ORIGINAL ARTICLE

Magnesium Sulfate for Fetal Neuroprotection in Women at Risk of Preterm Birth: Analysis of its Effect on Cerebral Palsy

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Abstract

Background: Magnesium sulfate ($MgSO_4$) can be used for the primary prevention of cerebral palsy in preterm infants less than 37 weeks of gestational age.

Aim and objective: To assess the effect of $MgSO_4$ given for fetal neuroprotection to women at risk of preterm birth.

Materials and Methods: This study was conducted on 100 women admitted to labor room in the Department of Obstetrics and Gynecology, S.N. Medical College, Agra, between August 2018 and December 2020. These women were randomly distributed into two groups. Women taken for study underwent detailed history, examination, and baseline investigations. In group 1, 50 women at risk of preterm birth before 37 weeks (gestational age, 28–36 weeks 6D) of gestation were given $MgSO_4$, 4 g bolus over 20–30 minutes followed by 1 g/hour, whereas in group 2, 50 women were not given $MgSO_4$.

Results: In our study, the majority of the patients were between the gestational age of 31 and 34 weeks. The mean gestational age was 30.1 weeks in group 1 and 31.5 weeks in group 2. The difference in terms of birth weight between the two groups is statistically insignificant. Neonatal outcomes among women administered $MgSO_4$ and women not administered $MgSO_4$ include the following: Neonatal seizures (2 vs 4%), respiratory distress (46 vs 60%), mechanical ventilation (48 vs 62%), and neonatal enterocolitis (6 vs 0.5%). The difference between Apgar scores of the two groups is statistically insignificant. Resuscitation was needed, 4 versus 6%, in group 2. There were 1 mortality in group 1 and 2 in group 2. In group 1, 44% of neonates needed neonatal intensive care unit (NICU) admission, whereas in group 2, 62.5% of neonates needed NICU admission with a *p* value of 0.03095, which is found to be not significant between the two groups. In neonates of group 1, the cases administered $MgSO_4$ did not show the sign of intraventricular hemorrhage or periventricular leukomalacia, while on the contrary, in neonates of group 2, 4% had ultrasonography suggestive of intraventricular hemorrhage and 6% had periventricular leukomalacia with a *p* value of 0.14, which is statistically insignificant.

Maternal side effects, such as flushing (66 vs 6%), nausea (16 vs 2%), sweating (28 vs 4%), hypotension (2%), tachycardia (4% in group 1), and postpartum hemorrhage, were seen in 4% of women administered $MgSO_4$ and 2% of cases in group 2. No serious side effects were attributed to $MgSO_4$, and the commonest side effect was flushing. Administering $MgSO_4$ with a large margin of safety in preterm births may help to prevent the development of cerebral palsy in preterm infants. As $MgSO_4$ is a safe, readily available inexpensive drug even if there are modest benefits for its use, the risk-benefit is in favor of its use.

Conclusion: $MgSO_4$ is the drug currently administered to mothers at the risk of preterm labor for fetal neuroprotection. Further multicenter studies with larger sample sizes exploring immediate adverse outcomes in magnesium-exposed neonates correlated with their serum magnesium concentrations are needed. Further prospective studies must be performed to determine the optimal dose of maternal magnesium for different subgroups of mothers to provide fetal neuroprotection with minimal neonatal adverse outcomes. In the meantime, there is a need for guidelines on the use of $MgSO_4$.

Keywords: Cerebral palsy, Fetal neuroprotection, Magnesium sulfate, Preterm labor.

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Introduction

Preterm birth is a major risk factor for cerebral palsy, and the risk increases markedly with decreasing gestational age. Currently, infants born at less than 34 weeks of gestation constitute about 25% of all new cases of cerebral palsy. Multiple pregnancy is associated with an increased risk of cerebral palsy, attributed partly to preterm birth.[1]

The prevalence of cerebral palsy reported in recent population-based studies ranges between 1.5 cases and 3.6 cases per 1,000 live births. The United Cerebral Palsy Foundation estimates nearly 800,000 children and adults of all ages in the United States have cerebral palsy. There is a modest increase in the prevalence of cerebral palsy over the last 40 years attributed to a substantial increase in cerebral palsy in very low birth weight infants, attributable to their increased survival reflecting improvements in a neonatal intensive care unit (NICU).

