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To assess and compare the efficacy of Nebulised Salbutamol and Nebulised l-Adrenaline in wheeze associated respiratory tract infection in children in the age group of 2 months to 2 years.

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Abstract

Aims and Objectives: 1).To determine the effect of nebulized salbutamol and nebulised L-adrenaline on clinical severity score in wheeze associated respiratory tract infection in children in the age group of 2 months to 2 years. 2). To compare the efficacy of these two nebulized bronchodilators in these patients.
DESIGN: randomized controlled trial. SETTING: tertiary care teaching hospital.
Materials and Methods: 200 children in age group of 2 months to 2 years with their 1st episode of wheezing in association with fever and/or coryza were enrolled. Of these, 100 received salbutamol (0.1mg/kg/dose) (Group A) 100 received L-adrenaline (0.1ml/kg/dose in 1 in 10,000 solution) (Group B). Three doses of each drug were given, nebulized with oxygen at 20 minutes intervals. Respiratory rate, CS score, clinical status and pulse oxymetry was recorded before intervention and 10 minutes after each dose. Patients who showed significant relief were discharged after an observation period of three hours while those who did not were admitted.
Results: Both L-adrenaline and salbutamol caused significant improvement in mean symptom score and oxygenation. However, the adrenaline group showed a significantly better improvement in the study parameters than the salbutamol group. More children in the adrenaline group could be sent home after the emergency treatment.
Conclusion: Adrenergic agonists both specific and non specific are beneficial in WARTI. Adrenaline is more effective than salbutamol and is thus a better, inexpensive and relatively safe alternative.

Keywords: Wheeze Associated with respiratory tract infections (WARTI), Clinical Severity Score (CS Score)

Introduction

Wheeze associated with respiratory tract infection (WARTI) is a very common problem in children less than five years of age. The reported attack rates in the western literature being as high as 11.4per 100 children in the first year and 6 per100 in the second year of life. Viral respiratory infection in young children is often associated with small airway narrowing, secondary to an inflammatory process and/or spasm of the bronchial musculature. Bronchiolitis, wheezy bronchitis, infantile asthma and WARTI are common diagnosis in such infants.[1-3] Majority of cases of WARTI include both pneumonia and acute viral bronchiolitis. Pneumonia and bronchiolitis are major cause of hospitalization in higher socio-economic regions of the world. Pneumonia is the leading cause of death in children, under 5 years of age, in developing countries.[4-7]

Bronchiolitis is a disease caused by respiratory viral infections, with little evidence of bacterial coinfection.[8] However, there may be viral-bacterial co-infections.[9] RSV is the only respiratory virus to produce a predictably sizeable outbreak of infection each year.[10] It is well known that RSV infection only confers partial immunity from subsequent infections; hence re-infection with RSV is frequent and occurs throughout life. However, after three years of age, infections are generally milder and confined to the upper respiratory tract.[11-13]

The role of bronchodilators in this set of small children has been shrouded with controversy and there are a lot of contradictory reports regarding the efficacy of bronchodilators in this setting.[14-16] The efficacy of beta 2 agonists in bronchiolitis has found improvement in oxygen saturation and heart rate, but the results were not clinically significant.[17] Earlier research showed that children below two years did not respond to bronchodilator therapy whereas later studies have shown that beta-2 receptor stimulants like salbutamol have a definite role in the treatment of such conditions in the younger age group.[18-19]

Of late there has been renewed interest in the role of adrenergic drugs in WARTI.[20] One of the issues in the current debate is whether an alpha agonist, either in combination with beta agonist, or even alone, will be as effective as beta-2 agonist used alone due to its added effect on decreasing the inflammatory edema. Although different nebulized bronchodilators such as albuterol sulfate, ipratropium bromide and epinephrine are being used in the treatment of bronchiolitis, research to date supports epinephrine as the bronchodilator of choice.[3] The little data available so far, reflects that perhaps a non selective agonist which combines both alpha and beta stimulating properties may be a better choice in treating this condition than a selective beta agonist.[21]

Traditionally recemic epinephrine has been used as a non-selective adrenergic agonist of choice in wheezy infants due to its supposedly fewer side effects than the more active and more readily available natural laevorotatory form of epinephrine. However, there seems to be no pharmacological basis for this belief. In addition, L-epinephrine is readily available in all countries while racemic epinephrine is not available in countries like India. Even in countries where both forms are available the racemic form is much more expensive.[22] Since racemic form is not available in India we used L- adrenaline.

