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Original Research Article

The Advantageous Impact of Intravenous Magnesium Sulphate in Full-Term Neonates Experiencing Perinatal Asphyxia

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Abstract:

Background: The primary aim of this research endeavour was to ascertain the efficacy of intravenous magnesium sulphate therapy in facilitating prompt recuperation and achieving a positive neurological prognosis upon discharge for neonates who have experienced asphyxia at birth.

Methods: Term neonates diagnosed with birth asphyxia were randomly allocated to receive either a magnesium sulphate infusion (Study group) or be part of the Comparison group. The neonates in both cohorts received treatment in accordance with the standard neonatal intensive care unit (NICU) protocol for birth asphyxia. The study group also underwent intravenous infusion of magnesium sulphate at a dosage of 250 mg/kg/dose (administered as 1 ml/kg/dose in 20 ml of 5% dextrose solution) over a duration of 1 hour, within 6 hours of birth. This was followed by the administration of 2 additional doses, repeated after 24 hours and subsequently at 48 hours. The vital signs were continuously monitored. Comprehensive clinical evaluations, encompassing thorough neurological examinations, were conducted on both cohorts until their release from the Neonatal Intensive Care Unit (NICU).

Results: Each cohort consisted of 60 neonates. A greater proportion of neonates within the study cohort exhibited successful seizure management through the administration of a solitary anticonvulsant, in contrast to the control group. Within the cohort under investigation, it was observed that a notable proportion of neonates, specifically 92%, achieved successful management of seizures within a span of 48 hours. In contrast, the comparison group exhibited a lower rate of seizure control, with only 70% of neonates achieving the same outcome. This discrepancy was found to be statistically significant, as evidenced by a p-value of 0.048. There was a notable occurrence of early implementation of nutritional intake among the study cohort in contrast to the control cohort, with a statistically significant difference observed. In the study cohort, a total of 47 neonates (84%) exhibited recovery from abnormal neurological examination within a span of four days, whereas in the comparison group, only 26 neonates (53%) demonstrated similar recovery. This disparity in recovery rates between the two groups was found to be statistically significant (p=0.0001).

Conclusions: The administration of intravenous magnesium sulphate to term neonates experiencing birth asphyxia within six hours of birth has been found to be beneficial in terms of early seizure management, prompt resolution of abnormal neurological manifestations, expedited initiation of enteral feeding, and reduced likelihood of neurological abnormalities upon discharge.

Keywords: Magnesium Sulphate, perinatal asphyxia, Neurological abnormalities.

Introduction

Perinatal asphyxia is a significant contributor to mortality in the early neonatal period. It pertains to the dysfunction in the process of respiratory gas exchange during the course of delivery, and the subsequent detrimental impact on the developing foetus. Perinatal asphyxia is ascertained through a multifaceted interplay of diverse maternal, placental, uterine, and foetal factors spanning the course of pregnancy until delivery. During the occurrence of perinatal asphyxia, there is an elevation in the extracellular levels of glutamate, which serves as the primary excitatory

neurotransmitter within the brain. Elevated levels of glutamate trigger the activation of NMDA (N-methyl-D-aspartate) receptors, resulting in the excessive entry of calcium ions into the neurons and leading to irreversible neuronal damage. I am experiencing severe pain in my lower back. It started a few days ago and has been getting Magnesium, a naturally present substance, acts as an antagonist to the N-methyl-D-aspartate (NMDA) receptor, thereby providing neuroprotection to the developing brain against glutamate-induced damage. Therefore, the utilisation of magnesium sulphate is being suggested for clinical application in order to counteract glutamate excitotoxicity and mitigate cerebral injury. The user's text does not provide any information to be rewritten in a medical or academic manner. The existing body of literature pertaining to postnatal magnesium therapy following birth asphyxia has demonstrated favourable outcomes in certain cases, while in other instances, no discernible beneficial effects were observed. The user's text, "[5-9]," could be rewritten in a medical and academic manner as Given the inconclusive findings regarding the involvement of magnesium in perinatal asphyxia and the limited number of Indian studies on the subject, this current investigation was conducted to assess the impact of intravenous magnesium sulphate therapy on expediting early recuperation and achieving positive neurological outcomes upon discharge for asphyxiated full-term neonates.

