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Antenatal Use of Ambroxol for the Prevention of Infant Respiratory Distress Syndrome

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Abstract

Objective: Our purpose was to evaluate the efficacy and safety of ambroxol for the prenatal prophylaxis of infant respiratory distress syndrome (IRDS).

Study Design: This was a prospective study with 2 groups of pregnant patients with premature labor or with premature rupture of membranes at an estimated gestation between 27 to 34 completed weeks. Ambroxol treatment group consisted of 39 subjects in whom 1,000 mg of ambroxol diluted in 500 m*l* of 5% glucose solution was given intravenously for 4 hours once a day for 3 days, while the control group consisted of 41 subjects in whom ambroxol was not administered. Main measures included Apgar scores, clinical signs of one or more of the following: respiratory rate of > 60/min, intercostal retraction, alar flaring, expiratory grunting, cyanosis on room air and radiological evidence of IRDS. Chi-square test was used to determine the statistical significance of the results.

Results: Tolerable maternal side effects were noted. Profile of newborns delivered were similar in both groups. Incidence of IRDS was significantly less in the treatment group ($p < 0.01$).

Conclusions: Antenatal administration of ambroxol resulted in a significant decrease in the incidence of IRDS as well as perinatal morbidity and mortality. Due to the efficacy and safety of this drug, it might be useful for the prevention of IRDS.

Key words: ambroxol, infant respiratory distress syndrome

Introduction

Infant respiratory distress syndrome (IRDS) is the most frequent death in newborns[1] and it was shown to be caused by deficiencies in lung surfactant.[2] It is a significant cause of mortality among preterm infants. Recovery may occur but late sequelae involving central nervous system and cardiopulmonary system may ensue.[3] The incidence among all newborns is 1.5%.[4] Research of drugs which may induce fetal lung maturation has been performed in many perinatal centers where prematurity has a high incidence and IRDS is a component of perinatal morbidity and mortality.

More than 20 years have passed after Liggins and Howie[5] first reported the antenatal treatment with corticosteroids which lead to a signifi-

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cant reduction in the incidence of IRDS even in newborns less than 35 gestational weeks. However, there are several attempts to discover other substances which can be used instead of glucocorticoids because of the following reasons: firstly, the mode of action of steroids is not yet fully understood.[6] However, there is experimental evidence that treatment with glucocorticoids might impose certain hazards in the fetus.[7-10] Moreover, some clinical reports have shown an increase in infection rate in both the mother and the newborn following prenatal administration of corticosteroids.[11,12] Steroids should be used with extreme caution in the presence of maternal infection, any form of gastrointestinal disorder, serious hypertension or diabetes.

Studies on the bromhexine metabolite, ambroxol, have shown a stimulating action on bronchial secretions and most importantly, ambroxol increases alveolar surfactant activity.[13] Ambroxol readily crosses the placenta and accumulates in the fetal lung and liver.[14] It stimulates the intracellular organelle involved in the surfactant secretion, thereby increasing the surfactant phospholipids in the amniotic and fetal tracheal fluids.[13] Treatment of IRDS with ambroxol is based on the fact that a progressive accumulation of saturated phosphatidylcholine in the fetal lung tissue precedes the presence of surfactant in the alveoli.[14] Therefore, the goal of medical treatment of IRDS is to stimulate both surfactant biosynthesis and secretion with the aim of improving lung function.

The question of whether alternative drugs such as ambroxol which might serve as a substitute for steroids is of rising interest. The data on its efficacy and side effects in humans are not yet as many as those of corticosteroids. We therefore carried out a prospective study to determine whether maternal ambroxol treatment given prenatally reduces the risk of IRDS and to assess its efficacy and safety in the prevention of IRDS.

Subjects and Methods

Women with premature labor or premature rupture of membranes who were admitted from February 1995 to August 1997 in the Department of Obstetrics and Gynecology, SLU Hospital of the Sacred Heart were eligible if the estimated gestation on admission was between 27 to 34 completed weeks. Most of the pregnancies were clinically and biophysically normal with some pathologic cases. First trimester sonography is not routinely performed in our institution hence the duration of gestation was computed from the last normal menstrual period and was confirmed by ultrasound using the biparietal diameter immediately before or during admission. The gestational age was checked at birth following the physical and neuromuscular criteria set by Ballard.[15]

The indications for initiating treatment were as follows: a) despite tocolysis, presence of premature rupture of membranes, progressive dilatation of the cervix and/or continued labor, b) possible premature termination of pregnancy in the event that immediate delivery is necessary as medically indicated.

