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Comparative study to evaluate the role of antenatal magnesium sulphate for neurological outcome in preterm neonates

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Abstract
Background: This study was carried out to compare the efficacy of antenatal Magnesium Sulphate for neurological outcome in preterm neonates.
Methods: A prospective comparative clinical study to evaluate the role of antenatal Magnesium Sulphate ($MgSO_4$) for neurological outcome in preterm neonates was carried out at the GMERS Medical College, Gotri, Vadodara from September 2020 to January 2022. The study comprised of total 100 patients who presented with preterm labour before 34 weeks of gestation, divided into two groups. All patients in group A were given Injection MgSO4 for Fetal Neuroprotection and in group Beware given placebo. After delivery, the outcomes were studied in terms of immediate APGAR (Appearance, Pulse, Grimace, Activity and Respiration) score, neurological abnormality at birth, features of neurodevelopment status of neonates at 1, 6, and 12 months of age.
Results: While comparing gestational age, there was significantly increased neuroprotective effect and survival in gestational age 32-34 weeks compared to 30-32 weeks and 28-30 weeks. In terms of the weight of the baby at birth, increased neuroprotective effect was seen with birthweight > 1.5 kg. In the MgSO4 group, the average APGAR score was 7 at 1 min v/s6 at 1 min in the placebo group. In the MgSO4group, the neurological developmental abnormalities at 1month was 10% in v/s 8% in the placebo group. The same at 6 and 12 months was 12% and 14% and 14% and 20%, respectively.
Conclusion: This study concludes that the Antenatal MgSO4given prior to preterm birth for fetal neuroprotection did not show significant difference between outcomes with those patients who did not receive MgSO4, except for the significant neuroprotective effect when administered between 32-34 weeks and when the birth weight is more than 1.5 kg.

Keywords: Preterm labour, magnesium sulphate for neuroprotection, preterm neonatal neurodevelopment.

Introduction
Magnesium Sulphate has been used in the management of eclamptic seizures and it is also the most familiar drug in obstetrics. Nelson and Grether was the one who identified the neuroprotective properties of magnesium in preterm infants first and they observed that Magnesium Sulphate given for pre-eclampsia and tocolysis in utero was having lower incidence of cerebral palsy in very-low-birth-weight infants (<1,500 g) compared to controls.
Preterm birth is one that occurs at <36+6 weeks of gestation or less than 258 days of gestation [1]. Amongst all the neonates diagnosed with cerebral palsy, 40% are related to preterm birth [2]. Damage to the immature brain is one of the central concerns. Typical lesions include peri-/intraventricular hemorrhages (PIVH) and periventricular leukomalacia (PVL) [3-6]. The resulting damage leads to spastic cerebral palsy of the legs. PIVH originates in the vascular bed of the germinal matrix, an area of the brain that almost completely disappears as the fetus matures. Blood vessels in this area of the brain burst very easily. Pre- and post-partum fluctuations of the cerebral blood flow can thus lead to the rupture of these blood vessels and induce PIVH [7]. In addition to perinatal mortality, a very preterm infant has a major risk of developing severe neurological problems such as damage of developing brain, cerebral palsy, cognitive dysfunction and cerebral hemorrhage [8].
Magnesium is an ionized mineral essential to hundreds of enzymatic processes, including hormone receptor binding, energy metabolism, muscle contractility as well as neuronal and neurotransmitter function [9]. It blocks calcium entry at the presynaptic junction, preventing excessive acetylcholine release and stimulation at the neuromuscular junction.

It also has a depressant effect at the postsynaptic membrane through the voltage-dependent block of N-methyl D-aspartate (NMDA) receptors [10]. This action as an NMDA receptor antagonist underpins one of the main proposed mechanisms of magnesium neuroprotection.

Materials and Methods

Study Setting: This is a prospective comparative study.

Study Area: The department of Obstetrics and Gynecology, GMERS Medical College and General Hospital, Gotri, Vadodara.

Study Period

This study was conducted for a period of 1.5 year in which follow up period was 1year

Sample Size

100 patients (50 cases &50 controls in each group).

Inclusion Criteria

Singleton pregnancy with alive fetus< 34 weeks, but > 28 weeks
Established Preterm labour

Exclusion Criteria

Any delivery beyond 34weeks of gestation

High risk conditions like:

- Preeclampsia/eclampsia
- Diabetes
- Cardiac disease
- Maternal renal insufficiency
- Maternal/fetal cardiac arrhythmia

Myasthenia gravis/maternal neuromuscular disease
Acute hemorrhage with possibility of hemodynamic instability.
IUFD
Fetal congenital anomalies

Methodology

From the eligible patients, informed consent was obtained after appropriate counseling.

All the patients were randomly divided into two groups: Group A, Injection Magnesium Sulphate Group and Group B, placebo group. The process of randomization was done by the random number software.

