

Combination of Magnesium Sulfate with Other Treatments in Managing Severe Preeclampsia: A Systematic Review

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ABSTRACT

Introduction: Preeclampsia is a pregnancy complication occurring after 20 weeks of gestation and characterized by blood pressure $\geq 140/90$ mmHg. It can cause serious maternal and fetal complications and remains an important contributor to maternal and fetal mortality. Magnesium sulfate ($MgSO_4$) and antihypertensive agents are commonly used to prevent seizures and control blood pressure in severe preeclampsia.

Objective: This study aimed to review the effectiveness of $MgSO_4$ combined with antihypertensive therapies in the management of severe preeclampsia and their effects on maternal and fetal outcomes.

Method: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist. Literature searches were conducted in PubMed, ScienceDirect, PMC Europe, and Springer Link. From 966 identified articles, 10 studies were selected based on the established selection criteria and analyzed through qualitative synthesis.

Result: The reviewed studies showed that $MgSO_4$ combined with antihypertensive agents, including labetalol, hydralazine, and nifedipine, effectively managed severe preeclampsia by preventing seizures and controlling blood pressure. These therapies were associated with improved maternal and neonatal outcomes, including reduced risks of premature birth and neonatal asphyxia. Additional therapies, such as sodium enoxaparin and Compound Danshen, were reported to support placental blood flow and fetal development.

Conclusion: The combination of $MgSO_4$ and antihypertensive therapy is beneficial in managing severe preeclampsia and improving maternal and fetal outcomes. Further research with well-designed studies is needed to strengthen evidence regarding the effectiveness and safety of these therapeutic approaches..

Keywords: *Preeclampsia, Magnesium sulfate, Maternal outcomes, Neonatal outcomes*

Kombinasi Magnesium Sulfat dengan Terapi Lain dalam Penatalaksanaan Preeklampsia Berat: Sebuah Tinjauan Sistematis

ABSTRAK

Pendahuluan: Preeklampsia merupakan komplikasi kehamilan yang terjadi setelah usia kehamilan 20 minggu dan ditandai dengan tekanan darah $\geq 140/90$ mmHg. Kondisi ini dapat menyebabkan komplikasi serius pada ibu dan janin serta menjadi salah satu penyebab penting morbiditas dan mortalitas maternal dan fetal. Magnesium sulfat ($MgSO_4$) dan obat antihipertensi umum digunakan untuk mencegah kejang dan mengendalikan tekanan darah pada preeklampsia berat.

Tujuan: Penelitian ini bertujuan untuk meninjau efektivitas $MgSO_4$ yang dikombinasikan dengan terapi antihipertensi dalam penatalaksanaan preeklampsia berat serta pengaruhnya terhadap luaran maternal dan fetal.

Metode: Tinjauan sistematis dilakukan berdasarkan Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Pencarian literatur dilakukan melalui PubMed, ScienceDirect, PMC Europe, dan Springer Link. Dari 966 artikel yang teridentifikasi, 10 studi dipilih berdasarkan kriteria seleksi yang telah ditetapkan dan dianalisis menggunakan sintesis kualitatif.

Hasil: Studi yang ditinjau menunjukkan bahwa $MgSO_4$ yang dikombinasikan dengan obat antihipertensi,

termasuk labetalol, hidralazin, dan nifedipin, efektif dalam menangani preeklampsia berat dengan mencegah kejang dan mengendalikan tekanan darah. Terapi tersebut berkaitan dengan perbaikan luaran maternal dan neonatal, termasuk penurunan risiko kelahiran prematur dan asfiksia neonatal. Terapi tambahan, seperti natrium enoksaparin dan Compound Danshen, dilaporkan dapat mendukung aliran darah plasenta dan perkembangan janin.

Kesimpulan: Kombinasi $MgSO_4$ dan terapi antihipertensi bermanfaat dalam penatalaksanaan preeklampsia berat dan meningkatkan luaran maternal dan fetal. Penelitian lebih lanjut dengan desain yang baik diperlukan untuk memperkuat bukti mengenai efektivitas dan keamanan pendekatan terapi tersebut.

