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Antenatal Treatment of Ambroxol Hydrochloride and Dexamethasone for the Prevention of Respiratory Distress Syndrome

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= 국문초록 =

산전 Ambroxol Hydrochloride와 Dexamethasone 치료의 미숙아 호흡곤란증 예방에 대한 효과

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연구목적 : 미숙아에 대한 치료 한계가 점점 어린 연령, 적은 체중으로 하향되면서 미숙아에서 발생하는 호흡곤란증(respiratory distress syndrome)은 출생 후 치료 뿐만 아니라 출생 전 예방에 더 많은 관심을 가지게 되었다 이에 본 저자는 산전 ambroxol hydrochloride와 dexamethasone치료가 미숙아 호흡곤란증 예방과 신생아 감염에 미치는 영향을 알아보고자 본 연구를 시행하였다.

방 법 : 조기 진통으로 미숙아를 분만하게되는 101명의 산모에서 무작위로 ambroxol hydrochloride와 dexamethasone을 투여하였다. 이들에서 분만 된 113명의 신생아가 연구에 포함되었으며, 이들 환아를 대상으로 뇌실 내 출혈 및 신생아 감염의 빈도에 대한 평가도 이루어졌다.

결 과 : 대상 환아의 두 군간에 평균 재태연령, 출생시 체중, 조기양막파수의 빈도, 아프가 점수 등의 차이는 없었다. Ambroxol투여군에서 호흡곤란증후군의 발생 빈도가 20.6%로 dexamethasone군의 38%에 비해 낮았으나 통계적 의의는 없었다($p>0.05$). 또한 인공 폐포 활성물질의 투여를 요구하는 중증의 호흡곤란증후군 빈도나 인공호흡기, 산소 치료, 입원 기간도 두 군간에 차이가 없었다. 신생아 감염의 경우 ambroxol 투여군에서 4.8%로 dexamethasone군의 24%에 비해 의미있게 낮았다($p<0.05$).

결 론 : Ambroxol hydrochloride의 산전 치료 효과는 미숙아 호흡곤란증의 예방에는 dexamethasone과 비슷한 효과를 보였으며, 신생아 감염에서는 더 낮은 감염률을 보였다.

중심 단어 : Ambroxol · Dexamethasone · Respiratory distress syndrome (RDS) · Neonatal infection.

Introduction

Respiratory distress syndrome (RDS) is a well known disease caused by deficiency of pulmonary surfactant in preterm infants. RDS is a common cause of morbidity and mortality among preterm infants. An estimated 30% of all neonatal deaths results from RDS or its compli-

cations.

The administration of dexamethasone to women 48-72 hr before delivery, at 32 week of gestation or less significantly reduces the incidence and morbidity and mortality from RDS[1]. But antenatal corticosteroid treatment for premature labor and fetal lung maturation has a potential risk of fetal and maternal infection[2].

Various substances, such as corticosteroids, betamimetics, aminophylline, thyroid hormone, cyclic-AMP, ethanol, fibroblast pneumocyte factor, bromhexine etc. have been used to accelerate the fetal lung maturation and hence alveolar surfactant production during intrauterine life up to now[3].

Ambroxol hydrochloride (Mucosolvan®) readily crosses the placenta and accumulates in the fetal lung and liver. Ambroxol is a member of the benzylamine group and has a marked effect on the respiratory epithelium by stimulating synthesis and secretion of surfactant by acting selectively on type II pneumocytes[4][5]. This study was conducted to evaluate the effectiveness of ambroxol in the prevention of neonatal respiratory distress syndrome and in the reduction of intermittent mandatory ventilation and oxygen therapy. And to compare the effect of ambroxol and dexamethasone on neonatal infection

Methods

1. Patients

101 pregnant women who were admitted at 27 to 35 weeks of gestation with premature labor took part in our investigation. All pregnant women enrolled in this study were randomized either for treatment with ambroxol or dexamethasone. The ambroxol group received 1 gram of ambroxol, diluted in 500 mL saline which was infused intravenously for 3 hours for 3 to 5 days. The dexamethasone group received 4 doses of 5 mg of dexamethasone given intramuscularly with an interval of 6 hours. Tocolysis with a beta-mimetic agent was allowed to delay labor. Exclusion criteria for pregnant women were delivery done within 24 hours after starting treatment, or over 37 weeks of gestation.

