PERINATAL ASPHYXIA AND PROMISING BENEFIT OF MAGNESIUM SULPHATE AS NEUROPROTECTIVE AGENT.

ABSTRACT

INTRODUCRION: Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. Encephalopathy occurs in 50% to 60% of patients with severe perinatal asphyxia. Moderate HIE, 10% to 20% die and 30% to 40% develop neurodeficits, whereas 50% of those with severe HIE die and almost all survivors develop neurodeficits. The systematic administration of magnesium sulphate (MGSO4) after perinatal asphyxia has shown effective resolution of neuronal injury. We are conducted this study to validate effect in severely asphyxiated neonates, so as to utilize its benefits on poor outcome associated with severe perinatal asphyxia/HIE.

OBJECTIVE OF THE STUDY: To determine the effect of magnesium sulphate on neurological outcome in severe perinatal asphyxia

MATERIALS AND METHODS: A prospective interventional trial of magnesium sulphate effect on severely asphyxiated newborns were conducted over one year period from 1st August 2017 to 31st July 2018 was documented.

RESULTS: Of the 52 neonates, male 34 while there 18 female giving a ratio of (M: F is 1:1.8). There were 30 (57.7%) in-born and 22 (42.3%) out-born, the total asphyxia cases (30/144) giving the incidence of 20.8% among in born. About one half (55.8%) of the patients commenced MgSO4 therapy at < 6 hours after birth, while 30.6% and 16.6% commenced MgSO4 therapy at 6 - < 24 hours and > 24 hours after birth respectively. About one half (49.0 %) commenced enteral feeding within 5 – 7 days while 36.7 % and 14.3 % commenced enteral feeding at < days and at > 7 days respectively. Majority of the patients commenced full enteral feeding at either between 5 – 7 days or > 7days while only 36.7 % of the neonates commenced full enteral feeding before 5 days. Equally, primary outcome, fully recovered and initiation breast feeding (p=0.002, 0.001 and 0.033) were statistically significant.

CONCLUSION: Of the fifty two patients managed, 5 (9.6%) died during the treatment period after 8th day of admission and at follow up, while 47 (90.4%) survived. Among the survivors, HIE accounted for 26.9%, DIC was observed among 7.7%, the seizure episodes accounted for 26.9% and Apnoea was responsible for 17.3%. There is need to replicate the study at national level so at obtain generalizable results.

KEYWORDS: Perinatal asphyxia, HIE, Magnesium Sulphate, Neuroprotection, outcome

INTRODUCTION

Perinatal asphyxia is a major cause of early neonatal death. [1] It refers to the impairment in the exchange of respiratory gases during delivery, and the ensuing adverse effect on the fetus. Perinatal asphyxia is determined by a complex interaction of various maternal, placental, uterine and fetal factors from pregnancy to delivery. [1] World Health Organization defined perinatal

asphyxia as "the failure to initiate and sustain breathing at birth. [2] Perinatal asphyxia is a leading cause of neonatal mortality accounting for 23% of all deaths during the new born period and one million deaths worldwide. [3] According to the World Health Organization (WHO), the yearly incidence of birth asphyxia is about 9million, with a mortality of 1.2million and a similar number developing severe neurological consequences. [4] The incidence varies from country to country; in Cape Town, South Africa, has an incidence of 4.6 per 1000; while in Nigeria figures ranging from 26 to 84 per 1000 live births have been reported. [5-8]

