Original Article

Neurodevelopmental outcome of pre-term babies less than 34 weeks of gestation at corrected 2 years of age, with respect to their antenatal steroid status

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ABSTRACT

Objectives: The objective of this study was to determine the neurodevelopmental status of pre-term babies between <34 weeks of gestation and equal to or more than 25 weeks of gestation, at corrected 2 years of age with respect to their antenatal steroid status. **Materials and Methods:** This population-level prospective study was conducted over a period of 6 years from 2017 to 2023 in middle Kerala. Pre-term babies with gestational age at birth between <34 weeks and equal to or more than 25 completed weeks, presenting for follow-up within 3 months of delivery, were randomly enrolled for the study. A total of 150 children were followed up and neurodevelopmental assessment done using Bayley Scales of Infant and Toddler Development edition-3 at their corrected 2 years of age. Approval for this prospective observational study was obtained from the Institutional Ethics Committee, School of Behavioral Sciences, Mahatma Gandhi University, Kottayam, Kerala, dated September 22, 2017. **Results:** Eighty-one pre-term <34 weeks babies belonged to the antenatal steroid complete group, 40 pre-term <34 weeks babies belonged to the antenatal steroid partial group, and 29 pre-term <34 weeks babies belonged to the nil steroid group. Total neurodevelopmental status score and domain-wise, cognitive, language, motor, and social-emotional developmental scores show significantly higher scores for pre-term <34 weeks with antenatal history of complete course steroid administered before pre-term delivery compared to partial and nil antenatal steroid group. **Conclusions:** Antenatal steroids are having a significant impact on the overall neurodevelopmental outcome of pre-term babies equal to or more than 25 weeks of gestation and <34 weeks of gestation, at their corrected 2 years of age, the maximum benefit for complete antenatal steroid group pre-term babies, equal to or more than 25 weeks and <34 completed weeks of gestation when compared with pre-term babies, equal to or more than 25 weeks and <34 completed weeks of gestation without any antenatal steroids.

Key words: Ante natal steroids, Neurodevelopmental outcome, Pre-term <34 weeks

A major contributor to under-five morbidity and mortality is pre-mature labor. 10–15% of total deliveries are due to pre-term labor [1,2]. Antenatal steroids are having proven short-term benefits such as reduction of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intracranial hemorrhage, and sepsis. It is estimated that there is a 34% reduction of the incidence of RDS, 46% reduction of the incidence of intraventricular hemorrhage (IVH), 54% reduction in the incidence of NEC, and 31% reduction in mortality among live pre-term births 34-week gestation or less [2]. Hence, the Government of India recommends a single course of corticosteroid injection in anticipated pre-term labor between 24 and 34 weeks of gestation [2]. The World Health Organization (WHO) recommends corticosteroid injection either dexamethasone or betamethasone antenatally in anticipated pre-term delivery between 24 and 34 weeks of gestation [3]. Antenatal corticosteroid therapy is recommended by the WHO for women with pre-gestational and gestational diabetes when there is a high likelihood of pre-term birth, and this should be accompanied by interventions to optimize maternal blood glucose control [3]. Antenatal corticosteroid therapy is also recommended for women with a high likelihood of pre-term birth of a growth-restricted fetus. Antenatal corticosteroid therapy is also recommended for women with hypertensive disorders in pregnancy who have a high likelihood of pre-term birth [3]. Absolute contraindication for antenatal corticosteroid therapy is women with chorio amnionitis who are likely to give birth pre-term [2, 3]. In a few studies that examined long-term outcomes of antenatal corticosteroids, treatment was associated with a 51% reduction in developmental delay and a trend toward fewer children having cerebral palsy, the longest period of follow-up being 6 years [1]. The benefits of the administration

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of antenatal corticosteroids before 24 weeks of gestation are not well understood and studied [1].

Studies related to the long-term neurodevelopmental outcome of pre-term babies who have received antenatal corticosteroids and those pre-term babies who have not received antenatal corticosteroids are relatively less. The present prospective study was aimed at determining the neurodevelopmental status of pre-term babies <34 weeks of gestation at their corrected 2 years of age with respect to their antenatal steroid status. Total and domain wise neurodevelopmental assessment was done using Bayley scales of infant and toddler development edition-3 (BSID-111) at their corrected 2 years of age. The majority of delivery points admitting and conducting pre-term deliveries are usually following the practice of administering antenatal steroids either betamethasone or dexamethasone in expected pre-term deliveries between 24 weeks and above and <34 weeks of gestation. The dosage schedule for dexamethasone is 6 mg 12th h 4 doses. The dosage schedule for betamethasone 12 mg 24 h apart 2 doses. If delivery occurs 24 h or more after the last dose of steroid, it is considered a complete course group. Anything less than this is considered a partial course group. If no dose of steroid in any form of corticosteroid, dexamethasone, or betamethasone received, it is considered as nil antes natal steroid groups. Sometimes, obstetrician may not get time to administer steroids sufficiently early in an unexpected onset of pre-term labor [4,5].

