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ORIGINAL ARTICLE

Comparison of Effectiveness of Nebulized N-Acetylcysteine Solution (Mucolytic Therapy), Nebulized Salbutamol and Nebulized Ipratropium Bromide In Treatment of Children with Acute Bronchiolitis

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ABSTRACT

Background: Bronchiolitis is a viral mediated disease that results in acute inflammation in the lower respiratory tract. It occurs in infants and children under 2 years of age. The vast majority of infants' experience at least 01 episode of bronchiolitis and 2-3% of all infants can be hospitalized for bronchiolitis in the 1st year. With an increasing rate having risen by an average of 1.8% annually in European country and a small percentage even need critical care. Children who are hospitalized for bronchiolitis currently only receive fluid replacement, additional oxygen and respiratory support.

Bronchiolitis is most common motivator for hospital admissions in many nations. Respiratory syncytial virus (RSV) is most common virus causes bronchiolitis, and also causes infections during the winter months.

Objective: To determine the comparison of effectiveness of nebulized N-acetylcysteine solution (mucolytic therapy), nebulized salbutamol and nebulized ipratropium bromide in treatment of children with acute bronchiolitis at a tertiary care hospital.

Materials & Methods: All patients who fulfilled the inclusion criteria and visited to Baqai Medical University Hospital, Karachi from April 17, 2019 to October 16, 2019 were included in this Prospective Randomized Control Trial (lottery method). Informed consent was taken after explaining the procedure, risks and advantages of the study.

Children from either gender having provisional diagnosis of acute bronchiolitis between 2 to 24 months of age were included and divided in three groups in our study. Each group obtained three treatments every day, introduced at intervals of eight hours for three days. Patients had been tested on admission, at 8 hours and every morning for severity of disease. For assessing improvement, scientific severity score turned into used to peer the effectiveness of nebulized N-acetylcysteine solution (mucolytic therapy), nebulized salbutamol and nebulized ipratropium bromide in bronchiolitis. All the collected data were entered into the proforma attached at the end and used electronically for research purpose.

Results: 81 study cases of these, 44 (54.3%) were males while 37 (45.7%) were females. Our study cases mean age in Nebulized N-acetylcysteine was 9.4±6.3, in Nebulized Salbutamol and Ipratropium Bromide was 10.8±6.7 and 12.0±6.6 months, respectively. In group wise comparison of clinical severity score at baseline, 8, 24 and 72 hours, highly significant difference was found among the group at baseline, 8, 24 and 72 hours i.e., $P \leq (0.05)$ within the groups while on the other hand non-significant difference i.e., (0.633) was showed between the group at baseline among nebulized N-acetylcysteine, nebulized salbutamol and ipratropium bromide group respectively.

Conclusion: In the lights of our findings, it is to be concluded that nebulized salbutamol was more effective in improvement of clinical severity score with shorter duration of hospital stay. Furthermore, it is to be concluded that there is a need to have further studies with larger sample size in different centers in Pakistan to validate the findings of current study.

Keywords: N-acetylcysteine Solution, Nebulized Salbutamol, Nebulized Ipratropium Bromide, Acute Bronchiolitis

INTRODUCTION

Acute bronchiolitis is one of the most common hospitalizations in children, with 20% of hospitalizations for children under one year of age [6]. Bronchiolitis usually affects infants under two years of age and its prevalent in children. It increases between December and March [7].

The main cause of global bronchiolitis is respiratory syncytial viruses and in winter season can cause lower respiratory infections up to 70 or 80% [8]. Other viruses such as HIV and adenovirus, type 3 virus, influenza and rhinovirus can also cause bronchiolitis, which is not different from RSV [8,9].

A large UK study found that the admission rate for all children less than 12 months of bronchiolitis was 24.2 per 1,000 [10].

Bronchiolitis is usually seasonal, with recurrent infections occurring during the winter months [11]. For the RSV, the same seasonal pattern is observed worldwide, with the majority of cases occurring in the northern hemisphere between October and May [11].

N-acetylcysteine is an antioxidant that increases intracellular glutathione at the cellular level. Disulfide bonds are divided into two sulfite groups. This process results in the destruction of mucous proteins in the mucous membrane of the lung, which reduces the length of the chain and the rest of the mucus. NAC has been studied in the treatment of various pathological conditions, including cystic fibrosis, chronic bronchiolitis, and non-systemic fibrosis. Bronchiolitis, other idiopathic lung fibrosis, as well as many other complications [12,13].

Salbutamol is an agronomy of adreno-beta receptors. At a therapeutic level, it acts on beta-2 adrenoreceptors, which provide bronchial muscles. With its onset (within 5 minutes) it is serious for the management and prevention of seizures for patients with asthma and bronchiolitis. Although bronchodilators have been used for decades, there is no consensus in their favor [14].

