ORIGINAL ARTICLE

NATIONAL JOURNAL NJMR MEDICAL RESEARCH

Effects of Antenatal Steroids with Magnesium Sulphate on Intraventricular Hemorrhage and Periventricular Leukomalacia in Neonates Born below 32 Weeks of Gestation

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Keywords:
Intraventricular Hemorrhage,
Periventricular Leukomalacia,
Steroid,
Magnesium sulphate

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Date of Submission: 12-09-2023
Date of Acceptance: 05-12-2023
Date of Publication: 01-01-2024

DOI:
10.55489/njmr.14012024987

ABSTRACT

Introduction: The most important acquired brain injuries in very and extremely preterm infants born in developing Country are periventricular-Intraventricular haemorrhages and diffuse white matter injury. Antenatal corticosteroids play a crucial role in its development. A study was conducted to determine effects of antenatal steroids along with magnesium sulphate on Intraventricular Hemorrhage and Periventricular Leukomalacia in preterm neonates.

Methodology: A retrospective prospective cohort study conducted among premature newborn babies admitted in the hospital. Based on the antenatal medication subjects were divided in to three groups: **Group 1:** No Steroid and No MgsO4 in antenatal period; **Group 2:** Received complete and incomplete course of antenatal steroid; and **Group 3:** Received complete course of antenatal steroid and MgSO4. The Occurrence of IVH and/or PVL in the neonates during hospital stay in all 3 groups.

Results: Among the 144 cases, 8 patients had IVH and 1 had PVL. No intervention group (No antenatal steroids/ antenatal MgSo4) had highest chances of development of IVH/PVL. Significantly lower rate of IVH/PVL recorded in 'Steroid and MgSO4' group compared to only 'Steroid' group. The chances of development of RDS, BPD and NEC in no intervention group (No antenatal steroids and antenatal MgSo4) was significantly higher compared to steroid and and MgSO4 group and Steroid only group.

Conclusion: This study confirmed that antenatal steroids when used along with antenatal magnesium sulphate to deliver preterm babies reduce IVH and white matter brain injury significantly.

INTRODUCTION

The most important acquired brain injuries in very and extremely preterm infants born in developing Country are periventricular-Intraventricular haemorrhages (PIVH) and diffuse white matter injury. This brain injury may lead to cerebral palsy and learning difficulties, and can have major impact on the quality of life.[1] Intraventricular hemorrhage (IVH) is commonest type of neonatal intracranial hemorrhage and is accompanying with antag-

Publisher: Medsci Publications www.medscipublications.com ISSN: 2249 4995 Official website: www.njmr.in

onistic neurological outcomes. Epilepsy, cerebral palsy and future disabilities such as learning disability, visual and hearing impairments can be resulted due to IVH. Developments in neonatal care have led to a continuous decrease in the mortality related with prematurity. [2]

Among very low birth weight (<1500 g) infants, the incidence of IVH has been found at 20%. The occurrence of IVH among VLBW infants has dropped in the past few decades, from 40-50% in the early 1980s to around 20% in the late 1980s, then remaining comparatively stable for the past two decades. [3,4]

IVH is seen in almost half of infants born at extremely low birth weight (500-750 g).[5] Infants who are survived by severe IVH (Grade III or IV) may be at increased risk of substantial long-term or permanent neurological injuries/deficits, including mental retardation, cerebral palsy and post-hemorrhagic hydrocephalus.[6] Periventricular Leucomalacia (PVL) is the commonest white matter brain injury in preterm infants occurs because of ischemic injury to periventricular oligodendrocytes of the developing brain.

Many previously done studies have revealed that treatment of pregnant women with antenatal corticosteroids is linked with a decreased risk of adverse health outcomes, including IVH. Leggings et al.[7] conducted the first randomized controlled trial of antenatal betamethasone, exhibited decreased mortality and lower risks of respiratory distress syndrome in infants of treated mothers in comparison to controls and the need for respiratory support. In that study, none of infants of steroid-treated mothers had IVH while four of the infants of control mothers had IVH. Although their study didn't find statistically significant difference but this finding raised the likelihood that antenatal steroid use might decrease the incidence of IVH.