MATERIALS AND METHODS

This population-based prospective study was conducted in middle Kerala over a period of 6 years between 2017 and 2023, pre-term babies <34 weeks of gestation and equal to or more than 25 weeks of gestation at delivery, and presenting for follow-up within 3 months of delivery were randomly enrolled and followed up for the study up to corrected 2 years of age [6]. Pre-term babies who are admitted to tertiary care units (neonatal intensive care units/special newborn care unit) of both private and public institutions of Kottayam district and discharged for follow-up were the target population for the study. Detailed evaluation was made based on the history and discharge summary about the antenatal steroid administration status. Those children having any visual birth defects, congenital heart defects, syndromic or other genetic disorders were excluded from the study. Enrolled babies fulfilling the inclusion criteria were followed up. Sample size was determined using the Cochran formula assuming the prevalence of pre-term delivery 10% of total deliveries and found to be 138 at 95% confidence interval with 5% precision. One hundred and fifty pre-term <34 weeks of gestation at the time of delivery were randomly enrolled for the study, over a period of 3 years, and a final neurodevelopmental assessment done at their respective corrected 2 years of age. Approval for the prospective observational analytical study was obtained from the Institutional Ethics Committee, school of behavioral sciences, Mahatma Gandhi University, Kottayam, Kerala State, India, dated September 22, 2017.

Those pre-term babies having a history of receiving antenatal steroids full course either betamethasone or dexamethasone 24 h before delivery were considered complete (Group-1), those who received steroid but not full course were considered partial (Group-2), and those who did not receive steroid in either form betamethasone or dexamethasone were enrolled as nil steroid (Group-3). Those babies who were not brought for follow-up and those babies whose parents did not give consent for the study were excluded from the study. Neurodevelopmental assessment was done using BSID-111 under domains cognition, communication, motor, and social-emotional by the principal investigator at corrected 2 years of age. Statistical measures such as measures of central tendency standard deviation and parametric tests, one-way analysis of variance (ANOVA), and Bonferroni *post-hoc* test for pair-wise comparison were employed for analyzing the data.

RESULTS

Table 1 shows that pre-term children who got a complete course of ante-natal steroids 24 h before delivery (Group-1) and partial ante-natal steroid (Group-2) babies are having higher means of total and domain-wise (cognition, communication, motor and social-emotional) neurodevelopmental status scores compared to mean values of nil antenatal steroid (Group-3) babies.

Table 2 summary of one-way ANOVA shows that there are significant differences in means of total and domain wise (cognition, communication, motor, and social emotional) neurodevelopmental status scores of different groups of pre-term <34 weeks children at corrected 2 years of age with respect to their antenatal steroid status.

Table 3 pair-wise comparison of total neurodevelopmental status scores shows that mean scores of pre-term babies, who

Table 1: Mean values and standard deviations of total and domain-wise neurodevelopmental status scores of pre-term <34 weeks babies at 2 corrected years of age with respect to their antenatal steroid status

S. No.	Domains	Ante natal steroid status	n	Mean	SD
1	Total	1. Complete	81	357.07	28.81
		2. Partial	40	329.10	24.78
		3. Nil	29	305.21	30.58
		Total	150	339.59	24.75
2	Cognition	1. Complete	81	86.73	7.83
		2. Partial	40	80.88	6.09
		3. Nil	29	76.38	8.55
3	Communication	1. Complete	81	93.32	8.31
		2. Partial	40	88.23	7.93
		3. Nil	29	80.69	8.45
4	Motor	1. Complete	81	89.56	7.84
		2. Partial	40	81.25	10.25
		3. Nil	29	72.28	11.19
5	Social-Emotional	1. Complete	81	87.47	9.69
		2. Partial	40	78.75	6.07
		3. Nil	29	75.86	7.45

Table 2: Summary of one-way analysis of variance of total and domain-wise neurodevelopmental status scores of different groups of pre-term <34 weeks babies at corrected 2 years of age with respect to their antenatal steroid status

S. No.	Domains	Source of variation	Sum of squares	Df	Mean square	F	p
1	Total	Between groups	63446.46	2	31723.23		
		Within groups	116527.91	147	792.71	40.02	0.000
		Total	179974.37	149			
2	Cognition	Between groups	2573.61	2	1286.80		
		Within groups	8397.23	147	57.12	22.53	0.000
		Total	10970.84	149			
3	Communication	Between groups	3498.60	2	1749.30	25.7	0.00
		Within groups	9984.84	147	67.92	5	0
		Total	13483.44	149			
4	Motor	Between groups	6788.71	2	3394.35	39.8	0.00
		Within groups	12519.29	147	85.17	6	0
		Total	19308.00	149			
5	Social-emotional	Between groups	3816.38	2	1908.19		
		Within groups	10497.12	147	71.41	26.72	0.000
		Total	14313.50	149			

