Original Research

Association of Antenatal Corticosteroid use with Hypoglycaemia and Hyperbilirubinemia in Preterm Neonates Admitted in a Tertiary Hospital of Kolkata: A Longitudinal Study

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Abstract

Background: Timely use of antenatal corticosteroids in a mother of preterm labour decreases the rates of perinatal death, respiratory distress syndrome, intra-ventricular hemorrhage, necrotizing enterocolitis in the new borns. However it is reported to have a causative role in neonatal hypoglycemia and hyperbilirubinemia. So the present study attempts to determine the association between the use of antenatal corticosteroids with hypoglycaemiaand hyperbilirubinemia in newborns with less than 35 weeks of gestational age.

Methods: A prospective observational study was conducted during a time period of 24 months from January 2020 to December 2021 in a tertiary care hospital of Kolkata on 99 preterm neonates of less than 35 weeks of gestational age. Antenatal history of corticosteroid use, neonatal glucose level and bilirubin level were measured among others. Data were analyzed using MS-EXCEL.

Results: Majority of neonates' mothers (71.7%) had received antenatal corticosteroids. Only 4.0% of the cases had hypoglycaemia at birth. But there was no cases of hypoglycaemia at 12 hour and 24 hour after birth. In 58.6% of the cases bilirubin level was in the phototherapy range and double surface photo therapy was required. In 14.1% of the cases double volume exchange transfusion was required.

Conclusion: Antenatal corticosteroid administration is not associated with neonatal hypoglycaemia but it is significantly related to neonatal hyperbilirubinemia.

Key word: corticosteroid, preterm, hypoglycaemia, hyperbilirubinemia

Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality. The incidenceof preterm birth in India is 7-9%,[1] and the rates are constantly rising. Preterm birth and its complications are the leading cause of perinatal mortality.[2] Preterm neonate is defined as a neonate born before

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37 weeks of gestation irrespective of the birth weight.

Timely use of antenatal corticosteroids in a mother reports with preterm labourbefore 34 weeks of gestation has the following clinical impacts in newborns who receive good supportive care by decreasing the rates of perinatal death (31%), respiratory distress syndrome (34%), intra-ventricular hemorrhage (46%), necrotizing enterocolitis (54%) and intensive care admissions.[3]Administration of antenatal corticosteroids to mothers at high risk for preterm birth has been shown to markedly improve neonatal outcomes, beginning with the landmark study by Liggins and Howie in 1972.[4]

In contrast to the beneficial effects for the fetus, maternal corticosteroids administration can result in a time limited period of maternal hyperglycemia.[5] The mechanism for this corticosteroid induced hyperglycemia is due to increased hepatic gluconeogenesis, elevated plasma glucagon levels and decreased utilization of peripheral glucose, via transport and receptormodifications.[6] Many neonates are born within days of antenatal corticosteroid administration and are thus exposed to this period of maternal hyperglycemia acutely before delivery. The 1952 Pederson hypothesis that maternal hyperglycemia leads to a state of fetal hyperinsulinemia and subsequent neonatal hypoglycemia and this may have relevance in the setting of short course antenatal corticosteroid administration.[7]WHO defines neonatal hypoglycemia as blood glucose level less than 45 mg/dl. Among ELBW infants, hypoglycaemiaoccurs more frequently in SGA neonates. Hypoglycaemiais the commonest metabolic disorder of neonates. If not detected in time, it can lead to considerable morbidity and mortality and both symptomatic and asymptomatic hypoglycemia can lead to long term neurological sequelae[8]

Similarly Corticosteroid use can also lead to hyperbilibubinaemia in children. it is observed that those exposed to antenatal dexamethasone had higher levels of serum unconjugated bilirubin for the first week after birth compared to non exposed population and their high level of hyperbilirubinemia requiring treatment[9]. Pathological hyperbilirubinemia in neonates can occur due to various reasons in newborn babies and is important because bilirubin is neurotoxic in neonates and even healthy babies can sometime sustain irrveversible brain damage. If hyperbilirubinemia is not managed promptly, adverse consequences include the classic manifestations of kernicterus, isolated auditory impairment or subtle, processing disturbances can occur[10].

So the present study attempts to determine the relation between the use of antenatal corticosteroids with neonatal hypoglycaemiaand hyperbilirubinemia in newborns with gestational age less than 35 weeks.