$MgSO_4$ has been used in obstetrics for decades as a tocolytic agent and for the prevention or treatment of seizures in women with preeclampsia or eclampsia.[2]

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Magnesium sulfate ($MgSO_4$) preconditioning decreases the induced lesion's sizes and inflammatory cytokine levels, prevents cell death, and improves long-term behavior. In humans, some observational studies have demonstrated reduced risks of cerebral palsy with antenatal $MgSO_4$ therapy.[3–6]

Materials and Methods

Hundred and nine women with preterm labor admitted to the Department of Obstetrics and Gynecology, S.N. Medical College, Agra, were selected for the study, out of which nine did not gave consent for their participation. After detailed history and examination, these cases were randomly allocated into two groups.

- **Group 1:** Pregnant women in preterm labor who are administered $MgSO_4$.
  These women received 4 g bolus dose of $MgSO_4$ over 20–30 minutes followed by 1 g/hour (discontinued if not delivered by 12 hours)
- **Group 2:** Pregnant women in preterm labor who are not administered $MgSO_4$.

Type of study

Prospective randomized control study.

Inclusion Criteria

Pregnant women with single or multiple pregnancy less than 37 weeks (28–36 weeks 6D) of gestational age who are in labor if the birth was planned or expected within 24 hours.

Exclusion Criteria

- Women in the second stage of labor or when delivery is eminent within 2 hours.
- Women who have received $MgSO_4$ therapy in pregnancy for other reasons.
- If there is a contraindication to $MgSO_4$ (respiratory rate <100 mL during the previous 4 hours, any sign of renal failure or hypocalcemia, absent patellar reflex).
- Women who met at least one of the following criteria: hypotension, cardiac rhythm abnormalities, electrolyte abnormalities, ingestion of calcium channel blockers, indomethacin or digitalis in the last 24 hours, myasthenia gravis, or indication for emergency cesarean section.
- Women with growth restriction, hemolysis, elevated liver function test results, low platelet syndrome, and retro placental hematoma.
- Severe fetal malformation or chromosomal abnormalities.
- Intrauterine fetal demise.

Results

In our study, the mean gestational age in the group administered $MgSO_4$ is 30 weeks and group not administered $MgSO_4$ is 31.5 weeks (Table 1).

In our study, the maternal side effects, such as flushing and sweating, were more common among women administered $MgSO_4$ rather than in women not administered $MgSO_4$ and statistically significant with *p* values of 0.00 and 0.001, respectively (Table 2 and Fig. 1). These results can be compared with the studies of Crowther et al. In our study, there was no overall significant difference between the two groups.

In our study, there was no overall significant difference between the two groups in terms of birth weight; in group 1, 64% of neonates were in-between 1.6 and 2 kg, whereas in group 2, 56%

Table 1: Distribution of cases according to gestational age

Gestational age (weeks)	*Group 1*		*Group 2*	
	No.	*%*	*No.*	*%*
28–31	21	42	18	36
32–34	27	54	26	52
35–36.6	02	04	06	12
Total	50	100	50	100

Table 2: Maternal outcome

Maternal side effects	*Cases administered $MgSO_4$, N = 50 (%)*	*Cases not administered $MgSO_4$, N = 50 (%)*	*Test statistics, p value*
Flushing present	33 (66)	3 (6)	39.0, 0.00
Nausea present	8 (16)	1 (2)	5.9, 0.014
Sweating present	14 (28)	2 (4)	10.7, 0.001
Hypotension present	1 (2)	0	1.01, 0.31*
Tachycardia present	2 (4)	0	2.01, 0.15*
PPH	2 (4)	1 (2)	0.34, 0.55

