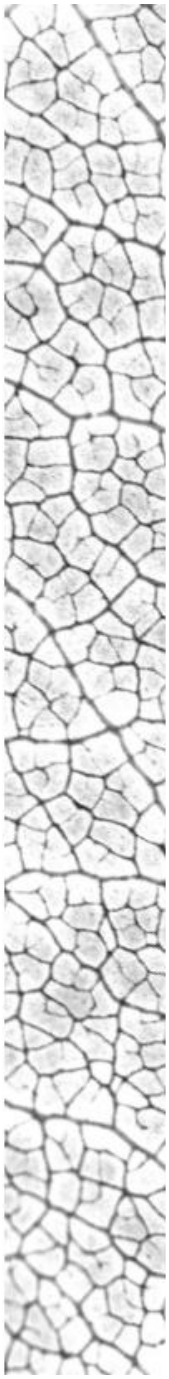

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Comparison of short-term outcome and serum magnesium levels in premature infants of mothers after magnesium sulfate therapy

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Abstract

Background: Magnesium sulfate ($MgSO_4$) is proven to be a neuroprotectant which functions to reduce the risk of cerebral palsy in premature infants, but the effects on the short-term outcome of newborns are still contradictory. This study aimed to analyze differences in short-term outcomes and serum magnesium levels in newborns after given $MgSO_4$ therapy.

Methods: This was a prospective cohort study. Subjects were divided into two groups involved preterm infants from mothers who received $MgSO_4$ and pregnant women who did not received $MgSO_4$ as a control.

Results: Among sixty subjects, there were significant differences in outcomes for gestational age infants and respiratory distress syndrome (RDS) between two groups ($p = 0.011$ and $p = 0.013$, respectively). Whereas, the significance results were found in birth weight ($p = 0.306$), Apgar scores 1 ($p = 0.816$) and 5 minutes ($p = 0.924$), the use of ventilators ($p = 0.335$), sepsis ($p = 0.276$), mortality ($p = 0.754$), and umbilical artery pH ($p = 0.123$). The magnesium serum levels of mothers who received MgSO4 and control were 3.45±1.65 mg/dl and 1.78±0.23 mg/dl, respectively ($p = 0.001$), and infants who received MgSO4 and control were 3.10±1.35 mg/dl and 1.74±0.19 mg/dl, respectively ($p = 0.001$).

Conclusion: There were significant differences in infant outcomes only at gestational age and RDS. The magnesium serum levels of newborns in therapy group were higher than control.

Keywords: MgSO4, short-term outcome, premature infant

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INTRODUCTION

In the late 1990s, studies of infants born to mothers given magnesium sulfate (MgSO4) to prevent eclampsia seizures or to tocolism showed decreased levels of Periventricular Cystic Leukcomalacia (PVL) and cerebral palsy (CP). The meta-analysis stated that the administration of MgSO4 as a neuroprotection is proven to prevent CP. Cochrane in 2009 also revealed that patients given MgSO4 could reduce the incidence of CP by 1.6% compared to those not given antenatal MgSO4. For moderate to severe CP levels, $MgSO_4$ shows the ability to reduce the risk of CP by a statistically significant difference (Salfi et al. 2019, Zeng et al. 2016).

The use of $MgSO_4$ as a neuroprotection begins with studies in preeclampsia patients where there is a decrease in CP in patients receiving $MgSO_4$ therapy. $MgSO_4$ can reduce blood pressure thereby reducing the risk of eclampsia and maternal death in which no adverse effects can be seen on the mother or baby in the short term. Thus, Magnesium sulphate for Prevention of Eclampsia trial (MAGPIE trial) concluded that the short-term effects on the administration of $MgSO_4$ therapy are safe (Group 2007, Pasaribu et al. 2016). Preterm birth is the leading cause of neonatal death (Sukatendel et al. 2018). The meta-analysis concluded that there is a reduced risk of developing CP in fetuses exposed to $MgSO_4$ to mothers at risk of giving

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birth to premature babies without increasing the risk of fetal or newborn death (Costantine et al. 2009).

However, if seen from the study conducted by Dwight in 2008, fetal exposure to $MgSO_4$ prior to the anticipation of early preterm labor does not reduce the combined risk of CP or death. Side effects have also been reported in several studies of neonates exposed to antenatal $MgSO_4$. The risk of respiratory distress, the need for resuscitation, neonatal seizures, and Apgar scores less than 7 at 5 minutes will increase with increasing $MgSO_4$ concentrations in the baby's body (Rouse et al. 2008).

