ORIGINAL RESEARCH PAPER

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USE OF MAGNESIUM SULFATE DURING PRETERM DELIVERY -EFFECT ON NEONATAL OUTCOME

KEY WORDS: Preterm birth, Magnesium sulfate, Neonatal outcome

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ABSTRACT

Objectives: Preterm birth is a major obstetric health care problem today. In India alone, the estimated number is 3.6 million per year. It is of key importance to predict and prevent preterm birth, or at least prevent crippling lifelong effects of preterm birth. The present study is carried out to evaluate the efficacy of Magnesium sulfate in anticipated preterm birth and on immediate neonatal outcome. **Methods and Materials:** An observational study was conducted on a sample size of 60 pregnant women admitted with preterm labor at Mediciti Institute of Medical Sciences, Telangana State, India. Thirty pregnant women were administered MgSo4 before delivery (group 1) and outcomes related to the immediate neonatal outcomes like APGAR scores at 1&5 minutes, need for NICU admission and neonatal resuscitation and neonatal death were measured and compared with women who did not receive MgSO4 (group 2). Data collected was exported to SPSS version 16 for analysis. Descriptive data was measured in percentages. For inferential statistics chi-squre test was applied .P value < 0.05 was considered significant. **Results:** In women who received MgSO4, NICU admission were required in 45.5% of babies whereas 93.8% of babies required NICU admissions in mothers who did not receive MgSO4. Only 3% of babies from group 1 required neonatal resuscitation whereas 34.4% of babies from group 2 required neonatal resuscitation (p=0.001).**Conclusions:** Magnesium sulfate when given to mothers diagnosed with preterm labor has been shown to improve immediate neonatal outcomes.

INTRODUCTION

Preterm labour is defined as the onset of labour prior to completion of 37 weeks of gestation, in a pregnancy beyond 20 weeks of gestation (WHO, 2014). Globally, more than 12% of all pregnancies are preterm (Fonseca, Damiao & Moreira, 2020). Preterm birth is important to achieve UN Sustainable Development Goal 3 to curtail preventable deaths of newborns and children under 5 years by the year 2030 (Walari, 2020). Preterm birth is the most important cause of neonatal mortality and the second-leading cause of death before age of 5 years (after pneumonia) worldwide. It also accounts for a great part of short- and long-term morbidity.

Maternal risk factors of preterm birth include pre-eclampsia, eclampsia, HELLP syndrome, previous caesarean section or uterine rupture, and maternal diseases (Gyamfi-Bannerman et al, 2011), while fetal indications are fetal growth restriction, oligohydramnios, intrauterine infection, poor umbilical blood flow, abnormal fetal heart rate, placental abruption, and placenta previa (Gyamfi-Bannerman et al, 2011; Gyamfi-Bannerman, 2012). Other risk factors include preterm mothers (Wilcox, Skjærven & Lie, 2008), sex of the child (Zeitlin et al, 2002), children with birth defects (Rasmussen et al, 2001), ethnicity of the mother (Patel et al, 2004) and socio-economic characteristics (Ganchimeg et al, 2014; Sukhov et al, 2011; Thompson et al, 2006). A common genetic susceptibility to preterm birth, autoimmune and inflammatory disease is also implicated (Coucerio et al, 2021).

The consequences of preterm birth include respiratory, neuro-developmental disability and mortality (Hibbard et al, 2010; McIntire & Leveno, 2008; Wang et al, 2004). Also, being born preterm increases the risk of developing chronic medical and functional disorders later in life including type 2 diabetes, hypertension, cardiovascular diseases and obesity (Annesi-Maesano, Moreau, & Strachan, 2001; Crump et al, 2011, Jaakkola et al, 2006; Mackay et al, 2013).

$MgSO_4$ has proven to be beneficial for neuroprotection in preterm births. Though the exact mechanism of action of antenatal MgSO4 on fetal neuroprotection is not clear, the mechanisms suggested were decreased neuroinflammation and raised seizure threshold (Johnson, Tremble & Chan, 2014), decreased haemorrhage in cerebellum (Gano & Partridge, 2016) and vasodilatation (Imamoglu, Gursoy & Karatekin, 2014) . Several observational studies showed infants whose mothers received $MgSO_4$ had a markedly decreased risk of developing cerebral palsy (Saigal & Doyle, 2008; Nelson & Grether, 1995; Stanley & Crowther, 2008; Marret, Marpeau & Bénichou 2008; Cahill, Stout & Caughey, 2010). However, there are conflicting reports on its effect on immediate neonatal outcomes. Studies on the effect of $MgSO_4$ on preterm births are non-existent in India. In light of these facts, our objective in this study was to determine whether treatment with $MgSO_4$ in preterm delivery affects immediate neonatal outcomes.

