

## Comparative trends and effectiveness of amlodipine and nifedipine as oral antihypertensives in preeclampsia management

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### ABSTRACT

The use of amlodipine in preeclampsia remains limited as it is not a treatment option officially. Whereas amlodipine's long half-life allows less frequent dosing in preeclampsia patients, potentially improving preeclampsia treatment more efficiently compared to nifedipine (standard medicine). Ensuring the effectiveness of amlodipine for preeclampsia is essential for optimizing delivery outcomes, in addition to efficiency aspects. However, the effectiveness study of amlodipine in preeclampsia patients is still not definitively known. This study aims to determine the prescription trends and effectiveness of amlodipine as an antihypertensive in preeclampsia. The study used a cross-sectional approach conducted at a one of the secondary healthcare facilities in Tasikmalaya, utilizing medical records from January 2019 to December 2023. The data were analyzed using Chi-Square test to determine the trends using and effectiveness of amlodipine compared to nifedipine in controlling blood pressure in preeclampsia. The study shows that the trends using of amlodipine in preeclampsia is decreasing over the past 5 years (2019 to 2023). This phenomenon may be influenced by limited evidence, established clinical practice guidelines, and priority of drug use. There was no significant difference in effectiveness of amlodipine compared to nifedipine in single therapy ( $p=0.698$ ) or dual therapy ( $p=0.1$ ). Furthermore, the study found that amlodipine and nifedipine exhibited comparable effectiveness in controlling blood pressure in preeclampsia. Therefore, amlodipine may be considered as an alternative antihypertensive option for controlling blood pressure in preeclampsia.

**Keywords:** amlodipine, antihypertensive, gestational hypertension, nifedipine, preeclampsia

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## INTRODUCTION

Abnormal changes in clinical profiles during pregnancy can occur, leading to complications (Sultana et al., 2022). Complications during pregnancy are significantly associated with the risk of worsening maternal health and adverse delivery outcomes (Mishra et al., 2024; Skytte et al., 2023). There are various risks of complications during pregnancy, but preeclampsia is one of the most commonly occurring pregnancy disorders (Sultana et al., 2022). According to literature reviews, 2-15% of pregnant women worldwide experience preeclampsia (Chang et al., 2023). Preeclampsia is a condition where the placenta in the uterus becomes dysfunctional due to systemic inflammation that occurs after 20 weeks of pregnancy (POGI, 2016). This dysfunction leads to organ impairment and elevated blood pressure (ACOG, 2020). Increased blood pressure during pregnancy is directly proportional to maternal health deterioration and adverse delivery outcomes, particularly in cases of severe hypertension (Abdurrahman et al., 2024; Magee et al., 2020).

Blood pressure is an important parameter for preeclampsia patient evaluation (ACOG, 2020). A study reported that uncontrolled blood pressure in preeclampsia patients significantly worsened delivery outcomes (Bugri et al., 2023). Additionally, other studies have shown that the use of antihypertensive medications can improve clinical outcomes in preeclampsia patients (Husna et al., 2023). A previous meta-analysis has found that different types of antihypertensive drugs yield varying levels of effectiveness in preeclampsia patients (Awaludin et al., 2022). Oral antihypertensive options for preeclampsia patients are still limited to methyldopa and nifedipine (Awaludin et al., 2022; PERKI, 2021). Other recommended antihypertensives are available as injectables, which can cause discomfort due to the associated pain (Awaludin et al., 2022; Kwatra et al., 2012; PERKI, 2021). Methyldopa is currently considered the safest antihypertensive for pregnant women (Drambarean et al., 2023). Additionally, calcium channel blockers such as nifedipine have been used as antihypertensive therapy in pregnancy for more than 30 years (Malha & August, 2019). Due to its long-standing use, nifedipine is often recommended as an antihypertensive during pregnancy, even though it does not have a specific license for pregnancy (ACOG, 2020; Malha & August, 2019). Nifedipine has a short half-life, which increases the risk of sudden drops in blood pressure, potentially causing placental perfusion issues (Elliott & Ram, 2011; Suhaimi et al., 2022).