Methods

The present research was a comparative study carried out on neonates diagnosed with perinatal asphyxia. The trial was conducted over duration of 12 months in the Neonatal Intensive Care Unit (NICU) of the Department of Paediatrics at Veer Surendra Sai Institute of Medical Sciences and Research, located in Burla, India. This medical facility is recognised as a tertiary-care hospital. A minimum sample size calculation was performed to determine the required number of term neonates (60 in the study group and 60 in the comparison group) with perinatal asphyxia. The incidence of perinatal asphyxia at our institution, based on live births, was found to be 2 out of every 100 births. The significance level for this calculation was set at 0.05. The utilised formula in this study was $n = z^2pq/d^2$, where z represents the critical value of 1.96, p denotes the probability of 0.02, q is the complementary probability of p (i.e., 1-p), and d signifies the desired margin of error set at 0.05. The enrolment of neonates occurred subsequent to obtaining informed consent from their parents, and the study received approval from the institutional ethical committee. The study's inclusion criteria consisted of term neonates diagnosed with perinatal asphyxia, as defined by the National Neonatal and Perinatal Database. Perinatal asphyxia was determined by an APGAR score of less than 7 at 1 minute after birth. A total of 10 neonates who had a documented history of maternal magnesium administration prior to delivery, as well as mothers who were administered Pethidine and Phenobarbitone, both of which have the potential to depress the neonate, were excluded from the study. Additionally, neonates presenting with any evident external congenital malformations were also excluded from the study.

Upon the infant's admission to the Neonatal Intensive Care Unit (NICU), pertinent information was recorded in a pre-established standardised form. This encompassed the historical data pertaining to antenatal risk factors associated with perinatal asphyxia, such as maternal age, a medical history of pregnancy induced hypertension, anaemia, bleeding, infection, and systemic disease. Intrapartum factors, such as the method of delivery, a previous history of prolonged rupture of membranes, the presence of meconium-stained amniotic fluid, malpresentation, and cord prolapse, were also included in the analysis. The comprehensive assessment encompassed the recording of vital signs and detailed anthropometric measurements. Additionally, a thorough neurological examination was conducted, along with other systemic evaluations. The neonates included in the study were allocated randomly, using computer-generated random numbers, to receive either a magnesium sulphate infusion (referred to as the Study group) or to be part of the Comparison group, as determined by investigator 1. The neonates in both cohorts were managed in accordance with the standard neonatal intensive care unit (NICU) protocol for birth asphyxia.

The study group also underwent intravenous infusion of magnesium sulphate at a dosage of 250 mg per kilogramme per dose (administered as 1 millilitre per kilogramme per dose in a 20 millilitre solution of 5% dextrose) over duration of 1 hour, within 6 hours of birth. This was followed by two additional doses administered after 24 hours and again at 48 hours. The vital signs were continuously monitored. The clinical assessments were conducted by investigator number 2, who maintained blinding with regards to the assignment of patients. During the neonatal period, the vital signs including heart rate, respiratory rate, blood pressure, and oxygen saturation were continuously monitored for the first 72 hours of life. The clinical evaluations encompassed regular assessments of the neurological condition conducted twice daily throughout the patient's hospitalisation. These assessments involved determining the severity of Hypoxic Ischemic Encephalopathy, categorising it into Stage I, Stage II, or Stage III. Additionally, the evaluations included determining the specific respiratory support required, identifying the

presence of seizures, assessing the extent of multiorgan dysfunction, measuring the time required for the patient to achieve full oral feedings through sucking, and conducting a comprehensive neurological examination at the time of discharge. The initial serum magnesium concentration was assessed shortly following delivery, and two subsequent measurements of serum magnesium were obtained at 24 hours and 48 hours for both study cohorts. The concentration of serum magnesium was determined using a commercially available magnesium kit provided by CREST Biosystems, employing the Calmagite method. The statistical analyses, including descriptive statistics, chi-square/contingency coefficient analysis, and independent samples t-test, were conducted using SPSS for Windows (version 16.0). A p-value of less than 0.05 was considered to be statistically significant in this study.

