

Pilot Study: Magnesium Sulphate Administration and Early Resolution of Hypoxic Ischemic Encephalopathy in Severe Perinatal Asphyxia

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Abstract

Introduction: Perinatal asphyxia is one of the leading causes of perinatal death and a recognized cause of neuromotor disability among survivors. About 20% - 30% of asphyxiated newborns who develop hypoxic ischemic encephalopathy (HIE) die during the neonatal period, and one third to one half of survivors are left with cerebral palsy and mental retardation. **Objective of the Study:** Was to determine the effect of magnesium sulphate as neuroprotective drug in hypoxic ischemic encephalopathy resulting from severe perinatal asphyxia. **Materials and Methods:** A prospective administration of magnesium sulphate to 52 severely asphyxiated newborns with hypoxic ischemic encephalopathy was conducted over one year period from 1st August 2017 to 31st July 2018. **Results:** Most (96.2%) of patients were term baby (GA ≥ 37 weeks). Most (90.4%) were in-hospital born, vaginal delivery accounted for 55.8% and 44.2% assisted delivery 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. Time of commencement of first enteral feeding (p = 0.018) and time to full enteral feeding (p = 0.015) showed significant correlation with the survival without neurological deficit. The earlier the commencement of MgSO₄ therapy, the better the proportion with strong palmar grasp, sucking reflex, tone and early resolution of encephalo-

pathy. **Conclusion:** All the study subjects treated with magnesium sulphate had impressive improvement; however there is a need to conduct randomized placebo-controlled trial treatment of severe perinatal asphyxia so as to determine its effects on early resolution of hypoxic ischemic encephalopathy/neuroprotective activity.

Keywords

Severe Perinatal Asphyxia, HIE, Magnesium Sulphate, Neuroprotection, Early Breastfeeding

1. Introduction

Perinatal asphyxia is a condition where hypoxaemia and acidosis are present in the foetus or the newborn infants. It is a failure newborn to initiate spontaneous, sustained, and vigorous respiration effort at birth. It is also defined as a failure to initiate spontaneous respirations and/or a 5-minute Apgar score of less than 7: the most commonly used indicator in the identification of birth asphyxia in resource limited settings [1]. Perinatal asphyxia is one of the leading causes of perinatal death and a recognized cause of neuromotor disability among survivors [2]. About 20% - 30% of asphyxiated newborns who develop hypoxic ischemic encephalopathy (HIE) die during the neonatal period, and one third to one half of survivors are left with cerebral palsy and mental retardation [3] [4]. Survivors present with several short and long term morbidities, including: seizure disorders, tone abnormalities, feeding difficulties, delayed developmental milestones, learning difficulties, cerebral palsy and mental retardation. The morbidities increase with asphyxia severity. The frequency of severe perinatal asphyxia complications, hypoxic ischemic encephalopathy (HIE) and incidence of up to 26.5/1000 live births is unacceptably high despite advances in perinatal care [5] [6]. Encephalopathy occurs in 50% to 60% of patients with severe perinatal asphyxia. Among patients with moderate HIE, 10% to 20% die, and 30% to 40% develop neurodevelopmental disorders, whereas 50% of patients with severe HIE die and almost all survivors develop neurodevelopmental deficits [7] [8] [9].

According to Onyearugha *et al.* [10], findings in some studies in Nigeria reported a prevalence of severe perinatal asphyxia between 46 - 63/1000 live births, and this is unacceptably high. The prevalence of severe birth asphyxia in any community is to a large extent dependent on prevailing risk factors, these in turn being influenced by the extent and impact of health education, literacy level, women empowerment, cultural and traditional beliefs affecting efficient utilization of health care services as well as the quality of antenatal, obstetric and neonatal care. Other factors including poverty, ignorance, poor communication network, harmful traditional and cultural practices with significant negative effect on utilization of appropriate health care services by women in pregnancy and labour are particularly rife in the developing countries like Nigeria

[9] [10].

