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Original Article

Evaluation of The Role of Ambroxol in Treatment of Respiratory Distress Syndrome: A Randomized-Controlled Trial

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Abstract

Background: RDS was reported to be the most common cause of morbidity and mortality among preterm neonates.

Objective: This study aimed to evaluate the effects of postnatal intravenous ambroxol for infant diagnosed with mild to moderate RDS.

Patients and methods: This study includes 40 preterm neonates, who were submitted to complete history taking, clinical examination, and initial investigations. All babies were followed up clinically, ABG testing, and x-ray imaging. All neonates in the intervention group (2nd group), (20 cases) were received i.v. ambroxol for 5 days beside routine RDS management, while the control group (1st group), (20 cases) were received the routine management for RDS.

Results: There were non-significant differences between the two groups as regard sex, birth weight, residence (urban or rural) mode of delivery and gestational age (P-values 0.752, 0.825, 0.749, 0.749, and 0.548 respectively). There were non-significant differences between the two groups as regard Apgar score at 1 and 5 minutes (P-values 0.879, 0.871 respectively). After treatment, there were significant differences between both groups as regard PCO2 (mmHg), SaO2%, PaO2 mmHg. The need for M.V and CPAP and its duration, hospital stay, and death rate significantly decreased in neonates who received ambroxol.

Conclusion: Giving intravenous ambroxol to preterm newborns with RDS improves gas exchange and reduces the requirement for and duration of mechanical ventilation, CPAP, oxygen therapy, and overall hospital stay.

Key words: RDS; Ambroxol; Preterm

Introduction

Insufficient surfactant production and structural immaturity in the lungs cause respiratory distress syndrome (RDS), also known as hyaline membrane disease [1]. According to the epidemiological survey, the incidence rate of NRDS is up to 7.8% with a fatality rate of 50% in premature infants, which is easy to cause chronic lung disease in children and affects the life safety and healthy growth of children [2]. RDS is more likely to occur when an infant's birth weight decreases; the condition is expected to affect 80 percent of infants weighing 750 gm at birth and 55 percent of infants weighing 1000 gm. [3]. Surfactant deficiency is the most common defect in RDS [4]. The ensuing greater surface tension in the preterm lung with insufficient surfactant activity causes lung instability at end-expiration, reduced lung volume, and impaired compliance [5]. Hypoxemia is caused by a mismatch between ventilation and perfusion as a result of the collapse of substantial sections of the lung (atelectasis), as well as additional contributions of ventilation/perfusion mismatch from intrapulmonary and extra-pulmonary right-to-left shunts [6]. Lung inflammation and respiratory epithelial damage are also caused by surfactant deficit, which can lead to pulmonary edema and increased airway resistance. These variables aggravate lung damage and deteriorate lung function even more [7]. At the same time, aberrant fluid absorption causes poor lung liquid clearance in the wounded, edematous lung, which obstructs gas exchange [6]. The goal of RDS management is to provide strategies that optimize survival while reducing negative consequences. Many treatments and medicines for the prevention and treatment of RDS have been developed and tested in clinical trials over the last 40 years [8].

Ambroxol is a secretolytic, mucokinetic, and promoter of surfactant synthesis and releases by type II pneumocytes via surfactant protein expression modulation [9]. Chemically the Ambroxol is a mucoactive medication with a variety of features, including secretolytic and secretomotoric effects that help to restore the respiratory tract's physiological clearance systems, which are critical in the body's natural defense mechanisms [10]. It encourages type II pneumocytes to produce and release surfactants. Surfactant functions as an anti-glue factor, reducing mucus attachment to the bronchial wall, increasing mucus transport and protecting against infection and irritating chemicals. Ambroxol improves the state of the patient by performing the following tasks: Histamine, which block the allergic reaction, and mucus clearance which aided by anti-inflammatory, antioxidant, and local anesthetic properties [9, 11]. Surfactant release from type II pneumocytes is stimulated. Cough syrups commonly contain Ambroxol as an active component [12]. Aside from its mucus-clearing effects, Ambroxol has antiviral, antibacterial, and antifungal activities. Ambroxol has direct and indirect anti-infectious actions (such as improving antibiotic absorption), according to various working groups [13-14]. Although an increasing numbers of studies have demonstrated its role in the prevention of RDS when given ante-natally with no adverse effects on the baby [15-16]. Few researchers have reported its postnatal effectiveness in the treatment of infants born with RDS [17-18]. Ambroxol 's protective impact on underdeveloped lungs of newborn newborns is supported by a meta-analysis of randomized controlled studies. According to the authors' conclusion, the relative risk of infant respiratory distress syndrome during Ambroxol medication was 0.38 when compared to control [19]. Further research into Ambroxol 's ability to avoid pulmonary problems in critically ill individuals has been reported [20-21].