Materials and Methodology

A prospective Observational Study was conducted in neonatal Care Unit (SNCU & NICU) Department of Paediatric Medicine R.G.Kar Medical College & Hospital, Kolkata from January 2020 to December 2021. 99 preterm babies with Gestational Age less than 35 weeks were included in the study. Among those babies with presence of lethal congenital anomalies or severe perinatal asphyxia were excluded.

For dependent variable of hypoglycaemia 12 hourly CBG monitoring was done. For hyperbillirubinemia, transcutaneous Bilirubin (prior to phototherapy) & total Serum Bilirubin (after 24 hours of phototherapy) were measured. Maternal factors like age, sex, gestational age, mothers' blood group, gravida & parity, mothers' diabetic status, whether antenatal corticosteroids received or not were considered as independent variable. Whether the baby has received double surface phototherapy (DSBT) or double volume exchange transfusion (DVET) was also taken into account. Calculated sample size was 90 (ref) which was further increased by 10% to compensate non response rate and exclusion criteria. Data were collected using case sheets, clinical examination and laboratory investigation findings about the above mentioned parameters. Data were compiled and analysed using MS_Excel and 'R' statistical package.

Mothers/care givers were informed about the study objectives and written informed consent was

signed by them. In case of illiterate mothers finger print of write thumb was taken in presence of a witness. Approval was taken for institutional ethics committee of R.G.kar Medical College, Kolkata (Registration number: ECR/322/Inst/WB/2013; memo no. RKC/173)

Result

Out of 99, 53.54% neonates were male and 46.46% of them were females. 37 (37.37%) out of 99 neonates had birth weight between 1 to 1.499 kg, which is very low and the remaining 62 neonates had low birth weight of 1.5 to 2.499 kgs. The mean birth weight of the neonates is 1.6 kgs with standard deviation of 0.3 kgs. No neonates were found to be extremely preterm. The distribution of neonates among very preterm, moderate preterm and late preterm were found to be 33, 36 and 30 neonates respectively. The lowest gestational age is 28 weeks and the highest is 34 weeks. The mean gestational age is 32.2 and median is 33 weeks.

38 neonates' mothers took 1 dose and 40 neonates' mothers took 2 dose of Antenatal Corticosteroid (ACS). The "Appearance, Pulse, Grimace, Activity, and Respiration" score (APGAR score) of about 25% neonates was less than 7 which meant that 1/4th of the neonates faced difficulty in tolerating the birthing process and needed medical attention. The mean APGAR score is 7.6 and median is 8.

We see that about 95.96% of the neonates had normal capillary blood glucose level at birth and only 4.04% of the neonates had hypoglycaemia with mean CBG level of 70.7 mg/dl. The lowest CBG level of neonates at birth was 28 mg/dl and highest was 118 mg/dl. Whereas after 12 hrs of birth no neonate had hypoglycaemia and all of them had normal CBG level. Again 24 hours after birth it was seen that the CBG level of 1 neonate decreased to <45 mg/dl and the rest 98 out of 99 neonates had normal CBG level with mean CBG level of 63.7 mg/dl. With time, the mean and the median capillary blood glucose level could be seen decreasing among the neonates. The lower range on one hand increases after 12 hours of birth than at birth on the other hand the upper range decreases. After 24 hours of birth the upper range further decreases and the lower range is also seen to be decreasing than that after 12 hrs.Prior to phototherapy 41 (41.41%) neonates had hyperbilirubinaemia as per transcutaneous Bilirubin measurement (TCB). All 41 of those neonates required double surface phototherapy (DSPT)whereas 14 (14.14%) out of 99 of the neonates required double volume exchange transfusion(DVET).

When comparison of number of ACS doses received by the neonates' mothers and CBG level at 0 hour, after 12 hours, and after 24 hours, transcutaneous bilirubin level, double surface phototherapy requirement and double volume exchange transfusion requirement done it was found that 50% of the mothers received 1 dose of antenatal corticosteroid and 50% of them received 2 doses of ACS when neonates had capillary blood glucose level at birth <45 mg/dl. No cases of hypoglycemia were found after 12 hours of birth. 1 case of hypoglycemia was found after 24 hours of birth and the mother received 2 doses of ACS in this case.