Neuro-science research has revealed our understanding of the mechanisms by perinatal asphyxia neuronal damage and adverse consequences. Asphyxia leads to two types of cerebral injuries: the primary neuronal injury that occurs at the time of hypoxic-ischemic insults and the secondary cerebral injury that occurs over hours to days after accumulation of excessive intra-neuronal calcium through stimulation of the excitatory N-methyl-D-aspartate (NMDA) glutamate receptors, which triggers apoptosis of the affected neurons [2].

Magnesium is a naturally occurring NMDA receptor antagonist that blocks neuronal influx of calcium within the ion channels. This block is voltage-dependent and is overcome during axonal depolarization that occurs in hypoxic-ischemic insults. If the extra-cellular magnesium concentration is increased, this blockade can be restored. Finding from earlier studies regarding the effects of magnesium sulphate after stimulated hypoxic-ischemic insults in several animal models revealed neuro-protective effects after administration of intravenous magnesium sulphate at a dose of 250 mg/kg daily at 24 hours interval within the first three days of delivery preferably of severely asphyxiated newborn [11] [12]. Magnesium sulphate may also have direct actions on mitochondrial activity, anticonvulsant properties and haemodynamic effects by increasing cerebral blood flow. Some data also suggest that MgSO₄ may serve an anti-apoptotic role and prevent neuronal cell loss [13] [14] [15]. Magnesium sulphate has wider use in critical care especially by Obstetrician in labour as tocolytic agents and for the suppression of pregnancy induced hypertension and has shown to be beneficial in neonates of treated mothers [7]. However, there is scanty work regarding the role of magnesium sulphate in severely asphyxiated newborn and even the few trials done are not widely circulated thus limiting knowledge and experience on its potential neuroprotective effects. We conducted this interventional trial to assess the potential neuroprotective effect of magnesium sulphate in treating severely asphyxiated newborns and improvement of the neurological outcome.

2. Justification/Problem Statements

Perinatal asphyxia especially the severe form is a common problem and contributes significantly to neonatal morbidity and mortality. Encephalopathy occurs in 50% to 60% of patients with severe perinatal asphyxia. Patients with moderate HIE 10% to 20% die and 30% to 40% develop neurodeficits, whereas 50% of patients with severe HIE die and almost all survivors develop neurodeficits. Magnesium sulphate administration to severely asphyxiated neonate prevent the complication associated with hypoxic-ischemic encephalopathy, so there is need to carry this study so as to encourage its wide application in affected neonates.

3. Objectives of the Study

1) General aim: To determine the benefit of magnesium sulphate on perinatal

asphyxia in neonates presenting UMTH Maiduguri North-Eastern Nigeria.

2) Specific objective:

a) Determine the effect of magnesium sulphate on neurological outcome in severe perinatal Asphyxia.

b) Determine the effect of magnesium sulphate on commencement of oral feed.

c) Determine the effect of magnesium sulphate on reduction of duration of Admission/hospitalization.

4. Methodology

4.1. Study Design

This was a prospective, interventional study.

4.2. 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° North and longitude 15° 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.

4.3. Inclusion Criteria

- 1) Neonates with severe perinatal asphyxia APGAR score < 3 at 1 min,
- 2) Neonates whose mother did not receive anticonvulsants,
- 3) Neonates whose mother did not receive MgSO₄.

4.4. Exclusion Criteria

- 1) Neonates with Apgar's score > 3 at 1 min,
- 2) Neonates with congenital malformations,
- 3) Neonates whose mother had general anaesthesia.

4.5. Sample Size

Fifty two (52) was recruited after fulfilling the inclusion criteria.

The sample size was determined using the formula for sample calculation by Glenn with attrition rate estimated at 10% [16].

4.6. Ethical Clearance

Ethical clearance was obtained from the University of Maiduguri Teaching Hospital Research and Ethics Committee.

