ORIGINAL ARTICLE

Maternal and perinatal outcomes of pre-referral magnesium sulfate treatment in severe preeclampsia patients

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ABSTRACT

Objectives: This study analyzed the association between pre-referral magnesium sulfate administration and maternal and perinatal outcomes in severe preeclampsia patients.
Materials and Methods: This was a retrospective observational analytic study using cross-sectional design. Samples were 132 pregnant women with preeclampsia referred to dr. Saiful Anwar, Hospital Malang, Indonesia in 2019. Data were taken from the patients' medical records. Maternal outcomes measured in this study were the incidence of eclampsia, ICU care, and maternal mortality, while the perinatal outcomes included the incidence of asphyxia, NICU care, and perinatal mortality.
Results: Patients' history of magnesium sulphate administration significantly associated with the incidence of eclampsia with p-value 0.035 and odds ratio (OR) 2.413, thus consumption of magnesium sulphate could reduce the risk of seizures. However, it did not associate with either maternal ICU care outcomes (p-value 0.087, OR 2.028), or maternal mortality (p-value 0.573). No relationship was found neither between history of magnesium sulphate administration in pregnant women with severe preeclampsia and perinatal outcomes nor with the incidence of asphyxia (p-value 0. 577, OR 0.795), with NICU treatment (p-value 0.205, OR 0.579), and with perinatal mortality (p-value 0.153, OR 3.259).
Conclusion: Magnesium sulfate reduced the risk of eclampsia, yet it did not affect either the rate of ICU care, maternal mortality, incidence rate of perinatal asphyxia, the rate of NICU care, or perinatal mortality.

Keywords: Pre-referral; magnesium sulfate; severe preeclampsia; maternal outcomes; perinatal outcomes; maternal health

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk menganalisis hubungan pemberian magnesium pra rujukan sulfat dengan luaran maternal dan perinatal pada pasien preeklampsia berat.
Bahan dan Metode: Metode penelitian ini adalah analitik observasional retrospektif dengan rancangan penelitian cross sectional. Sampel adalah 132 ibu hamil dengan preeklampsia yang dirujuk ke RSUD dr. Saiful Anwar, Malang, Indonesia, tahun 2019. Data diambil dari rekam medis pasien. Luaran maternal yang diteliti adalah kejadian eklampsia, perawatan ICU, dan kematian maternal. Luaran perinatal yang diteliti adalah kejadian asfiksia, perawatan NICU, dan kematian perinatal.
Hasil: Riwayat pemberian magnesium sulfat berhubungan signifikan dengan kejadian eklampsia p-value=0.035 dengan odds ratio (OR) 2.413. sehingga pemberian magnesium sulfat dapat menurunkan risiko kejadian kejang pada ibu dengan preeklampsia. Namun tidak terdapat hubungan dengan luaran maternal perawatan ICU (p-value 0.087, odds ratio (OR) 2.028). dan kematian maternal (p value 0.573). Tidak ada hubungan antara pemberian magnesium sulfat pra rujukan pada ibu hamil preeklampsia berat dengan luaran perinatal, antara lain kejadian asfiksia (p-value=0.577, odds ratio (OR) 0.795), perawatan NICU (p-value=0.182, odds ratio (OR) 0.579). dan kematian perinatal (p-value=0.153, odds ratio (OR) 3.259).
Simpulan: Penelitian ini menunjukkan magnesium sulfat pra rujukan dapat menurunkan risiko kejadian eklampsia namun tidak mempengaruhi tingkat perawatan ICU, kematian maternal. kejadian asfiksia perinatal, tingkat perawatan NICU dan kematian perinatal.

Kata kunci: Pra-rujukan; magnesium sulfat; preeklamspia dengan gejala berat; luaran maternal; luaran perinatal; kesehatan ibu

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INTRODUCTION

Preeclampsia-eclampsia is a pregnancy complication that has been the main cause of maternal and perinatal mortality and morbidity. Preeclampsia-eclampsia contributes to 14% of global maternal mortality.[1] In Indonesia, 25.25% of total maternal mortality rate is caused by preeclampsia-eclampsia, 31.15% of which occurred in East Java in 2019.[2]

Maternal mortality and morbidity rates can be lowered through the prevention of eclampsia occurrence. Nearly half of the total maternal mortality rate is due to eclampsia which should be preventable through the administration of precise treatment.[3]