Table 3: Bonferroni test for pair-wise comparison of total neurodevelopmental status scores, of different groups of pre-term (<34 weeks) babies at corrected 2 years of age, with respect to their antenatal steroid status

S. No.	Pair	Mean	Mean difference	p
1	1. Complete	357.07		
	2. Partial	329.10	27.97	0.000
2	1. Complete	357.07		
	2. Nil	305.21	51.86	0.000
3	1. Partial	329.10		
	2. Nil	305.21	23.89	0.002

Table 4: Bonferroni test for pair-wise comparison of cognitive scores of different groups of pre-term babies (<34 weeks) at corrected 2 years of age with respect to their antenatal steroid status

S. No.	Pair	Mean	Mean difference	p
1	1. Complete	86.73		
	2. Partial	80.88	5.85	0.000
2	1. Complete	86.73		
	2. Nil	76.38	10.35	0.000
3	1. Partial	80.88	4.50	0.048
	2. Nil	76.38		

Table 5: Bonferroni test for pair-wise comparison of language scores of different groups of pre-term (<34 weeks) babies at corrected 2 years of age with respect to their antenatal steroid status

S. No.	Pair	Mean	Mean difference	p
1	1. Complete	93.32		
	2. Partial	88.23	5.09	0.005
2	1. Complete	93.32		
	2. Nil	80.69	12.63	0.000
3	1. Partial	88.23		
	2. Nil	80.69	7.54	0.001

received full course antenatal steroids (Group-1) and partial course antenatal steroids (Group-2) are significantly higher when compared to those pre-term babies, who did not receive any antenatal steroids (Group-3). Complete antenatal steroid (Group-1) babies are having a significantly higher mean of total neurodevelopmental status score compared to partial antenatal steroid (Group-2) babies.

Table 4 pair-wise comparison shows that pre-term antenatal steroid complete course (Group-1) babies have significantly higher mean cognitive score values compared to antenatal steroid partial (Group-2) and antenatal steroid nil (Group-3) babies.

Table 5 pair-wise comparison shows that pre-term antenatal steroid nil (Group-3) babies have significantly lower mean language scores value at corrected 2 years compared with pre-term antenatal steroid complete (Group-1) and partial (Group-2) babies. Pre-term antenatal steroid status partial (Group-2) babies have significantly low mean language score value compared to the pre-term antenatal steroid status complete (Group-1) babies.

Table 6 pair-wise comparison shows that pre-term antenatal steroid nil (Group-3) babies have significantly lower mean motor score values at corrected 2 years compared with pre-term antenatal steroid complete (Group-1) and partial (Group -2) babies. Pre-term antenatal steroid status partial (Group-2) babies have significantly low mean motor score value compared to the pre-term antenatal steroid status complete (Group-1) babies.

Table 7 pair-wise comparison shows that pre-term antenatal steroid status complete (Group-1) babies have significantly higher mean social-emotional score values at corrected 2 years of age compared to pre-term antenatal steroid status partial (Group-2) and nil (Group-3) babies. Mean differences between partial (Group-2) and nil (Group-1) babies are not significant.

Table 6: Bonferroni test for pair-wise comparison, of motor scores of different groups of pre-term (<34 weeks) babies at corrected 2 years of age, with respect to their antenatal steroid status

S. No.	Pair	Mean	Mean difference	p
1	1. Complete	89.56	8.31	0.000
	2. Partial	81.25		
2	1. Complete	89.56	17.28	0.000
	2. Nil	72.28		
3	1. Partial	81.25	8.97	0.000
	2. Nil	72.28		

Table 7: Bonferroni test for pair-wise comparison of social-emotional scores, of different groups of pre-term (<34 weeks) babies at corrected 2 years of age, with respect to their antenatal steroid status

S. No.	Pair	Mean	Mean difference	p
1	1. Complete	87.47		
	2. Partial	78.75	8.72	0.000
2	1. Complete	87.47		
	2. Nil	75.86	11.61	0.000
3	1. Partial	78.75		
	2. Nil	75.86	2.89	0.490

DISCUSSION

Obstetrician Graham Liggins, while conducting experiments in pregnant sheeps, incidently noticed more structural maturity and survival in premature lamps born to pregnant sheeps who received antenatal steroids. Later Liggins and pediatrician Rose Howie conducted human trials of this type of antenatal interventions in anticipated pre-term deliveries and published it in an article in 1972. They found a significant reduction of RDS and neonatal mortality in pre-term babies due to this intervention [1]. Further studies established the effectiveness of this intervention in reducing the incidence of RDS, NEC, IVH, and overall neonatal mortality in pre-term babies [1]. The steroid used initially by Liggins and Howie was betamethasone, a 1:1 mixture of phosphate and acetate, two injection courses 12 mg given at 24 h intervals. The effectiveness due to its blood levels may be maximum during 2–7 days after the first injection [7,8]. The present study did not differentiate between betamethasone and dexamethasone, but only between, complete course, partial course, and nil.

