CLINICAL STUDIES

Effect of Prenatal T4 Treatment in Neonatal Morbidity: Preliminary Findings

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ABSTRACT. We report our experience with the use of intra-amniotic thyroxine to accelerate fetal maturation in preterm delivered infants. One hundred and fourteen infants who had received 500 µg of thyroxine weekly prenatally until an L/S ratio greater or equal to 2.0 was achieved, were compared to 113 premature infants who had not been given thyroxine or steroids prenatally. After stratification by weight, the relative incidence of respiratory distress syndrome (RDS), patent ductus arteriosus (PDA). necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH) were compared. A decrease in the incidence of RDS was observed in the infants with birth weight between 1000 and 1500g who had received more than one dose of intra-amniotic thyroxine. No difference in the incidence of RDS was observed in infants with birth weight of less than 1000g or over 1500g. One dose of thyroxine had no effect in decreasing the incidence of RDS , PDA, NEC, and IVH in any of the groups. We conclude intra-amniotic thyroxine seems to decreases the incidence of RDS in very low birth weight infants.
Keywords: prenatal thyroxine, respiratory distress syndrome, premature infant

Prematurity accounts for up to 80% of neonatal mortality and morbidity. Of all medical complications incurred by premature infants, respiratory distress syndrome (RDS) is the leading cause of morbidity and mortality. Although great advances have been made in the treatment of RDS, morbidity remains high. Antenatal steroids, have been effective in reducing the incidence of RDS. Other methods of accelerating fetal maturation are being explored (1-5). Thyroid stimulating hormone (TSH) in combination with corticosteroids has been used in a recent collaborative trial. A reduction in the incidence of chronic lung disease was reported but there was no effect on the relative frequency of RDS (6) The purpose of this communication is to report our experience with newborn infants with birth weight of less than 1750g and gestational age of less than 34 weeks who received more than one dose of thyroxine.

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Materials and Methods

One hundred and fourteen infants with birth weight of less 1750 and less than 34 weeks of gestational age who were given more than one dose of intra-amniotic thyroxine to accelerate fetal maturation were compared with a cohort of 113 infants- who had not received prenatal thyroxine or steroids- born in our hospital or at referring institutions during the same period of time (1984- 1989). Patients were matched for birth weight and gestational age. The gestational age of the infants ranged from 26 to 34 weeks in both groups. Treated infants had received from two to five doses of 500 g intra-amniotic T4 at weekly intervals starting at approximately 26 weeks gestation as previously reported by Romaguera et al (7). None of these patients received prenatal steroids or exogenous surfactant; which was not available at this time. For the purpose of analysis, infants were divided according to birth weight in three categories: less than 1000g, 1000-1500g and 1501- 1750g. The relative frequency of RDS, NEC and PDA and IVH was compared in the three groups. Comparison between groups was done using Chi Square and Fishers Exact Test. Unpaired t-student test was used to compared numeric variables between groups. Significance was established at $p<0.05$.

Results

Both groups of infants (treated versus untreated) were comparable regarding birth weight, gestational age and 5 minute Apgar Score (Table 1). The incidence of RDS

Table 1. General Characteristics

	<1000g		1001-1500g		1501- 1750g	
	Tx n=12	Not Tx n=36	Tx n=78	Not Tx N=41	Tx n=24	Not Tx n=36
Birth Weight (grams)	910±93	884±94	1326±170	1274±118	1616±101	1628±70
Gestational Age (wks)	29±2	29±2	31±3	31±2	32±2	31±2
Apgar 5 min	6±2	6±2	7±2	7±2	6±2	7±2
Male:Female	1:1	1:2	2:3	1:1	1:1	4:3

was significantly different in the treated group whose birth weight was between 1000 to 1500 g and who received more than one dose of thyroxine. No difference was observed on the relative frequency of RDS after only one dose of thyroxine There was no significant difference in the relative frequency of RDS in infants with birth weight less than 1000g, or among those between 1500g to 1750g who received more than one dose of intra-amniotic T4.(Table 2). The incidence of PDA, NEC or IVH was

Table 2. Incidence of RDS

Weight group (%)	Treated (%)	Untreated (%)	P
Less 1000g	6/12(50)	21/36(58)	NS
1001-1500g	24/78(31)	25/41(61)	0.002
1501-1750g	6/24(25)	9/36(25)	NS

not statistically different any of the groups.(Table3). Head sonograms were done in the most critically ill infants. The incidence of severe IVH Grade III and IV according to Papille)(8) was not different in both groups.

and the Consensus Conference Report in 1986, there has been resistance among some obstetricians regarding the use of steroids to enhance fetal lung maturation(11). Until recently only 12-18 percent of women who delivered prematurely were treated with antenatal corticosteroids (11). A recent meta analysis appears to confirm the effectiveness of steroids in accelerating maturation of the fetus (12). Relative contraindications exist for the use of steroids in certain maternal conditions such as insulin dependent diabetes, preeclampsia, premature rupture of membranes and multiple gestations (13).