WHO has recommended the consumption of magnesium sulfate in the prevention against eclampsia.[4] The MAGPIE Trial research showed magnesium sulfate administration to mothers with severe preeclampsia was effective in reducing the risk of eclampsia by more than 50%.[3] Magnesium sulfate can reduce maternal mortality,[5] maternal complications, need for intensive care and prevents long hospital stay due to eclampsia.[6]

The administration of magnesium sulfate to pregnant women with severe preeclampsia can prevent fetal brain injury due to hypoxia and prevent brain cell death.[7] However, Jordan (2003) found exposure to magnesium sulfate increased the risk of asphyxia in newborns due to its hypotonic effect that inhibited the blood flow to the fetus. This situation can bring complications such as asphyxia and death in newborns.[8] Furthermore, asphyxia has been the most dominant cause of the need for NICU care.[9] Thus, the administration of magnesium sulfate is assumed to increase the need for NICU. On the other hand, Shepherd et al. (2019) reported no significant gap in asphyxia prevalence between infants with mothers given magnesium sulfate and those were not.[10]

Magnesium sulfate is one of the standard services for the prevention and management of severe preeclampsia in Indonesia. Mothers who are diagnosed with severe preeclampsia must immediately consume magnesium sulfate, including those who will be referred.[11]

Health facilities that are unable to provide holistic magnesium sulfate treatment are required to give only loading dose before referring the patient to more advanced health facilities.[11] Pre-referral magnesium sulfate administration is the key to prevent fatalities to mothers and babies which might occur due to longer referral process to more advanced health facilities.[12]

dr. Saiful Anwar Hospital, Malang, Indonesia, is a tertiary hospital which is a main referral hospital for maternal and neonatal patients in East Java. In Java, pre-eclampsia/eclampsia was the top cause of maternal death in 2019. In this year, 95% of pregnant patients with severe preeclampsia were referred to dr. Saiful Anwar Hospital from other health facilities. However, some patients had not been given pre-referral magnesium sulfate due to various considerations, one of which was due to the fear of harmful drug reactions.[13] Analysis on quality of maternal and perinatal outcomes of patients with severe preeclampsia given pre-referral magnesium sulfate will improve the awareness regarding the importance of pre-referral of magnesium sulfate administration. The results of the analysis also provide a valuable insight in developing proper strategies to reduce maternal mortality and morbidity rates due to preeclampsia.

MATERIALS AND METHODS

This study was a retrospective observational analytic study with cross-sectional design in pregnant women with severe preeclampsia at dr. Saiful Anwar Hospital, Malang, Indonesia. The study population was pregnant women with severe preeclampsia who were referred to dr. Saiful Anwar Hospital from 1 January to 31 December 2019. The inclusion criteria were gestational age longer than 28 weeks, single pregnancy, and complete medical records. The exclusion criteria were pregnant women suffering from pre-eclampsia with contraindications to magnesium sulfate administration. The research sample was all pregnant women with severe preeclampsia who were referred to dr. Saiful Anwar Hospital from January 1, 2019 to December 31, 2019 who met the research requirements. Data used in this study were secondary data taken from the patient's medical records.

Pre-referral magnesium sulfate refers to the administration of magnesium sulfate by health facilities that referred the patients to dr. Saiful Anwar Hospital based on the standards of service. The history of magnesium sulfate administration was seen from the referral records in the medical records.

The maternal outcomes included the incidence of eclampsia, level of ICU care, and maternal incidence. The perinatal outcomes studied were incidence of asphyxia in newborn infants, rate of NICU care, and perinatal mortality. Data obtained were then processed, analyzed by statistical tests which results were presented in tables and narration.

RESULTS AND DISCUSSION

Table 1. Characteristics of pregnant wormen with severe pre-eclampsia referred to dr. Saiful Anwar Hospital, Malang, Indonesia, between 1 January and 31 December 2019.

