

## Assessing Role of Magnesium Sulphate on the Survival and Short-Term Neurologic Outcome of Neonate with Severe Perinatal Asphyxia

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### Abstract

**Aim:** The aim of the present study was to assess the role of magnesium sulphate and its timing of administration on the survival and short-term neurologic outcome (such as seizure, tone, reflex and death) of neonate with severe perinatal asphyxia.

**Methods:** The study was conducted in Department of Pediatrics, JLNMCB, Bhagalpur, Bihar, India for one year, and all neonates admitted into both inborn and out born units of the SCBU with APGAR score < 6 at 5 minutes or those referred from other health facilities with history of inability to establish spontaneous respiration (cry) at birth were enrolled after informed consent from the parents/caregivers. A total of 706 neonates were admitted and out of these neonates 136 (19.3%) had SPNA.

**Results:** Among those with SPNA 84 (61.8%) were male and 52 (38.2%) were female neonates, giving a M: F of 1.6:1. Majority 125 (91.9%) were delivered in health facility and 53 (29.0%) of them had no signs of hypoxic ischemic encephalopathy at presentation. Respiratory distress as evidenced by tachypnea (respiratory rate > 60) was the most common 73(53.7%) presenting symptom. Outcome showed that 104(76.5%) were treated and discharged while 32(23.5%) died. About equal number of mothers delivered term 70 (51.5) and preterm 66 (48.5%) babies. Most 114 (83.8%) mothers were booked and 55 (40.4%) of them were primiparous, 50 (36.8%) multiparous and 31 (22.8) grand multiparous. Majority of mothers received postpartum magnesium sulphate. There was statistically significant association between birth weight (0.001) and HIE (0.009) with outcome. However, admission heart rate, Spo<sub>2</sub>, BCS and gestational age were not significantly associated with outcome.

**Conclusion:** The findings of this study further strengthen the role of magnesium sulphate in improvement of short term neurologic outcome in asphyxiated neonates but there was no statistically significant difference in mortality with timing of administration of first dose of magnesium sulphate.

**Keywords:** magnesium sulphate, treatment, asphyxia

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### Introduction

Perinatal asphyxia is one of the major causes of neonatal mortality and long-term morbidity. Neurobiology research has extended our understanding of the mechanisms that culminate in neuronal loss after hypoxic-ischemic insult. Asphyxia leads to two types of cerebral insults: the primary neuronal injury that occurs at the time of the hypoxic-ischemic insult and the secondary neuronal injury that occurs over hours to even days following the accumulation of excessive intraneuronal calcium as a result of excitatory amino acid stimulation of the N-methyl-D-aspartate (NMDA) cell receptors. It has been shown that NMDA receptor antagonists block calcium ion entry and preserve neuronal function and structure. MK 801, a NMDA receptor antagonist, has been shown to be neuroprotective in immature animals with asphyxia, but is too toxic to be evaluated in the human neonate. [1] Magnesium

ion gates the NMDA channels in a voltage-dependent manner and may protect the brain from NMDA receptor-mediated injury. [2] In an earlier study, we have reported that a dose of 250 mg/kg and 125 mg/kg of magnesium sulfate given as an infusion is safe and well tolerated by asphyxiated neonates. [3]

The World Health Organization (WHO) defined severe perinatal asphyxia as failure to establish spontaneous respiration at birth or an APGAR score of 3 or less in the first minute of life in low resource settings. [4] While the American Academy of Pediatrics(AAP) and the American College of Obstetrics and Gynecology (ACOG) criteria for SPNA include profound mixed acidemia (PH < 7.0), APGAR score of 0-3 for longer than five minutes, neonatal neurologic sequel and multiple organ

dysfunction. [5] The catastrophic events following severe perinatal asphyxia such as acute encephalopathy (HIE), metabolic acidemia, circulatory collapse, and persistent pulmonary hypertension are sometimes neither predictable nor preventable. [5,6] This is because the timing of these events are difficult to establish for an individual infant as antepartum events may not lead to signs that are detectable in the fetus [7] Severe perinatal asphyxia leads to excessive release and reduced uptake of glutamate in the newborn brain. Increased glutamate concentrations open up N-Methyl-D-Aspartate (NMDA) channels allowing excessive calcium influx into the neurons which interferes with many enzymatic reactions including the activation of lipases, proteases, endonucleases and phospholipases, it also interferes with the formation of oxygen free radicals.<sup>8</sup> The cytosolic accumulation of calcium following hypoxia – ischemia has detrimental effect on neuronal cells leading to irreversible brain damage which occurs hours to days after the primary injury. [<sup>8,9</sup>]

