Sultan Qaboos University Medical Journal
December 2006 Vol 6, No. 2
Sultan Qaboos University©

ORIGINAL STUDY

# Evaluation of the Role of Postnatal Ambroxol in the Prevention and Treatment of Respiratory Distress Syndrome in Preterm Neonates

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# تقييم دور الامبروكسول بعد الولادة في منع وعلاج متلازمة الضائقة التنفسية عند المواليد الخدج

**الملخص: الهدف:** دراسة فعالية عقار الامبروكسول المعطى مباشرة بعد الولادة لمنع حصول مُتَلاَزِمَةُ الضَّائِقَةِ التَّنَفُّسِيَّة عند المواليد الخدج المعرضين للأصابة بها . وتقليل شدة المرض عند المصابين بها من هؤلاء المواليد . **الطريقة:** تم في هذه الدراسة العشوائية السريرية دراسة 120خديجا أدخلوا في وحدة الخدج بمستشفى جامعة قناة السويس (مصر) تراوحت أعمارهم بين 28 – 34 اسبوعا عند الولادة . استغرقت الدراسة من سبتمبر 2001 الى مارس 2003 . تم تقسيم الخدج عشوائيا الى مجموعتين . واعطاء المجموعة الاولى عقار الامبروكسول (بجرعة 20 ملجم/كجم/يوم) بالحقن الوريدي ولمدة خمسة أيام متوالية . بينما أعطيت المجموعة الثانية (العينة الضابطة) عقارا غُفْلا (كاذبا) اضافة الى الرعاية الخاصة بالخدج. **النتائج:** قلل الامبروكسول حدوث الاصابة بمُتَلاَزِمَةُ الضَّائِقَةِ التَّنَفُّسِيَّة . وأدى الى تخفيف الاعراض المصاحبة للمرض . مما أدى الى تقليص فترة التنفس الاصطناعية وكذلك قلل معدل الوفيات بينهم . **الخلاصة:** اثبتت هذه التجربة أن عقار الامبروكسول المعطى بعد الولادة للخدج يقلل من الاصابة بمُتَلاَزِمَةُ الضَّائِقَةِ التَّنَفُّسِيَّة . و يخفف من حدة الاعراض المصاحبة لها عند المصابين بها .

**المفردات المفتاحية:** متلازمة الضائقة التنفسية . الخداجة . أمبروكسول.

**ABSTRACT** ***Objective:*** to study the effect of the postnatal administration of Ambroxol in the prevention of respiratory distress syndrome in preterm neonates at risk and on the severity of the disease in those neonates already suffering from it. ***Methods:*** the study was a randomized clinical trial performed on 120 preterm neonates admitted to the neonatal unit of the Suez Canal University Hospital, Egypt, with gestational age of 28 to 34 weeks. It was performed in the period from September 2001 through March 2003. Half of the enrolled neonates received intravenous ambroxol (20 mg/kg/d), while the control group received the routine management of prematurity and a placebo. ***Results:*** Ambroxol decreased the incidence of Respiratory Distress Syndrome (RDS), improved the gas exchange, and decreased Continious Positive Airway pressure (CPAP) pressure, the length of mechanical ventilation and also the mortality rate. ***Conclusion:*** the study concluded that Ambroxol reduced the incidence of this disease in preterm neonates at risk of developing it, and improved the clinical course of RDS.

***Key Words:*** Respiratory Distress Syndrome (RDS), Prematurity, Ambroxol.

Respiratory distress syndrome (RDS) is the most common respiratory malfunction occurring in preterm newborns.[1] It is one of the most important factors determining neonatal morbidity and mortality.[2] In Egypt, RDS was reported to be the most common cause of morbidity (42.5%) among preterm neonates admitted to the Neonatal Intensive Care Unit (NICU) of Cairo University Hospital and is responsible for 70% of the neonatal mortality.[3] There are an estimated 40,000 cases of RDS annually in the United States, representing about 14% of all low-birth weight infants.[4]