The use of $MgSO_4$ for neuroprotection is not yet a fixed procedure in Indonesia. Short-term side effects are a concern because the infant mortality rate at less than 32 weeks' gestation in Indonesia is quite high. Premature infants with high exposure to $MgSO_4$ (≥4.5 Meq/L) can increase perinatal mortality due to lack of birth weight and gestational age (Basu et al. 2011). However, there are a number of studies of $MgSO_4$ for neuroprotection in the short term that show insufficient but not significant outcomes (Basu et al. 2011, Costantine et al. 2009). Thus, we aimed to analyze the differences in short-term outcomes and serum magnesium levels in newborns and mothers given $MgSO_4$ therapy and not treated with $MgSO_4$ (Kuchits S.S et al., 2019).

MATERIALS AND METHODS

This was an observational cohort study conducted in a group of newborns with a diagnosis of premature pregnant women. The study sample was selected from a population of infants with preterm pregnant women who received $MgSO_4$ taken from severe preeclampsia patients at 28-34 weeks gestational age who received $MgSO_4$, and the control sample was premature pregnant women at 28-34 weeks gestational age born at Dr. Soetomo Hospital in the period July 2018 to December 2018. This research had received ethical feasibility from the ethics commission for research at Dr Soetomo Hospital, Surabaya with the number 0403/KEPK/VII/2018.

Inclusion criteria included premature pregnant women who gave birth at a gestational age of more than 28 to 34 weeks, giving birth by vaginal delivery or by fetal delivery with a single pregnancy, no intrauterine asphyxia (Non Stress test (NST) category 1). Whereas, the exclusion criteria included major congenital abnormalities which are circulatory system malformations including congenital heart block, transposition of large arteries, left ventricular hypoplasia, pulmonary atresia and tetralogy of fallot. Abnormalities in the digestive system include abdominal defects, gastroschisis, central nervous system, and chromosomal abnormalities, mothers with cardiac abnormalities, smokers, consumption of opiates or alcohol during pregnancy, and autoimmune diseases.

A sample of 60 subjects was divided into groups who received MgSO4 therapy and controls who did not receive MgSO4 therapy. The group that received $MgSO_4$ therapy was given $MgSO_4$ therapy at a dose of 4 grams intravenously then continued with maintenance of 1 gram/hour of syringe pump up to 24 hours followed up until delivery was performed. The control group was not given $MgSO_4$ therapy but was followed up until delivery. In both groups, maternal and neonatal serum magnesium levels, postpartum infant blood gas analysis and short-term outcome assessments were performed, including first and fifth minute Apgar scores, respiratory distress syndrome (RDS), sepsis, type of oxygen support and infant mortality for 7 days of treatment. Data were analyzed using SPSS statistics 21 software. Chi-square analysis, Fisher's exact test, independent-samples test, and one-way Anova were used to analyze differences between variables.

RESULTS

There were 98 premature deliveries, with 9 babies born dead and excluded, 11 babies with congenital abnormalities, 18 babies with gestational age <28 weeks, then 60 samples that met the inclusion criteria were taken. Characteristics of mothers giving birth to premature babies during the study period are presented in **Table 1**. **Table 1** shows 30 patients with body mass index (BMI) above 30 (obesity). Of the 30 patients, 20 patients (83.3%) were diagnosed with severe preeclampsia and received $MgSO_4$ therapy, and an analysis using chi-square on BMI with $MgSO_4$ therapy showed a significance value of $p = 0.001$. Because the p value <0.05, there was a difference between BMI with $MgSO_4$ therapy. Of the 20 patients who received $MgSO_4$ therapy, 4 patients obtained BMI values above 40 (grade 3 obesity). Of the 19 infants with RDS outcomes, 5 were obtained in infants born to mothers who received $MgSO_4$ therapy.

Table 2 shows the comparison of infant outcomes between the two groups analyzed using chi-square. There were significant differences in outcomes for gestational age infants and respiratory distress syndrome ($p = 0.011$ and $p = 0.013$, respectively). Whereas, the significance value of $p > 0.05$ was found in birth weight, Apgar scores 1 and 2 minutes, the use of ventilators, sepsis, mortality, and umbilical artery pH.