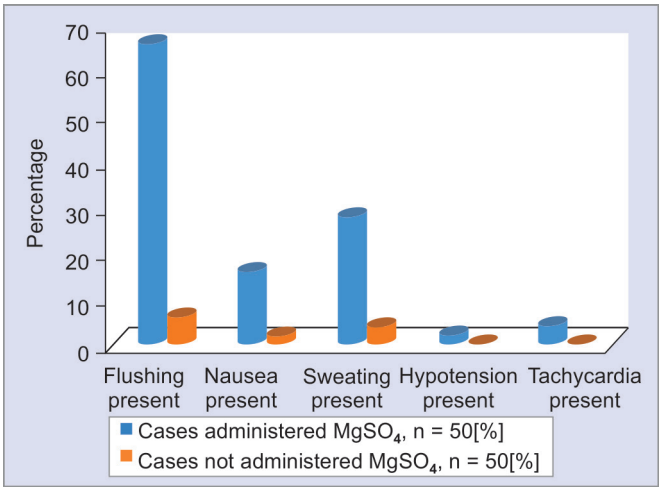

Fig. 1: Comparison of side effects between $MgSO_4$ administered and not administered $MgSO_4$ groups

Discussion

The first observational study in 1988 by Leviton et al.[4] discovered preterm infants born to mothers with severe preeclampsia had a lower incidence of adverse central nervous system outcomes. Very low birth weight babies (weighing less than 1751 g) who had been exposed to $MgSO_4$ in utero were found to have fewer germinal matrix hemorrhages. Six years later, in a case–control study derived from the California Cerebral Palsy project, Nelson and Grether[5] reported an association between antenatal $MgSO_4$ administration and reduction in the prevalence of cerebral palsy in infants born weighing less than 1500 g.

Antenatal $MgSO_4$ administration has demonstrated the neuroprotective effects for preterm births before 32 weeks of gestation. Owing to its biological properties, including its action as an N-methyl-d-aspartate receptor blocker and its anti-inflammatory effects, magnesium is a good candidate for neuroprotection.

of neonates were in-between 1.6 and 2 kg (Table 3). Apgar score at 1 and 5 minutes in majority of neonates in group 1 and group 2 was in-between 4 and 6 (Fig. 2). Neonatal adverse effect in the neonates of women administered $MgSO_4$. In preterm infants, $MgSO_4$ given for fetal neuroprotection decreased the need for NICU admission for respiratory distress, neonatal seizures, etc. (Tables 4 and 5; Figs 3 and 4). In the present study, neonates of the cases administered $MgSO_4$ did not show the sign of intraventricular hemorrhage or periventricular leukomalacia, while on the contrary, in neonates of group 2, 4% of neonates had the positive ultrasonography findings for intraventricular hemorrhage and 6% of neonates had ultrasound reporting periventricular leukomalacia (Table 6). Three trials (4,387 infants) reported cerebral palsy to severity (Rouse et al., Marret et al., Crowther et al.). Moderate or severe cerebral palsy was significantly reduced in the group who received $MgSO_4$. The risk of mild cerebral palsy was reduced by 26% in the group allocated

Table 3: Distribution of cases according to birth weight

	Group 1		*Group 2*	
Birth weight (kg)	*No.*	*%*	*No.*	*%*
<1.5	3	6	5	10
1.6–2.0	32	64	27	54
2.1–2.5	15	30	18	36
>2.5	0	0	0	0
Total	50	100	50	100

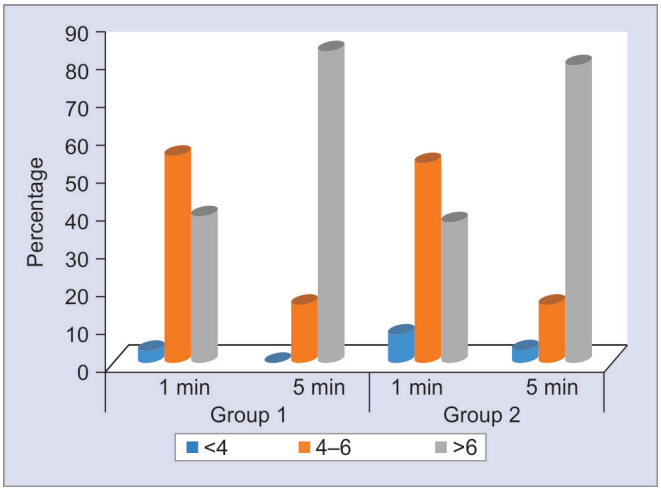

Fig. 2: Comparison between Apgar score at 1 minute and 5 minutes between the two groups