Characteristic	Total (n=132)	Percentage
Age (y.o)		
< 20	8	6.1
20-35	94	71.2
> 35	30	22.7
Education		
Elementary	38	28.8
Secondary	77	58.3
High	17	12.9
Parity		
Primipara	49	37.1
Multipara	75	56.8
Grandemulti	8	6.1
Referrer		
Doctor's Clinics	2	1.5
Health Care Center	16	12.1
Midwife Independent Service	24	18.2
Hospital	90	68.2
Eclampsia		
Yes	35	26.5
No	97	73.5
ICU care		
Yes	38	28.2
No	94	71.2
Maternal Death		
Yes	4	3.0
No	128	97.0
Asphyxia		
Yes	44	33.3
No	88	66.7
NICU Care		
Yes	41	31.1
No	91	68.9
Perinatal Death		
Yes	18	13.6
No	114	86.4

Medical records obtained from dr. Saiful Anwar Hospital from 1 January to 31 December 2019 showed that there were 132 samples that met the research criteria. Table 1 shows the characteristics of pregnant women with severe preeclampsia referred to dr. Saiful Anwar Hospital, Malang. Severe preeclampsia was mostly experienced by mothers of productive age between 20-35 years, as many as 94 mothers (71.2%), followed by 30 mothers aged >35 years, as many as 30 (22.7%). The lowest case occurred in the age group <20 years with 8 samples (6.1%).

In this study, pregnant women with severe preeclampsia were mostly secondary school graduates, 77 mothers (58.3%), followed by 38 primary school graduates (28.8%), and the least were 17 mothers with high school degrees (12.9%).

Based on parity, this study found that preeclampsia was mostly experienced by multiparous mothers amounting to 75 mothers (56.8%), followed by primiparous with a total of 49 mothers (37.1%), and grandemultipara as many as 8 mothers (6.1%). This study found that the highest number of patients with preeclampsia were referred from hospitals amounting to 90 mothers (68.2%). There were 24 mothers referred by independent midwife services (18.2%), followed by 16 mothers referred from public health centers (12.1%), then the lowest were 2 mothers referred from physicians' clinic (1.5%).

Most of mothers with severe preeclampsia (97 mothers) who were referred did not experience eclampsia (73.5%). Whereas, most of 94 mothers were not admitted to the ICU (71.2%), and 4 mothers died from severe preeclampsia (3%) (Table 1). Table 1 also shows that most newborns of mothers with severe pre-eclampsia did not experience asphyxia (88 babies or 66.7%), most of them (91 babies) were not referred to NICU (68.9%), and there were 18 newborns who died (86.4%).

Table 2. Relationship between pre-referral magnesium sulfate administration and maternal outcomes at dr. Saiful Anwar Hospital, Malang, Indonesia

Outcomes	Magnesium Sulfate Administration		*p-value*	*Odds ratio* (OR)	*Relative Risk* (RR)	
Eclampsia	Yes (n=97)	No (n=35)				
Yes	21	14	0.035	2.413	1.848	*Confidence Interval* (CI) 95%
No	76	21			0.766	
ICU Care						
Yes	24	14	0.87	2.028		
No	73	21				
Maternal Death						
Yes	4	0	0.573	-		
No	93	35				

Table 2 shows the statistical test results of the relationship between pre-referral magnesium sulfate administration with eclampsia incidence using the chi-square test with p-value 0.035 ≤ 0.05 with odds ratio (OR) 2.413 and RR value 1.848 (95% CI). These values indicated relationship between the history of magnesium sulfate administration with eclampsia. Mothers who did not receive pre-referral magnesium sulfate had a 2.413 greater risk of developing eclampsia than mothers who did not receive magnesium sulfate.

For ICU care variable, chi-square test revealed p-value of 0.087 with odds ratio of 2.028, which is higher than 0.05. Therefore, no relationship between the history of pre-referral magnesium sulfate administration and ICU care was found. Among pre-eclamptic pregnant women who received magnesium sulfate, 4 mothers died, while mothers who did not receive magnesium sulfate survived. Chi-square test with p-value = 0.573 indicated no relationship between the history of pre-referral magnesium sulfate administration and maternal mortality.

This study confirmed no relationship between magnesium sulfate administration in pregnant women with severe preeclampsia and perinatal outcomes. The details are presented in Table 3. Table 3 shows the results of bivariate analysis between pre-referral magnesium sulfate administration in preeclamptic pregnant women and perinatal outcomes. For the asphyxia variable, the chi-square analysis resulted in a p-value of 0.577 with an odds ratio=0.795, indicating that there was no relationship between pre-referral magnesium sulfate administration and the incidence of asphyxia in newborns of mothers with severe preeclampsia.