7.3% of the mothers whose neonate had hyperbilirubinemia and required DSPT did not receive any dose of antenatal corticosteroids. 46.3% of the mothers received 1 dose of antenatal corticosteroid and 46.3% of them received 2 doses of ACS when neonates had hyperbilirubinemia. On the other hand 14.3% of the mothers whose neonate required double volume exchange transfusion did not receive any dose of antenatal corticosteroids. 35.7% of the mothers received 1 dose of antenatal corticosteroid and 50% of them received 2 doses of ACS when neonates required double volume exchange transfusion.

Table 1: Number of corticosteroid doses received by the mothers and CBG level at 0 hour, after 12 hours, and after 24 hours, Transcutaneous Bilirubin level, DSPT and DVET requirement. (n=99)

Number (%)		0 dose	1 dose	2 doses	Total
		Number (%)	Number (%)	Number (%)	
0 hr CBG	Hypoglycaemia	0(0)	2(50)	2(50)	4(100)
	Normal	21(22.1)	36(37.9)	38(40)	95(100)
12 hr CBG	Hypoglycaemia	0(0)	0(0)	0(0)	0(100)
	Normal	21(21.2)	38(38.4)	40(40.4)	99(100)
24 hr CBG	Hypoglycaemia	0(0)	0(0)	1(100)	1(100)
	Normal	21(21.4)	38(38.8)	39(39.8)	98(100)
Average TCB level	Hyperbilirubinemia	3(7.3)	19(46.3)	19(46.3)	41(100)
	Normal	18(31)	19(32.8)	21(36.2)	58(100)
DSPT Requirement	Yes	3(7.3)	19(46.3)	19(46.3)	41(100)
	No	18(31)	19(32.8)	21(36.2)	58(100)
DVET Requirement	Yes	2(14.3)	5(35.7)	7(50)	14(100)
	No	19(22.4)	33(38.8)	33(38.8)	85(100)

Discussion

In this study, an association between antenatal treatment with corticosteroids and neonatal hypoglycemia and hyperbilirubinemia is established. Though the association between corticosteroid treatment and hypoglycaemia in neonates is not significant, it is found to be significant between neonatal hyperbillirubinaemia and corticosteroid use.

Previous studies by Spencer G Kuper et al.[11] on 2017 and John Ryan G et al.[12] on 2018 had not found any significant association between antenatal corticosteroids and neonatal hypoglycaemia.

However studies by Roy Zigron et al. on 2017, NurunUstun et al. on 2020, Olivia Jansen et al. on 2021[13-15] shows the significant association between antenatal cortico steroids and neonatal hypoglycaemia.In the present study 71.7% of mothers had received antenatal cortico steroids and only 4% neonates had hypoglycaemia which is considered as insignificant with p value=0.27.

A study by EyalKrispin et al[16] on 2018 shows no significant association between antenatal corticosteroids and neonatal hyperbilirubinemia. On the other hand, studies by Kate E Petit etal[17]On 2013 shows significant association between antenatal cortico steroids and neonatal hyperbilirubinemia. Present study showed a significant association between antenatal corticosteroids and neonatal hyperbilirubinemia (p value= 0.017) which requires further treatment in the form of DSPT and DVET.

The advent of routine corticosteroid administration to mothers at high risk for impending preterm delivery was an incredible milestone in the field of obstetrics. Since the sentinel study by Liggins and Howie in 1972,[4] many studies have been conducted to identify the short and long term neonatal effects of antenatal corticosteroids. However neonatal metabolic derangements after maternal betamethasone administration have only been evaluated in small trials. In 1979, a study reported on 23 preterm infants exposed to antenatal betamethasone and 52 control preterm infants and showed that there was no difference in the rates of hypoglycaemia or the mean glucose level at 2-8 hr of age [18]

Though this study shows significant association of hyperbilirubinemia with dexamethasone-exposure, these results are not at all intended to discount the substantial improvement in perinatal morbidity and mortality associated with antenatal corticosteroids. So instead of curtailing antenatal corticosteroid use there should be more emphasis and preparedness to combat possible hyperbilirubinaemia in case of dexamethasone exposure in antenatal period.

Conclusion

Antenatal corticosteroid administration is not significantly associated with neonatal hypoglycaemia but it is significantly associated with neonatal hyperbilirubinemia .