A Cochrane review in 2006 involving of a meta-analysis of randomized trials established a reduced risk of IVH (relative risk 0.54, 95% CI 0.43 to 0.69) when treatment with antenatal steroids given. Most of the trials included in that meta-analysis was done in the 1990's or early 2000's when IVH rates were greater, they were interested to understand if the positive impact of antenatal steroids would still be present. Furthermore, quality improvement efforts to upsurge use of antenatal steroid, along with other independent efforts to decrease IVH may have deteriorated this beneficial link.[8]

Numerous studies demonstrate that administration of magnesium sulphate to mothers betters the neurodevelopmental outcome of preterm fetuses.[9] Magnesium is essential for key cellular processes in humans. Magnesium has vasoactive properties, which upsurges cerebral blood flow because of cerebral vasodilatation. [10]

The fetal and neonatal brain appears more vulnerable to glutamate damage. Hence, delaying glutamate receptors through magnesium sulphate may decrease the risk of injury in perinatal period. Magnesium concentration increased in fetal serum within one hour of maternal intravenous administration surges Trans placental transfer of magnesium. [11] Magnesium sulphate given to mothers shortly before delivery reduces the risk of cerebral palsy and protects gross motor function in those infants born preterm. The effect may be greatest at early gestations and is not associated with adverse long-term fetal or maternal outcome.

The study was conducted to determine effects of antenatal steroids along with magnesium sulphate on Intraventricular Hemorrhage and Periventricular Leukomalacia in neonates born below 32 weeks of gestation compared to antenatal steroids alone and without antenatal steroids or magnesium sulphate.

MATERIAL & METHODS

The study was conducted in a tertiary care hospital in Setu Newborn Care Centre Ahmedabad over 12 months in 2021. This was a retrospective prospective cohort study conducted among premature newborn babies admitted in the hospital.

Eligibility criteria

Babies born at Gestational age of less than 32 weeks and being admitted immediately after birth were included in the study. Babies with congenital malformation, known chromosomal abnormality, severe perinatal asphyxia (defined as an Apgar score of 0-3 for more than 5 minutes, a cord blood pH of less than 7 or both) or expected to die shortly after birth were excluded.

Methodology

All the newborn babies prematurely admitted in the hospital were screened and those who fulfilled the inclusion criteria were included in the study. A detailed history was taken regarding gestational age at the time of delivery, birth weight, and gender. Mother's history was taken regarding antenatal medication, PIH, IUGR, Doppler findings. Details were taken regarding antenatal steroids and magnesium sulphate to mother including dosage and timings. After that thoroughly clinical examination was carried out which including recording of vital signs, general examination and systemic examination thoroughly.

Based on the antenatal medication subjects were divided in to three groups: **Group 1:** No Steroid and No MgsO4 in antenatal period; **Group 2:** Received complete and incomplete course of antenatal steroid; and **Group 3:** Received complete course of antenatal steroid and MgSO4

Complete course of Antenatal Steroid: A mixture (1:1) of betamethasone acetate and betamethasone phosphate: 12 mg every 24 hours, a total of 2 doses (24mg) and those who have received 1 dose has been considered incomplete course of steroids.

Complete course of Magnesium sulphate: IV bolus of 4 g followed by 1gm/hr infusion till delivery or 24 hours whichever is early.

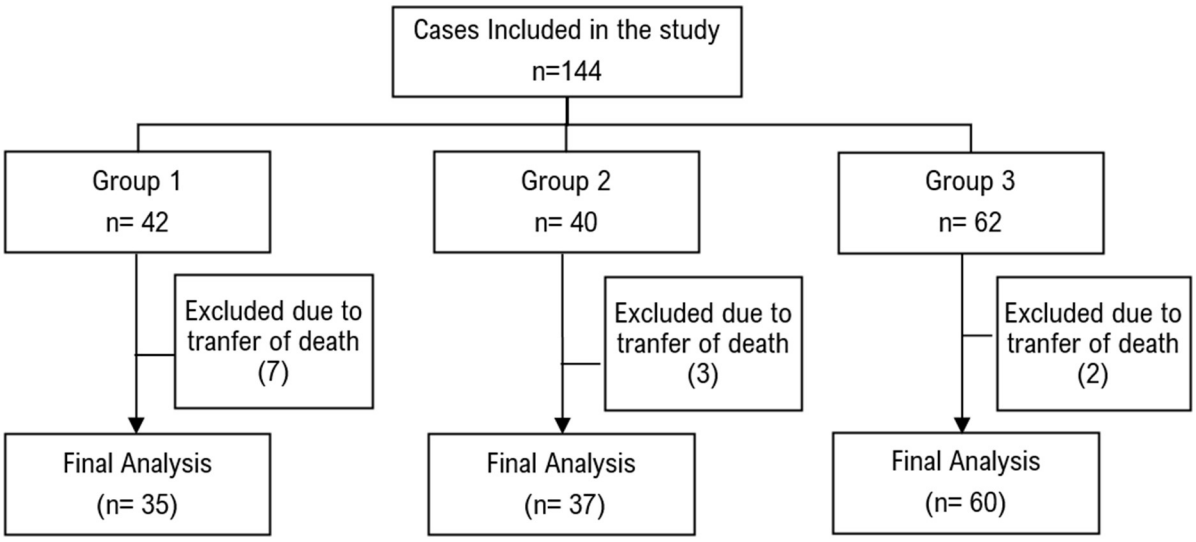
Sample Size: According to a study by Wei et al [12] The development IVH in preterm births was 23.7%. Hence, taking occurrence of IVH in 23.7%, average of 11.5%, absolute precision of 5% ad design effect of 1 the calculated sample size(n) is 140 according to the following formula: Sample size (n) = [DEFF*Np (1-p)]/ [$(d^2/Z^2_{1-\alpha/2}$*(N-1) +p*(1-p)]

