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RESEARCH ARTICLE

TO STUDY THE EFFECT OF ANTENATAL MAGNESIUM SULPHATE FOR NEUROPROTECTION IN PRETERM BABIES

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Key words:-

Magnesium Sulphate, Neuroprotection,
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Abstract

Background: Antenatal administration of magnesium sulfate is an important part of the neuroprotective strategy for preterm infants. Strong evidence from five randomized controlled trials and five meta-analyses has demonstrated that magnesium sulfate, when administered before preterm delivery, significantly reduces the risk of neurological disabilities. In our study, we aimed at assessing the effectiveness and safety of antenatal magnesium sulphate for neuroprotection in the preterm babies.

Methods: This was a prospective randomized controlled trial conducted on 586 women in preterm labour during the period of January 2019 to 2020 attending opd in the department of obstetrics & gynecology at Patna medical college and hospital in 2019. They were randomly allocated into 2 groups.

Group A : received magnesium sulphate as neuroprotective agent

Group B: received sodium chloride solution.

Procedure efficacy (defined as incidence of neurological disabilities, mortality and resuscitative measures in both groups), safety and side effects were assessed in both groups.

Results: Babies developing neurological disabilities were less in magnesium sulphate group than sodium chloride group which is statistically insignificant. Total mortality in group A was 137 whereas in group B is 169 which is statistically insignificant. 1 neonate had intraventricular hemorrhage in group A while 4 in group B which is statistically insignificant.

Conclusion: Although various studies have suggested that magnesium sulphate is cost effective and efficient neuroprotective agent in preterm babies but in our study we could not find significant difference between magnesium and placebo group, but it is proved to be efficient in preventing intraventricular hemorrhage.

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Introduction:-

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide. It accounts for 75% of neonatal deaths & 50% of long term morbidity including respiratory & neurodevelopmental impairment. According to WHO, across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born. Prevention of neurological

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disability associated with preterm birth is one of the major persistent challenge. The risk of morbidity & mortality is inversely related to gestational age at birth.

In observational studies, antenatal administration of magnesium sulphate has been considered as neuroprotective. The dose of 4g given intravenously over 15 min continued by 1g/h until maximum 24 hr & minimum 4 hr is standard regimen proposed in most guidelines. Owing to its biological properties, including its action on N-methyl-D-aspartate receptor blocker & its anti-inflammatory effects, magnesium is a good candidate for neuroprotection. Aim of this study is to determine the effectiveness of magnesium sulphate given for neuroprotection to women at risk of preterm birth before 32 week gestation in preventing neurological deficit.

Methods:-

This was prospective randomized controlled trial conducted during the period of January 2019 to 2020 in the department of obstetrics & gynecology at Patna Medical College and Hospital, Patna. The study recruited 586 patients admitted in labour ward. They were randomised into 2 groups.

Group A : 294 Patients in preterm labour receiving magnesium sulphate as neuroprotective agent

Group B: 292 Patients in preterm labour receiving sodium chloride solution.

These patients had regular antenatal checkup & routine blood investigations & satisfied the inclusion and exclusion criteria.

Inclusion Criteria

1. All pregnant women with single, twin fetus younger than 32 week gestational age with preterm labour.
2. Who consent to be part of the study

Exclusion Criteria

1. Women with gestational age more than 32 weeks
2. Women in second stage of labour
3. History of receiving magnesium sulphate therapy in this pregnancy (e.g magnesium sulphate used for eclampsia, hypertensive disease of pregnancy).
4. Contraindications to magnesium sulphate-
 - respiratory rate <16/min
 - Absent patellar reflex
 - Urine output <100ml in previous 4 hrs
 - Renal failure
 - Hypocalcemia

Eligible women who gave written informed consent were enrolled. Patients in both groups underwent through history taking, clinical examination, ultrasonography to confirm gestational age.

