

Randomised Trial: Adrenaline & Dexamethasone Vs. Adrenaline In Children With Bronchiolitis

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Abstract

Objective: To compare treatment outcomes with adrenaline and dexamethasone versus adrenaline alone in children with bronchiolitis.

Methods: It was a Randomized controlled trial parallel group ratio 1:1 with non-probability convenient sampling conducted at the Pediatrics Department, Benazir Bhutto Hospital, Rawalpindi from 1st September 2022 to 2nd March 2023. A total of 64 children were included. The clinical severity score was noted down at baseline. The patients were randomized into two groups with 32 in each group. Children in Group A received nebulized adrenaline and intramuscular dexamethasone and Group B received only nebulized adrenaline. Patients were assessed at every 30 minutes up to 120 minutes, then after every 4 hours & outcomes were assessed.

Results: The mean age of the patients in Group A versus B was 12.6±4.59 & 12.4±5.69 months respectively. In Group A versus B, the mean clinical severity score at the time of discharge was 3.3±0.88 & 4.4±0.61 with a p-value of 0.000, mean duration of hospital stay was 3.3±0.88 & 4.4±0.61 with a p-value of 0.000 and readmission at 7th day after initial treatment occurred in 3 (9.4%) & 9 (28.1%) patients with p value 0.05 respectively.

Conclusion: In children with bronchiolitis, a combination of adrenaline and dexamethasone was significantly associated with lower clinical severity scores, shorter duration of hospitalization and lesser rates of readmission compared to adrenaline alone.

Keywords: Adrenaline, Bronchiolitis, Dexamethasone.

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1. Introduction

Bronchiolitis is the most common respiratory tract infection in infants caused by viruses. Causative organisms include the respiratory syncytial virus accounts for 50 – 80 % of cases followed by the rhinovirus, influenza and para influenza virus. It is a major cause of hospitalization among infants.^{1,2} Its prevalence during the first 12 months and from 12-24 months of age varies from 18-32% and 9-17% respectively. Globally each year around 3% of otherwise healthy infants got hospitalized with a mortality of around 1-1.5%.³ Epidemics occur in winter with a peak from September to March. After getting an infection there is an acute onset of viral prodrome in the form of low-grade fever, cough and rhinorrhea followed by worsening of cough, fast breathing, lower chest indrawings and audible wheeze. There may be irritability, vomiting and poor feeding.^{4,5}

No definitive treatment exists for bronchiolitis. Most infants recover in 3 to 5 days but for some, symptoms worsen or persistent for a few days to a week time.^{6,7} Average hospital stay is from 3-5 days but it's prolonged in infants with severe disease and comorbidities. Heated Humidified oxygen is used for

sick hypoxemic hospitalized babies with pulse oximetry.⁸ Paediatricians use bronchodilators like beta 2 agonists, adrenaline, steroids, chest physiotherapy and antibiotics for superimposed bacterial infections.⁹ Researches were done in past on the role of bronchodilators but no consistent benefit was seen. It was observed in asthma management that synergy exists between bronchodilators and steroids and by using both, anti-inflammatory response is enhanced. Bronchodilators were found to be steroid-sparing and increase steroid efficacy.^{10,11}

Hartling et al carried out a study on the role of nebulized adrenaline in bronchiolitis and found that adrenaline decreases admission rate in infants and when combined with steroids results in a significant reduction in hospital admission at day 7 with no adverse effects.¹²

Faiza Yasin et al researched the role of adrenaline in bronchiolitis in infants and found that adrenaline nebulization results in a significant reduction in hospital stay.¹³

The rationale of the study is that it will give an idea about a better treatment strategy with a decreased hospitalization rate that would result in quick resolution of symptoms, improve respiratory distress earlier and decrease the duration of stay at the hospital.

That would not only benefit the family but the quick resolution of symptoms will improve the morbidity of the child and will help in reducing the mental stress of the parents. Most of the results of research conducted so far showed controversial results. Also scarcity of local literature exists on this topic.

