# Randomized controlled trial of antenatal magnesium sulfate for short-term neuroprotection in premature neonates

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## ABSTRACT

**Objective:** To test the hypothesis that antenatal magnesium sulfate ($MgSO_4$) has a short term neuroprotective role in the early neonatal period, when given to women considered at risk for preterm delivery in a developing country. **Study Design:** Randomized, placebo-controlled, open label, trial. **Participants:** A total of 126 mothers who delivered at or below 34 weeks gestation were randomized to receive either antenatal $MgSO_4$ (cases) or normal saline as placebo (controls). A total of 108 babies born were observed for the primary and secondary outcomes. **Primary Outcome:** The composite of the incidence of death and intraventricular hemorrhage (IVH) by cranial ultrasonography in surviving preterm infants. **Results:** There were 6 deaths in cases and 11 deaths in controls (relative risk [RR]: 0.54; 95% confidence interval [CI]: 0.2173-1.369; p=0.18). A statistically significant reduction in the number of IVH was observed in cases (n=1) compared to controls (n=9) (RR: 0.11; 95% CI: 0.0145-0.897; p=0.016) with a number needed to treat of 7. **Conclusion:** Antenatal $MgSO_4$ resulted in a significant reduction in the risk of IVH in preterm infants born at or below 34 weeks of gestation.

**Key words:** *Antenatal magnesium sulfate, Intraventricular hemorrhage, Neuroprotection, Preterm infants*

Preterm birth refers to delivery before 37 completed weeks of gestation. Its prevalence is increasing the worldwide and more than one in 10 babies are born preterm annually. The survival of preterm infants has greatly improved due to advances in neonatology. Significant neonatal complications are directly related to the gestational age at delivery and include chronic lung disease, intraventricular hemorrhage (IVH), and periventricular white matter disease; the latter two can result in cerebral palsy (CP) and neurodevelopmental delay. Antenatal corticosteroids, surfactant therapy, and gentle ventilation have reduced the respiratory complications of prematurity significantly [1].

In several observational studies, antenatal administration of magnesium sulfate ($MgSO_4$) for tocolysis or pre-eclampsia has been associated with a reduction in neonatal mortality and CP in low birth weight children [2,3]; however, these beneficial effects were not observed in other similar studies [4-6]. The beneficial effect of $MgSO_4$ in prevention of CP was first noted in a case–control study [7], where the incidence of CP in preterm babies was significantly reduced by exposure to antenatal $MgSO_4$ when compared to control subjects who did not receive the same (odds ratio [OR]: 0.14; 95% confidence interval [CI]: 0.05-0.51). It was postulated that in the vulnerable preterm brain, $MgSO_4$ may reduce vascular instability, prevent hypoxic damage, and reduce cytokine or excitatory amino acid damage [8].

Three randomized trials were undertaken in recent years in Australia and New Zealand, France, and the United States, to assess the effectiveness of $MgSO_4$ in reducing neonatal mortality, perinatal cerebral injuries and/or CP [9-11]. The results of the first trial, conducted by the Australasian Collaborative Trial of the $MgSO_4$ Collaborative Group showed short-term neuroprotective effects as well as significantly lower rate of major gross motor dysfunction at 2 years in children born preterm (<30 weeks of gestation) whose mothers had been given prenatal $MgSO_4$ infusions rather than placebo saline infusions [9].

While several western countries have formulated guidelines on the use of $MgSO_4$ as a neuroprotective agent, there are very few Indian studies regarding the antenatal use of $MgSO_4$ as a neuroprotective agent [12]. $MgSO_4$ is inexpensive and commonly used in the management of pre-eclampsia and for tocolysis. We undertook this study to test the hypothesis that antenatal $MgSO_4$ has a neuroprotective role in the early neonatal period, when given to women considered at risk for preterm delivery.

