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Magnesium Sulphate Treated Severely Asphyxiated Neonates, Their Characteristic and Outcome

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Authors' contributions

This work was carried out in collaboration between all the authors. Authors SP, MB and JPA designed the study, wrote the protocol and along with authors YM performed the statistical analyses and wrote the first draft. Authors SP, MB, RG, AYC and MIK managed the statistical analysis. Authors SP and MB managed the literature searches. All the authors read and approved the final manuscript.

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ABSTRACT

Introduction: 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 hypoxic ischaemic encephalopathy (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 ($MgSO_4$) after perinatal asphyxia has shown effective resolution of neuronal injury. We have conducted this study to validate the effect of $MgSO_4$ in severely asphyxiated neonates, so as to utilize its benefits on ameliorating the outcome associated with severe perinatal asphyxia/HIE.
Objective of the Study: To determine the characteristics and outcome of magnesium sulphate on neurological outcome in severe perinatal asphyxia
Materials and Methods: A prospective interventional study of magnesium sulphate treatment of neonates with severe perinatal asphyxia conducted over one year period from 1st August 2017 to 31st July 2018.

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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 $MgSO_4$ therapy at < 6 hours after birth, while 30.6% and 16.6% commenced $MgSO_4$ 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 4 < days and at > 7 days respectively. Majority of the patients commenced full enteral feeding at either between 5 – 7 days or > 7 days while only 36.7% of the neonates commenced full enteral feeding before 5 days. Equally, primary outcome, fully recovered and initiation breast feeding.

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. Also greater 50% of the survivors commenced breast feeding within five days of admission and were clinical normal at follow up clinic. Whether this coincidental or a true effect of $MgSo_4$, a future prospective randomized controlled trial may make the picture clearer

Keywords: Perinatal asphyxia; HIE; magnesium sulphate; neuroprotection; outcome.

1. 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 literature 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 may 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 prospective intervention to observe the effect treatment with intravenous magnesium Sulphate to selected neonates with severe asphyxia admitted to Special Care baby Unit (SCBU) of the University of Maiduguri Teaching Hospital, Maiduguri, North-eastern Nigeria.

2. PATIENTS, MATERIALS AND METHODS

2.1 Study Design

This is a Prospective, interventional study.

2.2 Study Location

The Study place is Special Care Baby Unit (SCBU), in the Department of Paediatrics University of Maiduguri Teaching Hospital (UMTH) Maiduguri, a tertiary health in the north-eastern Nigeria. 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 $MgSO_4$.

Exclusion criteria: 1. Neonates with APGAR score >3 at 1 min 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 were 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.

2.3 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 registrar entered into the proforma. Two separate venous blood sample was 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 was collected in Ethylene diamine tetracetic acid (EDTA) bottle for complete blood count and estimation of platelets value. Immediately the patient were administered three doses of intravenous magnesium sulphate infusion at a rate of 250 mg/kg/dose (1 ml/kg per dose in 20 ml of 5% dextrose solution) slowly over the period of one hour. The remaining two doses were given at intervals of 24 hours. Patients were administered other supportive care and their progress or otherwise were closely monitored. During the three days of treatment, oxygen saturation with the use of pulse oximeter was determined. Patient was assessed daily based on neurological status at 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.

2.4 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. Where applicable, associations were tested using chi square and $P < 0.05$ was considered statistically significant.

3. 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 (neonates born within the study center labour ward and admitted into neonatal unit) and 22 (42.3%) out-born (neonates delivered outside and referred to neonatal unit), 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).

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 had $MgSO_4$ administered at < 6 hours after birth, while 30.6% and 16.6% commenced $MgSO_4$ therapy at 6 - < 24 hours and > 24 hours after birth respectively.

Table 3 shows outcome of neonates with asphyxia treated with $MgSO_4$. A total of 5 (9.6%) out of 52 studied died while 47 (90.4%) were seen at 90 days in 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 4 < days and at > 7 days respectively. Equally, primary outcome, fully recovered and initiation breast feeding (p=0.002, 0.001 and 0.033) were statistically significant.

Table 1. Characteristics of mothers of asphyxiated 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

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 $MgSO_4$		
< 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. Outcome of neonate with asphyxia treated with $MgSO_4$

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

Fig. 2 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.