Ipratropium bromide has a relaxing effect on smooth bronchial muscle due to its effect on muscarinic receptors. The onset of ipratropium is slower than beta-2 stimuli; however, the duration of its factors may be slightly longer than those factors [15].

There was a paucity of literature available in Pakistan to assess the effectiveness of nebulized N-acetylcysteine in patients with bronchiolitis instead bronchodilators. Therefore, it has great importance to know the efficacy and safety of the drug in children with bronchiolitis. The proposed study assesses the effectiveness of nebulized N-acetylcysteine in children with bronchiolitis in comparison with nebulized salbutamol and ipratropium bromide for the further strategies to decrease the clinical severity and duration of hospital stays.

MATERIAL & METHODS

All patients who fulfilled the inclusion criteria and visited to Baqai Medical University Hospital, Karachi from April 17, 2019 to October

16, 2019 were included in this Prospective Randomized Control Trial (lottery method). Informed consent was taken after explaining the procedure, risks and advantages of the study. The total sample size of 81 patients, approved from ethical review committee was equally divided into three groups i.e., Nebulized N-acetylcysteine, Nebulized Salbutamol and Ipratropium Bromide.

The sample size was calculated via;

Formula $n= z^2p (1-P) /d^2$

Children from either gender aged between 2 to 24 months were made part of the study. All patients with provisional diagnosis of acute bronchiolitis with upper respiratory tract infection followed by wheezing on auscultation and a clinical severity score of > 4, on presentation were included.

Parents who did not give informed consent were excluded. Any patient who was found to have underlying bronco-pulmonary dysplasia, pneumonia, chronic lung disease, neuro-muscular impairment, immunodeficiency or congenital heart disease was also excluded from the study.

Clinical Severity Score consisted of respiratory rate, wheeze, cyanosis, and accessory respiratory muscle utilization, with scores for each sign ranging from 0 to 3, Tal et al [16]. The score was in the range 0–12, with a higher score indicating more respiratory distress. All measurements were taken when the child was awake and not crying.

Patients were randomly assigned to one of the three groups: group-1 received 20 mg N-acetylcysteine in 3 ml of 0.9% saline in nebulized aerolized form; group-2 received inhalation of 2.5 mg salbutamol in 3 ml of 0.9% saline solution as a nebulized Salbutamol and group 3 received inhalation of 250 ug ipratropium bromide in 3 ml of 0.9% saline solution as a nebulized Salbutamol.

SPSS version 23.0 was used for data analysis. Frequencies and percentages were computed for categorical variables while Mean±SD were calculated for quantitative variables. Anova was applied to compare the clinical severity score among groups using P ≤ 0.05 as significant.

RESULTS

In this study, the total of 81 patients 27 in each group as Nebulized N-acetylcysteine, Nebulized Salbutamol and Ipratropium Bromide had taken to determine the effects on clinical severity score among them 15 (55.6%) male and 12 (44.4%) females was enrolled in Nebulized N-acetylcysteine, 14 (51.9%) male and 13 (48.1%) females was enrolled in Nebulized Salbutamol while 15 (55.6%) male and 12 (44.4%) females were included in Ipratropium Bromide group. Average age in Nebulized N-acetylcysteine was 9.4±6.3, Nebulized Salbutamol 10.8±6.7 and Ipratropium Bromide 12.0±6.6 months, respectively. Average duration of hospital stay in Nebulized N-acetylcysteine was 4.8±1.0, Nebulized Salbutamol 4.1±0.8 and Ipratropium Bromide 5.7±1.4 days, respectively. Average duration of fever in Nebulized N-acetylcysteine was 4.2±1.2, Nebulized Salbutamol 3.4±1.3 and Ipratropium Bromide 4.4±1.0 days, respectively. In distribution of distress 81 (100%) patients having distress that were enrolled in all groups as shown in **Table 1**.

Table 1: Age, Duration of Hospital Stay & Gender among Groups

Group	Nebulized N-Acetylcysteine	Nebulized Salbutamol	Ipratropium Bromide	P-Value (b/w group)
Age	9.4±6.3	10.8±6.7	12.0±6.6	0.347
Duration of Hospital Stay	4.8±1.0	4.1±0.8	5.7±1.4	0.0001
Gender (Male)	15 (55.6%)	14 (51.9%)	15 (55.6%)	0.951
Gender (Female)	12 (44.4%)	13 (48.1%)	12 (44.4%)	

In group wise distribution of respiratory rate score at baseline, 8, 24 and 72 hours, highly significant difference was found within the group at baseline, 8, 24 and 72 hours i.e., P ≤ (0.0001) among nebulized N-acetylcysteine, nebulized salbutamol and ipratropium bromide group respectively, as shown in **Table 2.**