Table 3 also shows that the number of newborns of mothers who were given pre-referral magnesium sulfate admitted to the NICU was lesser than that of newborns from mothers who were not given magnesium sulfate. The chi-square analysis showed p-value 0.182 with odds ratio 0.579, so as the p-value was greater than 0.05, no relationship was found between the history of pre-referral magnesium sulfate administration with the level of NICU care among newborns of severe preeclamptic mothers.

The number of newborns of mothers with severe preeclampsia receiving magnesium sulfate who died was higher than those of newborns of mothers who were not given magnesium sulfate. The chi-square analysis obtained p-value 0.153 with odds ratio 3.259. Since the p-value was higher than 0.05, it indicated no relationship between magnesium sulfate administration for pregnant women with severe preeclampsia and perinatal mortality.

In this study, it was found that 26.5% of women with severe preeclampsia were not given magnesium sulfate before being referred, while magnesium sulfate administration as prevention of eclampsia had been a standard of care in severe preeclampsia management. This result was still better than the one of a study conducted in South Konawe, Indonesia, where 100% of severe preeclampsia patients were not given magnesium sulfate before being referred. The fear of side effects and drug reactions had made health workers reluctant to administer magnesium sulfate to women with severe pre-eclampsia.[13]

Table 3. The relationship between pre-referral magnesium sulfate administration and perinatal outcomes at dr. Saiful Anwar Hospital, Malang, Indonesia

Outcomes	Magnesium Sulfate Administration		*p-value*	Odds Ratio (OR)
Asphyxia	Yes (n=97)	No (n=35)		
Yes	31	13	0.577	0.795
No	66	22		
NICU Care				
Yes	27	14	0.182	0.579
No	70	21		
Perinatal Death				
Yes	16	2	0.153	3.259
No	81	33		

Magnesium sulfate is an anticonvulsant and neuro-protective drug that is the first recommendation for the prevention of eclamptic seizures in severe pre-eclampsia.[4] The specific mechanism of action of magnesium sulfate in preventing seizures in patients with severe preeclampsia is not yet well-known. Magnesium sulfate prevents seizures through its vasodilator properties that reduce the blood pressure. This vasodilator property is temporary, especially during loading the dose. Magnesium sulfate is a natural antagonist of calcium. An increase in magnesium levels in cells can reduce calcium levels needed for contraction.[14] Magnesium sulfate decreases the activity of N-methyl D-aspartate (NMDA) receptors that are associated with seizures. Hence, magnesium sulfate prevents seizures or eclampsia in mothers with severe preeclampsia.[15] Magnesium sulfate has been proven to significantly reduce the incidence of seizures and recurrent seizures compared to other anti-seizures such as phenytoin and nimodipine.[16]

The results of the chi-square analysis indicated a relationship between pre-referral magnesium sulfate administration with the incidence of eclampsia. Mothers who did not receive pre-referral magnesium sulfate had a higher risk of eclampsia (RR 1.848 95% CI), while mothers who received magnesium sulfate had a lower risk of eclampsia (RR 0.766 CI 95%). This finding was consistent with the results of The Magpie Trial which showed that magnesium sulfate administration for mothers with severe preeclampsia reduced the risk of eclampsia by half.[3] Another study done in Finland measuring the incidence of eclampsia in 2006-2010 also showed a very low incidence of eclampsia due to increased use of magnesium sulfate.[6]

Eclampsia is one of factors that worsens the condition of patients with severe preeclampsia who require intensive care. Magnesium sulfate administration is expected to reduce the level of intensive care requirement.[17] However, in this study, the history of magnesium sulfate administration was found to have no relationship with the level of ICU care. The results of studies done by Duley (2002) and Gordon et al. (2014) also showed that magnesium sulfate administration did not significantly associate with ICU care.[3,12] This study found that the number of patients admitted to the ICU exceeded the number of eclamptic patients, meaning that there were patients who did not experience eclampsia but requiring ICU care. Other factors might influence the need for ICU care in patients, such as the modes of delivery. Aryana and Manuaba (2015) stated that ICU deliveries in severe preeclampsia patients are the most common cause of ICU care in obstetric cases.[18]