4.7. Consent Form

A form explaining the type of Research, type of sample that was collected and

treatment given was presented to the parent in detail and to they agreed with the information and granted consent to be included in the study, blood sample was collected from the neonate for the appropriate analysis.

4.8. Detailed Procedure

The recruited patients were reviewed, detail history, thorough examination and a diagnosis of severe perinatal asphyxia (with/without) hypoxic ischemic encephalopathy grade I or II (HIE I or II) by one of the researcher or at least senior Paediatrics resident who entered into the proforma. Two separate venous blood sample was taken by the researchers or at least a resident Paediatrician; 1) The first sample of 4 mls was taken in plain bottle for estimation of electrolytes, serum Magnesium, Calcium, lactate dehydrogenase, creatine kinase levels and liver function tests including albumin, aspartate aminotransferases, and alanine aminotransferases. 2) The second blood sample of 1 ml was collected in Ethylene diaminetetracetic acid (EDTA) bottle to estimate the platelets amounts. Immediately after sample collection, the patient received three regimens of intravenous magnesium sulphate infusion at a dose of 250 mg/kg/dose (1 ml/kg per dose in 20 ml of 5% dextrose solution) slowly over the period of one hour and blood pressure was checked during this one hour. The remaining two doses repeated at intervals of 24 hours. Patients also received the other standard supportive care and their progress or otherwise was closely monitored. After the last dose of the treatment, serum electrolytes, magnesium, calcium, lactate dehydrogenase, creatine kinase levels and liver function tests including albumin, aspartate aminotransferases, alanine aminotransferases and platelet counts was done.

During these three days of treatment the following vital sings were documented; heart rate, respiratory rate, oxygen saturation with the use of pulse oximeter will be monitored administration of magnesium sulphate. Patient was assessed daily based on neurological status, the grade of hypoxic ischemic 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 by the same researcher at discharge. This assessment was repeated at follow up at two weeks, six weeks and 3 months after discharge. All these parameters were carefully enter into the proforma with the initial clinical finding documented.

4.9. Statistical Analysis

Data generated in this study was entered onto Microsoft Excel and was analyzed using Statistical Package for Social Sciences Version 20 (SPSS software Inc. Chicago, IL, USA). Tables and Charts were used to present frequencies and Prevalence rates. Associations were tested using appropriate statistical tools and P-value of less than 0.05 ($P \leq 0.05$) was considered statistically sig-

nificant.

5. Results

During the period of the study (1st August 2017 to 31st July 2018), a total of 52 patients were randomly recruited, comprising of 34 (65.4%) male and 18 (34.6%) females, with majority (82.7%) weighing ≥ 2500 g at birth. Most (96.2%) of patients were term baby (GA ≥ 37 weeks). Most (90.4%) were in-hospital born, vaginal delivery accounted for 55.8% and 44.2% assisted delivery 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. 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 primiparous, while 17 (32.7%) and 5 (9.6%) were multipara and grand multipara respectively. The percentage of mothers who did not have prenatal MgSO₄ and those who had prenatal MgSO₄ was approximately 88.5% and 11.5% respectively while 25 (48.1%) of the mothers presented with either preeclampsia or eclampsia. Only 14 (26.9%) of the mothers had antepartum haemorrhage.

Table 1 indicates an unadjusted analysis of factors predicting survival outcome of neonatal asphyxia treated with MgSO₄. It largely assessed features like Sex, birth weight, time of first MgSO₄ dose, gestation age, place of delivery, mode of delivery, anticonvulsant administration, and antibiotic-use showed no significant association with survival without neurological deficit. However, time to commencement of first enteral feeding ($p = 0.018$) and time to full enteral feeding ($p = 0.015$) showed significant correlation with the survival without neurological deficit (**Table 1**). When compared with patients who commenced enteral feeding after 7 days, patients who commenced enteral feeding before 5 days and patients who commenced enteral feeding between 5 - 7 days were about 2.6 and 5 folds more likely to survive without neurological deficit.