Recent research findings from various studies show that there are now some cases where oral amlodipine is used as an antihypertensive for preeclampsia (Awaludin et al., 2023; Yana et al., 2023). Even though amlodipine is generally used in cases of hypertension unrelated to pregnancy (Lowe et al., 2009; Untari et al., 2018). Amlodipine has a longer half-life and duration of effect compared to nifedipine, so it can be given as a single dose (Abernethy, 1992). Using a single-dose regimen can enhance treatment efficiency, potentially improving patient adherence and the effectiveness of antihypertensive therapy for preeclampsia (Ozyuncu & Erol, 2024). Previous research has found that the long half-life of amlodipine leads to more consistent bioavailability (Huang et al., 2019). The consistent bioavailability may substantially impact the efficacy of blood pressure control in preeclampsia patients who receive amlodipine, resulting in more stable blood pressure. Proper blood pressure control of preeclampsia is expected to extend the duration of pregnancy, leading to better delivery outcomes (ACOG, 2020; Garcia et al., 2023).

A meta-analysis has examined the effectiveness of amlodipine in hypertensive patients during pregnancy, showing that amlodipine has slightly better ability to lower blood pressure compared to nifedipine (Yin et al., 2022). However, research on the effectiveness of amlodipine use during pregnancy has not been conducted in more specific populations, such as preeclampsia patients. The results of several literature reviews report that data on the use of amlodipine during pregnancy are still limited, and thus its effectiveness needs further investigation (Kaye et al., 2019; Magee et al., 2022). Sufficient data availability could serve as a scientific basis for clinicians to consider amlodipine as an oral antihypertensive option for preeclampsia patients.

## MATERIALS AND METHOD

### Study design

This study is an observational analytic study with a cross-sectional approach. The research was conducted on preeclampsia patients at a secondary healthcare facilities in Tasikmalaya. The data used in this study are secondary data sourced from patient medical records. Data collection was carried out retrospectively from January 2019 to December 2023. The data obtained were then analyzed to determine the trends in the use of amlodipine and its effectiveness as an antihypertensive in preeclampsia patients compared to nifedipine. In this study, effective antihypertensive therapy was defined as achieving a target diastolic blood pressure of 80-100 mmHg within 24 hours of therapy (Magee et al., 2020).

### Sample study

The sample for this study consists of inpatient medical record at one of the secondary facilities in Tasikmalaya, involving pregnant women with preeclampsia who were treated with amlodipine or nifedipine from January 2019 to December 2023. The sample size was calculated using the Sample Size 2.0 application released by the World Health Organization (WHO). The minimum sample size calculation was based on hypothesis tests for two population proportions (two-sided test). For the single therapy category, the sample size was calculated with a significance level of 20% and a power test of 80%. Meanwhile, the sample size for the dual therapy category was calculated with a significance level of 5% and a power test of 90%. The population proportion used for the sample size calculation was obtained from the results of a pilot study. The minimum sample size for this study was 13 patients for each test group in the single therapy category and 24 patients for each group in the dual therapy category.

### Technique of sampling

The sample was selected using purposive sampling based on inclusion and exclusion criteria. The inclusion criteria included patients with an ICD-10 code for preeclampsia diagnosis (O14.0, O14.1, and O14.9), those receiving antihypertensive therapy, and patients with recorded blood pressure values after 24 hours of antihypertensive administration. The exclusion criteria included patients with multiple pregnancies, those receiving antihypertensive medications other than amlodipine or nifedipine, and patients with incomplete or missing medical records.