Exclusion criteria were as follows: a) more than 2 weeks disagreement in assessing gestional age using patient's history and ultrasound data, b) previous treatment during present pregnancy with other drugs enhancing fetal lung maturity such as aminophylline, thyroxine and corticosteroids,[16,17] c) history of hypersensitivity to ambroxol, d) history of convulsion, e) history of heart disease.

The patients were assigned into 2 groups namely, ambroxol treatment group and the control group. It is important to note that the institution where the research was conducted is a private catholic hospital hence several factors were considered as to the group assignment and these are as follows: attending physician's choice, patients' choice, cultural and religious beliefs. Even though the research was being conducted, we were not randomly assign specific patients into desired groups. Skepticism still played a role in the decision of both the physician and the patient since this drug is relatively a new regimen. Moreover, some patients adhered on the power of divine intervention or prayer by their ancestors and the administration of drugs were contradictory to their beliefs.

Fourty-six patients received ambroxol and formed the treatment group. However, 7 of the 46 patients were not included in the study because of one of the following reasons: lost to follow-up, non-institutional delivery, delivery at 35 weeks or at term, or delivery of < 3 days or > 14 days from the last administration of ambroxol. This is based on the fact that surfactant is normally detected in large quantities from 35 weeks of gestation and that the efficacy of the drug is evident after 72 hours but not more than 14 days after the last administration.[13] The control group comprised 41 patients, in whom ambroxol was not administered.

The study was approved by the Bioethics and

Research Committees of SLU Hospital prior to the trial study.

Admittance diagnosis of both groups is shown in Table 1. Most of the patients in both groups were admitted due to threatened preterm labor. There were more cases of hypertension/toxemia in the treatment group as compared to the control group. On the other hand, there were more cases of premature rupture of membranes in the control group. Profile of the subjects as well as that of the babies on delivery are shown in Table 2. There is no significant difference between the ambroxol and control group in all the parameters mentioned. Concurrent disorders in the mother were medically treated as required. Drugs concurrently used include antibiotics (amoxycillin, cephalexin and nitrofurantoin), antihypertensives (hydralazine, clonidine), tocolytics (isoxsuprine, terbutaline, salbutamol) and multivitamin supplements.

Patients in the ambroxol group were given daily for 3 days ambroxol 1,000 mg in 500 m*l* infusion of 5% glucose solution by slow intravenous infusion for 4 hours.[13] Once the solution for infusion was ready for use, it was not stored longer than 12 hours at room temperature. Informed consent was elicited from the patients. The patients in the treatment group were monitored for possible adverse effects and for progress of labor. Maternal vital signs were also recorded. The fetal heart rate was monitored and fetal movement counting was done by the patients at specified waking hours (i.e. 6–7 am, 11–12 pm, 3–4 pm, and 7–8 pm).

At delivery, the condition of the newborn was assessed. Apgar scores at 1, 5 and 10 minutes were recorded. After initial stabilization, infants were brought to the special care unit. All newborns were monitored for the development of IRDS using the following criteria: a) condition beginning 4 hours of life and lasting for more than 24 hours, b) clinical signs of one or more of the following: respiratory rate of > 60/min, intercostal retraction, flaring of alae nasi, grunting on expiration, cyanosis in room air, c) radiologic signs which are the presence of thoracic roentgenogram reticulogranular pattern and/or air bronchogram. All newborns with respiratory distress were examined by chest X-ray within the first 12 hours of life. Umbilical and arterial blood pH determination was not included in this study since there was no arterial blood gas machine available. Morbidity and mortality rates due to IRDS were recorded. Chi-square analysis was used to find the differences between the 2 groups.

Both groups received the same obstetrical care and were closely monitored. If the patient's condition was controlled, they were kept on weekly observation until child birth.

