

Effectiveness of nifedipine compared with other antihypertension on hypertension during pregnancy

Aisyah Nur Sapriati, Cyndi Yulanda Putri, Juwita Permata Sari, Satya Prima Kustanto, Umu Kholifah

Magister of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia

<https://doi.org/10.22146/ijpther.3248>

ABSTRACT

Submitted: 29/10/2021

Accepted : 12/03/2022

Keywords:

antihypertensive;
hypertension in
pregnancy;
nifedipine;
preeclampsia;
eclampsia

Hypertension is the most common complication of pregnancy. It is a major cause of maternal, fetal, and neonatal morbidity and mortality. In this article, the effectiveness of nifedipine compared with other antihypertensives in pregnant women with hypertension was reviewed. The randomized control trial (RCT) of nifedipine and other antihypertension in pregnancy without complications published from 2016 to 2021 in Google Scholar, Cochrane and PubMed were gathered. It was reported that antihypertensives administration to pregnant women with hypertension was very meaningful both for the mother herself and for the fetus or baby. Furthermore, nifedipine has better effectiveness in lowering blood pressure compared to other antihypertensives such as IV labetalol, oral labetalol, IV hydralazine, methyldopa in the treatment of preeclampsia, severe preeclampsia, severe pre-eclampsia/eclampsia, chronic hypertension, hypertension emergency, and severe hypertension.

ABSTRAK

Hipertensi merupakan komplikasi pada kehamilan yang paling sering terjadi. Hipertensi menjadi penyebab utama dalam morbiditas dan mortalitas ibu, janin dan neonatus. Pada artikel ini, dilakukan telaah terhadap efektivitas nifedipin dibandingkan antihipertensi lainnya pada wanita hamil hipertensi. Uji klinik secara acak (RCT) nifedipine dan antihipertensi lain pada wanita tanpa komplikasi yang dipublikasikan dari 2016-2021 di Googel Scholar, Cocharane dan PubMed dikumpulkan. Dapat dilaporkan pemberian antihipertensi pada wanita hamil dengan hipertensi sangat bermanfaat baik bagi ibu hamil sendiri atau pada janin atau anaknya. Selanjutnya terbukti nifedipin lebih efektif dalam menurunkan tekanan darah dibandingkan antihipertensi lain seperti labetolol IV, labetolol oral, hidralazin IV, metildopa dalam pengobatan preeklamsia, preeklamsia berat, preeklamsia/eklamsia berat, hipertensi kronik, kegawatdaruratan hipertensi dan hipertensi berat.

INTRODUCTION

Hypertension is the most common complication of pregnancy. Around 5% to 10% of pregnant women suffered hypertension in worldwide. Hypertension is a major cause of maternal, fetal, and neonatal morbidity and mortality. Maternal risks events such as stroke, placental abruption, multi-organ failure, and disseminated intravascular coagulation. In pre-eclampsia, the risk

of the fetus experiencing intrauterine growth retardation is (25%), premature birth (27%), and stillbirth around 4%.¹

A pregnant woman is categorized as hypertension if the blood pressure (BP) is > 140/90 mmHg. Furthermore, if BP between 140-159/90-109 mmHg it is categorized as mild hypertension and if BP > 160/110 mmHg, it is categorized as severe hypertension.^{1,2} Furthermore, hypertension in pregnancy can be classified into several parts, including

*corresponding author: juwita8566@gmail.com

1) pre-existing hypertension (chronic hypertension) that existed before pregnancy or before the 20th week, 2) gestational hypertension that occurs after the 20th week, 3) chronic hypertension and superimposed gestational hypertension with proteinuria, 4) pre-eclampsia, namely hypertension gestational hypertension accompanied by significant proteinuria, and 5) unclassified antenatal hypertension.¹⁻³

Labetalol, methyldopa, and nifedipine are the first-choice medications used in therapy for hypertension in pregnancy. The second choice medications are clonidine, hydralazine and thiazides. In emergency conditions of BP >170/110 mmHg, hydralazine is only used if other drugs failed to control BP targets. These drugs have been widely used in the treatment of hypertension in pregnancy.^{1,3}

Many studies have compared the effectiveness of therapy with antihypertensive drugs in pregnancy. Considering that labetalol is not available in Indonesia and methyldopa is avoided after delivery because of depression risk, this study aimed to focus

more on comparing the effectiveness of oral nifedipine compared to other antihypertensive therapies in pregnancy by looking at the length of time used to lower BP until the target BP is achieved.

