

## Research Article

# Effect of Intravenous Magnesium Sulphate on in-Hospital Mortality in Neonates with Perinatal Asphyxia: A Prospective Cohort Study

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### Abstract

**Background:** Early neonatal deaths in Pakistan account for 7% of global neonatal mortality rate, with perinatal asphyxia being responsible for 23% of these cases. Controversy exists in the literature regarding role of magnesium sulphate administration on reducing in-hospital mortality in newborns with perinatal asphyxia.

**Objectives:** To determine the effect of intravenous magnesium sulphate on in-hospital mortality in neonates with perinatal asphyxia.

**Methods:** This prospective cohort study was conducted at the Department of Pediatric Medicine, Nishtar Hospital Multan over a period of six months from January 2022 to June 2022. A total of 183 consecutive full-term neonates, weighing  $\geq 2500$  grams, with Apgar score  $< 7$  at 5-minutes after birth, presenting within 48-hours of life were included in the study. Neonates presenting within 6-hours after birth received intravenous magnesium sulphate ( $MgSO_4$ ) – exposed group and neonates presenting after 6-hours did not get  $MgSO_4$  – unexposed group. Baseline characteristics and survival outcome was recorded. Binary logistic regression analysis was run and Kaplan-Meier survival curve is constructed for the assessment of mortality.

**Results:** There were 90 neonates in exposed group and 93 in unexposed group. Males constituted 53% of the study population. Overall mortality rate was 15.8% (n=29). Severe asphyxia (RR 8.5, 95% CI 4.0 – 18.0;  $p < 0.001$ ) and spontaneous vaginal delivery (RR 1.8, 95% CI 1.1 – 2.9;  $p = 0.02$ ) were the independent predictors of mortality. Mortality (7.8% vs. 23.6%, p-value 0.003) was significantly higher in unexposed group compared to exposed group. In exposed group the median survival time was 16 days (95% CI- 8.7 – 23.3) compared to 11 days (95% CI 9.9 – 12.0) in unexposed group (Log-rank test:  $\chi^2 = 6.03$ , df-1,  $p = 0.01$ ).

**Conclusion:** Magnesium sulphate was effective in lowering neonatal mortality due to moderate-severe perinatal asphyxia. In order to further validate its impact on mortality, multi-center studies are suggested.

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### Introduction

Each year four million children die in their first 28 days of life, and perinatal asphyxia is the second most frequent reason.<sup>1</sup> Early neonatal deaths in Pakistan account for 7% of global neonatal mortality rate, with perinatal asphyxia being responsible for 23% of these cases.<sup>2</sup> Perinatal asphyxia is the term used to describe

the impairment in the exchange of lung gases during delivery and the subsequent hazardous effect on the fetus. From pregnancy till birth, a number of maternal, placental, uterine, and fetal variables interact to determine whether a baby experiences perinatal asphyxia.<sup>3</sup> Perinatal asphyxia results in Hypoxic Ischemic Encephalopathy (HIE). As asphyxia becomes more severe,

there is a corresponding rise in morbidity and death. Nearly all patients with severe HIE and 50–60% of children with mild HIE have neuro developmental abnormalities.<sup>4</sup>

The principal excitatory amino acid neurotransmitter glutamate, released in greater amounts into the extracellular compartment of the brain after fetal hypoxia, causes multi-organ failure. The other organs may recover, but the brain is permanently injured.<sup>5</sup> High glutamate concentration causes NMDA (N-methyl-D-aspartate) channels to open, enabling an excessive amount of calcium to enter the neurons and resulting in permanent neuronal damage. Since magnesium is a naturally occurring NMDA receptor antagonist, it protects the developing brain from harm brought on by glutamate.<sup>6</sup> Anti-excitotoxic (blocks the NMDA receptor), antioxidant (needed for glutathione biosynthesis), anti-cytokine (decreases levels of inflammatory cytokines), and anti-platelet (decreases platelet aggregation) effects are some of the mechanisms used in experimental work to support the potential role of magnesium sulphate.<sup>7,8</sup> The intravenous infusion of magnesium after a simulated hypoxic ischemic injury prevents neurological impairment in several animal models.<sup>9</sup> As a result, magnesium sulphate is recommended for usage in clinical settings to prevent brain damage and glutamate excitotoxicity. Studies on postnatal magnesium treatment for infants who had asphyxia at birth have shown some benefits while showing no benefits in others.<sup>10,11</sup>

The purpose of the current study was to ascertain the impact of intravenous magnesium sulphate treatment on the in-hospital mortality of asphyxiated term newborns.

