Original Article

THERAPEUTIC EFFICACY OF MAGNESIUM SULPHATE ON NEUROLOGICAL OUTCOME OF NEONATES WITH SEVERE BIRTH ASPHYXIA

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ABSTRACT:

BACKGROUND: In neonates, birth asphyxia is a serious condition. It results in high risk of morbidity and mortality. It is also associated with permanent neuro developmental deficits among survivors.
OBJECTIVES: The main objective of the study is comparing the efficacy of intravenous magnesium sulphate (MgSO4) with placebo in neonates with severe birth asphyxia in terms of neurological outcome.
METHOD: A total of 66 subjects were recruited in Pediatrics Medicine Unit-II, DHQ Hospital, Faisalabad from April 2011 to December 2011. Neonates divided into two groups A & B (33 patients in each group) with history of birth asphyxia. Neonates of group-A were given MgSO4 through I.V route(3 doses 250 mg/kg/dose, 24 hours interval) and group B received normal saline(3 doses 1 ml/kg/dose 24 hours interval). During stay in NICU all Neonates were regularly neurologically assessed.
RESULTS: Mean age (hour) was observed 2.82±1.35 and 3.24±1.60 in both A and B groups respectively. Total of 18(54.5%) subjects in group A and 19(57.6%) subjects in group B had 37-38 weeks while, 15(45.5%) and 14(42.4%) subjects had 39-40 weeks of gestational age respectively. At discharge time, neurological findings (neonatal reflexes) were improved in 25(75.8%) subjects in A group and 15(45.4%)subjects in B group. Statistically significant P value was found to be 0.002 for oral feed (sucking). Normal CT brain was seen in 28(84.9%) subjects in group A and 17(51.5%) subjects in group B.
CONCLUSION: Neurological outcome at discharge were improved with the treatment of postnatal I/V magnesium sulfate in neonates with severe birth Asphyxia when given early after birth having severe perinatal asphyxia.
KEY WORDS: Birth asphyxia, MgSO4, neurological outcome, Hypoxic ischemic encephalopathy.

INTRODUCTION:

Birth asphyxia or (perinatal asphyxia) is a major cause of neonatal mortality and morbidity. In this condition oxygen saturation become deficient before, during or just after birth[1]. Asphyxia remains a serious condition and cause significant mortality and long-term morbidity despite major advances in monitoring technology, obstetric care and fetal knowledge of neonatal emergencies[2,3].
Annually, seven million perinatal deaths were estimated mostly in developing countries[4]. It was reported by WHO that between 4 - 9 million new born suffer from birth asphyxia every year. It is also estimated that of these 1.2 million dies and at least the same number develop severe sequelae such as epilepsy, cerebral palsy and developmental delay pneumonia, diarrhea, neonatal infections and complications of pre term labor[5,6]. The prevalence of risk factors are increasing and it is believed that these results are increased incidence of asphyxia in the developing world. These risk factors are categorized as women with poor health and

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poor labor care, poor nutritional status of mothers and poor socio-economic conditions are also risk factors. Other risk factors are included often inadequate health and medical facilities[7].

One of the programme of South Africa namely Perinatal Problem Identification Program (PPIP) has identified seven per 1000 live births with the incidence of birth asphyxia in rural communities and six per 1000 live births in urban areas. In 1990, South Asia and Sub-Saharan Africa published a review of twenty studies and estimated that 24-61% of deaths during the perinatal period were caused by birth asphyxia. A possible neuro protective action has been attributed to magnesium in hypoxic ischemic insult[8]. Magnesium is naturally occurring N-methyl D-aspartate (NMDA) receptor antagonist. It works within the ion channels by blocking neuronal influx of Ca++[9]. This voltage dependent blockage occur with hypoxic-ischemia,is over come through out axonal depolarization. This block can be restored, if the extra cellular concentration of Mg is increased[10].

The rational of this study is to find out the therapeutic efficacy of MgSO4 infusion in severe birth asphyxia, which can improve neurological outcome at discharge for term neonates. Neonatal mortality and morbidity can also be decreased, Literature revealed beneficial effects of postnatal magnesium therapy significantly.

