

THE EFFICACY AND SAFETY OF MAGNESIUM SULPHATE FOR NEONATAL NEUROPROTECTION IN PATIENTS WITH IMMINENT PRETERM DELIVERIES: EXPERIENCE AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The study aimed to find the effect of 4 grams of intravenous bolus antenatal dose of magnesium Sulphate on maternal and neonatal outcomes in preterm births.

Material and Methods: In a one-year cross-sectional descriptive study, patients with active preterm labor or those with planned preterm birth at 28-34 weeks of gestation were included. Antenatal magnesium Sulphate was administered as a 4gm IV loading dose over 30 minutes. The data was analyzed with SPSS (version 20), where mean \pm standard deviation was used for numerical variables and frequency and percentages for categorical variables. The sample size was 88. A P value < 0.05 is used as a threshold for statistical significance.

Results: The mean age of patients was 28.78 (\pm SD of 6.038) and the mean period of gestation remained 32.04 (± 1.868). Similarly, the mean cervical dilatation at which magnesium Sulphate was given was 6.591 (± 1.358), the mean baby's weight was 1.655 (± 0.508) kg, and the mean Apgar score at 5 minutes was recorded as 7.11 (± 1.208). Regarding the period of gestation of the patients, 15 (17.04%) were at 28-30 weeks, 26 (29.54%) were at 30–32 weeks and 47 (53.4%) were at 32–34 weeks. Out of 88 patients, normal vaginal deliveries were conducted in 61 (69.38%) whereas, 27 (30.68%) patients had cesarean sections. Neonatal seizures were observed in 3 (2.6%), intraventricular hemorrhage in 2 (1.754%), Periventricular leukomalacia (PVL) 1 (0.877%), and neonatal mortality in 5 (4.38%).

Conclusion: Magnesium Sulphate is a safe drug that plays an important role in protecting immature brains. Four-gram bolus is a sufficient dose as compared with infusion, which requires additional human resources and risks attached to prolonged infusions.

Keywords: Magnesium Sulphate, Preterm Deliveries, Neonatal Neuroprotection, Intraventricular Hemorrhage

This article may be cited as: Mazhar T, Rauf S, Ambareen A, Nadir S. The efficacy and safety of Magnesium Sulphate for neonatal Neuroprotection in patients with Imminent preterm deliveries: Experience at a Tertiary Care Hospital. *J Med Sci* 2023 April;31(2):137-142

INTRODUCTION

Preterm labor is the leading cause of infant morbidity and mortality. The prevalence of preterm birth is increasing and so is cerebral palsy. 25% of all cases of cerebral palsy are in infants born at < 34 weeks of gestation. The risk of cerebral palsy is higher at early gestational ages and 30 to 50 % of children with CP are born preterm.¹ Magnesium Sulphate for fetal neuroprotection provides one of the first pre-natal evidence-based treatments to im-

prove the neurodevelopmental outcomes of children born at < 34 weeks of gestation. The most common pathological lesion associated with cerebral palsy in preterm infants is periventricular white matter injury. The NMDA (N-methyl-D-Aspartic acid) receptors on oligodendrocytes of white matter are potent neuroprotective agents. Magnesium Sulphate removes the harmful effects of hypoxic-ischemic brain injury by blocking the NMDA receptors acting as a calcium antagonist and reducing calcium influx into the cells^{2,3}. Between 24 and 32 weeks of gestational age, premyelinating oligodendrocyte progenitor cells are particularly vulnerable to hypoxic-ischemic damage, due to the interaction of immature blood flow autoregulation, immature vascular supply, and heart-rate-dependent cardiac output. Consequently, white matter injury occurs when other predisposing factors such as infections, inflammations, and disturbances in cerebral oxygenation overlap with the intrinsic vulnerability of the premature brain.