The aim of the present study was to assess the role of magnesium sulphate and its timing of administration on the survival and short-term neurologic outcome (such as seizure, tone, reflex and death) of neonate with severe perinatal asphyxia.

#### Materials and Methods

The study was conducted in Department of Pediatrics, JLNCH, Bhagalpur, Bihar, India for one year, and all neonates admitted into both inborn and out born units of the SCBU with APGAR score < 6 at 5 minutes or those referred from other health facilities with history of inability to establish spontaneous respiration (cry) at birth were enrolled after informed consent from the parents/caregivers. A total of 706 neonates were admitted and out of these neonates 136 (19.3%) had SPNA.

#### Data Collection

Neonatal parameters such as age, gender, weight, APGAR score at 1 and 5 minutes, pulse rate, respiratory rate, Spo2 and time of administration of first dose of magnesium sulphate were entered into a predesigned case report form by a member of the research team for neonates who met the eligibility criteria. The mother's booking status, parity, duration of labor and mode of delivery were also recorded. The main outcome variables which were death, discharge or neurologic status at day five were documented for each eligible participant. All Neonates were treated according to the standard unit protocol for severe perinatal asphyxia<sup>20</sup>, and in addition, received magnesium sulphate 250mg/kg/dose at admission, and was repeated after 24 and 48 hours respectively. Neurologic status which included the neonates' tone, posture, grade of HIE (Santa & Santa 1, 2, & 3), Blantyre coma score, Moro reflex, apnea, muscle tone, and seizures were assessed every 24 hours until 5 days of life.

#### Statistical Analysis

All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS)(IBM, NY, version 24), Categorical and continuous variables are summarized respectively as proportions and means (standard deviations). Cross tabulations with the outcome were performed using the  $\chi^2$  statistic for categorical variables, with statistical significance defined as  $\alpha < 0.05$  (two-sided).

Informed consent was obtained from each parent/care giver before patient was enrolled into the study.

#### Results

**Table 1: Sociodemographic characteristics of neonates**

Variable	Frequency (%) N=136
Sex	
Male	84(61.8)
Female	52(38.2)
Gestational age	
Term	70(51.5)
Preterm	66(48.5)
Place of Birth	
Facility	125(91.9)
Home	11(8.1)
Duration of Labor	
<12 hrs.	63(46.3)
12-24 hrs.	20(14.7)
>24 hrs.	10(7.4)
Presence and grade of HIE*	
1	14(10.3)

2	54(39.7)
3	15(11.0)
None	53(39.0)
Birth weight	
Normal	88(64.7)
Low birth weight	39(28.7)
Very low birth weight	9(6.6)
Admission Respiratory Rate	
<40 bpm	8(5.9)
40-60 bpm	55(40.4)
>60 bpm	73(53.7)
Admission SPO2	
<90	67(49.3)
90-95	18(13.2)
>95	34(25.0)
Missing entry	17(12.5)
Admission BCS	
0-2	10(7.4)
3-4	43(31.6)
	83(61.0)
Outcome	
Dead	32(23.5)
Alive	104(76.5)

Among those with SPNA 84 (61.8%) were male and 52 (38.2%) were female neonates, giving a M: F of 1.6:1. Majority 125 (91.9%) were delivered in health facility and 53 (29.0%) of them had no signs of hypoxic ischemic encephalopathy at presentation.

Respiratory distress as evidenced by tachypnea (respiratory rate > 60) was the most common 73(53.7%) presenting symptom. Outcome showed that 104(76.5%) were treated and discharged while 32(23.5%) died.