Table 2 shows crude analysis of maternal factors that could have an influence on neonatal outcome following administration of magnesium Sulphate; however none of the maternal factors demonstrated significant correlation with survival outcomes.

Table 3 presents adjusted analysis of factors with p value, 0.05 in the crude analysis. On adjusted analysis none of the factors showed significant correlation as independent predictors of survival outcome in asphyxia treated with MgSO₄.

Table 4 shows the survival outcome of asphyxiated neonate treated with MgSO₄ compared across various grades of HIE. There is no significant association between each grade of HIE and survival outcome.

Figure 1 presents percentage with strong suckling reflex distributed after the last dose of MgSO₄ dose. The earlier the commencement of MgSO₄ therapy the better the percentage with strong suckling reflex at 5 days.

Figure 2 presents percentage with strong Palma grasp distributed by the time

Table 1. Neonatal factors predicting survival outcome of MgSO₄-treated perinatal asphyxia.

Factors	Total	F (%) Alive without Neurological deficit	COR (95 CI)	p value
Sex				
Male	31	16 (51.6)	Reference	
Female	16	9 (56.2)	1.205 (0.358 - 4.055)	0.763
Birth weight				
1000 - <2500	8	5 (62.5)	1.583 (0.332 - 7.558)	0.564
≥2500	39	20 (51.3)	Reference	
Time of First MgSO₄ dose				
<6 Hours	23	12 (52.2)	1.818 (0.350 - 9.455)	0.477
6 - <24 Hours	13	9 (69.2)	3.750 (0.587 - 23.936)	0.162
≥24 Hours	8	3 (37.5)	Reference	
Gestation Age (weeks)				
<37	4	2 (50.0)	Reference	
≥37	43	23 (53.5)	1.150 (0.148 - 8.929)	0.896
Place of delivery				
In-hospital born	42	22 (52.4)	Reference	
Out-hospital born	5	3 (60.0)	1.364 (0.206 - 9.016)	0.748
Mode of delivery				
Vaginal delivery	26	12 (46.2)	Reference	
Non-vaginal delivery	21	13 (61.9)	1.896 (0.588 - 6.112)	0.284
Time of first enteral feeding				
<5	16	13 (81.2)	26.000 (2.219 - 304.702)	0.009
5 - 7	24	11 (45.8)	5.077 (0.528 - 48.855)	0.160
>7	7	1 (14.3)	Reference	
Time of commencement of full enteral feeding				
<7	13	11 (84.6)	7.857 (1.503 - 41.085)	0.015
≥7	34	14 (41.2)	Reference	
Anticonvulsant administered				
Yes	15	6 (40.0)	Reference	
No	32	19 (59.4)	2.192 (0.628 - 7.659)	0.219
Antibiotic administered				
Yes	41	23 (56.1)	1.917 (0.289 - 12.719)	0.500
No	5	2 (40.0)	Reference	

of first MgSO₄ dose. The earlier the commencement of MgSO₄ therapy the better the percentage with strong palmar grasp reflex at 5 days.

Table 2. Maternal factors predicting survival outcome of h MgSO₄-treated neonatal asphyxia.

Factors	Total	F (%) Alive without Neurological deficit	COR (95 CI)	p value
Booking status				
Not booked	11	5 (45.5)	Reference	
Booked	36	20 (55.6)	1.500 (0.386 - 5.825)	0.558
Parity				
Primiparous	27	14 (51.9)	1.615 (0.232 - 11.263)	0.628
Multipara	15	9 (60.0)	2.250 (0.285 - 17.759)	0.442
Grandmultipara	5	2 (40.0)	Reference	
Prenatal MgSO₄				
Yes	5	3 (60.0)	1.364 (0.206 - 9.016)	0.748
No	42	22 (52.4)	Reference	
Preeclampsia/Eclampsia				
Yes	23	14 (60.9)	1.838 (0.576 - 5.865)	0.304
No	24	11 (45.8)	Reference	
Antepartum Haemorrhage				
Yes	11	5 (45.5)	Reference	
No	36	20 (55.6)	1.500 (0.386 - 5.825)	0.558

Table 3. Adjusted analysis of factors predicting survival outcome of h MgSO₄-treated neonatal asphyxia.