## Methodology

This prospective cohort study was conducted over a period of six months from January, 2022 to June 2022 at Department of Pediatric Medicine Nishtar Hospital Multan, Pakistan after approval from institutional ethics committee (ERC#1163). Neonates with Apgar score < 7 at 5-minutes after birth and requiring active resuscitation were clinically categorized into mild, moderate and severe perinatal asphyxia based on Sarnat and Sarnat staging.<sup>12</sup> A total of 183 consecutive full-term neonates weighing  $\geq 2500$  grams with moderate to severe perinatal asphyxia presenting within 48-hours of life were enro-

lled in the study after informed consent provided by the parents. Neonates with congenital heart diseases (other than patent ductus arteriosus), with syndromic features and with C-reactive protein  $>6$  (neonatal sepsis) were excluded. Baseline characteristics including age, gender, gestational age, mode of delivery, birth weight and severity of perinatal asphyxia was noted. According to hospital protocol for the management of perinatal asphyxia neonates presenting within 6-hours after birth were given intravenous MgSO<sub>4</sub>, three doses 250 mg/kg/dose, 24 hours apart (exposed group). Neonates presenting after 6-hours of birth did not get intravenous MgSO<sub>4</sub> (un-exposed group) but were provided with routine neonatal care (oxygen, intravenous fluid, correction of electrolyte imbalance, prevention and treatment of seizures and complications of perinatal asphyxia and consideration of orogastric feeding if child is able to tolerate). The outcome was assessed in terms of in-hospital mortality, time to establishment of full oral feeding and duration of hospital stay.

A sample size of 183 neonates with perinatal asphyxia was calculated considering mortality rate of 35% in unexposed neonates as reported by Siddiqui MA et al<sup>13</sup>, and expected mortality of 15% in exposed neonates with power of 80%, confidence level of 95% and attrition rate of 10%. The data was analyzed using STATA 12.0. Descriptive statistics were run for numerical and categorical data. Comparison between exposed and un-exposed groups were through independent sample t-test and chi-square test for numerical and categorical data respectively. Unadjusted and adjusted binary logistic regression analysis were run for the assessment of risk factors for mortality between the two groups. A p-value of  $\leq 0.20$  was considered significant at bivariate level and  $\leq 0.05$  at multivariable level. Relative risk with 95% confidence interval is reported. The goodness of fit for the adjusted model was ascertained through the Hosmer-Lemeshow test. Kaplan-Meier method is used to construct the survival curves and mortality between neonates treated with and without MgSO<sub>4</sub> was compared through log-rank test.

## Results

Mean gestational age was  $38.1 \pm 0.9$  weeks and postnatal age was  $19.6 \pm 16.7$  hours. Males constituted 53% (n=97) of the study population and 54.6% (n=100) were

delivered through cesarean section. Mean birth weight of the neonates was  $3.1 \pm 0.4$  kg and 71.6% (n=131) suffered from moderate perinatal asphyxia. Mean time to start oral feeding was  $5.2 \pm 1.9$  days, inotropes were used in 21.8% (n=40) and mean hospital stay was  $6.5 \pm 2.6$  days. Overall mortality rate was 15.8% (n=29). Ninety neonates were received within six hours after birth and were given intravenous MgSO<sub>4</sub> and 93 neonates were received after this duration did not get MgSO<sub>4</sub> [Table 1].

