Original Article

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Efficacy of Maternal Magnesium Sulfate Administration on the Neurodevelopmental Outcome of Preterm Babies: A Randomised Controlled Trial

Paediatrics Section

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ABSTRACT

Introduction: Cerebral Palsy (CP) is a disability which shows an increased incidence with prematurity and Low Birth Weight (LBW). Many studies suggest that Magnesium Sulfate ($MgSO_4$) given to mothers expected to deliver preterm improves their neurodevelopmental outcome.

Aim: To assess the role of administration of $MgSO_4$ in improving neurodevelopmental outcome in preterm babies.

Materials and Methods: This was a hospital-based, prospective interventional study open label, randomised controlled trial conducted from December 2015 to May 2016 in the Department of Neonatology at Jubilee Mission Medical College in Central Kerala, India. Randomisation was done in deliveries expected to occur at or below 34 weeks. The mothers were then divided into two groups, those who would receive either $MgSO_4$ or a placebo (normal saline). A total of 83 babies were compared for their baseline characteristics, and the association of $MgSO_4$ administration on neonatal mortality, and on Amiel-Tison angle abnormalities and developmental delay at six months was studied. Either Chi-square test or Fisher's exact test was used to compare the percentages. Microsoft excel was used to enter data. IBM Statistical Package for the Social Science (SPSS) version 21.0 was used for analysis. Statistical significance was considered for p-value <0.05.

Results: Both groups were comparable on baseline characteristics. $MgSO_4$ use in mothers was not significantly associated with reduction in neonatal mortality (p-value=0.205). At six months of age, use of $MgSO_4$ was associated with significant reduction in Amiel-Tison angle abnormalities (p-value <0.001), and reduction in developmental delay as assessed by Trivandrum Development Screening Chart (TDSC) (p-value <0.001), showing that $MgSO_4$ has a neuroprotective role.

Conclusion: Although the percentage of neonatal deaths in the $MgSO_4$ group were less, it was not statistically significant. Amiel-Tison angle abnormalities were significantly less in the group which received $MgSO_4$. Neurodevelopmental outcome as assessed by TDSC was also significantly less in the group which received $MgSO_4$. This suggests that antenatal $MgSO_4$ protects preterm babies from cerebral palsy and neurodevelopmental disabilities. A larger study with a longer follow-up is suggested to confirm these findings.

Keywords: Amiel-Tison angle abnormalities, Cerebral palsy, Developmental delay, Newborns trivandrum development screening chart

INTRODUCTION

Cerebral palsy (CP) is a disability with enormous emotional and financial costs and its incidence increases with prematurity and LBW [1]. Many trials and meta-analyses suggest that giving $MgSO_4$ in the antenatal period has a favourable effect on the neurodevelopmental outcome of premature babies [2-5]. Excitatory stimuli are down-regulated by $MgSO_4$ and this is postulated to reduce nerve damage. $MgSO_4$ blocks N-methyl-D-Aspartate (NMDA) receptors and hence, reduces injury caused to the brain by glutamate. $MgSO_4$ also reduces calcium entering the cell and thus neuronal death [6]. Damage to preterm brain was reduced when $MgSO_4$ was given when proinflammatory cytokines were used to induce inflammation [7]. Another mechanism by which magnesium is thought to reduce damage to neurons is by reducing apoptosis [8]. Transplacental transfer of magnesium occurs within an hour of maternal intravenous administration [9].

The $MgSO_4$ is commonly used in the antenatal period for severe pre-eclampsia and for tocolysis [3]. Several studies have suggested that $MgSO_4$ given antenatally for pre-eclampsia or tocolysis is associated with a reduction in CP in Very Low Birth Weight (VLBW) and preterm babies and in deaths in the perinatal period [10-15]. This benefit by $MgSO_4$ given in the antenatal period is not seen however in all studies on the risk of Intraventricular Haemorrhage (IVH), CP or perinatal mortality [16-20].

