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Magnesium Sulphate: A New Frontier in Prevention of Intraventricular Hemorrhage in Premature Newborns

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A B S T R A C T

Introduction:Intraventricular haemorrhage (IVH) remains a catastrophic neurological complication with considerable mortality and neurodevelopmental disability in preterm neonates.Given that preterm birth is a major cause, many strategies have been put forth for its prevention . The newest on the present day list is Magnesium Sulphate (MgSo4).***Aims and Objectives:***To determine the effect of exposure of antenatal magnesium sulfate on intraventricular hemorrhage in premature newborns evaluated by cranial ultrasoundand other neonatal complications at birth.***Materials and Methods:*** This prospective interventional study was conducted on 70 women admitted to labor room in the Department of Obstetrics and Gynaecology, Sawai Mansingh Medical College, Jaipur. Women with singleton pregnancy between 28 to 32 weeks gestational age with expected delivery within 24 hours were included. Groups were allocated using flipcoin method into cases and controls, and the treatment group was administered with Magnesium Sulphate. Neonatal complications were reported at birth. On day 7, cranial ultrasound was done to evaluate IVH and its Papile grading.***Results:*** Our study concluded that the occurence of IVH was low in both groups, though there wasslightly higher occurence ofIVH in the group not receiving MgSO4compared to the groupreceiving MgSO4(11.4% vs 2.9%). HIE(22.9% vs 25.7%), RDS (20% vs 25.7%), ROP(0% vs 5.7%), Hydrocephalus (0% vs 5.7%), Neonatal seizures (5.7% vs 8.6%) and Neonatal mortality (8.6% vs 11.4%) were the neonatal outcomes reported among those administered MgSo4 and those not.***Conclusion:*** This study contributes to the body of evidence indicating that prenatal MgSO4 use on a large scale might be advantageousin prevention of IVH in preterm neonates. It offers a great deal of promise to lessen neurocognitive impairment and safeguard the growing fetal brain.

INTRODUCTION

The 2023 WHO *Born Too Soon Report* highlights that preterm birth (delivery at viability but before 37 weeks of gestation) remains the greatest contributor to neonatal and infant mortality worldwide and is one of the greatest contributors to lost human capital [1]. These infants are at the highest risk for poor neurodevelopmental outcomes.

Intraventricular hemorrhage, being an area of concern, is one of the most common types of brain injury in preterm infants [2]. IVH is primarily caused by destabilizing changes in cerebral blood flow inflicting to the microvasculature of the germinal matrix [3]. Infants most at risk are those born before 33 weeks of gestational age, as after this time, the germinal matrix involutes [4]. On the other hand, in preterm infants with immature cardiopulmonary systems, vital signs are considerably unstable during the first few days of life and complications such as respiratory distress syndrome can also occur. Therefore hypotension, hypoxia and hypercapnia are common. As cerebral autoregulation is also immature, CBF fluctuation can cause repeated ischemia-reperfusion events and a sudden increase in CBF can lead to excessive strain on fragile vessels in the GM, resulting in haemorrhage [5].

Studies have been conducted with many pharmacologic agents predicting that these agents could prevent IVH. However, the only pharmacologic agent that has been found to be efficient so far is antenatal steroids [6]. Recently,

Magnesium sulphate, which is being usedas a tocolytic and a prophylactic agent against convulsions in pre-eclamptic women, is gaining fame in the field of neuroprotection.

MgSO4 has been proposed to act as a neuroprotectant by reducing inflammatory cytokines or free radicals produced during hypoxic-ischemic reperfusion, preventing excitotoxic calcium-induced injury, membrane stabilization by preventing the membrane depolarization, inhibitingglutamate receptors involved in injury to preoligodendrocytes, stabilizing fluctuations in blood pressure that occur in neonates and an increase in cerebral blood flow [7].