Patients and methods

The study was a randomized controlled clinical trial involving 40 preterm newborns with gestational ages ranging from ≥ 32 to < 37 weeks, and classified into 2 groups, 20 infants for each. The first group was the control group and the 2nd group was the treatment group. This study was done at Al-Shefa General Hospital- Makkah- KSA, from period of October 2018 to August 2019.

We exclude any neonates with significant congenital abnormalities and illnesses that potentially cause respiratory distress in neonates. We also exclude preterm infants with maternal history of PROM (premature rupture of membranes) or chorio-amionitis, and neonates delivered with meconium aspiration syndrome.

Methods: All of the study's eligible subjects were subjected to the following: Through history taking (perinatal and natal). Examination: general examination which includes the New Ballard Score to determine gestational age [22], anthropometric measurements and vital signs. Systemic examinations includes the Down's score is used to assess respiratory distress [23], and complete systemic evaluation.

Investigations: Routine investigations, ABGs and a chest x-ray. Follow up of the two groups, in a clinical setting (signs of RD, CRT and other parameters of chest examination), SPO2 and blood pressure and laboratory settings by ABGs and chest – X-ray which done on admission and every 24 hours up to 5 days. Treatment: Half of the recruited neonates got i.v Ambroxol in a dose of 10 mg/kg, every 12 hours for 5 days as a slow intravenous infusion over 5 minutes, beside routine RDS management. While the other half received standard RDS care.

Ethical approval

Signed consent from the infants' guidance was obtained, and approval from local authority of Al-Shefa General Hospital.

Statistical analysis

Data was collected, coded, updated, and entered into IBM SPSS 20 (Statistical

Package for Social Science). For qualitative data, the data is displayed as a number and a percentage. Means, standard deviations, and ranges for parametrically distributed quantitative data. For quantitative data with non-parametric distribution, the median with interquartile range (IQR) was used, the Chi-square test was used to compare two groups with qualitative data, and the Fisher exact test was used instead of the Chi-square test when the expected count in any cell was less than 5.

The confidence interval was set at 95%, while the acceptable margin of error was set at 5%. As a result, the following p-value is considered significant: Significant if the P value is less than 0.05. (S) Highly significant if the P value is less than 0.01. (HS).

Results

There were non-significant differences between the two groups as regard sex, birth weight, residence (urban or rural) mode of delivery and gestational age and p-value 0.752, 0.825, 0.749, 0.749, and 0.548 respectively (table1 &2). There were non-significant differences between two groups as regard Apgar score at 1st and 5 min., and p-value 0.879, 0.871 respectively (table 3). After treatment, there were significant differences between both groups as regard PCO2 (mmHg), SaO2%, PaO2 mmHg (table 5). The need for M.V and CPAP and its duration, hospital stay, and death rate significantly decreased in the Ambroxol group (Tables 6 and 7).

Discussion

Ambroxol appears to improve lung maturation and the course of RDS in preterm newborns, according to a growing number of studies [2]. The exogenous surfactant can be directly installed or ambroxol can speed up endogenous surfactant manufacture in alveolar type 2 cells to increase surface-active material in the alveolar gaps [24]. There are also numerous studies that show its efficacy in preventing RDS in delivered neonates when given for pregnant women at risk of preterm labor, and it is recommended above corticosteroids to prevent neonatal RDS [19]. Despite the fact that exogenous surfactant therapy has improved survival in clinical RDS, chronic lung disease remains to be a major cause of death and morbidity [4]. Surfactant treatment of immature surfactant-deficient lungs in VLBW newborns failed to significantly reduce the incidence of BPD, contrary to expectations [25-26].

As a result, there is growing interest in the possible involvement of novel medicines in reducing or perhaps preventing lung injury in vulnerable premature neonates [27-28]. Surfactant could not be used as a routine treatment (for every case of RDS) in this country, because it is expensive. As a result, the standard treatment for the control group was only the usual management of preterm neonates, and surfactants were not used in either the control or intervention groups. This highlights the importance of using a less expensive product to support such cases as long as surfactants are not available, especially in low-income areas.