A Cochrane systematic review that studied $MgSO_4$ administration to mothers expected to deliver prematurely concluded that there is a need for evaluation of motor function of these babies later in childhood [21]. Another systematic review of studies evaluated the latest evidence regarding use of $MgSO_4$ to prevent neuronal injury when given to mothers expected to deliver prematurely and concluded that more studies are needed to formulate the most accurate regimens for protection of the preterm brain [22].

Although several developed countries have formulated guidelines for antenatal administration of $MgSO_4$ for neuroprotection, only a few Indian studies, and still less from Kerala have been conducted to assess the efficacy of the same in our population [23-28].

The authors studied the effect of two separate interventions (umbilical cord milking and $MgSO_4$ given to mothers expected to deliver prematurely) on the outcome of preterm babies with regard to their neurodevelopment. The data on the effect of milking of the cord on neurodevelopmental outcome at 6 months of age has already been published [29]. The present study aimed to identify whether preterm babies whose mothers received $MgSO_4$ had a better survival at discharge, and neurodevelopmental outcome at six months of age, when compared to those whose mothers did not.

MATERIALS AND METHODS

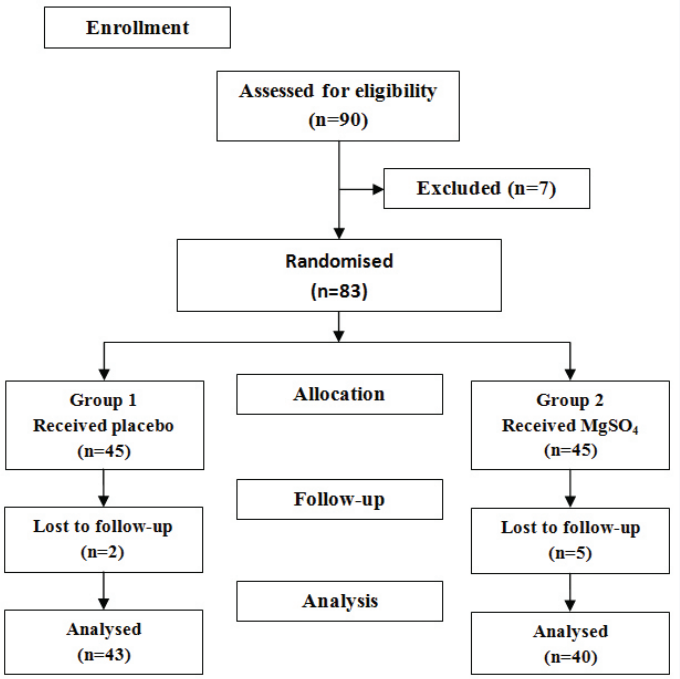
This was a hospital-based, prospective interventional study open label, randomised controlled trial that was conducted from December 2015 to May 2016 in the Department of Neonatology at Jubilee Mission Medical College in Central Kerala, India. The study was conducted after obtaining clearance from Institutional Ethical Committee (reference no. 03/15/IEC/IMMC and RI).

Inclusion and Exclusion criteria: Expectant mothers who were of the gestational age of 24-34 weeks were recruited into the study if birth was expected within 24 hours. Foetuses with severe malformations such as neural tube defects, and chromosomal abnormalities like trisomies, that would interfere with assessment of tone and developmental milestones were excluded, as were cases of maternal hypotension, renal insufficiency, hepatic insufficiency, and cardiac rhythm or electrolyte abnormalities.

The gestational age was calculated during recruitment to the study using the date of the last menstrual period and the results of the earliest available ultrasonogram.

Study Procedure

Eligible participants who gave consent were assigned randomly using sealed envelope method. The premature neonates who were born were then divided into two groups on the basis of their mothers receiving $MgSO_4$ or the placebo [Table/Fig-1].



[Table/Fig-1]: Flowchart.

- **Group 1 (n=40):** Mothers who received $MgSO_4$ as a 4 g intravenous bolus initially. Then an infusion of 1 g/hr was given for 24 hr or until birth, whichever came first.
- **Group 2 (n=43):** Mothers who was given a placebo infusion of normal saline.

The intervention was not concealed from the patients. The infusion was stopped if delivery did not take place within 24 hours.

