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Review Article

THE ROLE OF ANTIHYPERTENSIVE DRUGS IN PATIENTS WITH PREECLAMPSIA ANDHOW TO PREVENT IT: A REVIEW ARTICLE

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ABSTRACT

Treatment of hypertension in pregnancy, such as preeclampsia (PE), remains a challenging issue with adverse short and long-term implications for both of mother and baby. Screening for preeclampsia at 11-13 weeks' gestation with a combination of maternal demographic characteristics and medical history with measurements of biomarker can identify about 75% of women who develop premature preeclampsia with delivery at <37 weeks' gestation and 90% of those with early preeclampsia. Preeclampsia at <32 weeks has a 10% positive screen rate. Another major concern from administering Antihypertensive drugs during pregnancy is the potential adverse effects on the fetus. Some Antihypertensive drugs that are often used are methyldopa, hydralazine, labetalol, and nifedipine. The use of aspirin is often associated with a decrease in the prevention of early preeclampsia but must be accompanied by adherence to medication use, the use of aspirin can be combined with heparin. There is also a new combination from recent studies on the use of furosemide and nifedipine in preeclampsia.

Keywords: Antihypertensive, heparin, aspirin, preeclampsia, prevention.

INTRODUCTION

Preeclampsia (PE) is a disease characterized by new onset of hypertension and proteinuria or end-organ damage after 20 weeks of gestation. This disease is one of the main pregnancy-related hypertensive disorders and can occur after delivery. Additional clinical signs and symptoms include headache, visual disturbances, epigastric pain, thrombocytopenia, and abnormal liver function.[1] These clinical manifestations are induced by mild to severe microangiopathy in target organs, including the brain, liver, kidneys, and placenta. Potential maternal complications include pulmonary edema, cerebral hemorrhage, liver failure, renal failure, and even death. Potential fetal complications caused by placental hypo perfusion or the need for preterm delivery. Preeclampsia affects 3% to 5% of pregnancies in developed countries and is characterized by hypertension and new onset of proteinuria or organ dysfunction after 20 weeks of gestation.[3,4] Severe preeclampsia is characterized by organ damage or fetal growth restriction.[5] Preeclampsia increases not only the short-term risk for morbidity and maternal and child mortality but also the lifetime risk of cardiovascular disease (CVD). Women with severe preeclampsia can be up to 7 times more likely to develop CVD in the future than women with normotensive pregnancies.Recent studies have shown that PE patients have an increased postpartum cardiovascular risk. Therefore, patients with hypertension in pregnancy need to be monitored at postpartum for the development of other cardiovascular diseases. In this article, we review the Antihypertensive drugs that currently used to treat patients with PE and the advantages or disadvantages of using these drugs during pregnancy.

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PREECLAMPSIA DIAGNOSIS

The clinical diagnosis of PE is made when the new-onset of hypertension in the second half of pregnancy that associated with new-onset proteinuria. However, it was found that some patients showed evidence of multiorgan damage without proteinuria; under certain circumstances, PE can be diagnosed without proteinuria. In the absence of proteinuria, the diagnosis can be made if any of the following are present: abnormal liver function, thrombocytopenia, renal insufficiency, pulmonary edema, visual disturbances, or brain symptoms. According to 2013 report from the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy, PE can be diagnosed when the systolic blood pressure is greater than or equal to 140 mmHg or the diastolic blood pressure is greater or equal to 90 mmHg on two times examinations spaced at least 4 hours apart in previously normotensive patients or systolic blood pressure greater than or equal to 160 mmHg or diastolic blood pressure greater than or equal to 110 mmHg and hypertension can be confirmed within that time for facilitating timely Antihypertensive therapy.[1,7] Besides hypertension, proteinuria should be measured greater than or equal to 300 mg per 24-hour urine specimen, as the protein ratio is greater than or equal to 0.3, or as urine dipstick protein 1+ (if quantitative measurement is not available).[2]

