The Journal of Obstetrics and Gynecology of India (July–August 2022) 72 (S1):S36–S47
https://doi.org/10.1007/s13224-021-01531-9

ORIGINAL ARTICLE

Efficacy of Antenatal Magnesium Sulfate for Neuroprotection in Extreme Prematurity: A Comparative Observational Study

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Received: 13 February 2021 / Accepted: 15 July 2021 / Published online: 8 August 2021
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Abstract

Background Survival of preterm infants has improved drastically. In addition to significant contribution to neonatal mortality, impact of prematurity among survivors may continue through life impairing long-term physical life through neuro-disability and increased risk of cerebral palsy. Maternal administration of magnesium sulfate prior to impending preterm birth is an effective strategy to reduce neuromorbidity.

Aim To investigate the effectiveness of antenatal magnesium sulfate for neuroprotection in preterm infants between 26 and 34 weeks in preventing early neonatal morbidity and mortality. Secondary objective was to assess any adverse events with the use of magnesium sulfate on the mother and neonate.

Method This was a prospective observational comparative study for 2 years at our tertiary care hospital of 100 pregnant women who gave preterm births. Fifty infants each were born to mothers who were either not given $MgSO_4$ (Group 1) or given 4gm intravenous loading dose $MgSO_4$ (Group 2), preferably 4 h prior to preterm birth.

Results Among all the preterm in our study, 81% delivered between 30 and 34 weeks. There was no significant difference in terms of maternal mortality or serious morbidity including postpartum hemorrhage, caesarian section rates or length of hospital stay among women receiving $MgSO_4$ versus no $MgSO_4$. Mild maternal side effects secondary to magnesium sulfate were experienced in 8% cases. There were no significant differences between both groups for low 5 min APGAR, need for NICU admission, neonatal convulsions, hyperbilirubinemia, necrotizing enterocolitis, periventricular leukomalacia and septicemia. There was a trend toward reduced risk in the magnesium sulfate group for need for mechanical ventilation and ongoing respiratory support, intraventricular hemorrhage, neonatal hypotension, hypothermia, length of NICU stay. IVH was less frequent and less severe in babies exposed to antenatal $MgSO_4$ (8%) as compared to non-$MgSO_4$ group (16%). Neonatal morbidities were more when antenatal $MgSO_4$ was given less than 4 h from delivery.

Conclusion $MgSO_4$ is a safe drug to use in antenatal women at risk for impending preterm. Antenatal magnesium sulfate given to women in established preterm labor conferred significant neuroprotective advantage to the neonate. $MgSO_4$ also has protective effect on the need of invasive ventilatory support in preterm infants. Given the breadth of evidence in its favor, it is time for us to start using $MgSO_4$ in clinical practice for neuroprotective intent in all our extreme preterm births.

Keywords Neuroprotection · Preterm · Magnesium sulfate · $MgSO_4$

Introduction

Among 135 million neonates born each year worldwide, almost 14.9 million are preterm representing a preterm birth rate of 11.1% [1]. Approximately 70% of neonatal

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deaths, 36% of infant deaths and 25–50% of cases of long-term neurological impairment in the USA occur in these preterm live births [2].

With improved prenatal and neonatal care, survival of premature infants has increased significantly. However, these premature infants who survive exert a heavy burden on families, society and the healthcare system. Short-term complications of premature birth include respiratory and cardiovascular complications, intracranial hemorrhage, necrotizing enterocolitis, hypothermia and NICU admissions. Those who emerge from these initial obstacles may suffer from long-term sequelae of intellectual disability, cognitive dysfunction, hearing and visual impairments. These disabilities increase proportionally with decreasing gestational age at birth, lower birthweight and also decreasing quality of medical care facility [3].

Perinatal morbidity and death following preterm birth can be reduced not only by good neonatal care but by timely interventions provided to the mother in the form of antenatal steroids, antibiotics and $MgSO_4$ for improving lung maturity, susceptibility to infections and neuroprotection, respectively [4].

The exact mechanism of the role of magnesium sulfate ($MgSO_4$) in prevention of neuronal injury to fetal brain is unclear. Magnesium ions are involved in intracellular glycolysis, oxidative phosphorylation, protein synthesis and maintenance of cell membrane integrity. There is some evidence that magnesium reduces the production of pro-inflammatory cytokines and free radicles following hypoxic ischemic reperfusion and also prevents calcium-induced injury.

The use of $MgSO_4$ for seizure prevention in patients with pre-eclampsia and as a tocolytic agent in premature labor has been known and widely used for some time. Nelson and Grether were the first to suggest, in a case–control study of extremely low-birthweight infants in 1995, that there existed a link between the incidence of cerebral palsy and exposure to $MgSO_4$. It was serendipitously observed that infants exposed to $MgSO_4$ in pregnancy were less likely to develop cerebral palsy compared with those not exposed, all other factors remaining constant [5].

Since then three randomized trials, one each in Australia and New Zealand (Australia Collaborative Trial of the $MgSO_4$ group/ ACTOMAG), France (PREMAG) and USA (Beneficial effect of antenatal magnesium sulfate / BEAMS) have been conducted to assess the efficacy of $MgSO_4$ in preventing neonatal mortality, perinatal cerebral injury and cerebral palsy in premature births [6–8]. Subsequent meta-analysis of all available clinical trials in 2009 confirmed its neuroprotective effect [9, 10]. The Cochrane review in the same year also recommended the use of $MgSO_4$ for neuroprotection when birth is anticipated before 32 weeks of gestation [11].