Kata kunci: Preeklampsia, magnesium sulfat, luaran maternal, luaran neonatal

INTRODUCTION

Preeclampsia is a pregnancy-specific hypertensive disorder that generally develops after 20 weeks of gestation and may be accompanied by proteinuria, maternal organ dysfunction, or uteroplacental dysfunction. The condition can progress rapidly and is associated with serious maternal and fetal complications, including eclampsia, HELLP syndrome, fetal growth restriction, preterm birth, and maternal and perinatal morbidity and mortality. (Sakowicz et al., 2023) Current international recommendations emphasize early recognition, blood pressure control, prevention of seizures, and appropriate monitoring of maternal and fetal conditions. The pathophysiology of preeclampsia involves abnormal placentation, inflammation, oxidative stress, and endothelial dysfunction, which contribute to the progression of the disease (Magee et al., 2022)

Data indicate that hypertension occurs in 9.1% of pregnancies, with 5% of these being preeclampsia. In Indonesia, the maternal mortality rate (MMR) has shown a significant decline, from 305 per 100,000 live births in 2015 to 189 in 2020, surpassing the 2023 target. (Direktorat Jenderal Kesehatan Masyarakat. 2024) However, hypertension in pregnancy remains one of the leading causes of maternal mortality, accounting for 26.1% (Primadi, Oki, Didik, 2019)

Management of severe preeclampsia requires pharmacological interventions to control blood pressure and prevent neurological complications. Magnesium

sulfate ($MgSO_4$) is widely used for seizure prevention, while antihypertensive agents such as labetalol, hydralazine, and nifedipine are used to control severe hypertension. Evidence from clinical studies suggests that combination therapy may improve maternal and fetal outcomes. (Abdelrahman et al., 2019) evaluated labetalol or hydralazine combined with $MgSO_4$ in women with severe preeclampsia, while (Xiang et al., 2020) reported beneficial effects of $MgSO_4$ combined with nifedipine on blood pressure and other clinical parameters. These findings indicate the potential benefits of combining $MgSO_4$ with antihypertensive therapy in the management of severe preeclampsia (Wen et al., 2019).

Although several studies have reported beneficial effects of $MgSO_4$ combined with antihypertensive or adjunctive therapies, the available evidence involves different therapeutic combinations, study populations, and maternal and fetal outcomes (Abdelrahman et al., 2019). Therefore, the overall effectiveness of these therapeutic approaches in severe preeclampsia remains necessary to be systematically synthesized.

This study provides a systematic synthesis of recent evidence concerning $MgSO_4$ combined with antihypertensive and adjunctive therapies, with particular attention to maternal and fetal outcomes. The findings are expected to contribute to a clearer understanding of the therapeutic approaches reported in recent studies and identify areas requiring further investigation (Xiang et al., 2020). Accordingly, this study aimed to

evaluate the effectiveness of MgSO₄ combined with antihypertensive therapies and other adjunctive treatments in the management of severe preeclampsia and their effects on maternal and fetal outcomes.

METHOD

This study employed a systematic review design to evaluate the efficacy of magnesium sulfate in combination with other treatments for severe preeclampsia. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (Page et al., 2021). The study did not involve direct recruitment of human participants; baseline data consisted of published studies investigating magnesium sulfate combination therapy in patients with severe preeclampsia. The literature search was conducted through four electronic databases: PubMed, ScienceDirect, SpringerLink, and Europe PMC. Searches were performed on July 3–6 and December 2–4, 2024, using the keywords "Severe Preeclampsia" and "Magnesium Sulfate". The search was limited to studies published between 2019 and 2024, available in English or Indonesian, and with free full-text access.

Studies were included if they investigated the use of magnesium sulfate in combination with other treatments for severe preeclampsia, were published between 2019 and 2024, were available in English or Indonesian, provided an available abstract and full text, and possessed a Digital Object Identifier (DOI). Studies were excluded if they required paid access, were systematic reviews or meta-analyses, utilized qualitative research designs, or lacked a DOI.

The literature selection process consisted of identification, screening, eligibility assessment, and inclusion of relevant studies based on the predetermined criteria. The flow of study selection is illustrated in the PRISMA 2020 flow diagram

(Figure 1). Data were extracted from eligible articles, including study characteristics, interventions, comparator treatments where applicable, and reported maternal and perinatal outcomes. The primary outcomes assessed were changes in blood pressure and improvements in maternal and perinatal outcomes, including preeclampsia-related complications, maternal adverse effects, perinatal adverse effects, stillbirth, neonatal death, fetal growth restriction, and recurrence of preeclampsia.