Table 1. Principal admittance diagnosis

Diagnosis	Treatment group	Control group
Threatened premature labor	18	16
Premature rupture of membranes	3	13
Placenta previa	4	2
Abruptio placenta	0	2
Cervical incompetence	2	1
Hypertension/toxemia	6	2
Diabetes mellitus	2	2
Maternal infection i.e. UTI	4	3
Total	39	41

Results

Maternal side effects included: nasal congestion (17%), nausea, vomiting (7%) and slight tachycardia with a cardiac rate of 101–105 per min (3%). Hypotension (BP of 70–80 mmHg systolic and 40–50 mmHg diastolic) was recorded in 8 cases out of 16 in which ambroxol and tocolytic drug were used at the same time. The blood pressure readings taken prior to ambroxol ranged from 90–120 mmHg systolic and 60–90 mmHg. When used alone, ambroxol did not cause

Table 2. Profile of patients and newborns

Profile	Treatment group	Control group
Number of patients	39	41
Gestational age at trial start (weeks)	31.21 +/− 2.41	31.70 +/− 2.33
Age	26.02 +/− 6.3	30.98 +/− 4.7
Primipara	13	16
Gestational age at delivery (weeks)	31.46 +/− 2.32	31.97 +/− 2.31
Weight of newborn (g)	1943.11 +/− 331.47	2088.07 +/− 437.38
Number of infants	40	42
Number of liveborn infants	39	41

changes in the blood pressure. Fetal tachycardia (122–135 per min) was also recorded in 33% of cases. Fetal movement counting showed movement of more than 3 per hour in all cases.

Profiles of newborns delivered and the associated risk factors were compared in Table 3. IRDS, IRDS mortality, incidence of neonatal death and perinatal mortality were significantly less in the treatment group ($p < 0.01$ and < 0.05). Each of the suspected risk factors for IRDS was examined and found to be similar in both groups. Gestational age, birth weight and incidence of male babies and twin pregnancies were more or less similar in both groups. Moreover, the rate of cesarean section was more or less the same. Babies with Apgar scores less than 4 were more abundant in the control group.

The incidence of IRDS among those born before 34 weeks of gestation was examined in relation to various durations of membrane rupture prior to birth (Fig. 1). The time interval between the rupture of membranes and birth did not influence the frequency of IRDS in both groups.

Two-year follow-up of babies prenatally given with ambroxol showed no adverse effects.

Discussion

The incidence of IRDS in our present study was significantly less in the ambroxol group than in those subjects in whom no induction of fetal lung maturity was instituted. The gestational ages of the study population ranged from 27 to 34 weeks and the reason of admission varied from threatened premature labor to those having pathologic pregnancies.

Table 3. Profile of newborns delivered and risk factors

Profile/risk factor	Treatment group	Control group
IRDS	3	10*
IRDS mortality	1	6*
Fetal death	1	1
Neonatal death	3	8*
Perinatal mortality	4	9*
Surviving	36	33**
Male (%)	63.3%	57.9%
Twins (%)	3.3%	2.6%
Cesarean section	40.0%	42.1%
Diabetes mellitus	5.1%	5.3%
Apgar score < 4 (%)		
a) 1 min	17.5%	28.5%
b) 5 min	12.4%	22.1%
Labor suppressant use	46.2%	39.0%

* Indicates significance with a p value < 0.01.
** Indicates significance with a p value < 0.05.

The therapeutic regimen chosen in the present study is the one recommended in the ambroxol drug literature.[13] The use of ambroxol on the basis of such regimen resulted in a significant reduction in the incidence of IRDS. The safety of this drug has also been established. There was no reported adverse drug reaction, and the maternal side effects noted were tolerable and did not necessitate discontinuance of the treatment. A study done by Kimya *et al.*[3] showed that they were unable to detect any signs or symptoms of organ dysfunction with liver and renal function tests between the ambroxol and the control groups.

The clinical results of our present study substantiate previous reports[18,19] that antenatal infusion of large doses of ambroxol may be beneficial in reducing the risk of IRDS in prematurely born infants. Although the comparative analysis is difficult due to the fact that the gestational age and criteria of IRDS vary from one study to another, the findings obtained seemed to be similar.

Subjects with pathologic pregnancies were also included in this study. In the ambroxol group, those with preeclampsia, diabetes mellitus and premature rupture of membranes had decreased incidence of IRDS regardless of such complications compared to the control group. The maternal side effects were also minimal. The neonatal outcome was also favorable. These types of patients are the ones who will benefit a lot with the ambroxol regimen. The use of corticosteroids in the prevention of IRDS has gained wide popularity but it should be used with extreme caution if the gravida has maternal infection, serious hypertension or diabetes. Clinical reports have shown an increase in infection rate in both the mother and the newborn following prenatal administration of corticosteroids.[11,12] In this regard, patients who have premature rupture of membranes are at risk.

A study by Heytmanek *et al.*[20] found that transient and mild IRDS cases were slightly more frequent in the ambroxol group than in the betamethasone group among patients with pathologic pregnancies. Although betamethasone was not used in this present study, we did not find any case of mild or even transient IRDS in the ambroxol group.