**Table 2: Sociodemographic characteristics of Mothers**

Variable	Frequency (%) n=136
Gestational age	
Term	70(51.5)
Preterm	66(48.5)
Parity	
Primiparous	55(40.4)
Multiparous	50(36.8)
grand multiparous	31(22.8)
Booking History	
Booked	114(83.8)
Unbooked	22(16.2)
Duration of Labor	
<12 hrs.	63(46.3)
12-24 hrs.	20(14.7)
>24 hrs.	10(7.4)
Prenatal MgSO4 given	
Yes	132(97.1)
No	4(2.9)

About equal number of mothers delivered term 70 (51.5) and preterm 66 (48.5%) babies. Most 114 (83.8%) mothers were booked and 55 (40.4%) of them were primiparous, 50 (36.8%) multiparous and 31 (22.8) grand multiparous. Majority of mothers received postpartum magnesium sulphate.

**Table 3: Admission parameters associated with outcome of neonates**

Variable	Deadn=32 F (%)	Aliven=104F (%)	X2	p-value
Gestational age				
Preterm	19(28.8)	47(71.2)	1.971	0.160
Term	13(18.6)	57(81.4)		
Birth weight				
VLBW	4(44.4)	5(55.6)	20.521	<0.001
Normal weight	10(11.4)	78(88.6)		
LBW	18(46.2)	21(53.8)		
Admission RR				
<40bpm	1(12.5)	7(87.5)	2.528	0.283
40-60bpm	10(18.2)	45(81.8)		
>60bpm	21(28.8)	52(71.2)		
Admission BCS				
0-2	5(50.0)	5(50.0)	4.212	0.122
3-4	9(20.9)	34(79.1)		
5	18(21.7)	65(78.3)		
HIE				
Yes	26(31.0)	58(69.0)	6.728	0.009
No	6(11.5)	46(88.5)		

There was statistically significant association between birth weight (0.001) and HIE (0.009) with outcome. However, admission heart rate, Spo2, BCS and gestational age were not significantly associated with outcome.

**Table 4: Association Between Admission Oxygen Saturation and Time of Administration of First Dose of Mgso4 with Outcome**

Variable	Dead F (%)	Alive		p-value
		F (%)	X2	
<b>Time of administration of 1<sup>st</sup> dose MgSO4</b>				
<12 hrs.	16(30.8)	36(69.2)	4.184	0.123
12-24hrs	4(28.6)	10(71.4)		
>24hrs	9(15.0)	51(85.0)		
Total	n=29	n=97		
<b>Admission SPO2</b>				
<90	18(26.9)	49(73.1)	3.991	0.136
90-95	6(33.3)	12(66.7)		
>95	4(11.8)	30(88.2)		
Total	n=28	n=91		

Out of the 52 neonates that had the first dose of MgSO4 within 12 hours of delivery 16(30.8%) died while 36(69.2%) survived. Of the 14 that had the first dose between 12 to 24 hours, 4(28.6%) died while 10(71.4%) survived. Sixty (47.6%) of the patients received the first dose of MgSO4 after 24hours out of whom 9(15.0%) died and 51(85.0%)

survived. There was no statistically significant difference in mortality with time of administration of first dose of MgSO4 (p – 0.123). Most 67(56.3%) patients were admitted with SPO2 of < 90%, 18(26.8%) of them died and 49(36.0%) survived (p – 0.136).

