The Neuroprotective Effects of Antenatal Magnesium Sulphate in Preterm Infants: A Randomized Controlled Study

Original Article

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ABSTRACT

Objectives: This study aimed to determine whether magnesium sulfate (MgSO4) given to preterm fetuses during pregnancy had any influence on the neurological outcomes experienced by these newborns after birth.

Methods: 50 pregnant women, aged 20-34 years, were the subjects of this case-control research. The women had one or more children between 28 and 34 weeks of gestation, the women had discomfort during preterm labor, and the women had induced preterm labor for reasons related to the mother. Two groups were formed from the patients: one with impending preterm labor in active phase, cervical dilation of less than 4cm and effacement of less than 40%, and the other with patients who were equally distributed between the two categories.

Results: Intraventricular haemorrhage (IVH) incidence was considerably lower in study group than control group (P=0.042). At both 5 and 10 minutes, the study group had considerably lower Appearance, Pulse, Grimace, Activity and Respiration (APGAR) than the control group (P<0.05). APGAR scores were considerably higher in the study group compared to the control group after 5 and 10 minutes (P<0.05). Compared to the control group, the study group had significantly lower rates of Neonatal Intensive Care Unit (NICU) hospitalization, nasal CAPP, and mechanical ventilation (P < 0.05). Study group seizures were significantly lower than control group seizures (P=0.004).

Conclusion: When the mother consumes MgSO4 before preterm delivery, the child has better outcomes. It is possible that MgSO4 may dramatically reduce the following: seizures, Apgar score<7 at 5 minutes, NICU admission, and intravenous hydration.

Key Words: APGAR Score; intraventricular haemorrhage; magnesium sulphate; neuroprotective effects; preterm.

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INTRODUCTION

The World Health Organization (WHO) uses the following medical definitions of preterm labor: beginning of labor before 37 weeks of gestation and after 20 weeks[1]. To be classified as preterm, a baby must be born before the full 36 weeks and 6 days of gestation. Such a delivery would be equivalent to one that occurs at a gestational age lower than 258 days. The World Health Organization classifies preterm births as either very preterm (before 28 weeks), very preterm (between 28 and 32 weeks), or moderate to late preterm (between 32 and 37 weeks)[2].

Most preterm newborns will have one or more of the following neonatal complications: cerebral palsy, IVH, respiratory distress syndrome (RDS), or retinopathy of prematurity[3].

The risk of a premature delivery increases in the following situations: the presence of multiple foetal implants, infections within the uterus, long-term health problems in the mother, the mother's age (young or old), socioeconomic status, substance abuse, smoking, excessive bleeding before birth, and a previous cervical operation[4].

Brain damage, cerebral palsy, cognitive impairment, cerebral hemorrhage, and premature infant mortality are among the serious neurological problems that a preterm infant is at high risk of developing after delivery[5].

Magnesium is essential for several vital physiological activities in humans, such as glycolysis, oxidative phosphorylation, protein synthesis, DNA and RNA aggregation, and preservation of plasma membrane integrity[6,7].

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Although the precise mechanism by which MgSo4 protects neurons in growing brains remains unknown, it is believed to have a role. Magnesium ions are required for several biological activities, including maintaining cell membrane integrity, intracellular glycolysis, protein synthesis, and oxidative phosphorylation[8].

Magnesium acts as a voltage-dependent inhibitor of the N-methyl-D-aspartate receptor to glutamate, limiting calcium entrance into the cell and protecting it from excitotoxic calcium-induced damage[9,10].

It seems that glutamate-induced damage is more likely to occur in the developing brain during the prenatal and neonatal phases. It is feasible to reduce the risk of injury during the neonatal period by inhibiting glutamate receptors using drugs like magnesium sulphate. One of magnesium's beneficial hemodynamic characteristics is its capacity to keep the blood pressure of premature infants steady during the first two days of their lives[11]. It may also reduce the narrowing of the cerebral arteries, which increases blood flow to the brain[12].

Because of the rapid transfer of magnesium across the placenta, fetal circulation will have elevated magnesium levels within one hour following intravenous magnesium administration to the mother[13].

The World Health Organization has released new guidelines to help reduce the occurrence of complications during premature deliveries. These guidelines suggest MgSO4 to prevent cerebral palsy and intraventricular haemorrhage (IVH), antibiotics to prevent sepsis in premature membrane rupture, and prenatal steroid injections to prevent respiratory distress syndrome. Babies need to be provided with the correct care, including warmth, assistance with eating, and safe use of oxygen, according to the guidelines[14,15].