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Date Received: 08-05-2022

Date Revised: 29-04-2023

Date Accepted: 03-05-2023

Magnesium Sulphate given to mothers shortly before delivery reduces the risk of cerebral palsy and protects gross motor functions in those infants born preterm.⁴ The effect is greatest at early gestation and is not associated with adverse long-term fetal or maternal outcomes. This study is aimed at determining the effectiveness of Magnesium Sulphate in preventing fetal and maternal outcomes.

MATERIAL AND METHODS

This cross-sectional descriptive study is conducted at Khyber Teaching Hospital (KTH) in Peshawar, Pakistan. The study duration was from December 2020 to November 2021. All those patients included in the study who were admitted to the labor room with active preterm labor or \pm Preterm Premature Rupture of Membranes (PPROM) or those with planned preterm birth for fetal or maternal indication at 28-34 weeks of gestation. Imminent preterm labor is defined as a high likelihood of birth due to either active labor with cervical dilatation > 4 cm with or without preterm PROM or planned preterm birth for fetal or maternal indication. Women with severe preeclampsia and eclampsia with preterm labor are also included in the study.

Exclusion criteria are major fetal abnormalities or intrauterine fetal death, patients with relative contraindications for Magnesium Sulphate such as electrolyte disorders, and maternal cardiac or renal disease. Delivery was not delayed administering magnesium Sulphate to patients for fetal neuroprotection when there was a maternal or fetal indication for an emergency delivery. Informed consent was obtained from all patients. For women with imminent preterm birth between 28-34 weeks of gestation, Antenatal Magnesium Sulphate was administered as a 4gm IV loading dose over 30 minutes. The obstetrician and pediatrician drafted this protocol jointly. When the birth was delayed for > 12 hours after a bolus, it was recommended to repeat the bolus. However, in our study, there was no case of prolonged labor so a second bolus was not given.

Mothers and infants were monitored according to standard clinical guidelines. The protocol called for recording the pulse rate, BP, Respiratory rate, and tendon reflexes. Fetal heart rate was monitored throughout labor. Mothers and infants were followed up until hospital discharge. Five minutes Apgar score and neonatal well-being were assessed by the pediatricians. Nursery and Neonatal ICU monitoring was done in most cases. Monitoring for hypoxic-ischemic encephalopathy, irritability, and seizures noted in the neonates.

Intraventricular hemorrhage grading was done according to cranial ultrasound findings and Papiles criteria. Periventricular leukomalacia, which is hyperechoic lesions persisting to day 7 of life, was also recorded. Dependent variables were neonatal Apgar score, nursery, and NICU

admissions, monitoring for hypoxemic ischemic encephalopathy, frequency of occurrence of neonatal seizures, and neonatal cranial ultrasound findings of intraventricular hemorrhage.

Statistical data was analyzed by SPSS version 20. One-way ANOVA (Analysis of variance) was also applied. Mean \pm standard deviation was calculated for numerical variables and frequency, and percentages were calculated for categorical variables. The sample size was 88. P value < 0.05 is used as a threshold for statistical significance. Tukey $_b$ post hoc test was applied to check the interval / group-wise period of gestation difference.

RESULTS

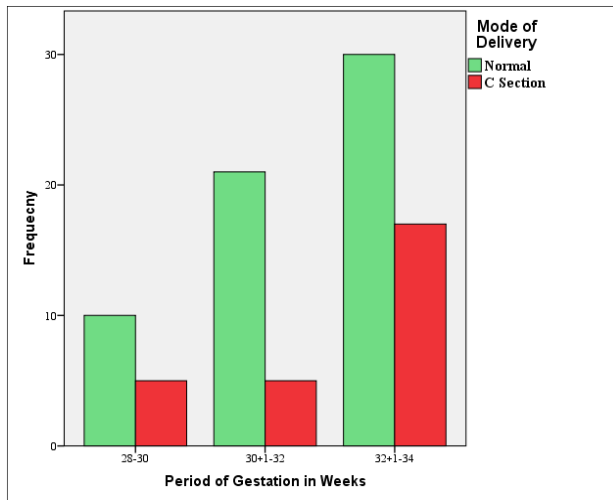
Out of a total of 114 neonates, 79 (69.2%) were resuscitated, and 76 (66.6%) were admitted to the nursery and NICU). Frequency of neonatal seizures observed in 3 (2.6%), intraventricular hemorrhage 2 (1.754%), periventricular leukomalacia (PVL) 1 (0.877%), and neonatal mortality 5 (4.38%). See table 1 and 2 for details.

