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A Study of Drug Interaction with Nifedipine and Magnesium Sulfate in the Management of Preeclampsia: An Observational Study

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Abstract: Maternal mortality rate (MMR) remains a major priority in global health. The World Health Organization (WHO) estimates that MMR will decrease to 70 per 100,000 live births by 2030. However, in 2015, MMR in Indonesia reached 305 per 100,000 live births. Drug Related Problems (DRPs) are undesirable events that occur due to drug therapy and can hinder the recovery process of patients. Identifying drug-related issues during treatment is crucial for reducing morbidity, mortality, and therapy costs, as well as enhancing the effectiveness of pharmacological therapy. This study aims to identify DRPs caused by the use of the combination of Nifedipine and Magnesium Sulfate in preeclamptic patients at RSIA Sitti Khadijah 1 Makassar. The research method employed is non-experimental (observational) with a descriptive (qualitative) approach. The results indicate that among 32 preeclamptic patients who consumed the combination of Nifedipine and Magnesium Sulfate, there were no reported DRPs or adverse effects that jeopardized the patients' lives. These findings suggest that the combination therapy is in accordance with the management guidelines for preeclampsia in pregnant women based on national medical service protocols.

Keywords: drug related problems; nifedipine; preeclampsia

1. INTRODUCTION

Drug Related Problems (DRPs) are prevalent in both primary and tertiary healthcare settings worldwide, impacting patients, their families, healthcare providers, and the entire healthcare system. Drug-related problems have the potential to negatively impact clinical outcomes in critically ill patients. These patients are typically seen as more susceptible to the adverse effects of drug-related issues due to the high frequency of medication-related incidents and their complex clinical situations. However, reports on drug-related problems identified by clinical pharmacists in medical intensive care units in Thailand are limited. This study presents clinically significant data, detailing the identified problems, common causes of drug-related issues, and the interventions carried out by pharmacists in real-world settings. The findings aim to serve as educational resources for pharmacists involved in providing pharmaceutical care and participating in medical intensive care units [1]. To provide safe and rational therapy, the selection of drugs during pregnancy must consider the balance of benefits and risks for both the mother and the fetus. The drugs used for managing preeclamptic

patients are antihypertensives (Nifedipine) and tocolytics (Magnesium Sulfate) [2]. The combination of Nifedipine and Magnesium Sulfate is the most commonly encountered treatment for patients diagnosed with preeclampsia. Awaluddin [3], states that the antihypertensive therapy used for preeclamptic patients in public hospitals shows that Calcium Channel Blockers (CCBs) are the most frequently used antihypertensives. This is because Nifedipine is the most commonly used antihypertensive drug, and the combination of Nifedipine and Magnesium Sulfate is frequently utilized in the treatment of preeclamptic patients, emphasizing pharmacodynamic and pharmacokinetic aspects [2]. Nifedipine is administered orally in doses ranging from 10 mg to 40 mg twice daily or 20 mg to 90 mg once daily. Nifedipine is easily absorbed from the gastrointestinal tract but undergoes first-pass metabolism. The oral administration of nifedipine capsules has a bioavailability of 45 to 75 percent [4].

Magnesium sulfate in conjunction with nifedipine is effective in relaxing smooth muscles, reducing blood pressure, and enhancing fetal nutrition. Furthermore, the combination therapy of magnesium sulfate and nifedipine shows a significant reduction in blood pressure and proteinuria compared to using nifedipine alone. This combination is also beneficial in managing hypertension during pregnancy, effectively controlling edema, blood pressure, proteinuria, and providing protection to the kidneys [5]. In the use of nifedipine, it is often combined with magnesium sulfate therapy to prevent and manage seizures, with a mechanism of action similar to that of other calcium antagonists. Magnesium sulfate is recommended for women with severe symptomatic preeclampsia. The intravenous route is advised, starting with an initial dose of 4–6 grams, followed by a maintenance dose of 1–2 grams per hour, typically administered during active labor and for 24 hours postpartum without mandatory serum monitoring. In addition to intravenous administration, magnesium sulfate can be given intramuscularly with an initial dose of 10 grams, followed by 5 grams every 4 hours. When a cesarean section is indicated, it is recommended to continue magnesium during the procedure, as discontinuation of magnesium may increase the risk of postpartum eclampsia [6]. The infusion of $MgSO_4$ should be stopped, and serum magnesium levels should be checked immediately if deep tendon reflexes are lost, respiratory rate decreases to less than 12 breaths per minute, or urine output drops below 30 mL per hour. Overdose and maternal death can occur due to improper administration of $MgSO_4$. The antidote for $MgSO_4$ overdose is 10 mL of 10% calcium gluconate administered intravenously over 10-20 minutes [7].