METHOD

The method used in this study is a literature study using the search engine method, namely Google Scholar, Cochrane, and PubMed. The keywords used in this literature search were “hypertension in pregnancy” or “hypertensive in pregnancy”, “nifedipine”, “efficacy”, and “randomized control trial (RCT)”. The literature that can be used in this study is the journal RCT with a publication range of 2016-2021. The inclusion criteria in this study were the journal RCT, hypertension in pregnancy without other complications, receiving nifedipine therapy, and having a comparative outcome of the length of time in lowering blood pressure (BP) to reach the therapeutic target. Exclusion criteria in this study were complications, did not receive nifedipine therapy, and non-RCT articles.

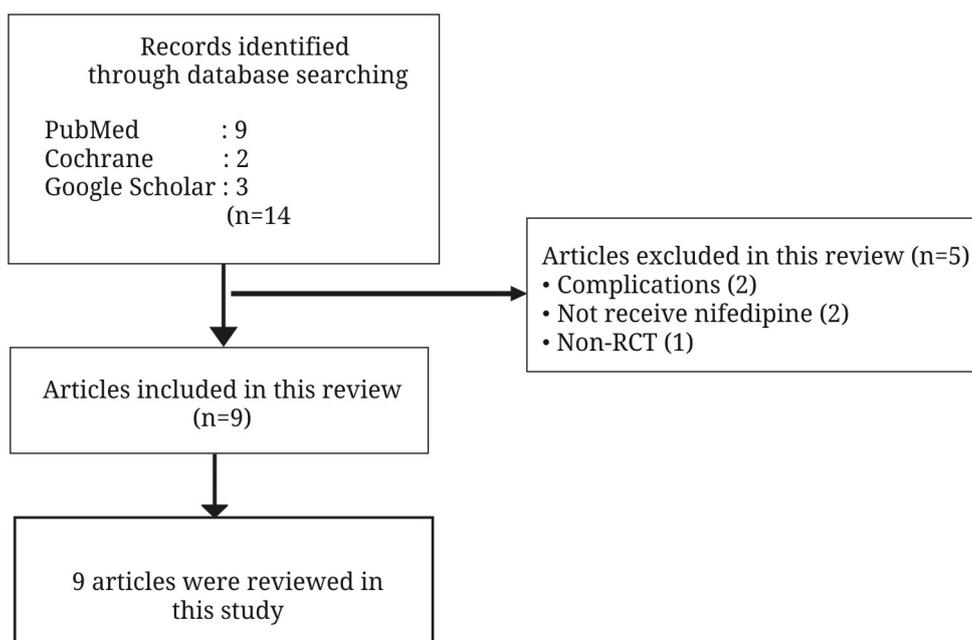


FIGURE 1. Flowchart diagram of article selection process

RESULT

All the main articles used to discuss the effectiveness of nifedipine on hyper-

tension in pregnant women compared with other drugs have different results. The outcome of each of these journals presented in TABLE 1.

TABLE 1. The outcome of the use of nifedipine with other hypertension drugs for pregnant women

