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RESEARCH ARTICLE

Fetomaternal outcome in patients with early preterm labour following administration of magnesium sulphate - a hospital based prospective study

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ABSTRACT

Objective: To assess the effectiveness of magnesium sulfate as a neuroprotective agent in early preterm labour (28 to 32 weeks). To assess any maternal or fetal adverse effects after giving magnesium sulfate. **Methods:** Hospital based prospective observational study. Initially 72 pregnant women with preterm labour, planned preterm birth due to maternal or fetal indication between 28 to 32 weeks of gestation were selected. Among them 37 women received $MgSO_4$, out of which 2 women could not be followed up. So, the study was conducted between 35 women as study group (Group A), who received $MgSO_4$ and 35 women as control group (Group B), who did not receive $MgSO_4$. Corticosteroid was given to both groups. **Results:** The number of babies who developed IVH in the non-$MgSO_4$ group was significantly greater (5/35, 14.3 %) than in the $MgSO_4$ group (3/35, 8.6%) (p Value = 0.452). In this study 3 (8.6%) ELBW babies in non$MgSO_4$ group had IVH compared to 2 (5.7%) in $MgSO_4$ group. 2 (5.7%) VLBW babies in non$MgSO_4$ group had IVH while 1 (2.9%) VLBW babies in $MgSO_4$ group had IVH. According to the gestational age in non$MgSO_4$ group 20% (7/35) of the babies between 28 to 30 weeks required intubation compared to 11.4% (4/35) babies in $MgSO_4$ group. 14.3% (5/35) of the babies between 30 to 32 weeks in non$MgSO_4$ group required intubation where only 5.7% (2/35) babies in $MgSO_4$ group required intubation. (p Value = 0.017). 5.7% (2/35) babies between 30 to 32 weeks of gestation in non$MgSO_4$ group had delayed milestones, while no baby showed delayed milestones in $MgSO_4$group**. Conclusions**: Antenatal $MgSO_4$ appears to minimize the likelihood of invasive mechanical ventilation, the need for continuing respiratory support, intraventricular hemorrhage. Antenatal $MgSO_4$ has similar effects across a range of preterm gestational ages.

Keywords: Preterm, neuroprotective, magnesium sulfate.

Preterm birth is the world's leading cause of infant morbidity and mortality. Every year, 15 million babies are born prematurely, accounting for more than one-tenth of all newborns born worldwide [1]. There are no recent precise data on the prevalence of preterm birth globally, but estimates range from 5% in affluent countries to 25% in impoverished countries [2]. The burden of preterm birth is mainly borne by emerging nations like India [2]. Preterm birth occurs at a rate of 23.3% in India [3]. Preterm birth (before 32 weeks) accounts for 1-2% of all births and is responsible for 60% of perinatal death and nearly all neurological morbidity [4]. Preterm birth is becoming more common around the world, possibly as a result of rising maternal age, increased rate of induction due to maternal indication like PIH and diabetes. However, preterm baby survival has improved as a result of better ICU care and therapies such as prenatal corticosteroids and surfactant. But their long-term neurological outcome remains a major concern as preterm birth is associated with neurodevelopmental impairments such as neuromotor deficits, cognitive deficits, learning disabilities, behavioral and psychiatric disorders and neurosensory deficiencies [5, 6]. Short-term complications of premature birth include respiratory and cardiovascular complications, intracranial hemorrhage, necrotizing enterocolitis etc. Those who emerge from these initial obstacles may suffer from long-term sequelae of intellectual disability, cognitive dysfunction, hearing and visual impairment [7 - 9]. In Indian settings, abnormal neurological outcomes were observed in 25% of extremely low birth weight infants observed for two years [10]. Two recognized patterns of injury appear to be at the root of preterm newborn central nervous system complications: 1. Intraventricular hemorrhage (IVH); and 2. White matter damage. Later in childhood, these can lead to cerebral palsy (CP) and neurodevelopmental problems. CP affects 2 to 2.5