Distribution of gender, gestational age, mode of delivery, birth weight and severity of perinatal asphyxia did not

**Table 1:** Characteristics of neonates with perinatal asphyxia (N=183)

Characteristics	All (N=183)	MgSO <sub>4</sub> group (n=90)	No MgSO <sub>4</sub> (n=93)	P-value*
Age (hours)	19.6 ± 16.7	4.0 ± 1.6	34.7 ± 8.9	< 0.001
<b>Gender</b>				
Male	97 (53)	49 (50.5)	48 (49.5)	0.70
Female	86 (47)	41 (47.7)	45 (52.3)	
Gestational Age (weeks)	38.1 ± 0.9	38.2 ± 0.9	38.1 ± 0.8	0.18
<b>Mode of delivery</b>				
Normal vaginal	83 (45.4)	40 (48.2)	43 (51.8)	0.81
Cesarean section	100 (54.6)	50 (50)	50 (50)	
Birth weight (kg)	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.3	0.98
<b>Perinatal asphyxia</b>				
Moderate	131 (71.6)	61 (46.6)	70 (53.4)	0.26
Severe	52 (28.4)	29 (55.8)	23 (44.2)	
Use of Inotropes (Yes)	40 (21.8)	27 (67.5)	13 (32.5)	0.01
Time to start oral feed (days)(n=154)	5.2 ± 1.9	4.4 ± 1.9	6.2 ± 1.5	< 0.001
Hospital Stay (days)	6.5 ± 2.6	5.8 ± 3.1	7.2 ± 1.8	< 0.001
Mortality (yes)	29 (15.8)	07 (7.8)	22 (23.6)	0.003

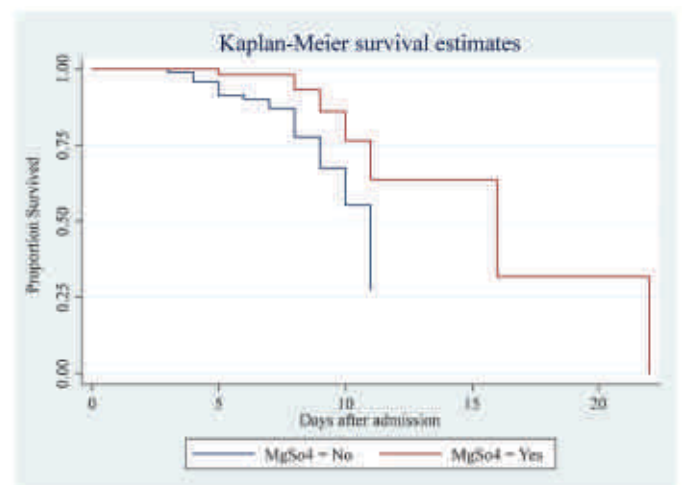
\*chi-square test for categorical variables and t-test for quantitative variables

differ significantly between exposed and unexposed groups. Nevertheless, use of inotropes (67.5% vs. 32.5%, p-value 0.01) was higher in exposed group. Mortality (7.8% vs. 23.6%, p-value 0.003) was significantly higher in unexposed group compared to exposed group. Similarly, mean time to start oral feed ( $4.4 \pm 1.9$  vs.  $6.2 \pm 1.5$  days) and hospital stay ( $5.8 \pm 3.1$  vs.  $7.2 \pm 1.8$ ) were significantly (p-value < 0.001) low in exposed group compared to unexposed group respectively [Table 1]. Most of the demographic characteristics were comparable in expired and alive neonates. However, proportion

of severe asphyxia was significantly high in neonates who expired (75.9% vs. 19.5%) compared to alive neonates. On the other hand, proportion of neonates reaching hospital within 6-hours of delivery was higher in surviving neonates (53.8% vs. 24.1%) compared to neonates who expired [Table S1].