The study was planned to compare treatment outcomes with adrenaline nebulization and intramuscular dexamethasone versus adrenaline alone in children with bronchiolitis.

2. Materials & Methods

It was a Randomized controlled trial parallel group ratio of 1:1 with non-probability convenient sampling conducted at the Pediatrics Department, Benazir Bhutto Hospital, Rawalpindi. The study was conducted from 1st September 2022 to 2nd March 2023. A total of 64 children were enrolled in the study. The sample size was calculated by using the WHO formula for the sample size for two population means with the following values: Level of significance = 5%. Power of test = 80%. The mean reduction in the clinical severity score by a value of 2.30 ± 0.69 in the adrenaline and dexamethasone group. Mean reduction in the clinical severity score in the adrenaline alone group by a value of 1.75 ± 0.86 . Pooled SD = 0.78. Children were divided into two equal groups. Children of age 2 months to 2 years of both genders fulfilling criteria of acute bronchiolitis as per operational definition were included in the study. Children with history of inhaled or systemic corticosteroids given to the infants over last 4 weeks, cardiopulmonary condition, history of a continuous (>4 weeks) or severe respiratory disease, children with congenital abnormalities, history of recurrent wheezing, history of asthma, history of previous bronchodilator use, infants in severe distress (defined as a pulse rate >200 beats per minute, a respiratory rate >80 breaths per minute, or an RDAI score >15)⁹ or with profound lethargy, and infants who had been exposed to varicella within the preceding 3 weeks were excluded from study. Acute bronchiolitis in an infant is characterized by an episode of wheezing, respiratory distress and signs of respiratory infection. It was labelled as mild, moderate and severe according to the Wang bronchiolitis clinical severity score.¹¹ The primary outcome was the mean reduction in the clinical severity score as assessed by Wang bronchiolitis clinical severity score. Wheezing,

respiratory rate, chest retraction, and general state are the four components of the WRS. With the exception of the overall state, which received a score of zero for normal or three for irritability or lethargy, each clinical indicator was given a number between 0 and 3. The overall score could be between 0 and 12. The secondary outcome were; 1. The mean duration of hospital stay (in hours)-it was considered starting from the enrollment point and till the time that an infant was considered for discharge if the child fulfilled one of the following criteria: If no supplemental oxygen was given for 10 hours, An oxygen saturation of >90% on room air, Wang clinical severity score of <5, Adequate feeding i.e. taking 75% of the normal intake, 2. Duration (in hours) of supplemental oxygen. 3. Admission rate on the 7th day after initiation of the treatment. Approval was taken from the Ethical Review Board of the institution. Children were enrolled in the study after taking written informed consent from parents. Demographic details, clinical history and physical examination of all children were taken and findings were noted down on proforma. Bronchiolitis Clinical severity score of all patients was noted down at baseline. The patients were randomly divided into two groups with 32 in each group. To ensure concealment of the treatment assignment, randomization was carried out independently of the investigator by another doctor who was not part of the study and the nebulization solution was labelled with a unique colour code as allotted by that doctor of which the researcher was not aware. Children in Group A received adrenaline and dexamethasone and children in Group B received only adrenaline. In Group A, children received a single dose of intramuscular dexamethasone injection; 0.6 mg/kg (max 10mg) and nebulized adrenaline and in Group B, children received nebulized adrenaline, 0.5 ml in 1:1000 solutions (undiluted) per treatment every 6 hourly till discharge. Both groups received nebulization for a maximum of 4 times over a period of 2 hours and the interval between the next nebulization was at least 30 minutes. Supportive treatment was given to all infants irrespective of their group according to the recommended guidelines which are elevation of the head end of the bed, if oxygen saturation drops to <94% then provision of supplemental oxygen, if fever was present then acetaminophen was given and a nasal lavage was done with sterile saline before and after giving the nebulized solutions. If at any