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out of every 1000 live births[11]. Various studies showed that infants born preterm to women with eclampsia had a lower incidence of adverse central nervous system outcomes due to routine use of magnesium sulfate in eclamptic patients [12,13]. The neuroprotective effects of magnesium in preterm newborns were originally discovered by Nelson KB and Gretter JK, who discovered that magnesium sulphate administered for pre-eclampsia and tocolysis in utero was lower in very-low-birth-weight infants (less than 1.5 Kg) with cerebral palsy than in controls (7.1 vs. 36%). As a result, prospective research has been carried out in order to uncover a potential prophylactic medicine with neuro-protective effects that can minimize the incidence of preterm neurodevelopmental problems, with magnesium sulphate ($MgSO_4$) studies proving to be promising [14]. Magnesium sulfate reduces brain metabolism, stabilizes blood pressure, reduces constriction in the cerebral arteries, restoring infusion in preterm infants [12]. Based on the evidences that magnesium sulfate has neuroprotective effects with minimal and tolerable side effect [2,12,15], we hypothesize that the use of intravenous magnesium sulfate in patients with early preterm birth, can reduce the risk of neurological complications of preterm infants and thereby reduces neonatal mortality and morbidity.

Materials and methods

Hospital based prospective observational study was conducted in the Obstetrics and Gynecology department of Fakhruddin Ali Ahmed Medical College and Hospital during the study period of one year from September 2020 to August 2021. Initially 72 pregnant women with preterm labour, planned preterm birth due to maternal or fetal indication between 28 to 32 weeks of gestation were selected. Among them 37 women received $MgSO_4$, out of which 2 women could not be followed up. So, the study was conducted between 35 women as study group (Group A), who received $MgSO_4$ and 35 women as control group (Group B), who did not receive $MgSO_4$. Corticosteroid was given to both groups. Diagnosis of preterm labour was based on clinical history, clinical examination and ultrasonography. Predesigned proforma was used to assess the demographic, obstetric and medical history of the patients.

A 4gm intravenous loading dose was given over 15 minutes, followed by a 1g/hr. infusion until birth or up to 24 hours, whichever came first (FOGSI FOCUS- Prevention of preterm labour, 2017). Hot flushes, nausea, vomiting, muscle weakness, and discomfort at the injection site, as well as respiratory depression were among the maternal side effects evaluated. Birth weight, Apgar score at 1 minute and 5 minutes, NICU admission, requirement for respiratory support, presence of IVH (Diagnosed by cranial USG done within 14 days of birth), neonatal morbidities, maternal adverse effects, neonatal signs and symptoms (weak cry, tachypnoea, chest retraction, lathery, seizure, hypotension, apnea, sepsis), neonatal morbidities (RDS, NEC, septicemia), baby's condition at discharge were all investigated and was used for comparison. A six-month follow-up was performed to assess any early neurological complications. We compared the achievement of milestones of these babies at two months, four months, and six months of corrected gestational age. At 2 months (social smile), 4 months (neck holding), and 6 months (sitting with support), these milestones were used for comparison.

Statistical analysis - Bar diagram and Pie-chart were used to describe the descriptive statistics. Chi square or Fishers exact test is used to evaluate association between categorical variables. Data were checked for normality using Kolmogorov-Smirnova and Shapiro-Wilk test. Independent T test is used to compare mean difference between two groups depending on fulfillment of normality assumption for continuous variables.

Results

In present study 5 (14.3%) of the babies born to mother who did not receive $MgSO_4$ developed IVH compared to 3 (8.6%) of the babies born to mother who received $MgSO_4$ (table 1). In this study 3 (8.6%) ELBW babies in non$MgSO_4$ group had IVH compared to 2 (5.7%) in $MgSO_4$ group. 2 (5.7%) VLBW babies in non$MgSO_4$ group had IVH while 1 (2.9%) VLBW babies in $MgSO_4$ group had IVH (table 2). 12 (34.3%) out of 35 babies required intubation in non$MgSO_4$ group whereas 6 (17.1%) out of 35 babies in $MgSO_4$ group required intubation. CPAP requirement was similar in both groups according to gestational age. 3(8.6%) out of 35 babies