References	Drug use	Patients, population and problem	Outcome target	Result
Adebayo <i>et al.</i> ⁴	Oral nifedipine vs IV hydralazine	Persistent severe hypertension in pregnancy with gestational age >28 weeks, maternal age 18–45 yo, and BP 160/ 110 mmHg or higher, maternal HR 60–120 beats/min and presence of a reassuring fetal heart rate	Doses of the drug needed to achieve targeted BP The time needed to achieve target BP Recurrence and retreatment of hypertension within 24 h and after 24 h of achieving BP control Maternal adverse effects and perinatal outcomes.	Nifedipine significantly reduced both the BP more than hydralazine following the 2 nd dose of the drugs. Acute control of BP was faster in the hydralazine arm when compared with nifedipine Dosages required to achieve BP control was significantly different in both arms (p<0.05) Recurrence and retreatment of hypertension was lower in the nifedipine when compared to hydralazine group (p<0.05) No significant difference in BP control after 24 h, the risk of recurrence and retreatment of severe hypertension, in the rate of induction of labor, and mode of delivery (p>0.05) Participants in the nifedipine group were 4 times more likely to have headache and 3 times more likely to experience nausea when compared with those in the hydralazine group
Easterling <i>et al.</i> ⁵	Initial dose of 10 mg oral nifedipine or 10 mg dose could be provided each hour versus initial dose of 200 mg oral labetalol or an additional 200 mg dose could be provided each hour versus 1000 mg methyldopa	Women with severe hypertension in pregnancy, aged at least 18 y.o, they were pregnant with fetuses that had gestational age of at least 28 wk, and were able to swallow the oral medications	BP control within 6 h with no adverse outcomes The need to change drug regimen or provide additional medications, placental abruption, maternal side effects, caesarean delivery.	The frequency of neonatal admission was significantly higher in babies born to women assigned to nifedipine versus labetalol and methyldopa. Women receiving nifedipine were more likely to achieve the BP target at 6 h than those receiving labetalol or methyldopa. BP control within the 6 h study period, with no adverse outcomes was significantly more common in women in the nifedipine group than in those in the methyldopa group. Slightly less than half of women in the nifedipine and labetalol groups received a second dose of their allocated medication Women receiving methyldopa were more likely to receive an additional or second hypertensive drug than those receiving nifedipine or labetalol Women in labetalol group more frequently received a third dose of study treatment than those in the nifedipine group
Zulfeen <i>et al.</i> ⁶	IV labetalol versus oral nifedipine	Gestational age >28 wk, BP of 160/110 mmHg or higher with severe hypertension in pregnancy.	Target BP 150/100 mm Hg Number of doses required Adverse effects Maternal and perinatal outcomes.	Mean time taken to achieve the target BP for intravenous labetalol was 36.75 and 27.25 min for oral nifedipine The nifedipine group also required a significantly lower number of doses than labetalol to reach the target BP Here was a drop in maternal HR in labetalol group compared to nifedipine group though the difference was not significant (p > 0.05). Urine output was significantly higher in nifedipine group (p < 0.001) None of the patients in nifedipine group required additional drug using the opposite treatment of labetalol. More women in labetalol group who had eclampsia, whereas more women in nifedipine group had abruption and HELLP syndrome, although it was not significant (p>0.05)

TABLE 1. cont.