Sample size calculation: Based on the proportion of neurodevelopmental delay observed in an earlier publication by Nelson KB and Grether JK, that investigated whether antenatal $MgSO_4$ had an association with a lower prevalence of CP in newborns who had a weight of less than 1500 g, among the 42 VLBW infants who developed CP, only 7.1% had received $MgSO_4$ in the antenatal period when compared 36% of the 75 controls with 95% confidence level and 90% power, the minimum sample size came to 40 in each group [30].

The formula used and the calculation done are as follows:

$$n=\frac{[Z_{(1-\alpha/2)}\sqrt{2p(1-p)}+Z_{(1-\beta)}\sqrt{p_1(1-p_1)+p_2(1-p_2)}]^2}{2\,(p_1-p_2)^2}$$

n=[1.96* √({2*0.215*0.785})+1.28* √{0.07*0.93+0.36*0.36}]^2/(0.07-0.36)^2

n=40

Total of 45 babies were selected for each group. However, two babies in group 1 who were born to women not exposed to antenatal $MgSO_4$, and five babies in group 2 who were born to women exposed to $MgSO_4$ were lost for follow-up. Hence, 43 infants in group 1 and 40 infants in group 2 were included in the study. The 83 infants thus selected were then followed-up from birth upto six months.

Parameters Assessed

1) Birth weight: This were assessed in two ways i) those who were above 1500 g are Very Low Birth Weight (VLBW) [31] and ii) those below 1500 g.

2) Gestational age: This was recorded in two ways i) those above 32 weeks of gestational age, and ii) those below 32 weeks.

3) Baseline characteristics: The babies in the two groups were also compared regarding gender, Premature Rupture of Membranes (PROM), previous abortions, Gestational Diabetes Mellitus (GDM), pregnancy induced hypertension (PIH), and infections like neonatal sepsis. Data was collected from hospital records and physical examination of babies.

4) Number of neonatal deaths: Primary outcome was measured by comparing the number of neonatal deaths in the two groups.

5) Amiel-Tison angles [32,33]: It was used for detecting abnormalities of tone at six months of corrected gestational age for all the babies enrolled in the study.

6) Trivandrum Development Screening Chart (TDSC) [34]: TDSC was used to detect developmental delay. There are 17 test items in the validated tool called TDSC. Lines are drawn vertically at the corrected chronological ages of babies. If the baby has not achieved the developmental milestones that are on the left of the line, then that baby is diagnosed to have delay in development.

STATISTICAL ANALYSIS

Microsoft excel was used to enter data. Data was expressed as percentages and frequencies. Either the Chi-square test or the Fisher's exact test was used to compare the percentages. IBM SPSS Statistics for Windows version 21.0 was used for statistical analysis. Statistical significance was considered for p-value <0.05.

RESULTS

In the present study, most babies had a gestational age of 32-34 weeks. There was one baby less than 28 weeks gestational age in each of the 2 groups (who received and did not receive $MgSO_4$). The babies in each group were divided into those below 32 weeks and above, and the difference between the two groups was not significant (Pearson's Chi-square test, p-value=0.50).

In this study, most babies were in the VLBW group. The number of babies below 1500 g and above 1500 g in each group was comparable, and the difference between the two groups was not significant (Pearson's Chi-square test, p-value=0.670).

There were more male children in the group who did not receive $MgSO_4$ and more female children in the group who received $MgSO_4$. However this was not statistically significant (Pearson's Chi-square test, p-value=0.225).

Mothers in both groups were comparable with regard to the incidence of PROM, PIH, previous abortions, and GDM, and the incidence of infections like neonatal sepsis [Table/Fig-2].