Table 1: Incidence of IVH in $MgSO_4$ (Group A) and non$MgSO_4$ group (Group B)

IVH	Group A	Group B	Total	Total %	Group A (%)	Group B (%)	p value
Absent	32	30	62	89	91	86	0.452
Present	3	5	8	11	9	14	
Total	35	35	70	100	100	100	

Table 2: Incidence of IVH in comparison to weight of the baby

Categories	Weight of baby (kg)	No	Yes	Total	No (%)	Yes (%)	Total %	p value
Group A (MgSO4 group)	<1 Kg	3	2	5	8.6	5.7	14.3	<0.001
	1-1.5 KG	17	1	18	48.6	2.9	51.4	
	>1.5 Kg	12	0	12	34.3	0.0	34.3	
	Total	32	3	35	91.4	8.6	100.0	
Group B (nonMgSO4 group)	<1 Kg	4	3	7	11.4	8.6	20.0	0.033
	1-1.5 KG	13	2	15	37.1	5.7	42.9	
	>1.5 Kg	13	0	13	37.1	0.0	37.1	
	Total	30	5	35	85.7	14.3	100.0	

Table 3: Comparison of respiratory support with gestational age in babies born to mother who received MgSO4 and those who did not

Categories		Gestational age						
	Respiratory support	28-30 wks	30-32 wks	Total	28-30 wks (%)	30-32 wks (%)	Total %	p value
Group A (MgSO4 group)	CPAP	7	2	9	20.0	5.7	25.7	
	Intubated	4	2	6	11.4	5.7	17.1	
	Not required	2	3	5	5.7	8.6	14.3	
	O2 by hood	9	6	15	25.7	17.1	42.9	
	Total	22	13	35	62.9	37.1	100.0	
Group B (nonMgSO4 group)	**CPAP**	7	2	9	20.0	5.7	25.7	
	Intubated	7	5	12	20.0	14.3	34.3	
	Not required	0	4	4	0.0	11.4	11.4	
	O2 by hood	3	7	10	8.6	20.0	28.6	
	Total	17	18	35	48.6	51.4	100.0	
Total	CPAP	14	4	14	20.0	5.7	20.0	
	Intubated	11	7	13	15.7	10.0	18.6	
	Not required	2	7	16	2.9	10.0	22.9	
	O2 by hood	12	1	27	17.1	1.4	38.6	
	Total	39	31	70	55.7	44.3	100.0	

Table 4: Requirement of respiratory support according to birth weight in babies born to mothers who received $MgSO_4$ and those who did not

		Weight of baby								
Group A (MgSO4 group)	Respiratory support	<1 Kg	1-1.5 Kg	>1.5 Kg	Total	<1 Kg (%)	1-1.5 Kg (%)	>1.5 Kg (%)	Total %	p value
	CPAP	2	5	2	9	5.7	14.3	5.7	25.7	0.011
	Intubated	2	2	0	4	5.7	5.7	0.0	11.4	
	Not required	0	3	3	6	0.0	8.6	8.6	17.1	
	O2 by hood	0	9	7	16	0.0	25.7	20.0	45.7	
	Total	4	19	12	35	11.4	54.3	34.3	100.0	
Group B (nonMgSO4 group)	CPAP	1	5	4	10	2.9	14.3	11.4	28.6	0.002
	Intubated	5	4	2	11	14.3	11.4	5.7	31.4	
	Not required	0	2	1	3	0.0	5.7	2.9	8.6	
	O2 by hood	0	5	6	11	0.0	14.3	17.1	31.4	
	Total	6	16	13	35	17.1	45.7	37.1	100.0	
Total	CPAP	3	10	6	14	4.3	14.3	8.6	20.0	<0.001
	Intubated	7	6	2	13	10.0	8.6	2.9	18.6	
	Not required	0	5	4	16	0.0	7.1	5.7	22.9	
	O2 by hood	0	14	13	27	0.0	20.0	18.6	38.6	
	Total	10	35	25	70	14.3	50.0	35.7	100.0	

