CLINICAL STUDIES

Comparative Study of the Effectiveness of Thyroxine and Steroids on Reduction of Neonatal Morbidity: Outcome at 20 Months Follow-up

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This study analyzes health, growth and neurodevelopmental outcome of infants who received prenatal corticosteroids with or without thyroxine for fetal lung maturation. During a 12 month period infants from a prospective double blind study who received either steroids or steroids combined with thyroxine for pulmonary maturation and who had reached 18 months of age were recalled for evaluation of health status, growth parameters and neurodevelopmental outcome using the Bayley Scales 2nd edition (BSID-II). Mental developmental index (MDI), psychomotor developmental index (PDI), language developmental age (LDA), cognitive developmental age (CDA), and behavioral rating scales (BRS) were compared for the two treatment groups. The Hollingshead Socioeconomic Status Index was determined for each infant. Of a total of 134 patients enrolled during the study period, 66 patients return for follow up. Data from 60 patients was included in the final analysis. Of these, 32 had received the combination regimen and 28 had solely received only steroids. Demographics and neonatal morbidity were similar in both groups. No statistical differences in growth parameters, hospital admissions, respiratory problems, surgical procedures or frequency of infections were found. Neurodevelopmental parameters (MDI, PDI) were similar in both treatment groups, although, below normal in both groups. Language delay was more common in infants who received prenatal corticosteroids. There were no difference in the incidence of neurologic abnormalities. The addition of thyroxine to steroids did not affect growth or neuro-developmental outcome of the infants at 18 to 22 postnatal age.

Key words: Respiratory distress syndrome, Corticosteroids, Thyroxine, Neurodevelopment, BSID-II

Little success has been achieved in reducing the incidence of premature births in the last 20 years. While mortality of premature infants has decrease remarkably, morbidity remains high. Respiratory distress syndrome (RDS) with its sequel continues to burden the physicians who care for these infants. Emphasis has been placed in accelerating fetal lung maturation with hormones. Steroids have been used for this purpose with variable success (1,2). Studies done by Ballard and co-workers in animals and in fetal lung tissue demonstrated that thyroid hormone has an additive effect when combined with glucocorticoids in inducing fetal lung maturation (3,5). A collaborative trial to investigate the effect of adding thyroid releasing hormone (TRH) to glucocorticoids to enhance fetal pulmonary maturation in women with preterm labor was done in the United States. This resulted in no decrease in the incidence of RDS (6). In 1997, the Australian Collaborative Trial of Antenatal Thyrotropin-Releasing Hormone (ACTOBAT) reported a higher incidence of premature babies when TRH was used in combination with corticosteroids in women with premature labor. Furthermore, a follow up study done at 12 month of age in infants from the ACTOBAT trial, whose mothers had received TRH combined with steroids reported detrimental effects on neurodevelopment outcome. TRH administration was associated with an increased risk of developmental delay in motor, social, fine motor, and sensory milestones as well as early language impairment (7). To this end we designed a follow up study of infants who participated in a double blind randomized trial comparing the effectiveness of corticosteroids alone or

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combined with intra-amniotic thyroxine in enhancing fetal lung maturation and thus reducing the incidence of RDS (8).

Method

Patients were selected from a Comparative Study of the Effectiveness of Thyroxine and Steroids on Reduction of Neonatal Morbidity at the Department of Obstetrics and Gynecology of the University of Puerto Rico School of Medicine (8). Infants who would reached 18 months of age during the period from July 1997 to December 1998 were contacted by telephone and by mail six weeks ahead of the planned appointment. They were invited to the University of Puerto Rico School of Medicine Clinical Research Center for medical and neurodevelopmental evaluations. Of the 134 infants identified, 66 patients came for evaluation. Data from 60 patients was employed after excluding the second pair of each pair of twins and infants who did not complete the evaluations. Each infant underwent a complete physical and neurological examination by a neonatologist or neonatology fellow blinded to the treatment protocol. Growth parameters, weight, height, and head circumference were plotted on the National Center for Health Statistics Charts. Percentiles were determined for each growth parameter. Information regarding medical complications, hospital admissions, medications, infections, immunizations, respiratory problems and surgical procedures were recorded.

