ROLE OF MAGNESIUM SULPHATE IN SHORT TERM NEUROLOGICAL OUTCOME OF PERINATAL ASPHYXIA

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Background: Perinatal asphyxia or Hypoxic Ischemic Encephalopathy (HIE) is a condition of impaired blood gas exchange during the intrapartum period that leads to progressive hypoxemia and hypercapnea with a metabolic acidosis resulting ischemic encephalopathy. Now a days many therapeutic interventions are tried to reduce the morbidity and mortality in Hypoxic ischemic encephalopathy. Magnesium sulphate is one of them. Reduced morbidity with such an inexpensive and easy to administered drug is appreciable especially for resource limited countries. Objective: To compare Magnesium sulphate to placebo in short term neurological outcome of the full term newborns presented with perinatal asphyxia. Study design: It was a randomised control trial. Methodology: 200 term neonates with moderate to severe perinatal asphyxia admitted in NNU were studied in a prospective, longitudinal placebo control trial. Patients were randomly assigned in two groups. One group received 3 doses of Mgso4 infusion at 250 mg/kg per dose 24 hr apart (treatment group A) and second group received 3 doses of normal saline infusion 1 ml/kg per dose 24 hr apart (placebo group B) . Both groups received same supportive care according to unit protocol. Results: Showed a significant difference in short term outcome in the form of early discharge and oral feeding. 71% of the patient in treatment group were discharged on oral feeding up to 2 weeks comparative to 23% patients in placebo group. Mortality in treatment group(A) was 13% and in placebo(B) 23%. Conclusion: The study concluded that the Magnesium sulphate is an effective drug for the management of morbidity in perinatal asphyxia.
Key words: Perinatal asphyxia, Magnesium sulphate, Hypoxic ischemic encephlopathy, Neurological outcome.

INTRODUCTION

Four million children die each year in first 28 days of life and the perinatal asphyxia is the second most common cause.[1] Neonatal mortality is much greater in developing countries than in developed. Pakistan is amongst the first three countries, Pakistan accounts for 7% of the global neonatal deaths and the 23% of these are due to perinatal asphyxia.[2,3]

Perinatal asphyxia leads to Hypoxia ischemic encephalopathy (HIE). As the severity of Asphyxia increases morbidity and mortality also increases. Neuro developmental abnormalities occur in 50-60% of patients with moderate HIE and in almost all of the patients with severe HIE.

Perinatal asphyxia leads to multi-organ dysfunction, while the other organs may recover but brain is often permanently damaged by a pathophysiological process that progress over many days [4]. Research suggest that the excessively increased intracellular calcium is the main culprit of cellular damage through the activation of lipases, proteases and endonucleases. Neurotransmitter glutamate is the main reason behind this excessive calcium influx. Glutamate acts on N methyl D aspartate (NMDA) receptors and causes Ca influx into neurones thus inducing irreversible neuronal damage.[5,6,7] Cascade of cell damage that occur after reperfusion is thought to be caused by release of oxygen free radicals and an imbalance between excitatory and inhibitory neurotransmitter system. Some of the damage is also caused by activation of a cellular suicidal programme known as apoptosis.

Magnesium sulphate (Mgso4) is a NMDA receptor antagonist. It blocks the influx of Ca within the ion channels. This blockade is voltage dependant and is overcomed due to hypoxic ischemia in perinatal asphyxia. If the extracellular concentration of Mgso4 is increased, this block can be restored. Mgso4 also has an antiapoptotic, antioxidant, anti inflammatory and anticonvulsant properties, which also help in preventing neuronal damage.[8,9] The trial of this drug when administered in hypoxia induced injury in animal models has shown beneficial effect in some studies.[10]

We have conducted this study on role of Mgso4 in perinatal asphyxia to prove the beneficial fact in neurological outcome as if it proved to be effective in improving neurological outcome that would be very useful for developing countries like Pakistan as it is cheaper drug, easily available and easy to administer.

METHOD

This was a randomised control trial conducted in NICU of Lahore General Hospital, Lahore. 200 full term neonates of both gender with perinatal asphyxia, having HIE II and HIE III were selected. Newborns eligible for study were gestation age of ≥36 weeks and Perinatal asphyxia with neonatal encephalopathy stage II & III.

Newborns who were IUGR, having congenital anomalies, presented after 6 hour of life and who have history of maternal administration of Mgso4 during labour were excluded from the study.