Factors	Total	F (%) Alive without Neurological deficit	AOR (95 CI)	p value
Time of first enteral feeding				
<5	16	13 (81.2)	12.491 (0.722 - 216.075)	0.083
5 - 7	24	11 (45.8)	4.864 (0.504 - 46.947)	0.171
>7	7	1 (14.3)	Reference	
Time of commencement of full enteral feeding				
<7	13	11 (84.6)	2.906 (0.302 - 27.955)	0.356
≥7	34	14 (41.2)	Reference	

Figure 3 shows a resolution of encephalopathy and normalization of muscle tone after administration of three doses of magnesium Sulphate.

Figure 4 shows general posture normalization as results of administration of 3 doses of intravenous magnesium Sulphate the severely asphyxiated with hypoxic-ischemic encephalopathy.

We also observed resolution of encephalopathy, normalization of muscle tone and posture. At 3 month in the follow up clinic, greater 50% were normal without neurodeficits.

Table 4. Primary outcome of asphyxiated neonates with HIE treated with MgSO₄.

HIE	Total	F (%) Alive	p value
Grade 1			
Yes	3	3 (100.0)	0.561
No	49	44 (89.8)	
Grade 2			
Yes	36	32 (88.9)	0.583
No	16	15 (93.8)	
Grade 3			
Yes	14	13 (92.9)	0.714
No	38	34 (89.5)	

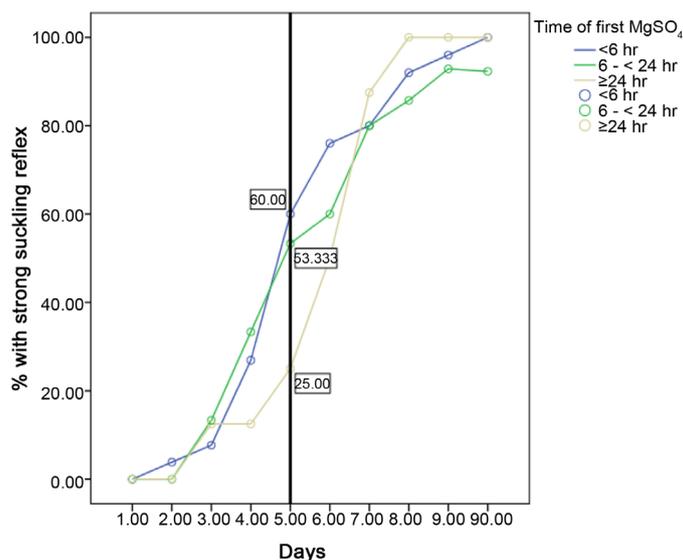


Figure 1. Restoration of sucking reflex after last dose of MgSO₄.

