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Role of magnesium sulphate in the treatment of severe perinatal asphyxia: Experience from a tropical tertiary hospital

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Abstract

Introduction: Perinatal asphyxia is a major global cause of neonatal morbidity and mortality. In Nigeria, despite the improvement in perinatal care, perinatal mortality is still responsible for about 27% on neonatal mortality. The use of magnesium sulphate to antagonize the excitotoxicity and subsequent brain damage in severe perinatal asphyxia is increasingly being employed.

Objective: To assess the role of magnesium sulphate and the timing of administration of the first dose on survival and short term neurologic outcome of neonates with severe perinatal asphyxia (SPNA) treated at Federal Teaching Hospital, Gombe

Methodology: This was a prospective cross sectional observational study conducted at Special Care Baby Unit (SCBU) of Federal Teaching Hospital, Gombe. Neonatal parameters such as age, gender, weight, pulse SpO2 APGAR score and time of administration of first dose of magnesium sulphate were recorded. Mothers booking status, parity, place of delivery and prepatum administration magnesium sulphate were also recorded. The neonates tone, reflexes, seizures and grade of HIE was assessed daily for five days.

Results: Out of 706 neonates admitted 136 had SPNA giving a prevalence of 19.3%. There were 84(61.8%) males and 52(38.2%) female M: F 1.6:1. Respiratory distress was commonest presenting symptom and mortality was 23.5%. Birth weight and HIE had statistically significant association with outcome but there was no difference in mortality with time of administration of first dose.

Conclusion: Magnesium sulphate significantly improved the short term outcome of neonates with HIE but there was no difference in mortality in relation to timing of administration of first dose.

Keywords: magnesium sulphate, treatment, asphyxia, tropical setting

Introduction

Perinatal asphyxia continues to present a major global health challenge especially in low-and middle-income countries [1]. Globally, it remains a common cause of neonatal morbidity and mortality, leading to about 4 million deaths annually [1, 2]. The prevalence of severe perinatal asphyxia (SPNA) ranged from 6.1% in Malawi [3], 17% in Ethiopia [4], and 30.9% in Tanzania [5] based on observational studies. In Nigeria, despite the improvement in perinatal care, the burden of perinatal asphyxia still remains high, accounting for 27% of neonatal mortality [4] according to one study. The prevalence of SPNA was reported as 30.1% from Gusau [6], 32.0% at Central hospital Benin City [7] and 20.8% from Maiduguri [8] in Northern east, Nigeria.

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 [1, 9]. While the American Academy of Pediatrics(AAP) and the American College of Obstetrics and Gynecology (ACOG) criteria for SPNA include profound mixed academia (PH < 7.0), APGAR score of 0-3 for longer than five minutes, neonatal neurologic sequel and multiple organ dysfunction [10]. 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 [10, 11]. 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 [12] 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 [10, 13]. 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 [13, 14].

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 [15]. Mushtaq et elp [16] showed that magnesium sulfate treatment improves neurologic outcomes at discharge for term neonates with severe perinatal asphyxia. One report [17] from Bangladesh suggests that magnesium sulphate is safe and has neuroprotective effect on neonates with severe perinatal asphyxia. Savitha *et al* [18] reported that magnesium sulfate infusions were well tolerated without significant alterations in heart rate, oxygen saturations, respiratory rate, or mean arterial blood pressure during intravenous infusions. However, Tagin *et al* [19] in a meta-analysis showed that magnesium sulphate treatment for newborns with HIE does not significantly reduce disability but was associated with increase trend in mortality which is a cause for concern.

Magnesium is increasingly being employed to combat the excitotoxicity and brain damage associated with SPNA in the newborn. In view of limited experience, conflicting reports with the use of magnesium in low resource setting and the dearth of published data on the use of magnesium sulphate from Northern Nigeria, this study aims to assess the role of magnesium sulphate and it's 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

Study setting

The study was conducted at Special Care Baby Unit (SCBU) of the Federal Teaching Hospital, Gombe. The SCBU has two sections, the inborn which has capacity to admit 17 patients (12 cots and 3 incubators) with an average monthly admission of 15 neonates. The outborn unit which has 10 cots and 3 incubators, and has an average monthly admission of 19 neonates. The two sections are equipped with similar facilities (Resuscitaire, incubators, radiant warmers, phototherapy, suction machines, piped oxygen and oxygen concentrators). Each unit has the full complement of nursing and support staff but managed by the same team of Pediatricians that includes a Consultant neonatologist, 2 senior registrar, 5 registrars and house officers.