## MATERIALS AND METHODS

### Study Design and Participants

We conducted an open label randomized controlled trial in a tertiary care teaching hospital in India from February 1, 2014

to November 30, 2015. Pregnant women with singleton, twin, or triplet fetuses between 24 and 34 weeks of gestational age were eligible for recruitment if birth was expected or planned within 24 h. Exclusion criteria include fetus with severe malformations or chromosomal abnormalities, maternal hypotension, cardiac rhythm or electrolyte abnormalities, renal or hepatic insufficiency, maternal contraindications to $MgSO_4$, unwillingness of the obstetrician to intervene for fetal benefit, and receipt of $MgSO_4$ within the previous 12 h. The duration of gestation was calculated at an entry to the trial according to a previously described algorithm [13] that makes use of the date of the last menstrual period (if reliable) and the results of the earliest available ultrasonogram. The study was approved officially by the Institutional Research Committee and Ethical Review Board. All participants gave written informed consent before enrolment.

### Procedure

Eligible, consenting women were randomly assigned to receive either intravenous $MgSO_4$ (a 4 g bolus followed by a constant infusion of 1 g/h for 24 h or until birth, whichever comes first) or matching placebo (normal saline). The study was single blinded, and allocation was concealed by sequentially numbered opaque sealed envelopes, in which the treatment for next person recruited for the study was mentioned, and the intervention was not concealed from the patients. If delivery did not occur after 24 h and was no longer considered imminent (e.g., if the woman was not having regular uterine contractions), the infusion was discontinued. Imminent preterm birth was defined as a high likelihood of birth, due to one or both of the following conditions: Active labor with ≥4 cm of cervical dilation with or without preterm premature rupture of membranes and planned preterm birth for fetal or maternal indications.

Preterm babies born to eligible women were recruited into the study and assigned to one of the two groups depending on whether their mothers received $MgSO_4$ or not. Members of the investigating team collected information regarding the mother's demographic features, medical history, and social history at the time of enrolment in the study. The members also obtained data about maternal and neonatal outcomes at delivery. During admission to the neonatal intensive care unit, clinical assessment of neurological status was done by the principal investigator (first author) and repeated daily until discharge. Apart from the detailed clinical examination, Hammersmith Short Neurological Evaluation Score was used for daily assessment of neurological status and the full version of the Hammersmith Neonatal Neurologic Assessment was used to evaluate the infants at the time of discharge and thereafter [14].

Neonatal cranial ultrasonography was performed on all neonates by a single radiologist specialized in neurosonography who was blinded to group allocation on day 0-3, day 7, and day 28 for assessment of IVH and classified as per Volpe's classification [15].

### Outcomes

The primary outcome was the composite incidence of the death and IVH by cranial ultrasonography in surviving preterm infants. Neonatal death until discharge was considered significant for the study. The secondary outcomes studied were resuscitation at birth, respiratory distress syndrome, surfactant administration, type and duration of ventilator support, hypoxic ischemic encephalopathy, apnea of prematurity, sepsis, anemia requiring transfusion, necrotizing enterocolitis, and patent ductus arteriosus. We estimated that the primary outcome would occur in 20% of the control group [9] and calculated the sample size, by Fleiss formula using OpenEpi software, version 3.03. Thus, a total sample of 134, equally divided into two groups was deemed sufficient for the detection of a 22% reduction in this outcome, with a Type I error (two-sided) of 5% and a power of at least 80%.

### Statistical Analysis

All statistical analyses were calculated on an intention to treat basis to avoid overestimation of clinical effectiveness. The data from all patients were analyzed according to the group to which they were assigned randomly. Categorical variables were summarized as percentages and were analyzed by relative risk (RR) assessment. We performed analysis of the primary outcome and its components, excluding infants with major congenital anomalies noted at birth. Infants with blood culture proven or with definite clinical evidence of severe sepsis as the primary cause of death were also excluded from the study. Statistical analysis was performed using IBM SPSS Statistics 20.0 software. A p<0.05 was considered statistically significant.

### RESULTS

A total of 126 mothers were randomly assigned to treatment or placebo group. Of the 134 neonates born to these mothers (including 8 sets of twin pregnancy), 16 had to be excluded as shown in Fig. 1. Remaining 118 neonates were randomized into two groups and out of them, 108 eligible neonates were included in the final analysis. There were 54 cases and 54 controls in the study group of preterm infants as depicted in the participant flowchart (Fig. 1). No adverse events were observed in the mothers included in the study.