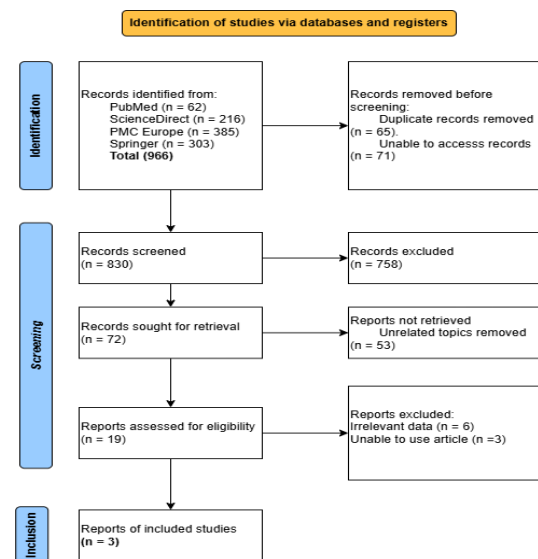


Figure 1. PRISMA flowchart

Data were analyzed descriptively and narratively by comparing the findings across the included studies. Due to heterogeneity in study characteristics, interventions, and reported outcomes, the findings were synthesized qualitatively rather than through statistical meta-analysis. As this systematic review did not involve primary data collection or direct human-subject intervention, ethical approval was not applicable.

RESULT

A total of 966 studies were identified through database search most of which were excluded after a thorough evaluation of duplicates, title and abstract matching, availability of full text, and the application of

relevant variables. Studies that met the inclusion criteria for this systematic review were included. Ten articles met the inclusion criteria. The studies included in this systematic review involved studies conducted in various countries, mainly in China, some from Egypt and United States. Assessment of study characteristics which include authors, title, study design, study location, study population, intervention, comparison group, outcome measures, and main findings are presented in **Table 1**.

Table 1. Characteristics of Enrolled Studies

Author (Year)	Number of Participants	Intervensi	Outcome
(Abdelrahman et al., 2019)	50 pregnant women with severe preeclampsia and a gestational age of ≥ 32 weeks. Participants were randomized into two equal groups, with 25 patients in each group.	Group A: 25 women received $MgSO_4$ and intravenous labetalol infusion. Group B: 25 women received $MgSO_4$ and intravenous hydralazine infusion.	- Intravenous infusion regimen of labetalol and hydralazine, when combined with $MgSO_4$, has proven effective in controlling severe hypertension in pregnant women with severe preeclampsia. - Both medications are well tolerated and do not show significant changes in fetoplacental circulation. - Labetalol demonstrates a more significant reduction in post-treatment systolic blood pressure and maternal heart rate compared to hydralazine.
(Wang et al., 2022)	70 patients with severe preeclampsia were involved. Participants were divided into two groups: the control group (n=35) and the observation group (n=35).	Observation Group: included Low Molecular Weight Heparin (LMWH) at a low dose combined with $MgSO_4$. Control Group: received only $MgSO_4$. 20 mL of 25% $MgSO_4$ was added to 100 mL of 5% glucose.	- This study demonstrates that the use of LMWH combined with $MgSO_4$ in the treatment of severe preeclampsia can effectively control the disease, improve hypercoagulability in pregnant women, reduce systolic blood pressure, enhance placental microcirculation, promote fetal growth, and improve clinical outcomes. - This combination therapy has been found to have high efficacy and safety, indicating its potential for clinical application and promotion in the management of severe preeclampsia.
(Lu et al., 2024)	80 patients with severe preeclampsia were involved. Participants were divided into two groups: the control group (n=40) and the observation group (n=40).	Single Group (received $MgSO_4$ only) Combination Group (received magnesium sulfate combined with sodium enoxaparin)	- The combination of sodium enoxaparin and $MgSO_4$ has been found to be more effective in regulating cytokine levels, improving pregnancy outcomes, and enhancing neonatal APGAR scores compared to $MgSO_4$ alone. - This combination therapy shows a lower incidence of side effects, demonstrating its safety and efficiency in the treatment of severe preeclampsia.
(Zhou et al., 2022)	60 patients with severe preeclampsia were divided into two groups (30 patients in the control group and 30 patients in the therapy group).	Control Group: Received $MgSO_4$ as standard treatment. Therapy Group: Received Danshen injection (16 ml) plus $MgSO_4$.	Compound Danshen injection can enhance kidney function, reduce blood hypercoagulability, and lower oxidative stress levels, providing better therapeutic effects in patients with severe preeclampsia compared to standard treatment with $MgSO_4$ alone.