required oxygen by hood in non $MgSO_4$ group while, 9 (25.7%) out of 35 babies in $MgSO_4$ group between 28 to 30 weeks of gestation. 7 (20%) out of 35 babies required oxygen by hood in non$MgSO_4$ group between 30 to 32 weeks of gestation. 6 (17.1%) out of 35 babies in $MgSO_4$ group between 30 to 32 weeks of gestation required oxygen by hood (table 3). 5 (14.3%) ELBW babies (<1kg) required intubation born to mother who received $MgSO_4$ compared to the 2 (5.7%) babies whose mother did not receive $MgSO_4$. 4 (11.4%) VLBW babies required intubation in non$MgSO_4$ group compared to 2 (5.7%) babies in $MgSO_4$ group. 2 LBW babies (>1.5 kg) in non$MgSO_4$ group required intubation compared to $MgSO_4$ group where none of the babies' required intubation (table 4).

At the end of six months, 3 (8.6%) of babies in the $MgSO_4$ group had delayed milestones, whereas 5 (14.3%) of babies in the non$MgSO_4$ group had delayed milestones. In the present study 3 (8.6%) babies were between 28 to 30 weeks of gestation who did not achieve milestones in both $MgSO_4$ and non$MgSO_4$ group. 2 (5.7%) babies between 30 to 32 weeks gestation in non$MgSO_4$ group had delayed milestones, while none of the babies between 30 to 32 weeks of gestation in $MgSO_4$ group had delayed milestones (table 5).

Table 5: Comparison of gestational age with achievement of milestones at the end of 6 months in $MgSO_4$ and non $MgSO_4$ group

		Outcome (milestone) 6 months						
Categories		**28-30wks**	**30-32wks**	**Total**	**28-30wks (%)**	**30-32wks (%)**	**Total %**	**p value**
Group A	Achieved	19	13	32	54.3	37.1	91.4	0.357
(MgSO4	Not Achieved	3	0	3	8.6	0.0	8.6	
group)	Total	22	13	35	62.9	37.1	100.0	
Group B	Achieved	14	16	30	40.0	45.7	85.7	0.729
(nonMgSO4	Not Achieved	3	2	5	8.6	5.7	14.3	
group)	Total	17	18	35	48.6	51.4	100.0	

At the end of six months, none of the LBW babies in the $MgSO_4$ group had delayed milestones, whereas 1(3%) of babies in the non$MgSO_4$ group had delayed milestones. 2 (6%) VLBW babies who did not achieve milestones in $MgSO_4$ and 3 (9%) in non$MgSO_4$ group. 1(3%) ELBW babies in both $MgSO_4$ and non$MsSO_4$ group had delayed milestones (table 6).

Table 6: Comparison of birthweight with achievement of milestones at the end of 6 months

		Weight of baby							
Group	Outcome (Milestone) 6 Months	**<1 Kg**	**1-1.5 Kg**	**>1.5 Kg**	**Total**	**<1 Kg (%)**	**1-1.5Kg (%)**	**>1.5 Kg (%)**	**Total (%)**
A	Achieved	3	17	12	32	9	49	34	91
(MgSO4	Not Achieved	1	2	0	3	3	6	0	9
group)	Total	4	19	12	35	11	54	34	100
Group B	Achieved	5	13	12	30	14	37	34	86
(nonMgSO4	Not Achieved	1	3	1	5	3	9	3	14
group)	Total	6	16	13	35	17	46	37	100

In present study 5 (14.3%) babies out of 35 not antenatally exposed to $MgSO_4$ developed IVH compared to $MgSO_4$ group where 3 (8.6%) babies out of 35 had IVH. 4 (11.4%) of the babies born to mothers who received $MgSO_4$ and who did not receive $MgSO_4$ had NEC. 15 (42.9%) of the babies in $MgSO_4$ group had RDS compared to 17 (48.6%) babies in non$MgSO_4$ group. 3 (8.6%) of the babies in $MgSO_4$ group had septicemia compared to 2 (5.7%) of the babies in non$MgSO_4$ group (table 7).