Baseline characteristics	Groups	$MgSO_4$ Not received (n=43)	$MgSO_4$ Received (n=40)	Total	p-value
Gestational age (in weeks)	>32	26 (60.5%)	27 (67.5%)	53 (63.9%)	0.505
	≤32	17 (29.5%)	13 (32.5%)	30 (36.1%)	
Gender	Male	24 (55.4%)	17 (42.5%)	41 (49.4%)	0.225
	Female	19 (44.2%)	23 (57.5%)	42 (50.6%)	
Birth weight (in grams)	>1500	24 (55.8%)	30 (75.0%)	54 (65.0%)	0.670
	≤1500	19 (44.2%)	10 (25.0%)	29 (34.9%)	
Previous abortions	No	36 (83.7%)	29 (72.5%)	65 (78.3%)	0.215
	Yes	7 (16.3%)	11 (27.5%)	18 (21.7%)	
PIH	No	34 (79.1%)	30 (75.0%)	64 (77.4%)	0.659
	Yes	9 (20.9%)	10 (25.0%)	19 (22.9%)	
GDM	No	38 (88.4%)	33 (82.5%)	71 (85.5%)	0.447
	Yes	5 (11.6%)	7 (17.5%)	12 (14.5%)	
PROM	No	31 (72.1%)	31 (77.5%)	62 (74.7%)	0.571
	Yes	12 (27.9%)	9 (22.5%)	21 (25.3%)	
Neonatal sepsis	No	41 (95.3%)	38 (95.0%)	79 (95.2%)	Fischer's exact test, p-value=1
	Yes	2 (4.7%)	2 (5.0%)	4 (4.8%)	

[Table/Fig-2]: Baseline characteristics.
PIH: Pregnancy induced hypertension; GDM: Gestational diabetes mellitus; PROM: Premature rupture of membranes; p<0.05* statistically significant; p<0.001** statistically highly significant

The percentage of neonatal deaths in the $MgSO_4$ group was 2.5% when compared to 9.3% in those who did not receive $MgSO_4$. However, this was not statistically significant (p-value 0.361, Fisher's exact Test) [Table/Fig-3].

Immediate outcome	$MgSO_4$ Not received (n=43)	$MgSO_4$ Received (n=40)	Total (N=83)	p-value
Survived	39 (90.6%)	39 (97.5%)	78	0.361
Not survived	4 (9.3%)	1 (2.5%)	5	

[Table/Fig-3]: Immediate outcome.
Fisher's exact test

At six months corrected gestational age, 25/43 (58.1%) of those who had not received $MgSO_4$ had Amiel-Tison angle abnormalities when compared to 9/40 (22.5%) of those who received $MgSO_4$. This was statistically significant (p-value <0.001) [Table/Fig-4].

Amiel-Tison Angle group	$MgSO_4$ Not received (n=43)	$MgSO_4$ Received (n=40)	Total (N=83)	p-value
Normal	18 (41.9%)	31 (77.5%)	49 (59.0%)	0.001
Abnormal	25 (58.1%)	9 (22.5%)	34 (41.0%)	

[Table/Fig-4]: Amiel-Tison Angle.
Pearson's Chi-square test

At six months corrected gestational age, on neurodevelopmental evaluation of all surviving infants using TDSC, 23/43 (53.5%) of those who did not receive $MgSO_4$ had developmental delay as assessed by TDSC when compared to 3/40 (7.5%) of those who received $MgSO_4$. This was statistically significant (p-value <0.001) [Table/Fig-5].

TDSC score	$MgSO_4$ Not received (n=43)	$MgSO_4$ Received (n=40)	Total (N=83)	p-value
No delay	20 (46.5%)	37 (92.5%)	57 (68.7%)	0.001
Delayed	23 (53.5%)	3 (7.5%)	26 (31.3%)	

[Table/Fig-5]: Trivandrum Development Screening Chart (TDSC) score.
Pearson's Chi-square test; TDSC: Trivandrum development screening chart

DISCUSSION

The present study was conducted to identify whether preterm babies whose mothers received $MgSO_4$ had a better neonatal survival and neurodevelopmental outcome at six months of age, when compared to those whose mothers did not. The two groups were comparable regarding gestational age. This is important as extreme prematurity is an added risk factor for the presence for neurodevelopmental delay [1-2].

