Original Research Article

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Comparison of nebulized Salbutamol versus Adrenaline in the treatment of wheeze associated respiratory tract infection

Sireesha S.1*, B. S. Prasad¹, Suresh J.²

¹Department of Pediatrics, S. S. Institute of Medical Sciences and Research Centre, Davangere, Karnataka, India ²Department of Forensic Medicine, JJM Medical College, Davangere, Karnataka, India

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*Correspondence:

Dr. Sireesha S.,

E-mail: sireeshdr@gmail.com

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ABSTRACT

Background: Wheezing related to respiratory infections is common in infancy and early child hood. In 1-3% of all infants these infections are severe enough to require hospitalization. Most episodes of wheezing in early life are of viral origin and form a heterogeneous group with different outcomes. The objectives of this study were to assess the efficacy of bronchodilators in wheeze associated respiratory infection and to comparing the efficacy of a nebulized nonspecific adrenergic agonist -1 adrenaline with a nebulized beta-2 specific agonist salbutamol for the treatment of the wheeze associated respiratory tract infection.

Methods: The study was conducted in children reporting to the Pediatric Department Government General Hospital in Kakinada. The study period was 6 months from January to June 2014. Children between the ages of two months to two years attending the hospital with the clinical diagnosis of bronchiolitis were enrolled.

Results: 30 children were enrolled. 22 (73.3) were in age group of 2 months to 1 year and 8 (26.7%) were in age group of 1-2 years. There is no added advantage of decreasing the respiratory rates, wheezing and retractions of one over the other groups.

Conclusions: It can be inferred that bronchodilators, both nebulized adrenalin and salbutamol are useful in relieving symptoms and improving oxygenation in wheezy infants with clinical diagnosis of WRTI. No drug is said to be better over the other.

Keywords: Epinephrine, Nebulization, Respiratory tract infection, Wheezing

INTRODUCTION

Wheezing related to respiratory infections is common in infancy and early child hood. In 1-3% of all infants these infections are severe enough to require hospitalization. There is evidence that most episodes of wheezing in early life are of viral origin and wheezing infants form a heterogeneous group with different phenotypes and outcomes. In early life approximately 20% of all children will suffer from wheezing illnesses. There is evidence that most episodes of wheezing in early life are due to viral in origin and most commonly diagnosed as acute

viral bronchiolitis or wheezy bronchitis infantile asthma and wheeze associated respiratory tract infection. Recent clinical trials have provided conflicting evidence regarding the benefit of pharmacological interventions. The role of bronchodilators is controversial. The efficacy of beta 2 agonists in bronchiolitis has found improvement in oxygen saturation and heart rate, but the results were not clinically significant.

Few beta2 agonists and epinephrine hydrochloride were found short term improvements in clinical score among children with mild and moderate severity.

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

Respiratory distress due to wheezing is often associated with respiratory tract infection in the first two years of life. It is difficult to make an exact diagnosis in the absence of viral cultures and pathologic findings and usually clinical diagnoses of bronchiolitis, wheezy bronchitis, wheeze associated respiratory infection, etc. are made. The main aim of the clinician in such a situation is to provide long lasting relief to respiratory distress by decreasing wheezing and improving air entry. The present study has attempted to verify the efficacy of bronchodilators in WRTI and compare the benefits of a beta-2 specific agonist with a combined alpha and beta (nonspecific) agonist among children presenting with a first or second episode of wheezing and respiratory distress in association with fever and/or coryza, without any family history of atopy or asthma.

Objectives of this study were to assess the efficacy of bronchodilators in wheeze associated respiratory infection and to compare the efficacy of a nebulized nonspecific adrenergic agonist 1- adrenaline with a nebulized beta-2 specific agonist salbutamol for the treatment of the wheeze associated respiratory tract infection.

METHODS

The study was conducted in children reporting to the Pediatric Department Government General Hospital in Kakinada. The study was done over a period of 6 months extending from January to June 2014. It was conducted in children between the ages of two months to two years attending the hospital with the clinical diagnosis of bronchiolitis, i.e. children with their first or second episode of respiratory distress associated with wheezing and clinical evidence of viral respiratory illness in the form of temperature 38°C and or coryza, were included. Study participants were grouped in Group A and Group B to study the results nebulizing agents.

Exclusion criteria

- 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.
- A history of prematurity or mechanical ventilation in the new-born period.

