International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Treatment with $MgSo_4$ of Babes in Term with Serious Asphyxia at Birth

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Abstract: ***Perinatal encephalopathy is a significant public health issue. It is associated with high mortality, serious morbidity and significant costs. Most of this cost is related to long - term neurodevelopmental disabilities, such as cerebral palsy (CP). Magnesium sulfate ($MgSO_4$) is one of the most commonly used drugs in obstetric medicine. Its first reported use was in 1925 for control of eclamptic seizures. The patholphysiology of perinatal hypoxic - ischemic stroke has been extensively studied in order to find the components to be inhibited to reduce cerebral damage. Among the possible therapeutic strategies MgSO4 has been the subject of experimental studies and recently of many clinical studies.***

Keywords: magnesium, HIE, perinatal, neuroprotection, treatment

1. Introduction

Perinatal Asphyxia is the second largest contributor to global neonatal mortality rate. It is a major cause of disability despite public health interventions targeted at its reduction in the past four decades (1). The burden of Perinatal asphyxia (PA) in some countries is assuming epidemic proportions. The typical presentation is failure of the new - born to resume or sustain spontaneous respiration after complete delivery with hypoxaemia, hypercapnia and acidosis (2). Survivors present 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 the most severe complication, hypoxic ischaemic encephalopathy (HIE), incidence of up to 26.5/1000 live births is unacceptably high despite advances in perinatal care (5, 6). This is many times the international incidence of 2 - 6/1000 live births (3). Perinatal asphyxia leads to excessive release and reduced uptake of glutamate in the newborn brain. Increased glutamate concentrations open N - Methyl - D - Aspartate (NMDA) channels allowing excessive calcium influx into the neurons and causes irreversible neuronal injury. Magnesium is a naturally occurring NMDA receptor antagonist that blocks neuronal influx of calcium within the ion channels. Without interruption of calcium influx, neuronal injury or death is the result, manifesting either as mortality or survival with sequelae; hence the neuroprotection strategy (4).

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 antiapoptotic role and prevent neuronal cell loss.

More recently, attention has been drawn to many pharmacologic agents with anti - inflammatory and neuroprotective properties. These include erythropoietin, melatonin, magnesium sulphate (MgSO4), topiramate, xenon, and allopurinol. These agents have specific pathways in the pathophysiology of perinatal asphyxia. Antioxidants have also been tried in animal models for the prevention of post asphyxia brain injury syndrome. These have provided evidence that led to the different trials with antioxidants or their combined use with other modalities of therapy (18 - 20). In fact, the clinical use of Magnesium sulphate to counteract the effect of glutamate and provide additional pharmacologic neuroprotection to hypothermia in the Mag Cool study is one of such (5). Similar experience has also been extended to the use of Magnesium sulphate and antenatal corticosteroids for preterm mothers. The neuroprotection properties of magnesium sulphate (MgSO4) have been documented in several animal studies. Magnesium has also shown beneficial effect in reducing cerebral palsy in infants of mothers that received prenatal magnesium sulphate for other perinatal indications. Its usefulness in the management of persistent pulmonary hypertension of the newborn, one of the common comorbidities associated with perinatal asphyxia may be an added advantage and usefulness in resource limited setting like ours (6). Magnesium sulphate was shown to improve neurologic outcome of severely asphyxiated newborns in a randomized, placebo controlled trial, which is in tandem with previous observational studies which advocated for more studies and multicenter trials (7). This low cost, low technology, readily available intervention could be a possible coping strategy for stemming the tide of perinatal asphyxia and hypoxic ischemic encephalopathy in low resource settings. The aim is to study whether postnatal application of $MgSo_4$ can improve neurological output at discharge, in infants in term with severe asphyxia at birth.

2. Material and Methods

This is a prospective study conducted at the University Obstetric - Gynecological Hospital "Koço Gliozheni", in Tirana, - Albania, during the period January 2012 to December 2015.

Thirty two term babies (gestational age> = 37 weeks) with severe asphyxia at birth were included in this prospective, longitudinal placebo - control study. Patients were randomly selected to receive 3 doses of $MgSo_4$ infusion 250 mg / kg dose (1 ml / kg dose) with a 24 hour difference (treatment group) or 3 doses of Sol infusion. Physiological 0.9% (1 ml / kg dose) with 24 hours difference (placebo group). Both groups received supportive care according to the protocol of our intensive unit for perinatal asphyxia.

3. Results and Discussion

In the treatment group, moderate HIE was present in 18% (3 of 16 cases) of patients and, severe EHI in 31% (5 of 16 cases, 3 of which are deceased babies) of patients in admission. In the placebo group, 25% (4 out of 16) of patients had moderate HIE, and 37.5% (6 out of 16, 2 deceased babies) had severe HIE (figure 1). At discharge, 25% (4 of 16) had neurological impairement in the treatment group, compared with 37.5% (6 of 16) in the placebo group. Also neuroimaging carried out on the 14^{th} day, resulted in abnormal findings in fewer children of the placebo treatment group (31% vs 37.5%). Children in the treatment group were more predisposed to start oral feeding (absorption) faster (within the first week) than those in the placebo group (69% vs.63%). Early neurological output was better in the treatment group 62.5% compared to that placebo 43%.