Author (Year)	Number of Participants	Intervensi	Outcome
(Xiang et al., 2020)	118 pregnant women with gestational hypertension were divided into two groups.	Control Group: Received MgSO ₄ only. Observation Group: Received MgSO ₄ plus nifedipine for one week.	The combination of MgSO₄ and nifedipine is effective in controlling edema, lowering blood pressure, reducing proteinuria, and protecting kidney function in patients with gestational hypertension.
(Wen et al., 2019)	This study involved 103 participants with severe preeclampsia, divided into two groups.	Control Group (low-dose intravenous MgSO ₄) Observation Group (MgSO ₄ plus 5000 U of LMWH heparin).	Studies indicate that low molecular weight heparin combined with MgSO₄ is more effective than MgSO₄ alone in treating severe preeclampsia, thereby improving maternal health and neonatal outcomes.
(Mowafy & Medhat, 2023)	This study involved a total of 60 pregnant women suffering from severe preeclampsia.	Group M: Initial intravenous dose of 4 grams of MgSO ₄ over 20 minutes + 1 gram per hour for 24 hours. Group L: Intravenous labetalol starting at a dose of 20 mg/hour.	This research concludes that MgSO₄ and labetalol effectively reduce cerebral perfusion pressure (CPP) in patients with severe preeclampsia while maintaining cerebral blood flow (CBF). However, labetalol may offer advantages in achieving target blood pressure and reducing the need for additional antihypertensive agents.
(Liu, Y.; Zhou, M.; Cheng, H.; Du, 2021)	This study included a total of 124 pregnant women with early-onset severe preeclampsia (EOSP). The participants were divided into two groups, with 62 women in each group.	Control Group: received MgSO ₄ with labetalol Observation Group: received a regimen of MgSO ₄ , labetalol, and LMWH 5000 IU	In conclusion, this study provides evidence that the combination of LMWH, MgSO₄, and labetalol can effectively manage severe preeclampsia by reducing blood pressure, improving coagulation and vascular function, and decreasing adverse pregnancy outcomes.
(Wen et al., 2019)	This study included a total of 160 patients with gestational hypertension.	Control Group: received MgSO ₄ only Observation Group: received MgSO ₄ with phentolamine	This study concludes that MgSO₄ combined with phentolamine and nifedipine is a more effective therapeutic approach for gestational hypertension compared to MgSO₄ alone. This combination not only regulates blood pressure more effectively but also increases serum levels of LIF and Apelin.
(Wang, Y.; Bao, J.; Peng, 2020)	A total of 164 participants were enrolled in the study, comprising 83 participants in Group A and 81 participants in Group B	Group A: received MgSO ₄ with labetalol Group B: received a regimen of MgSO ₄ without labetalol	This research supports the use of MgSO₄ combined with labetalol as an effective and safe treatment option for severe preeclampsia occurring in the early stages.

Note: MgSO₄: magnesium sulphate, LMWH: low molecule weight heparin, LIF: leukimia inhibition factors, IU: international unit, EOSP: early onset severe preeclampsia

The authors assessed bias in a study using the Cochrane Risk of Bias 2.0 (RoB 2) tool. across six domains, and the data were analyzed using Review Manager software version 5.4.1. The evaluation results indicated that the majority of studies had a low risk of bias for selection bias, appropriate randomization procedures were implemented. For performance bias, several studies also showed a low risk, indicating effective blinding regarding the intervention. However, detection bias was mostly rated as unclear, reflecting insufficient information regarding the blinding of outcome assessors.

Regarding attrition bias, six studies had a low risk, but three studies were unclear and one study showed a high risk, indicating potential issues with the completeness of outcome data. All studies were assessed to have a low risk of reporting bias, demonstrating comprehensive reporting of findings without evidence of selective outcome reporting.

