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Evaluation of Role of Ambroxol in Treatment of Bronchiolitis

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ABSTRACT

Background: Bronchiolitis is the most common reason for hospital admission in infants, accounting for 20% of hospitalization at < 1 year of age. The recently discovered human meta pneumo-virus and other viruses like adenovirus, parainfluenza virus type-3, influenza virus and rhinovirus also cause bronchiolitis that is indistinguishable from respiratory syncytial virus (RSV) disease. It is more common in males, those who are not breast fed and living in crowded conditions.

Objective: The aim of the work was to assess role of Ambroxol inhalation in treatment of Bronchiolitis.

Patients and Methods: This randomized controlled clinical trial included a total of included 40 children with bronchiolitis, attending at Department of Pediatrics, Sohag General Hospital. They were randomly divided into two groups, the **control group** consisted of 20 cases who were given bronchodilators, inhaled or systemic steroids, antibiotics if needed, or supportive measures and oxygen supplementation if needed. The **intervention group** consisted of 20 cases who were treated with Ambroxol inhalation in addition to supportive measures mentioned above.

Results: There was insignificant differences between two groups regarding the need of oxygen and duration of oxygen therapy (p-value 0.337, 0.536 respectively). In the current study, we found that there was insignificant differences between two groups regarding degree of RD on admission but after treatment there was significant improvement in interventional group with p-value <0.001. In the current study, we found that there was significant difference between two groups regarding length of hospital stay as in interventional group was lower than control (p-value 0.002).

Conclusion: It could be concluded that Ambroxol gives a good improvement in cases with bronchiolitis and decreases hospital stay. Furthermore, Ambroxol is safe, cheap and easy to administer.

Keywords: Coronary artery bypass graft, chronic obstructive pulmonary disease, positive end expiratory pressure

INTRODUCTION

Bronchiolitis is a disorder most commonly caused in infants by viral lower respiratory tract infection (LRTI). It is the most common lower respiratory infection in this age group. It is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm. Signs and symptoms are typically rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring [(1)].

Many viruses cause the same constellation of symptoms and signs. The most common etiology is the respiratory syncytial virus (RSV), with the highest incidence of RSV infection occurring between December and March [(2)]. Ninety percent of children are infected with RSV in the first 2 years of life and up to 40% of them will have lower respiratory infection [(3)].

The cost of hospitalization for bronchiolitis in children less than 1 year old is estimated to be more than 700 million dollars per year. Several studies have shown a wide variation in how bronchiolitis is diagnosed and treated [(4)].

Ambroxol is a secretolytic, mucokinetic and stimulator for synthesis and release of surfactant by type II pneumocytes via modulation of surfactant protein expression [(5)] and it is shown that it can improve the respiratory system symptoms of bronchiofitis and reduce the time of hospital stay.Ambroxol has remarkable and predictable effect [(6)].

The aim of this study was to assess role of Ambroxol inhalation in treatment of Bronchiolitis.

PATIENTS AND METHODS

This randomized controlled clinical trial included a total of included 40 children with bronchiolitis, attending at Department of Pediatrics, Sohag General Hospital.

Ethical approval:
Written informed consent of all the subjects was obtained. **Approval of the ethical committee of Al-Azhar university was obtained.**

The included subjects were randomly divided into two groups; the **control group** consisted of 20 cases who were given bronchodilators, inhaled or systemic steroids, antibiotics if needed, or supportive measures and oxygen supplementation if needed and the **intervention group** consisted of 20 cases who were

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treated with Ambroxol inhalation in addition to supportive measures mentioned above.

Inclusion criteria: All children aged more than 6 months and presented by acute bronchiolitis.

Exclusion criteria: Infants aged less than 6 months or presented by respiratory distress due to other causes e.g. pneumonia, bronchial asthmas, and others.

All eligible patients assigned to the study were submitted to:

Full history taking: Personal history (name, age, sex, address, order of birth). History of present illness (onset, course, duration, associated symptoms, symptoms suggesting other system affection, foreign body exposure and other).