Randomized studies comparing magnesium sulfate with placebo for women with preeclampsia have demonstrated that magnesium sulfate administration can reduce the risk of seizures in preeclampsia by 58%. Magnesium sulfate is the drug of choice that can reduce coronary artery spasm (CAS), also known as coronary artery vasospasm, which is a type of heart attack without blockage in the arteries. This condition occurs when one of the heart arteries spasms, drastically reducing blood flow to the heart, even temporarily stopping it [8].

The best therapy for seizures is magnesium sulfate, as it has neuroprotective effects by reducing nerve inflammation and cerebral edema while lowering blood pressure. However, its short duration of action cannot guarantee stable blood pressure for the patient [9]. Normally, the required magnesium levels in the body range from 1.7 to 2.3 mg/dL. The body experiences excess magnesium

when levels exceed 2.6 mg/dL (hypermagnesemia), which is characterized by symptoms such as nausea, vomiting, unusually low blood pressure, headaches, diarrhea, neurological disturbances, muscle weakness, respiratory issues, irregular heartbeat, and lethargy. Other signs of magnesium intoxication include double vision, low blood pressure, loss of consciousness, and respiratory distress. If magnesium concentration rises above 30 mg/dL, it can lead to cardiac arrest [10].

Hypertensive disorders in pregnancy is a general term used for conditions such as preeclampsia and eclampsia. According to Youssef & Crispi [11], pregnant women with hypertension and long-term preeclampsia have a fourfold increased risk of developing chronic hypertension and a twofold increased risk of ischemic stroke and heart disease compared to those who are not pregnant. Women at higher risk of developing preeclampsia include primigravida, those with multiple pregnancies, obesity, diabetes mellitus, kidney disease, or autoimmune diseases (i.e., systemic lupus erythematosus, antiphospholipid syndrome) [11].

2. MATERIALS AND METHODS

The type of research used in this study is non-experimental (observational) employing a descriptive (qualitative) method. Data collection was conducted retrospectively.

2.1. Determination

Thirty-two hospitalized preeclamptic patients at RSIA Sitti Khadijah 1 Makassar during the period from August 2021 to August 2022, who have received combination therapy with Nifedipine and Magnesium Sulfate, were designated as the sample for this study.

2.1.1. Inclusion Criteria

a. Patients diagnosed with preeclampsia who have used a combination of Nifedipine (antihypertensive) and Magnesium Sulfate (tocolytic)
b. Patients who have used a combination of Nifedipine at a maximum dose of 30 mg per day and Magnesium Sulfate with an initial dose of 4 grams within 5–10 minutes, followed by a maintenance dose of 1–2 grams per hour for 24 hours
c. Patients who have been prescribed more than two medications
d. Patients without comorbid diseases
e. Patients with a gestational age of >20 weeks (second trimester)
f. Patients with blood pressure ≥140/90 mmHg up to ≥160/110 mmHg
g. Patients aged <20 and >35 years
h. Patients who are hospitalized
i. Patients who have died
j. Patients with complete medical record data, including medical record number, patient name, patient address, patient occupation, patient age, gestational age, and birth order of the child

2.1.2. Exclusion Criteria

a. Patients without a diagnosis of preeclampsia who are using a combination of Nifedipine (antihypertensive) and Magnesium Sulfate (tocolytic)
b. Preeclamptic patients who are not using the combination of Nifedipine and Magnesium Sulfate
c. Preeclamptic patients who are only using Nifedipine therapy
d. Preeclamptic patients who are only using Magnesium Sulfate therapy

e. Patients with blood pressure of 120/80 mmHg
f. Patients who do not have complete medical record data