The role of endogenous pulmonary surfactant in the maintenance of alveolar stability has been reported since 1950.[4] The deficiency of surfactant in newborns was attributed to pulmonary atelectasis and hyaline membrane disease, the condition now known as respiratory distress syndrome.[5]

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**Table 1:** ***Distribution of the enrolled neonates according to their birth weight (gm)***

| | Ambroxol Group | | Control Group | | Total | | t - test | *p* value |
|---|---|---|---|---|---|---|---|---|
| Birth weight (gm) | Mean | S.D | Mean | S.D | | | | |
| | 1547.7 | 241.3 | 1590.6 | 305.1 | | | 1.290 | >0.05 |
| | No | % | No | % | No | % | Chi -2 Test | *p* value |
| 1100 - 1400 | 26 | 43.4 | 23 | 38.3 | 49 | 40.83 | 0.14 | >0.05 |
| >1400 - 2000 | 34 | 56.6 | 37 | 61.6 | 71 | 59.17 | | |
| **Total** | 60 | 100.0 | 60 | 100.0 | 120 | 100.00 | | |

**Not statistically significant difference at 0.05 level**

Although exogenous surfactant therapy has dramatically improved survival in clinical RDS, chronic lung disease continues to cause significant mortality and morbidity, thus there is an increasing interest in the potential role of newer therapies that may further decrease lung injury in susceptible premature newborns[6,7] and even prevent its occurrence.

Although glucocorticoids are effective in the prevention of RDS and in the treatment of chronic lung disease,[8] their action depends on the repetition of the dose every seven days, which leads to a rise in cumulative side effects.[9] There are now growing concerns, based on animal and human data, that repeated antenatal doses could lead to growth retardation, decreased fetal brain size and abnormal neuronal development.[10]

Ambroxol, is a relatively new promoter of fetal lung maturity, the data on its efficacy are not yet as numerous as those of corticosteroids, although an increasing number of studies reported its role in the prevention of RDS, when given antenatally, with no side effects on the newborn.[11,12,13,14] The effectiveness of postnatal intravenous Ambroxol in the treatment and the prevention of RDS remains an area of concern and needs more research. Therefore, this study was conducted to evaluate the role of post-natal intravenous administration of Ambroxol in the treatment of RDS and its effects on the course and severity of the disease among Egyptian neonates.

**Table 2:** ***Distribution of the enrolled neonates according to Apgar score at 5 minutes***

| APGAR Score | Ambroxol Group | | Control Group | | Total | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| < 5 | 2 | 3.33 | 0 | 0.0 | 2 | 1.67 |
| ≥ 5 | 58 | 96.67 | 60 | 100.0 | 118 | 98.33 |
| **Total** | 60 | 100 | 60 | 100 | 120 | 100 |

**Statistically not significant difference at 0.05 level**
**Fisher exact test (2-tailed) *p*=0.49**

## METHODS

The sample size of our study was 120 preterm neonates with gestational ages between 28 to 34 weeks, admitted to the Neonatal Unit of Suez Canal University Hospital between September 2001 and March 2003. The study Protocol was approved by the ethical committee of researches in the Faculty of Medicine in Suez Canal University in Egypt before the launch of the study and an oral consent was taken from every parent before inclusion in the study in which the goal and the nature of the study was explained. The study was funded by University of Science and Technology, Sanaa Republic of Yemen in 2003.

Neonates with major congenital malformations or diseases that could cause respiratory distress in the neonates (e.g. congenital diaphragmatic hernia, congenital heart disease, congenital pneumonia, congenital emphysema, etc.) were excluded, as well as those neonates with a history of maternal conditions that are associated with increased risk of RDS (e.g. toxemia of pregnancy, diabetes mellitus, placenta previa, etc.).

Randomisation was done immediately after inclusion. All eligible patients assigned to the study were submitted to an initial assessment regarding gestational age, then a complete clinical examination, with particular attention paid to signs of respiratory distress, chest auscultation and cardiac and radiological examinations.