A key translational consideration for testing neuroprotectants is when to treat. The majority of preclinical studies surveyed (20/22; 91%) started the intervention before the insult or immediately after the insult (within the first 30 min). Just 2 out of 22 studies initiated treatment within the first hour after the insult, one showed MgSO4 was not associated with neuroprotection, while the other suggested a modest improvement. Scientifically, the mechanisms of intra - insult cell death, particularly in the setting of HI, are different from those after treatment. Furthermore, it is well - established that inflammation (sterile or infective) is a key contributor to perinatal encephalopathy and is an important target for any neuroprotective intervention, particularly delayed therapy (8). Therefore, efficacy during pretreatment does not necessarily indicate the treatment will be effective if the insult has already started to evolve.

In an elegant study by Koning et al., pretreatment with MgSO4 from 6 days to 12 h before HI in P7 rats was associated with reduced oxidative stress and inflammation, and reduced severity of neural injury, likely due to preconditioning of mitochondrial resistance (9). As previously reviewed (10), preclinical and clinical studies have shown that antenatal preconditioning is associated with improved tolerance to subsequent insults (11). Conversely, preconditioning can induce sensitization to subsequent insults (12). Thus, translating preconditioning into improved outcomes is complex and requires careful further investigation before it can be applied in practice.

Clinically it is difficult to identify fetuses who are at risk of developing encephalopathy in advance, since the positive predictive value of fetal heart rate monitoring for predicting adverse neurodevelopmental outcomes is low (13). Furthermore, it remains a formidable challenge to start any intervention within the first 4–5 h after birth (14). None of the human studies surveyed reported a beneficial effect of MgSO4 on neurodevelopment after antenatal treatment, two of these studies were sub - analyses of a randomized controlled trial that focused on infants exposed to clinical chorioamnionits (15). Two relatively small studies in preterm infants that received antenatal MgSO4 reported a reduction in the incidence of cerebral or cerebellar hemorrhage, however, neurodevelopmental outcomes were not reported (16). Postnatal treatment (30 min to 6 h) with MgSO4 alone or as an adjuvant to therapeutic hypothermia did not improve short - term outcomes in term infants with HIE, however, both studies were based on relatively small cohorts and one of these trials is ongoing (The MagCool Study; NCT01646619) (17).

These data are broadly consistent with data from a study in piglets that suggests MgSO4 was associated with only modest improvement in histological outcomes with no effect on magnetic resonance spectroscopy markers of long - term outcomes (18). This suggests that more pre - clinical research is essential before large multicenter RCTs of MgSO4 for neonatal encephalopathy at term should be considered. Furthermore, three of the preclinical studies surveyed reported negative effects of MgSO4 on cell survival and oligodendrocyte development (19, 20), and one clinical study reported higher cord blood magnesium levels were associated with an increased risk of neonatal mortality, thus highlighting potential safety considerations. Collectively, these data indicate that we must improve our understanding of the optimal treatment regimen and patient population that are most likely to demonstrate benefit from MgSO4, before progressing further down the translational pipeline.

4. Conclusions

Postnatal magnesium alone or combined with respiratory support improves survival of asphyxiated babies and babies with encephalopathy. Intravenous magnesium sulphate within few hours of postnatal life to term neonates with birth asphyxia helps in early seizure control, early recovery from abnormal neurological signs, early establishment of feeds and fewer chances of neurological abnormalities at discharge.

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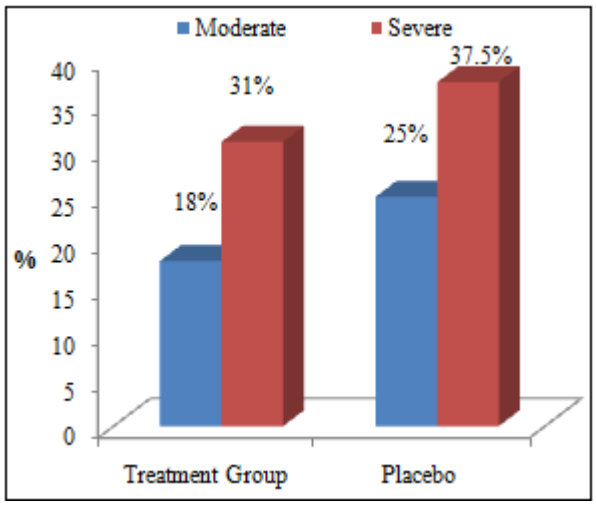

Figure 1: Comparison of the HIE frequency among treatment group and placebo