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

Outcome of intervention with magnesium Sulphate treatment of severely asphyxiated newborn who were admitted into the unit and followed up to 3 month after discharge. 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 was observed among 26.9%, DIC was observed among 7.7%, The seizure episodes among 26.9% and Apnoea was recorded in 17.3% of patients.

4. 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], 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 complication [10,27,28].

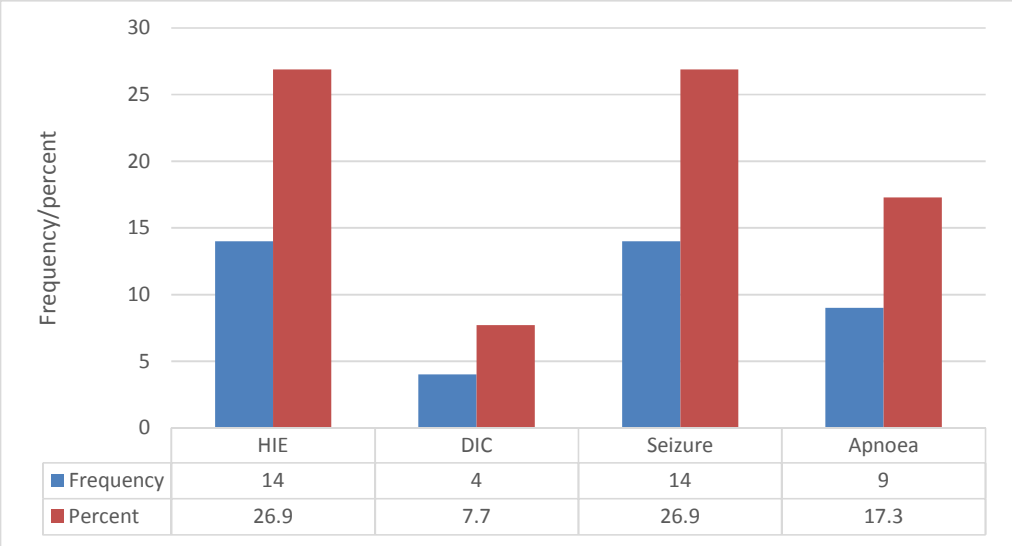

Fig. 1. Asphyxia-associated complications

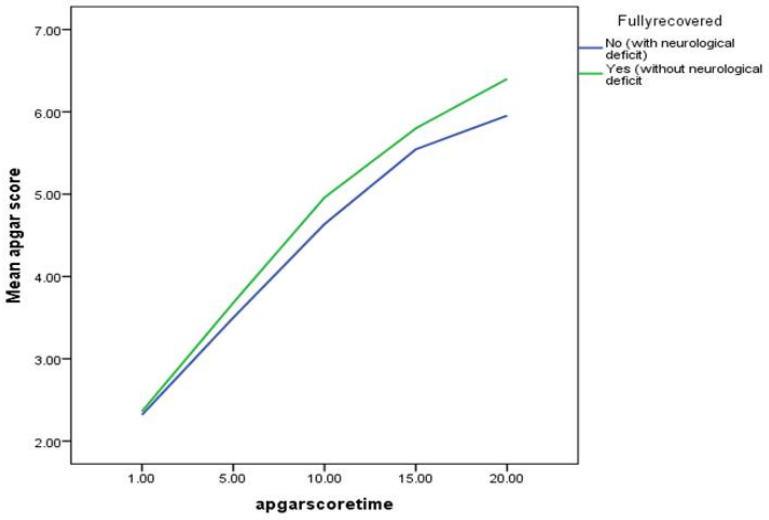

Fig. 2. APGAR acore vs time distributed by survival outcomes

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 find 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 12.9.0%, 10.0%, 14.7.0% respectively [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 electroence-phalogram 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.

5. 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. Also greater 50% of the survivors commenced breast feeding within five days of admission. 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%. Whether this coincidental or a true effect of $MgSo_4$, we suggest a future prospective randomized placebo controlled trial may make the picture clearer.

6. LIMITATIONS

The limitations of the study include; the study not being a placebo-controlled study and duration of the follow up lasted only for 3 months. It would have been more robust if the study was extended to 18-24 months in addition to being controlled study. If given the opportunity we can continue with the study with these limitations taken into account. Otherwise we strongly recommend future placebo-controlled study for at least 24 months and we have the capacity do conduct the study if we have the sponsorship.

CONSENT AND ETHICAL APPROVAL

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.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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