Although the goal of all the three randomized trials was to evaluate the effect of magnesium sulfate on neurodevelopmental outcomes and mortality in preterm neonates, comparisons between trials are difficult due to differences in population studied, gestational age at treatment, inclusion and exclusion criteria, $MgSO_4$ regimes and outcome variables assessed. $MgSO_4$ regimes have varied from a loading dose of 4gm in 15 min to 6 gm in 20 min with maintenance dose varying from none to 3 gm/ hour and duration of infusion from 12 to 24 h.

On the contrary, few studies on early outcomes among preterm infants treated with $MgSO_4$ for neuroprotective intent have demonstrated increased risk of intraventricular hemorrhage, impaired intestinal blood flow in the few hours after birth, increased spontaneous bowel perforation, increased neonatal intensive care admissions and need for intubation [12].

In spite of the recommendations, drug being inexpensive, clinicians experienced with its use in eclampsia, it is still not being widely practiced, and to my knowledge, there are no known Indian comparative studies on use of magnesium sulfate for neuroprotection.

We decided to use magnesium sulfate for fetal neuroprotection in patients with imminent preterm delivery as a standard of care in our unit in a tertiary care hospital. However, all the other units of our hospital were still not convinced of its efficacy as well as worried about its maternal and neonatal complications. We planned to compare the perinatal outcome in 100 cases. The Institutional Ethics Committee granted approval for the study.

Aims and Objectives

1. To investigate the effectiveness of antenatal magnesium sulfate for neuroprotection in preterm infants between 26 and 34 weeks in preventing early neonatal morbidity and mortality.
2. To assess any adverse events with the use of magnesium sulfate on the mother and neonate.

Methodology

This was a prospective comparative observational study from April 2016 till March 2018 at our tertiary care referral hospital of 100 pregnant women who gave preterm births between 26 and 34 weeks either due to spontaneous preterm labor and / or planned preterm birth for fetal or maternal indications.

Out of these, 50 infants were born to mothers who were not given injection $MgSO_4$ (Group 1) and 50 infants were born to mothers in impending preterm delivery who were

given injection $MgSO_4$ (Group 2) 4gm intravenous loading dose in 100 ml normal saline over 30 min preferably 4 h prior to preterm birth as per standard of care. No maintenance dose was given. If delivery was imminent, it was still given irrespective of 4-h window period. We excluded from both groups, women who delivered before they could get the benefit of two doses of steroids for lung maturity, multiple pregnancies and those with a major fetal abnormality.

Pregnant women and neonates were cared for according to standard clinical practice. Outcome of these preterm infants and their mothers were analyzed through information collected from patient record till postnatal 1 month or hospital discharge whichever was later and was used for comparison.

Results

Among the 100 women in our study, average age of the mothers was 28.2 ± 4.74 years with a range of 19–41 years. The average mothers' age in Group1 was 29.0 ± 4.88 and in Group 2 was 27.3 ± 4.49 [t (98) = 1.747, $p = 0.084$].

Maximum delivery occurred between 30 and 34 weeks of gestation (n-81, 81%) (Fig. 1). Gestational age at birth was similar in the $MgSO_4$ (31.1 ± 1.73 weeks) and non-$MgSO_4$ group (31.4 ± 1.49 weeks) [t (98) = 1.084, $p = 0.281$].

Pregnancy-induced hypertension, fetal growth restriction (FGR) and history of previous preterm delivery or second trimester abortion were found to be the major risk factors for preterm delivery. Eighty-three percent of all patients had 1 or more risk factors and only 17% were low-risk pregnancies.

Fifty-two percent patient went into spontaneous preterm labor (n-30) or spontaneous premature rupture of membranes (PROM) (n-22) and 48% were indicated preterm deliveries due to maternal medical disease such as hypertensive disorders, placental causes (placental abruption and previa) and fetal causes (FGR and oligohydramnios). The single most common indication for preterm delivery was abnormal Doppler flows (27%) barring patients in spontaneous labor.

Seventy percent preterms delivered by LSCS (lower segment cesarean section) (Table 1). There were more number of LSCS in non-$MgSO_4$ group (57%) compared to $MgSO_4$ group (42%) which was statistically significant [$\chi(1) = 4.762$, $p = 0.029$]. The most common indication for LSCS being abnormal Color Doppler 26% followed by PIH 15% and prolonged PPROM 11%.

The average time elapsed between $MgSO_4$ and delivery was 3.74 ± 1.675 h with the maximum time being 6 h and minimum time being 1 h (Fig. 2). Almost equal numbers delivered in less than and more than 4 h ideal protocol (24/26) (Table 2).