The Government of India, the Ministry of Health and Family Welfare issued operational guidelines in 2014, regarding the use of antenatal corticosteroids in anticipated pre-term births [2].

Studies on long-term neurodevelopmental status of pre-term babies <34 weeks with respect to their antenatal steroid status are less and mostly inconclusive 2. The majority of studies compare neurodevelopmental status of pre-term babies with term babies. In this study, comparison is made between pre-term <34 weeks and equal to more than 24 weeks of gestation with completed antenatal steroid group babies with pre-term <34 weeks with partial antenatal steroid group and pre-term <34 weeks without antenatal steroid group babies of their neurodevelopmental status at corrected 2 years of age. Domains for assessment included cognition, communication (receptive and expressive), motor (gross motor and fine motor), and social-emotional using BSID-111 [4,9]. The objective of the present study was to compare the neurodevelopmental status, at corrected 2 years of age, of three different pre-term <34 weeks groups babies, with respect to their antenatal steroid status.

Results of a meta-analysis study [7] lead to a conclusion that exposure to a single course of antenatal steroids is associated with a significantly lower risk of neurodevelopmental impairment in children with extremely pre-term birth but a significantly higher risk of neurocognitive and psychological outcomes in children with late pre-term and full-term birth.

Results of the present study clearly show that mean neurodevelopmental status scores of domains cognition, language, motor, and social-emotional of pre-term <34 weeks and >24 weeks of gestation with complete course of antenatal steroid group babies are significantly better compared to the pre-term <34 weeks and >24 weeks of gestation without antenatal steroid group babies and pre-term with partial antenatal steroid group babies. Thus pre-term <34 weeks with complete antenatal steroid group babies had the maximum benefit compared to the other two groups of pre-term <34 weeks babies, indicating the need for starting antenatal steroid in any form betamethasone or dexamethasone in all anticipated pre-term deliveries, sufficiently early to complete the full course, 24 h before pre-term deliveries. One-way ANOVA and Bonferroni pair-wise comparison indicates significant differences in means of different groups of pre-term babies <34 weeks of gestation with respect to their antenatal steroid status. Even in those pre-term <34 weeks of gestation group babies who received only a partial course of antenatal steroid had significantly better neurodevelopmental mean values in all domains compared to the pre-term <34 weeks with nil antenatal steroid group babies. Better neurodevelopmental status outcomes at corrected 2 years of age in pre-term <34 weeks and >24 weeks of gestation with completed/partial antenatal corticosteroids status group babies may be attributed to the reduced incidence of RDS, NEC and IVH when compared to pre-term<34 weeks and >24 weeks without antenatal steroid status group.

Implications of the present study for clinical practice are that corticosteroids either betamethasone or dexamethasone should be administered to all antenatal women <34 weeks of gestation where pre-term delivery is anticipated within 1 week unless there are any absolute contraindications like chorioamnionitis, considering the huge benefit of it for the pre-term babies <34 weeks of gestation. Future research concentrating on whether any significant differences exist between the betamethasone group and dexamethasone group, related to neurodevelopmental outcome at corrected 2 years of age, can be carried out.

Limitations of the study out of the total 150 children who were finally assessed for neurodevelopment, antenatal steroid nil group babies were only 29 compared to 40 antenatal steroid partial group and 81 antenatal steroid complete group.

CONCLUSIONS

Pre-term <34 weeks and more than 24 completed weeks of gestation with a history of receipt of full course of antenatal steroids have significantly better neurodevelopmental outcome at corrected 2 years of age compared to pre-term <34 weeks and >24 weeks of gestation babies without history of antenatal steroids. Pre-term <34 weeks and more than 24 weeks of gestation babies, with a history of antenatal steroid partial administration, are having better neurodevelopmental status at corrected 2 years of age compared to pre-term babies <34 weeks and >24 weeks of gestation without antenatal steroid. Relatively better neurodevelopmental outcome of pre-term babies <34 weeks gestation with a history of antenatal steroid when compared to pre-term babies <34 weeks gestation without antenatal steroids may be attributed to decrease neonatal insults from RDS, NEC, and IVH in antenatal steroid group pre-term babies.

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