The incidence of RDS was assessed in 113 neonates, including 12 sets of twins, who were born at less than 37 weeks of gestation. Neonatologists who participated in this study were blinded to the antenatal treatment. Exclusion criteria for neonate were early neonatal death within 24 hours, severe congenital anomaly, neonatal transfer to another hospital, and neonates who were discharged against medical advice. 63 neonates were enrolled in the ambroxol group and 50 neonates were enrolled in the dexamethasone group.

2. Methods

Criteria for the diagnosis of RDS were as follows. 1) symptom onset within the first 4 hours of life 2) symptom duration more than 24 hours 3) tachypnea more than 50 per minute 4) intercostal retractions and flaring of the alae nasi 5) grunting on expiration 6) cyanosis and arterial oxygen pressure less than 60 mmHg 7) reticulogranular pattern and/or air-bronchograms on chest x-rays. Severe RDS was defined as Bomsel radiological classification of RDS grade 3 and over with alveoloarterial oxygen gradient on ABGA less than 0.35 on mechanical ventilation. We used the Radiological grading of intraventricular hemorrhage by Papile. Our parameters for evaluation were incidence of RDS and severe RDS, incidence of neonatal infection, incidence of neonatal complications such as IVH, PIE, pneumothorax, Pulmonary hemorrhage, NEC, ROP, BPD, duration of admission, and neonatal death.

3. Statistical analysis

The study was designed to test the hypothesis that infants of ambroxol treated mothers would have a risk of RDS or neonatal infection in infants of steroid treated mothers. In a previous study, among infants born at less than 37 weeks of gestation inclusive, the risk of RDS among infants of steroid treated mothers would be 31% and among infants of ambroxol treated mothers, 13%. Further, the study was designed to expose no more than the minimum number of mother-fetus pairs to the experimental therapies. Calculations indicated that sequential design would require a much larger sample size (150 to 250 total) than that needed for the fixed sample size design (126 total). For a type I error of 5% (two-tailed), a type II error of 20% (implying power of 80% to detect a treatment difference if one, in fact, did exist), and a

hypothesized risk difference of 18% (31% to 13%), the sample size calculated for each treatment group was 63. But in a few case of study group, they are excluded by some reason. Thus, a total of 113 infants were studied. Statistical analysis were done by student's t-test and the Chi-square test or the Fisher exact test with SAS program, if the cell frequencies in the 2×2 tables were smaller than 5. A level of statistical significance of $p<0.05$ was accepted.

Results

1. Characteristics of patients

Comparing the study population on pretreatment variables, there were no significant differences between each group of neonates in gestational age, birth weight and sex ratio. There were also no significant differences in the clinical characteristics of study groups regarding main factors affecting the development of RDS (Table 1).

2. Incidence of rds and neonatal outcome

Thirteen of 63 patients in the ambroxol group and nineteen of 50 patients in the dexamethasone group had RDS. The incidence of RDS was slightly lower in the ambroxol group than the dexamethasone group, but there was no statistical significance. The incidence of severe RDS, which was defined as Bomsel radiological classification above grade three and alveolo-arterial oxygen gradient less than 0.35, was also slightly higher in the dexamethasone group than the ambroxol group (Table 2).

Total duration of admission in the ambroxol group was slightly shorter than the dexamethasone group, but there was no statistical significance. Total incidence of IVH in the ambroxol group was significantly lower than the dexamethasone group ($p<0.01$), but the incidence of severe IVH above grade three was similar in each group (Table 3). In the ambroxol group two patients died of RDS, sepsis and DIC. In the dexamethasone group one patient died of RDS and sepsis (Table 4).