With regards to the duration of admissions in nursery and NICU, 44 (57.8%) were retained for 48-72 hours, 19(25%) for 1-2 weeks, and 13 (17.1%) for 2-4 weeks. Sixteen parents and attendants didn't bring their neonates for follow-up. The rest of the cases were followed up for a month either by checkups in the Pediatrics unit or were contacted by mobiles for the neonatal outcome. Three neonates had seizures. One newborn who was delivered at 28 weeks had a seizure after 1st week of birth. Two others who delivered at 28⁺⁴ and 29⁺² weeks of gestation had fits after 3-7 days of birth. 2 cases of IVH were seen after 7 days of birth. Both were the same neonates who had fits. One case of PVL was seen in the newborn who delivered at 30 weeks of gestation. 5 babies expired. One was the case who had IVH. 4 babies expired in 3rd and 4th weeks of life due to chest infection and fever but didn't have seizures.

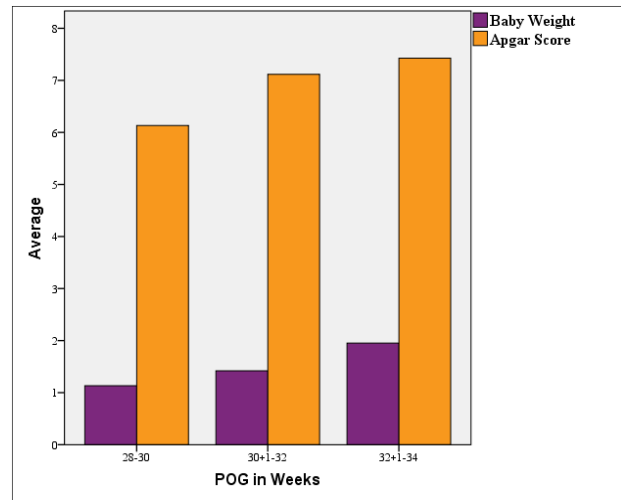
No major side effects were observed with Magnesium Sulphate use. However, two patients with eclampsia presented with disseminated intravascular coagulation. Side effects observed were hypotension 8 (9.09%), flushing and sweating (4.54%), palpitation 3 (3.04%), headache 2 (2.27%), nausea and vomiting 2 (2.27%) and hyporeflexia seen in one eclamptic case (1.13%). For the mode of delivery, indications of C- Section, and associate conditions see Figure 1 and Tables 3-5.

DISCUSSION

Magnesium Sulphate for fetal neuroprotection is the first prenatal evidence-based treatment and is given to mothers shortly before delivery as it protects gross motor functions and is associated with decreased incidence of echo-densities and lucencies i.e. periventricular leukomalacia on cranial ultrasound and cerebellar hemorrhage on



Picture-1 (A): Mode of Delivery in Relation to the Period of Gestation



Picture-1 (B): Baby's weight and Apgar score according to the period of gestation

Table 1: Maternal and Neonatal Demographics

| Mean Period of Gestation (POG) (weeks) | Mean Age of Patients (years) | Mean APGAR Score | Mean Baby's Weight (Kg) | Mean Cervical Dilatation at Magnesium Sulphate administration (cm) |
|--|------------------------------|------------------|-------------------------|--|
| 32.04 (±1.86) | 28.78 years (±6.038) | 7.11 (±1.208) | 1.65 (±0.508) | 6.591 (±1.358) |