### Data Analysis

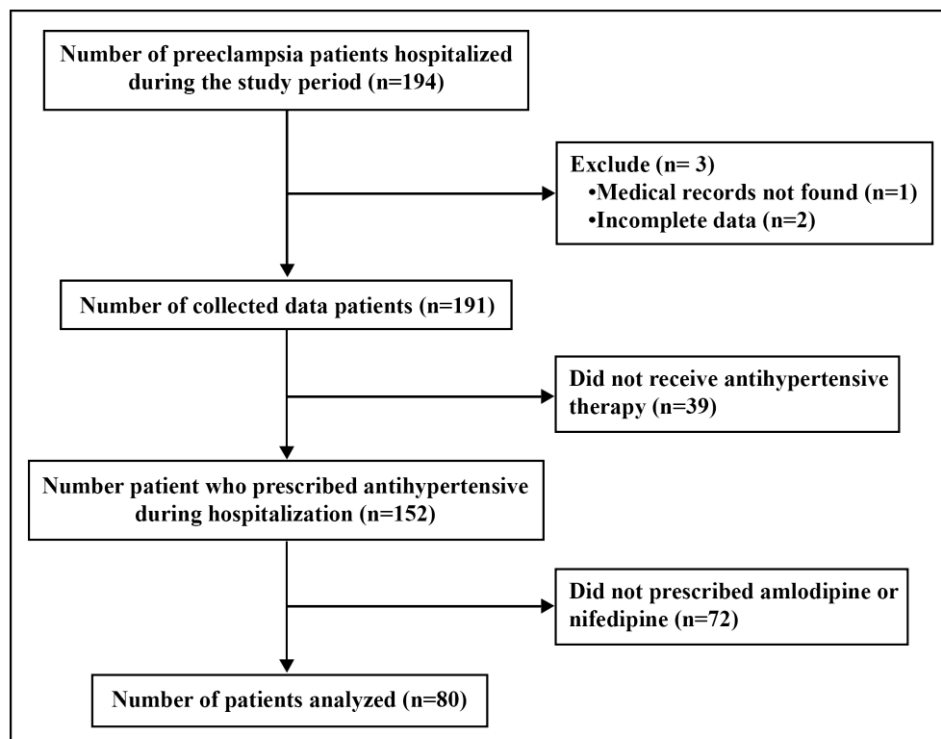
The collected data were sorted, cleaned, and coded, then exported to the Statistical Package for Social Science (SPSS) version 23.0. Missing data were handled using mean substitution method. Descriptive analysis was performed on the demographic and clinical characteristics of the patients using cross-tabulation between the two groups, presented as frequency and percentage. The Chi-square test was used to analyze differences in patient characteristics and drug effectiveness between groups. Odds Ratio (OR) and 95% Confidence Interval (CI) were used to describe the trends in the use of amlodipine and its effectiveness as an antihypertensive in preeclampsia. The last blood pressure recorded in medical record during the 24-hour therapy were used to analyze the achievement of the target blood pressure in patients. Statistical significance was determined based on a p-value <0.05.

### Ethical approval

This study was conducted with ethical approval from the Health Research Ethics Committee of Bhakti Tunas Husada University, under approval number 265-01/E.01/KEPK-BTH/VII/2024, granted on July 15, 2024.

## RESULT AND DISCUSSION

A total of 194 preeclampsia patients were hospitalized during the study period. However, 3 patients were excluded from the study population due to incomplete and missing data. As a result, 191 medical records were successfully collected for the study. Of these, 111 were not included in the analysis because 39 patients did not receive antihypertensive medication, and 72 patients were given antihypertensive drugs other than amlodipine or nifedipine. The final sample size analyzed in this study was 80 patients consisted of 41 patients in amlodipine group and 39 patients in nifedipine group (Figure 1). According to the sample size calculation, the number of samples used in this study met the required minimum sample size.



**Figure 1. Preeclampsia patient selection flowchart from January 2019 to December 2023**

The sociodemographic and clinical characteristics of the patients in this study are shown in Table 1. Based on age, 75% of preeclampsia patients were within 20–35 years, which is generally recommended for pregnancy. A study in Indonesia found that pregnant women in 20–35 years have a lower risk of preeclampsia compared to those over 35. Older pregnant women (>35 years) are three times more likely to experience maternal and perinatal complications due to preeclampsia (Tias et al., 2019). Another study in China confirmed that advanced maternal age is an independent risk factor for preeclampsia (Hou et al., 2024). However, other factors such as body mass index (BMI), medical history, and lifestyle also play a significant role in the risk of preeclampsia (Hou et al., 2024; Mayrink et al., 2019). In this study, 69% of preeclampsia patients were covered by the National Health Insurance (NHI). This indicates that the healthcare costs for the majority of preeclampsia patients are borne by NHI. A study reported that hospital care costs for more than 93% of preeclampsia patients exceeded the capitation provided by NHI, which is the excess costs having to be fully covered by the hospital (Akbar et al., 2018). Thus, preeclampsia can be a significant financial burden for both hospitals and NHI in Indonesia.

The study found that 31% of patients did not use National Health Insurance to cover their healthcare services. Of these, 26% were self-funded, while 6% utilized private health insurance. The findings of this study align with those of previous studies that have analyzed health insurance coverage in Indonesia. The study found that certain individuals did not utilize national health insurance due to various factors, including educational and socioeconomic status (Sukartini et al., 2021). Low educational attainment can result in limited access to information about health insurance coverage despite being enrolled in the National Health Insurance program (Putri et al., 2023). This is because individuals with lower levels of education may not fully understand how to utilize the NHI system to access healthcare services (Putri et al., 2023; Wulandari et al., 2023). Additionally, private healthcare insurance users are typically accessed by individuals with higher-income who desire more comprehensive coverage (Agustin et al., 2023).