Table 1 Mode of delivery among $MgSO_4$ and non-$MgSO_4$ group

Mode of delivery	Weeks of gestation	Non-$MgSO_4$ group	$MgSO_4$ group	Total
LSCS	< 30 weeks	7	2	9
	30.1–32 weeks	15	13	28
	> 32–34 weeks	18	15	33
	Total	40	30	70
PTVD	< 30 weeks	2	8	10
	30.1–32 weeks	3	7	10
	> 32–34 weeks	5	5	10
	Total	10	20	30

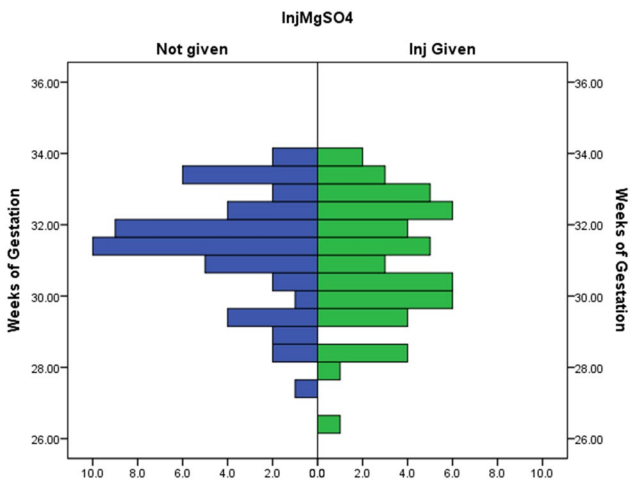

Fig. 1 Distribution of mothers according to weeks of gestation

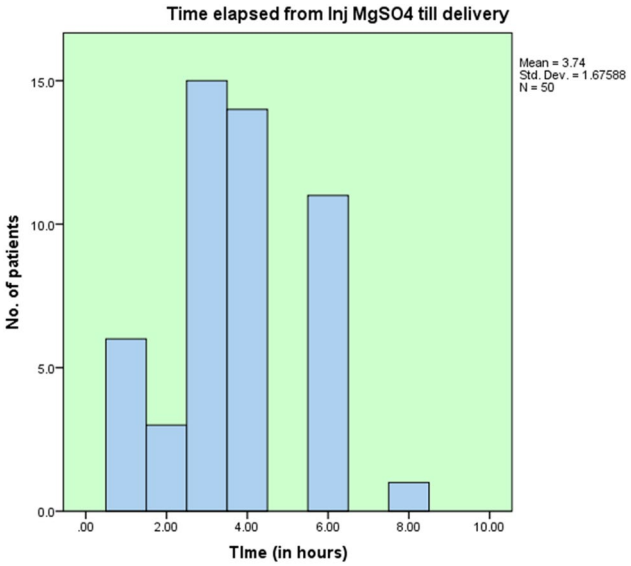

Fig. 2 Hour-wise time elapsed from $MgSO_4$ infusion till delivery

Table 2 Duration between $MgSO_4$ and mode of delivery

Duration between $MgSO_4$ and delivery	LSCS	PTVD	TOTAL
Less than 4 h	10	14	24
More than 4 h	16	10	26
Total	26	24	50

Table 3 Distribution of birthweight among $MgSO_4$ and non-$MgSO_4$ group

Birthweight	Non-$MgSO_4$ group	Inj $MgSO_4$ given	Total (%)
ELBW (1 kg & less)	10	15	25
VLBW (1–1.5 kg)	26	23	49
LBW (1.5–2.5 kg)	14	12	26
Total	50	50	100

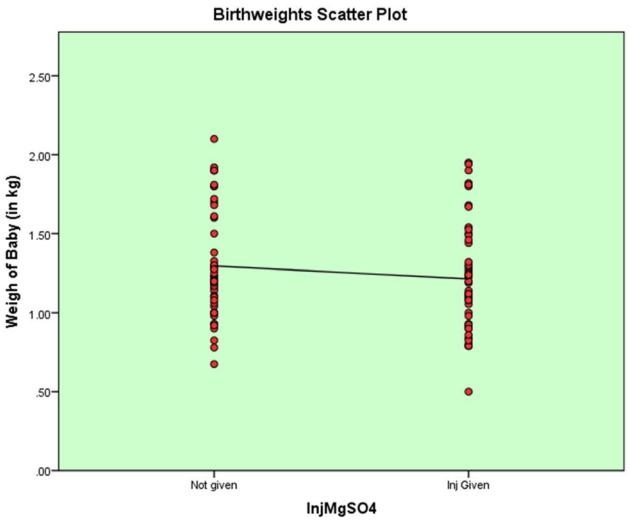

Fig. 3 Distribution of neonates according to birthweight among $MgSO_4$ and non-$MgSO_4$ group

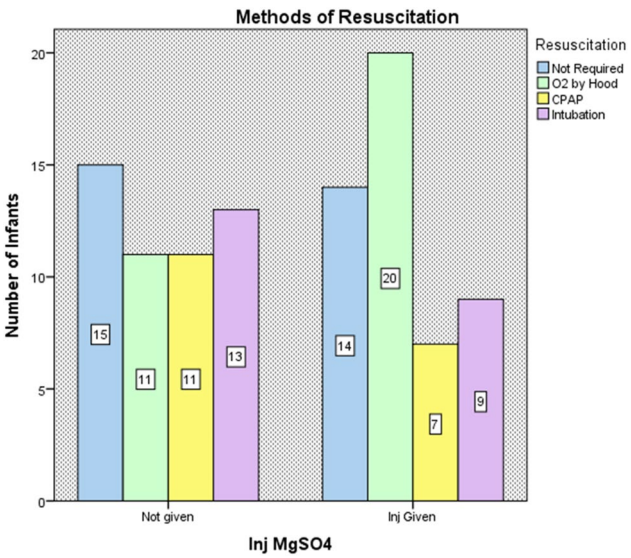

Fig. 4 Distribution of infants among $MgSO_4$ and non-$MgSO_4$ according to the method of resuscitation

Only 4 out of the 50 women (8%) who received $MgSO_4$ had mild side effects, including nausea (1), dizziness (1), flushing (1) and tachycardia (1), which subsided spontaneously after 1- 3 h, none required medications or cessation of $MgSO_4$ therapy. Out of the 50 patients in Group 1 (non-$MgSO_4$), 6 (12%) patients had atonic postpartum hemorrhage (PPH), all of which had cesarean deliveries. Two women who received $MgSO_4$ for neuroprotection had PPH (4%), both of which had vaginal deliveries. Atonic PPH was more seen in non-$MgSO_4$ group; however, it was not statistically significant ($p = 0.269$). None had estimated blood loss > 1000 ml (Massive postpartum hemorrhage) and all were controlled with uterotonics with no increased morbidity.

