-invasively using pulse oxymeter, and those with values less than 92% were designated as having significant hypoxia.

The cases were then randomly (one case to salbutamol group and next case to adrenaline group) assigned into two groups designated as A (salbutamol group) and B (adrenaline group). Group A (salbutamol group) received salbutamol in a dose of 0.15 mg/kg body weight (minimum dose 1 mg)[7] diluted in normal saline to make a total volume of 3 ml. Cases in group B (adrenaline group) received nebulization with 0.1 ml/kg body weight of 1 in 10,000 solution of adrenaline (1 ampoule 1:1000 injection diluted with 9 ml of normal saline to make it 1 in 10000 solution) [7]. The drug was further mixed with normal saline to make a total volume of 3 ml. Nebulization in each groups were given at 20 minutes intervals. Pulse oxymetry (NBP-40, Nellcor-Puritan Benett, Ireland) was done during this period and SaO_2 values were recorded before and after nebulization. No other drugs like antibiotics, steroids, intravenous fluids, etc were given during this period. In febrile cases only hydrotherapy was given.

Ten minutes after administration of the last dose, respiratory rate, MRDAI score and oxygen saturation (by pulse oxymetry) were evaluated again to assess the response to therapy. The decision for further management was taken on the basis of this evaluation. Children who showed a sustained decrease in tachypnea and respiratory distress (wheezing and retractions), and were accepting well orally after an observation period of 1 hour, were sent home with oral medication. Children who did not improve admitted in hospital for further management.

Supportive measures like propped up positioning, fluid, feeding and antibiotics (whenever indicated) and counseling was done. MRDAI score was chosen to assess the clinical outcome of nebulized salbutamol and adrenaline because it is clinically relevant and has undergone validation and reliability measurement in randomized controlled trials involving patients with bronchiolitis[4].

Data was analyzed by using SPSS statistical software employing appropriate statistical tests like paired and unpaired Student's "t" test.

Table-I

Respiratory distress assessment instrument[9]

	0	1	2	3	4	Points
Wheezing						
Expiratory	None	End	1/2	3/4	All	4
Inspiratory	None	Partial	All			2
Location	None	2 of 4 lung fields	3 of 4 lung fields			2
Retraction						
Supraclavicular	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked		3
Subcostal	None	Mild	Moderate	Marked		3
Respiratory Rate	20-25	26-35	36-45	>45		3
Total						

Results

The study included 52 cases, 25 (male-15, female-09) in nebulized salbutamol group, 27 (male-17, female-10) in nebulized adrenaline group. Most of the cases (salbutamol group-25, adrenaline group-24) in both the groups were born at term and 42 (salbutamol group-21, adrenaline group-21) infants were delivered normally. Body weight of the cases ranged from 4.5 kg to 13 kg (mean-6.7kg).

Majority in salbutamol (17/25; 68%) and adrenaline group (17/27; 63%) were exclusively breastfed up to 4 months of age. Only 2 cases in both groups had combined breast feeding and complementary feeding. Only complementary feeding was given to 6 cases (6/25; 24%) in salbutamol group versus 8 cases (8/27; 29.6%) in adrenaline group.

Twenty cases (20/25; 80%) in salbutamol group and 23 cases (23/27; 85%) in adrenaline group live in urban area and 05 cases (5/25; 20%) in salbutamol group and 4 cases (4/27; 15%) live in rural area. Majority of the cases (salbutamol group-19/25; 76% and adrenaline group-23/27; 85%) live in normal environment. Minority of the cases (salbutamol group-6/25; 24% and adrenaline group-4/27; 15%) lives in crowded environment. Majority of the cases (salbutamol group-21/25; 84% and adrenaline group-24/27; 89%) lives in well-ventilated rooms. Ventilation of the rest of the families was poor. In salbutamol group 12 (11/25; 44%) family members were smokers while it was 6 (6/27; 22.2%) in adrenaline group. Majority of the family members 34(13/25; 52% in salbutamol group and 21/27; 77.8% in adrenaline group) were non-smokers.

Table-II

Residence of the family, crowded living and ventilation status distribution

		Salbutamol group (n=25) No. (%)	Adrenaline group (n=27) No. (%)
Residence	Urban	20 (80)	23 (85.2)
	Rural	05 (20)	04 (14.8)
Crowded living	Present	06 (24)	04 (14.8)
	Absent	19 (76)	23 (85.2)
Ventilation	Good	21 (84)	24 (89)
	Poor	04 (16)	03 (11)

Table-III
Clinical presentation

	Salbutamol group (n=25) No. (%)	Adrenaline group (n=27) No. (%)
Cough	25 (100)	27 (100)
Fever	16 (64)	16 (59.3)
Respiratory distress	25 (100)	27 (100)
Feeding difficulties	21 (84)	26 (96.3)
Running nose	24 (96)	27 (100)

All the cases presented with cough but 98% of the cases presented with running nose (salbutamol group-24/25; 96% and adrenaline group-27/27; 100%). Difficulty of feeding was a presenting feature in 21 (84%) patients of salbutamol group and 26 (96%) patients in adrenaline group. Only in 16 cases in both groups (salbutamol group-16/25; 64% and adrenaline group-16/27; 59%) presented with fever (98ºF -103ºF). All the cases were presented with wheeze and respiratory distress.