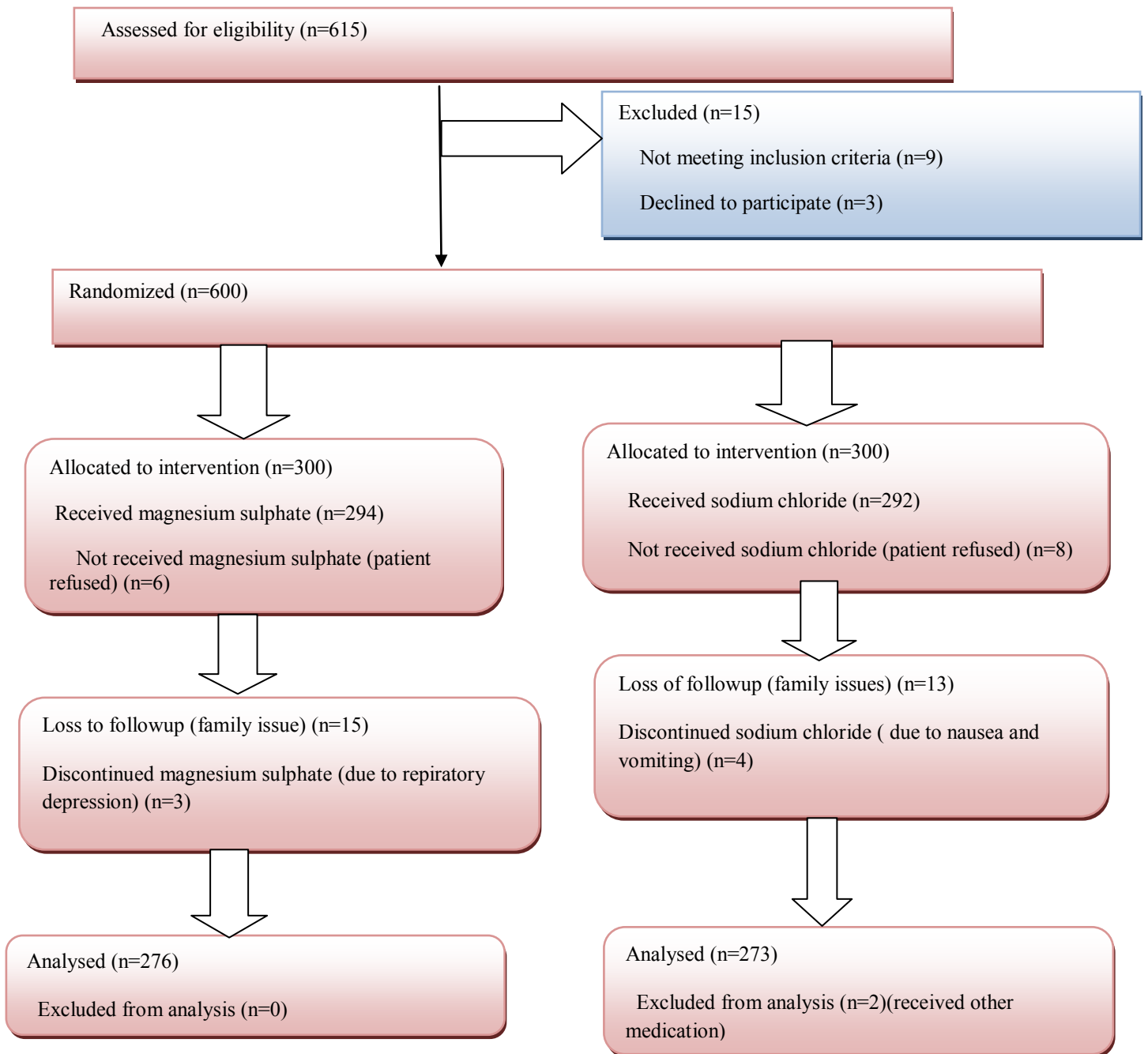
Intervention

In group A patients were given a loading infusion of 8ml (4g) [16mmol] of magnesium sulphate for 20 mins followed by a maintenance infusion of 2ml/h until birth (if occurred within 24 hr) or upto 24 hrs.

In group B patients were given infusion of 8 ml of sodium chloride solution for 20 min followed by maintenance infusion of 2ml/h until birth (if occurred within 24 hr) or upto 24 hrs.

Pulse rate, blood pressure, respiratory rate, knee jerk, urine output were monitored throughout infusion and any adverse effects were recorded. The loading and maintenance dose were stopped if respiratory rate decrease more than 4 min, bp fall more than 15 mm hg below baseline.

All surviving infants had a cranial ultrasound performed within first 7 days of life to detect intraventricular hemorrhage & a later ultrasound (beyond 4 week at age or at time of discharge) to identify periventricular leukomalacia.



Statistical Analysis

Data analysis used χ^2 or Fisher’s exact test, as appropriate, for categorical variables and the ANOVA test for continuous variables. P value <0.05 is applied as statistically significant.