The mean birthweight in Group 1 was 1.29 ± 0.346 and in Group 2 was 1.21 ± 0.348 (Table 3) with no statistically significant difference, $p = 0.249$ (Fig. 3).

Infants with 5 min Apgar score less than 5 were not seen in the $MgSO_4$ group. However, 2 neonates in non-$MgSO_4$ group had 5 min Apgar less than 5 due to cord prolapse in one and extreme prematurity (26 weeks) in the second. The correlation of the effect of $MgSO_4$ on APGAR scores was not significant with almost equal number of neonates with 5 min Apgar less than 7 in both groups (36%vs 38%) [rpb = 0.52, $p = 0.611$]. The average APGAR score for Group 1 was 7.1 ± 1.54 and for Group 2 was 7.2 ± 1.38.

The methods of resuscitation are summarized in the clustered bar chart (Fig. 4). Thirteen out of 50 neonates (26%) not exposed to antenatal magnesium sulfate required intubation whereas 9 out of 50 infants (18%) exposed to antenatal magnesium sulfate required intubation. Need for CPAP (continuous positive airway pressure) or full ventilation was seen in 24/50 (48%) neonates in non-$MgSO_4$ group and only 16/50 (32%) in the MgSO4 group.

75% (6/8) neonates in non-$MgSO_4$ group who delivered before 30 weeks of gestation required intubation when compared to 47% (8/17) in $MgSO_4$ group. Among neonates who delivered after 30 weeks 16% required intubation in non-$MgSO_4$ when compared to only 3% in $MgSO_4$ group. Twenty-three percent neonates more than 1.5 kg in non-$MgSO_4$ group required intubation compared to $MgSO_4$ group whereas none of the neonates more than 1.5 kg required intubation (Table 4).

Table 4 Distribution of infants according to method of resuscitation in relation to weeks of gestation and birthweight

Groups	Variables		Need for respiratory support				Total
Non-$MgSO_4$	Weeks of gestation		Intubated	CPAP	O2 By Hood	Not required	
		26–27.6 Weeks	1	0	0	0	1
		28–29.6 Weeks	5	2	0	0	7
		30–31.6 Weeks	5	6	4	5	20
		32–34 Weeks	2	3	7	10	22
		TOTAL	13	11	11	15	50
	Birthweight	Less than 1 kg	6	2	0	0	8
		1–1.5 kg	4	8	9	8	29
		More than1.5 kg	3	1	2	7	13
		Total	13	11	11	15	50
$MgSO_4$	Weeks of gestation	26–27.6 weeks	4	0	0	0	4
		28–29.6 weeks	4	3	6	0	13
		30–31.6 weeks	1	4	4	3	12
		32–34 weeks	0	0	10	11	21
		Total	9	7	20	14	50
	Birthweight	Less than 1 kg	5	3	0	0	8
		1–1.5 kg	4	4	13	10	31
		More than 1.5 kg	0	0	7	4	11
		Total	9	7	20	14	50

Among the 100 live births, 90 neonates required NICU admission. Excluding the 7 infants in which death occurred before discharge, 83 infants were evaluated for the number of days they stayed in the NICU. The average number of days in NICU for infants in Group 1 (non-$MgSO_4$) was 24.1 ± 23.46 days and for Group 2 ($MgSO_4$ group) was 22.1 ± 21.18. There was no statistically significant correlation rpb = 0.44, $p = 0.673$.

Twenty percent (10/50) neonates not exposed to antenatal $MgSO_4$ required respiratory support for more than 10 days as compared to 12% (6/50) neonates in $MgSO_4$ group. Three neonates not exposed to antenatal $MgSO_4$ required respiratory support for more than 25 days whereas no infants exposed to antenatal $MgSO_4$ required more than 25 days of respiratory support, hence protecting the neonates from adverse effect of excessive oxygenation such as retinopathy of prematurity (Table 5).

Fourteen percent neonates who delivered after 30 weeks of gestation in non-$MgSO_4$ group required ventilator support for more than 10 days when compared $MgSO_4$ group where none of the neonates required ventilator support after 10 days. A point-biserial correlation was run to determine if infants exposed to antenatal $MgSO_4$ required less days on ventilator than controls. The correlation was significant, [rpb = 0.031, $p = 0.780$]. Infants with antenatal exposure to $MgSO_4$ had more days free of respiratory support in the first 28 days of life. Similar correlation was found with regard to birthweight and need for ventilator support.