Children ill enough to require immediate admission, intravenous fluids and injectable drugs such as those with altered sensorium or dehydration, heart rate >180/minute, respiratory rate more than 100/minute or lethargy or

suspected to be in incipient respiratory failure. No child was included in the study twice.

RESULTS

Thirty children in the age group of two months to two years were included in the study. Out of thirty 16 (53.3%) were males and 14 (46.7%) were females. The mean age of the children was 10.6 months in Group A and 11 months in Group B.

Table 1: Distribution of study groups.

Age	Male	Female	Total
2 months to 1 year	12	10	22 (73.3%)
1 year to 2 years	4	4	8 (26.7%)
Total	16	14	30 (100%)

The post intervention values for adrenaline (Group A) and salbutamol (Group B) were compared. There is no added advantage of decreasing the respiratory rates, wheezing and retractions of one over the other groups. In the present study both adrenaline and salbutamol groups responded well to the nebulization therapy but when salbutamol is compared with the adrenaline in relieving the distress, wheezing and all there is no statistically significant benefit of one over the other.

Table 2: Parameters in Group A before and after nebulization.

Variables	Before treatment Mean (SD)	After treatment Mean (SD)	P value
RDAI	6.93 (1.67)	3.47 (1.06)	0.0001
HR	121 (13)	142 (20.4)	0.0017
RR	50.1 (16)	36.9 (7.93)	0.0081
SPO_2	91.3 (3.77)	96.8 (1.57)	0.0001

Table 3: Parameters in Group B before and after nebulization.

Variables	Before treatment Mean (SD)	After treatment Mean (SD)	P value
RDAI	7.67 (1.35)	3.53 (0.834)	0.0001
HR	122 (13.8)	148 (22.7)	0.0008
RR	54.7 (12.3)	40.2 (6.99)	0.0005
SPO_2	92.6 (4.05)	95.8 (2.62)	0.016

The oxygen saturation, measured by pulse oxymeter showed no significant difference between the mean values of the two groups at the start of the study (SPO₂-1) and ten minutes after the first dose (SPO₂-2). Subsequently, however, there was a significant improvement in the values recorded after the second and third doses (SPO₂-3 and SPO₂-4 respectively) of nebulization in both the groups. In the adrenaline group, it increased from a mean value of 91.3 to 96.8, while in

the salbutamol group it increased from 92.6 to 95.8, (p <0.001). Also, the mean oxygen saturation in the adrenaline group was significantly higher than that of the salbutamol group after the 2nd and 3rd doses.

Table 4: Comparison of serial recording of pulse Oximetry values of study participants.

Pulse Oximetry	SP02 - 1	SP02-2	SP02-3	SP02-4
Group A (n)	(15)	(15)	(15)	(15)
Mean±SD	91.3 (3.77)	93.1 (2.77)	95.3 (1.59)	96.8 (1.57)
Group B (n)	(15)	(15)	(15)	(15)
Mean±SD	92.6 (4.05)	93.7 (3.20)	94.8 (2.37)	95.87 (2.62)
P value	0.7918	0.1218	< 0.001	< 0.001

DISCUSSION

Primarily the study was focusing on wheezing in association with RTI, epidemiologically and clinically presumed to be of viral origin and attempts were made to exclude children with atopy.⁴

Use of Bronchodilators in bronchiolitis has been controversial. Many randomized control trials were done to evaluate the effect of salbutamol on bronchiolitis of which few have shown that bronchodilators have no effect.⁴ Recently few randomized trials evaluated the effect of nebulized epinephrine on bronchiolitis have shown significant clinical improvement with reductions in oxygen requirement respiratory rate and wheeze after nebulized epinephrine.⁵

Ray and Singh randomized 91 children, age 0 to 2 years, with "wheezing associated with respiratory tract infection to receive either epinephrine or salbutamol." In this study, patients treated with epinephrine had significantly greater improvement in mean RA02 and a significantly lower mean RDAI score and admission rate compared with those treated with salbutamol. By enrolling children up to 2 years of age and not excluding those with a history of wheezing, it is likely that Ray and Singh's study population included some children with asthma who may respond differently to epinephrine than do those with bronchiolitis. We attempted to exclude children with asthma by not enrolling children older than 2 years and/or those with a history of wheezing. Furthermore, since Ray and Singh's study subjects were severely ill (mean RDAI score, >13; mean RA02, 91%), their results may not be generalizable to a moderately ill population.⁶