Results

A cohort of 142 neonates underwent screening, from which 22 neonates were excluded. Among the excluded neonates, 14 were found to have met the exclusion criteria, 5 parents declined participation, and 3 neonates were discharged against medical advice prior to the completion of the intervention. A total of 60 neonates were randomly allocated to the study group, while another 60 neonates were assigned to the comparison group. The pre-intervention baseline data of the study groups is presented in Table 1. The study group exhibited a male to female ratio of 1:1.5, while the comparison group had a ratio of 2.15:1 (p=0.341). In the study cohort, the average age of the mothers was found to be 21.9 years. Furthermore, it was observed that 73.3% of the participants were primiparas, while the remaining participants were classified as multiparas. Within the comparison group, the average maternal age was 21.5 years, with 76.7% of the participants being primiparas and the remaining individuals being multiparas. The presence of meconium stained amniotic fluid emerged as the predominant risk factor for birth asphyxia, followed by premature rupture of membranes and prolonged labour. Other factors observed in the study encompassed nuchal cord, gestational hypertension, and antepartum haemorrhage. The majority of neonates were delivered via spontaneous vaginal delivery and exhibited appropriate growth and development for their gestational age. There was no statistically significant disparity observed in the method of resuscitation between the two cohorts, and a majority of the neonate's necessitated endotracheal intubation during the resuscitation process. The majority of children in both groups exhibited stage 2 hypoxic ischemic encephalopathy (HIE). Therefore, the initial data in both groups exhibited a similar level of comparability. The post-intervention comparison between the study group and the comparison group is presented in Table 2. The mean serum magnesium level of the study group after the intervention was found to be greater than 2.4 milliequivalents per litre (Meq/L), a value within the therapeutic and neuroprotective range. This observation is supported by previous research (reference 11). No untoward effects associated with increased levels of magnesium were observed in any of the neonates. During the duration of the hospitalisation, the study group exhibited superior management of seizure activity. The average duration of seizures was found to be lower in the study group compared to the comparison group, and this difference was determined to be statistically significant. A greater proportion of neonates within the study cohort exhibited successful seizure management through the administration of a solitary anticonvulsant, in contrast to the control group. In the research cohort, a notable 92% of neonates exhibited successful seizure control within a span of 48 hours, in contrast to the comparison group where only 70% achieved the same outcome. This discrepancy was found to be statistically significant, as indicated by a p-value of 0.048. There was a significant difference in the early implementation of nasogastric tube feeding (p=0.001), palladai feeding (p=0.0001), and direct breast feeds (p=0.0001) between the study group and the comparison group. In the study cohort, a total of 47 neonates (84%) exhibited recovery from abnormal neurological examination within a span of 4 days, whereas only 26 neonates (53%) in the control group demonstrated similar improvement. This observed difference in recovery rates between the two groups was found to be statistically significant (p=0.0001). The study group consisted of 32 neonates, while the comparison group included 22 neonates. It was observed that normal neuromotor tone was present in the study group, which was statistically significant when compared to the comparison group (p=0.019). The occurrence of shock (5 cases in the study group and 6 cases in the placebo group), need for ventilator support (1 case in the study group and 2 cases in the placebo group), development of acute kidney injury (6 cases in the study group and 12 cases in the placebo group), and mortality (1 case in both the study and placebo groups) did not demonstrate statistical significance.