The 14 signs and symptoms recorded were analyzed to check whether there were any $MgSO_4$ attributable adverse signs and symptoms. Although we expected hypotension in the neonate given $MgSO_4$ due to transplacental passage of the drug, infants were four times less likely to develop hypotension when $MgSO_4$ was given (χ 2(1) = 6.353, $p = 0.012$, 95% CI 1.201 to 13.319). Hypothermia (3 from 50 neonates) was also less in infants exposed to antenatal $MgSO_4$ as compared to infants (8 from 50 neonates) not exposed, although not statistically significant (Table 6).

All surviving infants (n-93) underwent a cranial ultrasound within the first 14 days of life. On neurosonogram, 2 infants showed (periventricular leukomalacia) PVL, one each in $MgSO_4$ and non-$MgSO_4$ group and 12 infants had IVH (Intraventricular hemorrhage). IVH was more often seen in non-$MgSO_4$ group (8/12) as compared to $MgSO_4$ group (4/12).

IVH was seen in 9 out of 19 neonates (47%) born before 30 weeks and 3 out of 81 neonates (3.7%) born after 30 weeks of gestation. No IVH was seen in baby weighing more than 1.5 kg.

In the infants not antenatally exposed to $MgSO_4$, 5 neonates delivered before 30 weeks of gestation had IVH and 3 neonates delivered after 30 weeks of gestation also had IVH, which were between 1 and 1.5 kg weight. IVH was seen in only 4 antenatal exposed $MgSO_4$ neonates all of whom were less than 30 weeks of gestation and extremely low birthweight (less than 1 kg) (Table 7).

Table 5 Cross-tabulation between method of ventilatory support, weeks of gestation and no. of days of ventilatory support in $MgSO_4$ and non-$MgSO_4$ group

Group	Need for ventilatory support			No of days in need of ventilatory support						Total
				5 days and less	6–10 days	11–15 days	16–20 days	21–25 days	More than 26 days	
Non- $MgSO_4$	Positive pressure ventilation and intubation	Weeks of gestation	26–27.6 wks	0	0	0	0	0	1	1
			28–29.6 wks	0	0	0	2	1	2	5
			30–31.6 wks	5	0	1	0	0	0	6
			32–34 wks	1	0	0	0	0	0	1
			Total	6	0	1	2	`1	3	13
		Birthweight	1 kg and less	0	0	0	1	0	2	3
			1–1.5 kg	5	0	1	1	1	1	9
			More than 1.5 kg	1	0	0	0	0	0	1
			Total	6	0	1	2	1	3	13
	CPAP	Weeks of gestation	26–27.6 weeks	0	0	0	0	0	0	0
			28–29.6 weeks	2	0	0	0	0	0	2
			30–31.6 weeks	0	1	2	0	0	0	3
			32–34 weeks	4	1	0	1	0	0	6
			Total	6	2	2	1	0	0	11
		Birthweight	1 kg and less	0	0	0	1	0	0	1
			1–1.5 kg	5	2	1	0	0	0	8
			More than 1.5 kg	1	0	1	0	0	0	2
			Total	6	2	2	1	0	0	11
Group	Need for ventilatory support			No of days in need of ventilatory support						Total
				5 days and less	6–10 days	11–15 days	16–20 days	21–25 days	More than 26 days	
$MgSO_4$	Positive pressure ventilation and intubation	Weeks of gestation	26–27.6 weeks	1	0	0	0	0	0	1
			28–29.6 weeks	1	2	2	0	0	0	5
			30–31.6 weeks	1	1	0	0	0	0	2
			32–34 weeks	0	1	0	0	0	0	1
			Total	3	4	2	0	0	0	9
		Birthweight	1 kg and less	1	2	0	0	0	0	3
			1–1.5 kg	1	2	2	0	0	0	5
			More than 1.5 kg	1	0	0	0	0	0	1
			Total	3	4	2	0	0	0	9
	CPAP	Weeks of gestation	26–27.6 weeks	0	0	1	0	0	0	1

Table 5 (continued)

Group	Need for ventilatory support		No of days in need of ventilatory support						Total
			5 days and less	6–10 days	11–15 days	16–20 days	21–25 days	More than 26 days	
		28–29.6 weeks	1	0	0	0	0	0	1
		30–31.6 weeks	2	0	0	1	0	0	3
		32–34 weeks	1	1	0	0	0	0	2
		Total	4	1	1	1	0	0	7
	Birthweight	1 kg and less	2	0	0	1	0	0	15
		1–1.5 kg	1	1	1	0	0	0	7
		More than 1.5 kg	1	0	0	0	0	0	1
		Total	4	1	1	1	0	0	7

Of the 4 neonates with IVH in the $MgSO_4$ group, only 1 had grade 2 IVH while 3 had grade 1 IVH, all amenable to resolution. None of the neonates antenatally exposed to $MgSO_4$ had grade 3 or grade 4 IVH, which may have long-term neuromorbidity. Out of 8 neonates with IVH in the non-$MgSO_4$ group, 3 had severe grade 3 IVH and 2 neonates had grade 2 IVH and 3 neonates had grade 1 IVH.

It is seen that all IVH in the $MgSO_4$ exposed group were in pregnancies where $MgSO_4$ was given less than 4 h before delivery where probably the protective effect was inadequate. It may be beneficial to give $MgSO_4$ more than 4 h prior to intention of delivery.

The study found no statistical significant difference in neonatal morbidities like neonatal jaundice and need for phototherapy, septicemia, seizures and necrotizing enterocolitis (NEC) in neonates exposed to antenatal $MgSO_4$ as compared to those not given $MgSO_4$ (Table 8).