The major consequence of perinatal asphyxia is hypoxic ischaemic encephalopathy (HIE). Diagnosis of HIE requires abnormal findings on neurological examination after birth. The clinical spectrum of HIE is described as mild, moderate or severe according to the Sarnat stages of HIE. Infants can progress from mild to moderate and/or severe encephalopathy over the 72 hours following the hypoxic-ischaemic insult. [9] About 20-30% of asphyxiated newborns who develop hypoxic ischaemic encephalopathy (HIE) die during the neonatal period, and one third to one half of survivors are left with cerebral palsy and mental retardation [9, 10] In perinatal asphyxia, glutamate, the main excitatory amino acid neurotransmitter, is released in increased concentrations into the extracellular compartment of the brain. Two mechanisms of glutamate induced neuronal death are identified. [11-13] First is rapid cell death initiated by glutamate receptor activation. The second is initiated principally by activation of the N-methyl D-aspartate (NMDA) receptor. Magnesium is a naturally occurring NMDA receptor antagonist which is recommended for clinical use to combat glutamate toxicity and brain damage. [14] Some literatures regarding postnatal magnesium therapy after birth asphyxia revealed beneficial effects in some while no beneficial effects in others. [15] A series of various maternal, obstetrical, and foetal risk factors causes foetal and newborn asphyxia. Therefore, the risk factors are associated with decreased blood flow and oxygenation to the tissues [16]. So perinatal asphyxia can be caused by events that have their roots in 50% of cases primarily antepartum in origin, 40% cases intra-partum and remaining 10% of cases are postpartum periods or combinations thereof [16-18]. Lack of standard referrals and inadequate and inappropriate resuscitation measures and lack of modern obstetric care, and lack of trained birth attendants; lack of basic paediatric critical care and effective paediatric advanced life support Neonatologist/paediatric residents; inadequate resuscitation efforts; paediatrician's inabilities to recognize critically ill neonates; lack of modern or advanced equipment; and lack of transport services to facilitate movement of babies from

peripheral hospitals to neonatal units will contribute to increased risks of neonatal asphyxia [18,19]. Magnesium sulphate was shown to improve neurologic outcome of severely asphyxiated newborns in a series of randomized, placebo controlled trial, which was documented in previous observational studies that advocated for more studies and multicenter trials. This low cost, low technology, readily available intervention could be the strategy for turning the tide of perinatal asphyxia and hypoxic ischemic encephalopathy in low resource settings. [20] We embarked on the intervention trial of the beneficial activity of intravenous magnesium Sulphate administration to selected severely asphyxiated neonates admitted and managed in the Special Care baby Unit (SCBU) of the University of Maiduguri Teaching Hospital, Maiduguri, North-eastern Nigeria.

PATIENTS, MATERIALS AND METHODS

Study design:

This is a Prospective, interventional study.

Study location:

The Study place is Special Care Baby Unit (SCBU), in the Department of Paediatrics University of Maiduguri Teaching Hospital (UMTH) Maiduguri, the state capital. Borno state is the largest of the six states in the north eastern zone of Nigeria. It lies on latitude 11^{o} North and longitude 15^{o} East. It occupies an area of 50,778 square kilometer. Borno state shares borders with republic of Niger to the North, Chad to the North East and Cameroun to the East.

The study population consisted of randomly selected fifty two (52) severely asphyxiated neonates who fulfilled the criteria for enrolment and were recruited as a study subjects. **Inclusion criteria:** 1. Babies with history of foetal distress, meconium stained amniotic fluid requiring resuscitation with bag-mask-valve device or endotracheal intubation during resuscitation; Neonates with severe perinatal asphyxia Apgar's score <3 at 1min or <7 at 5 min 2. Neonates whose mother did not receive anticonvulsants, 3. Neonates whose mother did not receive MgSO4. **Exclusion criteria: 1.** Neonates with APGAR score >3 at 1min and subsequently improved, **2.** Neonates with congenital malformations, **3.** Neonates whose mother had general anaesthesia. Only those who met the above criteria and the parents had consented to the research was administered magnesium Sulphate after appropriated specimens had been

collected.[21] The sample size was determined using the formula for sample calculation by Glenn with attrition rate estimated at 10%. [22] Ethical clearance was obtained from the University of Maiduguri Teaching Hospital Research and ethics committee.