Table 1: baseline characteristics of the study group and comparison group before intervention

Baseline characteristics	Study group Number (percentage)	Comparison group Number (percentage)	'P' value
1.Male: Female	1:1.5	2.15:1	0.341
2. Mean age of mothers(years)	21.9	21.5	
3.Primipara	73.3%	76.7%	
4. Mode of delivery			
a. Normal vaginal	40(66.7)	41(68.3)	0.845
b. Cesarean section	11(18.3)	11(18.3)	1.00
c. Assisted vaginal delivery	9 (15.0)	8 (13.3)	0.794
5.Major risk factors			
a. Meconium stained amniotic fluid	27(45)	29(48.3)	0.714
b. Premature rupture of membranes	12(20.0)	15 (25.0)	0.512
c. Prolonged labor	13(21.7)	7 (11.7)	0.142
d. Others(cord around the neck, pregnancy induced hypertension and antepartum hemorrhage)	12(20.0)	10(16.7)	0.637
6.Weight for gestational age			
a. Appropriate for gestational age(AGA)	56(93.3)	58(96.7)	
b. Small for gestational age(SGA)	3 (5.0)	2 (3.3)	0.539
c. Large for gestational age(LGA)	1 (1.7)	0	
7. Physiological variables	Mean±SD	Mean±SD	
a.Non-invasive BP(mm Hg)	45.6±3.22	45.5±2.98	0.860
b. Heart rate(per min)	147±14.57	148±3.21	0.535
c. Respiratory rate(per min)	46±7.89	46±5.92	0.620
d. Oxygen saturation(percentage)	96.6±3.40	97.5±1.82	0.238
8.Methods of resuscitation	Number(percentage)	Number(percentage)	
a. Bag and mask ventilation	21(35.0)	19(31.7)	
b. Endotracheal intubation+ Positive pressure ventilation	38(63.3)	41(68.3)	
c. Endotracheal intubation + Positive pressure ventilation + chest compression	1 (1.7)	0	0.545
9.Sarnat and Sarnat HIE staging			
Mild (HIE stage 1)	24(40.0)	27(45.0)	
Moderate(HIE stage 2)	34(56.7)	32(53.3)	0.752
Severe(HIE stage 3)	2 (3.3)	1 (1.7)	

Table 2: Post intervention characteristics of the study group and the comparison group

Characteristics	Study group	Comparison group	'P' value
1. **Mean serum magnesium levels (Meq/L)**	Mean±SD	Mean±SD	
a. Preintervention baseline level	1.52±0.3022	1.59±0.1384	0.0648
b. Post intervention at 24 hours	2.63±0.5584	1.58±0.1454	0.0001
c. Post intervention at 72 hours	2.72±0.4948	1.62±0.1338	0.0001
2. **Events associated with seizures**	Number (percentage)	Number (percentage)	
a. Seizures present	25 (69.4)	27 (81.8)	0.233
b. Mean duration of seizures ± SD (days)	1.52±0.653	2.29±1.564	0.026
c. Seizure control with only one anticonvulsant	24 (96.0)	20 (74.0)	0.029
d. Seizure control within 2 days	23 (92.0)	19 (70)	0.048
3.Mean duration of recovery (days)±SD, from neurological abnormalities	Mean±SD 3.36±1.12	Mean±SD 4.96±1.54	0.0001
4. **Mean duration for initiation of feeding**			
a. Duration (days) for initiation of nasogastric tube feeding	3.02±0.985	3.9±1.254	0.001
b. Duration (days) for initiation of Palladai feeding	3.5±1.378	5.6±2.019	0.0001
c. Duration (days) for initiation of direct breast feeding	4.6±1.358	6.0±1.511	0.0001
5. **Feeding pattern and neurological findings**	Number (percentage)	Number (percentage)	

at discharge			
a. Normal suck and on direct breast feeding	32(91.4)	21(65.6)	0.009
b. Neurologically clinically normal	32(91.4)	21(65.6)	0.009
c. Normal neuromotor tone (Amiel Tison criteria)	32(91.4)	22(68.75)	0.019
d. Normal neuroimaging	28(80.0)	20 (62.5)	0.112