The majority of patients in this study presented to the hospital with a gestational age of more than 37 weeks. At this stage, termination is the recommended management for preeclampsia patients, as it reduces the risk of complications for both the mother and the baby (Chappell et al., 2020). This study found that the majority of the sample study had an elevated BMI, indicating overweight (31%) and obesity (56%). Previous studies have shown that higher maternal BMI during pregnancy is associated with high blood pressure levels compared to normal BMI (Hissen et al., 2024). The study suggests that high BMI may be an additional factor, beyond antihypertensive efficacy, that influences the attainment of target blood pressure levels in preeclampsia. Controlling BMI could be another focus area in managing preeclampsia patient's blood pressure.

The study found that 81% of preeclampsia patients had severely elevated blood pressure, exceeding 160/110 mmHg (Table 2). Reducing elevated blood pressure in preeclamptic patient with severe hypertension is vital to prolonging the time to delivery and mitigating adverse maternal outcomes. Prolonging the pregnancy until fetal maturity is essential to optimize fetal outcomes (ACOG, 2020). Preeclampsia with severe hypertension during delivery has the highest risk of maternal death compared to other types of hypertension in pregnancy (Ackerman et al., 2019). Additionally, 85% of preeclampsia patients were new cases with no prior history of preeclampsia, which could increase their risk of developing preeclampsia in future pregnancies. A study reported that patients with a history of preeclampsia are significantly more likely to experience it in subsequent pregnancies (Njoroge et al., 2021). Therefore, the number of preeclampsia cases is always at risk of increasing in the future. Early detection and prompt management are crucial to preventing complications associated with preeclampsia (Pramana et al., 2020). Primary healthcare facilities play a key role in preventing preeclampsia and its worsening. The use of aspirin and the potential exploration of statins may be beneficial for preeclampsia prevention (Voto & Zeitune, 2022).

The analysis results show no relationship between sociodemographic or clinical characteristics of preeclampsia patients with the antihypertensive therapy administered. Pre-eclampsia patients who were treated with amlodipine or nifedipine were commonly prescribed these drugs in combination with methyldopa. The combination of antihypertensive medications during pregnancy is recommended in cases of persistent hypertension (Magee et al., 2022). Previous research has shown that combination therapy can be more effective in reducing blood pressure in preeclampsia (Wijaya et al., 2023). However, another study reported that combination antihypertensive therapy in preeclampsia patients resulted in worse delivery outcomes compared to single therapy (Al Ismaili et al., 2022). Although combination antihypertensive therapy may be necessary in some preeclampsia cases, the risks to both mother and fetus should be carefully considered with close monitoring and management.

Previous studies have shown that amlodipine is one of the calcium channel blockers increasingly used to manage preeclampsia, alongside nifedipine. The study reported that amlodipine accounted for 17% of antihypertensive use in preeclampsia cases (Wijaya et al., 2023). However, this study shows that over the five-years (2019 to 2023), the trend of using amlodipine as an antihypertensive in preeclampsia patients has declined. Although there was a significant increase of amlodipine use in

2020, its selection as an antihypertensive decreased in the following three years. It was found that the amount of preeclampsia in 2020 significantly decreased, making it the year with the fewest cases compared to other years. This acts as a confounding factor that may bias the analysis results. The year 2020 was the peak of the Covid-19 pandemic, during which a study reported a decline in antenatal care visits (Hazfiarini et al., 2022). The decrease in preeclampsia cases in 2020 might be related to the reduced number of antenatal care visits, leading to undetected cases.

**Table 1. Preeclampsia patient based on characteristics and antihypertensive therapy**

Variable	Therapy Group				Total		p-value
	Amlodipine (N= 41)		Nifedipine (N=39)				
	n	%	n	%	n	%	
Age-year							1
20-35	31	76	29	74	60	75	
>35	10	24	10	26	20	25	
Employment							0.146
Employed	13	32	6	15	19	24	
Unemployed	28	68	33	85	61	76	
Payment Methods							0.332 <sup>a</sup>
Self-funded	10	24	10	26	20	25	
NHI	30	73	25	64	55	69	
PHI	1	2	4	10	5	6	
Gravidity							1
Primigravida	9	22	9	23	18	23	
Multigravida	32	78	30	77	62	78	
Parity							0.483 <sup>a</sup>
Nullipara	10	24	11	28	21	26	
Primipara	12	29	15	38	27	34	
Multipara	19	46	13	33	32	40	
History of Abortion							0.38
Yes	10	24	14	36	56	70	
No	31	76	25	64	24	30	
BMI-kg/m <sup>2</sup>							0.646 <sup>a</sup>
Underweight	0	0	1	3	1	1	
Normal	4	10	5	13	9	11	
Overweight	12	29	13	33	25	31	
Obesity	25	61	20	51	45	56	
Gestational age at admission							0.386
<37 weeks	14	34	18	46	13	16	
≥37 weeks	27	66	21	54	67	84	
Single Therapy	17	41	14	36	31	39	
Dual Therapy	24	59	25	64	49	61	