Table 2: Neonatal Apgar score in relation to POG and Cervical dilatation at which Magnesium Sulphate given

| Period of Gestation (POG) (weeks) | Mode of Delivery | | APGAR Score (mean ± SD) | Baby's Weight (kg) (mean ± SD) | Cervical Dilatation at Magnesium Sulphate administration (cm) (mean ± SD) |
|-----------------------------------|------------------|-------------|-------------------------|--------------------------------|---|
| | Vaginal | Caesarean | | | |
| (POG) | | | | | |
| (N=88) 28-30 | 10 (16.4%) | 5 (18.52%) | 6.13 (1.598) | 1.113 (0.3374) | 6.8 (1.4757) |
| 30+1 - 32 | 21 (34.43%) | 5 (18.52%) | 7.12 (0.711) | 1.419 (0.3238) | 6.913(1.3455) |
| 32+1 - 34 | 30 (49.18%) | 17 (62.96%) | 7.43(1.137) | 1.951 (0.4338) | 6.303 (1.3106) |

Table 3: Mode of Delivery in Patients with preterm delivery (n=88)

| Period of Gestation (POG) (Weeks) | Mode of Delivery | | | |
|-----------------------------------|--------------------|------------------------------|--------------------------------|-------------------------------|
| | Vaginal (Number/%) | Caesarean Section (Number/%) | Emergency C Section (Number/%) | Elective C Section (Number/%) |
| (N=88) 28-34 | 61 (69.38%) | 27 (30.68%) | 24 (88.8%) | 3 (11.11%) |

Table 4: Indications of Cesarean Sections in Patients with preterm delivery.

| Indication of Emergency Cesarean Section | (N=24) |
|---|----------------------------------|
| Eclampsia | 5 (20.8%) |
| Severe preeclampsia with poor bishops | 2 (8.33%) |
| Previous 2 or > C sections in preterm labor | 4 (16.66%) |
| Breech presentation | 3(12.5%) |
| Multiple pregnancy with malpresentation | 3 (12.5%) |
| Chorio Amnionitis | 2 (8.33) |
| Fetal distress | 2 (8.33%) |
| Transverse lie | 1 (4.16%) |
| Uncontrolled Diabetes and BOH | 1 (4.16%) |
| Placenta previa | 1 (4.16%) |
| Indication of Elective C Section (N=3) | IUGR 2 BOH and Raised SD Ratio 1 |

MRI. Clement Chollat performed meta-analyses of various Randomized Control Trials (RCTs) such as Magnesium Sulphate and neurological endpoints trial (MAGNET), use of Magnesium Sulphate in preterm deliveries (PREMAG), which to date reported that antenatal Magnesium Sulphate given to women at risk of preterm delivery is associated with significantly reduced risk of cerebral palsy (CP) in children exposed in utero with RR ranging from 0.61- 0.70 and no impact on mortality⁵. The Cochrane review of trials concluded that antenatal MgSO₄ therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy (CP) in their children with a relative risk of 0.68 (95% CI 0.54-0.87). There was also a significant reduction in the rate of periventricular leukomalacia and substantial motor dysfunction (RR 0.61, 95% CI 0.44 – 0.85).^{6,7,8}

Pierre Emmanuel Bouet conducted a one-year study on 126 patients who had preterm delivery. He concluded that the mean period of gestation at Magnesium Sulphate administration was 29.6 weeks \pm 2.1 days (24 – 32 weeks). 60 (74%) received maintenance infusions. The main reasons for preterm birth were preterm labor, preterm rupture of membranes (PROM), peripartum hemorrhage, and preeclampsia.⁹

Rates of emergency delivery, abnormal CTG, general anesthesia, neonatal cord PH < 7.10 at birth, Apgar score < 7, neonatal external cardiac massage, and use of epinephrine were significantly higher in the group of women who didn't receive Magnesium Sulphate before birth.^{10, 11}