stage during the trial, the clinical condition of the child worsened, then that child was excluded from the study to escalate further care. Patients were assessed every 30 minutes up to 120 minutes, then every 4 hours for vital status, oxygen saturation, parenteral fluids and requirement of additional nebulization. Reduction in the severity score was observed as per operational definition and the scores were compared to that at baseline and other secondary outcomes were assessed too. All findings were noted down on a predesigned proforma and were subjected to statistical analysis. Data was analyzed using SPSS version 25.0. Quantitative data such as age, clinical severity score at baseline, after 20 minutes of nebulization and at discharge, oxygen saturation and duration of hospital stay (in hours) were presented as mean and standard deviation. Qualitative data such as gender, severity of bronchiolitis, admission rate within 7 days of first discharge and need of oxygen supplementation were presented as frequency and percentages. Data was stratified for mean clinical severity score and mean duration of hospital stay concerning age, gender and severity of bronchiolitis. Post-stratification t-test was applied and a p value of ≤ 0.05 was considered as significant. Data was stratified for frequency of admission on the 7th day after first discharge concerning age, gender and severity of bronchiolitis. Post-stratification chi-square test was applied and a p-value of ≤ 0.05 was considered significant. Comparison of outcome i.e. mean reduction in clinical severity score and mean duration of hospital stay between the two groups was made by Independent t-test and a p-value of ≤ 0.05 was considered as significant. The Chi-square test was used to compare the rates of admission on 7th day between the two groups and a p-value of ≤ 0.05 was considered significant.

3. Results

A total of 64 children were included in the study. The mean age of the children in Adrenaline plus dexamethasone group A and Adrenaline-only group B was 12.6 ± 4.59 and 12.4 ± 5.69 months respectively. Males and females were 35(54.7%) and 29(45.3%) respectively. The mean bronchiolitis clinical severity score at baseline, after 20 minutes of nebulization and at the time of discharge is shown in Table 1.

The mean oxygen saturation in Group A and Group B was 94 ± 3.66 and 93 ± 3.98 % respectively. The mean duration of hospital stay in Group A was 3.3 ± 0.88 and in Group B it was 4.4 ± 0.61 . The comparison of both groups revealed that the difference was statistically significant with $t = -4.088$ and a value of less than 0.05. The severity of bronchiolitis is shown in Figure 1. The Frequency of patients according to the need for supplemental oxygen in both groups was 9 (28%) & 10 (31%) in Groups A & B respectively.

Table 1: Comparison of Mean Bronchiolitis Clinical Severity at Baseline, After 20 Minutes Of Nebulization And At Time Of Discharge In Both Groups:

Duration	Group	Mean $\pm$ Standard Deviation	T-Test	p-value
At baseline	A	8.3 ± 1.69	-0.745	0.459
	B	8.9 ± 1.65		
After 20 minutes of nebulization	A	5.7 ± 1.03	-2.863	0.006
	B	6.6 ± 1.54		
At the time of discharge	A	3.3 ± 0.88	-6.093	<0.05
	B	4.4 ± 0.61		

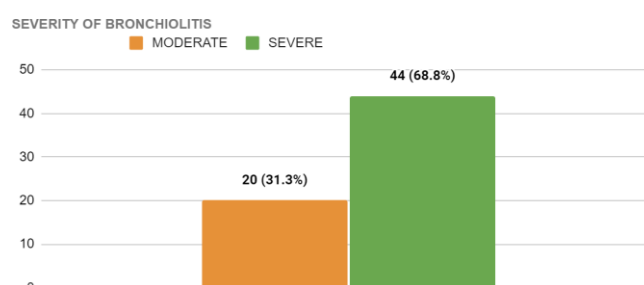


Figure 1: Severity Of Bronchiolitis Among Patients

Readmission on the 7th day after initial treatment in both groups is shown in Figure 2 and a comparison of both groups revealed that there was a significant difference between the two groups as indicated by a p-value of 0.05.