Sample size calculated using openepi software available on http://www.openepi.com.

Primary outcome: Primary outcome was measured as occurrence of IVH and/or PVL in the neonates during hospital stay in all 3 groups

Secondary outcome: Secondary outcome was measured occurrence of other morbidities like RDS, NEC, Broncho Pulmonary Dysplasia (BPD), Retinopathy of Prematurity (ROP), Patent Ductus Arteriosus (PDA), and also mortality in all 3 groups.

Statistical analysis: All collected information was entered in to excel sheet and analysed using software Epi Info™ For Windows version 7.2. All qualitative data were presented by frequency and percentage. All quantitative data were presented by mean and standard deviation. Initially baseline profile were compared among all three groups. This was followed by comparison of outcome variable in all three groups. Statistical difference between two groups were assessed using chi-square for study variable was qualitative and ANOVA test when study variable was quantitative. P value below 0.05 indicate statistically significant difference in two groups.



RESULTS

This study was conducted among 144 cases to assess effectiveness of antenatal steroid and/ or MgSO4 on IVH / PVL in preterm babies. Out of Total 144 patients 12 patients were transferred or died (within 12 hours) so data was not available hence 132 patient details were available for analysis. Table 1 shows comparison of gestational age at the time of delivery, gender of the baby and birth weight among the three study groups. All these three indicators were comparable in all the study groups and these was no significant difference among them (p>0.05). Certain selected clinical variables were compared among three groups (table 2). There was no statistical difference in PIH, IUGR and doppler abnormality. Mortality was statistically differed among three groups. Mortality was 4 (9.5%) in group 1 (No antenatal steroids and antenatal MgSo4), 4 (10%) in group 2 (only steroids) and 2 (3.2%) in group 3 (Steroid and MgSO4).

Table 1: Comparison of basic characteristics of study participants

Study Variables	Study Groups			P value
	No Steroid or No MgSO4 (n=42) (%)	Steroid (n=40) (%)	Steroid+MgSO4 (n=62) (%)	
Gestational Age				
24-26	4 (9.5)	4(2.5)	4(6.5)	0.500
27-29	13 (31)	13(25)	13(21)	
30-32	25 (59.5)	25(72.5)	45(72.6)	
Sex				
Female	14 (33.3)	16(40)	29(46.8)	0.388
Male	28 (66.7)	24(60)	33(53.2)	
Birth Weight (mean (kg) ±SD)	1.12 ± 0.453	1.33 ± 0.474	1.21 ± 0.484	0.145

Table 2: Comparison of clinical characteristics of study participants

Study Variables	Study Groups			P value
	No Steroid or No MgSO4 (n=42) (%)	Steroid (n=40) (%)	Steroid+MgSO4 (n=62) (%)	
PIH				
Yes	18 (42.9)	12(30)	25(40.3)	0.44
No	24 (57.1)	28(70)	37(59.7)	
IUGR				
Yes	13 (31)	6(15)	20(32.3)	0.128
No	29 (69)	34(85)	42(67.7)	
Doppler				
Abnormal	13 (31)	7(17.5)	25(40.3)	0.055
Normal	29 (69)	33(82.5)	37(59.7)	
Mortality				
Yes	4 (9.5)	4(10)	2(3.2)	0.013
No	32 (76.2)	34(85)	60(96.8)	
Transferred	6 (14.3)	2(5)	0(0)	