DETAILED PROCEDURE

The recruited patients were reviewed, detail history, thorough examination and a diagnosis of severe perinatal asphyxia (with/without) hypoxic ischaemic encephalopathy grade I or II or III (HIE I or II or III) by one of the researcher or at least senior Paediatrics resident are entered into the proforma. Two separate venous blood sample will be taken by the researchers or at least a resident Paediatrician; Samples for investigations were taken for estimation of electrolytes and other metabolic profiles. The second blood sample of 1ml will be collected in Ethylene diamine tetracetic acid (EDTA) bottle for complete blood count and estimation of platelets value. Immediately the patient will receive three regimens of intravenous magnesium sulphate infusion at a rate of 250 mg/kg/dose (1ml/kg per dose in 20ml of 5% dextrose solution) slowly over the period of one hour and blood pressure will also be checked during this one hour. The remaining two doses repeated at intervals of 24 hours. Patients will also receive the other standard supportive care and their progress or otherwise will be closely monitored. During the three days of treatment the following vital signs were monitored; oxygen saturation with the use of pulse oximeter was determined. Patient was assessed daily based on neurological status, during the stay on admission, the grade of hypoxic ischaemic encephalopathy (HIE) moderate or severe, the presence of convulsions and the time of establishment of full oral breastfeeding by way of sucking or accepting expressed breast milk with cup and spoon, as well as full neurological examination was done at discharge. This assessment was repeated at follow up at six weeks and 3 months after discharge at the neonatology follow up clinic.

Ethical clearance was obtained from the University of Maiduguri Teaching Hospital Research and ethics committee. A consent form was signed by each parents of the enrolled patients after explaining the type of Research in detail and after agreeing with the information. The blood sample and other was carried out.

Statistical Analysis

Data generated in this study was entered onto Microsoft Excel and was analyzed using Statistical Package for Social Sciences Version 16 (SPSS software Inc. Chicago, IL, U.S.A). Tables and Charts were used to present frequencies and Prevalence rates. Associations were tested using appropriate statistical tools and $P < 0.05$ was considered statistically significant.

Results

During the study period, a total 52 severely asphyxiated neonates were consecutively recruited and administered magnesium Sulphate after meeting eligibility criteria. Of the 52 neonates, male 34 while there 18 female giving a ratio of (M: F is 1:1.8). There were 30 (57.7%) in-born and 22 (42.3%) out-born, the total asphyxia cases (moderate and severe) were 144 (30/144) giving the incidence of 20.8% among in born. Table 1 shows the characteristics of mothers of neonates studied. Majority (73.1 %) of the mothers were booked and most were booked in either PHC (18 .5%), General hospital (14.8 %) or tertiary hospital (33.3 %). About 58 % were primapara while 17 (32.7 %) and 5 (9.6 %) was multipara and grand multipara respectively. The percentage of mothers who presented with either preeclampsia or eclampsia were (48.1 %). Only 14 (26.9 %) of the mothers had antepartum haemorrhage. Majority of the mothers were either overweight (23.5 %), obese (29.4 %) or morbidly obese (14.7 %) while only 29.4 % presented with normal BMI (18 - < 25 kg/m^2).

Table 1: characteristics of mothers of preterm babies

Factors		**Frequency**	**Percent**
Booking status			
	Not booked	14	26.9
	Booked	38	73.1
Place of booking			
	PHC	10	18.5

	Private clinic	2	3.7
	General Hospital	8	14.8
	Tertiary Hospital	18	33.3
	Missing	16	29.6
Parity			
	Primipara	30	57.7
	Multipara	17	32.7
	Grand multipara	5	9.6
Preeclamsia/Eclampsia			
	Yes	25	48.1
	No	27	51.9
Antepartum Haemorrhage			
	Yes	14	26.9
	No	38	73.1
BMI status			
	< 18.0	1	2.9
	18.0 - < 25.0	10	29.4
	25.0 - < 30.0	8	23.5
	30.0 - < 35.0	10	29.4
	≥ 35.0	5	14.7

Forty seven (90.4%) were in born while the remaining (9.6%) were out born. Majority (82.7%) weighed ≥ 2500 g at birth as shown in table 2. Most (96.2%) of patient were term baby (GA ≥ 37 weeks). The percentage delivered through vaginal and non-vaginal was 55.8% and 44.2 % respectively. About one half (55.8%) of the patients commenced MgSO4 therapy at < 6 hours after birth, while 30.6% and 16.6% commenced MgSO4 therapy at 6 - < 24 hours and > 24 hours after birth respectively.