BMI: Body Mass Index; NHI: National Healthcare Insurance; PHI-Private Healthcare Insurance

<sup>a</sup>Pearson Chi-Square test



**Tabel 2. Clinical characteristics of preeclampsia patient and antihypertensive therapy**

Variable	Therapy Group				Total		p-value
	Amlodipine (N= 41)		Nifedipine (N=39)				
	n	%	n	%	n	%	
History of Preeclamsia							1
Yes	8	20	7	18	15	19	
No	33	80	32	82	65	81	
Chronic Hypertension							0.684
Yes	5	12	7	18	12	15	
No	36	88	32	82	68	85	
Type of Hypertension							0.107
Mild <sup>a</sup>	11	27	4	10	15	19	
Severe <sup>b</sup>	30	73	35	90	65	81	
Drug administrated							0.779
Single Therapy	17	41	14	36	31	39	
Dual Therapy	24	59	25	64	49	61	

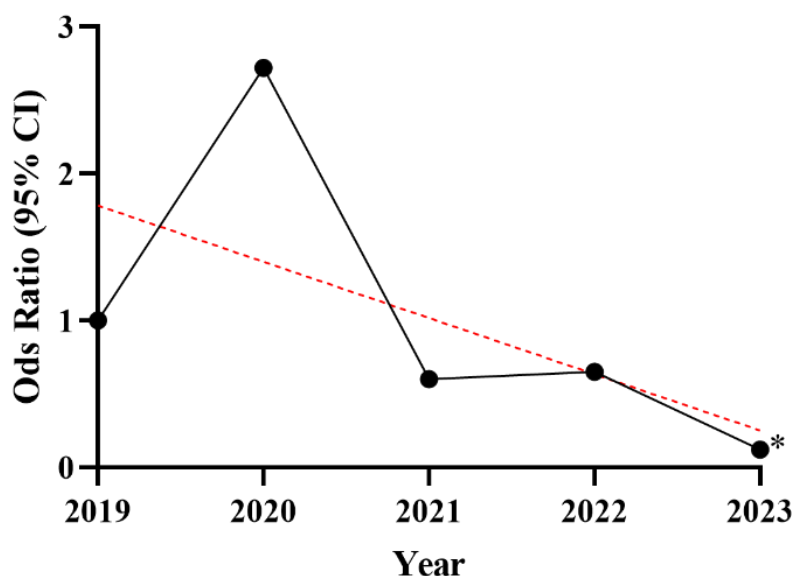
<sup>a</sup>Systolic blood pressure 140-159 mmHg and/or diastolic blood pressure 90-109 mmHg

<sup>b</sup>Systolic blood pressure  $\geq 160$  mmHg and/or diastolic blood pressure  $\geq 110$  mmHg

Statistical analysis shows a significant change in the prevalence of amlodipine use in 2023 compared to the previous four years (Figure 2). This suggests that, despite the initial rise in amlodipine use as an antihypertensive for preeclampsia, clinicians eventually tended to favor nifedipine as the antihypertensive therapy of choice for preeclampsia. This is potentially attributable to clinician preferences and established clinical practice guidelines. This is potentially attributable to clinician preferences and established clinical practice guidelines. The current evidence for using amlodipine to manage preeclampsia remains limited, leading clinicians to be cautious about prescribing it. In addition, Amlodipine was the calcium channel blocker most commonly prescribed for inpatient non-pregnant hypertension (Khumaeni et al., 2023). Furthermore, beyond limited evidence-based, the tendency might be associated with the management of drug supplies and prescribing practices. The supply prioritization of amlodipine for the treatment of hypertension in non-pregnant hypertension pregnancy may contribute to its underutilization in preeclampsia management. A study in Japan reported that amlodipine was the third most prescribed antihypertensive during pregnancy, with no significant changes in prescription trends over the last eight years (2013 to 2020) (Kikuchi et al., 2022). Conversely, the prescription trend for nifedipine during pregnancy significantly increased over the study period (Kikuchi et al., 2022).