**Table 2:** Risk Factors of mortality in neonates with perinatal asphyxia (N=183)

Characteristics	Unadjusted Risk Ratio (95% CI)	p-value	Adjusted Risk Ratio (95% CI)	p-value
Use of MgSO <sub>4</sub> (No)	3.1 (1.4 – 6.7)	0.006	3.5 (1.7 – 7.0)	0.001
Grade of asphyxia (Severe)	7.9 (3.6 – 17.4)	<0.001	8.5 (4.0 – 18.0)	<0.001
Mode of delivery (SVD)	1.7 (0.8 – 3.4)	0.12	1.8 (1.1 – 2.9)	0.02
Use of Inotropes (Yes)	1.6 (0.8 – 3.3)	0.19	-	-
Gestational Age (> 38-week)	1.4 (0.7 – 2.7)	0.39	-	-
Gender (Female)	1.1 (0.5 – 2.1)	0.88	-	-
Weight (> 3.0 kg)	0.7 (0.4 – 1.4)	0.24	-	-



**Figure-1:** The Kaplan-Meier survival estimates of neonates with perinatal asphyxia (N=183)

In the unadjusted model it is evident that the risk of mortality was three times higher in unexposed group, 7.9 times in neonates with severe asphyxia, 1.7 times in neonates born by SVD, 1.6 times with the use of inotropes and 1.4 times in neonates born after 38 weeks of completed gestation. In multivariable model, the independent predictors (in the presence of exposure variable) of mortality in the study were severe asphyxia (RR 8.5,

95% CI 4.0 – 18.0; p-value < 0.001) and spontaneous vaginal delivery (RR 1.8, 95% CI 1.1 – 2.9; p-value 0.02) [Table 2].

The Kaplan-Meier survival estimates of children receiving MgSO<sub>4</sub> showed median survival time of 16 days (95% CI- 8.7 – 23.3) compared to median survival of 11 days (95% CI 9.9 – 12.0) in neonates who did not get MgSO<sub>4</sub> and this was significantly high (Log-rank test:  $\chi^2 = 6.03$ , df -1, p-value 0.01) [Figure 1].

**Table S1:** Comparison of characteristics between neonates with perinatal asphyxia who survived and expired (N=183)

Characteristics	Survived (n=154)	Expired (n=29)	p-value
Age (hours)	18.1 ± 16.6	27.7 ± 15.3	0.004
<b>Gender</b>			
Male	82 (53.2)	15 (51.7)	0.88
Female	72 (46.8)	14 (48.3)	
Gestational Age (weeks)	38.1 ± 0.9	38.4 ± 0.9	0.12
<b>Mode of delivery</b>			
Normal vaginal	66 (42.9)	17 (58.6)	0.12
Cesarean section	88 (57.1)	12 (41.4)	
Birth weight (kg)	3.1 ± 0.4	3.0 ± 0.3	0.16
<b>Perinatal asphyxia</b>			
Moderate	124 (80.5)	7 (24.1)	< 0.001
Severe	30 (19.5)	22 (75.9)	
Reached hospital within 6-hours (Yes)	83 (53.8)	7 (24.1)	0.003
Use of Inotropes (Yes)	31 (20.1)	9 (31.0)	0.19
Hospital Stay (days)	6.2 ± 2.2	8.2 ± 3.9	< 0.001

## Discussion

Overall mortality in our study was 15.8%. Mortality was high in neonates not treated with MgSO<sub>4</sub> (23.6%), compared to neonates treated with MgSO<sub>4</sub> (7.8%). Pakistan is one of the nations with the highest neonatal mortality rates, with birth asphyxia being one of the dominant underlying causes.<sup>14</sup> Regarding therapeutic hypothermia, whole body cooling seems to be more effective at reducing death compared to selective head cooling, but both modalities are efficacious at decreasing severe disability.<sup>15</sup> There is supportive treatment of respiratory distress, pulmonary hypertension, coagulopathy and myocardial dysfunction. Intubation, surfactant, oxygen and inhaled nitric oxide are used to treat respiratory distress and pulmonary hypertension. Vasopressors are needed to manage myocardial dysfunction. Renal dysfunction may cause oliguria or anuria; so, crystalloids and blood pro-

ducts should be used cautiously.<sup>16</sup>

Although neonates have been observed to show improvement by practicing therapeutic hypothermia in cases of moderate birth asphyxia, the cases of severe birth asphyxia do not respond well to the treatment.<sup>17</sup> As a result, additional research is required to identify adjuvant therapeutic approaches for providing neuroprotection and reducing mortality. By closing the NMDA channels, magnesium sulphate prevents brain damage in newborns who have had perinatal asphyxia.<sup>18,19</sup>