It is not completely elucidated whether MgSO4 has an effect on the cerebral lesions detected during the neonatal period or whether the reduction of the risk of IVH is through some other pathway. This study was conducted to describe the important neonatal clinical outcome and the neurodevelopment of neonates exposed to antenatal MgSO4 therapy during this period with the aim of developing local data, to encourage the practitioners to adopt antenatal magnesium into practice.

MATERIAL AND METHODOLOGY

This is a prospective interventional study conducted in department of Obstetrics and Gynecology, SMS Medical College, Jaipur, Rajasthan, India planned over a period of 1 year (December 2022 to December 2023). It included 70 women admitted in labour room with singleton pregnancy between 28 to 32 weeks gestational age with preterm labor and cervical change (dilatation >or=1 cm, 80% effacement) andexpected delivery within 24 hours. Following the acquisition of appropriate written and informed consent, a thorough medical history, standard ANC exams, and standard ANC investigations were carried out. The flipcoin approach was utilized to divide the groups into treatment and control groups.

- Treatment group- Loading dose with 4g of magnesium sulphate over total of 20-30 minutes followed by maintenance dose of 1g per hour through infusion pump until delivery or 24 hours whichever was earliest and given routine standard treatment according to our hospital protocols for preterm labor.
- Control group-Women given routine standard treatment according to our hospital protocols for pretemlabor.

Inclusion Criteria:

1. Singleton pregnancy 28 to 32 weeks gestational age.
2. Preterm labor with cervical change and expected delivery within 24hours.
3. Patient who understands and willing to participate in the study and give written informed consent.

Exclusion Criteria:

1. Major Congenital malformations.
2. Pregnancy with chronic medical disorders (including severe preeclampsia).
3. Maternal contraindications to magnesium sulfate (eg:myasthenia gravis, renal failure).

Neonatal complications were observed at birth.
A cranial ultrasonography was performed on the seventh day after delivery to check for intraventricular hemorrhage (Papile grading [8]).

RESULT AND DISCUSSION

- **Distribution of participants according to different variables**

In the present study, the mean age of participants administered with MgSO4 was 25.4 ± 2.38 years while the mean age of participants not administered with MgSO4 was 26.26 ±2.08 years.

The RCOG [9] and NG25 [10] recommended offering magnesium sulfate to women who are in established labour or having a planned preterm births within 24 hours before 30 weeks of gestation (as benefit is greatest). FIGO good practice recommendations [11] on magnesium sulfate administration for preterm fetal neuroprotection recommnends its use in pregnancies below 32-34 weeks of gestation (2021). In our cases, the mean gestational age was 29.84 ± 1.19 weeks, while in our control group, it was 29.97 ± 1.14 weeks. Our study included the participants in the recommended age group parameters for them to be eligible for the greatest therapeutic benefits of antenatal MgSo4 for fetal neuroprotection.

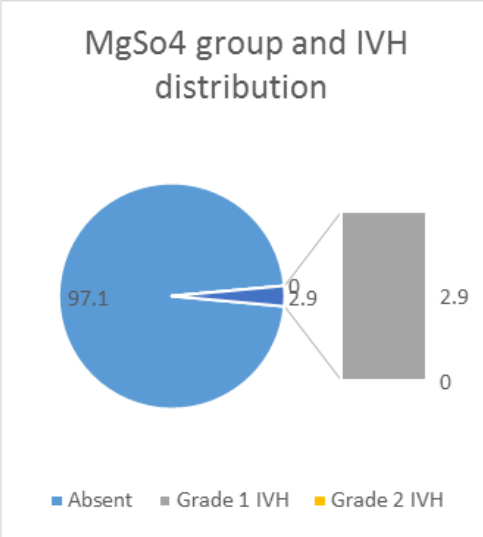
The mean birth weight of infants in study group was 1.39 ±0.21 kg whereas in control group it was 1.33±0.17 kg.