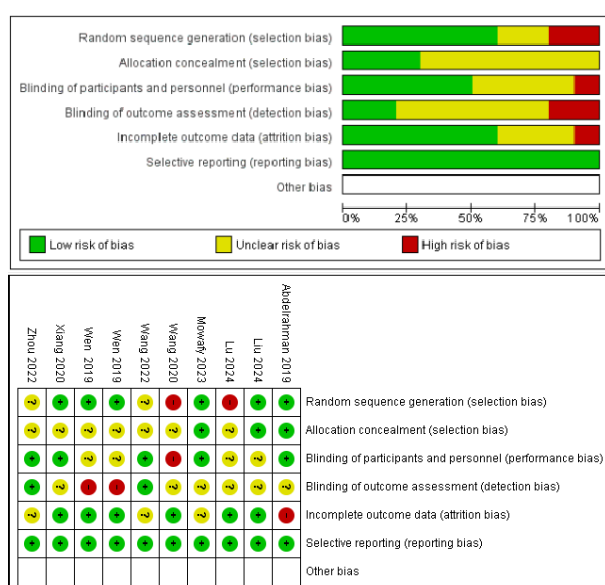


Figure 2. The results of the risk of bias assessment using RoB2 from the included journals

DISCUSSION

In the management of severe preeclampsia, magnesium sulfate (MgSO₄) is the first-line treatment for prevention and

management of eclamptic seizures significantly reducing the incidence of seizures compared to other therapies. The administration of MgSO₄ is also associated with a decrease in maternal mortality rates and a reduction in risks associated with this condition. The advantages of MgSO₄ lie in its low cost, widely available, and ease of administration and monitoring. Although its mechanism is not yet fully understood, MgSO₄ is believed to exert neuroprotective effects through the stabilization of neuronal membranes and inhibition of neurotransmitter release, as well as inducing vasodilation through the relaxation of vascular smooth muscle and the uterus, contributing to lower blood pressure (Padda et al., 2021).

In addition to MgSO₄, antihypertensive therapies such as nifedipine, hydralazine, and labetalol are also used to control hypertension that often accompanies severe preeclampsia. Research by Xiang et al. indicates that the combination of MgSO₄ and nifedipine is more effective in managing hypertensive disorders of pregnancy compared to the use of MgSO₄ alone. Nifedipine, as a calcium channel blocker, relaxes the smooth muscle of blood vessels, thereby increasing blood flow and reducing vascular resistance.

The combination of these two medications has been shown to more effectively reduce levels of proteinuria and blood viscosity, as well as increase serum levels of LIF (leukemia inhibitory factor) and Apelin, which are crucial for the improvement of maternal and fetal conditions (Xiang et al., 2020) These findings, supported by Wen et al., also demonstrate that the combination of MgSO₄ with phentolamine

and nifedipine provides significant benefits, creating a more supportive hormonal environment for pregnancy and resulting in a safer delivery process with better health outcomes for both mother and baby.

Wang et al. highlight the effectiveness of the combination of MgSO_4 and labetalol in managing hypertension and preventing complications in eclampsia, recommending serum levels of sFlt-1 and PlGF as biomarkers to guiding individualized treatment and assess the severity of preeclampsia. Post-treatment results show a significant decrease in serum levels of sFlt-1 and the sFlt-1/PlGF ratio, along with an increase in PlGF levels, indicating a restoration of the angiogenic balance essential for endothelial function (Wang, Y.; Bao, J.; Peng, 2020).

Abdelrahman et al. found that the combination of MgSO_4 with labetalol or hydralazine is effective in controlling hypertension in women with severe preeclampsia. Here, MgSO_4 acts as a neuroprotective agent to reduce the risk of seizures, while labetalol and hydralazine lower blood pressure without compromising placental blood flow, thereby maintaining hemodynamic stability for both mother and fetus (Abdelrahman et al., 2019). The incidence of adverse reactions was found to be comparable, indicating that this combination therapy is safe for pregnant women and may potentially reduce the risk of eclampsia.