Result:-

Table 1:- Maternal characteristics.

| Maternal characteristics | Group A (magnesium sulphate group) | Group B (Placebo group) | P value |
|-----------------------------|------------------------------------|-------------------------|---------|
| Mean maternal age(years) | 28.37 | 29.21 | >0.05 |
| Parity | 2.7+-0.91 | 2.6+-1.27 | >0.05 |
| Mean gestational age(weeks) | 27.6+-2.12 | 26.1+-1.39 | >0.05 |

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Table 2:- Principal reasons for preterm birth.

| Reason for preterm birth | Group A (magnesium sulphate group) N=294 | Group B (Placebo group) N=292 | P value |
|-------------------------------|--|-------------------------------|---------|
| Preterm labour(spontaneous) | 78 | 72 | >0.05 |
| Premature rupture of membrane | 48 | 48 | >0.05 |
| Preeclampsia | 27 | 30 | >0.05 |
| Polyhydraminos | 42 | 46 | >0.05 |
| Twin pregnancy | 26 | 22 | >0.05 |
| Maternal & fetal infections | 73 | 74 | >0.05 |

Table 3:- Complications due to intervention.

| complications | Group A (magnesium sulphate group) N=294 | Group B (Placebo group) N=292 | P value |
|------------------------|--|-------------------------------|---------|
| Headache | 31 | 24 | >0.05 |
| Hypotension | 11 | 8 | >0.05 |
| Nausea & vomiting | 16 | 11 | >0.05 |
| Flushing&sweating | 12 | 9 | >0.05 |
| Respiratory depression | 3 | 0 | >0.05 |
| Hyporeflexia | 0 | 0 | >0.05 |
| Palpitation | 6 | 2 | >0.05 |
| Post partum hemorrhage | 9 | 4 | >0.05 |

Table 4:- Characteristics at birth & neonatal morbidities.

| Characteristics | Group A (magnesium sulphate group) N=294 | Group B (Placebo group) N=292 | P value |
|-----------------------------------|--|-------------------------------|---------|
| Gestational age(weeks) | 29.41+-1.92 | 30.36+-2.73 | >0.05 |
| Birth weight(gm) | 1115+-333 | 1037+-833 | 0.012 |
| Head circumference(cm) | 24.76+-1.6 | 21.24+-0.8 | 0.051 |
| Total NICU admission, n(%) | 254(86.3) | 256(87.6) | >0.05 |
| Neurological disabilities, n(%) | 167(56.8) | 162 (55.4) | >0.05 |
| APGAR AT 5' <7 | 226(76.8) | 270(92.4) | <0.05 |
| Intubation, n(%) | 197(67) | 199(68.1) | >0.05 |
| External cardiac massage, n(%) | 213(72.4) | 257(88) | <0.05 |
| Epinephrine, n(%) | 181(61.5) | 216(73.9) | <0.05 |
| Mortality, n(%) | 137(46.6) | 169(57.4) | >0.05 |
| Necrotising enterocolitis, n(%) | 1(0.3) | 2(0.68) | >0.05 |
| Intraventricular hemorrhage, n(%) | 1(0.34) | 4(1.37) | >0.05 |
| Fetal infection, n(%) | 164(55.8) | 172(58.5) | >0.05 |

Result:-

Total 586 women were randomly selected who were in gestational age < 32 weeks, attending opd or emergency of patna medical college and hospital, patna with preterm labour. They were divided into two groups. Group A (n=294) received magnesium sulphate & group B(n=292) received sodium chloride infusion.

The descriptive statistics of maternal demographics & obstetrics characteristics are described in **Table 1**. Both groups are comparable and showing no significant differences ($P > 0.05$). Most of the cases in group A belonged to gestational age 27 to 29 weeks & in group B belonged to gestational age 28-30 weeks ($p > 0.05$).

Table 2 shows different reasons for preterm birth. In group A out of 294 cases, 78 had spontaneous preterm labour, 48 had preterm premature rupture of membrane, 27 had preeclampsia, 42 had polyhydramnios, 26 had twin pregnancy, 73 had maternal & fetal infections whereas in group B, out of 292 cases, 72 had spontaneous preterm labour, 48 had preterm premature rupture of membrane, 30 had preeclampsia, 46 had polyhydramnios, 22 had twin pregnancy, 74 had maternal & fetal infections. Both the groups are comparable with respect to the reasons of preterm birth but statistically insignificant ($p > 0.05$).

Table 3 shows complications due to intervention in both groups like nausea & vomiting, headache, flushing & sweating, hypotension, palpitation, it was found that complications noted in both the groups were statistically insignificant. There was no hyporeflexia in any group. There was 1 case of respiratory depression in group A that led to termination of intervention. In 9 cases, postpartum hemorrhage occurred in group A & 4 cases in group B which was successfully managed conservatively.