Table 3 shows the mean serum magnesium levels of mothers in those receiving $MgSO_4$ therapy of 3.45±1.65 mg/dl with a significance value of $p = 0.001$. Because the p value <0.05, the effect of $MgSO_4$ administration on maternal serum magnesium levels was obtained. The mean magnesium level of infants in those receiving $MgSO_4$ therapy was 3.10±1.35 mg/dl with a significance value of $p = 0.001$. Because the p value <0.05, the effect of MgSO4 administration on infant serum magnesium levels was obtained.

Table 1. Characteristics of mothers and infants with or without $MgSO_4$ therapy

Variables	Therapy		Control		P-Value
	N	%	n	%	
Characteristics of Mothers					
Mothers' Age					
16-35 years	21	50	21	50	1.000
>35 years	9	50	9	50	
Age of Pregnancy					
28 - <32 weeks	6	40.0	10	62.5	0.375
32 - ≤34 weeks	24	54.5	20	45.5	
Parity					
Multiparous	22	51.2	21	48.8	1.000
Primiparous	8	47.1	9	52.9	
Body Mass Index (BMI)					
BMI <30	10	27.8	26	72.2	0.001
BMI ≥30	20	83.3	4	16.7	
Lung Maturation					
Yes	22	51.2	22	51.2	1.000
No	8	47.1	8	47.1	
Labor Method					
Abdominal	28	50.9	27	49.1	1.000
Vaginal	2	40	3	60	
Characteristics of Infants					
Breathing					
Spontaneous	17	58.6	12	41.4	0.389
CPAP	11	44	14	56	
Ventilator	2	33.3	4	66.7	
Mortality					
No	29	50	29	50	1.000
Yes	1	50	1	50	
Respiratory distress syndrome					
Yes	5	26.3	14	73.7	0.013
No	25	61	16	39	
Sepsis					
Yes	9	60	6	40	0.552
No	21	46.7	24	53.3	

Table 2. Outcomes of infants born prematurely with or without MgSO4 therapy

Variables	Therapy (n = 30)	Control (n = 30)	P-Value
Birth Weight (grams)	1743.33±334.19	1880.40±642.86	0.306
Pregnancy Age (weeks)	33.43±1.25	32.2±2.23	0.011
AS in first minute	5.73±1.83	5.83±1.46	0.816
AS in fifth minute	7.10±1.51	7.13±1.16	0.924
CPAP	11 (36.67)	14 (46.67)	0.432
Ventilator	2 (6.67)	4 (13.33)	0.335
Respiratory distress syndrome	5 (16.67)	14 (46.66)	0.013
Sepsis	9 (30)	6 (20)	0.276
Mortality	1 (3.33)	1 (3.33)	0.754
Umbilical arterial pH	7.19±0.09	7.23±0.08	0.123

Data presented as Mean±SD and number (%)

Table 3. Maternal and infant magnesium levels of each group

Variables	Therapy (n = 30)	Control (n = 30)	P-Value
Maternal Magnesium Levels (mg/dl)	3.45±1.65	1.78±0.23	0.001
Infant Magnesium Serum Levels (mg/dl)	3.10±1.35	1.74±0.19	0.001

Table 4. Outcome of infants in groups based on magnesium levels

Groups based on magnesium levels (n = 60)	Group A (<2.5 mg/dl) n = 41	Group B (>2.5 - <3.5 mg/dl) n = 10	Group C (>3.5 mg/dl) n = 9	P-Value
AS in first minute	5.8±1.61	6.30±1.05	5.11±2.20	0.499
AS in fifth minute	7.10±1.28	7.60±0.69	6.67±2.00	0.608
CPAP	18 (43.9)	3 (30)	4 (44.44)	0.714
Ventilator	5 (12.19)	0 (0)	1 (11.11)	0.619
Respiratory distress syndrome	16 (39.02)	0 (0)	3 (33.33)	0.013
Sepsis	9 (21.95)	4 (40)	2 (22.22)	0.487
Mortality	2 (4.87)	0 (0)	0 (0)	0.619
Umbilical arterial pH	7.23±0.07	7.22±0.10	7.15±0.11	0.106

Data presented as Mean±SD and number (%)

Table 4 shows the outcomes of respiratory distress syndrome in Group A (<2.5 mg/dl) of 16 patients (39.02%) and Group C (≥3.5 mg/dl) of 3 patients (33.33%). Analysis using chi-square with a significance value of p = 0.013 was performed. Because the p value <0.05, differences in respiratory distress syndrome outcomes with groups of serum magnesium levels in infants were obtained.

DISCUSSION

In this study, there were significant differences in infant outcomes only in gestational age and RDS between the two groups. For serum magnesium levels, there was a statistically significant difference between serum magnesium levels both in the group receiving $MgSO_4$ therapy and those not receiving $MgSO_4$ therapy.