Table 2. Demographic characteristics of the asphyxiated neonates studied

Factors		**Frequency**	**Percent**
Sex			
	Male	34	65.4
	Female	18	34.6
Birth weight (grams)			
	1000 - < 2500	9	17.3
	> = 2500	43	82.7
Gestation Age [GA] (weeks)			
	< 37	5	3.8
	> = 37	47	96.2
Age at commencement of MgSO4			
	< 6hr	26	53.1
	6 - < 24hr	15	30.6
	>= 24hr	8	16.3
Place of Birth			
	In-hospital Born	47	90.4
	Out-hospital Born	5	9.6
Mode of delivery			
	Vaginal Delivery	29	55.8
	Non-Vaginal Delivery	23	44.2

Table 3: shows outcome of neonates with asphyxia treated with MgSO4. A total of 5 (9.6 %) out of 52 studied died while 47 (90.4 %) were at the end of 90 days follow-up. Among the 47 alive, 25 (53.2 %) recovered fully while 22 (46.8) recovered with neurological deficit. About one half (49.0 %) commenced enteral feeding within 5 – 7 days while 36.7 % and 14.3 % commenced enteral feeding at < days and at > 7 days respectively. Majority of the patients commenced full enteral feeding at either between 5 – 7 days or > 7days while only 36.7 % of the neonates commenced full enteral feeding before 5 days. Equally, primary outcome, fully recovered and initiation breast feeding (p=0.002, 0.001 and 0.033) were statistically significant.

Table 3: Outcome of neonate with asphyxia treated with MgSO4

Outcome indicators		**Frequency**	**Percent**	**P value**
Primary outcome				0.002
	Alive	47	90.4	
	Death	5	9.6	
Fully recovered				0.001
	Yes (without neurological deficit)	25	53.2	
	No (with neurological deficit)	22	46.8	
Trial of enteral feeding				0.033
	< 5	18	36.7	
	5 - 7	24	49.0	
	> 7	7	14.3	
Commencement of Full enteral feeding				0.133
	< 5	24	49.0	
	5 - 7	18	36.7	
	> 7	7	14.3	

Figure 3: Presents graph of APGAR scores vs. time distributed by neurological outcomes. Patients who survived with neurological deficit consistently demonstrated lower APGAR score across time when compared with patients who survived without neurological deficit. However, mean APGAR score increases with time for both groups.