The developmental status was evaluated using the 2nd edition of the Bayley Scales of Infant Development (BSID-II) that yield scores for mental developmental index (MDI) and psychomotor developmental index (PDI) with a standardization mean of 100 and a standard deviation of 15 points. Development was considered mildly impaired if scores were between 70 to 84, moderately impaired if they were between 55 to 69 and severely impaired if they were less than 55. The Cognitive Developmental Age (CDA), Language Developmental Age (LDA), Behavioral Rating Scales (BRS), were determined for each infant. The standardization of the Bayley Scales of Infant Development (BSID-II) included a representation of the Hispanic population living in the Continental U.S. (9). No correction was done for prematurity. All infants underwent hearing screening using the Natus Automated ABR. Hearing loss was considered present if the hearing threshold was more than 75 decibels.

All preterm infants underwent ophthalmologic evaluation at 8 weeks of age. Full term infants had routine ophthalmologic evaluation at 12-24 months. Significant visual defect was defined as any patient who required surgical intervention. Blindness was diagnosed if vision could not be corrected to better than legal blindness. Socioeconomic status was classified according to the Hollingshead Socio-economic Status Index. The Hollingshead Index considers the social status to be a multidimensional concept. It takes into consideration education, occupation, sex, and marital status of parents. Stratas are classified from 1 to 5. The 5^{th} is difine as the highest socioeconomic strata and the 1^{st} is the lowest (10). For analysis we pooled the Hollingshead Scores into two groups: mid high to high (strata 4 and 5) versus low to middle (strata 1 to 3) because of the small number of patients in each strata.

Statistical analysis. Descriptive statistics for continuous variables including mean, standard deviation, median and range (min.-max.) were computed. Frequency distribution and percents were obtained for categorical variables. The Shapiro Wilk test was used to verify the normal assumption of continuous variables, as well as box plots and quantile plots. The Student t-test or Mann-Whitney test, when appropriate was used to compare continuous variables. Pearson's chi-square or Fischer's exact test, when appropriate, was used to determine statistical associations among categorical variables. Pearson's correlation analysis was used to correlate MDI and LDA, and BRS with CDA in both study groups. Odds ratio and 95% confidence interval (95% CI) were calculated to estimate the magnitude of the associations among study groups with MDI, PDI, infections, respiratory problems and hospitalizations. Variables with a p-value <0.10 in the univariate analysis were included in the unconditional logistic regression analysis. The accepted level of significance was $p<0.05$. All statistical test were two sided. Data entry was performed using Epi-Info 6.04 (1). The SAS package was used to perform the statistical analysis. (SAS software Version 8.0 (2).

Results

Of 134 infants born during the study period, 66 came for follow up. There were four pair of twins in the study group of which only twin # 1 was included in the analysis, although both underwent the same evaluation; two other patients did not complete the evaluations. Data from 60 patients was employed for final analysis. The characteristic of both treatment groups were similar except for the time on mechanical ventilation which was statistically significantly longer in the infants who received the combination of thyroxine and steroids. The incidence of RDS was statistically similar in both groups (Table I). There was no significant difference in health status variables. Neurodevelopmental variables, MDI, PDI, although similar in both groups, were below normal range. LDA and CDA showed no significant difference between the two

Tables 1. Characteristics of the study group participating in the follow-up study

	Steroids/T4* (n=32)	Steroids (n=28)	p-value
Age (mo)			
Mean (SD)	20 ± 4.6	19.5 ± 2.6	ns
Birth weight (g)			
Mean (SD)	2332 ± 801	2465 ± 589	ns
Gestation (wk)			
Mean (SD)	36 ± 3.5	37 ± 2.5	ns
Male gender			
Apgar score (5min)	9	9	
IVH (I-III)	3 (9)	3 (11)	
RDS	8 (25)	7 (25)	ns
NEC	4	0	
Mechanical ventilation (days)	8 (25)	1 (3)	0.03
Hollistead score:			
1-3	15 (47)	12 (43)	ns
4-5	17 (53)	16 (57)	ns

Plus-minus values are means ± standard deviation (SD)
( ) represent percentages
* steroid in combination with intra-amniotic thyroxine

treatment strategies. Although language delay was more frequent in infants who received only prenatal steroids it was not statistically different (Table 2). There was a strong correlation in both study groups between MDI with LDA

Table 2. Developmental Scores of Infants in the Follow-up Study Using the Bayley Infant Scales II.