This study aimed to evaluate the impact of administering prenatal MgSO4 on the neuroprotection of preterm fetuses and the subsequent neurological outcomes of these newborns.

PATIENTS AND METHODS

Preterm labor pain with progressive cervical effacement and changes, as well as cases planned for induced preterm labor for maternal indication, were observed in 50 pregnant women, ranging in age from 20 to 34 years, during the 28th through the 34th week of gestation. The women were carrying either singletons or twins. Following clearance from the Ethical Committee of Tanta University Hospitals in Tanta, Egypt, the research was conducted from November 2022 to November 2023. The informed written consent of every single patient has been obtained.

Renal or hepatic failure, cardiac arrhythmia in the mother, calcium channel blocker uses in the last two hours, major fetal abnormalities or death, and severe pulmonary difficulties in the mother were all reasons for exclusion from the study.

The patients were split into two equal groups. One group was treated for early preterm labor in its latent phase, which is defined as cervix dilatation less than four cm and cervical effacement less than 40%. The other group was treated for imminent preterm labor in its active phase, which is defined as cervix dilatation ≥ 6 cm and cervical effacement more than 70%.

Each patient had a comprehensive evaluation of their medical history, along with laboratory testing such as a complete blood count (CBC) and C-reactive protein (CRP), in addition to an ultrasound examination to exclude any fetal abnormalities. In addition, the maternal pulse, blood pressure, respiration rate, tendon reflexes, and urine output were continually monitored to identify any indications of MgSO4 poisoning. The individuals in the study group received an initial dosage of 4 g of intravenous magnesium sulphate administered over a period of 20 to 30 minutes. This was followed by a continuous infusion of 1 g per hour for a duration ranging from four to 24 hours.

The administration of the infusion was paused and resumed as needed, based on the reevaluation of the need for immediate delivery, such as the presence of contractions, in cases where the baby had not been delivered within 24 hours and was not expected to be born imminently[16].

After delivery assessment of the neonate

Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at five and ten minutes, clinical examination, seizure activity, cranial ultrasound, and neonatal outcomes at delivery, scheduled follow-up visits, and discharge from the neonatal unit.

Sample Size Calculation

The sample size was determined using G*Power 3.1.9.2 from the Universitat Kiel in Germany. It was determined by considering the 0.475 effect size, 95% confidence limit, and 95% power of the trial. A prior study found that the placebo group had an average Apgar score of 5, while the MgSO4 group had an average of 5.7, with a common standard deviation of ±1.6. This led to the recruitment of 25 patients per group.

Statistical analysis

The statistical study was conducted using IBM's SPSS v26 program, which is headquartered in Chicago, IL, USA. An unpaired Student's t-test was used to compare the two

groups. This statistical test provides the quantitative data as the mean and standard deviation (SD). We used either the Chi-square test or Fisher's exact test to evaluate the qualitative variables, which were presented as percentages and represented as frequencies, depending on the specific conditions. The statistical significance was established using a two-tailed *P value* that was below 0.05.

RESULTS

The eligibility for participation in this study was determined via an examination that 93 people completed. Of them, 31 did not fulfil the requirements, and 12 more declined to participate in the study. The remaining patients were divided into two equal groups of 25, with each group selected at random. Statistical methods were used to monitor and evaluate each assigned patient (Figure 1).