Table 7: Comparison of incidence of neonatal morbidities in babies born to mother who received $MgSO_4$(Group A) and those who did not (Group B)

Neonatal morbidities	**Group A**	**Group B**	**Total**	**Group A (%)**	**Group B (%)**	**Total %**
Necrotising enterocolitis	4	4	8	11.4	11.4	11.4
RDS	15	17	32	42.9	48.6	45.7
Septicaemia	3	2	5	8.6	5.7	7.1
IVH	3	5	8	8.6	14.3	11.4

Discussion

A hospital based prospective study was conducted in Fakhruddin Ali Ahmed Medical College and Hospital to assess the effectiveness of $MgSO_4$ as a neuroprotective agent in early preterm labour (28 to 32 weeks) and to assess any maternal and fetal adverse effect. Although several clinical trials and current guidelines from several countries support the use of magnesium sulphate for the prevention of cerebral palsy in preterm infants, usage of $MgSO_4$ in preterm birth is not routinely employed in clinical practice, including at our institution. We studied the neurological outcome of preterm babies (28-32 weeks) following administration of $MgSO_4$. The neurological outcomes studied were in terms of, complications at birth such as intraventricular hemorrhage, requirement of respiratory support, Apgar score at 1 and 5 minutes and achievement of milestones till 6 months of age. Also, we studied various adverse effect of magnesium sulphate like hot flushes, nausea, vomiting, dizziness, etc. among the mothers. We looked at the incidence of neonatal morbidities (NEC, RDS and septicemia) to check whether there were any MgSO4 attributable adverse effects.

The number of babies who developed IVH in the non-$MgSO_4$ group was greater (5/35, 14.3 %) than in the $MgSO_4$ group (3/35, 8.6%) (p value = 0.452). In the non$MgSO_4$ group, 8.6% (3/35) of the ELBW babies developed IVH, while 5.7% (2/35) in the $MgSO_4$ group. IVH occurred in 5.7% (2/35) of VLBW babies in the non$MgSO_4$ group and 2.9% (1/35) in the $MgSO_4$ group, [(Group A) p value = <0.001] [(Group B) p value = 0.033]. In present study, the main risk factor for IVH was an infant's extremely low birth weight (p value = <0.001). Kuban and colleagues in 1992, and subsequently Van de Bor et al and Levitron, found that giving $MgSO_4$ to pre-eclamptic women reduced the risk of intraventricular hemorrhage in very low birthweight infants [16]. Crowther 2003 and Rouse 2008 RCTs both found a protective effect similar to what we found in our study [17,18].

Antenatal $MgSO_4$ exposure demonstrated a protective effect against the requirement for respiratory support. Despite lower birth weight or lower gestational age, $MgSO_4$ had protective effect on the need of invasive ventilation in our study. According to the gestational age in non$MgSO_4$ group 20% (7/35) of the babies between 28 to 30 weeks

required intubation compared to 11.4% (4/35) babies in $MgSO_4$ group.

14.3% (5/35) of the babies between 30 to 32 weeks in non$MgSO_4$ group required intubation where only 5.7% (2/35) babies in $MgSO_4$ group required intubation (p value = 0.017). In the non$MgSO_4$ group, 14.3% (5/35) of ELBW babies and 11.4% (4/35) of VLBW babies needed intubation, compared to 5.7% (2/35) of ELBW and 5.7% (2/35) VLBW babies in the $MgSO_4$ group (p value = 0.011). Crowther et al (2017) in his meta-analysis found no significant differences in terms of use of respiratory support after birth, Apgar score at 5 minutes < 7 [17]. Hypotonia, lowers 1-minute and 5-minute Apgar score, intubation, admission to NICU were elevated in a study on the newborn consequences of $MgSO_4$ given to 6654 mothers with preeclampsia by Mina Abbassi [19].