The study shows no significant difference in the effectiveness between amlodipine and nifedipine in achieving blood pressure target in preeclampsia patients, whether as single therapy ( $p= 0.698$ ; OR 0.654, 95% CI 0.125-3.403) or in dual therapy ( $p= 0.1$ ; OR 3.25, 95% CI 0.967-10.922) (Table 3). However, other studies have reported different outcomes, with amlodipine demonstrating better blood pressure control during pregnancy compared to nifedipine (Yin et al., 2022). This discrepancy may be due to the heterogeneity of the study population in the previous study, which included patients with hypertension during pregnancy in general. In contrast, this study included only preeclampsia patients, who tend to have more severe conditions and prognosis compared to general pregnancy hypertension.

In this study, the use of amlodipine in combination with methyldopa resulted in a higher percentage of blood pressure target achievement (75%) compared to the combination use of nifedipine (48%). Preeclampsia patients who did not achieve their target blood pressure levels were at a substantially elevated risk of experiencing unfavorable delivery outcomes (Bugri et al., 2023).



**Figure 2. Time trends of amlodipine prescriptions compared to nifedipine as antihypertensive for preeclampsia patients from 2019 to 2023 while 2019 as a reference. \*Statistically significant ( $p < 0.05$ )**

Amlodipine and nifedipine both belong to the same drug class, Dihydropyridine Calcium Channel Blockers (DHP-CCBs). DHP-CCBs are vascular-selective as potent vasodilators (Lee, 2023). These two drugs exert their pharmacological effects by inhibiting the movement of calcium ions into the cytoplasm through transmembrane calcium channels, thereby reducing the contractility of blood vessels and the heart, as well as modulating the activity of pacemaker cells (Bain, 2019). This mechanism of action results in vasodilation, a decrease in blood pressure, and other cardiovascular effects. Theoretically, drugs within the same pharmacological class are likely to have similar effectiveness. However, clinical evidence shows that drugs in the same class do not always provide the same efficacy or safety profile (Gordon, 2013).

This study has limitations that can serve as references for improvement in future research. This study relied on retrospective data and was performed at a single healthcare facility. Although the sample size used met the minimum required, the number of study samples was still had suboptimal power of test. The study did not exclude patients with a history of cardiovascular disease and metabolic disorders, such as chronic hypertension and diabetes mellitus, which could potentially bias the results. Furthermore, the study could not analyze clinical outcomes after delivery to describe the impact of amlodipine use on delivery outcomes in preeclampsia. Nevertheless, the study used a sufficiently long database over five years, allowing the findings to serve as an approximation of the actual situation within the study population. This study is expected to provide an initial overview of the trends and effectiveness of amlodipine use in preeclampsia patients; a topic that has not been widely researched. The findings are also expected to inform clinical decisions regarding the use of amlodipine to treat hypertension in preeclampsia patients. Amlodipine is similar to nifedipine in effectiveness, but it may be easier to administer.



**Table 3. Effectiveness between amlodipine compared with nifedipine based on achievement of blood pressure target in preeclampsia**

Administration Method	Drugs	Efficacy of therapy				OR [95% CI]	p-value
		Achieve BP Target		Not Achieved BP Target			
		n	%	n	%		
Single Therapy							
	Amlodipine	12	70.6	5	29.4	0.654 [0.125-3.403]	0.698 <sup>b</sup>
	Nifedipine	11	78.6	3	21.4		
Dual Therapy <sup>a</sup>							
	Amlodipine	18	75	6	25	3.25 [0.967-10.922]	0.1
	Nifedipine	12	48	13	52		

BP: Blood pressure; OR: Odds Ratio; CI: Confidence interval.

<sup>a</sup>Drugs combined with methyldopa

<sup>b</sup>Fisher exact test

## CONCLUSION

The application of amlodipine in preeclampsia management has tended to decrease over the past five years. The limited evidence, clinical practice guidelines, and priority of drug use may be possible factors. Meanwhile, this study demonstrates that amlodipine and nifedipine have comparable effectiveness, indicating that utilization of amlodipine as an antihypertensive may be a viable option for preeclamptic patients. Furthermore, amlodipine potentially as an alternative antihypertensive agent alongside nifedipine in the therapeutic algorithm for preeclampsia. Further studies on delivery outcomes resulting from the use of amlodipine in preeclampsia are needed to provide a more comprehensive overview.

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