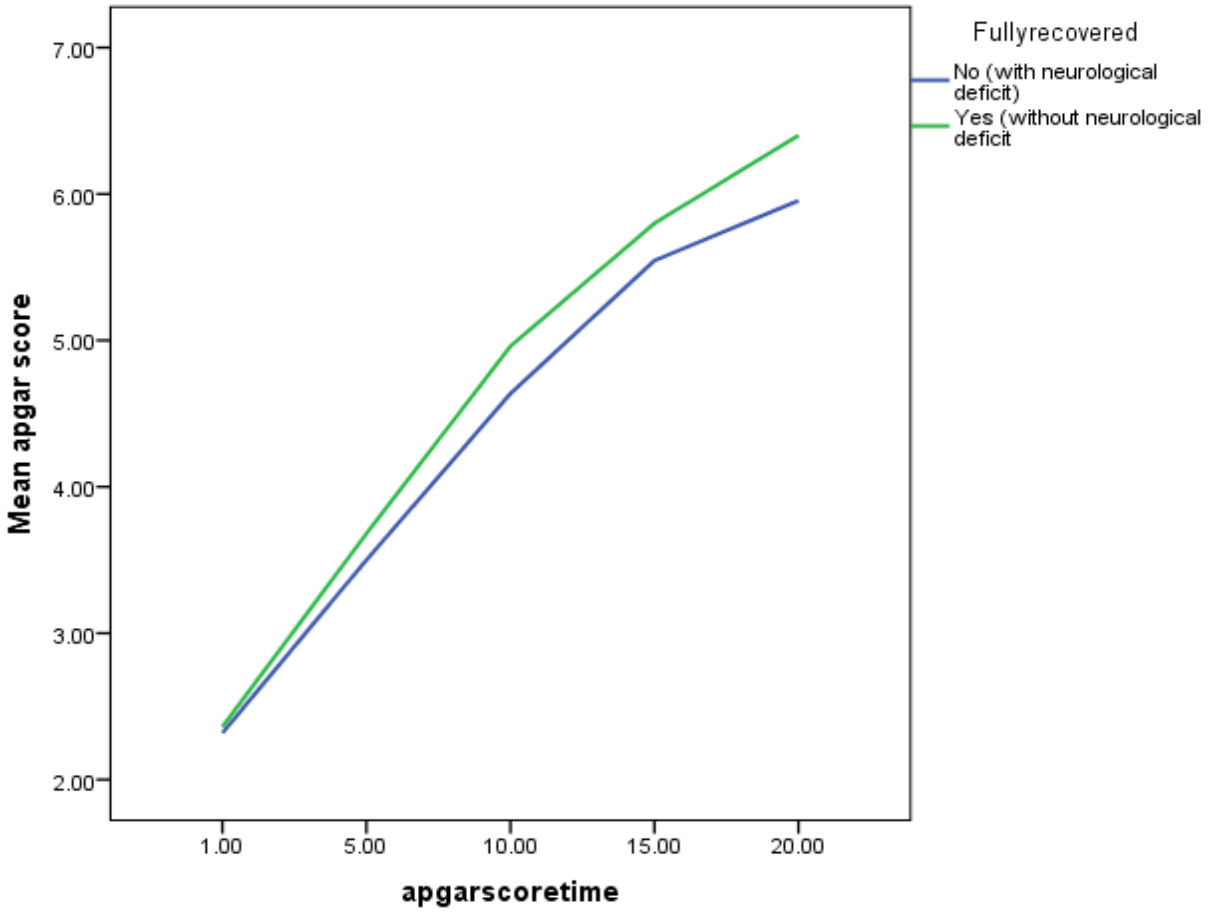

Figure 3: APGAR acore vs time distrubuted by survival outcomes

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201 Figure 1: Presented documented complications associated with neonatal asphyxia in this study. A
202 total of 14 (26.9 %), 14 (26.9 %), 9 (17.3) and 4 (7.7 %) presented with HIE, DIC, Seizure and
203 apnoea respectively.
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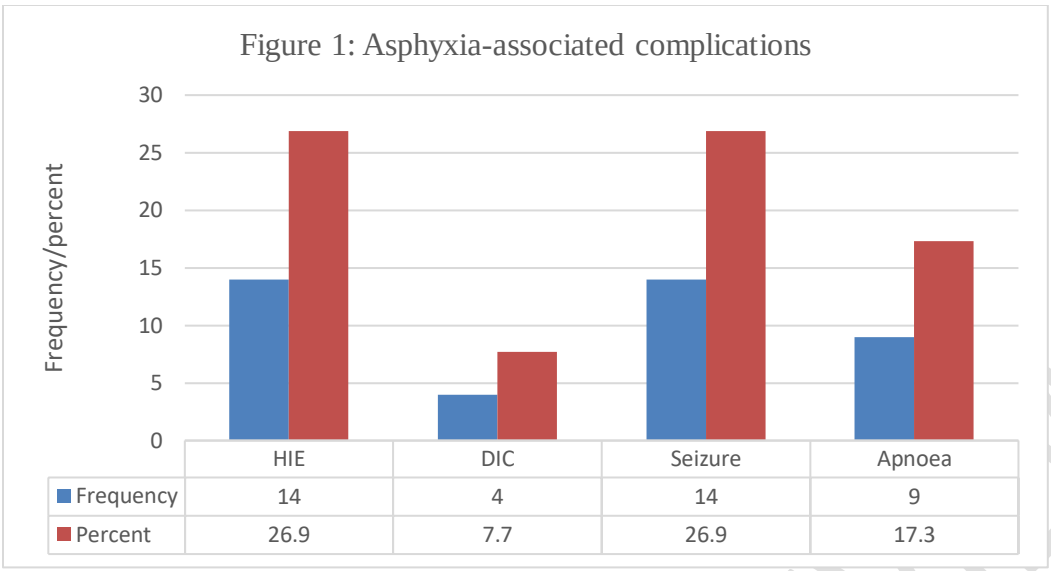

Outcome of intervention with magnesium Sulphate treatment of severely asphyxiated newborn who were admitted into the unit and followed up to 3 month after discharged. Of the fifty two patients managed, 5 (9.6%) died during the treatment period after 8th day of admission and at follow up, while 47 (90.4%) survived. Among the survivors, HIE accounted for 26.9%, DIC was observed among 7.7%, The seizure episodes accounted for 26.9% and Apnoea was responsible for 17.3%.