In present study we found delayed milestones more in non$MgSO_4$ group (14%) compared to $MgSO_4$ group (6%) at the end of 6 months. In a follow-up study of 24 months, Rouse et al (2008) found substantial gross motor dysfunction was significantly less frequent among surviving children in the magnesium sulfate group (3.4% vs. 6.6%; relative risk, 0.51; 95% CI, 0.29 to 0.91) [18]. Marret et al [20] reported 2-year outcomes of a trial that involved 573 mothers. Infants of women assigned to receive magnesium sulfate had non-significantly lower rates of cerebral palsy among survivors (7.0% vs. 10.2%; relative risk, 0.69; 95% CI, 0.41 to 1.16). Present study shows improved neuroprotection in babies weighing more than 1.5 kg. In both groups, the newborns' mean birthweight was comparable. In this study 10.5% of VLBW babies had delayed milestones in $MgSO_4$ group and 18% of VLBW babies in nonMgSO4 group had delayed milestones at the end of 6 months. 7.6% of the LBW babies had delayed milestones in non$MgSO_4$ group while no LBW babies in $MgSO_4$ group had delayed milestones. Nelson KB (1995) found 7.1% of the 42 VLBW infants with CP and 36% of the 75 VLBW controls were exposed to $MgSO_4$ [21]. 8.6% (3/35) of babies between gestational age of 28-32 weeks had delayed milestones in both groups. 5.7% (2/35) of the babies in non$MgSO_4$ group between 30 to 32 weeks of gestation had delayed milestones [Group A (p value = 0.357), Group B (p value = 0.729)] whereas, no babies in $MgSO_4$ group between 30 to 32 weeks of gestation had delayed milestones. Jung EJ et al (2017) showed there was no significant difference in developmental delay between the two groups for patients in the subgroup of 28-30 weeks and 28-30 weeks. Rouse et al (2008) found that 3.5% in $MgSO_4$ group and 2.5% in placebo group of the babies belonging to 28-30 weeks had cerebral palsy at 24 months [18].

There were no incidences of major adverse effects requiring magnesium sulphate infusion to be discontinued prematurely. In line with the previous findings, our investigation found that $MgSO_4$ can be safely provided to women for neuroprotection with no clinically significant effect on maternal morbidity. No statistically significant difference was seen in analysis of neonatal morbidities. In this study, among the 8 newborns who had NEC 4 (11.4%) belonged to $MgSO_4$ and 4 (11.4%) belonged to non $MgSO_4$ group. No association between use of $MgSO_4$ and NEC was found. In his meta-analysis, Agustn Conde-Agudelo found a non-significant but higher incidence of necrotizing enterocolitis in the $MgSO_4$ group [22]. The MagNET experiment prompted some worries regarding $MgSO_4$ harming babies because their analysis revealed that newborns whose mothers got MgSO4 (32%) had more adverse events than those whose mothers received placebo (19%), however the difference was not statistically significant [23].

Strength of the study - This was a case control study with matching controls. In the study group only two patients (<5%) dropped out. We could follow-up as per our methodology up to 6 months without further dropout in both the groups.

Limitation of the study – With the limited resources, the present design of the study served the purpose; however, the study had some limitations:

- Due to the COVID-19 pandemic during our study, we could not take larger sample size. So, the sample size was only 35.
- We have followed up the babies only till 6 months of age due to limitation of time, ideally this type of study needs longer follow up to pick up all the neurological complication.

Recommendation -

- Similar studies should be done in different health care settings with a larger sample size and better methodology like RCT.
- Routine use of MgSO4 in clinical practice can reduce the burden of CP facing babies born very preterm.

Conclusion

The administration of magnesium sulfate prior to preterm birth for fetal neuroprotection may prevent cerebral palsy and reduce the risk of fetal or infant death. Following a

series of large randomized control trials, antenatal $MgSO_4$ is now well established as a neuroprotective agent to reduce the risk of cerebral palsy in preterm infants. The beneficial effects are observed regardless of the cause of preterm birth, the protective effect being seen regardless the gestational age. Magnesium sulphate has great potential for use in resource restricted settings due to its ease of storage, widespread availability and low cost. We believe that the introduction of such an inexpensive, easy-to-administer treatment with no significant maternal side effects, in the national guidelines, may lead to an important improvement of the preterm infant prognosis and it should be considered a component part of the prenatal prophylactic treatment of preterm infants.

Conflict of interest: None. **Disclaimer:** Nil.

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