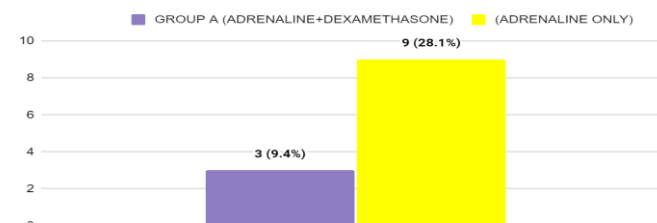


Figure 2: Comparison Of Frequency Of Readmission On 7TH Day After First Treatment In Both Groups: P Value<0.05

Stratification of mean bronchiolitis clinical severity score at discharge in both groups concerning age, gender, and severity is shown in Table 2. Stratification of the mean duration of hospital stay in both groups concerning age, gender, and bronchiolitis severity is shown in Table 3. Stratification of frequency of

readmission on the 7th day after the first treatment concerning age, gender, and severity of bronchiolitis is shown in Table 4. No side effects of drugs were observed in any patient. No children were excluded from the study.

Table 2: Stratification of Mean Bronchiolitis Clinical Severity at Discharge in Both Groups Concerning Age, Gender, severity

Variable		N	Mean $\pm$ Standard Deviation	t-Test Value	p-value
Age	≤ 12 Months	35	3.9 $\pm$ 0.95	0.004	0.997
	>12 Months	29	3.8 $\pm$ 0.96		
Gender	Males	35	3.7 $\pm$ 0.95	-0.785	0.436
	Females	29	3.9 $\pm$ 0.96		
Bronchiolitis Severity	Moderate	20	3.5 $\pm$ 1.1	-1.897	0.063
	Severe	44	4 $\pm$ 0.85		

Table 3: Stratification of Mean Duration Of Hospital Stay in Both Groups concerning Age, Gender, Bronchiolitis Severity

Variable		N	Mean $\pm$ Standard Deviation	t-Test Value	P-Value
Age	≤ 12 Months	35	3 $\pm$ 0.74	-0.836	0.406
	>12 Months	29	3.2 $\pm$ 0.61		
Gender	Male	35	3 $\pm$ 0.68	-0.468	0.642
	Female	29	3.1 $\pm$ 0.69		
Bronchiolitis Severity	Moderate	20	2.7 $\pm$ 0.47	-3.349	0.001
	Severe	44	3.3 $\pm$ 0.69		

Table 4: Stratification Of Frequency Of Readmission At 7TH Days After First Treatment Concerning Age, Gender, Severity Of Bronchiolitis

Readmission On 7 th Day After The First Treatment	Age Group		Total	P VALUE
	≤12 Months	>12months		
Yes	5 (7.8%)	7 (10.9%)	12 (18.7%)	0.315
No	30 (46.9%)	22 (34.4%)	52 (81.3%)	
Gender				
	Male	Female		0.778
Yes	7 (10.9%)	5 (7.8%)	12 (18.7%)	
No	28 (43.8%)	24 (37.5%)	52 (81.3%)	
Severity				0.01
	Moderate	Severe		
Yes	0 (0%)	12 (18.7%)	12 (18.7%)	
No	20 (31.3%)	32(50%)	52 (81.3%)	
Total	20 (31.3%)	44 (68.7%)	64 (100%)	

4. Discussion

The current study revealed that in children with bronchiolitis, there was a significant difference between children who had adrenaline plus dexamethasone versus adrenaline alone in terms of bronchiolitis clinical severity score after 20 minutes of nebulization ($p=0.006$)

and at the time of discharge ($p<0.05$). Furthermore, the two groups differed significantly in terms of mean duration of hospital stay ($p<0.05$) and the rate of readmission at 7th after initiation of first treatment ($p=0.05$). Duration of hospital stay and the frequency of

readmission were significantly associated with the severity of the bronchiolitis.