3. RESULTS AND DISCUSSION

This research used secondary data in the form of medical records of preeclampsia patients who had used a combination drug therapy of nifedipine as an antihypertensive and magnesium sulfate as a tocolytic in the inpatient ward of RSIA Sitti Khadijah 1 Makassar during the period from August 2021 to August 2022. Out of the total inpatients at RSIA Sitti Khadijah 1 Makassar, there were 47 cases of preeclampsia patients. There was a sample size of 32 patients who met the inclusion criteria with complete and clear medical records. Based on the results of the research that has been carried out, there were 47 cases of preeclampsia patients who had used a combination drug therapy of nifedipine and magnesium sulfate and met the inclusion criteria in this study. However, from the results of the Slovin formula calculation, the sample size in this study was 32 samples. Table 1 shows the age group, where in the age group of preeclampsia patients, the <20 years age group showed 13 cases of preeclampsia (40.6%), and the >35 years age group showed 19 cases of preeclampsia (59.3%). Fifi [12], states that pregnancy at age <20 years can cause many problems because at this age, there is a risk of anemia, high blood pressure, miscarriage/abortion, anxiety, and the mother not being ready for pregnancy. Mothers in this age group tend to have thoughts of fear, isolation, or feeling alone. This condition will affect the psychological development of the mother and the fetus in her womb.

The educational background of the mothers in preeclampsia cases shows that in the junior high school (SMP) education group, in the high school (SMA) group there were 16 cases (50%). This is in line with the research conducted by Nurnaningsih Yunus [13], whose research results state that education teaches a person various abilities, including mastering knowledge. The higher a person's level of education, the higher their level of knowledge, and the easier it is for them to accept and develop technological knowledge. Someone with a higher level of education will find it easier to understand information on how to prevent preeclampsia/eclampsia.

The effect of parity on the incidence of preeclampsia based on the number of cases shows that in the primigravida (first pregnancy) group, there were 9 cases (28.1%), in the multigravida (2-4 pregnancies) group, there were 18 cases (56.2%), while in the grand multigravida (>5 pregnancies) group, there were 5 cases (12.6%). The incidence of primigravida is almost 2 times higher; genetic factors are most likely caused by recessive inheritance, and pre-existing conditions such as hypertension are one of the predisposing factors for the occurrence of preeclampsia. The first pregnancy and childbirth increase the health risks that arise because the mother has never experienced pregnancy before, and the birth canal will be tried for the first time by the fetus. On the other hand, if giving birth too often, the uterus will become weaker due to the scarring of the uterine tissue caused by repeated pregnancies.

The effect of occupation on the incidence of preeclampsia can be seen from the number of cases, where: Housewives (IRT) had 21 cases (65.6%). The research by Sumampow [14], suggests that high levels of stress or anxiety experienced by pregnant women can affect their pregnancy. Specifically, Stressful jobs or high mental pressure can increase stress hormones like cortisol and corticotropin-

releasing hormone (CRH) in pregnant women. These elevated stress hormones can influence the implantation of the embryo and the formation of the placenta. This indicates that the type of occupation and associated stress levels can be a contributing factor to the development of pregnancy complications like preeclampsia. Jobs that place a high mental or emotional burden on pregnant women may increase their risk of adverse pregnancy outcomes. The chart above shows the length of stay for patients with preeclampsia, 13 patients (40.6%) had a 3-day stay. The factors that influence the length of stay include is presence of comorbidities - Patients with additional medical conditions may require a longer recovery time, fetal abnormalities - complications with the fetus can prolong the mother's hospital stay, maternal health after delivery - the mother's post-partum condition can also affect the length of hospitalization. These factors can lead to a longer or shorter hospital stay for preeclampsia patients, depending on the specific circumstances of each case.

Table 1. Demographic data of patients

Criteria	Category/Class	Number of Cases	Percentage (%)
Age	<20	13	40.6
	>35	19	59.3
Total		32	100
Education	Junior High School	4	12.5
	High School	16	50
	Diploma	4	12.5
	Bachelor's	8	25
Total		32	100
Pregnancy	Primigravida	9	28.1
	Multigravida	18	56.2
	Multigravida Grade	5	12.6
Total		32	100
Occupation	Housewife	21	65.6
	Private Employee	3	9.37
	Civil Servant	7	21.8
	Contract Worker	1	3.12
Total		32	100
Length of Stay	3 days	13	40.6
	4 days	10	31.2
	5 days	4	12.5
	6 days	3	9.37
	7 days	2	6.25
Total		32	100

Table 2. Frequency of preeclampsia patients based on potential drug interactions

Potential Drug Interaction (www.drugs.com)	Number of Cases	Percentage (%)
Interaction occurred	120	96.7
No interaction occurred	4	3.22
Total	124	100

Based on table 2, the potential for drug interactions in preeclampsia patients is high, with 120 cases (96.7%) experiencing interactions, while only 4 cases (3.22%) had no interactions. This can be attributed to the complex treatment regimens required by preeclampsia patients, who often need multiple medications to manage their condition, increasing the risk of drug-drug interactions. Additionally, preeclampsia patients frequently have other medical conditions that require additional treatments, further elevating the potential for interactions. Furthermore, the physiological changes during pregnancy, such as alterations in drug metabolism, distribution, and elimination due to hormonal and organ function changes, can modify the body's response to medications, leading to increased interaction risks. The close monitoring and comprehensive management of preeclampsia patients may also contribute to the higher detection and reporting of potential drug interactions.