The effect of ambroxol can be expected within 24-48 h. Since during that period most of the life-threatening complications of RDS occur, the effect of Ambroxol was expected mainly in RDS survivors [2]. Therefore, the sample size was calculated for that population and the results document the benefit of a 5 day treatment of ambroxol in preterm infants with established RDS.

There were non-significant differences between the two groups as regard sex, birth weight, residence (urban or rural) mode of delivery and gestational age and p-value 0.752, 0.825, 0.749, 0.749, and 0.548 respectively. There were non-significant differences between two groups as regard Apgar score at 1st and 5 min., and p-value 0.879, 0.871 respectively, these results in accordance to results of study done in 2006 by El-Sayed., et al [17].

After the introduction of Ambroxol to the studied groups, there were statistically significant differences between the two groups, as the requirement for CPAP was utilized as a measure of severity (morbidity of RDS). Ambroxol reduced the requirement for and duration of CPAP. Furthermore, Ambroxol reduced the need for mechanical ventilation onset and duration during the course of the illness [2]. In our study, we found these beneficial effects because there were statistically significant differences between two groups in terms of need for M.V (p-value 0.025), and its duration (p-value 0.001), and need for CPAP (p-value 0.04) and its duration (p-value 0.001 as this preventive impact of CPAP correlates with the effect reported by [18, 29 - 30]. In general, Ambroxol reduced the severity of RDS in the neonates who took part in the study [24].

Ambroxol also reduced the fraction of inspired oxygen (Fio2) required to maintain appropriate oxygen saturation, as well as the duration of oxygen therapy and hospital stay, and we found statistically significant differences between two groups in terms of oxygen therapy duration (hours) and hospital stay duration (days) p-value 0.001 and 0.020 respectively. As regard Fio2, there were statistically significant variations between two groups at 3, 6, 12, 24, 48 hours, and the p-values were, 0.005, 0.009, 0.047, 0.042, and 0.043, respectively; these findings are consistent with those reported by [16, 31].

Our findings demonstrated that the total death rate was considerably reduced in the Ambroxol -treated group (p-value 0.020), which is similar to Baranwal, et al, [21].

Radiologically, Ambroxol exerts its benefits on x-ray pictures after the period of treatment where significant improvement on x-ray was pictures of the Ambroxol group, and we found that non-statistical significant differences between two groups as regard severity of RDS in x-ray before treatment (p-value 0.3423), but there were statistically significant differences between the two groups after treatment (p-value 0.0251).

As regard ABGs findings after treatment, there were significant changes between the two groups as regard PCO2 (mmHg), SaO2%, PaO2 mmHg (all p-value <0.001) as PaO2 and SaO2% increased and PCO2 decreased in Ambroxol group after treatment than control group [32 - 33].

The inhalation form of Ambroxol is less available than intravenous form and its efficacy was studied before, in the treatment of RDS in comparison with intravenous form and did not show significant differences between the two dosage forms as regard efficacy and incidence of complications (p-value < 0.05), so we used the intravenous form because is the easy availability in our locality [11, 35].

Fan and Wen, 2009 reported a dose range for treatment of RDS in preterm neonates, 15 mg/kg/day as a conventional dose and 30 mg/kg/day as a high dose, [35]. The results of studies that used a high dose (30 mg/kg/day) such as Wauer and Schmalisch, 1992, [18], as regard efficacy and outcome were relatively similar to the results which used lower dose (20 mg/kg/day) such as Elsayed, et al., 2006, [17], for this reason, we selected a lower dose protocol (20 mg/kg/day) to minimize possible adverse effects.

Limitations: Extreme premature and infants with severe RDS were not included in the study.

Conclusions

Giving Ambroxol to preterm newborns with RDS improves gas exchange and reduces the requirement for and duration of mechanical ventilation, CPAP, oxygen therapy, and overall hospital stay, as well as the mortality rate. It is also safe, inexpensive, and simple to administer, allowing it to benefit newborns that are managed without intubation.

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Author's contributions

AH AND ME equally contributed in the study concept, design, supervision, methodology, statistical analysis and data collection. WE performed the investigations and laboratory workup and wrote the first draft of the manuscript.