Examination: General look. Vital signs. Detailed chest examination including: Skin color (Pink, cyanotic, pale, dusky, mottled or jaundiced). Breathing pattern (Unlabored or labored, grunting, nasal flaring, or retraction). Chest wall (Deformity, symmetrical or asymmetrical movements). Breath sounds (Distant, shallow, stridor, wheezing, or diminished, equal or unequal). Apnea / bradycardia / desaturation (Lowest observed heart rate, color, oximeter reading and duration of episode). Secretions (Amount, color, consistency). Downes' score to evaluate respiratory distress. Complete systemic examination from head to toe specially heart examination to detect possible cardiac causes of respiratory distress.

Investigations: Routine investigations (CBC, CRP, kidney function tests). ABG. Chest x-ray and echocardiography if needed. Others.

Follow up the two groups of study clinically**:** Continuous monitoring by pulse oximetry. ABG. Chest x-ray. The outcome of the study (the of oxygen needs to maintain the optimum oxygen saturation and PaO2, the length of hospital stay and the incidence of complications.

Treatment: The intervention group was treated with nebulized ambroxol 2ml (7,5mg/ml) twice daily for 5 days.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)

- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Table (1): Comparison between the two studied groups according to demographic data

	Intervention (n = 20)		**Control (n = 20)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Sex						
Male	10	50.0	10	50.0	χ^2=0.0	1.000
Female	10	50.0	10	50.0		
Age (month)						
Min. – Max.	6.0 – 24.0		6.0 – 24.0		t=0.117	0.907
Mean ± SD.	14.65 ± 5.51		14.45 ± 5.26			
Median	13.0		13.0			

This table shows that there were insignificant differences between two groups as regard sex, age (p-value 1.0, 0.907 respectively).

Table (2): Comparison between the two studied groups according to main complaint

Main complain	**Intervention (n = 20)**		**Control (n = 20)**		**χ^2**	**p**
	No.	**%**	**No.**	**%**		
Cough	8	40.0	8	40.0	0.0	1.000
Breathing difficulties	12	60.0	12	60.0		

This table shows that there were insignificant differences between two groups regarding cough and breathing difficulties (p-value 1.00)

Table (3): Comparison between the two studied groups according to duration of illness

Duration of illness	Intervention (n = 20)	Control (n = 20)	U	p
Min. – Max.	6.0 – 40.0	6.0 – 45.0		
Mean ± SD.	16.35 ± 8.20	16.4 ± 8.20	200.0	1.000
Median	13.0	14.0		

This table shows that there were insignificant differences between two groups regarding duration of illness (p-value 1.00).

Table (4): Comparison between the two studied groups according to respiratory rate.

Respiratory rate	Intervention (n = 20)	Control (n = 20)	t	p
On admission				
Min. – Max.	40.0 – 65.0	40.0 – 65.0		
Mean ± SD.	51.45 ± 6.45	51.65 ± 6.50	0.098	0.923
Median	53.0	54.0		
After treatment				
Min. – Max.	38.0 – 55.0	38.0 – 55.0		
Mean ± SD.	44.35 ± 4.15	46.35 ± 5.42	1.310	0.198
Median	44.0	45.0		
P_1	<0.001*	0.003*		

This table shows that there was insignificant differences between two groups regarding respiratory rate on admission and after treatment (p-value 0.923) but in the same group there was significant reduction in respiratory rate from admission to after treatment.

Table (5): Comparison between the two studied groups according to O2 saturation.

O2 saturation	Intervention (n = 20)	Control (n = 20)	U	p
On admission				
Min. – Max.	85.0 – 96.0	85.0 – 96.0		
Mean ± SD.	93.15 ± 2.70	93.15 ± 2.70	200.0	1.000
Median	94.0	94.0		
After treatment				
Min. – Max.	90.0 – 98.0	85.0 – 96.0		
Mean ± SD.	95.10 ± 1.65	93.30 ± 2.49	89.0*	0.002*
Median	95.0	94.0		
	<0.001*	0.257		

This table shows that there were insignificant differences between two groups regarding oxygen saturation on admission (p-value 1.00), but after treatment interventional group shows significant improvement than control (p-value 0.002).