Drug interactions are categorized into three levels based on their severity: major, moderate, and minor. Major severity indicates the presence of clinically significant interaction effects, thereby increasing the risk of interaction beyond what is indicated by the therapeutic needs. The recommended management in this case is to avoid the combination of drugs [15].

In the case of moderate severity, there is a potential for clinically significant interactions. Preventive strategies generally involve avoiding the drug combination and using the medications only under specific conditions. Meanwhile, minor severity indicates that the interaction effects are clinically minimal. Possible solutions may include assessing the risk to minimize it, reviewing alternative treatment options, and taking steps to avoid potential interaction risks, including planning appropriate monitoring [16].

Table 3. Frequency based on drug interaction classification level

Classification Of Drug Interaction (www.drugs.com)	Number of Cases	Percentage (%)
Major	5	4.03
Moderate	95	76.6
Minor	20	16.1

Based on Table 3, the classification levels of drug-drug interactions are presented. The data indicates the percentage of interaction classification levels, with 5 cases (4.03%) classified as major, 95 cases (76.6%) classified as moderate, and 20 cases (16.1%) classified as minor interactions.

The high proportion of moderate-level interactions, accounting for 76.6% of the cases, suggests that the majority of the drug interactions observed in preeclampsia patients are of moderate severity. These interactions may require close monitoring and potential dose adjustments, but may not necessarily lead to severe adverse outcomes if properly managed. The relatively lower percentage of major interactions (4.03%) indicates that a smaller subset of the drug interactions in this patient population are of greater clinical significance, potentially requiring more immediate intervention or changes in the treatment regimen. The presence of minor interactions (16.1%) suggests that some drug combinations may result in less clinically relevant interactions, which may not necessitate significant changes in the medication management plan. Overall, the classification of drug interactions in preeclampsia patients, as shown in Table 3, provides valuable insights into the severity and potential clinical impact of the observed drug-drug interactions. This information can guide

healthcare providers in prioritizing their monitoring and management strategies to ensure the safe and effective use of medications in this patient population.

Managing preeclampsia poses considerable clinical challenges due to the associated risks for both the mother and the fetus. The results indicating that the combination of Nifedipine and Magnesium Sulfate does not lead to Drug Related Problems (DRPs) or life-threatening side effects are encouraging. Magnesium sulfate (MgSO4) is the preferred medication for managing hypertension during pregnancy, functioning by suppressing the central nervous system and inhibiting conduction at the peripheral neuromuscular junction [17]. MgSO4 has calming effects, alleviates seizures, and relaxes skeletal muscles, which helps lower intracranial pressure and promotes peripheral relaxation [18]. Nevertheless, the standard monotherapy with magnesium sulfate has not shown significant improvements in the patient's condition, and discontinuing treatment may cause blood pressure to rise again [5]. Consequently, recent studies have indicated that combining magnesium sulfate with nifedipine can produce favorable outcomes [19]. Nifedipine acts as a calcium antagonist, relaxing the smooth muscles of blood vessels, dilating them, and decreasing peripheral vascular resistance [20]. The lack of DRPs underscores the safety of this combination, which enhances the confidence of both healthcare providers and patients. Nifedipine functions as a vasodilator, while Magnesium Sulfate acts as an anticonvulsant and antihypertensive, indicating a synergistic effect in alleviating preeclampsia symptoms. These findings support the wider use of this drug combination in clinical settings. However, additional research with larger and more diverse populations is necessary to confirm these results and refine treatment protocols. In summary, the combination of Nifedipine and Magnesium Sulfate appears to be a safe and effective strategy for managing preeclampsia, warranting further exploration to improve clinical outcomes

4. CONCLUSION

From the 32 preeclampsia patients who consumed the combination of Nifedipine and Magnesium Sulfate, there were no Drug Related Problems (DRPs) or life-threatening side effects observed. This indicates that the combination of these two drugs can be used safely in the management of preeclampsia without causing significant issues related to medication. This success is important to ensure patient safety and the effectiveness of therapy in addressing preeclampsia.

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