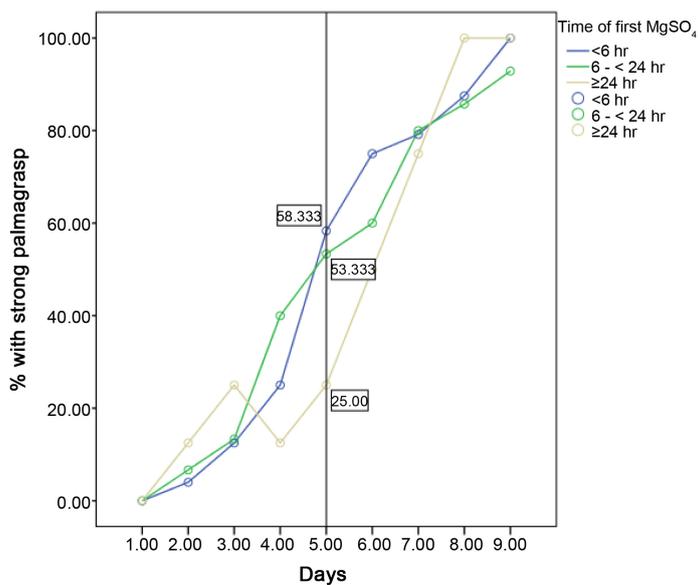


Figure 2. Restoration of palmgrasp after the last dose of MgSO₄.

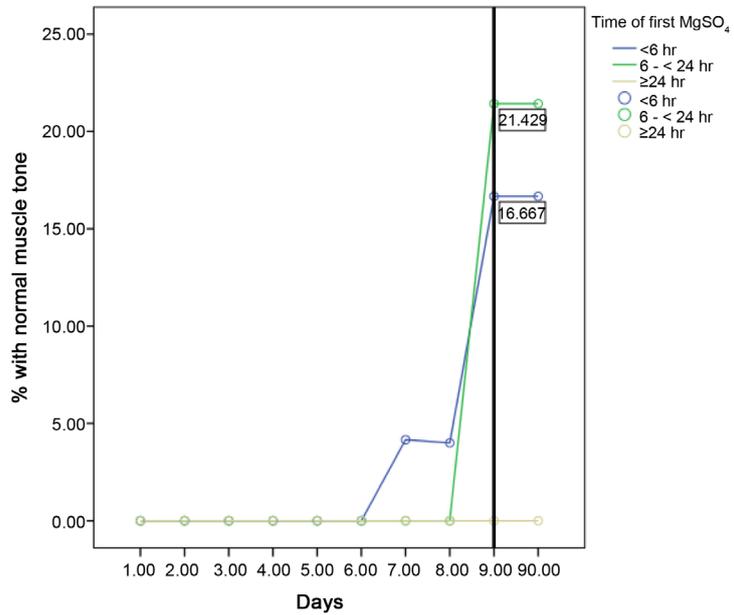


Figure 3. Restoration and normalization of muscle tone as consequence of MgSO₄.

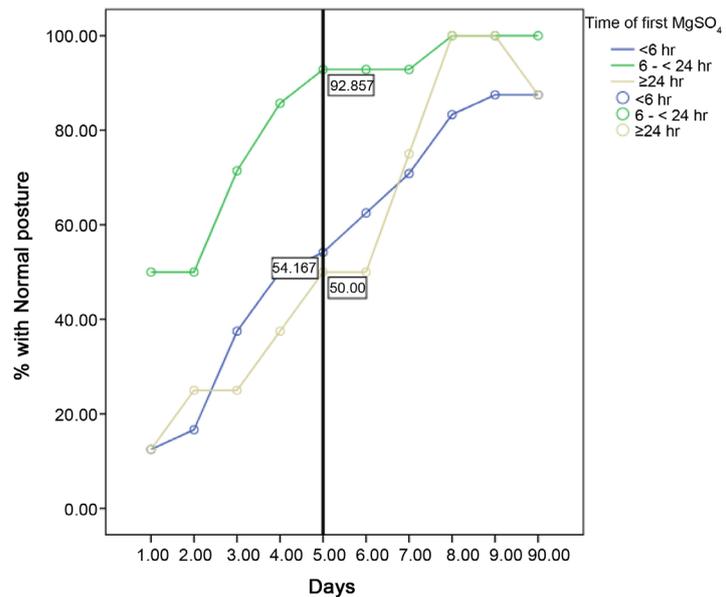


Figure 4. Patients that were treated with MgSO₄ and normal tone.