Table 4 shows characteristics at birth & neonatal morbidities. Mean gestational age in group A was 29.41 ± 1.92 weeks while it was 30.36 ± 2.73 weeks in group B. Mean birth weight in group A was 1115 ± 333 g & in group B was 1037 ± 833 gm. ($p > 0.05$). The number of babies getting NICU admission with prior antenatal magnesium sulphate was 254 as compared to with sodium chloride infusion was 256, however this difference was statistically insignificant.

Babies developing neurological disabilities were 167 in magnesium sulphate group whereas 162 in sodium chloride group. (P value > 0.05). APGAR in 5 min < 7 was 226 in magnesium sulphate group as compared to 270 in sodium chloride group which is statistically significant. Neonates requiring intubation was 197 in magnesium sulphate group whereas 199 in sodium chloride group. (P value > 0.05). Neonates requiring external cardiac massage were 213 in magnesium sulphate group whereas 257 in sodium chloride group. (P value < 0.05). Epinephrine was given 181 in magnesium sulphate group whereas 216 in sodium chloride group (P value < 0.05). Total mortality in group A was 137 whereas in group B is 169 which is statistically insignificant. 1 neonate developed necrotizing enterocolitis in group A while 2 in group B. 1 neonate had intraventricular hemorrhage in group A while 4 in group B which is statistically insignificant. Fetal infection developed in 164 of magnesium sulphate group whereas 172 in sodium chloride group. (P value > 0.05).

Discussion:-

In the late 1990s studies of infants born to mother given magnesium sulphate to prevent eclamptic seizures or as tocolysis showed reduction in rate of cerebral palsy. Although exact mechanism of action of magnesium sulphate as neuroprotective agent is unknown but it is seen that it acts as NMDA (N-methyl-D-aspartic acid) receptor antagonist present on oligodendrocyte which is important in glial injury process. Magnesium sulphate may reverse the harmful effects of hypoxic/ischemic brain injury by blocking NMDA receptors, acting as calcium antagonist and reducing calcium influx in cells. It also protects from free radical injury & acts as vasodilator, prevents hypoxic injury, attenuates cytokine or excitatory amino acid induced cell damage and has anti-apoptotic activity. Magnesium forms complex with adenosine triphosphate which is required for activity of ion pumps, enzymes, proteins and various transporters.

Five randomized controlled trials, three meta-analyses, and a Cochrane review were conducted. On the basis of these studies, the university of Adelaide issued, in March 2010, a guideline on best practice for clinical care in the use of antenatal magnesium sulphate prior to preterm birth for the neuroprotection of fetus, infant and child.

In 2002, Mittendorf et al. randomized trial there was no significant difference in neonatal outcome between control and treatment groups.

In 2003 by Crowther et al. showed that magnesium sulfate had a protective effect on the risk of IVH; however, this effect was not statistically significant. In our study, 1 out of 294 cases in group A developed intraventricular hemorrhage while 4 out of 292 cases in group B developed IVH which is statistically insignificant ($p > 0.05$).

In 2008, Marret et al. showed that although $MgSO_4$ has a protective effect on IVH, this effect was not statistically significant.

In a systematic review study conducted by Doyle et al. in 2009 with the aim of studying the effect of antenatal MgSO₄ on neurologic outcomes in preterm infants, the results showed that use of MgSO₄ dramatically reduced the risk of cerebral palsy in the children of women at risk of preterm birth also, a significant decrease was observed in the rate of substantial gross motor dysfunction but no statistically significant effect on pediatric mortality, or on other neurologic impairments or disabilities, in the early years of life of children. In general, there are many reports that show that MgSO₄ increases the antioxidant properties of the brain, protects the brain cells against hypoxia and apoptosis, and normalizes platelet aggregation.

Since 2010, an increasing number of obstetrical societies have recommended its use to improve the neurological outcomes of preterm infants, especially the International Federation of Gynecology and Obstetrics and World Health Organization in 2015, and France in 2017.

A study by Petrova and Mehta in 2012 revealed that there was no significant association between the use of magnesium sulfate, IVH, and parenchyma injury.

The Cochrane review of trials concluded that antenatal magnesium sulphate therapy given to mother at risk of preterm birth substantially reduced the risk of cerebral palsy in their children, there was also significant reduction in rate of gross motor dysfunction.

Conclusion:-

Although various studies have suggested that magnesium sulphate is cost effective and efficient neuroprotective agent in preterm babies but in our study we could not find significant difference between magnesium and placebo group, but it is proved to be efficient in preventing intraventricular hemorrhage and overall mortality.

More study is needed to clarify the impact of magnesium on the cognitive outcome.

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