Gohil JR et al researched the role of adrenaline and steroid and adrenaline alone in bronchiolitis in the paediatric population. They enrolled 100 patients. Results found that a decrease in clinical severity was seen in the group that received adrenaline and dexamethasone versus the group that received adrenaline alone with 2.30 ± 0.68 and 1.75 ± 0.86 respectively. The mean duration of hospitalization was also decreased in the group that received adrenaline and steroids versus adrenaline alone with 4.78 ± 1.83 and 4.93 ± 1.95 respectively with a difference of stay was 1.02 ± 0.58 . There was a 22% reduction in hospital stays with the adrenaline and steroid group. They concluded that combining adrenaline and steroids has a good response in decreasing disease severity and duration of hospitalization. These are all consistent with our study results.¹⁴

Our study results found no side effects related to adrenaline & steroids. Systemic review and meta-analysis conducted by Fernandes RM et al on acute respiratory conditions and the safety of steroids found no side effects related to steroids in acute conditions for short duration either in oral or inhaled form.¹⁵

Plint AC et al conducted a double-blind multicenter placebo control trial on the role of adrenaline and steroids. They included 800 paediatric patients presenting with bronchiolitis. Results found that infants who received steroids and adrenaline were significantly less likely to be hospitalized on day 7 when compared to Adrenaline alone and placebo with no significant side effects observed. These are all consistent with our study results.¹⁶

Verma et al conducted prospective research on the role of adrenaline and steroids and adrenaline alone and included 120 children presenting with bronchiolitis. The mean RDAI score decreased significantly in the group that received adrenaline and steroids compared to the other group 2.37 ± 0.80 and 26.4% decrease in hospitalization when compared to the other group. They concluded that adrenaline and dexamethasone have a significant role in decreasing disease severity and hospitalization with no side effects. These are all consistent with our study results.¹⁷

Gelbart B et al carried out multicenter randomized control trials on the role of steroids and adrenaline. They included 210 children. They found that combination therapy of adrenaline and steroids has a significant role

in decreasing severe bronchiolitis and patient duration on CPAP and mechanical ventilation was decreased with no significant side effects. These are consistent with our study results.¹⁸

Bawazeer et al carried out a double-blind trial on the effect of steroids and adrenaline on bronchiolitis. They included children presenting with moderate to severe bronchiolitis and assessed primary outcomes (hospitalization rates within 7 days of treatment) and secondary outcomes (respiratory distress, changes in heart and respiratory rate and fluctuations in oxygen saturation). Results found that treatment with adrenaline and dexamethasone resulted in a significant difference in hospitalization rate with a significant p-value of less than 0.005. The authors revealed that in terms of the rate of admission on the 7th day after receiving the first treatment, the children in the combination group had an admission rate of 31.1% compared to 30.77% in the adrenaline group alone with a p-value equal to 0.926. These findings are inconsistent with our study results in that our study showed that there was a significant difference between the two groups and lesser rates were observed in the combination group.¹⁹

The current study findings support the use of a combination of adrenaline and dexamethasone in children with bronchiolitis. This combination resulted in quick resolution of symptoms, improved respiratory distress earlier decreased the duration of stay at the hospital and also reduced the rates of readmission, thus improving morbidity and decreasing anxiety of the parents. Further studies must be carried out on a larger sample size for validation of current study findings.

The current study had certain limitations. Firstly, the sample size was small and the study was carried out at a single centre so there is an issue of generalization of the results. Secondly, a comparison with other available options was not made so the findings cannot be validated when other treatment options are used.

5. Conclusion

In children with bronchiolitis, a combination of adrenaline and dexamethasone was significantly associated with lower clinical severity scores, shorter duration of hospitalization and lesser rates of readmission compared to adrenaline alone.

Institutional Review Board Approval

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Contributions:

S.C, I.L, S.T.M - Conception of study

- Experimentation/Study Conduction

J.N, M.M - Analysis/Interpretation/Discussion

S.T.M - Manuscript Writing

R.A, J.N, M.M - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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