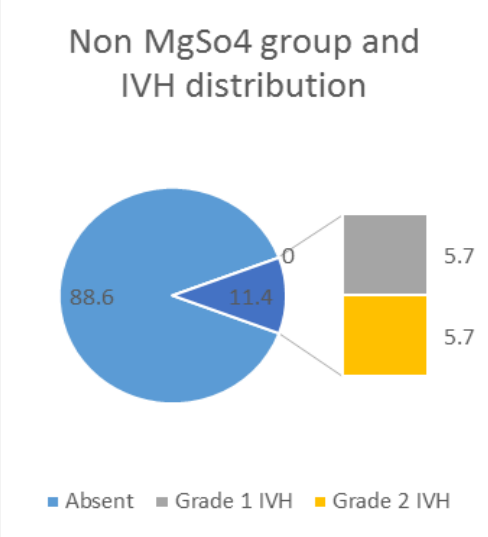
Variables	Cases	Controls	p value
Age of participants (Years)	25.4±2.38	26.26±2.08	0.113
Weight of neonates (kgs)	1.39±0.21	1.33±0.17	0.149
Gestational age(Weeks)	29.84±1.19	29.97±1.14	0.642

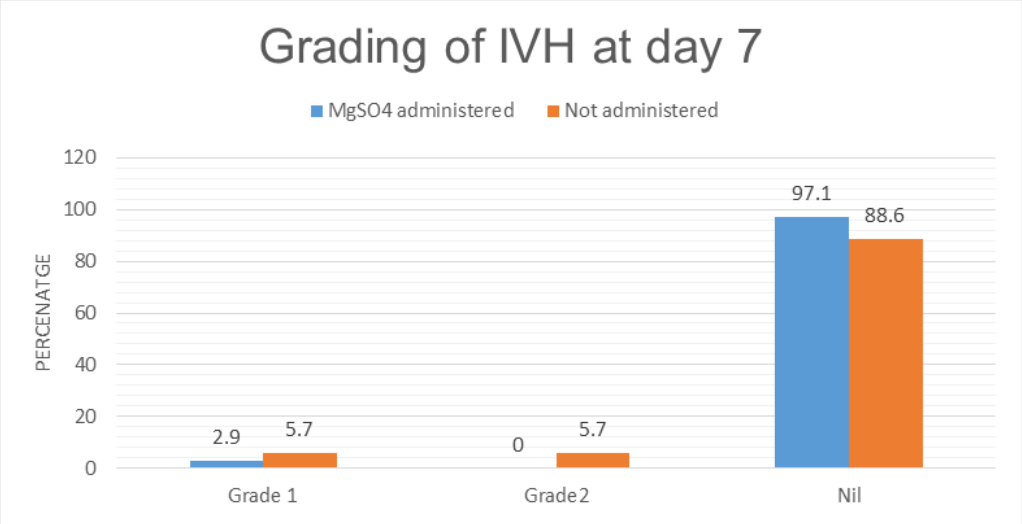
- **Distribution of participants according to grading of IVH in neonatal ultrasound at day 7**

IVH grading	Cases	Controls
Grade 1	1(2.9)	2(5.7)
Grade2	0	2(5.7)
Nil	34(97.1)	31(88.6)
Total	35(100)	35(100)

Among participants administered with MgSo4, oneneonate had (2.9%) grade 1 IVH on cranial ultrasound whereas the rest of the neonates (97.1%) had no features of IVH. Among participants not administered with MgSo4, 4 neonates had IVH, 2 neonates (5.7%) each had grade 1 and grade 2 IVH while the majority (88.6%) had no features suggestive of IVH. Thissuggests that the occurence of IVH was low in both groups although there's a slightly higher occurence ofIVH in the group not receiving MgSO4compared to the groupreceiving MgSO4(11.4% vs 2.9%) (P=0.363).