On examination of the lungs, 33 (63.5%) patients had no significant auscultatory finding and spleen was palpable in 10 (19.2%) patients. Asthma, eczema and allergic rhinitis (atopic conditions) were present in only 9 (17.3%) families.

After nebulized salbutamol therapy, mean respiratory rate (52.5±4.9), oxygen saturation (97.1±1.5) and RDAI score (6.4±1.7) had significantly improved in comparison to respiratory rate (67.5±6.1), oxygen saturation (93.9±1.6) and RDAI score (14.6±1.3) of before nebulization (p=<.001 in all parameter). Heart rate also significantly increased after nebulization (151.8±10.6 versus 109.4±0.4) (p=.004)

After nebulized adrenaline therapy mean respiratory rate (50.0±2.9), oxygen saturation (97.9±0.8), RDAI score (7.7±0.1) had also significantly improved in comparison to respiratory rate (64.9±5.9), oxygen saturation (94.11±2.9) and RDAI score (15.04±0.8) before nebulization (p=<.001 in all parameter). Mean heart rate was significantly increased after nebulization (160 ±10.1 versus 105, ±10.04) (p=<.001).

In comparison between two modalities of treatment, adrenaline was found to be significantly more efficacious than salbutamol in every parameter except in MRDAI score after nebulization where p value was 0.08. But in respiratory rate (p=.03), oxygen saturation (p=.03) and MRDAI score reduction (.004) was significantly better in adrenaline group after 3rd nebulization.

We have done RSV antigen of nasal swab in 25 (48%) patients of both groups and found only 4(16.0%) patients were positive for RSV antigen. Here group difference not shown.

Table-IV
Comparison of response to therapy with nebulized salbutamol versus adrenaline

	Before therapy			After therapy		
	Salbutamol (No.=25) mean(±SD)	Adrenaline (No.=27) mean (±SD)	P	Salbutamol (No.=25) mean (±SD)	Adrenaline (No.=27) mean (±SD)	P
Respiratory rate	67.5 (±5.4)	64.9 (±5.9)	.12	52.5 (±4.9)	50 (±2.9)	.03
Heart rate	104.4 (±5.4)	105.4 (±10)	.17	151.8 (±10)	160.2 (±10.2)	.005
Oxygen saturation	93.9 (±1.6)	94.1(±1.4)	.63	97.1 (±1.5)	97.9 (±0.8)	.03
RDAI score	14.6 (±1.3)	15 (±0.8)	.13	6.4 (±1.7)	7.7 (±1.0)	.08
RDAI score reduction				6.12 (±1.7)	7.33 (±1.1)	.004

Discussion

The present study included 52 cases, 25 (male-15, female-09) in nebulized salbutamol group, 27 (male-17, female-10) in nebulized adrenaline group. Male infants are predominantly affected with bronchiolitis in both the groups[7,10]. Most of the cases in both the groups were born at term and delivered normally. Body weight of the cases ranged from 4.5 kg to 13 kg (mean-6.5 kg). In an Indian study mean age was 5.6 months[7]. Majority cases in both salbutamol and adrenaline groups were exclusively breast-fed up to 4 months. Only 2 cases in both the groups had mixed feeding. Only complementary feeding was given to 6 cases in salbutamol group versus 8 cases in adrenaline group. Though breast feeding has a protective effect against infection the present study showed that breast fed babies also suffer with bronchiolitis. Twenty cases (80%) in salbutamol group and 23 cases (85.2%) in adrenaline group live in urban area and few cases live in rural area. Here urban infants are affected more and it is established inference for bronchiolitis[2]. Majority of the cases live in normal environment and in well-ventilated rooms. Though living in well-ventilated room, majority of the cases had attack of bronchiolitis.

Forty-seven mothers are housewives and only 4 mothers work outside home. In salbutamol group only 12 family members were smokers versus 6 in adrenaline group. Majority of the family members of both the groups were non-smokers. Though smoking is a recognized risk factor for bronchiolitis, particularly maternal smoking[11,12].