DISCUSSION

The incidence of severe perinatal asphyxia among in born in this study is 20.8 % which was lower compared to (24.3%) reported by West and colleagues [23], Okechukwu et al [24] and from Abuja, however it similar to the report by Ilah et al [25] from Gusau North-western Nigeria. The management of severe perinatal asphyxia in Nigeria generally is symptomatic despite advances achieved in care asphyxiated neonates in the advanced society and this because prohibitive high cost such technologies [15, 20]. This has left most neonates in this part of the world with high mortality rate and the few survivors remain with unacceptable complications like cerebral palsies, mental retardation among others. [20]

Magnesium Sulphate, a potent tocolytic and anti-convulsants drug used extensively among women in labour complicated by eclampsia with effective neuro-protection activity after the

eclampsia storm, and many reports show evidence of neuroprotection among their babies evidenced by fewer needs of admission to Neonatal Intensive Care Units (NICU). [26] In this same vein, many clinical placebo-trial studies put forward its efficacy in ameliorating severe perinatal asphyxia and neuroprotective activity among those with hypoxic ischaemic encephalopathy (HIE) following perinatal asphyxia and has proven to prevent even the long term complications. [10,27,28]

In this study we administered three doses of magnesium Sulphate infusion at 250 mg /kg /dose in 5% dextrose infusion and first dose within 6 hours after birth but preferably at birth of severely asphyxiated neonates, the subsequent 2 doses were administered at 24 hours interval. Patients that presented after 24 hours was also included and given the same regimen of magnesium Sulphate. The finding in this study was plausible as we had discharge among 47 (survival, (90.4%), mortality 5, (9.6%), (p=00.02), also patients who achieved full recovery (without neurological deficit) were 25 (53.2%), while 22 (46.8%) (p= 0.001), recovered some various degree of neurodeficit, it was statistically significant.

Test feed (initiation of breast milk feed using expressed breast milk); among those commenced <5 day of onset asphyxia, 7 (14.9%) tolerated, 5-7 days 18 (38.3%), > 7 days 24(51.1%) and full enteral feeding (accepting direct or cup and spoon breastfeeding), <5 days 18(36.7%), 5-7 days 29 (59.2%) and > 7days 2(4.1%), p= 0.033 and was significant. The finding in this was consistent with the work by Bhat and colleagues [29] from India, who in their study administering 3 doses regimen of intravenous infusion of magnesium Sulphate 24 hours apart starting within 6 hour of birth asphyxiated newborn revealed significant neuroprotection among these patients with HIE injuries. Also in this study, we did not found any adverse events as result of administration of magnesium Sulphate as respiratory rate, heart rate, blood pressure oxygen saturation by handheld pulse oximeter monitoring remained constantly within normal range both during intravenous infusion and immediately after administration, this concur with report by some workers. [1,28,30] Magnesium Sulphate was neuroprotective on asphyxiated with HIE as evidenced by the finding in this study, of the 52 severely asphyxiated neonates studied there were 5 death (9.6%) and the 47 (90.4%), this was significantly lower than most mortality reported by others. [1,29, 30]

The diagnosis of perinatal asphyxia this study was principally on low Apgar score (<3 and <5 at 1 and 5 minutes respectively). We know that other parameters like umbilical cord PH, and base deficit in addition to clinical parameters is standard, however we had limitation in determining them which would have been helpful quantifying the severity of the asphyxia. Also neuroimaging studies like diffusion weighted imaging and amplitude integrated electroencephalogram were also not done, however we so all the discharged neonates in the follow up neonatal clinic at 3 months were found to be neurological stable with no neurodevelopmental sequel even among those that had mild difficulty sucking at immediate discharge period.

CONCLUSION

In this study, magnesium Sulphate has shown a promising benefit on ameliorating neuronal damage due to severe perinatal asphyxia. However there is dire need to replicate this study at the national level as multicenter study where large pull of patients can be studied in order to have large results that can infer on the general application in the care of patients with hypoxic ischaemic encephalopathy due severe perinatal asphyxia.

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