Therefore, this study was carried out with the primary objective of finding out the comparison and effectiveness of salbutamol nebulization and adrenaline nebulization in WARTI among Indian children.

Materials and Methods

This prospective hospital based study was carried out in the outpatient Department of Pediatrics, Government Medical College, Amritsar. The study sample consisted of 200 cases of WARTI in the age group between 2 months to 2 years during the time period of twenty months from February 2016 to October 2017.

Selection of Cases

Inclusion criteria

All children with first episode of WARTI having the following features were included in the study:

- Infants and children between two months to two years of age.
- First episode of respiratory distress associated with wheezing and clinical
- evidence of viral respiratory illness in the form of fever,cough and or coryza.
- Clinical severity score≥ 3.

Exclusion criteria

- Age < 2 months or > 2 years.
- History of two or more episodes of respiratory distress in the past.
- The presence of chronic cardiovascular or respiratory conditions like congenital heart disease, lung cysts etc.
- Family history of asthma/atopy.
- Clinical evidence of bacterial infection.
- Children presenting with altered sensorium or dehydration, heart rate >180/min, respiratory rate >100/min, or in incipient respiratory failure.

This study included 200 patients in the age group of 2 months to 2 years presenting in the outdoor patient department with different respiratory tract symptoms like cough, fever, wheezy chest and respiratory distress. The patients were grouped into 2 random groups A and B. The randomisation was done using random number generator. Children in group A was given nebulised salbutamol in a dose of 0.1 mg/kg/dose for 3 times over 20 min interval. Children in group B were given nebulised L-adrenaline(1:10000) in a dose of 0.1ml/kg for 3 times over 20 min interval .The response to nebulisation after one hour was assessed using clinical severity (CS) score, which includes respiratory rate, chest retractions, wheeze/ronchi and general condition of the patient. Heart rate and sp02 was also be assessed in both groups at the time of enrollment before intervention, 10 minutes after each dose and three hours after the first nebulisation. Similarly, observation was made of any evidence of tremors, occurring or worsening of restlessness or any other side effects after nebulisation in both the groups. After an observation period of three hours patients showing improvement in CS score i.e whose CS score comes less than 3 were sent home, while those who did not showed such response were admitted in the ward. The comparative efficacy were assessed and Data was recorded on a predetermined proforma and analyzed using Epi-info-5, Microstat, Instat and SPSS statistical software employing appropriate statistical tests like Student's test, Chi square test and proportions test and P < 0.001 was considered significant. The data of all the cases was recorded on a predetermined proforma. The diagnosis of acute bronchiolitis was clinical, based on the history and physical examination. The severity of the illness was assessed by using CS score described by Wang et al.[23]