	Steroids/thyroxine (n=32)	Steroids (n=28)	p-value
MDI	80 ± 17	80 ± 16	0 .54
PDI	84 ± 14.5	85 ± 16	0.93
BRS	84 ± 24	75 ± 30	0.04
LDA	16 ± 6	14 ± 3	0.38
CDA	18.3 ± 5.88	16.6 ± 3.10	0.25

Plus-minus values are means SD; all scores were included
BRS (behavioral), LDA (language developmental age) and CDA (cognitive developmental age) were calculated from the 2nd edition Bayley Infant Scales

and CDA. (Table 3) Infants who received the combination of steroids with thyroxine did not have higher risk of having a low MDI or PDI, nor more infections or respiratory problems than infants who only received steroids. No statistical difference was observed among the incidence of impairment between the two treatment groups (Table 4). No ophthalmological or hearing abnormalities were detected in any of the study patients. Only one patient in each group was diagnosed with a serious neurological abnormality; a patient of combined treatment had congenital ventriculomegaly and a patient in the steroid treatment group had hypotonia of congenital origin.

Table 3. Correlation of CDA vs MDI and LDA vs MDI Between Steroids and Thyroxine-steroid Treatments.

Correlation	Steroids Treatment	p-value	Steroids and Thyroxine Treatment	p-value
CDA vs MDI	0.64	0.0002	0.59	0.0004
LDA vs MDI	0.82	0.0001	0.67	0.0001

CDA Cognitive developmental age
MDI Mental developmental age
LDA Language developmental age

Table 4. Comparison of grade of neurodevelopmental using the MDI scores

	Steroids	Combined T†	*p value
Normal (scores>84)	12 (20)	14 (23)	ns
Mild Impairment (scores 70-84)	9 (20)	10 (17)	ns
Moderate Impairment (scores 55-69)	3 (5)	5 (8)	ns
Severe Impairment (scores <54)	3 (5)	4 (7)	ns

*Fisher's Exact Test
†Steroid - Thyroxine combined treatment

Discussion

The ACTOBAT study has been critized because it did not use an established developmental instrument. They established their own domains of development that cannot be paralleled with other established measures (11). To avoid this pitfall we used the Bayley Infant Scales to evaluate all of our patients. This approach is a more expensive one requiring infants to come into the clinics for evaluation and the availability of specialized personnel. This limits the number of patients evaluated but at the same time a more objective evaluation can be done. We also chose to evaluate patients at a later age to avoid dealing with the effects of prematurity in neuro-development since we were not correcting for prematurity. We were able to reclute 49% of the patients in the study window. This is a limitation of the study that has to do with the fact that patients needed to come to the hospital for formal objective evaluations while the ACTOBAT study used questionnaires sent by mail. Many parents agreed to bring their child because they were worried that the treatment could have caused some problem to their child. Others thought there was no need to come because the child, according parent's perception, was doing fine. We think this could have biased the study towards the most affected infants coming for evaluation. Other reasons for patients attrition was that family moved out of the geographic area leaving no information, telephone disconnected, transportation problems, etc.

The low MDI and PDI scores obtained by our patients was an area of concern. We have previously reported the results of MDI and PDI in a group of babies who had

received intrauterine thyroxine using the 1st edition Infant Bayley Scales. The MDI scores were 92±12 in the treated group compared to 89.7±22 in an untreated group of premature infants (12,13). Garcia Coll reports lower MDI and PDA scores using the 2nd edition Bayley Scales in a population of homeless and low income housed infant and toddlers from Massachusetts. She reports 12 points lower in the MDI and 7 points lower in the PDI scores when the BSID-II was used (14). Glen, et al. found that the effect of additional language items in the BSID-II has adverse effects on performance (15). In our study we demonstrated that language developmental age (LDA) had a strong effect on MDI. Many of the patients with low MDI had low LDA. We speculate that a catch up of language had not occurred yet in these infants. A lower language score was obtained in the group that only received steroids when compared with those that received the combined therapy. We have no explanation for this finding. A similar finding has not been reported in other studies which have followed infants exposed to prenatal corticosteroids. The small number of infants in our study preclude any conclusions for this finding. Bayley Scores were not corrected for gestational age as other authors suggest (16). We think this has little impact in our result because most of our patients were large premature babies and were evaluated at a later age where the impact of prematurity should be negligible.This neurodevelopmental follow-up study of infants exposed to antenatal thyroxine and glucocorticoids as part of assessing of the effectiveness of the treatment showed no significant difference in outcome between the two treatment strategies. Although the number of patients evaluated was small, we could not detect any adverse effects on neurodevelopment of infants exposed to intrauterine thyroxine.

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