At the time of the study (2003) and, as in many Arabic countries, surfactant could not be given as standard treatment (that is given for every case of RDS) because it was and still is very expensive. Therefore, the standard treatment for the control group was only the usual management of preterms. Once RDS appeared,

**Table 3:** ***Vital signs of the enrolled neonates at the initial assessment***

| Neonates Characteristics | Ambroxol Group | | | Control Group | | | t- Test | *p* value |
|---|---|---|---|---|---|---|---|---|
| | Range | Mean | ±SD | Range | Mean | ±SD | | |
| Respiratory rate | 45-80 | 64.17 | 7.86 | 50-80 | 66.77 | 6.29 | 1.555 | >0.05 |
| Heart rate | 110-180 | 146.33 | 22.40 | 120-180 | 144.50 | 23.10 | 0.466 | >0.05 |
| Temperature | 35.5-37 | 36.44 | 0.34 | 35.5-37 | 36.52 | 0.39 | 1.497 | >0.05 |
| $SaO_2$ | 88-100% | 94.83 | 4.34 | 66-95% | 94.13 | 3.80 | 0.944 | >0.05 |

**Not significant at 0.05 level**
**$SaO_2$: Oxygen Saturation at room air.**

respiratory support was given with either continuous positive airway pressure (CPAP) in mild cases or mechanical ventilation if not responding and according to the mentioned indications in the methods. Therefore surfactant was not used in both the control and intervention groups and from here comes the importance of using a cheaper product to support such cases as long as surfactants are not available, especially in poor communities.

The treatment protocol in our study was as follows:

1. Resuscitation and supportive care by giving sufficient inflation pressures through CPAP in mild cases, and by endotracheal intubation and mechanical ventilation in severe cases with hypoxia despite CPAP
2. Blood gas monitoring by taking arterial blood samples.
3. Monitoring of blood pressure and adequate circulatory support.
4. Other general supportive measures like temperature control and minimal handling.

The intervention group received, in addition to the above mentioned protocol, intravenous Ambroxol (Mucosolvan, Boehringer, Ingelheim am Rhein, Germany) in a dose of 10 mg /kg, repeated every 12 hours for a duration of 5 days as infusion over 5 minutes, as early as possible after birth. Ambroxol was available in ampoules containing 15 mg diluted in 2 ml saline. The control group received a placebo, which was available as similar indistinguishable ampoules in dose and duration.

Antenatal steroids were given for every woman with threatened premature labour and in our patients it was given prenatally to all cases of both groups (at least one dose of betamethasone was given)

### Outcome measurements

The diagnosis of respiratory distress syndrome was based on clinical, radiological and blood gas examinations according to Kimya et al., (1995)[11] ie. onset of respiratory distress within the first four hours of life, with a duration of more than 24 hours, tachypnea of more than 60 beats/minute, intercostal retractions, grunting on expiration, cyanosis and/or $PaO_2$ less than 60mmHg at room air temperature, reticulogranular pattern and/or air bronchogram on chest x-ray.

**Table 4:** ***Result of assessments after 24 hrs of admission***

| Incidence of RDS at 24hrs | Ambroxol Group | | | Control Group | | | Chi 2 test | *p* value |
|---|---|---|---|---|---|---|---|---|
| | No | % | | No | % | | | |
| Yes | 20 | 33.3 | | 29 | 48.4 | | 2.21 | 0.049* |
| No | 40 | 66.7 | | 31 | 51.6 | | | |
| | | Mean | ±SD | | Mean | ±SD | t- Test | *p* value |
| $paO_2$ mmHg | | 94.03 | 5.24 | | 76.75 | 16.72 | 7.971 | 0.0007* |
| $pCO_2$ mmHg | | 35.57 | 3.58 | | 42.62 | 8.44 | 5.933 | 0.0003* |
| $SaO_2$ % | | 95.94 | 3.77 | | 83.25 | 9.14 | 9.798 | 0.008* |
| PH | | 7.34 | 0.03 | | 7.31 | 0.5 | 0.463 | >0.05 |