In group wise comparison of clinical severity score at baseline, 8, 24 and 72 hours, highly significant difference was found among the group at 8, 24 and 72 hours i.e., P ≤ (0.0001) within the groups & between the groups while on the other hand non-significant difference i.e., (0.633) was showed between the group at baseline among nebulized N-acetylcysteine, nebulized salbutamol and ipratropium bromide group respectively, as shown in **Table 3.**

Table 2: Respiratory Rate at baseline, 8, 24 & 72 hours among Groups

Group	Nebulized N-Acetylcysteine	Nebulized Salbutamol	Ipratropium Bromide	P-Value (b/w group)
At baseline	63.7±13.4	60.3±9.4	58.3±9.6	0.193
At 8 hours	63.0±10.1	54.4±12.2	55.3±10.3	0.008
At 24 hours	46.8±9.2	43.0±9.3	48.2±9.5	0.112
At 72 hours	34.5±5.4	32.3±6.0	36.1±6.2	0.064
P-Value (within group)	0.0001	0.0001	0.0001	

Table 3: Clinical Severity Score at baseline, 8, 24 & 72 hours among Groups

Group	Nebulized N-Acetylcysteine	Nebulized Salbutamol	Ipratropium Bromide	P-Value (b/w group)
At baseline	8.3±1.0	8.1±1.1	8.2±1.0	0.633
At 8 hours	6.4±1.5	4.9±1.3	6.5±1.4	0.0001
At 24 hours	4.9±1.5	3.7±1.7	5.7±1.8	0.0001
At 72 hours	2.9±1.0	1.6±1.2	3.9±1.3	0.0001
P-Value (within group)	0.0001	0.0001	0.0001	

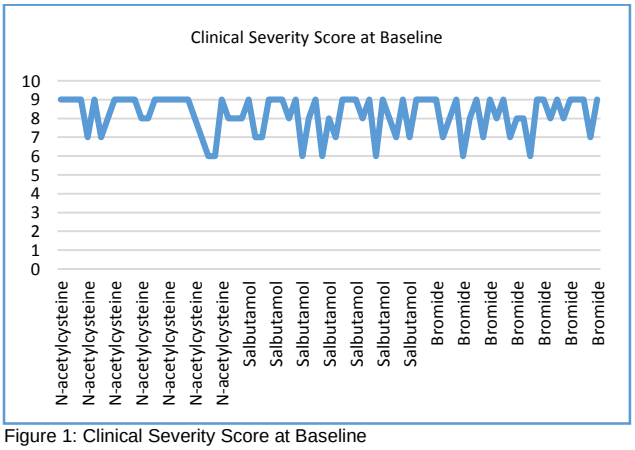

Figure 1: Clinical Severity Score at Baseline

Clinical severity score at baseline among patients with nebulized n-acetylcysteine, nebulized salbutamol and ipratropium bromide as shown in Figure 1.

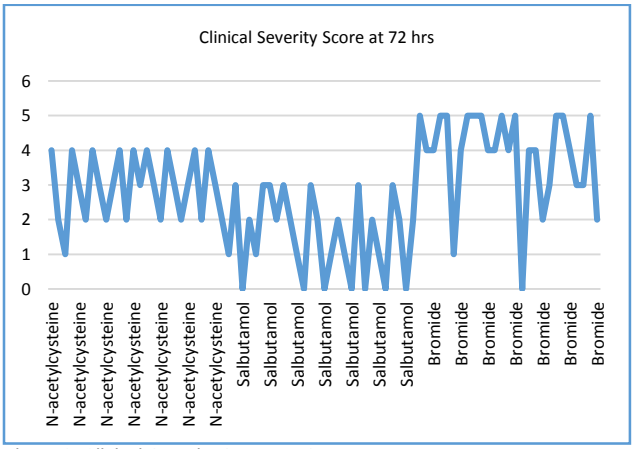

Figure 2: Clinical Severity Score at 72 Hours

Clinical severity score at 72 hours among patients with nebulized n-acetylcysteine, nebulized salbutamol and ipratropium bromide as shown in Figure 2.

DISCUSSION

Bronchiolitis is an acute inflammation of children's lower respiratory tract caused by viruses, cough, flu and distress are the main symptoms. A large percentage of infants will experience at least 01 case of bronchiolitis.

Bronchiolitis is one of the most common causes of hospitalized babies in many nations, and is difficult for the economy, the region and for pediatric personnel. RSV is a common virus that causes bronchiolitis and occurs in winter season [17].

Acute bronchiolitis is often a viral infection, and RSV causes more than 50% of cases. Other major viral causes include adenovirus, influenza and parainfluenza viruses, human metapneumovirus, and nasal (rhino) virus. Sometimes Mycoplasma pneumonia may be associated with bronchiolitis.