PIH – Pregnancy induced hypertension; IUGR – Intra uterine growth retardation

Table 3: Comparison of outcome among the three study groups

Outcome variables	Study Groups			P value[a]	P value[b]
	No Steroid or No MgSO4 (n=35) (%)	Steroid (n=37) (%)	Steroid+MgSO4 (n=60) (%)		
IVH/PVL					
No	29 (82.9)	34(91.9)	60(100)	0.005	0.025
Yes	6 (17.1)	3(1PVL) (8.1)	0(0)		
Respiratory Distress Syndrome					
No	5 (14.3)	15(40.5)	23(38.3)	0.025	0.828
Yes	30 (85.7)	22(59.5)	37(61.7)		
Brocho-Pulmonary Dysplasia (BPD)					
No	25 (71.4)	33(89.2)	55(91.7)	0.001	0.683
Yes	10 (28.6)	4(10.8)	5(8.3)		
Necrotizing enterocolitis					
No	31 (88.6)	35(94.6)	60(100)	0.04	0.034
Yes	4 (11.4)	2(5.4)	0(0)		
Patent ductus arteriosus (PDA)					
No	25 (71.4)	30(81.1)	50(83.3)	0.368	0.776
Yes	10 (28.6)	7(18.9)	10(16.7)		
ROP position					
No	32 (91.4)	36(97.3)	59(98.3)	0.2168	0.727
Yes	3 (8.6)	1(2.7)	1(1.7)		
Sepsis					
Yes	2 (5.7)	1(2.7)	1(1.7)	0.2168	0.727
No	33 (94.3)	36(97.3)	59(98.3)		

[a] Comparison among all three study groups

[b] Comparison between Only steroid group and steroid + MgSO4 group

IVH - Intraventricular Hemorrhage; PLV - Periventricular Leucomalacia

The data showed that total 8 patients had IVH and 1 had PVL. In group 1 with no antenatal steroids or MgSO4 cover had 6 patients of IVH of which 2 had of grade 2, 2 had of grade 3 and 2 had of grade 4 IVH. In group 2, with antenatally (complete or incomplete) steroids group had 1 case of severe PVL and 2 had IVH of grade 1. Group 3 who had both antenatally complete steroids and MgSO4 cover, had no cases of IVH and PVL. And The difference was significant ($p < 0.05$) which means that no intervention group (No antenatal steroids/ antenatal MgSo4) had highest chances of development of IVH/PVL compared to steroid only group and Steroid and MgSO4 group. Comparison of development of IVH/PVL between 'Steroid' and 'Steroid and MgSO4' group, indicated that there is significantly lower rate of IVH/PVL development in 'Steroid and MgSO4' group compared to only 'Steroid' group with P value 0.025.

RDS was diagnosed by clinical signs and confirmed with x-ray findings. The chances of development of RDS in no intervention group (No antenatal steroids and antenatal MgSo4) was significantly higher compared to steroid and and MgSO4 group and Steroid only group.

BPD found in 10 (28.6%) cases, 4(10.8%) cases and 5 (8.3%) cases in group 1 (No antenatal steroids and antenatal MgSo4), in group 2 (only steroids) and in group 3 (Steroid and MgSO4) respectively. The difference was statistically significant ($p < 0.05$) which means that presence of BPD was higher in in group 1 (No antenatal steroids and antenatal MgSo4) compared to rest two group. Comparison between 'Steroid' and 'Steroid and MgSO4' group indicate no statistical difference in development of BPD between these two groups($p > 0.05$).

NEC develop in 4 (9.5%) cases, 0 cases and 1 (1.67%) case in group 1 (No antenatal steroids and antenatal MgSo4), in group 2 (only steroids) and in group 3 (Steroid and MgSO4) respectively. The difference was statistically significant ($p < 0.05$) which means that development of NEC was significantly higher in no intervention group (No antenatal steroids and antenatal MgSo4) compared to steroid and MgSO4 group and Steroid only group. Comparison between 'Steroid' and 'Steroid and MgSO4' group indicate that 'Steroid' only group had higher chances of developing NEC compared to 'Steroid and MgSO4' group ($p < 0.05$).