In the present study running nose, cough, wheeze, fever and feeding difficulty were predominant presenting features in both the groups (Table-III). All the cases (100%) of the present study presented with cough and 94% cases presented with running nose. Difficulty of feeding was a presenting feature in 75% cases in salbutamol group and almost all cases in adrenaline group. Only 16 cases in both the groups presented with fever (up to 103^0F). One study in Bangladesh observed that clinical presentations were almost similar to our study[10]. L kabir et al found that spleen was palpable in 42% cases while it was only 19% in present study[10].

We tested only 25 samples of nasal swabs out of total 52 cases for RSV where only nasal swabs of 4 patients had RSV antigen positive. A previous study in Bangladesh showed 45.0% anti RSV antibody (IgM) positive cases[10]. A study in England reported that 60% of cases had RSV positive antigen in their nasal swab[13].

Comparing nebulized salbutamol with adrenaline there was significant improvement of respiratory rate and O_2 saturation and difference of improvement between the two groups after 3rd nebulization was statistically significant. One study in neighbouring country also observed significant improvement by nebulized salbutamol and adrenaline therapy and the efficacy of nebulized adrenaline was significantly superior to salbutamol[7]. Menon et al observed no significant difference between nebulized salbutamol and adrenaline[14].

In the present study (Table-IV) mean O_2 saturation before nebulization were 93.9% and 94.1% in salbutamol and adrenaline group respectively. After nebulization mean oxygen saturation raised upto 97.1% and 97.8% in salbutamol and adrenaline group respectively, which is statistically significant. In another Indian study SaO_2 before nebulization was 91.1% and 90.6% in salbutamol and adrenaline group respectively and after nebulization these score raised to 93.9% and 98.0% respectively[7], similar to our study.

In a canadian study there was no significant improvement in O_2 saturation when compared with before and after nebulization salbutamol versus adrenaline[14]. Ainiune AA et al compared the efficacy of nebulized adrenaline with nebulized normal saline and concluded that adrenaline is not superior to normal saline[13]. An earlier trial on croupy infants had revealed that the peak effect of nebulized epinephrine appeared in 30 minutes and lasted for 60-90 minutes[15]. In this study even though the continued effect of the drugs was seen after the third dose, the maximal change in SaO_2 appeared in both groups after the second nebulization, i.e., about 30 minutes after the onset of nebulization. This may perhaps explain why certain authors who used only a single dose of adrenaline failed to observe any significant improvement[16].

MRDAI (Respiratory Distress Assessment Instrument) score reduction in our study was 6.1 and 7.3 in salbutamol and adrenaline group respectively, which is statistically significant. Reduction of MRDAI score in adrenaline group is significantly better than salbutamol group in our study which was also shown by a previous Indian study where mean score reduction was 8.8 and 5.9 in adrenaline and salbutamol groups respectively[7]. A study in Canada, MRDAI score

reduction was 7.5 and 6.6 in salbutamol and adrenaline groups respectively, which did not have any statistical significance[14]. Ainine AA has also shown no significant difference regarding RDAI score reduction between adrenaline and saline nebulization[13].

In our study, we have used a combination of MRDAI score and oxygen saturation to assess the respiratory functional status and degree of distress. These score are non-invasive, have low inter-observer variation and can be easily evaluated in the OPD set-up. Arterial oxygen saturation by pulse oxymetry has suggested being the best objective criterion to assess degree of distress in children[17].

Analysis of the present study also revealed that the children in both the groups had similar clinical profile during the time of inclusion in the study. After nebulization for three times consecutively, within 20 minutes interval both the adrenaline and salbutamol groups showed significantly improvement which was more marked in the adrenaline group in comparison to salbutamol group in all parameters. Not only the mean score and mean SaO_2 levels were better in the adrenaline group but also more proportion of patients significantly improved both in clinical scores as well as oxygen saturation in adrenaline group compared to salbutamol group ($p< 0.03$).

The cardiac side effects of drugs used were also assessed because the chronotropic action of adrenegric agents on the heart is often a matter of concern. Both salbutamol as well as adrenaline showed a significant increase in heart rate that was more in case of adrenaline group. However, this study did not have any adverse clinical effects like increased irritability, tremors, facial blanching, arrhythmia, congestive heart failure and none of the children required drug withdrawal or intervention for tachycardia or any other intervening measures.

Bronchodilator, both specific (β_2 agonist e.g, salbutamol) and nonspecific agonist (adrenaline) are useful in relieving symptoms and improving oxygenation in bronchiolitis.

Conclusion

The study concluded that both salbutamol and l-adrenaline are useful in relieving symptoms and improving oxygenation in bronchiolitis. When comparative efficacy was evaluated it was observed that nebulized l-adrenaline was superior to nebulized salbutamol in bronchiolitis. Nebulized adrenaline can be safely used in reliving of symptoms in bronchiolitis without any major side effects. Larger, multicentre, double blind, randomized controlled trials are required to validate our study results.

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