MATERIALS AND METHODS:

The study was conducted on sixty pregnant women admitted with preterm labor in the labor ward of MediCiti Institute of Medical Sciences in Ghanpur, Telangana, from January 2017 – July 2018.

Women admitted were evaluated based on a selection criteria and considered for the study. The selection criteria were as follows: pregnant women with diagnosis of imminent preterm labour, preterm premature rupture of membranes with regular uterine contractions, medical or obstetric condition necessitating preterm delivery and singleton or multiple pregnancy. Women with singleton or twin pregnancies were eligible if they were admitted with a viable fetus at less than 36 weeks of gestational age. Women with

non-reassuring fetal status, presence of any infection, in their second stage of labour, contraindication to MgSO4, anticipated delivery in less than 2 hrs, any known major fetal anomalies and cases with intrauterine fetal death were excluded from the study. In our protocol the contraindications for MgSO4 are renal failure, maternal cardiac arrhythmia during this pregnancy, myasthenia gravis, and urgent delivery. We considered urgent delivery for any maternal or fetal emergency that required delivery in the shortest time such as abnormal fetal heart rate tracing, severe antepartum hemorrhage. Eligible women were informed regarding details of the study protocol, and the adverse effects and benefits of $MgSO_4$. Written informed consent was taken from willing participants and institutional ethical clearance was obtained. For purposes of this study, imminent preterm birth was defined as high likelihood of birth due to either active labour with cervical dilatation>4cms, with or without preterm premature rupture of membranes, or planned preterm birth for fetal or maternal indications or other situations such as significant vaginal bleeding. The gestational age at presentation was determined preferably by first trimester scan. If a first trimester scan was not available, then menstrual dating and/or a second trimester scan was considered. Other routine investigations were performed. The 60 women considered for this study were divided randomly into two groups with 30 in each group. Demographic data such as age, BMI and other variables were collected with the patient's consent. Group 1 were those in whom $MgSO_4$ was given. A 4g loading dose of $MgSO_4$ was given IV slowly over 20-30 min. No $MgSO_4$ was given to those in group 2. There were five primary outcomes for this study: (1) need for NICU admission, (2) APGAR scores at one and (3) five minutes, (4) need for neonatal resuscitation and (5) neonatal death.

Statistical Analysis:

Information collected was entered into MS-Office Microsoft excel 2010 spread sheet. This raw data was exported to SPSS version 16 for analysis. Descriptive data was presented in measured in percentages. For inferential statistics chi-square test was applied. P value < 0.05 was considered significant.

Results and Observations:

The present study was conducted in a rural teaching hospital - the cultural practice in this area is women get married at a younger age and conceive soon after marriage. Table 1 shows the baseline characteristics of women in the study. The age distribution was studied across four different spectra (younger than 20, 21-25, 26-30 and older than 31) with equitable distribution across the two different groups with the highest numbers (just above 50% in both groups) being in the 21-25 category. For the same reasons as above, majority of women belonged to low socio-economic status with low literacy levels. Women were categorized according to Asian BMI classification. Most of the women (46.6% in both groups) were in the normal-weight category (18.5 – 22.9 kg/m^2). Gestational age was used to categorize the population into two time-periods (28-32 weeks and 33-36 weeks) with very preterm births constituting 26.6% and 13.3% in groups 1 and 2 respectively. Multigravida women constituted majority of the present study with primigravida women accounting for 43.3% and 26.6% across the two groups. Previous history of one miscarriage was found only in 16.6% and 13.3% of women respectively in group 1 and 2 respectively. Past history of two miscarriages was found only in one woman in both the groups.