While evaluating neonatal outcomes with regard to duration of $MgSO_4$ infusion prior to delivery, 15% infants exposed to antenatal $MgSO_4$ for less than 4 h had seizures whereas no seizures were seen in infants exposed to antenatal $MgSO_4$ for more than 4 h. Eighteen percent infants exposed to antenatal $MgSO_4$ for less than 4 h had NEC whereas no NEC was seen in infants exposed to antenatal $MgSO_4$ for more than 4 h.

Out of 100 preterm neonates studied, there were 7 early neonatal deaths in NICU. Two among the neonatal mortality were in less than 28 weeks of gestation and rest 5 neonatal deaths occurred in 28–30 weeks gestation. All neonatal deaths occurred in extremely low-birthweight babies (less than 1 kg) born at less than 30 weeks maturity.

In the 50 patients in whom $MgSO_4$ was given, there were 5 (10%) NICU deaths as against 2(4%) deaths in the non-$MgSO_4$ group. A Fischer's Exact test was run which showed that NICU deaths were not significantly associated with $MgSO_4$, $p = 0.436$.

Discussion

Prevalence of cerebral palsy worldwide has shown a modest increase secondary to increased survival of very low-birthweight infants [13]. White matter injury and intraventricular hemorrhage are the main developmental stage-specific brain disease responsible for these neuro-disabilities [14]. Risk of IVH increases inversely with the gestational age at birth [15].

Although multiple clinical trials and available guidelines from several countries endorse the use of magnesium sulfate for prevention of cerebral palsy in preterm infants [16–18], its clinical use for this purpose has undergone limited evaluation outside the context of these trials.

Table 6 Neonatal signs and symptoms in $MgSO_4$ and non-$MgSO_4$ group

Signs and symptoms		Inj $MgSO_4$ not given (n = 50)	Inj $MgSO_4$ Given (n = 50)	Total (n = 100)	Percentage
1	Weak cry	13	15	28	28.0
2	Tachypnoea	24	23	47	47.0
3	Chest retraction	15	16	31	31.0
4	Hypoglycemia	11	10	21	21.0
5	Hypothermia	8	3	11	11.0
6	Hypocalcemia	1	0	1	1.0
7	Lethargy	11	9	20	20.0
8	Hypotension	12	3	15	15.0
9	Bradycardia	12	12	24	24.0
10	Apnea	7	8	15	15.0
11	Seizure	6	7	13	13.0
12	Weak suck	9	13	22	22.0
13	Nasal flaring	2	1	3	3.0
14	Sepsis	1	1	2	2.0

Table 7 Incidence of IVH in $MgSO_4$ and non-$MgSO_4$ group in relation to weeks of gestation and birthweight

Variables		Intraventricular hemorrhage Non-$MgSO_4$ group	Intraventricular hemorrhage $MgSO_4$ group	Total
Weeks of gestation	26–27.6 weeks	0	0	0
	28–29.6 weeks	5	4	9
	30–31.6 weeks	3	0	3
	32–34 weeks	0	0	0
Total		8	4	12
Birthweight	Less than 1 kg	5	4	9
	1–1.5 kg	3	0	3
	More than 1.5 kg	0	0	0
Total		8	4	12

Table 8 Incidence neonatal morbidity in $MgSO_4$ and non-$MgSO_4$ group

Neonatal morbidity		Inj $MgSO_4$ not given ($n = 50$)		Inj $MgSO_4$ given ($n = 50$)		Total ($n = 100$)	Percentage
		No.	%	No.	%		
1	Neonatal Jaundice	12	24.0	11	22.0	23	23.0
2	Septicemia	1	2.0	1	2.0	2	2.0
3	Seizures	6	12.0	7	14.0	13	13.0
4	Necrotizing Enterocolitis	7	14.0	7	14.0	15	15.0

Even in our institution at the time of conducting the study, only our clinical unit was using $MgSO_4$ as a standard of care in women delivering preterm while there was still resistance to its use from all other units. So we decided to undertake this comparative prospective observation study where the obstetric management was performed by the respective consultants, while the NICU and the clinical treatment of the neonates were under a common neonatal team. We planned to compare short-term maternal and perinatal outcomes and safety of use of $MgSO_4$ in routine clinical practice. Given the prospective nature of our study and the strictly defined exposure status and outcomes, information bias was minimized.

From April 2016 to March 2018, 100 cases of preterm birth were studied of which 50 women expecting preterm delivery were given $MgSO_4$ for fetal neuroprotection and 50 women were not given. In all the RCT, different regimens of antenatal $MgSO_4$ have been used for neuroprotection [6, 8, 19]. We have not addressed the issues of different regimens

in our study and used the lowest dosage regime which is less likely to lead to maternal side effects.

Baseline maternal characteristics and reasons for preterm birth were similar in both groups. Preterm birth was seen more in the age group of 26–34 years (53%) as that is the most common reproductive age group.

Eighty-one percent of preterm deliveries occurred between 30 and 34 weeks of gestation suggesting the need for concentrating our resources on survival in this age group. However, those that survive in the less than 30 weeks (19%) are the ones at extremely high risk for early and late neonatal morbidity. Steps need to be taken in preventing the burden of neurological sub-normality in these very tiny babies who have braved their way to survival.