Table 4: Distribution of cases according to Apgar score at the time of birth

	$MgSO_4$ administered group				*$MgSO_4$ not administered group*			
	1 min		*5 min*		*1 min*		*5 min*	
Apgar score	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
<4	4	8	5	0	6	12	16	4
4–6	14	28	18	16	27	54	17	16
>6	32	64	37	84	27	38	17	80
Total	50	100	50	100	50	100	50	100

Table 5: Distribution of cases according to the neonatal outcome

Neonatal outcome	*Cases administered $MgSO_4$, N = 50 (%)*	*Cases not administered $MgSO_4$, N = 50 (%)*	*Test statistics, p value*
Neonatal seizures	1 (2)	2 (4)	0.344, 0.54
Respiratory distress	23 (46)	30 (60)	1.9, 0.16
Mechanical ventilation	24 (48)	31 (62)	1.9, 0.15
Neonatal enterocolitis	3 (6)	1 (0.5)	0.12, 0.72
Intensive resuscitation	2 (4)	3 (6)	0.21, 0.64
IUGR	3 (6)	2 (4)	0.2, 0.64
Neonatal mortality	1 (2)	2 (4)	0.344, 0.54
NICU admission required	*No.*	*%*	*No.*	*%*
Yes	22	44.8	32	66.6
No.	27	55.2	16	33.3
Total	49	100	48	100

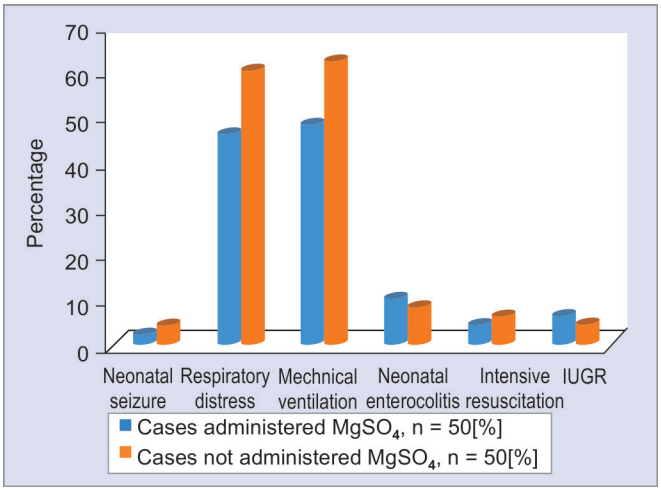

Fig. 3: Comparison between two groups according to the neonatal outcome

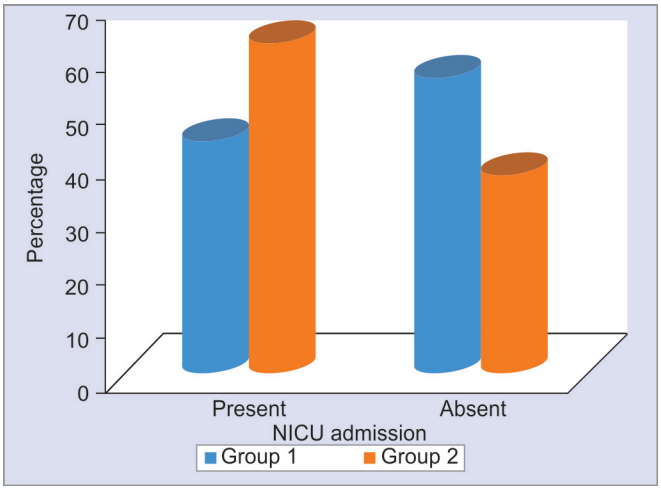

Fig. 4: Comparison between neonates of group 1 and group 2 according to the need for NICU admission

Table 6: Distribution of cases according to trans cranial ultrasound findings

Transcranial ultrasound	*Group 1*				*Group 2*			
	Present		*Absent*		*Present*		*Absent*	
Intraventricular hemorrhage	0	0	49	100	2	4	46	96
Periventricular leukomalacia	0	0	49	100	3	6	48	100