- **Distribution of participants according to neonatal complications at birth**

Neonatal complications	Cases	Controls	P value
Hypoxic Ischemic Encephalopathy (HIE)	8(22.9)	9(25.7)	1.000
Neonatal seizures	2(5.7)	3(8.6)	1.000
Respiratory Distress Syndrome (RDS)	7(20)	9(25.7)	0.776
Hydrocephalus	0	2(5.7)	0.473
Retinopathy of Prematurity (ROP)	0	2(5.7)	0.473
Mortality	3(8.6)	4(11.4)	1.000

No complications	20(57.1)	21(60)	1.000

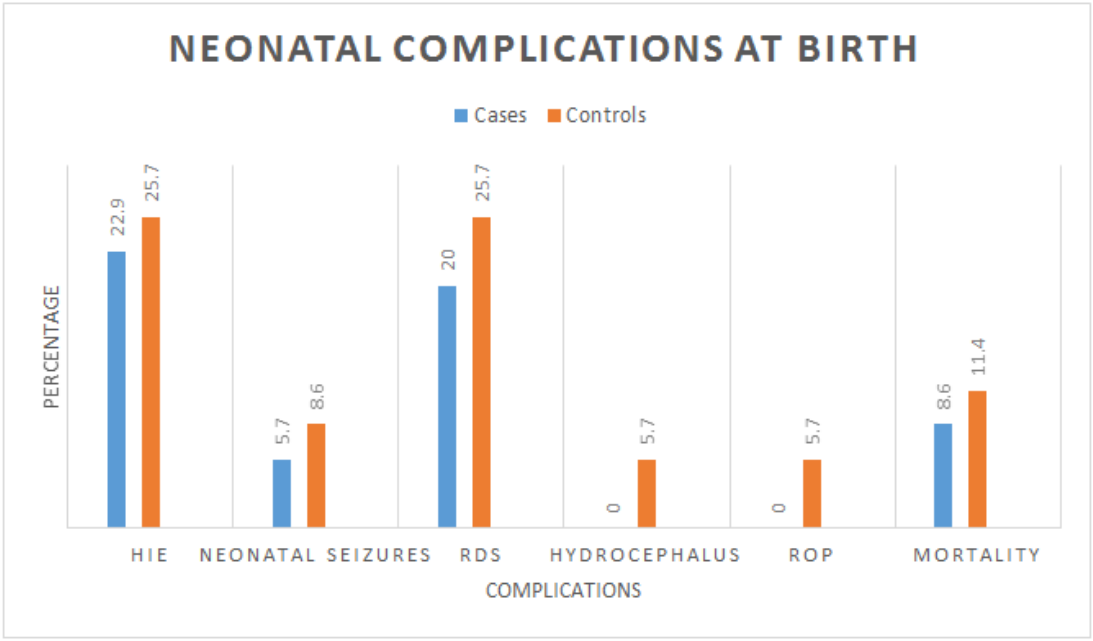
Among participants with MgSO4, majority neonates (57.1%) developed no complications. Eight neonates (22.9%) developed Hypoxic ischemic encephalopathy (HIE) in study group as compared to nine (25.7%) in control group.

Seven neonates (20%) developed Respiratory distress syndrome (RDS) in study group as compared to nine neonates (25.7%) in control group.

In the control group, two neonates (5.7%) experienced Retinopathy of Prematurity (ROP), and the equal percentage (5.7%) experienced hydrocephalus. The intervention group did not experienced any of these complications. Neonatal seizures occurred in 5.7% cases as compared to 8.6% neonates in control group.

In terms of neonatal death, the study group experienced 8.6% neonatal mortality, while the control group experienced 11.4%. This implies that antenatal MgSo4 therapy can reduce newborn mortality by around 3% and shield neonates from certain potentially fatal problems.

Hence, our analysis revealed that there were no noteworthy variations among the groups concerning the likelihood of unfavorable neonatal consequences. However, a non-significant rise in the danger of hypoxic ischemic encephalopathy, respiratory distress syndrome, neonatal seizures, retinopathy of prematurity and hydrocephalus was observed in the control group, indicating its advantageous influence on the prognosis of premature infants.