Patients were divided in to two groups (group A & group B) each having equal no of patients that was 100. Group A was trial group and group B was control. An informed consent was taken for assigning them to a particular procedure, and using their data for the research. For each patient detailed history was taken including demographic information. Trial of Mgso4 was started within the 6 hour of life. Group A patients received 3 doses of Mgso4 infusion in 20 ml normal saline with the dose of 250 mg/kg/dose at zero, 24 and 48 hour interval. Infusion was given over 1 hour through syringe pump. Group B patients received 20 ml normal saline infusion at the same interval.

During the infusion monitoring was done in the form of BP, vitals and pulse oximetry. This was also continued up to 72 hour of life. Both groups of patients were given same supportive care as per NICU protocol. The outcome was measured in the term of establishment of oral feeding at discharge or at 14 day of life which ever come earlier and at the time of discharge. Patients who get neurologically stable early were shifted on oral feeding early and their hospital stay was also shorter.

The collected data was analyzed by using SPSS version 10. Descriptive statistics were calculated. Quantitative variable was age of the patient and it was presented as mean±SD. Frequency and percentage for qualitative variable like oral feeding (sucking) at discharge was noted. The outcome of two groups was compared by applying chi-square test. $P \leq 0.05$ was considered as significant.

RESULTS

A total of 200 neonates fulfilling inclusion/ exclusion criteria were selected. Hundred neonates were randomly assigned to treatment group (Group A) and hundred in control group (Group B). In Group A 43 were male and 57 were females, while in Group B 49 were male and 51 females. There was no significant difference regarding gender among both groups. (Table 1)

Table No. 1: Gender Distribution of The Patients (n=200)

Gender	**Group-A (n=100)**		**Group-B (n=100)**	
	No. of patients	**%**	**No. of patients**	**%**
Male	43	43	49	49
Female	57	57	51	51
Total	**100**	**100**	**100**	**100**

Table No. 2: Compare Between Magnesium Sulphate And Placebo (n=200)

Outcome (Feeding at discharge)	**Group-A (n=100)**		**Group-B (n=100)**	
	No. of patients	**%**	**No. of patients**	**%**
Yes	72	72	31	31
No	28	28	69	69
Total	**100**	**100**	**100**	**100**

In group A 66% neonates had moderate and 33% had severe encephalopathy. In group B 69% neonates were having moderate and 31% having severe encephalopathy. There was no statistically significant defence in grades of encephalopathy among both groups.

Treatment group received Mgso4 infusion and control group placebo at the same interval with similar monitoring protocol and supportive care.

Comparison between both groups was done which shows that 72% (n = 72) neonates in treatment group discharged on oral feeding as compare to only 31% (n=31) in placebo group which were taking oral feed on discharge. P value calculated was as 0.001 i.e. < 0.05 which is significant. (Table 2).

In Group A, 15% neonates were on NG feed on day 14 of life and 13% were expired. In Group B, 46 neonates were still on NG feed till the 14 day of life and 23% were expired. There was a significant difference in mortality among both groups.

DISCUSSION

The overall incidence of Perinatal asphyxia is 1% to 1.5% of live births in developed countries.[11] This incidence is more common in developing countries. A database report shows an incidence of 5% among studies conducted in 16 medical institutes.[12] Encephalopathy occurs in 50% to 60% of patients with severe perinatal asphyxia. Moderate/severe hypoxic-ischemic encephalopathy (HIE) causes significant morbidity and death in the neonatal period and permanent neuro developmental handicaps among survivors. At discharge neurological abnormality is a strong predictor of long-term neurodevelopmental delay. Magnesium sulphate blocks neuronal influx of calcium within the ion channels.

This study was conducted considering the fact that no data regarding therapeutic effects of magnesium in newborn is available in Pakistan and hypothesized that magnesium sulphate is more effective than placebo in the improvement of short term neurological outcome in full term newborns presenting with perinatal asphyxia. The results of the study set borderline data on the topic that magnesium sulphate ultimately reduces the morbidity and mortality among neonates. In our study, comparison between magnesium sulphate and placebo was done which shows the efficacy as 72%(n=72) in Group-A and 31%(n=31) in Group-B while rest of the patients i.e. 28%(n=28) in Group-A and 69%(n=69) in Group-B had no feeding & discharge, p value was calculated as 0.001 i.e. ≤0.05. The results of the study are in agreement with a study that shows infants in the group treated with magnesium sulphate were more likely to be receiving oral feedings (sucking) at discharge than were those in the placebo group (77% vs. 37%).[13] Another study by Ichiba H and colleagues who determined whether postnatal MgSO(4) infusion (250 mg/kg per day) for 3 days is both safe and able to improve outcome in infants with severe birth asphyxia and concluded that "Postnatal MgSO(4) infusion as above is safe and can improve short-term outcome in infants with severe birth asphyxia".[14]