***Statistically Significant difference at p< 0.05.**

**Table 5:** ***Results of the analysis of CPAP settings***

| Effect of Ambroxol | | Ambroxol | | Control | | Chi 2 Test | *p* value |
|---|---|---|---|---|---|---|---|
| | | No | % | No | % | | |
| Need for CPAP | Yes | 9 | 15.00 | 27 | 45 | 11.47 | 0.0007* |
| No | | 51 | 85.00 | 33 | 55 | | |
| | | Mean | ±SD | Mean | ±SD | *t*-test | *p* value |
| Pressure of CPAP Cm $H_2O$ | | 5.78 | 1.09 | 7.71 | 1.45 | 8.540 | 0.0006* |

***Statistically significant difference at p< 0.05.**

The severity of the disease was determined by the following indices:

1. The need for continuous positive air way pressure (CPAP), defined as the presence of mild respiratory distress requiring a fraction of inspired oxygen ($FIO_2$) below 0.40 to maintain a pressure of arterial oxygen of 50-80 mmHg.
2. The need for mechanical ventilation was defined as $PaO_2 \leq 50$ mmHg at oxygen concentration of 70-100% and CPAP 8-10 $cmH_2O$, arterial blood $PCO_2$ of 60mmHg or more or persistent apnea.
3. The main airway pressure (MAP) needed during the ventilation to keep $PaO_2$ at an adequate limit at the initial settings was calculated by the specific formulas as well as the oxygenation index ($O_I$).

## RESULTS

The mean gestational age in the intervention group was 30.23 weeks, while in the control group was 30.63 weeks. The mode of delivery was lower segment cesarean section in 11.67% of the neonates in the intervention group, while 13.33 % of the control group delivered by cesarean section.

The distribution of the enrolled neonates according to their birth weight, APGAR score at 5 minutes, is shown in the Tables 1 and 2 respectively. Fisher Exact Test (2-tailed) P= 0.49

Unfortunately, the cause of preterm delivery was not recorded as part of the research.

The result of the initial assessment of the enrolled neonates regarding respiratory rate, heart rate, temperature and oxygen saturation percentage are shown in Table 3. It shows no significant differences in the two groups of the neonates.

The incidence of RDS was significantly lower in the Ambroxol group (33.3%) compared with the control group (48.4%) as shown in Table 4. This table shows also the blood gas analysis to be significantly better in the Ambroxol group.

The main pressure of CPAP needed during the course of the treatment was found to be significantly lower in the Ambroxol group [Table 5].

The need for and the duration of mechanical ventilation were lower in the Ambroxol group. The oxygenation index as an indicator of gas exchange during the mechanical ventilation was lower in the Ambroxol group [Table 6].

**Table 6:** ***Results of the analysis of the need for mechanical ventilation and its settings***

| Ambroxol | | | | Control | | | Chi 2 test | *p* value |
|---|---|---|---|---|---|---|---|---|
| Need for M.V | No | % | | No | % | | | |
| **Yes** | 4 | 6.67 | | 20 | 33.33 | | 11.72 | 0.0006* |
| **No** | 56 | 93.33 | | 40 | 66.66 | | | |
| | | Mean | ±SD | | Mean | ±SD | T-Test | P-value |
| **OI during M.V** | | 10 | 0.1 | | 12.42 | 1.85 | 8.593 | 0.0001* |
| **MAP during M.V** | | 9 | 0.1 | | 10.24 | 0.97 | 9.850 | 0.0001* |
| **Duration of M.V(hrs)** | | 84 | 12.70 | | 169.60 | 32.0 | 2.923 | 0.004* |

*** Statistically Significant difference at p< 0.05.**
**For Duration of M.V, two-sample Wilcoxon Rank-Sum for equality of medians was used.**
**M.V: Mechanical Ventilation.**
**OI: Oxygenation Index.**
**MAP: Mean Airway Pressure.**

**Table 7:** ***Mortality among the two studied groups***

| Death rate | Ambroxol Group | | Control Group | | Chi-2 test | *p* value |
|---|---|---|---|---|---|---|
| | No | % | No | % | | |
| **Yes** | 11 | 18.33 | **21** | 35 | 3.261 | 0.039* |
| **No** | 49 | 81.66 | **39** | 65 | | |

*** Statistically Significant at p< 0.05.**
**HMD: Hyaline Membrane Disease. Hypo: Hypotension.**
****FE: Fisher Exact Test (2 tailed)**

The present study shows also that the mortality rate was significantly lower in the Ambroxol group (18.3%) compared with the control group (35%) [Table 7].