Total 10 mortality were recorded. The common causes of mortality include extreme prematurity (3), intraventricular haemorrhage (IVH) (1), prematurity with sepsis and respiratory distress (1), renal failure (2), respiratory distress and prematurity (1), and sepsis (2).

Mean ventilation days for no steroid no MgSO4 5.85 days (sd 5.242), for steroid only group 2 days (sd 0.707), and Steroid + MgSO4 group 2.29 days (sd 1.799). Mean CPAP treatment days in no Steroid no MgSO4 group was 9.63 days (sd 9.251), in steroid group 8.67 days (sd 11.388), and in steroid + MgSO4 group 12.07 days (sd 10.815).

DISCUSSION

It has been observed that intra-periventricular hemorrhage (IVH-PVH) is the most common type of intracranial hemorrhage in premature babies. It is also the chief cause of neurodevelopmental disabilities in premature babies. Factors influencing to IVH-PVH are: respiratory distress syndrome (RDS), prematurity, hypoxic-ischemic lesions, reperfusion, disturbances of the cerebral blood flow, lesions of the blood vessels, pneumothorax, hypertension and hypovolaemia.[13] These factors lead to breach in the blood vessels of the germinal matrix, where the early location of intracranial bleeding for premature newborns is. In 80% of these patients haemorrhageprogress into the ventricles and 10-15% of patients have hemorrhage into periventricular regions.[14] In most cases, IVH leads to acute dilatation of the ventricles. In 10-15% infants with low-birth-weight hydrocephalus is being developed which is stable in 65% cases. Progressive hydrocephalus accompanying with intra-parenchyma hemorrhage and ventricular-peritoneal shunt is related with critical neurodevelopmental consequence. Newborns having IVH with intra-parenchyma echogenicity more than 1 cm is linked with increased rate of mortality and increased risk of motor and cognitive disabilities. In cases where the IVH grade I and grade II are not having with intra-parenchyma bleeding and periventricular leucomalacia (PVL), they have decreased risk of long-term neurodevelopmental sequels. Administration of corticosteroids to the pregnant women who are with higher risk of preterm labour have decreased the incidence of IVH, RDS and neonatal mortality.

In this study, no intervention group (No antenatal steroids and antenatal MgSo4) had highest chances of development of IVH/PVL compared to steroid only group and Steroid and MgSO4 group. The difference between steroid only group and Steroid and MgSO4 group was statistically significant (pa value <0.05) which means lower rate of IVH/PVL development in 'Steroid and MgSO4' group compared to only 'Steroid' group.

In this study, chances of development of RDS in no intervention group (No antenatal steroids and antenatal MgSo4) was significantly higher compared to steroid and MgSO4 group and Steroid only group. The difference between steroid only group and Steroid and MgSO4 group was statistically non-significant (pa value >0.05) which means RDS development in 'Steroid and MgSO4' group 'Steroid' group were same.

Previous studies have revealed that exposure to antenatal steroids was related with a reduction in the risk of IVH in newborns born between 29 to 34 weeks gestational age when studied as an overall collective cohort.[8] In general though, my findings are constant with previous studies on historic cohorts. In a study done by Shankar an et al. re they reported an unadjusted odds ratio of 0.39 (95% CI: 0.27 - 0.57) for the relationship of a whole course of steroids with the development of grades 3 and 4 IVH in a huge cohort of singleton VLBW infants (i.e. birth weight between 501 to 1500 g).[15] In a study done by Wright et al., they observed the association between complete, partial and any course of

antenatal steroids and the consequences of any or severe IVH in around ten thousand VLBW infants in fourteen NICUs with varied populations and management strategies. Receiving complete or any antenatal steroid was found to be related with a statistically significant decrease in the possibility of IVH.[15] In a meta-analysis of Crowley et al. which was placebo controlled randomized trials, they established that steroid therapy decreases the chances of periventricular hemorrhage. Odds ratio of 0.38 (95% CI: 0.23 - 0.94) was found in their results.[16] These evidences led the National Institutes of Health Consensus Development Panel to issue a statement that antenatal steroids decrease incidence and mortality of IVH in newborn infants and suggested that mothers at risk for preterm delivery should be given steroids. Women between 24-34 weeks gestation be candidates for the treatment.[17]