Conflict of interest

Authors declare they have no conflict of interest

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Table (1): Socio-demographic data of patients in control and Ambroxol group

	Group I (control) (n = 20)		Group II (treatment group), (n = 20)		Test of significance	P value
	No.	%	No.	%		
Sex						
Male	9	45	10	50	χ^2= 0.100	0.752
Female	11	55	10	50		
Residence						
Urban	12	60	11	55	χ^2= 0.1023	0.749
Rural	8	40	9	45		
Birth weight(kg) Mean ± SD.	2.53 ± 0.56		2.51 ± 0.46		t = 0.222	0.825

*Statistically Significant difference at $p < 0.05$

Table (2): Obstetric data of patients in control and Ambroxol group

Obstetrics data	Group I (n= 20)		Group II (n= 20)		Test of sig.	P value
	No.	%	No.	%		
Mode of delivery						
C.S	9	45.0	8	40.0	χ^2= 0.102	0.749
NVD	11	55.0	12	60.0		
Gestational age (Weeks)						
Mean ± SD	33.60 ± 2.27		33.55 ± 2.23		t = 0.126	0.900

*Statistically Significant difference at $p < 0.05$

Table (3): Apgar score of neonates in control and Ambroxol group

APGAR score	Group I (n= 20)	Group II (n= 20)	Test of significance	P value
At 1st min				
Mean ± SD	5.23 ± 1.15	5.29 ± 1.12	0.153	0.879
At 5 min				
Mean ± SD	8.42 ± 1.04	8.47 ± 1.08	0.164	0.871

*Statistically Significant difference at $p < 0.05$

Table (4): Arterial blood gases "ABGs" before treatment

Arterial blood gases "ABGs"	Group I (n= 20)	Group II (n= 20)	Test of significance	P value
PH				
Mean ± SD	7.34 ± 0.12	7.31± 0.14	0.135	0.821
PCO_2(mmHg)				
Mean ± SD	41.04 ± 2.48	39.04 ± 2.37	0.147	0.723
PaO_2 mmHg				
Mean ± SD	74.55 ± 6.14	76.35 ± 5.34	0.158	0.634
SaO_2%				
Mean ± SD	85.65 ± 5.22	83.65 ± 6.78	0.162	0.542

*Statistically Significant difference at $p < 0.05$

Table (5): Arterial blood gases "ABGs" after 48 hours of treatment

Arterial blood gases "ABGs"	Group I (n= 20)	Group II (n= 20)	Test of significance	P value
PH				
Mean ± SD	7.40 ± 0.32	7.44 ± 0.34	0.3831	0.7038
PCO_2(mmHg)				
Mean ± SD	43.04 ± 4.48	34.41 ± 1.64	8.094	< 0.001*
PaO_2 mmHg				
Mean ± SD	80.55 ± 9.14	93.45 ± 3.41	5.914	< 0.001*
SaO_2%				
Mean ± SD	83.65 ± 4.55	95.58 ± 1.89	10.834	< 0.001*

*Statistically Significant difference at p< 0.05

Table (6): The need for mechanical ventilation and CPAP and death rate among cases versus control

	Group I (n= 20)		Group II (n= 20)		Test of significance	P value
	No.	%	No.	%		
Need for M.V						
No	8	40.0	15	75.0	□^{2}=5.013*	0.025*
Yes	12	60.0	5	25.0		
Duration of M.V. (hours)	**Mean ± SD** **170±31.2**		**Mean ± SD** 83**±11.7**		t = 5.966	0.001*
Need for CPAP						
No	10	50.0	14	70.0	□^{2}=3.956*	0.047*
Yes	10	50.0	6	30.0		
Duration of CPAP (hours)	**Mean ± SD** **145±26.85**		**Mean ± SD** **95±14.51**		t = 4.172	< 0.001*
Death rate						
No	14	70.0	20	100.0	□^{2}=7.059*	0.020*
Yes	6	30.0	0	0.0		

*Statistically Significant difference at p< 0.05

Table (7): Oxygen therapy and duration of hospital stay

	Group I (n= 20)	Group II (n= 20)	Test of significance	P value
Duration of oxygen therapy (hours)				
Mean ± SD.	98.80 ±13.86	86.15 ± 6.30	3.716*	0.001*
FiO2 needed to keep SpO2 between 92-95%				
At 3hours	0.87 ± 0.28	0.63 ± 0.23	2.962*	0.005*
At 6hours	0.88 ± 0.32	0.63 ± 0.28	2.753*	0.009*
At 12hours	0.63 ± 0.25	0.48 ± 0.21	2.055*	0.047*
At 24hours	0.73 ± 0.27	0.54 ± 0.30	2.105*	0.042*
At 48hours	0.52 ± 0.23	0.38 ± 0.19	2.099*	0.043*
Duration of hospital stay (days)				
Mean ± SD.	19.30 ± 5.68	15.50 ± 4.07	2.433*	0.020*

*Statistically Significant difference at $p < 0.05$

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