Method

A total of 66 subjects were recruited by randomized clinical trial in Pediatrics Medicine Unit-II, DHQ hospital, Faisalabad. This study was conducted for six months from April 2011 to December 2011. Ethical approval was obtained from institution ethics committee. Sample size was calculated by using WHO sample size calculator formula for 2 proportions. To collect sample consecutive sampling technique (non-probability) was used. Neonates were randomly divided into two groups; each group has 33 subjects, group-A and B by using random number tables generated by computer. Neonates of group-A were given MgSO4 through I/V, 3 doses 250mg/kg/dose, 24 hours apart and group-B were given I/V normal saline, 3 doses 1 ml/kg/dose after 24 hours. According to the ward protocol supportive care was also provided for perinatal asphyxia.

Neonates of either sex presenting with moderate to severe birth asphyxia, gestational age of >37 weeks, HIE (moderate to severe), has severe perinatal asphyxia, CT scan brain were included in the study. While, patients with intrauterine growth retardation (weight at birth <2.0 kg),maternal prenatal Mg administration (on the basis of history),congenital malformation (on the basis of clinical examination), neonates with CT brain showing congenital brain malformations at admission were excluded from the study. Exclusion criteria was strictly followed to control confounding variables. The purpose, procedure, risks and benefits were explained to the parents of neonates and informed consent was taken. After detailed history and examination, data was registered as per proforma. At discharge complete data was obtained.

CT scan of brain was done at admission and at discharge from hospital radiology department and it was reported by hospital radiologist (MRI facility was not available).The criteria of treatment efficacy were an improvement in neurological findings (neonatal reflexes), establishment of oral feeding (sucking)on the basis of clinical examination and findings of normal CT brain.

Statistical analysis

Statistical package of social sciences (SPSS) version 23 was used for statistical analysis. For all variables descriptive statistics was considered. Quantitative variables were measured by calculating mean and standard deviation. For qualitative variables frequency and percentages were calculated. To compare efficacy in two groups, Chi square test was used as a test of significance. Statistical significance was defined as $P < 0.05$.

RESULTS:

In group-A and B, 20(60.6%)subjects and 18(54.5%)subjects were males while 13(39.4%)subjects and 15(45.5%)subjects were females respectively. Regarding age distribution, 15(45.4%)subjects in group-A and 14(42.4%)subjects in group-B were 1-2 hours of age. In group-A, 12(36.4%)subjects and in

group-B, 7(21.2%)subjects were 3-4 hours old while 6(18.2%)subjects in group-A and 12(36.4%)subjects in group-B were 5 hours old. Mean age (in hour) was observed 2.82±1.35 and 3.24±1.60 in group-A and B, respectively. In group-A and B, 18(54.5%) and 19(57.6%) subjects had 37-38 weeks while, 15(45.5%) and 14(42.4%) subjects had 39-40 weeks of gestation age respectively. (Table-1).
Neurological findings (neonatal reflexes)at discharge were improved in 25(75.8%)subjects in group-A and in 15(45.4%)subjects in group-B. Significant difference between two groups was observed with p value (P=0.011). Oral feed (sucking) was significantly established in group-A 25(75.7%)as compared to group-B 13(39.4%). P value (0.002) was considered statistically significant. Normal CT brain was seen in 28(84.9%) subjects in group A while in group-B in 17(51.5%) subjects. Between groups statistically significant difference was observed(P=0.003) (Table-2).

Table 1: Distribution of cases by sex, age (hour) andgestational age (week)

Distribution of cases by	Group-A (Treatment) Total=33, n (%)	Group-B (Placebo) Total=33, n (%)
Sex		
Male	20(60.6%)	18(54.5%)
Female	13(39.4%)	15(45.5%)
Age (hours)		
1-2	15(45.4%)	14(42.4%)
3-4	12(36.4%)	07(21.2%)
5	6(18.2%)	12(36.4%)
Mean ± SD	2.82±1.35	3.24±1.60
Gestational age (week)		
37-38	18(54.5%)	19(57.6%)
39-40	15(45.5%)	14(42.4%)
Mean±SD	39.5±3.1	39.1±3.5