Thyrotropin releasing hormone combined with steroids has been evaluated recently in a large collaborative trial. A decrease in the relative frequency of RDS was similar in the control and treated groups; however, a significant decrease in the incidence of chronic lung disease was reported (6) Recently a large collaborative study in Australia using a lower dose of TRH reported adverse effects from the combined treatment corticosteroids and TRH (14). Thyroxine has been known to improve lung function and accelerate the synthesis of surfactant phospholipids in animals studies (15) In vitro and in vivo studies provided strong evidence for the role of thyroid hormones in fetal maturation.

Triiodothyronine and thyroxine receptors have been known to increase during the second trimester in human pregnancies suggesting a role for thyroid hormones in lung maturation (4,5). Since thyroxine does not cross the placenta it needs to be given directly to the fetus either into the amniotic sack for the fetus to swallow or by intramuscular injection to the fetus (7,16) Increase in T4 in fetal blood has been observed after intra-amniotic administration of thyroxine (17,18). At present a limited number of human clinical trial have utilized the therapeutic application of thyroid hormone given intra-amniotic to accelerate fetal maturation (19,20,21).

Table 3. Morbidity

	<1000		1501-1750		1501-1750		
	Tx (%)	Not Tx (%)	Tx (%)	Not Tx (%)	Tx (%)	Not Tx (%)	P
Patent Ductus Arteriosus	3/10(25)	19/35(52)	17/78(22)	12/41(30)	4/24(16)	3/36(8)	NS
Necrotizing Enterocolitis	3/12(25)	15/35(42)	13/78(17)	6/41(15)	3/22(13)	9/36(25)	NS
Intraventricular Hemorrhage (Grade III & IV)	2/15(13)	1/36(3)	6/41(15)	3/26(12)	.....	4/18(22)	NS

Discussion

The use of corticosteroids for accelerating pulmonary maturation has been the standard of care since Liggins reported its effectiveness in 1972(9). For years, and specially after the National Collaborative Trial in 1981(10)

Maschiach was the first to report the use of intra-amniotic thyroxine to enhance pulmonary maturity (21). Romaguera et al, reported an increase in fetal lung maturation measuring the L/S ratio in the amniotic fluid of women given intra-amniotic thyroxine in anticipated premature deliveries.(19). In our study, we have observed

a decrease in the incidence of RDS in very low birth weight infants.

Our experience is not based on a randomized control trial since all patients were considered potential candidates for treatment and only patients who refused treatment or who came into the service too advance in labor did not receive treatment. Since our service is a tertiary referral center, most, if not all of the untreated patients were patients who were being treated for premature labor else where. They were referred to our service when conservative management failed. Romaguera et al, reported the use of prenatal thyroxine to enhance pulmonary maturation in pregnant cancer patients . She found that delivery could be planned and still permit early antineoplastic therapy of the mother.(21). She also observed beneficial results in a limited group of patients with diabetes, preeclampsia and severe RH hemolytic anemia (7).

We suggest that some groups of patients, where the use of steroids has been considered controversial, could benefit from this treatment modality. A disadvantage of this treatment may be the need of amniocentesis. In our center this is a routine procedure for all premature labors.

We conclude that the intra-amniotic administration of thyroxine accelerates fetal maturation expressed in lowering the frequency of RDS of preterm newborn infants. For this reason, we believe that thyroxine may have a place in the induction of fetal maturation in the preterm fetus. Besides, the additive effect of T4 and corticosteroids demonstrated in vitro and in animal studies needs to be address. We are currently undergoing a double blind randomized trial comparing the effect of thyroxine combined with steroids to steroids alone in reducing neonatal morbidity.

Resumen

Reportamos nuestra experiencia con el uso de tiroxina intra-amniótica para acelerar maduración fetal en infantes nacidos prematuramente. Ciento catorce infantes que recibieron tiroxina prenatal, 500 g semanal, hasta lograr una razón de lecitina a esfingomielina (L/S) mayor de 2.0, se compararon con 113 infantes prematuros que no habían recibido tiroxina o esteroides prenatales. Después de estratificar por peso de nacimiento, se determinó la incidencia relativa del síndrome de angustia repiratoria del recién nacido, ducto arterioso patente, enterocolitis necrotizante y hemorragia intraventricular. Se observó una disminución significativa en la incidencia del síndrome de angustia respiratoria en infantes con pesos de nacimiento entre 1000 y 1500gramos. No se observó disminución estadísticamente significativa en la incidencia de ducto arterioso patente, enterocolitis necrotizante y hemorrágia intraventricular. Tampoco se observó disminución en la incidencia del síndrome de angustia respiratoria en infantes con pesos de menos de 1000 gramos ni en infantes con peso mayor a 1500 gramos. Una sola dosis de tiroxina intra- amniotica no produjo efecto alguno en la incidencia del sindrome de angustia respiratoria, ni en la morbilidad neonatal. Concluímos que tiroxina intra-amniotica disminuye la incidencia del sindrome de angustia respiratoria en infantes prematuros de bien bajo peso.

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