Preceding data regarding the relationship between the occurrence of IVH in infants delivered at less than 29 weeks gestational age and use of antenatal steroids had been contradictory. In a systematic review by Roberts et al. in which 21 studies were included, they reported that antenatal steroids decrease the occurrence of IVH in infants born before 28 weeks.[8] In contrast, a systematic review of Onland et al. including nine randomized trials determined that there was no indication to back or refute recommending antenatal steroids to women with risk of preterm birth at less than 26 weeks of gestation. [18] Meanwhile these reviews were available, Mori et al. found that introduction of antenatal steroids was linked with a noteworthy reduction in the risk of IVH and severe IVH frequency in infants born between 24 to 29 weeks of gestational age. [19] Likewise, a retrospective cohort study done in Australia by Wong et al. established a considerably lower frequency of severe IVH in infants of 24 to 28 weeks of gestational age who got a whole course of antenatal steroids.[20] My findings are consistent with these latest cohort studies.

In a study done by Abbasiet. al, including 117 neonates, they described those mothers of infants less than 24 weeks of gestational age with antenatal steroids treatment had a significantly lesser incidence of grade 3 and 4 IVH (16.7% vs. 36%, p <0.05, relative risk (RR) = 0.46).[21] Studies related to these subjects in infants born before 24 weeks of gestational age are rare. The odds ratio for the relationship between antenatal steroids and the consequences of IVH and severe IVH found by Mori et al. in infants of 22-23 weeks gestational age was found insignificant.[19] Nevertheless, Hayes et al. established that in neonates born at 23 weeks gestation, the incidence of severe IVH in infants given antenatal steroids wasn't significantly dissimilar in comparison to the frequency of IVH in infants not exposed to antenatal steroids (23.1% in comparison to 57.1%, p =0.17).[22]

Mothers with preeclampsia with proteinuria were more likely to receive magnesium sulphate &other investigators have revealed that preeclampsia in the mother may itself belinked with a lesser risk of CP and other neonatal brain lesions. [9,23] We also should be concerned that women with magnesium sulphate usage might be more likely to be given, a factor that hasbeen revealed in some studies to be related with decreased risk of brain lesions.[24]

Other studies have inspected the association between magnesium sulphate use and either neonatal brain lesions or CP. Hauth et al.[25] found a considerable decrease in CP in magnesium sulphate–treated infants weighing < 1 kg in Alabama, but a more fresh report from the same authors established, in a different group, no association of magnesium sulphate to neonatal brain lesions.[26] Likewise, Lemons et al.[27] examined the data from the Neonatal Research Network and found no significant protecting effect of $MgSO_4$exposure in VLBW infants on risk of neonatal brain lesions. Certainly, in an analysis limited to singleton extremely LBW infants without preeclampsia or maternal diabetes, magnesium sulphate use was related with a substantial excess of brain lesions. Magnesium sulphate, was, however associated with lower mortality in that study. In their study Leviton et al.[28] have now revealed, in comparison to their findings from an earlier data group[9], that magnesium sulphate isn't associated with decreased risk of brain lesions in neonates. In our study it has been observed that antenatal when mgso4 when it was given along with antenatal steroids has significantly reduced preterm IVH/PVL occurrence.

In my study, difference in PDA rate was non-significant in all three study groups. However, the development of NEC and BPD were significantly higher in no intervention group (No antenatal steroids and antenatal MgSo4) compared to steroid and MgSO4 group and Steroid only group. NEC development rate is significantly lower in 'Steroid and MgSO4' group compared to only 'Steroid' group.

Data from the Cochrane review revealed that there are reductions in IVH, RDS, neonatal death, and NEC in the infants whose mothers were given antenatal corticosteroids.[8]

In this study, Mortality was lowest in Steroid and MgSO4 group compared to 'No antenatal steroids and antenatal MgSo4' group and Steroid only group. In the Cochrane review by Roberts D et al., of randomized controlled trials of antenatal corticosteroids administration showed that rates of neonatal death were not significantly decreased by the intervention (relative risk 0.82)[8] This was similar to findings of my study.

CONCLUSION

This study confirmed the association that antenatal course of steroids reduces IVH. It demonstrated that Antenatal steroids when used along with antenatal magnesium sulphate to mother expected to deliver preterm babies reduce IVH and White matter brain injury significantly than mothers receiving only antenatal steroids. It was also observed that antenatal steroids and MgSO4 combination offers more protection against NEC, and reduces mortality significantly.

Funding agency: None
Conflict of interest: No

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