Following the earliest primary neuronal injury, when oxygen and glucose supply to brain is interrupted, there is a latent period of up to six hours before a secondary phase of injury starts. This is the period when the injured area is re-perfused, and damaged cells are lysed, releasing toxic neurotransmitters. The goal of magnesium sulphate therapy is to intervene during the latent period and reduce damage from the secondary neuronal injury.<sup>20</sup>

The current study revealed increased use of inotropes and lower mean time to start oral feed, and hospital stay in exposed group compared to unexposed group. Our results are comparable with those reported by Iqbal N et al. In their study, compared to placebo group the feeding was commenced earlier (p-value 0.002), mean duration of stay was shorter (p-value 0.003), and mortality was low (2 deaths versus 4 deaths, p-value 0.39) in the magnesium sulphate group.<sup>4</sup> Sajid NK et al also found that oral feed (sucking) was established in 75.7% cases who were given MgSO<sub>4</sub> as compared to 39.4% patients who were given normal saline (p-value 0.002).<sup>21</sup> In another study, more number of infants in group A (MgSO<sub>4</sub>) had established sucking at the time of discharge as compared to group B (Placebo) (71.4% vs 40%; p-value 0.008).<sup>22</sup>

Comparable to results of our study, Bhat MA et al, observed that the overall mortality rate was 10% (equal percentage in both treatment and placebo group). Thirty-five percent of patients in the treatment group required presser support compared with 25% of patients in the placebo group (p-value > 0.05). Seventy-seven percent of infants in the treatment group were taking oral feeds at the time of discharge in comparison to 37% in the placebo group.<sup>11</sup> The study by Hossain MM et al reported an overall mortality rate of 26%. They found that at the time of discharge, experimental group was receiving more (78% vs. 44%) oral feeds compared with the

control group.<sup>23</sup> Concordant to our results, another study from Pakistan reported mortality rate of 13% in treatment group (A) and 23% in placebo (B).<sup>24</sup> The relatively low mortality rate in our study could be due to the reason that significant percentage of patients (71.6%) were experiencing moderate asphyxia instead of severe asphyxia.

Due to increased production of prostacyclin and inhibition of angiotensin-converting enzymes, magnesium causes vasodilation and hypotension.<sup>25,26</sup> So, to overcome magnesium-induced hypotension, inotropes were used largely in patients receiving magnesium sulphate and we observed favorable outcome in the form of survival. Ichiba H et al observed that postnatal infusion of MgSO<sub>4</sub> when given along with dopamine did not produce any physiological changes including mean arterial pressure.<sup>10</sup>

Severe perinatal asphyxia was the independent risk factor of mortality in our study. More than half of the neonates received MgSO<sub>4</sub> yet the mortality rate in severe asphyxia was 42.3% (n/N=22/52). This finding indicated that MgSO<sub>4</sub> could not provide much benefit to neonates with severe asphyxia. This is supported by another study from Bangladesh<sup>27</sup> where mortality rate in severe perinatal asphyxia was comparable between MgSO<sub>4</sub> treated and placebo group (50% vs. 55.5%).

Hypothermia (selective or whole body) is current standard of care for neonates with perinatal asphyxia. This treatment modality could not be provided to our patients due to lack of proper equipment and expertise in using locally improvised methods of cooling. Other limitations are lack of long-term follow-up for the assessment of neurological and developmental outcomes in surviving newborn, lack of randomization and inability to compare exposed vs un-exposed group within 6 hours of life. Mode of delivery was comparable in both the surviving and expired neonates but we did not have data on perinatal factors like duration of labour, obstructed labour, neonatal resuscitation and premature rupture of membrane.

## Conclusion

Postnatal magnesium sulfate infusion, when given within 6 hours, is not only effective in reducing the mortality but it also reduces mean time to start oral feeding and hospital stay for neonates with moderate to

severe perinatal asphyxia. More studies with large sample sizes, longer follow-up period and preferably multicenter trials, are required to validate these results.

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