On the other hand, a study by Luerti *et al.*[9] showed that ambroxol is more effective than steroids in twin births and in female infants. Our present study showed that ambroxol is also effec-

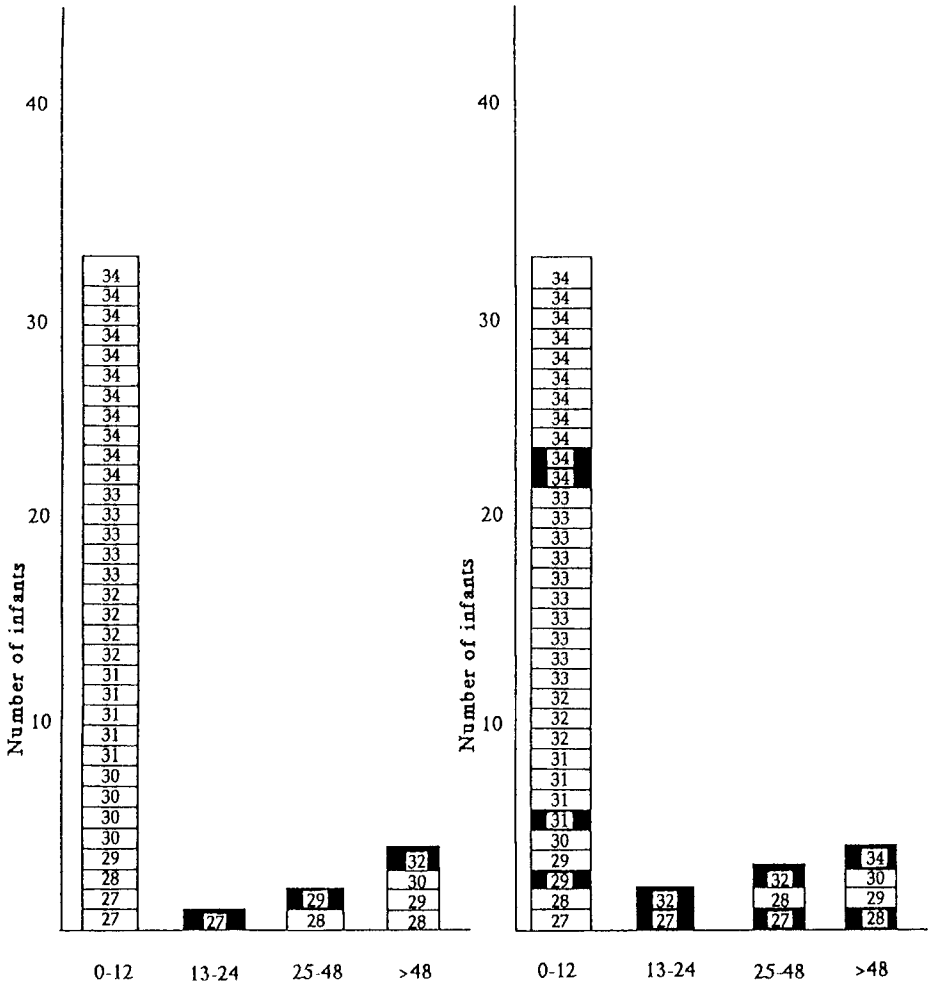

Fig. 1. Relationship between duration of membrane rupture before birth and number of infants born with or without IRDS in the ambroxol group (left, $n = 40$) and the control group (right, $n = 42$). Number of infants born is shown in ordinase. Abscissa shows duration of membrane rupture prior to birth. Each box indicates a single infant. The number in the box is the week of gestation at birth. Shaded box designates that the infant had IRDS, while unshaded box implies that IRDS was not present. Mortality due to IRDS occurred at 29 weeks in the treatment group. IRDS mortality in the control group were as follows: 2 at 27 weeks, 1 at 28 weeks, 1 at 31 weeks and 2 at 34 weeks gestational ages. Mortality due to IRDS at 34 weeks occurred in infants born with rupture of membranes at 0–12 hours and the other at > 48 hours.

tive in twin pregnancies. However, most of the liveborn infants in the ambroxol group consisted of males. The male sex as a risk factor for the development of IRDS was not evident in the present study.

Our results indicate that ambroxol is effective and has no significant maternal and perinatal side effects. In this regard, ambroxol may be used as a valuable alternative to corticosteroids in the prevention of IRDS. However, because of the relatively small sample size, further studies involving a larger sample size will be needed.

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