RSV is highly contagious, with a 98% infection in first stage of infection. This reduces the rate of infection to 75% rate for second infection. The spread usually requires close contact and effects of mucus and nasal infections. Therefore, very isolated precautions can be effective in reducing the number of infections [18].

Some children, especially those with risk factors, have a more severe course of bronchiolitis. The most common medical reason for including children in intensive care units (ICUs) is bronchiolitis, ventilation, fluid balance and general support. This can be a particular challenge for the ICU, which does not have a special children's unit.

Acute viral bronchiolitis is one of most common medical emergencies in childhood & clinics providing care for critically ill children will continue to do so. The main pillars of viral bronchiolitis treatment are oxygen and fluid, and "minimal treatment" is generally recommended. Nebulized epinephrine is common in some countries, but there is little evidence. Inhalation of hypertonic saline solution has recently been offered as a voluntary treatment. If medical treatment cannot stabilize the baby, severe ventilation is needed to prevent and support breathing problems. Appropriate treatment methods are needed that apply to all levels of the treatment chain & reflect local considerations and conditions [19].

Our study included only 81 babies with bronchiolitis who met the criteria of our study. Of these cases, 44 (54.3%) were boys & 37 (45.7%) were girls. Various studies have documented male sex prevalence with bronchiolitis. Arif et al [17] from Lahore showed 68% of males have acute bronchiolitis which is similar to the results of our study. Other studies by Ahmad and others from Faisalabad [21] indicated that the male to female ratio was 1.4:1 indicating male superiority. These findings are consistent with the results of our study, by Ahmad et al [18]. Jacobs and others [22] reported that 69% of boys have acute bronchiolitis, which is better than male sex. This is consistent with our findings. However, Naz and others from Lahore [15] noted that 40% of boys had acute bronchiolitis and 60% of girls, completely different from the results of our study.

The mean age in our study in group A: 9.4±6.3 months for Nebulized N-acetylcysteine, mean age of group B: Nebulized Salbutamol was 10.8±6.7 months and group C: ipratropium bromide, mean age was 12.0±6.6 months. Our study results show that most cases in our study were < 1 year. Arif et al. from Lahore [20] noted that the average age of children with bronchiolitis was 5.43±9.44 months, which is close to the results of our study. Ahmad and others from Faisalabad [21] reported that the average age was 7.6±4.7 months. Jacobs et al. [19] reported that the mean age was 6.0±3.9 months, which is in line to our results. Naz et al [15] have noted that the average age is 3 months and that this is slightly less than the expected length of the results of our study.

In this study, the majority of mothers of children were illiterate, i.e. 58 (71.7%) mothers. Ahmad et al [21] reported similar results from Faisalabad.

In the present study, the average hospital stay for Nebulized N-acetylcysteine was 4.8±1.0 days, Nebulized Salbutamol was 4.1±0.8, and Ipratropium Bromide 5.7±1.4 days, respectively. Flores et al [23] reported that 5.4±2.1 days in hospital with acute bronchiolitis were in the immediate vicinity of the results of this study. Naz et al [15] reported 4.67±2.2 days, making the hospitalization equivalent to the duration of the study results.

In current study, mean clinical severity score at 8 hours, in Nebulized N-acetylcysteine, Nebulized Salbutamol and Ipratropium Bromide were 6.4±1.5, 4.9±1.3 and 6.5±1.4, respectively. Mean clinical severity score at 24 hours, in Nebulized N-acetylcysteine, Nebulized Salbutamol and Ipratropium Bromide were 4.9±1.5, 3.7±1.7 and 5.7±1.8, respectively. Mean clinical severity score at 72 hours, in Nebulized N-acetylcysteine, Nebulized Salbutamol and Ipratropium Bromide were 2.9±1.0, 1.6±1.2 and 3.9±1.3, respectively. Naz et al [15] also reported mean score in group A (treated with N – acetylcysteine) as 0.88±1.08 while in group B treated with salbutamol as1.90 ± 1.32. Ejaz et al. [24] reported a clinical severity score of 5.68±0.73, consistent with the results of our study. Jacobs et al. [22] reported an average score of 5.7±1.8.

Ipratropium bromide is an anticholinergic bronchodilator with no superior efficacy for RSV Bronchiolitis. Treatment of Bronchiolitis is mainly supportive and the role for bronchodilator is still controversial in the latest guideline release by the American Academy of pediatrics.

CONCLUSION

In the lights of our findings, it is to be concluded that nebulized salbutamol was more effective in improvement of clinical severity score with shorter duration of hospital stay. Furthermore, it is to be concluded that there is a need to conduct more studies with larger sample size in different centers in Pakistan to validate the findings of current study.

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