6. Discussion

Following severe perinatal asphyxia, hypoxic-ischemic injury of neonatal brain ensues and which said to occur in two phases. The primary phase respond to active resuscitative measures when carried promptly while the secondary phase lingers several hours to days and cause severe irreversible neuronal damages to the developing brain [7]. Glutamate acts on the N-methyle-D-aspartate (NMDA) receptor, a post-synaptic ion channel in the brain, and during asphyxia process, there excessive release and reduced uptake of glutamate in the newborn

brain [17]. High concentrations of glutamate open channels, allowing excessive calcium influx into the neurons and induce irreversible neuronal. Magnesium Sulphate is a naturally occurring NMDA receptor antagonist that blocks neuronal influx of calcium within the ion channels. It has been found in several researches that when the extracellular concentration of magnesium is increased, then this block is restored thereby halting further brain damages [18].

In this study, we administered to 52 severely asphyxiated neonates that were recruited consecutively after meeting the selection criteria magnesium Sulphate at 250 mg/kg/dose daily for the first 72 hours and monitored patients responses to the effects of the drug on the neurological resolution by way of restoration primitive reflexes and regain of consciousness. Approximately half (48%) of the mothers of asphyxiated babies had intrapartum pre/eclampsia, 26.9% had antepartum haemorrhages while more than 50% of the asphyxiated babies were born to obese mother. It was observed that magnesium Sulphate had neuroprotective effects on the study subjects of patients this was evidenced by early restoration of sucking reflexes. In this study majority of the subjects commenced initial feeding with nasogastric tubes (test feed), while full enteral feed by cup and spoon or direct breast feeding were commenced in less than 7 days in most of the patients, these were independent factors that also predicted the survival without neurodeficit as at the time of discharge from the hospital and follow up clinic at 6 weeks. This findings was similar to the reports by Bhat *et al.*, [7] and Ichiba *et al.* [19].

In this study we evaluated and monitored parameters in addition early breast-feeding by way of early resumption of sucking reflex includes; normalization of palmar grasp, muscles and resolution of hypoxic ischemic encephalopathy, which was observed in more than 50% of the patients and was associated survival without neurologic abnormalities as at discharge and at 6 weeks follow in the clinic [20]. Just like in this study, magnesium Sulphate use in human neonates are few and many of the stated neuroprotective role of magnesium Sulphate has been largely done in animal models, with many evidence of favourable results in terms of amelioration of secondary neuronal injury [7] [21]. Unlike study by Bhat and colleagues [7], this index study was randomized non-controlled interventional study, which included all asphyxiated neonates, however, during the study we did not encountered any adverse effects in the neonates; there was no bradycardia, no hypotension and even the few that had apnoea we attributed to severity of the hypoxic-ischemic brain damage before the interventions were instituted. Other workers have also reported similar findings where they found a rapid and good neurological improvement among moderately to severely asphyxiated neonates treated with 3 days daily doses of magnesium Sulphate infusion at 250 mg/kg [22]. Even though is an interventional trial, it shown a good effect on rapid resolution of hypoxia-ischaemia encephalopathy among magnesium Sulphate treated neonates HIE stage I-III.

7. Conclusion

We believe from our interventional trial, magnesium Sulphate has neuroprotect-

tive effect on severely asphyxiated neonates. If the treatment is administered early after the onset of asphyxia, it surely will halt and probably reverse the secondary neuronal damage due to hypoxic ischemic injury following severe perinatal asphyxia.

8. Limitation

This study was non-controlled randomized magnesium Sulphate interventional trial; it will have been better if it were placebo-controlled trial but were unable to do that for ethical reasons. Also we stopped follow up at 3 months, preferably if the patients were followed up to 18 - 24 months post-magnesium study, so that the first two years of the subject growth and development would have more defined with respect to neuromotor deficits as consequences of severe perinatal asphyxia complication. Therefore we suggest further placebo-controlled trial be undertaken to make it robust and more detailed.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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