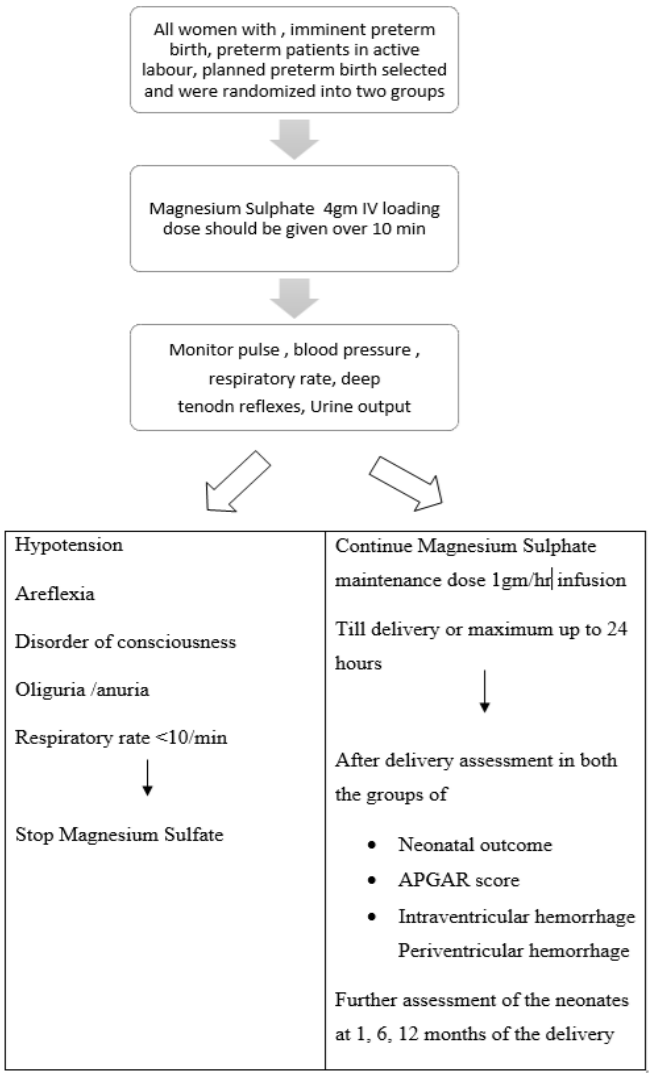
Group A was consist of the patients who were given th antenatal Magnesium Sulphate.

All the patients were allowed to proceed for either vaginal delivery or Caesarean section as per the obstetric indications, as per the protocol of the department. All the patients in group A were given Injection Magnesium Sulphate as per the following regimen:

- Dose: A loading dose of 4 gm diluted in total 20 ml Normal saline, IV slowly, followed by a maintenance infusion of 1gm per hour,
- Starting point: The timing is adjusted to be preferably within 4-6 hours prior to delivery. So, the administration is started at the beginning of the active stage of labor i.e. around 4-5 cm of dilatation of the cervix for vaginal delivery, and 4-6 hours prior to planned Caesarean Section.
- Stopping point: Immediately after the delivery or up to 24 hours, whichever is earlier.

Patients of group B were administered placebo in a similar way.

The broad flowchart of the methodology is shown here:



Results

Table 1: Comparison of 24 hours follow up APGAR score between Magnesium Sulphate and Placebo

24 hours follow up APGAR score	Magnesium Sulphate (N=50)	Placebo (N=50)	Total	P-Value
Mean ± SD	6.36 ± 0.83	6.18 ± 0.94	6.27 ± 0.89	0.312‡
Median (25^{th} -75^{th} percentile)	7(6-7)	6(6-7)	7(6-7)	
Range	4-7	4-7	4-7	

‡ Independent t test

Table 2: Comparison of outcome at follow up between Magnesium Sulphate and Placebo

Outcome at follow up	Magnesium Sulphate (N=50)	Placebo (N=50)	Total	P-Value
At 1 month				
Milestone achieved	35 (70%)	37 (74%)	72 (72%)	0.898*
Complication	5 (10%)	4 (8%)	9 (9%)	
Died	10 (20%)	9 (18%)	19 (19%)	
At 6 months				
Milestone achieved	33 (66%)	34 (68%)	67 (67%)	0.864†
Complication	6 (12%)	7 (14%)	13 (13%)	
Died	11 (22%)	9 (18%)	20 (20%)	
At 12 months				
Milestone achieved	32 (64%)	31 (62%)	63 (63%)	0.689†
Complication	7 (14%)	10 (20%)	17 (17%)	
Died	11 (22%)	9 (18%)	20 (20%)	

* Fisher's exact test, † Chi square test

Table 3: Comparison of outcome with gestational age

Outcome at follow up	28 weeks to 29 weeks + 6 days (N=11)	30 weeks to 31 weeks + 6 days (N=16)	32 weeks to 34 weeks (N=73)	Total	P-Value
At 1 month					
Milestone achieved	4 (36.36%)	5 (31.25%)	63 (86.30%)	72 (72%)	<.0001*
Complication	0 (0%)	3 (18.75%)	6 (8.22%)	9 (9%)	
Died	7 (63.64%)	8 (50%)	4 (5.48%)	19 (19%)	
At 6 months					
Milestone achieved	3 (27.27%)	5 (31.25%)	59 (80.82%)	67 (67%)	<.0001*
Complication	1 (9.09%)	3 (18.75%)	9 (12.33%)	13 (13%)	
Died	7 (63.64%)	8 (50%)	5 (6.85%)	20 (20%)	
At 12 months					
Milestone achieved	1 (9.09%)	3 (18.75%)	59 (80.82%)	63 (63%)	<.0001*
Complication	3 (27.27%)	5 (31.25%)	9 (12.33%)	17 (17%)	
Died	7 (63.64%)	8 (50%)	5 (6.85%)	20 (20%)	