**Table 5: Comparison of neonates’ neurologic parameters on day 1 and day 5**

Variable	Day 1	Day 5	X2	p-value
Moro reflex				
Normal	110(88.7)	62(83.8)	0.981	0.322
Abnormal	14(11.3)	12(16.2)		
Total	124(100)	74(100)		
Tone				
Normal	93(68.9)	66(78.6)	2.429	0.119
Abnormal	42(31.1)	18(21.4)		
Total	135(100)	84(100)		
Seizure				

Present	19(15.6)	1(1.3)	<0.001*
Absent	103(84.4)	76(98.7)	
Total	122(100)	77(100)	
Apnoea			
Present	6(4.9)	1(1.3)	0.969*
Absent	115(95.1)	75(98.7)	
Total	121(100)	76(100)	

Assessment of the neurologic status shows that 14/124(11.3%) had absent Moro reflex on day one compared to 12/74 (16.2%) on day 5 ( $p = 0.322$ ). The muscle tone was abnormal in 42/135(31.1%) on day 1 compared to with 18/84 (21.4%) on day 5 ( $p = 0.119$ ). Seizures were present in 19/122 (15.6%) on day 1 compared to 1/77(1.3%) on day 5 ( $p=0.001$ ) and Apnea was observed in 6/121 (4.9%) on day1 compared to 1/76 (1.3%) on day 5 ( $p = 0.963$ ).

### Discussion

Magnesium is an NMDA receptor antagonist that blocks neuronal influx of calcium within the ion channels which is voltage dependent and is overcome during axonal depolarization if the intracellular magnesium is increased then this block will be restored. [10] Mushtaq et al [11] showed that magnesium sulfate treatment improves neurologic outcomes at discharge for term neonates with severe perinatal asphyxia.

A total of 706 neonates were admitted and out of these neonates 136 (19.3%) had SPNA. The similarity could be because the reported studies were carried out in tertiary setting like that of this study and they used similar diagnostic criteria and recruited only those with SPNA. However, higher rates of 30.1%, 32.0% and 56.9% were reported from earlier studies in Gusau [12], Benin city [13] and Bangladesh<sup>6</sup> respectively. The higher rates in those studies may be due to differences in study design, diagnostic criteria, recruitment of all grades of asphyxia or it may indeed reflect a substantial improvement in perinatal care over time.

Out of the 52 neonates that had the first dose of MgSO<sub>4</sub> within 12 hours of delivery 16(30.8%) died while 36(69.2%) survived. Of the 14 that had the first dose between 12 to 24 hours, 4(28.6%) died while 10(71.4%) survived. Sixty (47.6%) of the patients received the first dose of MgSO<sub>4</sub> after 24hours out of whom 9(15.0%) died and 51(85.0%) survived. There was no statistically significant difference in mortality with time of administration of first dose of MgSO<sub>4</sub> ( $p = 0.123$ ). [13] Most 67(56.3%) patients were admitted with SPO<sub>2</sub> of < 90%, 18(26.8%) of them died and 49(36.0%) survived ( $p = 0.136$ ). In this study 39.0% of the patient with SPNA did not show any sign of HIE, this rate is lower than 42.0% reported by Chauhan et al [14] in India and 45.8% from Ethiopia. [15] These differences could be accounted for by use of one minute Apgar score in both studies as diagnostic

criteria and the inclusion of patients with mild and moderate asphyxia.

Assessment of the neurologic status shows that 14/124(11.3%) had absent Moro reflex on day one compared to 12/74 (16.2%) on day 5 ( $p = 0.322$ ). The muscle tone was abnormal in 42/135(31.1%) on day 1 compared to with 18/84 (21.4%) on day 5 ( $p = 0.119$ ). Seizures were present in 19/122 (15.6%) on day 1 compared to 1/77(1.3%) on day 5 ( $p=0.001$ ) and Apnea was observed in 6/121 (4.9%) on day1 compared to 1/76 (1.3%) on day 5 ( $p = 0.963$ ). Eclampsia in this study reflected that the number of women who received magnesium sulphate before delivery. There was statistically significant association between birth place ( $p = 0.001$ ), HIE ( $p = 0.009$ ) with outcome. This finding is similar to other reports [16,17] that showed that low birth weight and HIE are poor prognostic factors. However, admission heart rate, SpO<sub>2</sub>, BCS, and gestational age were not statistically significantly associated with outcome.

### Conclusion

The findings of this study further strengthen the role of magnesium sulphate in improvement of short-term neurologic outcome in asphyxiated neonates but there was no statistically significant difference in mortality with timing of administration of first dose of magnesium sulphate.

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