Results

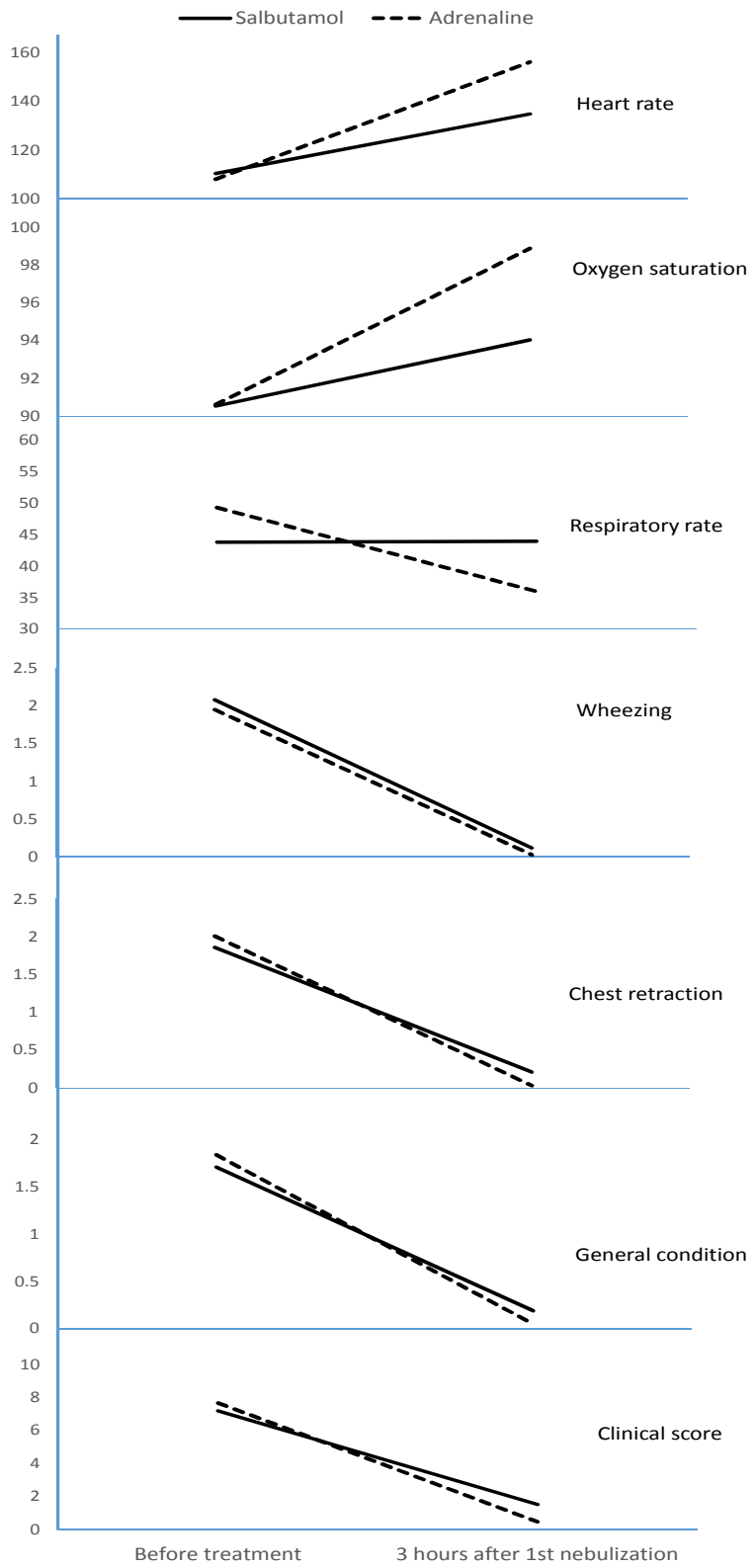
A total of 200 children in the age group of 2 month-2 year were enrolled in the study. There were 100 each children in the salbutamol group and in adrenaline group. The mean age of the patients was 6.418±4.023 months. The youngest patient was 2 months and the oldest was 24 months old.

Both the groups were comparable in their age, gender, mean initial HR, RR, RDAI scores, and SpO2. All the children were assessed for their HR, RR, SpO2, and CS Score at the time of enrollment and then every 20 minutes of nebulization thrice over one hour and then after 3 hours of first nebulization and the scores were plotted. On analysis, the two groups were matched in age, gender, and the all the study parameters at the time of admission.

Comparison of Initial and Final Parameters in Both Groups

S.No.	Variable	Group (n=100)	Before treatment		After treatment	
			(Mean + SD)	p value	(Mean±SD)	p value
1.	Heartrate	A	110.37±18.55	0.371	134.85± 25.35	<0.001
		B	107.97±19.34		156.30±11.17	
2.	SPO2	A	90.53±5.09	0.99	94.04±2.53	<0.001
		B	90.61±2.53		98.88±0.85	
3.	Respiratory rate	A	47.83±6.824	0.136	43.99±7.252	0.001
		B	49.32±7.445		36.01±4.968	
4.	Wheezing	A	2.08±0.442	0.083	0.12±0.31	0.027
		B	1.95±0.601		0.03±0.262	
5.	Chest retraction	A	1.86±0.45	0.551	0.21±0.4	0.0001
		B	2.01±0.628		0.03±0.171	
6.	General condition	A	1.71±0.68	0.09	0.19±0.56	0.0001
		B	1.84±0.35		0.05±0.22	
7.	Clinical score	A	7.19±1.64	0.676	1.52±0.82	0.0001
		B	7.67±2.03		0.47±0.91	