* Fisher's exact test

Table 4: Association of outcome at follow up with birth weight(kg)

Outcome at follow up	<1.5 kg (N=37)	>=1.5 kg (N=63)	Total	P-Value
At 1 month				
Milestone achieved	12 (32.43%)	60 (95.24%)	72 (72%)	<.0001*
Complication	7 (18.92%)	2 (3.17%)	9 (9%)	
Died	18 (48.65%)	1 (1.59%)	19 (19%)	
At 6 months				
Milestone achieved	9 (24.32%)	58 (92.06%)	67 (67%)	<.0001*
Complication	9 (24.32%)	4 (6.35%)	13 (13%)	
Died	19 (51.35%)	1 (1.59%)	20 (20%)	
At 12 months				
Milestone achieved	11 (29.73%)	52 (82.54%)	63 (63%)	<.0001†
Complication	7 (18.92%)	10 (15.87%)	17 (17%)	
Died	19 (51.35%)	1 (1.59%)	20 (20%)	

* Fisher's exact test, † Chi square test

Discussion

Both the groups were comparable as regards the birth weight of the neonates. While comparing different gestational age groups with neonatal outcome, significantly better neuroprotective effect and survival were seen in gestational age 32-34 weeks compared to gestational age of 30-32 weeks and 28-30 weeks. In terms of the birth weight, increased neuroprotective effect was seen with baby weight > 1.5 kg. Regarding duration of Magnesium Sulphate infusion, comparison was made between those who got infusion >6 hours and those who got infusion< 6 hours. There was no significant difference between the two groups. Comparing APGAR score among Magnesium Sulphate group and Placebo group, the Magnesium Sulphate group had average APGAR score of 7 at 1 min compared to placebo group with average APGAR score of 6 at 1 min. This does not appear to be statistically significant.

Overall, at 1 month follow up, 10% of the Magnesium Sulphate group showed neurological developmental abnormalities compared 8% patients of the placebo group. This difference is statistically not significant. While at 6months these numbers are 12% and 14% for Magnesium Sulphate group and Placebo group respectively. And similarly, at 12 months follow up, the result is showing 14% and 20% neurological abnormalities neurological for Magnesium Sulphate group and Placebo group respectively. All these differences are statistically not significant.

Specifically, for those who were given Magnesium Sulphate at > 32 weeks of gestation and whose birth weight was > 1.5 kg, at 6months and 12 months follow up, there was improved neuroprotection and reduced complications.

In preterm babies, Caroline A, et al., studied Magnesium Sulphate as a neuroprotector. In Australia and New Zealand, a randomized controlled trial at 16 tertiary hospitals with

stratification by center was carried out. Total 1062 women in total with fetuses younger than 30 weeks' gestation for which birth was planned or expected within 24 hours were enrolled from February 1996 to September 2000 with follow-up of surviving children at a corrected age of 2 years. These studies demonstrated neuroprotective effects of Magnesium Sulphate while administered antenatally.

In 2009, Cochrane review was published on the topic. The five prospective randomized studies included a total of 6145 children and it was covered between 2002 to 2008. The neuroprotector, Magnesium Sulphate was tested on patients at risk of preterm birth before the end of 37th week of pregnancy. The incidence of infantile cerebral palsy (relative risk 0.68; 95% confidence interval 0.54 to 0.87), as well as in the incidence of gross motor skill dysfunction (relative risk 0.61; 95% confidence interval 0.44 – 0.85) among children whose mother has been treated with Magnesium Sulphate has a significant reduction in the study.

To prevent cerebral palsy, Dane a. *et al*. done a study in Canada regarding Magnesium Sulphate as a neuroprotector in preterm babies with recruitment of 3752 mothers over 4 years. 84% increase in the odds of optimal use, a reduction in the odds of underuse and an increase in suboptimal use were concluded in this study.

Conclusion

This study shows Antenatal Magnesium Sulphate given prior to preterm birth for fetal neuroprotection did not show any significant difference in the outcomes in comparison to those patients who do not receive Magnesium Sulphate, except for the significant neuroprotective effect when administered between 32-34 weeks and when the birth weight is more than 1.5 kg.

This study also suggests antenatal administration of Magnesium Sulphate for neuroprotection doesn't show any side effect or complication to mother and newborn so it is safe for mother and newborn.

Considering the different ethnic origin of Indian patients, vastly different labour care and neonatal units in India, such outcome may have been observed. Further randomized, multicentric studies with larger sample size are needed in Indian population to establish the efficacy of antenatal Magnesium Sulphate for neuroprotection in preterm neonates**.**

Conflict of Interest

Not available

Financial Support

Not available

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