With respect to co-morbid conditions, majority of women (43.3%) in group 1 were mildly anaemic, whereas in group 2, 40% of women were not anaemic. The onset of labour was spontaneous in majority of the women in both the groups (77% and 83% respectively). Vaginal delivery was seen in most of the women in group 1 (67%) and group 2 (57%), followed by emergency caesarean section. Table 2 shows the time interval between the administration of MgSO4 and delivery was studied across time (in hours) categories (0-6, 6-12, 12-18, 18-24, 24-30, 30-36, 36-42, 42-48). It was less than 6 hours for most of the women in group 1 (43.3%). Table 3 shows the neonatal outcomes of both the groups. For the sex of the neonate, there was preponderance of females in group 1 (62.8%) and males in group 2 (63.3%). Finally the birth weight of the neonates was studied across 4 weight (in kg) categories (<1.5, 1.51-2.50, >2.51) with most of the neonates weighing between 1.51-2.5 kg in both the groups at 81.8% and 56.2% respectively. In Group 1, APGAR Score was 7-10 at 1minute and at 5 minutes in all the babies. NICU admissions were required in 45.5% of babies in group 1 and 93.8% of babies in group 2.Only 3% of babies from group 1 required neonatal resuscitation whereas 34.4% of babies from group 2 required neonatal resuscitation (p=0.001).

DISCUSSION :

The study was carried out to find out neuroprotective effect of MgSO4 on immediate neonatal outcomes. The primary outcome measures were need for NICU admission, APGAR scores, need for neonatal resuscitation and neonatal deaths. The study setting was in a rural teaching hospital in an area where generally marriages and pregnancies happen at an earlier age. Hence the mean maternal age was 23.7±3.9 years in group 1 and 24.7±4.2 years in group 2 which was lower compared to PreMag (Marret et al, 2007) (29.3±5.3& 29.5±5.1 years) and Rouse et al (2008) (26.1±6.3& 25.9±6.2 years). The mean gestational age in the present study was 33 weeks in both the groups which was higher compared to other studies as women were included from 28 weeks of gestation. The mean gestational age in PreMag study (Marret et al, 2007) was 30 weeks in both the groups. The mean gestational age in Beam study (Rouse et al, 2008) was 28 weeks in both the groups and in ACTOMgSO4 study (Crowther et al, 2003), mean gestational age in both groups was 27 weeks,` as women were included from 22 weeks. The prepregnancy maternal BMI is a modifiable risk factor for preterm birth. With regard to BMI, in the present study women were classified based on Asian BMI classification and the mean BMI is low (20.6±4.04kg/m2 in group 1 and in group 2 was 20.4±2.97kg/m2) as most of these women were from low socio-economic status and with low literacy levels and hence malnourished. In Rouse et al (2008), mean BMI of group 1& group 2 was 26±6.7kg/m2 and 26.4±6.9kg/m2 respectively. In the present study most common cause for preterm in group 1 was PPROM, and in group 2, hypertensive disorders of pregnancy. PPROM causes about 30-40% of preterm births (Mercer, 2003). The cause for preterm may be spontaneous or either iatrogenic for various obstetric indications. Similar findings were seen in Rouse et al (2008) and Marret et al (2007). In the present study mean birth weight of neonates in group 1 was 1.96±0.4kgs and in group 2 was 1.8±0.5kgs which was higher when compared to Rouse et al (2008) (1.4kg in both groups) and Marret et al (2007) (1.3kg and 1.4kg in group 1 and group 2 respectively) as women in present study were included from 28 weeks to 36 weeks of gestational age whereas in other studies the women were recruited from 22 weeks gestation till 33 weeks gestation. The primary outcomes studied were NICU admission, APGAR scores, need for neonatal resuscitations and neonatal deaths. In the present study 45.4% of neonates in group 1 and 93.7% of neonates in group 2 were admitted in NICU and 3.03% of neonates in group 1 and 34.3% of neonates in group 2 required resuscitation after birth like chest compressions, intubation and oxygen mask where as in Beam study (Rouse et al, 2008), 16.6% & 15.8% of neonates in group 1&2 respectively did not require resuscitation. The difference in need for neonatal resuscitation in present study and in Rouse et al (2008) was due to difference in sample size in both the studies and less number of women were included in the present study. The Apgar score is a standardized score that provides information on the condition of the baby when the baby is born. A score 7 or above is normal, while a score below 7 indicates distress. In the present study ,none of the neonates who received MgSO4

had APGAR <7 at the end of 5 minutes and in group 2 , 3.12% of neonates had lower scores However, in Beam study ,there was not much significance (18.1% & 18.5% in group 1 & 2 respectively) CP was not included in primary outcome in the present study because duration of study period was short ,hence immediate neonatal outcomes were only included to know neuroprotective effects of MgSO4 whereas in other studies CP was taken as major primary outcome In Rouse et al (2008), when risk of CP was examined, CP was less in MgSO4 treated group (1.9% vs 3.5%). In the present study there were no neonatal deaths in MgSO4 group and in group 2 there were 18.7% of neonatal deaths. This is in contrary to Rouse et al (2008) where the neonatal mortality was similar in 2 groups,9.5% in MgSO4 group and 8.5% in placebo group. Also in Drassinower et al (2002) study, the neonatal deaths after 30 weeks was 3.4% and 1.5% respectively in 2 groups and concluded that MgSO4 did not affect immediate neonatal outcomes or initial neonatal resuscitation. Indeed, the three large RCTs on neuroprotection did not show any adverse outcomes among MgSO4 exposed neonates.