Almost equal numbers of preterm delivery were following spontaneous labor (52%) and iatrogenic preterm deliveries in our study that is similar to the National Centre for Health Statistics which also states that preterm labor precedes almost 50% of all preterm births [2]. In the first Australian randomized trial the primary reason for preterm birth was spontaneous labor (63%) and more than half were primigravidas with no risk factors [6]. Since our institution is a tertiary referral center for high-risk pregnancies hence the high numbers of indicated preterm births and few (17%) low-risk pregnancies.

Non-$MgSO_4$ group saw more LSCS (57%) as compared to those given $MgSO_4$ (42%) which was statistically significant. This result was contrary to the three trials [6, 8, 19] which reported no significant difference in mode of birth. Our results may be skewed toward more vaginal delivery in $MgSO_4$ group due to different obstetric teams working in the two groups with our unit ($MgSO_4$ group) protocol of giving a fair trial to all preterm labor.

More patient delivered vaginally in the group where the 4 h could not be completed probably due to preponderance of spontaneous active labor in these patients. Relation of timing of $MgSO_4$ with the mode of delivery was not statistically significant (Table 2).

$MgSO_4$ was given only when the delivery was inevitable or decision for LSCS was taken. None of the patient had a prolongation of gestation due to the tocolytic effect of magnesium sulfate. Four grams $MgSO_4$ in neuroprotective dose used in the Premag trial also failed to prevent preterm labor [19].

Maternal adverse effects from $MgSO_4$ therapy are an important issue in administering antenatal $MgSO_4$. Due to its peripheral vasodilator effect when given intravenously, Magnesium sulfate may cause a sensation of warmth, flushing and sweating. It may also cause side effects like nausea, vomiting, headache, dizziness palpitation, tachycardia, hypotension and hypocalcemia. Intravenous $MgSO_4$ if given too rapidly or in too high dosage may accentuate muscle relaxation of respiratory muscles leading to collapse due to its neuromuscular blocking effect. $MgSO_4$ in above recommended range could lead to severe postpartum hemorrhage, respiratory depression, pulmonary edema and cardiac arrest.

No serious adverse events occurred leading to stoppage of the magnesium sulfate infusion prematurely in our study. Minor maternal side effects were encountered in the three major trials, however no serious maternal complications like cardiac arrest, respiratory failure or death were seen [9–11]. Consistent with the above evidence, our study has also shown that $MgSO_4$ can be safely administered to women for neuroprotection as there is no clinically significant effect on maternal morbidity.

The mean birthweight of the infants and the weeks of gestation in the two groups were comparable. Extreme preterm and extreme low-birthweight infants that are principal risk factors for IVH and cerebral palsy in our study constituted about a quarter of the total. The rate of CP in very low-birthweight (VLBW) infants reported in literature is 4–8% [20].

$MgSO_4$ has been used for obstetric indication for many decades. Despite the familiarity and comfort of use, there are concerns about the potential adverse effects of antenatal $MgSO_4$ on preterm infants. Mina Abbassi in a study on neonatal effects of $MgSO_4$ given to 6654 women with pre-eclampsia suggested hypotonia, lower 5 min apgar, intubation and admission to NICU were all significantly increased [21]. Five-minute Apgar score <7 which quantitates clinical signs of neonatal depression showed no difference between the two groups in our study which is similar to the Cochrane systematic review [11].

It is found in our study that the infants who received antenatal $MgSO_4$ were less likely to require invasive mechanical ventilation on either day 1 or day 3 of life compared to the group not received antenatal $MgSO_4$, despite lower birthweight or lower gestational age. $MgSO_4$ had protective effect on the need of invasive ventilation in preterm infants.

Neonates with antenatal exposure to $MgSO_4$ had more days free of respiratory support in the first 28 days of life hence protecting the neonates from adverse effect of excessive oxygenation such as retinopathy of prematurity. Additionally, the beneficial effect of antenatal treatment was uniform between those recruited between 30 and 34 weeks and also those less than 30 weeks. Thus, it appears that the treatment should not be restricted to only the latter.

MagNET trial raised some concerns about MgSO causing harm to the neonates as their analysis showed more adverse events in infants whose mothers received $MgSO_4$ (32%) compared with those where mothers received placebo (19%) although not statistically significant [22]. A Binomial Logistic Regression was performed in our study to ascertain the effects of $MgSO_4$ on 14 neonatal signs and symptoms. Hypotension and hypothermia were significantly less with $MgSO_4$ exposed neonates. $MgSO_4$ exposed neonates

were more likely to have poor sucking reflex than their non-$MgSO_4$ counterparts although not statistical significant.

Agustín Conde-Agudelo in his meta-analysis suggested a non-significant but increased risk of necrotizing enterocolitis in the $MgSO_4$ group [10]. Another recent publication by Rattray also reported possible association between antenatal exposure to $MgSO_4$ in extremely low-birthweight infants less than 25 weeks and spontaneous intestinal perforation [23]. Among the 14 infants in our NICU who had NEC, our study demonstrated no association between $MgSO_4$ and NEC (7 vs 7) although we had no babies < 25 weeks in our inclusion criteria.

Prevention of IVH is of prime importance in preterm infants as it is associated with neuro-disability, death and cerebral palsy. Risk of IVH increases with lower gestational age at birth as seen in our study as well. Neonates in our study who developed IVH were significantly more in non-$MgSO_4$ group (8/50, 16%) as compared to $MgSO_4$ group (4/50, 8%). IVH in the neonates born after 30 weeks was only seen in the non-$MgSO_4$ group. Additional protection was seen with regard to the severity of the IVH in our $MgSO_4$ exposed neonates.