References	Drug use	Patients, population and problem	Outcome target	Result
Webster <i>et al.</i> ⁷	Labetalol vs nifedipine	Women with prenatal chronic hypertension or BP 140/90 mmHg, ≤20 weeks gestation, need treatment antihypertensive, aged >18 years	To assess feasibility and to evaluate mechanical treatment effects, To examine the impact of ethnicity on efficacy of nifedipine with labetalol	Labetalol and nifedipine effective in controlling BP in women with chronic hypertension in pregnancy More women receiving nifedipine developed superpenalized preeclampsia than those allocated labetalol The same number of women in each group were diagnosed with early onset superimposed preeclampsia in 34 wk gestation The number of women requiring additional oral antihypertensive agents and women requiring induction of labor and caesarean section were comparable Adverse maternal outcomes and adverse neonatal outcomes were reported 6 women and 11 infants in the labetalol arm compared with 8 women and 17 infants in the nifedipine arm Late miscarriages are 1 in the labetalol and 3 in the nifedipine. There were 2 stillbirths in the labetalol group and 1 in the nifedipine group and no difference in mean birthweight
Salama <i>et al.</i> ⁸	Methyldopa vs nifedipine	Pregnancy woman with mild to moderate chronic hypertension, no medication and without features of end organ affection as renal or hepatic impairment, fundal changes, BP 140–159/90–109mmHg	Maternal outcome based by ultrasound confirmed, mode of delivery, hospital admissions for BP . Fetal-neonatal outcome: SGA defined as a birth weight < 10 th percentile, 5 min Apgar score, preterm labor, gestational age at delivery, IUFD, NICU, and neonatal deaths.	No significant difference between the methyldopa versus nifedipine groups regarding maternal demographic data in terms of age, parity and BMI, BP at enrollment, gestational age at enrollment, duration of chronic hypertension and past history of adverse obstetric outcome (p > 0.05) No significant difference between the methyldopa and nifedipine groups regarding the development of hepatic impairment, venous thromboembolism and cesarean delivery (p > 0.05) Neonates in the nifedipine group were more prone to prematurity, low Apgar score < 7 at 5 min and admission to neonatal ICU (p < 0.001) with no differences in the rates of small for gestational age, birth weight, gestational age at delivery, intrauterine fetal demise and neonatal death (p > 0.05) when compared to methyldopa group
Shi <i>et al.</i> ⁹	Oral nifedipine vs intravenous labetalol	Gestational age is ≥30 wk, severe pre-eclampsia who need to control BP with drug, the latest BP 160/110 mmHg	The main outcome of time needed to achieve the effective BP control and adverse effects on maternal or fetal	No significant difference between time taken to achieve the effective BP, number of dosages of medication needed to achieve target BP, newborn's Apgar scores, birthweight, and total number of dosages of medication needed to achieve effective BP control No severe adverse effects associated with either drug treatments and on maternal or fetal were reported, and the response to drugs was also similar in two treatment groups. Ten (13.5%) newborns in the oral nifedipine group and 12 (16.4%) in the intravenous labetalol group had Apgar scores of 4–6.

TABLE 1. cont.

References	Drug use	Patients, population and problem	Outcome target	Result
Thalamati, <i>et al.</i> ¹⁰	Nifedipine oral 10 mg versus dose escalation of labetalol in the regimen 20, 40, 80, 80, and 80 mg, done every 15 min	Sustained severe hypertension in pregnancy with BP 160/110 mmHg, pregnant women at 20 wk of gestation	The time required for BP to reach the target value. The number of doses required to achieve the target value. Adverse effects i.e. nausea, vomiting, dizziness, palpitations, chest pain, sweating and shortness of breath. The mode of delivery, maternal and perinatal morbidity, mortality. The neonates if admitted in NICU were followed up till discharge.	The mean time taken to achieve the target BP 36.61±5.2 min in labetalol group and 34.77±4.8 min in nifedipine group (p = 0.29). The labetalol group needed three doses and the nifedipine group required two doses to control the BP to target level. No significant difference in the number of doses required (p=0.43). The side effects like dizziness, sweating, nausea, vomiting, palpitations, headache and shortness of breath showed no statistical significance among the two drugs. No significant differences about mode of delivery, average birth weight, Apgar score of <7 at 5 min and APGAR score of 7 at 5 min. The neonatal complications like prematurity, NICU admissions, respiratory distress hyperbilirubinemia was comparable among the two groups. There were 2 IUD's and 2 neonatal deaths among the labetalol group and 2 IUD's and 3 neonatal deaths in the nifedipine group (p>0.05).
Havle & Havle, ¹¹	Oral labetalol versus oral 10 mg nifedipine	Pregnant women with BP 160/100 mmHg, severe pre-eclampsia/ eclampsia	Maternal BP, primary and secondary outcome and neonatal outcome	Time required achieving normal BP control in group labetalol was 35.4 h and in group nifedipine was 31.2 h. Sustained BP control for 72 h was seen in 24 patients in the labetalol group and 35 patients in the nifedipine group (p< 0.05). Additional hypertensive drugs required in group labetalol was 5 and in group nifedipine was 4. Length of hospital stay was 3.2 d in labetalol group and 3.5 d in nifedipine group. Side effect dyspnea was present 2 in group labetalol, 1 in group nifedipine, bronchospasm 1 in group labetalol, palpitations 2 in group labetalol and 1 in group nifedipine, flushing 1 in group labetalol and 2 in group nifedipine (p<0.05).