Table (6): Comparison between the two studied groups according to degree of RD.

Degree of RD	Intervention (n = 20)		Control (n = 20)		χ^2	p
	No.	%	No.	%		
On admission						
G2	12	60.0	12	60.0	0.00	1.000
G3	8	40.0	8	40.0		
After treatment						
G1	7	35.0	0	0.0		^{MC}p
G2	13	65.0	12	60.0	15.912	<0.001*
G3	0	0.0	8	40.0		
^{MH}p	0.003*		1.000			

This table shows that there was insignificant differences between two groups regarding degree of RD on admission but after treatment there was significant improvement in interventional group with (p-value <0.001).

Table (7): Comparison between the two studied groups according to chest –ray on admission.

Chest –ray on admission	Intervention (n = 20)		Control (n = 20)		χ^2	MCp
	No.	%	No.	%		
NAD	20	100.0	20	100.0	-	-

This table shows that all patients shows no abnormality on chest X ray.

Table (8): Comparison between the two studied groups according to length of hospital stay

Length of hospital stay	Intervention (n = 20)	Control (n = 20)	t	P
Min. – Max.	45.0 – 80.0	52.0 – 89.0		
Mean ± SD.	68.0 ± 10.01	77.70 ± 8.78	3.258*	0.002*
Median	70.0	80.		

This table shows that there were significant differences between two groups regarding length of hospital stay as in interventional group lower than control p-value 0.002

Table (9): Comparison between the two studied groups according to need oxygen therapy

	Intervention (n = 20)		Control (n = 20)		Test of Sig.	p
	No.	%	No.	%		
Need oxygen therapy						
No	13	65.0	10	50.0	X^2=	0.337
Yes	7	35.0	10	50.0	0.921	
Duration of oxygen therapy (hours)						
Min. – Max.	24.0 – 72.0		24.0 – 72.0		U=	
Mean ± SD.	40.0 ± 15.87		44.20 ± 16.67		28.0	0.536
Median	36.0		42.0			

This table shows that there was insignificant differences between two groups regarding need oxygen and duration of oxygen therapy p-value 0.337, 0.536 respectively.

DISCUSSION

Bronchiolitis is an acute respiratory illness that is the leading cause of hospitalization in young children less than 2 years of age in the UK. Respiratory syncytial virus is the most common virus associated with bronchiolitis and has the highest disease severity, mortality and cost [(7)].

Bronchiolitis is a common lung infection in young individuals. The viral infection involves the lower respiratory tract and can present with signs of mild to moderate respiratory distress. Bronchiolitis is a mild, self-limited infection in most children but may sometimes progress to respiratory failure in infants. Bronchiolitis is managed supportively with hydration and oxygen. No specific medications treat the infection. It is important to know that respiratory syncytial virus is just one cause of bronchiolitis. The infection can occur in individuals of any age, but overall, the most severe symptoms tend to be common in infants [(8)].

In the current study we aimed to assess role of Ambroxol inhalation in treatment of Bronchiolitis. This study conducted on 40 cases divided into two groups interventional and control group.

In the current study we found that there were insignificant differences between two groups as regard sex, age, past and family history and regarding duration of illness.

In agreement with our results, **Yakoot *et al.*** [(9)] showed that the two groups were almost matched at baseline in terms of age, smoking history, lung function, oxygen saturation.

Another study by **Guyatt *et al.*** [(10)] agree with our results showed that the groups are comparable, and none of the small differences observed reached conventional levels of statistical significance.

In the current study, we found that there were insignificant differences between two groups regarding cough and breathing difficulties (**p-value 1.00**).

This is in consistent with **Yakoot *et al.*** [(9)] who showed that there were insignificant differences between two groups regarding severity of cough, and breathlessness.

In the current study, we found that there were insignificant differences between two groups regarding respiratory rate on admission and after treatment but in the same group there was significant reduction in respiratory rate from admission to after treatment.

Yakoot *et al.* [9] showed that there was a statistically significant improvement of breathlessness and cough scoring in both groups when compared before and after treatment at day 3 and at day7, using a nonparametric related samples Friedman test (**P, 0.05**).