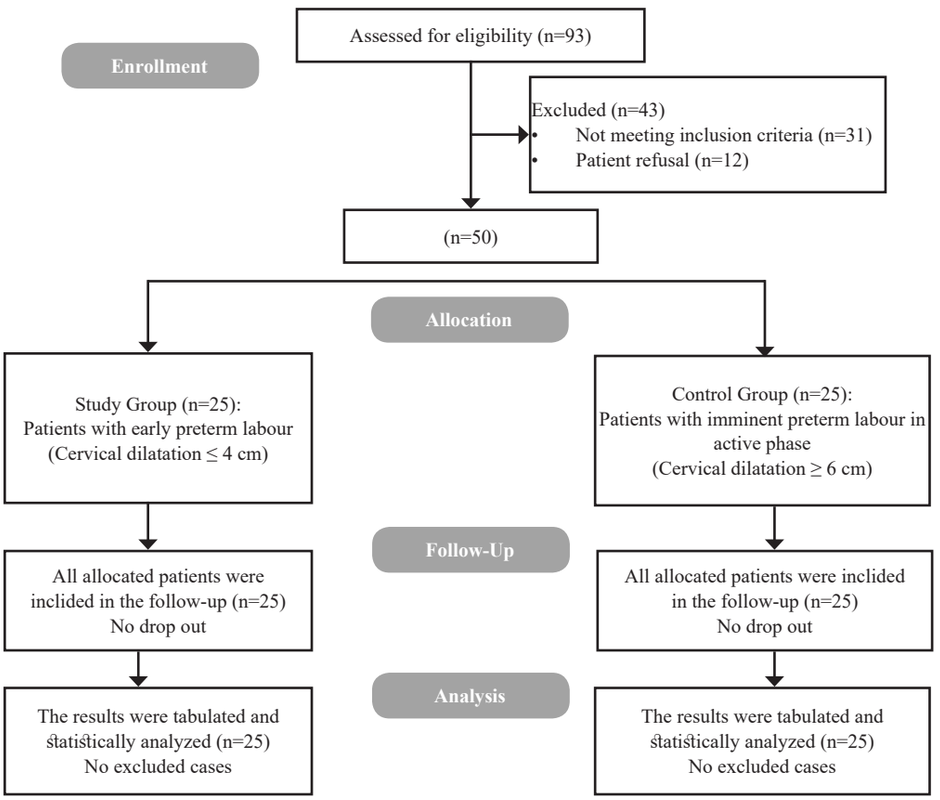

Fig. 1: CONSORT flow diagram of the participants through each stage of the trial

In terms of demographics, systolic and diastolic blood pressure, and respiratory rate, there were no apparent distinctions between the two groups (Table 1).

There was no statistically significant difference in the number of fetuses between the two groups. The study group exhibited a significantly lower occurrence of IVH in comparison to the control group (P= 0.042) (Table 2).

At 5 minutes, the research group's APGAR score was lower than the control groups, coming in at less than 7. Even after 10 minutes, with a score below 7 (P <0.05), this disparity was still evident. At both the 5-minute and 10-minute points, the study group's APGAR score was significantly higher than the control group's (P< 0.05) (Table 3).

NICU hospitalization, Nasal continuous positive airway pressure (NCPAP), and Mechanical Ventilation (MV) were considerably decreased in study group compared to control group (P < 0.05). Seizures were considerably fewer in the study group than in the control group (P = 0.004). Neither group had substantially higher mortality (Table 4).

Table 1: Demographic data, systolic blood pressure, diastolic blood pressure and respiratory rate of the studied groups

	Study group (n=25)	Control group (n=25)	*P*
Age (years)	27.64 ± 2.84	28.24 ± 3.93	0.539
Weight (kg)	76.32 ± 9.36	79.36 ± 9.24	0.254
Height (m)	1.65 ± 0.06	1.65 ± 0.07	0.918
BMI (kg/m^2)	28.13 ± 4.04	29.21 ± 3.98	0.346
Gestational age (weeks)	32.36 ± 1.41	31.8 ± 1.61	0.197
Parity	2.16 ± 1.43	1.6 ± 1.5	0.184
Systolic blood pressure (mmHg)	117.92 ± 4.26	120 ± 4.12	0.086
Diastolic blood pressure (mmHg)	67.36 ± 3.88	69.24 ± 4.38	0.115
Respiratory rate (breaths/min)	21.52 ± 3.07	22.6 ± 2.94	0.210

Data are presented as mean±SD, BMI: body mass index.

Table 2: Number of fetuses and incidence of IVH of the studied groups

		Study group (n=28)	Control group (n=27)	*P*
Number of fetuses	Single	22 (78.57%)	23 (85.18%)	0.814
	Twin	6 (21.43%)	4 (14.82%)	
Incidence of IVH		3 (10.71%)	9 (33.33%)	0.042*

Data are presented as frequency (%), * significant $p \leq 0.05$, IVH: intraventricular haemorrhage.