The baseline characteristics of the study population are displayed in Table 1, the primary outcome in Table 2 and the secondary outcome in Table 3. There were 6 deaths in cases and 11 deaths in controls (RR: 0.54; 95% CI: 0.2173-1.369; p=0.18). Two babies in the control group who died did not receive antenatal steroids. There was only one case of IVH (Grade 1) seen in the study group whereas there were four cases of Grade 1 IVH, three cases of Grade 2 IVH, and three cases of Grade 3 IVH seen in controls. There was no case of periventricular echodensity seen in both the groups (as per Volpe's classification) [15].
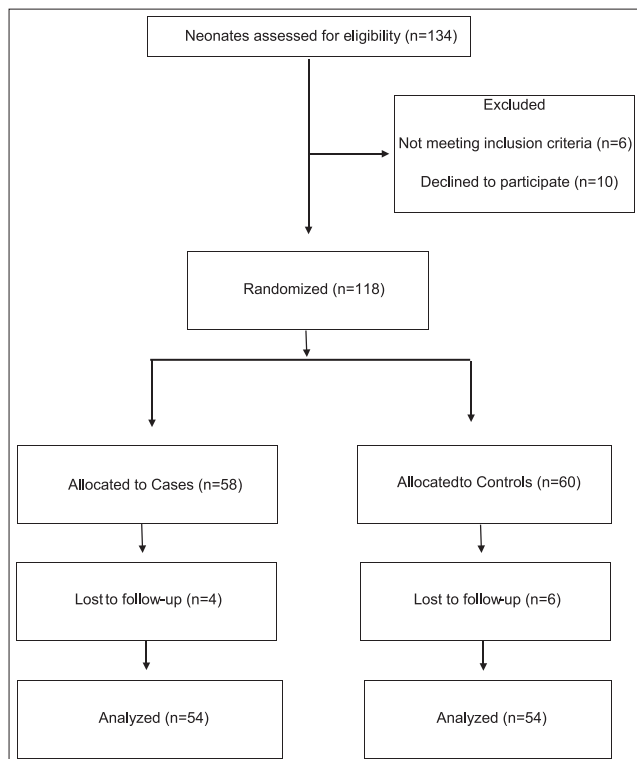
**Figure 1: Participant flowchart**

**Table 1: Baseline characteristics of the study population**

| Characteristic | Cases | Controls | p value |
|---|---|---|---|
| Gestational age | | | >0.99 |
|   <28 weeks | 3 | 3 | |
|   28-32 weeks | 31 | 28 | |
|   32-34 weeks | 20 | 23 | |
| Sex | | | 0.84 |
|   Male | 32 | 33 | |
|   Female | 22 | 21 | |
| Antenatal steroids received | | | 0.07 |
|   Complete | 39 | 30 | |
|   Incomplete | 8 | 14 | |
|   Nil | 7 | 10 | |
| Mode of delivery | | | 0.56 |
|   Vaginal | 25 | 22 | |
|   Cesarean | 29 | 32 | |
| Birth weight | | | 0.30 |
|   <1000 g | 11 | 7 | |
|   1000-1499 g | 22 | 33 | |
|   >1500 g | 21 | 1 | |

**Table 2: Primary outcome**

| Characteristic | Cases | Controls | RR | 95% CI | p value |
|---|---|---|---|---|---|
| Death | 6 | 11 | 0.54 | 0.2173-1.369 | 0.18 |
| IVH | 1 | 9 | 0.11 | 0.0145-0.897 | 0.016 |

RR: Relative risk, CI: Confidence interval, IVH: Intra ventricular hemorrhage

A statistically significant reduction in the number of IVH was observed in cases (n=1) compared to controls (n=9) (RR: 0.11; 95% CI: 0.0145-0.897; p=0.016) with a number needed to treat of 7. One baby in the control group who did not receive antenatal steroids developed IVH.

## DISCUSSION

We found that antenatal administration of $MgSO_4$ in women at imminent risk for delivery between 24 and 34 weeks of gestation resulted in a significant reduction in the primary outcome of the IVH but not death. None of the cases developed a significant degree of IVH. Analysis of both primary and secondary outcomes ruled out any neonatal complications in the group that received antenatal $MgSO_4$. The number of women needed to treat with $MgSO_4$ to prevent IVH in one preterm infant is 7 and hence, highly significant for a prophylactic intervention. $MgSO_4$ is inexpensive and commonly used in obstetric practice. Unlike corticosteroids, which need to be given at least 24 h before delivery to obtain a maximum beneficial effect, the window of opportunity for the administration of $MgSO_4$ is shorter, about 4 h before birth.