Kuban and colleagues in 1992 and later Van de Bor et al. and Levitron noted a decrease in incidence of intraventricular hemorrhage in very low-birthweight infants born to pre-eclamptic women who received $MgSO_4$ [24–26]. Crowther 2003 and Rouse 2008 RCT also suggested a similar protective effect as was seen in our study. However, they conjectured that perhaps the protective effect of $MgSO_4$ is beneficial only in neonates of earlier gestational age [6, 8]. Our study suggests significant benefit of $MgSO_4$ for both 30–34 weeks and < 30 weeks with regard to IVH.

The presumed mechanism of action of $MgSO_4$ for neuroprotection is dependent on adequate fetal levels of magnesium at the time of delivery. Animal studies evaluating placental transfer of magnesium sulfate have shown that it crosses fetal blood brain barrier within 2 h of sustained maternal infusion but its concentrations increase in the forebrain only after 4 h of treatment [27]. All neonatal outcomes that is 5 min Apgar score, need for resuscitation, hypotension, sepsis, seizures, IVH, NEC and number of days in NICU were better when time interval between $MgSO_4$ and delivery was more than 4 h in our study. With this evidence, one should aim to commence $MgSO_4$ at least 4 h prior to delivery. However, where it is not possible to achieve the 4-h window period, $MgSO_4$ should still be administered, as it is likely to show some benefit.

Infant death during hospitalization was higher in the $MgSO_4$ group [5] as compared to control [2] although not statistically significant. All the 7 neonatal deaths whether exposed or not exposed to antenatal $MgSO_4$, were extremely premature and extremely low birthweight and hence the detrimental outcomes on neonates may be difficult to attribute directly to the effects of $MgSO_4$. While Crowther, Magpie, Marret and Rouse showed no significant mortality difference between infants exposed to antenatal $MgSO_4$ and infants not exposed to antenatal $MgSO_4$, Mittendorf showed significant more death in $MgSO_4$ group than non-$MgSO_4$ group [6–8, 22, 28]. The neonatal mortality in our study was lesser with increasing gestational age and birthweight with no death in infants more than 1 kg.

Conclusion

$MgSO_4$ is a safe drug to use in antenatal women at risk for impending preterm birth. There is no significant difference in terms of maternal mortality or serious morbidity among women receiving $MgSO_4$ versus no $MgSO_4$. Additionally, no significant increase in postpartum hemorrhage, caesarian section rates or length of hospital stay is expected in women who receive $MgSO_4$. Timing of $MgSO_4$ had no significant association with the mode of delivery.

No significant difference regarding neonatal 5 min APGAR, convulsions, hyperbilirubinemia, necrotizing enterocolitis, periventricular leukomalacia, septicemia and need for NICU admission is seen with antenatal $MgSO_4$ use.

A trend toward reduced risk for invasive mechanical ventilation on day 1 of life, requirement for ongoing respiratory support, intraventricular hemorrhage, neonatal hypotension and hypothermia and length of hospital stay are additional beneficial effects of antenatal $MgSO_4$.

Prenatal $MgSO_4$ was protective with regard to frequency and severity of neonatal IVH both before 30 weeks and after 30 weeks of gestation.

Intraventricular hemorrhage, 5 min Apgar score less than 7, need for resuscitation, neonatal seizures and other neonatal morbidities were seen more in infants exposed to antenatal $MgSO_4$ for less than 4 h as compared to more than 4 h. It may be beneficial to give $MgSO_4$, at least 4 h prior to intention to delivery. However, benefit of antenatal $MgSO_4$ should not be denied to women where anticipated birth is earlier and the 4 h gap is not available.

Limitations

Firstly, only a small number of cases were studied. Larger cases are required to document a significant reduction in adverse outcome with magnesium therapy and to assess the neuroprotective role of injection $MgSO_4$ in neonatal outcomes.

Secondly, because of limited period of study and other practical constraints, the babies were not followed up, to document the long-term effects of such therapy. Controlled trials with larger number of babies with follow-up for

defined period to document long-term neurodevelopmental outcome is required.

Among pregnant women at risk of imminent preterm birth between 26 and 34 weeks, magnesium sulfate therapy is effective in protecting the fetus from neurological complications and is safe both for the mother and the neonate. Magnesium sulfate for neuroprotective intent should only be given if preterm birth is likely within the next 24 h. Minimum dosage of 4gm IV in infusion over 30 min may be given even if delivery is imminent and 4 h are not available.

In spite of various recommendations and guidelines, drug being inexpensive, clinicians vast experience with its use in eclampsia, it is still not being widely practiced in India. With our Indian study of comparison between use and non-use of $MgSO_4$ in women with preterm birth between 26 and 34 weeks for neuroprotection in surviving infants showing promising results, we anticipate widespread use of antenatal $MgSO_4$ in our country. Magnesium sulfate can protect the developing fetal brain and so has significant potential to reduce disability.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Human and animal rights Research involves human participants but since it is a prospective observational study, there has been no direct risk to participants. Study has been approved by the hospital ethics committee.

Informed consent Informed consent has been taken from all participants. Informed consent document (ICD) has been attached at the end of the manuscript as annexure.

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