TABLE 1. cont.

References	Drug use	Patients, population and problem	Outcome target	Result
Sharma <i>et al.</i> ¹²	Hydralazine doses of 5 and 10 mg vs flat dose of nifedipine 10 mg every 20 min to a maximum of 4 doses	Sustained severe hypertension in pregnancy with BP $\geq 160/110$ mmHg, 18-45 years of age, ≥ 24 wk of gestation, HR was between ≥ 60 and <120 beats/min, and had a reassuring fetal HR	Time needed to achieve target BP of $\leq 150/100$ mmHg Total number of antihypertensive dosages required to achieve the target BP Maternal HR profile during the first 100 min, maternal hypotension (BP $<90/60$ mmHg), side-effects profile, and perinatal outcome	Median time to achieve target BP was 40 min in both groups All women in the study required a median of 2 doses for acute control of BP and no woman in the study required the cross-over treatment. The mean maternal HR at the end of the treatment were 78 and 88 beat/min in the hydralazine and nifedipine groups. Two women had tachycardia (heart rate >90 beat/min), both in the nifedipine group No statistically significant difference in mean HR of women in the hydralazine group ($p>0.05$) Maternal vomiting which was significantly more frequent in the hydralazine group (hydralazine vs nifedipine 9 vs 2, $p = 0.042$). One case of precipitous decrease in maternal BP during the trial period in the hydralazine group. No maternal or fetal death during the study.

DISCUSSION

Severe hypertension is usually treated with fast-acting antihypertensive agents, which are usually administered parenterally, and therefore, require expertise in constitution and administration. Antihypertensive agents have a role in controlling hypertension to avoid maternal and fetal complications. The efficacy of drugs in controlling high blood pressure is important in the prevention of complications in both the woman and the fetus. In addition, the availability of drugs is also an important factor in the management of hypertension to save lives. In studies related to severe hypertension conducted by Adebayo *et al.*⁴, Easterling *et al.*⁵ Zulfeen *et al.*⁶ and who compared the effectiveness of nifedipine with other antihypertensives, namely IV labetalol, methyldopa, oral labetalol, and IV hydralazine. The results showed that nifedipine has better effectiveness than other antihypertensives. This can be seen from the faster reduction in blood pressure achieved with nifedipine, and

also the lower dose required compared to other antihypertensives.

A study related to chronic hypertension conducted by Webster *et al.*⁷ Salama *et al.*⁸ showed that nifedipine vs labetalol and nifedipine vs methyldopa both could lower blood pressure to the therapeutic target with no significant difference. This means that both have the same effectiveness in lowering blood pressure to the therapeutic target in chronic hypertension. However, nifedipine has better tolerance.

A study related to pre-eclampsia conducted by Shi *et al.*⁹ found that oral nifedipine lowered the patient's blood pressure faster than IV labetalol in pregnancies with severe pre-eclampsia, although there were no significant differences in the time interval, dose of administration, and side effects of therapy. Meanwhile, in a study related to severe pre-eclampsia conducted by Thalamati *et al.*¹⁰ which compared the effectiveness of oral nifedipine and IV labetalol, the results obtained were that oral nifedipine is more effective than IV labetalol. Regarding the study of severe

pre-eclampsia/eclampsia conducted by Havle & Havle.¹¹ namely comparing oral labetalol and oral nifedipine were found that the effectiveness of oral nifedipine was better than oral labetalol in severe pre-eclampsia/eclampsia.

In a study related to hypertension emergency conducted by Sharma *et al.*¹² that is, comparing IV hydralazine with oral nifedipine, the results show that IV hydralazine and oral nifedipine have the same effectiveness in controlling the patient's blood pressure, but oral nifedipine has better tolerance than IV hydralazine, so oral nifedipine is recommended as first-line therapy in hypertensive emergencies in pregnant women.