3. Neonatal infection

The incidence of culture proven sepsis was significantly higher in the dexamethasone group than the am-

Table 1. Clinical characteristics of study groups

Characteristics	Groups	
	Ambroxol (n=63)	Dexamethasone (n=50)
Gestational age (weeks)	33.6 ±2.2	33.5 ±2.5
<34 weeks (%)	19 (30.2)	22 (44.0)
≥34 weeks (%)	44 (69.8)	28 (56.0)
Male : Female	28 : 35	25 : 25
Multiple pregnancy (%)	8 (14.5)	4 (7.1)
Cesarean section (%)	32 (50.8)	34 (68.0)
PROM at delivery (%)	31 (49.2)	23 (46.0)
A/S 1min	7.2 ±2.5	6.8 ±2.6
5min	8.6 ±1.8	8.4 ±2.0
Asphyxia	13 (19.1)	14 (28.0)
Initial arterial PH	7.28±0.1	7.23±0.1

Mean±SD (%)

Table 2. Incidence of RDS

RDS	Groups	
	Ambroxol (n=63) (%)	Dexamethasone (n=50) (%)
RDS total	13 (20.6)	19 (38.0)
△aAO2≥0.35	6 (9.5)	9 (18.0)
△aAO2<0.35	7 (11.1)	10 (20.0)
Surfactant Tx.	5 (7.9)	8 (16.0)

Table 3. Outcome of study groups

	Groups	
	Ambroxol (n=63) (%)	Dexamethasone (n=50) (%)
Duration of adm. (days)	25.8±17.3	31.2±27.3
IVH total	30 (47.6)	42 (84.0)*
Grade≥III	3 (4.8)	2 (4.0)
NEC	1 (1.6)	2 (4.0)
ROP	1 (1.6)	2 (4.0)

* : p<0.01

Table 4. Neonatal deaths

Group	Sex	GP (WKS)	BWt (Kg)	Cause of death	Day of death (days)
Ambroxol	F	27.4	1.05	RDS, Sepsis	79
	M	32.5	1.80	Sepsis, DIC	33
Dexame-thasone	M	27.3	1.01	RDS, Sepsis	36

broxol group ($p<0.05$). Organisms isolated from blood culture in the ambroxol group were staphylococcus epidermidis, S. maltophilia, and enterobacter cloca. Organisms isolated from blood culture in the dexamethasone group were staphylococcus epidermidis, streptococcus maltophilia, enterobacter cloca, pseudomonas, and candida albicans (Table 5).

Discussion

Insufficient surfactant production in newborns, the so-called respiratory distress syndrome (RDS), is an important cause of mortality among preterm infants. Exogenous surfactant instillation and high frequency ventilator treatment have been introduced in neonatal RDS. Late sequeale of the CNS and cardiopulmonary systems are common even after recovery from RDS. Therefore therapeutic strategies focused on antenatal prevention of RDS with the aim to accelerate fetal lung maturation in women at risk of premature birth. In 1972 Liggens and Howie[6] found a significant decrease in the incidence of RDS following antenatal treatment with bethamethasone. Numerous clinical studies in humans supported their findings[7-9]. However, the most widely used agent, corticosteroids, though reducing the incidence of RDS, increases the morbidity and mortality from neonatal sepsis[10]. Pueperal endometritis also arises more frequently in such cases. The potential risk of maternal and fetal infection, which is extremely life threatening for the preterm newborn, has been a controversial subject[2][11-13].