Table 2: Distribution of cases by neurological findings (neonatal reflexes), oral feed (sucking) and CT brain at discharge

Distribution of cases by	Group-A (Treatment) Total=33, n (%)	Group-B (Placebo) Total=33, n (%)	P value
Neurological findings (neonatal reflexes) at discharge			
Improved	25(75.8%)	15(45.4%)	0.011
Not improved	08(24.2%)	18(54.6%)	
Oral feed (sucking) at discharge			
Established	25(75.7%)	13(39.4%)	0.002
Not established	08(24.3%)	20(60.6%)	
CT brain at discharge			
Normal	28(84.9%)	17(51.5%)	0.003
Abnormal	05(15.1%)	16(48.5%)	

DISCUSSION:

In the current study, birth asphyxia was improved with the treatment of MgSO4. Significant results were observed with neurological findings (neonatal reflexes), oral feed (sucking) and CT brain at discharge time. In India, similar study has done in 2009 for the use of MgSO4 in severe birth asphyxia. It improves the overall neurological outcome, CT scan and oral feeding (sucking) in treatment group at discharge time as compared to placebo group[11]. In another study, for the first 3 days of life three doses of magnesium sulfate infusion was given daily at the 250mg/kg per dose. In neonates, this strategy also improved the neurologic outcomes at discharge with severe perinatal asphyxia[12]. Previously, Ichibia et al. conducted a multi center, randomized controlled trial. He also observed the improved outcomes in babies with severe birth asphyxia with the treatment of postnatal magnesium sulfate infusion (250 mg/kg/day) for 3 days[13,14]. It was also estimated that significant results occurred more often in the magnesium group than in the control group on cranial CT, EEG and for establishment of oral feeding by day 14 of age.

Neurobiology research is done to understand the mechanisms that culminate in neuronal loss after hypoxic-ischemic insult[15]. In animal model, the systemic administration of magnesium after a simulated hypoxic ischemic insult has been shown to limit neuronal injury[16]. Previously, the plausibility of Mg in the prevention of delayed neuronal death following perinatal asphyxia in the human neonate has also been discussed[17]. The potential value of magnesium are supported by experimental work by several mechanisms, i.e. anti-excitotoxic (block the NMDA receptor), antioxidant (required for glutathione biosynthesis), anti-cytokine (inflammatory cytokineslevels are decreased) and antiplatelet (platelet aggregation are decreased) effects[18].

Infusion of postnatal magnesium sulfate was neuro protective in this study. Fewer neonates are reflected with neurologic abnormalities and at discharge oral feedings are received by more infants in the treatment group. In previous study, a lower incidence of cerebral palsy was observed in pre term infants born to mothers who had received magnesium sulfate before delivery[19]. Magnesium supplementation is also recommended to mother in this study. Similar to other study, in which lower incidences was reported for fetal heart rate deceleration and term stillbirths for mothers who received magnesium during pregnancy[20].

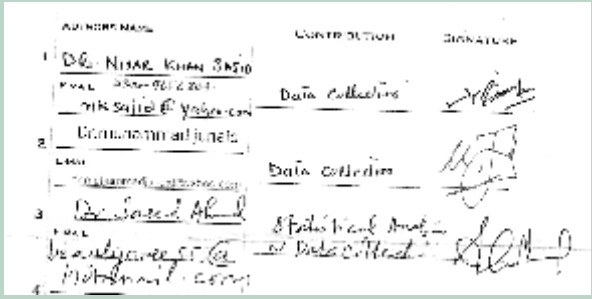
CONCLUSION:

Magnesium has beneficial effects in babies with severe asphyxia. This study concludes that neurologic outcomes can be improved at discharge time with the treatment of postnatal magnesium sulfate for neonates having perinatal asphyxia in severe condition. To the best of our knowledge, very few studies at present from Pakistan with small sample size based on single center. However, a large multi center trial should be conducted to validate our hypothesis.