Discussion

In the current study, the comparisons of baseline parameters exhibited similar characteristics in both groups prior to the implementation of the intervention. A loading dose of 250 mg/kg of magnesium was administered, followed by two subsequent infusions of the same dosage, with a 24-hour interval between each administration. According to the pharmacokinetics and estimated plasma half-life of magnesium sulphate as documented by Levene M et al, this prescribed dosage regimen will effectively maintain a plasma concentration of magnesium within the neuroprotective range for a duration of 72 hours. The neuroprotective range of serum magnesium levels is typically observed to be between 2.4 and 5 milliequivalents per litre (Meq/L).The user's text is too short to be rewritten in a medical and academic manner. In the current study, all physiological variables, including heart rate, respiratory rate, blood pressure, and oxygen saturation, exhibited no significant changes before and after the intervention when comparing the two groups. Therefore, no deleterious effects of Magnesium were observed in the present investigation. This finding aligns with the observations made in numerous other studies. The patient presents with a cluster of symptoms including 5-7, 11, and 12 this phenomenon can be attributed to the manifestation of comprehensive neuromuscular blockade, respiratory cessation, and muscular relaxation, which were observed exclusively at a dosage of 400mg/kg per administration. The user's text is not sufficient to be rewritten in a medical and academic manner.

The potential positive outcome associated with the management of seizures may be attributed to various characteristics of magnesium. These include its notable anticonvulsant effect on seizures occurring in the hippocampus, its ability to dilate blood vessels in the brain, its capacity to decrease the entry of calcium by regulating the NMDA receptor in the brain, and its ability to counteract the harmful effects of excessive glutamate activity. The user's text is already concise and does not require any additional medical or academic language. However, in contrast to the findings of our study, Ichiba H et al. observed no statistically significant difference in the occurrence of clinical seizures between the two groups. The user's text is too short to be rewritten in a medical and academic manner. This incongruous outcome may be attributed to the utilisation of a limited sample size. This study elucidates that neonates within the experimental cohort exhibited expedited recovery from atypical neurological manifestations. Additionally, in the context of a hospitalisation, the initiation of feeding was observed to occur at a notably earlier time frame within the study group. The aforementioned findings provide substantial evidence to suggest that magnesium offers clear neuroprotective benefits in neonates who have experienced asphyxia. Previous investigations have not assessed the impact of magnesium on the prompt initiation of enteral nutrition.

In the current study, a significantly lower proportion of neonates in the study group exhibited neurological abnormalities upon discharge. Consistent findings were observed in previous research endeavours. The patient presents with a numerical expression of "5,7." In the current study, a statistically significant proportion of infants in the study group demonstrated the ability to successfully establish normal suckling and feeding patterns upon discharge. Bhat et al. (year) reported comparable findings in their study. The numerical value provided by the user is insufficient to generate a medical or academic response. Please provide a present study exhibited a lower mortality rate in comparison to previous studies. The potential explanation for this discrepancy could be attributed to the relatively limited sample size in previous studies, as well as the higher number of neonates diagnosed with Hypoxic-Ischemic Encephalopathy (HIE) stage 1 in both experimental groups.

Several limitations were observed in the current study. Firstly, the utilisation of umbilical cord pH and base deficit for the diagnosis and quantification of asphyxia was not implemented. Additionally, specialised investigations including diffusion weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and amplitude-integrated electroencephalography were not conducted. Additionally, the absence of extended-term monitoring to evaluate potential neurologic consequences in the future represents another constraint.

Conclusion

Based on our findings, it is determined that the administration of intravenous magnesium sulphate to term neonates with birth asphyxia within 6 hours of postnatal life has demonstrated efficacy in facilitating prompt seizure control, expediting the resolution of abnormal neurological manifestations,

promoting early initiation of enteral feeding, and reducing the likelihood of neurological abnormalities upon discharge.

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