DISCUSSION

Animal and human observational studies have suggested that $MgSO_4$ is neuroprotective for the immature brain (Marret *et al*., 1995; Wolf *et al*., 2012). Although the exact processes underlying this neuroprotective effect are unknown, research have pointed to a number of potential explanations.According to Nowak *et al*., (1984) and Kang *et al*., (2011), magnesium can lessen excitotoxicity by inhibiting the N-methyl-D-aspartic acid (NMDA) receptor and reducing extracellular glutamate. Furthermore, by modulating pro-inflammatory cytokines and oxidative stress, magnesium may exhibit anti-inflammatory effects (Mazur *et al*., 2007; Burd *et al*., 2010; Rayssiguier *et al*., 2010) [12]. Magnesium sulfate has since been the subject of numerous sizable randomized prospective clinical trials aimed at assessing its effectiveness for prenatal and neonatal neuroprotection.

Nidhi *et al*., (2021) [13] suggested that incontrol group ,4% had IVH and 6% had periventricular leukomalaciacompared as compared to nil cases of IVH in MgSo4 group (p=0.14).

Bansal *et al*., [14] (2021) conducted a study in whichall surviving infants (n-93) underwent a cranial ultrasound within the first 14 days of life. On neurosonogram, 2 infants showed (periventricular leukomalacia) PVL, one each in

$MgSO_4$ and non-$MgSO_4$ group and 12 infants had IVH (Intraventricular hemorrhage). IVH was more often seen in non-$MgSO_4$ group (8/12) as compared to $MgSO_4$ group (4/12).

The incidence of cerebellar hemorrhage was significantly less in the MgSO4 group (0% vs. 16%, p value = 0.002) in a study conducted by Ayed *et al.*, (2022) [15]. Neonates who received MgSO4 had lower risks of grade 3–4 intraventricular hemorrhage (IVH) (17% in MgSo4 group vs 39% in controls) p = 0.006; moderate-severe white matter injury (WMI) p = 0.046.

All of these studies and inquiries contribute to the growing body of proof regarding the therapeutic value of this miraculous medication.

Over the past decade, adoption of magnesium sulfate for preterm neuroprotection has ensued across the globe. Across high-income countries, professional bodieshave provided committee opinions and clinical practice guidelines. The long-term prognosis for newborns with IVH varies considerably depending on the severity of IVH, complications of IVH or other brain lesions, the birth weight/gestational age and other significant illnesses that affect the neurologic outcome.

Particularly infants born at an earlier gestational age are at higher risk for cerebral palsy. The incidence of CP is much higher in children born extremely prematurely, occurring in approximately 20% of children born at ≤26 weeks gestational age but in only 4% of children born at 32 weeks' gestational age [16]. Three trials (Rouse *et al.*, (2008), Marret *et al*., (2006), Crowther *et al.*, (2003) consisting of 4387 infants was conducted and they showed that moderate or severe cerebral palsy was significantly reduced in the group who received $MgSO_4$. The risk of mild cerebral palsy was reduced by 26% in the group allocated $MgSO_4$ rather than placebo, although this did not achieve statistical significance (Haslam *et al*.,). If these results are extrapolated to a neonate's long-term neurodevelopmental outcomes, it will substantially enhance his or her prognosis.

Therefore the studies suggeststhat antenatal magnesium sulfate given to women in established preterm labor conferred neuroprotective advantage to the neonate. Although no significant results were obtained but these paved a way for further multicentric large sample size studies for defining its certain neuroprotective effect.

CONCLUSION

Magnesium is a substance which has been used for decades in the field of obstetrics as a prophylaxis for eclamptic seizures and tocolysis. Likewise, benefits of magnesium have been extrapolated to the area of premature newborns' neuroprotective deficit.

Furthermore, our study contributes to the body of evidence indicating that prenatal MgSO4 use on a large scale might be advantageous.

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