Alternative treatments of equal efficacy without severe adverse reaction were requested. Among them, we have studied the effect of ambroxol, a bromhexine metabolite, has been experimentally proven as a lung surfactant inducer[14] with very low toxicity even in high dosages. Valaquez and Sepulveda[15] have shown that ambroxol stimulates the synthesis of not only surfactant but also the intracellular organelles selectively in mice. Wauer, et al[5] found a more significant improvement of the PaO_2/FiO_2 ratio, mean airway pressure, phospholipid profile of tracheal effluent and pulmonary profiles of spontaneously breathing infants in the ambroxol group than control group. In addition, the incidences of bronchopulmonary dysplasia (29% Vs 54%), intraventricular hemorrhage (25% Vs 44%) and postnatally acquired pneumonia (15% Vs 36%) were significantly reduced in the ambroxol group as compared to the control group. No adverse events attributed to ambroxol treatment were reported. However the efficacy of ambroxol in the prevention of neonatal RDS showed much controversy. Luerti, et al[3] reported significantly better results with ambroxol than with bethamethasone treatment in infants born between 27 and 34 weeks of gestation. But, Heytmanek, et al[16] reported no significant difference for the prevention of RDS with ambroxol and bethamethasone treatment in infants born between 27 and 34 weeks of gestation. Furthermore, recently, Dani C, et al[17] reported negative results in 88 mothers whose infants were born between 24 and 34 weeks of gestation and who were randomized either for treatment with ambroxol (group A=42) or served as control (group B=46). This study did not show the efficacy of antenatal ambroxol treatment both for the prevention of neonatal respiratory distress syndrome and for the reduction of its severity.

We wanted to determine whether ambroxol, a drug which stimulates the release of surfactant by type II pneumocytes, decreases the incidence of neonatal RDS and affect the incidence of neonatal infection. In our study,

Table 5. Incidence and cause of sepsis in study groups

		Ambroxol (n=63) (%)	Dexamethasone (n=50) (%)
Suspected sepsis		37 (58.7)	22 (44.0)
Provened epsis		3 (4.8)	12 (24.0)*
Organism	Sta. epidermydis	1	4
	Strept. maltophilia	1	3
	Enterobacter cloaca	1	3
	Pseudomonas		1
	Candida. albicans		1

* : $p<0.05$

the total incidence of RDS and severe RDS, which was defined as Bomsel radiological classification of RDS grade 3 and over and alveolo-arterial oxygen gradient on ABGA less than 0.35 on mechanical ventilation, were slightly lower in ambroxol group. But there was no statistical significance.

Antenatal treatment with steroid, especially in pregnant women with premature rupture of membrane for the prevention of RDS, demonstrated an increase in maternal or fetal infection. Taeusch, et al[12] reported that antenatal treatment with steroid increased the incidence of neonatal infection. In our study, about 22 to 25% of the ambroxol group had mild side effects, such as nausea and vomiting, headache, and chest tightness etc. But, the side effects were transient, and none had serious side effects, such as anaphylaxis, fever, and respiratory distress. However, in the dexamethasone group, about 20% had mild side effects and about 30% had a puerperal infection. Furthermore, the incidence of confirmed neonatal infection was significantly higher in the dexamethasone group than the ambroxol group.

During the past few years, the most popular theory for one of the causes of preterm labor has been intrauterine infection even though silent infection[17]. In our study, mothers with premature labor were included, and antenatal treatment with dexamethasone may have increased the risk of maternal or fetal infection. On the contrary, ambroxol has a contributory factor in infection prevention, especially that of the respiratory system as it increases mucocilliary transport by the stimulation of cilliary motility[19]. Hence the attachment of the pathogenic organism to the target organ is prevented. Furthermore, one of the most advantageous features of ambroxol may be its direct antimicrobial activity[20].

As a final result of our study, the incidence of confirmed neonatal infection was significantly higher in the dexamethasone group than the ambroxol group, which may be associated with a decreased incidence of bronchopulmonary dysplasia(BPD). Because many reports supported the correlation of BPD with infection[21)22)]. Further study is needed for the long-term outcome, including the incidence of BPD.

In summary, the incidence of RDS did not differ between the ambroxol and the dexamethasone group. But one of the outcomes, the incidence of IVH, and the incidence of neonatal infection in the ambroxol group were less than the dexamethasone group. Ambroxol is at least as effective as dexamethasone in reducing the incidence and severity of RDS with less infection. We speculate that further evaluation in optimal dosage and duration of antenatal treatment of ambroxol would be needed to design new treatment strategies preventing RDS and neonatal infection.

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