Table 3: APGAR score of the studied groups

	Study group (n=28)	Control group (n=27)	*P*
5 min	8.21±1.93	5±2.34	<0.001*
10 min	9.11±1.73	6.56±2.49	0.009*
APGAR at 5 min <7	8 (28.57%)	17 (62.96%)	0.01*
APGAR at 10 min <7	4 (14.29%)	12 (44.44%)	0.014*

Data are presented as mean±SD or frequency (%), * significant $p \leq 0.05$, APGAR: Appearance, Pulse, Grimace, Activity and Respiration

Table 4: NICU admission, need for NCPAP, MV, seizures and mortality of the studied groups

	Study group (n=28)	Control group (n=27)	*P*
NICU admission	4 (14.29%)	12 (44.44%)	0.014*
Need for NCPAP	3 (10.71%)	10 (37.04%)	0.022*
Need for MV	1 (3.57%)	6 (22.22%)	0.038*
Seizures	5 (17.86%)	15 (55.56%)	0.004*
Mortality	1 (3.57%)	3 (11.11%)	0.282

Data are presented as frequency (%), * significant $p \leq 0.05$, NICU: Neonatal Intensive Care Unit, NCPAP: Nasal continuous positive airway pressure, MV: Mechanical Ventilation

DISCUSSION

Magnesium functions as an endogenous agent that counteracts excitotoxicity by binding to the magnesium site on the N-methyl-D-aspartate (NMDA) receptor, therefore decreasing the activity of these glutamatergic channels[17].

Under ischemia situations, magnesium could lower the levels of extracellular glutamate, which may result in a reduction of excitotoxicity. Magnesium regulates the entry of calcium via voltage-gated channels, potentially decreasing the initiation of apoptosis[18]. Consequently, there is a growing interest in using MgSO4 as a neuroprotective therapy for premature infants. In our results, we observed that the incidence of IVH, APGAR score, NICU admission, need for NCPAP and MV, and seizures were significantly lower in the study group than control group. In the present study, the incidence of IVH was significantly lower in the study group than control group. In agreement with our results, Petrova and Mehta[19] found that Neonates who were exposed to tocolytic MgSO4 were less likely to develop IVH compared to neonates with comparable clinical features who were not exposed to IVH. This suggests that prenatal exposure to MgSO4 may have a protective effect against IVH. In disagreement with our results, Rouse *et al*.[20] found that the incidence of intra-ventricular hemorrhage didn't significantly differ between study group and control group. This difference may be attributed to different inclusion criteria, different gestational age as they included women at imminent risk for delivery between 24 and 31 weeks, and different sample size.

At five and ten minutes, the study group's APGAR score was significantly lower than the control groups. Like our findings, Lin *et al*.[21] showed that among newborns without this background, the probability of poor Apgar score increased by 6.390 times compared to those who administered MgSO4 before delivery (95% CI = 0.832–49.053; $P = 0.020$).A study by Morag *et al*.[22] demonstrated that the Apgar 5 min <7 score was significantly lower in Mg-exposed infants compared with controls. In disagreement with our results, Shepherd *et al*.[23] revealed that Newborns who were exposed to prenatal magnesium sulphate had a 67% higher chance of having an Apgar score less than 7 at 1 minute compared to those who were not exposed. Additionally, they had more than twice the risk of requiring volume expansion. This discrepancy might be attributed to variations in sample sizes and variations in the concentration of maternal MgSO4 exposure.

The current research found that compared to the control group, the group under investigation had much fewer seizures. Magnesium binds to the NMDA glutamate receptor ion channel at the magnesium site to reduce the harmful effects of excitotoxicity. Evidence suggests it may help reduce inflammation and harm that follows. Cardiovascular stability is improved, and free radical production is prevented by stabilized cell membranes[24]. The findings of Shokry *et al*.[25] confirmed our findings, showing that the control group had a higher rate of seizures than the MgSO4 group ($p = 0.011$). There was no difference in the frequency of seizures between the control group and the group treated with MgSO4, according to Conde-Agudelo *et al*.[26]. Differences in sample size might explain this discrepancy.

In this study, the two groups did not vary significantly with respect to mortality. Our results are in line with those of Shepherd *et al*.[27], who also found no significant difference between MgSO4 and placebo/no therapy in terms of the major review outcome of perinatal mortality, stillbirth, neonatal death (no apparent imbalance could be seen when looking at the funnel plot), and death after 28 days. The neonatal mortality rate was not significantly different between the control group and the group that received MgSO4, according to Shokry *et al*.[25].

The small sample size is a limitation of this research. An isolated location was used to conduct the investigation. Consequently, we advocate for a more comprehensive investigation with a bigger sample size and the use of several criteria to support the validity of our findings in future research. More research is needed to determine the possible long-term benefits of magnesium and to confirm its safety, given the improved immediate outcomes with no increase in negative effects.

CONCLUSION

The results for the child are better when the mother takes MgSO4 before a very premature birth. Apgar score <7 at 5 minutes, seizures, NICU hospitalization, and IVH may all be significantly decreased by MgSO4.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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