Preeclampsia is one of the top causes of global maternal death. In developing countries, in which resources are limited, maternal mortality rate is mostly affected by eclampsia, seizures that cause severe maternal hypoxia, trauma, and aspiration pneumonia.[3] Prevention against eclampsia through magnesium sulfate administration is expected to reduce maternal mortality. The Magpie Trial study noted lower maternal mortality among patients with preeclampsia who received magnesium sulfate than in patients who did not. The study also found that magnesium sulfate administration did not affect maternal mortality since no maternal deaths were found in patients who were not given magnesium sulfate while 4% of patients given magnesium sulfate died.[3]

Such condition may occur due to other factors that can reduce the risk of maternal death, such as advanced health facilities.[19] dr. Saiful Anwar Hospital, Malang, Indonesia, is a tertiary hospital with better and more complete facilities. However, more accurate studies which involve greater number of subjects are needed to analyze factors that can reduce the risk of maternal death in mothers with severe preeclampsia.

The chi-square analysis showed no relationship between magnesium sulfate administration and perinatal outcome, including the incidence of asphyxia, NICU care, and perinatal mortality. Hallak and Cotton in their study on animals found that magnesium sulfate could enter fetal blood brain barrier through the placenta.[20] Greater intracellular magnesium concentration inhibits the calcium from entering the cells, which can block calcium channels and lead to decreased uterine contractions or hypotonia. The effect of hypotonia reduces the blood flow to the fetus and cause fetal hypoxia. Fetal output, that is the sign of fetal hypoxia prior to delivery, is the occurrence of metabolic acidosis, asphyxia, and complications that can lead to fetal death.[8]

The chi-square analysis performed in this study indicated no relationship between magnesium sulfate administration and the incidence of perinatal asphyxia. Other studies also found that magnesium sulfate administration did not affect the incidence of asphyxia in newborns.[3,10] Severe preeclampsia itself is one of the risk factors for asphyxia in newborns. The risk increases 4 times higher in pregnant women with severe preeclampsia than preeclamptic pregnant women without severe symptoms.[21] In other words, even without magnesium sulfate administration, newborns of mothers with severe preeclampsia have higher risk of experiencing asphyxia.

Asphyxia is the most common factor that makes newborns required to be admitted to NICU.[9]

Theoretically, magnesium sulfate may increase the risk of developing asphyxia, thereby increasing the need for intensive care for newborns. However, in this study, the results of the chi-square analysis showed that pre-referral administration of magnesium sulfate did not affect the level of NICU care. Similarly, other studies also showed no association between magnesium sulfate administration and NICU treatment levels.[3,10]

One of the factors that can reduce the level of NICU care is good quality neonatal resuscitation. Proper asphyxia management can minimize the need for NICU care.[9] On the other hand, other factors can also increase the need for NICU care including preeclamptic pregnant women who deliver by sectio caesaria, babies with low birth weight, and prematurity.[23]

The use of magnesium sulfate is accused of increasing the incidence of perinatal mortality, but some other studies have shown no relationship between the use of magnesium sulfate in pregnant women with pre-eclampsia and the perinatal mortality rate.[3,10] Meanwhile, in this study, chi-square analysis showed no relationship between magnesium sulfate administration and the incidence of perinatal mortality. Therefore, other factors might influence perinatal mortality including quality of newborn management. Proper resuscitation can help reduce the risk of perinatal death.[22]

Other factors also possibly influence perinatal maternal outcome in patients with severe preeclamptic patients. However, this study only investigated their association with magnesium sulfate administration. The quality of referrals, including response time, the tiered referral system, and the quality of antenatal care can also affect the quality of maternal and perinatal outcomes. Secondary data sources in this study could be biased due to the possibility of documentation error. Therefore, further and more accurate research is needed.

CONCLUSION

Pre-referral injection of magnesium sulfate reduced the risk of eclampsia, yet it did not affect either the rate of ICU care or maternal mortality. Pregnant women with preeclampsia who did not get pre-referral infection of magnesium sulfate had a higher risk of eclampsia, while pregnant women with magnesium sulfate preeclampsia had a lower risk of eclampsia. The administration of pre-referral magnesium sulfate to pregnant women with severe preeclampsia neither affected the incidence rate of perinatal asphyxia, the rate of NICU care, nor the perinatal mortality. Health workers at the primary health facility level are recommended to continue giving magnesium sulfate prior to hospital referrals to prevent eclampsia from occurring during the referral process. Future researchers are encouraged to involve larger sample size in order to obtain more comprehensive results.

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