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Reference

1. Oliveira LL, Gonçalves AD, Costa JS, Bonilha AL. Maternal and neonatal factors related to prematurity. Revista da Escola de Enfermagem da USP. 2016 May;50:382-9.
2. Iacovidou N, Varsami M, Syggellou A. Neonatal outcome of preterm delivery. Annals of the New York Academy of Sciences. 2010 Sep;1205(1):130-4.
3. Kankaria A, Duggal M, Chauhan A, Sarkar D, Dalpath S, Kumar A, Dhanjal GS, Kumar V, Suri V, Kumar R, Kumar P. Readiness to provide antenatal corticosteroids for threatened preterm birth in public health facilities in Northern India. Global Health: Science and Practice. 2021 Sep 30;9(3):575-89.
4. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants .Pediatrics 1972;50:515-25.
5. Barondiot C, Morel O, Vieux R, Sery GA, Floriot M, Hascoet JM. Antenatal betamethasone during pregnancy with severe diabetes: is better worse than good?. Archives de pediatrie: OrganeOfficiel de la SocieteFrancaise de Pediatrie. 2007 Apr 24;14(8):989-92.
6. Olefsy JM, Kruszynsa YT. Insulin resistance. In: Shanahan J, Noujaim S, Holton B, eds. Ellenberg and Rifkin's diabetes mellitus. 6 th ed. New York: McGraw-Hill Companies; 2003:367-400.
7. Pedersen J. Diabetes and pregnancy; blood sugar of newborn infants during fasting and glucose administration. Ugeskrift for laeger. 1952 May 22;114(21):685.
8. Saini A, Gaur BK, Singh P. Hypoglycemia in low birth weight neonates: frequency, pattern, and likely determinants. Int J Contemp Pediatrics. 2018 Mar;5(2):7.
9. Ne'meth I, Szeleczki T, Boda D. Hyperbilirubinemia and urinary D-glucaric acid excretion in premature infants following antepartum dexamethasone treatment. J Perinat Med 1981;9:35-9.
10. Parthasarathy A, Menon PS, Nair MK. IAP Textbook of pediatrics. Jaypee Brothers Medical Publishers; 2019 Feb 4.
11. Kuper SG, Baalbaki SH, Parrish MM, Jauk VC, Tita AT, Harper LM. Association between antenatal corticosteroids and neonatal hypoglycemia in indicated early preterm births. The Journal of Maternal-Fetal& Neonatal Medicine. 2018 Dec 2;31(23):3095-101.
12. Viar JR, Cunanan EC. The Association of Antenatal Steroids and Hypoglycemia in Preterm Neonates. Journal of Medicine, University of Santo Tomas. 2021 Jul 31;5(1):604-10.
13. Zigron R, Rotem R, Erlichman I, Rottenstreich M, Rosenbloom JI, Porat S, Rottenstreich A. Factors associated with the development of neonatal hypoglycemia after antenatal corticosteroid administration: It's all about timing. International Journal of Gynecology& Obstetrics. 2022 Aug;158(2):385-9.
14. Üstün N, Hocaoğlu M, Turgut A, Arslanoğlu S, Ovalı F. Does antenatal corticosteroid therapy improve neonatal outcomes in late preterm birth?. The Journal of Maternal-Fetal& Neonatal Medicine. 2022 Jan 2;35(1):11-7.
15. Janssen O, Ratner V, Lin J, Fox N, Green R. Respiratory and glycemic control outcomes of late preterm infants after antenatal corticosteroid exposure. Journal of Perinatology. 2021 Nov;41(11):2607-13.
16. Krispin E, Hochberg A, Chen R, Wiznitzer A, Hadar E, Borovich A. Neonatal outcome in gestational-diabetic mothers treated with antenatal corticosteroids delivering at the late preterm and term. Archives of Gynecology and Obstetrics. 2018 Oct;298:689-95.
17. Pettit KE, Tran SH, Lee E, Caughey AB. The association of antenatal corticosteroids with neonatal hypoglycemia and hyperbilirubinemia. The Journal of Maternal-Fetal& Neonatal Medicine. 2014 May 1;27(7):683-6.
18. Sann L, Burnod J, Lasne Y, Bethenod M. Antenatal administration of betamethasone. Effects upon neonatal blood glucose in premature infants (author's transl). La Nouvelle Presse Medicale. 1979 Oct 1;8(39):3147-8.