Study design

This was a prospective cross-sectional observational study conducted from March, 2017 to February, 2020. All neonates admitted into both inborn and outborn units of the SCBU with APGAR score < 6 at 5minutes 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.

Data collection

Neonatal parameters such as age, gender, weight, APGAR score at I 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[20], 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).

Ethical consideration

Ethical approval was obtained from the research and ethics committee of Federal Teaching Hospital, Gombe before commencement of the study. Informed consent was obtained from each parent/care giver before patient was enrolled into the study.

Results

A total of 706 neonates were admitted in the inborn and out born units of SCBU at Federal Teaching Hospital, Gombe from March, 2017 to February, 2020. Out of these neonates 136 (19.3%) had SPNA. 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 I.

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 II. 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 as shown in Table III.

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) see table IV.

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) as shown in table V.

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)

We need to put a note under here to reference what grading system was used for this. Sp02=oxygen saturation, BCS= Blantyre comma score, HIE=Hypoxic, Ischaemic Encephalopathy.

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)

Table 3: Admission parameters associated with outcome of neonates.

Variable	Dead n=32 F (%)	Alive n=104 F (%)	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)		

RR= respiratory rate, BCS=Blantyre comma score

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

Variable	Dead F (%)	Alive		
		F (%)	X2	p-value
Time of administration of 1st dose MgSO4				
<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	
Admission SPO2				
<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	

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)	

*Fischers exact NB The total number (n) for each parameter was different on day I and 5 due to discharge, death and DAMA before re-assessment on day 5.

Discussion

Magnesium sulphate is increasingly being employed as a neuroprotective agent in neonates with severe perinatal asphyxia but the effect of timing of administration of the first dose on survival and short term neurological outcome is not fully described. The finding of this study shows that 19.3% of neonates admitted at the SCBU during the study period had SPNA. This rate is comparable to reports from other centres [8, 4, 11]. 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[6], Benin city[7]and Bangladesh[11]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.

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* [21] in India and 45.8% from Ethiopia[5]. 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. Additionally, these are retrospective reviews as against this study which is prospective and 91.9% of the patients were delivered in health facilities where they had access to oxygen given by bag and mask within minutes of delivery. This could have reduced the risk of brain hypoxia and injury resulting in fewer cases developing acute encephalopathy. Most 132(97.1%) mothers in our study also received antepartum magnesium sulphate for the treatment of eclampsia which has been reported [22] to reduce the incidence of HIE.

The findings of about equal number of term and preterm in this study is not in keeping with reports from Maiduguri[8] and Benin [4] this may be because there were high number of babies delivered following Eclampsia in this study as reflected by 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 [23, 19, 24] that showed that low birth weight and HIE are poor prognostic factors. However, admission heart rate, Sp02, BCS, and gestational age were not statistically significantly associated with outcome.

The finding that there was no statistically significant difference in timing of administration of the first doze of magnesium sulphate between those who survived and those who died (p = 0.123) is not in keeping with previous reports [15, 24]. This might be due to differences in study population and methodology because the reported studies recruited only new-borns within the first six hours and commenced treatment immediately in contrast to this study that involved both inborn and outborn babies thus even patients who presented after 24hours were also included.

The proportion of neonates with seizure on day one was significantly higher than on day 5 (p=0.001) this improvement can be attributed to central seizure control property of magnesium sulphate on the hippocampus it also causes cerebral vasodilation, reduction in calcium influx and antagonizing glutamate exitotocity. Other neurologic parameters such muscle tone, moro reflex and apnea had higher proportion of neonate who had normal parameters on day 5 compared to day one (admission) although, it was not statistically significant. Similar findings of neuroprotive effect of magnesium sulphate have been previously reported [18, 22].

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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