The gestational age at which Magnesium Sulphate administration has its greatest effect has been debated. An intervention immediately pre-delivery is more likely to be effective at earlier gestation as perinatal and neonatal factors are more prominent in the etiology of cerebral palsy (CP) in less mature infants. So, the number needed to treat will increase significantly with advancing gestational age.¹² This concept is supported by data from Rouse et al showing a significant reduction in moderate or severe CP in babies recruited at less than 28 weeks of gestation (RR 0.45, 95% CI 0.23 – 0.87) but not in those between 28 and 31 weeks of gestation.⁴

Constantine et al looked at those trials addressing outcomes at less than 34 weeks of gestation and concluded that the number needed to treat at < 30 weeks of gestation was 46 (95% CI 26-187) and rose to 56 (95% CI 34 – 164) before 32-34 weeks of gestation¹³. Conde- Agudelo et al and Mittendorf's study concluded that in women at risk of preterm delivery before 34 weeks of gestation, the number of mothers needed to prevent one case of cerebral palsy in their child was 52 (95% CI 31-159).¹⁴⁻¹⁶ Many related studies and trials included multiple pregnancies, those with PROM, chorioamnionitis, abruption, hypertensive disorders of pregnancy, and gestational diabetes mellitus.^{17,18,19} Rouse et al. excluded women with hypertension

or preeclampsia. This suggests that irrespective of the indication any infant delivering preterm might be expected to benefit from it. All used a loading dose of Magnesium Sulphate that varied between 4 and 6gm. Not all trials administered a maintenance infusion. These studies indicated persistent benefits of Magnesium Sulphate regardless of dose and support the use of low dose 4gm loading \pm 1 g/hr) maintenance dose for 12 h compared with high doses (6 gm loading dose + 2 gm hour maintenance for 24 hrs).^{20,21} J Bisht, Lawrence Impay concluded that from 22⁺¹ - 31⁺⁶ weeks of gestation, 4 grams is a sufficient dose because of lack of evidence of better outcomes with other dosages and infusions in conjunction with manpower and risk issues with prolonged infusions. Also, the loading dose is effective when given even one hour before delivery and the bolus dose can be repeated if birth is imminent after 12 hours.²² In our study mean cervical dilatation at which Magnesium Sulphate was given is 6.591 (1.3585) cm or an average of 4 hours before delivery. Mittendorf reported different doses in two arms of the study.¹⁵

Regarding timing of Magnesium Sulphate administration, Rous et al suggested discontinuing therapy if the delivery was not achieved in 12hrs.⁴ He excluded women who had more than 8cm cervical dilatation or less than 2 hours from delivery and women who were at risk of delivery more than 6 hours after stopping a further bolus was given.^{22,23} Australian guideline suggests that ideally dose should be commenced at least 4 hours before birth but agrees that there may still be a benefit if given less than 4 hours before delivery.²⁴ Median time from randomization to birth in the Magnesium Sulphate group of these trials was between 1.6- 3.7 hrs. Antenatal administration enables the prompt transfer of Magnesium Sulphate. It should be commenced as close as possible to 4 hours before birth and if delivery is expected to occur sooner than 4 hrs still it must be administered as there is likely to be an advantage from administration within this time.^{24,25}

In our study, we found no major side effects as we didn't give the maintenance infusions except in severe preeclampsia and eclampsia cases. Its use is now recommended by the pediatrics and obstetrics society as well as by the strong recommendation of WHO for women at risk of imminent birth before 34 weeks. 4 gm bolus is sufficient because of a lack of evidence for better outcomes with infusion, in conjunction with manpower and risk issues with prolonged infusions.²⁴

CONCLUSION

Magnesium Sulphate is a safe and effective molecule that plays a key role in protecting the immature brain. Further large-scale multicenter trials are needed to signify the dose, duration, and effectiveness of this regimen.

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CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE: NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

- Mazhar T:** Main Idea, Research proposal
- Rauf S:** Data Collection and writing
- Ambareen A:** Review and proofreading
- Nadir S:** Data Collection

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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