Mowafy et al. compared the effectiveness of labetalol and magnesium sulfate (MgSO_4) in the management of preeclampsia, finding that both medications successfully lowered blood pressure, although labetalol acted more quickly, showing effects after one hour. Neither had a negative impact on cerebral blood flow (CBF), which is crucial for avoiding cerebral complications. While MgSO_4 remains the standard prophylaxis for seizures, labetalol presents a safe and effective alternative (Mowafy & Medhat, 2023).

Liu et al. examined the use of Low Molecular Weight Heparin (LMWH) in conjunction with MgSO_4 and labetalol in patients with Early Onset Severe Preeclampsia (EOSP) before 34 weeks of gestation. The results indicated an improvement in endothelial function, monitored through increased nitric oxide levels and decreased endothelin-1, as well as a reduction in oxidative stress, reflecting the potential protective effects of LMWH against pathogenic damage in preeclampsia. This combination has the potential to enhance maternal and fetal health and reduce the incidence of adverse pregnancy outcomes (Liu, Y.; Zhou, M.; Cheng, H.; Du, 2021).

Wang et al. reported that the combination of MgSO_4 and LMWH contributed to improved coagulation function, reduced hypercoagulability, and enhanced microcirculation in the placenta (Wang et al., 2024). This combination also lowered both systolic and diastolic blood pressure and proteinuria, reflecting anti-inflammatory effects and improvements in vascular function (Lu, D.; Yu, J.; Sang, 2024). Increased expression of kininase and Tumor Growth Factor Beta-1 ($\text{TGF-}\beta 1$) indicated improvements in hemodynamic conditions that support fetal growth and enhance overall clinical outcomes. The findings of Liu et al. align with those of Wen et al., emphasizing that sodium LMWH and MgSO_4 may serve as effective strategies in the management of severe preeclampsia, where it is important to consider the addition of LMWH when MgSO_4 alone may be insufficient (Wen et al., 2019).

Lu et al. investigated the combination of MgSO_4 with sodium enoxaparin, demonstrating a reduction in D-dimer and sFlt-1 levels, as well as an increase in PlGF levels and the APGAR score of newborns. Sodium enoxaparin aids in improving blood flow and placental perfusion, supporting fetal development, while MgSO_4 plays a role in lowering blood pressure and reducing vascular spasms, thereby maintaining hemodynamic

stability. The synergy between these two medications enhances pregnancy outcomes and reduces adverse reactions, making it an effective therapeutic option for severe preeclampsia (Lu, D.; Yu, J.; Sang, 2024).

Zhou et al. found significant benefits from the combination of MgSO₄ with Compound Danshen injection in managing severe preeclampsia, where the reduction in Tumor Necrosis Factor-alpha (TNF- α) levels and the increase in nitric oxide (NO) levels contribute to decreased inflammation and endothelial cell damage, as well as improved blood flow and placental tissue perfusion (Zhou et al., 2022). The increase in NO as an endogenous vasodilator supports blood pressure reduction, while this combination also improves kidney and liver function and reduces hypercoagulability, which is crucial for preventing complications.

Overall, the combination of MgSO₄ with either sodium enoxaparin or Compound Danshen shows great potential in enhancing the management of severe preeclampsia, each offering distinct yet complementary mechanisms to improve maternal and fetal conditions.

CONCLUSION

The findings of this systematic review suggest, with a combination of MgSO₄ and various other therapies such as nifedipine, phentolamine, labetalol, hydralazine, sodium enoxaparin, and Compound Danshen, may provide greater therapeutic benefits. Magnesium sulfate and labetalol are relatively accessible medications in Indonesia, making them practical choices for the management of preeclampsia. This combination has proven effective in lowering blood pressure and reducing the risk of complications, as well as providing faster control over pregnancy-induced hypertension. Research indicates that the combination of MgSO₄ with sodium enoxaparin can improve blood flow and placental perfusion, which is crucial for fetal

health.

Additionally, this combination also helps reduce the hypercoagulable state often seen in pregnant women, thereby decreasing the risk of further complications. Combination therapy not only focuses on blood pressure control but also contributes to increased serum levels of LIF and Apelin, which are important for placental function and fetal growth. This suggests that this approach can lead to safer and more effective delivery processes, as well as reduce the incidence of preterm birth and neonatal asphyxia. Given the research findings supporting the use of this drug combination, it is important for medical practitioners in Indonesia to consider this approach in the management of severe preeclampsia.

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