## DISCUSSION

There are increasing numbers of studies that report the improving effect of Ambroxol on lung maturation and on the course of RDS in preterms.[15] It is possible to increase surface active material in the alveolar spaces either by direct installation of exogenous surfactant or by accelerating endogenous surfactant biosynthesis in the alveolar type 2 cells by Ambroxol.[16]

In this work, the prevalence of RDS at 24 hours of administration was significantly lower in the group of neonates who received Ambroxol group. This preventive effect coincides with the effect reported by Wauer et al.,[17] Leurti et al.,[18] Laoag et al.[17,18,19] Ambroxol generally reduced the severity of RDS among the enrolled neonates. The need for CPAP was used as an index for severity (morbidity of RDS). Ambroxol reduced the need for CPAP and its mean pressure. Moreover Ambroxol reduced the need for the initiation of mechanical ventilation during the course of illness and the initial ventilator setting. This coincides with the results of Wauer et al.[20]

Ambroxol also reduced the oxygenation index (OI) which reflects a better gas exchange, a lower mean airway pressure (MAP) and a lower fraction of inspired oxygen ($FIO_2$). The MAP was also lower in the group treated with Ambroxol. This reflects a reduced peak inspiratory pressure (PIP) and peak expiratory end pressure (PEEP), as well as reduced inspiratory time. This result goes with those reported by Durisova,[21] Sackdy et al.,[12] and Schmalisch et al.[14]

Our study showed the overall death rate to be significantly lower in the group treated with Ambroxol. This is consistent with the results concluded by Duresova in 1992.[21]

Ambroxol efficacy is probably dependent not only on lung pathology, but also on the dose administered and the duration of administration. Our choice of 20mg/kg/day was the minimal dose reported in the literature; larger doses could be used safely.

The Ambroxol used in this study was safe and caused no complications. According to literature no significant complications were attributed to this drug during 30 years of research and it has been used in neonates intravenously for pneumonias to improve

**Table 8:** ***Mortality and cause of death among the two studied groups***

| | | Ambroxol Group | | Control Group | | Chi-2 test | P-value |
|---|---|---|---|---|---|---|---|
| | | No | % | No | % | | |
| **Yes** | | 11 | 18.33 | 21 | 35.0 | 3.261 | 0.039* |
| **No** | | 49 | 81.66 | 39 | 65.0 | | |
| **Cause of death** | HMD | 4 | 36.4 | 8 | 38.1 | 0.01 | 0.993 |
| | Hypo | 1 | 9.1 | 2 | 9.5 | | |
| | Sepsis | 6 | 45.5 | 11 | 52.4 | | |
| **Death at day** | <14 | 6 | 54.5 | 12 | 57.1 | FE** | 1.000 |
| | ≥14-28 | 5 | 45.5 | 9 | 42.9 | | |

*** Statistically Significant at p< 0.05**
**HMD: Hyaline Membrane Disease. Hypo: Hypotension**
****FE: Fisher Exact Test (2 tailed)**

thick secretions, so we were looking for simple complications such as frothy secretions as well as it is being mucolytic. Moreover, its administration is simple in comparison with surfactant administration and is cheaper.

## CONCLUSION

Finally, we could conclude that Ambroxol administration to preterm neonates at risk of/or suffering from RDS improves gas exchange, and decreases the length of mechanical ventilation, as well as the incidence of RDS and of mortality. Furthermore, Ambroxol therapy could be considered as a therapeutic option in cases of at risk neonates for RDS and for those neonates with established RDS. It is also safe, cheap and easy to administer, so that infants who are managed without intubation can benefit from it, which is a major advantage of Ambroxol.

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