There was a highly statistically significant difference in improvement in breathlessness score, as well as cough score in favor of Farcosolvin treatment when the two groups were compared using an independent samples Kruskal Wallis test [9]**.**

In the current we found that there were insignificant differences between two groups regarding oxygen saturation on admission but after treatment interventional group shows significant improvement than control. There was insignificant differences between two groups regarding need oxygen and duration of oxygen therapy (**p-value 0.337, 0.536)** respectively.

Elsayed *et al.* [11] showed that there were no significant differences observed between both groups at baseline regarding respiratory rate, temperature and oxygen saturation.

Ambroxol decreased the incidence of respiratory distress syndrome (33.3% vs. 48.4%,**p<0.05**), improved the gas exchange (**p<0.05**), and decreased continuous positive airway pressure(**p<0.001**), the length of mechanical ventilation (**p<0.001**) and also the mortality rate (18.3% vs.35%, **p<0.05**) [11]**.**

Moreover, **Li *et al.*** [12] showed that on the 3rd and 5th days, the oxygenation index in the high-dose ambroxol group (291.02 ± 34.96 and 301.28 ± 37.69; **p<0.05**) was significantly higher than in the control group (230.08 ± 26.25 and 253.82 ± 26.26; **p<0.05**), with significant differences between the two groups (p<0.05).

He [13] study goes with our result in that after 14 day of treatment, the PaO2 index of the observation group was (76.23 ± 9.33) mmHg, and the control group was (71.22 ± 8.92) mmHg. The PaO2 index of the observation group was higher than that of the control group, and the difference was significant, **p< 0.05.**

Ericsson *et al.* [14] have reported a double-blind RCT in which 11 of 32 placebo treated patients, 18 of 31patients treated with 60 mg of ambroxol daily, and 20 of 32 patients treated with 120 mg of ambroxol daily, reported improved chest symptoms. The difference between the placebo and high-dose ambroxol group was statistically significant **(p=0.046**).

Moreover **Malerba *et al.*** [15] showed that Cough (frequency/ intensity), difficult expectoration and dyspnea were evaluated as secondary endpoints. Score distribution at baseline appeared comparable between two groups for all symptom categories.

A greater number of patients had absent or mild symptoms at the entry: cough frequency was absent or mild in 84% of patients taking ambroxol and in 87% of those taking placebo; a similar trend can be referred to difficult expectoration, defined as absent or mild in 90% of subjects in both treatment groups; 50% of ambroxol treated patients and 53% of placebo treated patients did not complain of dyspnea. All symptom scores slightly decreased during the treatment course without any significant difference between groups [16]**.**

In the current we found that there was insignificant differences between two groups regarding degree of RD on admission but after treatment there was significant improvement in interventional group with **p-value <0.001.**

In an open, long term multicenter study including 5635 patients, ambroxol was effective and well-tolerated for the prophylaxis of exacerbations of chronic bronchitis [16]**.**

Positive effects have been seen with the use of ambroxol in patients with early hyper secretory CB, including improvement in coughing; dyspnea; color and consistency of sputum; and ease of expectoration, when compared to a control **(P, 0.05)** [14]**.**

A systemic review by **Su *et al.*** [6] showed that the recovery of respiratory system symptoms in ambroxol group was earlier than that in the control group **(P < 0.01**)**.**

In the current we found that there was significant differences between two groups regarding length of hospital stay as in interventional group lower than control **p-value 0.002.**

In agreement with our result **Su *et al.*** [6] showed that the time of hospital stay was obviously shorter than the control group [RR-1.38,95% CI(-1.67, -1.08), P < 0.00001].

On the other hand, **Malerba *et al.*** [15] showed that no difference in the time course of antibiotic treatments in the number of working days lost and number of days of hospitalisation was reported.

CONCLUSION

It could be concluded that Ambroxol gives a good improvement in cases with bronchiolitis and decreases hospital stay. Furthermore, Ambroxol is safe, cheap and easy to administer.

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