Previous research concluded that the biggest risk factor for RDS was premature birth; from 86.5% of preterm infants, the incidence rate of RDS ranged from 86% at 24 weeks gestation compared to 39 weeks gestation which was only 1% (Qari et al. 2018). Obese mothers have long been considered a risk factor for neonatal morbidity and mortality. Neonatal morbidity is defined as an adverse outcome in the first four weeks of a baby's life. The assessed outcomes can be injuries at birth, low Apgar scores, RDS, sepsis, hypoglycemia, neonatal seizures, treatment at the NICU and even death (Burn et al. 2018). RDS is also a complication of sepsis (Dewi et al. 2016). However, previous study stated antenatal corticosteroid therapy might be a protective factor that can reduce the incidence of RDS in prematurity (Zenita et al. 2018).

A study measured blood magnesium levels. This found that umbilical cord blood magnesium levels were found to increase significantly with an increase in maternal serum magnesium levels (Das et al. 2015). In addition to the dosage regimen, several other factors such as gestational age, birth weight, and maternal serum magnesium levels, can affect higher serum levels of fetal magnesium. Another factor that may contribute to high fetal serum on the umbilical cord is the ability of the placenta to actively transport magnesium to the fetus. Furthermore, magnesium renal clearance in the early days of life is reduced in neonates and especially in preterm neonates, causing magnesium levels to remain high for a long time (Basu et al. 2011).

In this study, no statistically significant differences were found in the umbilical artery pH between groups with or without $MgSO_4$ and groups with various levels of $MgSO_4$ levels. Cord blood is the most objective way to assess the metabolic condition of the fetus at birth. Association has been investigated between umbilical artery pH and important clinical outcomes in the prenatal period. Although there is debate about definite pH levels to determine the significance of acidemia, in this study we used pH <7.14 as suggested as a pathological marker of premature infants with acidemia (Simhan 2018).

A study comparing umbilical cord blood gas analysis in premature neonates born to healthy mothers versus preeclampsia mothers found lower pH compared to those in healthy mothers and higher BE in the preeclampsia group. In addition, metabolic acidosis was more detectable in preterm neonates born to preeclampsia women compared to those born to healthy women (22.2% versus 8.4%, p=0.001) (Sheikh et al. 2016).

In the first and second minute Apgar scores, the use of ventilators, sepsis, mortality and umbilical arterial pH did not differ significantly between groups with or without $MgSO_4$ and groups with various levels of $MgSO_4$ levels. This is consistent with WHO recommendation that there is no statistically significant difference between the group that receives $MgSO_4$ and the group that does not receive active treatment. One measure of infant morbidity reported: RDS, neonatal infection, severe IVH or periventricular leukomalacia, NEC, and use of mechanical ventilation did not have a significant difference in those who used MgSO4 therapy and those who did not receive therapy (World Health Organization 2015).

The main results from other studies were neonatal morbidity, which is defined as a 5 minute Apgar score of less than 7, hospitalization for more than 5 days, being treated at the NICU, and diagnosed with hypoglycemia, RDS, sepsis, and infant mortality. Results showed a statistically significant increase ($P < 0.001$) in the overall incidence of neonatal morbidity with increasing BMI (Burn et al. 2018). Similiar with other studies that infant experienced neonatal mortality occurred with APGAR score ≤ 6 which indicates asphyxia (Putri et al. 2018, Yudrika et al. 2018).

In another study, there was no significant difference between the first and fifth minute score scores and the need for resuscitation, both in groups with and without administration of $MgSO_4$ or in groups with different levels of $MgSO_4$ (Basu et al. 2011). A similar review was found in a systematic review that $MgSO_4$ given specifically to the fetus as neuroprotection did not affect the incidence of Apgar score of 5 minutes <7 (RR 1.03; 95% CI 0.90 in 4387 infants) and hypotonia (RR 1.02 95% CI 0.77 in 2444 infants). Similar to these findings, our study also found no significant differences in the Apgar score (Magee et al. 2011).

This research has various limitations that might be anticipated when conducting further research or other similar research. The limitations include the use of populations with preeclampsia mothers so that the outcomes of $MgSO_4$ could not be fully evaluated.

CONCLUSION

Significant differences in infant outcomes were only found in gestational age and RDS. Magnesium levels in the blood of newborns with mothers given MgSO4 therapy were higher than those not treated with $MgSO_4$.

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