$MgSO_4$ rather than placebo, although this did not achieve statistical significance (Haslam et al.[7])

Forty-two percent of cases administered $MgSO_4$ had cesarean delivery, while 58% delivered vaginally. Among cases not administered $MgSO_4$, 44% had cesarean delivery and 56% had vaginal delivery. There was no statistical significance in-between the two group ($p = 0.16, 0.688$). In a study by Marret et al.,[8] 40.6% of cases in group administered $MgSO_4$ delivered by cesarean section and 34.7% by cesarean section in placebo group with a p value of 0.15, which is also statistically not significant between both groups.

The results of secondary neonatal outcome can be compared with the study Rouse et al., Marret et al., and Crowther et al. There were no significant differences in-between the groups in the risk of adverse neonatal outcomes, although a nonsignificant increase was seen in the risk of necrotizing enterocolitis in the magnesium group. In this study, pediatric follow-up was done to evaluate neurodevelopmental process in infants of women exposed to prenatal $MgSO_4$ and compare them with the infants of the women not exposed to $MgSO_4$. Seven children are still in our follow-up who have not completed their 24 months of age. These findings are consistent with the results obtained from the study by Crowther et al. who reported that substantial gross motor dysfunction or delayed milestones was decreased with the $MgSO_4$ that was statistically insignificant with a p value of 0.29. Marret et al. reported no significant difference in gross motor dysfunction between $MgSO_4$ group and placebo group (p-value,-0.41). With the findings of our study and comparison with several other studies, antenatal $MgSO_4$ should be considered for use in women at high risk of preterm delivery.

Conclusion

$MgSO_4$ is the drug currently administered to mothers at the risk of preterm labor for fetal neuroprotection. Further multicenter studies with larger sample sizes exploring immediate adverse outcomes in magnesium-exposed neonates correlated with their serum magnesium concentrations are needed. Further prospective studies must be performed to determine the optimal dose of maternal magnesium for different subgroups of mothers to provide fetal neuroprotection with minimal neonatal adverse outcomes. In the meantime, there is a need for guidelines on the use of $MgSO_4$.

References

1. Agustin CA, Roberto R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants <34 weeks' gestation: a systematic review and metaanalysis. Am J Obstet Gynecol 2009;200(6):595–609. DOI: 10.1016/j.ajog.2009.04.005.
2. Clark GD, Rothman SM. Blockade of excitatory amino acid receptors protects anoxic hippocampal slices. Neuroscience 1987;21(3):665– 671. DOI: 10.1016/0306-4522(87)90027-3.
3. McIntosh TK, Vink R, Yamakami I, et al. Magnesium protects against neurological deficit after brain injury. Brain Res 1989;482(2):252–260. DOI: 10.1016/0006-8993(89)91188-8.
4. Leviton A, Kuban KCK, Pagano M, et al. Maternal toxemia and neonatal germinal matrix hemorrhage in intubated infants less than 1751 g – In reply. Obstet Gynecol 1989;73:683.
5. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? Pediatrics 1995;95:263–269.
6. Rouse DJ, Hirtz DG, Thom EA, Eunice Shriver Kennedy National Institute of Child Health and Human Development Maternal - Fetal Medicine Units Network. Magnesium sulfate for the prevention of Cerebral Palsy. Rply N Engl J Med 2009;360:190.
7. Crowther CA, Hiller JE, Doyle LW, Haslam RR. Australasian Collaborative Trial of Magnesium Sulphate (ACTO MgSO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. JAMA 2003;290:2669– 2676. DOI: 10.1001/jama.290.20.2669.
8. Marret S, Marpeau L, Follet-Bouhamed C, Cambonie G, Astruc D, Delaporte B. et al. [Effect of magnesium sulphate on mortality and neurologic morbidity of the very-preterm newborn (of less than 33 weeks) with two year neurological outcome: results of the Bibliography [69] prospective PREMAG trial]. Gynecol Obstet Fertil 2008;36:278–288. DOI: 10.1016/j.gyobfe.2008.01.012.