Some of the strengths of the study was the prospective nature of the study. Also, the results were compared with a control group. Health care personnel performing neonatal assessment after birth and resuscitation were blinded to treatment assignment, thus limiting bias. The limitations of the study were the small size of the women recruited, and Cerebral Palsy which has a high incidence in preterm infants was not studied.

CONCLUSION:

Three major conclusions can be drawn from the results of the present study. *Firstly*, it has been shown that there is significant reduction in need for NICU admission in those who received $MgSO_4$ as neuroprotective. *Secondly*, there is a statistically significant reduction for need of neonatal resuscitation among cases who were given $MgSO_4$. *Finally*, there is a reduction in number of neonatal deaths in those who were given $MgSO_4$. The conclusions from this study demonstrate that magnesium sulfate has been shown to improve several immediate neonatal outcomes when given before delivery in the case of preterm births.

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Conflicts of interest:None declared

Table1: Baseline characteristics of study population

Variables	Group 1	Group 2	P value
Age (Years)			
≤20	6 (20%)	5 (16.6%)	0.77
21- 25	17 (56.7%)	16 (53.3%)	
26-30	6 (20%)	6 (20%)	
>31	1 (3.3%)	3 (10 %)	
Literacy			
Illiterate	8 (27%)	9 (30%)	0.77
Literate	22 (73.5%)	21(70%)	
Socioeconomic status			
Lower,Lower middle	10(33.3%)	8(26.7%)	0.58
Middle	11(36.7%)	15(50%)	
Upper,Upper Middle	9(30%)	7(23.3%)	
BMI (Kg/m2)			
≤ 18.4	9(30%)	10(33.3%)	0.54
18.5-22.9	14(46.7%)	14(46.7%)	
23-27.4	5(16.7%)	6(20%)	
≥ 27.5	2(6.7%)	-	
Gravida			
Primi	13(43.3%)	8(26.7%)	0.18
Multi	17(56.7%)	22(73.3%)	
Gestational age in weeks at birth			
28-32	8(26.7%)	4(13.3%)	0.197
33-36	2273.3%)	26(86.7%)	
Previous H/O miscarriage			
yes	6(20%)	5(16.7%)	0.74
no	24(80%)	25(83.3%)	
Anaemia			
Yes	19(63.3%)	12(60%)	0.79
No	11(36.7%)	18(40%)	
Labor			
Spontaneous	23(76.7%)	25(83.3%)	0.52
Induced	7(23.3%)	5(16.7%)	
Mode of delivery			
Elective LSCS	3(10%)	2(6.7%)	0.61
Emergency LSCS	7(23.3%)	11(36.7%)	
Vaginal	20(66.7%)	17(56.7%)	
Sex of the neonate			
Female	22(66.7%)	13 (40.6%)	0.04
Male	11(33.3%)	19(59.4%)	

Table 2: Time interval between administration of MgSo4 and delivery

Time interval in hours	Number n= 30 (%)
0-6	13 (43.3%)
6- 12	5 (16.6%)
12-18	-
18-24	2 (6.6%)
24-30	3 (10%)
30- 36	2 (6.6%)
36-42	2 (6.6%)
42-48	3 (10%)

Table 3: Neonatal Outcomes in both the groups

Variable	Group 1 (n=33)	Group 2 (n=32)	P value *
Birth weight (Kg)			
< 2.5	29 (96.7%)	27(90%)	0.61
≥ 2.5	1(3.3%)	3(10%)	
APGAR score at 1 m			
7-10	33(100%)	25(78.1%)	0.005
<7		7 (21.9%)	
APGAR score at 5 min			
7-10	33 (100%)	31(96.9%)	0.49
<7	-	1(3.1%)	
NICU admission			
yes	15(45.5%)	30(93.8%)	0.00
no	18(54.5%)	2(6.2%)	
Need for neonatal resuscitation			
yes	1(3%)	11(34.4%)	0.001
no	32(97%)	21(65.65)	
*Chi square test			

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