This significant protective role of magnesium sulfate has been based largely on studies with animal models, many of which showed favorable results in terms of amelioration of secondary neuronal injury. A few studies with pregnant women showed beneficial effects for neonates also. Nelson and Grether observed a lower incidence of cerebral palsy in preterm infants born to mothers who had received magnesium sulfate before delivery.[15] Schendel et al and Grether et al observed the relationship of intrapartum magnesium sulfate administration to mothers and cerebral palsy in newborns.[16,17] They showed significant effects of magnesium sulfate in preventing cerebral palsy. Harrison et al[18] reported lower incidences of fetal heart rate deceleration and term stillbirths for mothers who received magnesium supplementation during pregnancy.

However, the findings of our with the support of other studies are of the view that hypothesis of the study "Magnesium sulphate is more effective than placebo in the improvement of short term neurological outcome in full term newborns presenting with perinatal asphyxia" and the drug may be used in future for the management of perinatal asphyxia.

CONCLUSION

Magnesium sulphate is an effective drug to improve the short term neurological outcome for infants with moderate to severe perinatal asphyxia. It also reduces the mortality according to our study. However many of the other studies do not favour the reduction in mortality. So we suggest multi-centre trials to confirm its effects on mortality.

REFERENCES

1. World Health Report 2005: Make every mother and child count. Geneva: WHO; 2005.
2. Imtiaz Jehan , Hillary Harris , Sohail Salat, Amna Zeb , Naushaba Mobeen , Omrana Pasha, et al. Neonatal mortality, risk factors and causes: a prospective population-based cohort study in urban Pakistan.. Bulletin of the World Health Organization 2009;87:130-138.
3. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet 2005; 365: 891-900.
4. Dixon G, Badawi N, Kurinczuk JJ, et al. Early developmental outcomes after newborn encephalopathy. Pediatrics. 2002; 109(1):26 –33
5. Choi DW, Harley DM, Waxman SG. Calcium and Glutamate induced cortical neuronal death. Molecular and cellular approaches to the treatment of Neurological Disease. New York;sRaven Press, 1993; 122-129.
6. Nowak L, Bregestovski P, Ascher P, Herbert A, Prochiantz A. Magnesium gates glutamate activated channels in mouse central neurons. Nature 1984; 307 : 462-465.
7. McIntosh TK, Vink R, Yamakami I, Faden AI. Magnesium neuroprotects against neurological

deficit after brain injury. Brain Res 1989; 482 : 252-260.
8. McDonald JW, Silverstein FS, Johnston MV. Magnesium re- duces N-methyl-D-aspartate (NMDA)-mediated brain injury in perinatal rats. Neurosci Lett. 1990;109(1–2):234–238
9. Hoffman DJ, Marro PJ, McGowan JE, Mishra OP, Delivoria- Papadopoulos M. Protective effect of MgSO4 infusion on NMDA receptor binding characteristics during cerebral cortical hypoxia in the newborn piglet. Brain Res. 1994;644(1):144–149
10. Hartley R. Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia. Arch Dis Child Fetal Neonatal Ed. 1995;73(3):F174 –F177
11. Adcock LM, Papile LA. Perinatal asphyxia. In: Cloherty JP, Eichenwald EC, Stark AR, eds. Manual of Neonatal Care. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:518–28
12. Paul VK. Neonatal morbidity: report of the National Neonatal and Perinatal Database. Indian Pediatr.1999;36 (2):167– 9
13. Bhat MA, Shah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal functions in term neonates with perinatal asphyxia; a randomized placebo controlled trial. J Pediatr. 2006;149(2):180– 4.
14. Ichiba H, Tamai H, Negishi H, Ueda T, Kim TJ, Sumida Y. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int. 2002;44(5):505-9
15. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birth weight infants? Pediatrics.1995;95(2):263–9.
16. Schendel DE, Berg CJ, Yeargin-Allsopp M, Boyle CA, Decoufle P. Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. JAMA.1996;276 (22):1805–10.
17. Grether JK, Hoogstrate J, Selvin S, Nelson KB. Magnesium sulfate tocolysis and risk of neonatal death. Am J Obstet Gynecol.1998;178 (1):1–6.
18. Harrison V, Fawcus S, Jordaan E. Magnesium supplementation and perinatal hypoxia: outcome of a parallel group randomised trial in pregnancy. BJOG.2007;114 (8):994–1002.