REFERENCES:

1. Natarajan G,Shankaran S, Laptook AR, ctal. APGAR Score at 10 min and outcome at 6 – 7 years following hypoxic ischemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 2013; 98(6): F 473 – 479.
2. Sreenivasa. B, Lokeshwar K, Joseph, N. Role of magnesium sulphate in management and prevention of short term complications of birth asphyxia. Sri Lanka Journal of Child Health, 2017; 46 (2): 148 - 151
3. Namasivayam A, Waldemar AC. Hypoxic Ischemic Encephalopathy in: Behrman RE, Kleigman RM, Jensen HB editors. Nelson Text book of Pediatrics. First South Asia edition. Philadelphia: Saunders Publishers, 2015: 569 – 570.
4. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. Lancet 2005; 365:1147-52
5. Leone CR, Barbosa NO. Magnesium and perinatal asphyxia. Neo Rev 2007;8:e387-93.
6. Gathwala G. Neuronal protection with Magnesium. Indian J Pediatr 2001; 68:417-9.

7. Gathwala G, Khera A, Singh J, Balhara B. Magnesium for neuroprotection in birth asphyxia. Journal of pediatric neurosciences. 2010 Jul; 5(2):102.
8. Hoffman DJ, Marro PJ, McGowan JE, Mishra OP, Delivoria-Papadopoulos M. Protective effects of MgSO4 infusion on NMDA receptor binding characteristics during cerebral cortical hypoxia in the newborn piglet. Brain Res 1994; 644:144-9
9. Bhat MA, Charoo BA, Bhat JI, Ahmed SM, Ali SW, Mufti MU.magnesium sulfate in severe Perinatal asphyxia: a randomized placebo – Controlled Trial. Pediatrics 2009; 123: e 764 – 9
10. Huang Z, Filipovic Z, Ung C, Troy EL, Colburn RW, Iaci JF, Hackett C, Button DC, Caggiano AO, Parry TJ. AC105 increases extracellular magnesium delivery and reduces excitotoxic glutamate exposure within injured spinal cords in rats. Journal of neurotrauma. 2017 Feb 1;34(3):685-94
11. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birth weight infants? Pediatrics 1995; 95:263–9
12. Harrison V, Fawcus S, Jordaan E. Magnesium supplementation and perinatal hypoxia: outcome of a parallel group randomised trial in pregnancy. BJOG 2007;114:994–1002
13. Ichiba H, Tamai H, Negishi H, Keda T, Kim TJ, Sumida Y, et al. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int. 2002; 44:505-9.
14. Mehmood T, Zulfiqar R, Faran T, Saeed T. Effect of PostnatalMagnesium Sulfate Infusion on Neurological Outcome of Term Neonates with Severe Perinatal Asphyxia. Journal of Rawalpindi Medical College (JRMC); 2015;19(3):193-196.
15. Shankaran S. hypoxic-ischemic encephalopathy and novel strategies for neuroprotection. Clin perinatal 2012, 39: 919-929.
16. Clowcry, G.J, Basuodan, R, Chan, F. what are the best animal models for testing early intervention in cerebral palsy? Front. Neurol 2014, 5, 258.
17. Shaikh H, Lechpammer, M, Jonson, F.E warfield, S.K, Hansen, A.H, Kosaras, B, Shevell, M., Winter Mark P. Increased brain perfusion persist over the first month of life in term asphyxiated newborn treated with Hypothermia. Does it reflect activated angiogenesis? Transl stroke Res. 2015, 6, 224 – 233.
18. Jasim Anabrees. Magnesium sulphat for newborns with HIE, Synopsis of evidence from a systematic review. J.clin Neonatal. 2013 Jul – Sep : 2 (3): 114 – 116
19. Chan, A., Xiong, L.J., Tong, Y, Mao, M.Neuroprotective effect of brain derived Neuro trophic factor mediated by autophagy through the PI3K/Akt/motor pathway. Vol. Med. Rep 2013, 8, 1011 - 1016.
20. Brandon J. Dixon, Cesar Reis, Wing Mann HO, Jiping Tang etal. Neuroprotection Strategies after Neonatal Hypoxic Ischemia Encephlopathy. Int J. Volmol Sci 2015, 16, 22368 – 22401.



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