In a more recent study Abual-ainine and Luyt failed to find a significant difference between the mean RDAI scores of infants treated with epinephrine and of those treated with an isotonic saline. However, because there were just 19 children in each study group and because they were treated with just one dose of epinephrine or placebo it is possible that a clinically significant difference might have been missed.⁷

Khashabi J, et al in Iran 2005 conducted a randomized clinical trial with 72 infants with moderately severe bronchiolitis were enrolled. 3 doses of epinephrine salbutamol and normal saline as a placebo were nebulized with oxygen at 20 minutes intervals. They concluded that both nebulized epinephrine and salbutamol improved oxygenation and decreased respiratory distress better than normal saline. L-epinephrine was more effective in relieving respiratory distress and improving oxygen saturation as well as the need for hospitalization than nebulized salbutamol.⁸

Menon et al also noted that infants receiving nebulized epinephrine had a significantly lower heart rate than did a similar group receiving nebulized salbutamol. Same results were found in our study.

The drug chosen for comparison with salbutamol in the present study (L- adrenaline) is also different from those used by most researchers in the past. The earliest study by Lenney and Milner using both nebulized adrenaline and nebulized phenylephrine, showed no advantage of, either drug as compared to placebo, in children with bronchiolitis. However, this study, suffered from many drawbacks. ¹⁰

Subsequently, Lowell et al used injectable epinephrine in wheezy infants and found it to be of benefit.¹¹ Several studies, thereafter, compared the effects of Beta-2 agonists such as salbutamol with normal saline in wheezy children and found salbutamol to be more advantageous. More recently, the focus has shifted back to the role of nonspecific adrenergic agonists for their possible effect on reduction of mucosal edema in addition to bronchodilator, thereby possibly providing greater relief than that given by Broncho-dilation alone. But earlier workers have used racemic adrenaline as the nonspecific adrenergic agent of choice. 12 Kristjansson and Wennegren compared racemic adrenaline with placebo for the treatment of bronchiolitis and concluded that racemic adrenaline was more efficacious than nebulized salbutamol.¹³ Similarly, Reijonen et al also found nebulized racemic epinephrine to be better than nebulized salbutamol for the treatment of bronchiolitis. 14

Thus, while several authors have shown that nonspecific adrenergic agonists are superior to beta-2 specific agonists, almost all of them used racemic adrenaline, the selection of which as the nonspecific agonist of choice is debatable.

There perhaps is no sound pharmacologic basis for the belief that racemic adrenaline is safer than L-adrenaline. Also, racemic adrenaline is not manufactured in India and is thus difficult to obtain and expensive, thus making L-adrenaline a more viable option. To the best of our knowledge there is only one earlier study that has

compared L-adrenaline with salbutamol in bronchiolitis. In this study, L-adrenaline was found to be more effective though the dose used by the authors (3 ml of 1 in 1000 solution per dose) is much higher than in the present study. In view of the reports of facial blanching by nebulized adrenaline reported by them, we decided to use a lower dose (same as the standard subcutaneous dose 0.1 ml/kg 1 in 10,000 solution) for nebulization and found it to be safe and effective.

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. In this study, even though the continued effect of the drugs was seen after the third dose, the maximal change in SPO₂ appeared in both groups after the second dose of 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 adrenergic agonist nebulization did not find it superior to a placebo. In the present study too, maximum effect of the drugs was observed after the second dose.

Analysis of results revealed that the children in both the groups had similar clinical profile at the time of inclusion in the study. After three doses of nebulization, both the adrenaline and salbutamol groups showed significant improvement in mean respiratory rate, RDAI score, clinical score as well as oxygen saturation.

However, these changes were not statistically significant correlation that one is more advantageous over the other 0.02). Thus, both drugs showed good efficacy with adrenaline being better than salbutamol.

CONCLUSION

It can be inferred that bronchodilators, both nebulized adrenalin and salbutamol are useful in relieving symptoms and improving oxygenation in wheezy infants with clinical diagnosis of WRTI, who present with respiratory distress and wheezing in association with coryza. No drug is said to be better over the other.

Larger, multi centric, double blinded randomized controlled trials are required to confirm these results.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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