Historically, the positive association between in utero exposure to $MgSO_4$ and a reduction in perinatal morbidity was first reported by Kuban et al. in 1992 [16]. They conducted a prospective study of 449 babies delivered with birth weight <1501 g and found that maternal receipt of $MgSO_4$ was associated with a decreased incidence of IVH. Petrova and Mehta in 2012 studied 89 IVH cases and 89 controls that were comparable for parity, mode of delivery, antenatal exposure to corticosteroid, and surfactant administration. They found that among the IVH cases,

30.3% of infants were exposed to tocolytic $MgSO_4$ as compared to 47.2% of the controls (OR adjusted: 0.471; 95% CI: 0.241-0.906), thereby suggesting that antenatal exposure to $MgSO_4$ may have a protective effect against IVH [17].

The Cochrane review of $MgSO_4$ for women at risk of preterm birth for neuroprotection of the fetus [18] showed no significant reduction in pediatric outcomes of IVH (RR: 0.96; 95% CI: 0.86-1.08; four trials; 4552 infants). Subgroup analysis revealed that when $MgSO_4$ was given with the intent for neuroprotection, the magnesium group compared with placebo, showed a significant decrease in the risk of death or CP (RR: 0.85; 95% CI: 0.74-0.98; four trials; 4446 infants) and a significant decrease in substantial gross motor dysfunction (RR: 0.60; 95% CI: 0.43-0.83; three trials; 4387 children). All the primary outcome variables of our study (death and IVH) were considered among the secondary outcomes in the Cochrane review. It is interesting to note that though the secondary outcomes were not significantly different between treatment groups, these were not always reported. Limitations of our study include relatively small sample size and a lack of double blinding and long-term follow-up. At present, Indian protocols do not recommend routine antenatal administration of $MgSO_4$ to mothers at risk of preterm delivery. Like most experimental studies, the significance of our findings needs to be validated by conducting large multicenter trials with long-term follow-up so as to adapt the same in the routine management of mothers at risk of preterm labor.

**Table 3: Secondary outcome**

| Characteristic | Cases | Controls | RR | 95% CI | p value |
|---|---|---|---|---|---|
| Resuscitation | | | | | |
| Not required | 24 | 22 | | | |
| PPV | 9 | 12 | | | |
| Advanced resuscitation | 3 | 2 | 1.5 | 0.261-8.622 | >0.99 |
| 5' APGAR<6 | 4 | 5 | 0.8 | 0.227-2.819 | >0.99 |
| RDS | 51 | 49 | 1.04 | 0.935-1.158 | 0.71 |
| Surfactant therapy | 41 | 43 | 0.95 | 0.779-1.167 | 0.64 |
| Ventilation | | | | | |
| CPAP | 43 | 44 | | | |
| Invasive ventilation | 14 | 15 | 0.93 | 0.500-1.74 | 0.82 |
| HIE | 3 | 5 | 0.6 | 0.150-2.387 | 0.71 |
| Apnea | 17 | 15 | 1.13 | 0.632-2.33 | 0.67 |
| Sepsis | 13 | 10 | 1.3 | 0.624-2.706 | 0.48 |
| Anemia requiring transfusion | 9 | 8 | 1.12 | 0.469-2.69 | 0.79 |
| NEC** stage 2 or more | 6 | 5 | 1.2 | 0.389-3.69 | 0.75 |
| PDA | 4 | 6 | 0.66 | 0.199-2.23 | 0.50 |

PPV: Positive pressure ventilation, RDS: Respiratory distress syndrome, CPAP: Continuous positive airway pressure, HIE: Hypoxic ischemic encephalopathy, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus

## CONCLUSION

We conclude that antenatal $MgSO_4$ resulted in a significant reduction in the risk of IVH and may be considered for the primary prevention of IVH in preterm infants of gestational age 34 weeks and below. The above treatment is cost-effective, without neonatal side effects and clinically significant for a prophylactic intervention.

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