CONCLUSION

It is found that giving antihypertensives to pregnant women with hypertension conditions is very meaningful both for the mother herself and also for the fetus or baby. Studies' results found that nifedipine as an antihypertensive agent of the calcium channel blocker class has higher effectiveness than other hypertension agents, namely IV labetalol, oral labetalol, IV hydralazine, methyldopa in the treatment of pre-eclampsia, severe pre-eclampsia, severe pre-eclampsia/eclampsia, chronic hypertension, hypertensive emergencies, and severe hypertension. Although in chronic hypertension, the antihypertensive effect of nifedipine with labetalol and IV hydralazine is similar, nifedipine has better tolerance in lowering blood pressure to the therapeutic target.

AKNOWLEDGEMENT

We would like to thank our colleagues whom support to finish this article.

REFERENCES

1. PERKI. Guidelines for the management of cardiovascular disease in pregnancy, 1st Edition. Jakarta: Indonesian Association of Cardiovascular Specialists, 2021.
2. Tinawi M. Hypertension in pregnancy. Arch Intern Med Res 2020; 3(1): 010-7. <http://doi.org/10.26502/aimr.0018>
3. Brown MA, Magee LA, Kenny LC, Karumanchi AS, McCarthy FP, *et al.* Hypertensive disorders of pregnancy ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018; 72:24-43. <https://doi.org/10.1161/HYPERTENSIONAHA.117.1083>
4. Adebayo JA, Nwafor JI, Lawani LO, Esike CO, Olaleye AA, Adiele NA. Efficacy of nifedipine versus hydralazine in the management of severe hypertension in pregnancy: a randomized controlled trial. Niger Postgrad Med J 2021. 27(4):317-24. https://doi.org/10.4103/npmj.npmj_275_20
5. Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, *et al.* Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomized controlled trial. Lancet 2019; 394(10203):1011-21. [https://doi.org/10.1016/S0140-6736\(19\)31282-6](https://doi.org/10.1016/S0140-6736(19)31282-6)
6. Zulfeen M, Tatapudib R, Sowjanya R. IV labetalol and oral nifedipine in acute control of severe hypertension in pregnancy—a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2019; 236:46-52. <https://doi.org/10.1016/j.ejogrb.2019.01.022>
7. Webster LM, Myers JE, Piercy CN, Harding K, Cruickshank JK, Coote IW, *et al.* Labetalol versus nifedipine as antihypertensive treatment for chronic hypertension in pregnancy a randomized controlled trial. Hypertension 2017; 70(5):915-22. <https://doi.org/10.1161/>

- hypertensionaha.117.09972
8. Salama M, Rezk M, Gabera W, Hamza H, Marawan H, Gamal A, *et al.* Methyldopa versus nifedipine or no medication for treatment of chronic hypertension during pregnancy: a multicenter randomized clinical trial. *Pregnancy Hypertens* 2019; 17:54-8.
<https://doi.org/10.1016/j.preghy.2019.05.009>
 9. Shi DD, Yang FZ, Zhou L, Wang N. Oral nifedipine vs. intravenous labetalol for treatment of pregnancy-induced severe pre-eclampsia. *J Clin Pharm Ther* 2016; 41(6):657-61.
<http://doi.org/10.1111/jcpt.12439>
 10. Thalamati S, Bandaru S, Bhumireddy D. Assessment of safety and efficacy of oral nifedipine and intravenous labetalol in management of increased blood pressure in severe preeclampsia. *Int J Reprod Contracept Obstet Gynecol* 2018; 7(7):2645-9.
<http://doi.org/10.18203/2320-1770.ijrcog20182465>
 11. Havle PA and Havle PA. Efficacy of oral labetalol and oral nifedipine in management of hypertensive disorders of pregnancy. *J Nat Remed* 2020; 21(3):60-3.
 12. Sharma C, Soni A, Gupta A, Verma A, Verma S. Hydralazine vs nifedipine for acute hypertensive emergency in pregnancy: a randomized controlled trial. *Am J Obstet Gynecol* 2017; 217(6):687.e1-e6.
<http://doi.org/10.1016/j.ajog.2017.08.018>