In the present study, neonatal deaths in the $MgSO_4$ group was 2.5% when compared to 9.3% in those whose mothers did not receive $MgSO_4$. However, this was not of statistical significance (p-value=0.361). Bansal V and Desai A, also concluded that antenatal magnesium sulfate given to women in established preterm labour was not associated with increase in neonatal deaths. There were 5 (10%) neonatal deaths amongst the 50 whose mothers received antenatal $MgSO_4$ while there were only 2 (4%) deaths in the neonates whose mothers did not receive $MgSO_4$ and the results were not significantly associated with $MgSO_4$ (p-value=0.436) [27]. A Cochrane review in 2009 by Doyle LW et al., examining the impact of $MgSO_4$ on CP in five trials had also concluded that $MgSO_4$ given to expectant mothers did not significantly alter the incidence of neonatal deaths (RR 1.04; 95% CI 0.92-1.17; 5 trials, 6145 infants) [21]. A 2019 systematic review and meta-analysis of 197 studies by Shepherd E et al., found no clear difference for perinatal deaths in randomised trials between those given $MgSO_4$ and those who were not (RR 1.01; 95% CI 0.92 to 1.10; 8 trials, 13,654 babies) [35].

Abnormalities in Amiel -Tison angles were found in 58.1% of those who had not received $MgSO_4$ while it was found in 22.5 % of those who did. This was statistically significant (p-value=0.001). In a study in Mysore by Prakash R et al., $MgSO_4$ was given for neuroprotection in the postnatal period for babies with birth asphyxia. Amiel-Tison assessment did not reveal much difference in tone abnormality (out of 22 infants in the group given $MgSO_4$, 3 had abnormal Amiel-Tison angles while abnormalities wer only found in 4 out of the 19 who were not given $MgSO_4$ In this study the relative risk was 0.65; 95% CI, 0.16-2.54; p-value=0.53.

At six months corrected gestational age, 53.5% of those who did not receive $MgSO_4$ had developmental delay as assessed by TDSC when compared to 7.5% of those who received $MgSO_4$. This was statistically significant (Chi-square test, p-value <0.001). A previous study by Prakash R et al., on babies with birth asphyxia given postnatal $MgSO_4$, developmental delay measured by TDSC at 12 months of age did not show a statistically significant difference. The incidence of delay in development was found in three infants who were given $MgSO_4$ out of a total of 22 while five infants were found to have delay amongst the 19 infants who were not given $MgSO_4$ (relative risk, 0.51; 95% CI,0.14-1.88; p-value=0.32) [36]. Cochrane review in 2009 by Doyle L et al., [21] concluded that there was a decrease in CP when $MgSO_4$ was given (RR 0.68; 95% CI 0.54-0.87). There were four trials where $MgSO_4$ was given specifically for protecting the brain, and these too showed a significant reduction in CP. (RR 0.71; 95% CI 0.55-0.91). There was a decrease in both CP (RR 0.64; 95% CI 0.44-0.92) as well as a dysfunction of the gross motor functions (RR 0.61; 95% CI 0.44-0.85).

The present study had assessed babies for tone using Amiel-Tison angles and developmental delay using TDSC at six months of age. This may be too early an age for diagnosis of cerebral palsy, as postulated by Kato T et al., who in their study of the popliteal angle found that babies weighing less than 2 kg had higher tone of the legs when they were four months of age [37]. The authors concluded that this may hence be too early an age for diagnosis of spastic CP. They concluded that the popliteal angle is a much better predictor of CP in babies with periventricular leukomalacia at one year of age.

Antenatal $MgSO_4$ is a relatively inexpensive treatment. This study adds to the body of evidence supporting the role of $MgSO_4$ in reducing the incidence of cerebral palsy in preterm infants and emphasises the need for large multicentric trials in India.

Limitation(s)

The sample size was relatively small. The follow-up for neurodevelopmental outcome was only for six months. The significance of our findings maybe validated by larger, blinded, multicentric studies with a longer follow-up.

CONCLUSION(S)

Although the percentage of neonatal deaths in the $MgSO_4$ group were less, it was not statistically significant. Amiel-Tison angle abnormalities were significantly less in the group which received $MgSO_4$. Neurodevelopmental outcome as assessed by TDSC was also significantly less in the group which received $MgSO_4$.

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