Graphical Representation of clinical parameters before and after treatment



At the end of the intervention period it was seen that four out of hundred patients in the adrenaline group had either shown no improvement or deteriorated and had to be admitted for further treatment, while the rest could be sent home on oral medication. Correspondingly in the salbutamol group, 12 out of 100 required admission as they failed to respond to therapy ($p = 0.03$).

Discussion

The present study was conducted to assess the efficacy of bronchodilators in WARTI and compare the benefits of a beta-2 specific agonist with a combined alpha and beta (non specific) agonist among children presenting with first episode of wheezing and respiratory distress in association with fever and/or coryza, without any family history of atopy or asthma. So primarily the study was focusing on wheezing in association with RTI and clinically presumed to be of viral origin.

The data and observations were analysed to compare efficacy of nebulized salbutamol and nebulized adrenaline. The efficacy was assessed with regard to both drug parameters as well as patient characteristics. Drug parameters taken into consideration were total clinical severity score (respiratory rate, wheeze, chest retraction and general condition), SPO2 values and immediate adverse effects like tremors and increase in heart rate were also assessed. After three doses of nebulization significant improvement was noted in both sabutamol and adrenaline groups in SPO2, CSS and respiratory scores. However, these changes were significantly more marked in the adrenaline group as compared to the sabutamol group for all parameters ($p<0.001$ for each parameter). As per our study 12 out of 100 patients in salbutamol group showed CS score $\geq$ 3 compared to 4 out of 100 patients in adrenaline group with calculated p value = 0.03 which was significant. Therefore number of patients requiring hospitalization after adrenaline nebulization was significantly less than that of salbutamol group.

Adverse effects of both the drugs were also studied, the two major side effects seen during the course of study were tremors and tachycardia. Six patients out of 100 in salbutamol group experienced tremors and none in adrenaline group and both salbutamol as well as adrenaline showed a significant increase in heart rate, more so in the case of adrenaline. However, this had no adverse clinical effects like increased irritability, facial blanching, arrhythmia, congestive heart failure. None of the children required drug withdrawal or intervention for tachycardia or its consequences no cardiac symptoms observed in any patient.

Sanchez et al in a study of 24 infants with acute bronchiolitis, concluded that raecemic adrenaline is better than salbutamol[24], similar results were found by Ray et al with L- adrenaline having upper hand over salbutamol nebulization[25].

Modaressi et al in 2012 in one month to 2 years concluded that epinephrine group showed significant improvement in RDAI index (P=0.03) and less duration of hospital stay.(3.3±1.1 and 3±0.9 in the patients receiving salbutamol and epinephrine respectively)[26].

Gayati et al in 2017 in a double blind randomized control trial showed reduction in mean RR from 85.14/min and 84.14/min to 69.47/min and 65.1 in salbutamol and adrernaline groups respectively. Adrenaline arm resulted in better respiratory status with significant improvement in RR, RDAI score and SpO2, decreased oxygen requirement and shorter hospital stay. There were no significant side effects in either group[27].

Conclusion

Thus we conclude from this study that in children suffering from WARTI, both salbutamol neblulization and L-adrenaline nebulization are significantly effective in the treatment of this disease. But when the efficacy of these two drugs is compared L-adrenaline nebulization, despite showing comparable side effects, shows better efficacy than salbutamol nebulization. There was not only significant improvement in SPO2 levels and the CS score but also significant reduction in the hospital admissions. However further studies are needed in this regard by taking greater sample size and more precisely comparing the patients with similar clinical severity scores and similar disease pathology.

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