CLASSIFICATIONOF PREECLAMPSIA

Previously, PE was classified in terms of severity as mild, moderate, or severe. Recently, because of morbidity and mortality can be significant for severe asymptomatic PE, a 2013 report from the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy recommended that this classification be avoided.[2] Otherwise, the term “preeclampsia without severe symptom” should be used to differentiate from "preeclampsia with severe symptom" that more severe.Based on gestational age at delivery, PE is broadly classified into early-onset, with signs and

symptoms developing at <34 weeks' gestation, and late-onset in patients with new-onset hypertension and proteinuria at 34 weeks gestation, and occasionally during labor (Table 1). Although the data are limited, it has been suggested that maternal and perinatal mortality varies within the preeclampsia subgroup.[8,9] Early-onset of PE comprises approximately 10% of total PE cases, and placental dysfunction is more likely in this subgroup than late-onset PE, which is more common. PE can cause complications for patients with preexisting chronic hypertension or chronic kidney disease (CKD). Preexisting chronic hypertension is a major risk factor for PE and usually signifies a poorer prognosis for the patient and fetus.[10] The diagnosis can be made when new-onset proteinuria and/or end-organ dysfunction occurs after 20 weeks gestation in a woman with chronic hypertension / previously diagnosed. For women with chronic preexisting hypertension / previously diagnosed who had proteinuria before or in early pregnancy, a sudden exacerbation of hypertension or the need to increase Antihypertensives, especially when blood pressure was previously controlled on these drugs, will lead to an overlapping diagnosis of preeclampsia. The relationship between preeclampsia and the subsequent development of kidney disease is well known, but because CKD and PE can coexist with hypertension and proteinuria in pregnancy, it is usually difficult to differentiate between the two. Several attempts are being made to accurately differentiate CKD from PE, including using uteroplacental flow and tyrosine kinase-1 such as tyrosine kinase-1 that soluble in maternal circulation to placental growth factor ratio.[11] Until now, there is no curative treatment for PE; therefore, primary management includes precautions for those at risk and, when PE occurs, stabilization of the mother and fetus followed by delivery at the optimal time.[12]

Table 1. Characteristics of the Preeclampsia Subgroup

Preeclampsia Subgroup	Signs and Symptoms
Early-onset PE (<34 weeks of gestation)	Only ±PE case Often due to placental dysfunction, increased of IUGR, maternal and perinatal mortality. Renal function indicators (Cr, BUN, and Uric Acid) increased significantly, but alkaline phosphate was low
Late-onset PE (≥34 weeks gestation)	Most cases of PE Severe during normal or large term labor

TREATMENT OF HYPERTENSION

All antihypertensive drugs have the potential to cross the placenta. Currently, there are no randomized controlled trials that underlie the recommendation for the use of one antihypertensive agent over another. However, certain drugs are effective in lowering blood pressure with an acceptable safety profile in pregnancy. The choice of therapy depends on the severity of hypertension. In addition, the choice of parenteral or oral therapy should be considered when selecting a particular drug.

1. Methyldopa

Methyldopa stimulates central alpha-adrenergic receptors by the neurotransmitter(α-methyl norepinephrine), which results in a decreased sympathetic outflow of norepinephrine to the heart, kidneys, and peripheral blood vessels. Methyldopa has been used extensively in the management of high blood pressure in pregnant women. In addition, its long-term safety for the fetus has been demonstrated. In the CHIPS (Control of Hypertension in Pregnancy Study) trial, preeclamptic women treated with methyldopa may have better outcomes than those treated with Labetalol.[13] However, methyldopa has only a mild antihypertensive effect with a slow onset of action (3 to 6 hours). Many preeclamptic women will not achieve the target of blood pressure on these oral agents alone.

2. Labetalol

Labetalol lowers blood pressure by blocking β- and α-adrenergic receptors. In addition, it can maintain uteroplacental blood flow better than other β-blockers. It has a rapid onset of action (2 hours) compared to methyldopa. Randomized clinical trials comparing labetalol with methyldopa or nifedipine have shown that labetalol to be safe for use in pregnancy.[14,15] Labetalol has been shown to cause maternal hepatotoxicity; it is important to recognize this side effect because it can be confused with HELLP syndrome. Most cases of labetalol-induced hepatotoxicity are reversible, but death has been reported.[16]

3. Nifedipine

Nifedipine is a calcium channel blocker that has been used in pregnancy without major problems. Long-acting nifedipine is preferred over short-acting nifedipine because the short-acting version of the drug can cause a significant decrease in blood pressure. However, some more recent studies suggest that short-acting oral nifedipine, under certain conditions, may be considered for safely reducing blood pressure. Long-acting nifedipine can be given as a tablet in a dose of 30-90 mg once daily. The dose may be increased at 7 to 14-day intervals, reaching a maximum dose of 120 mg daily.[17]

4. Hydralazine

Hydralazine is a direct arteriolar vasodilator. Intravenous hydralazine has been used extensively in the acute treatment of severe hypertension associated with preeclampsia. Although meta-analyses showed a slightly increased rate of adverse events from hydralazine compared with labetalol, the evidence is not strong enough to recommend one drug over the other.[18] However, the hypotensive effect of hydralazine is less predictable than with other parenteral agents. The oral version of hydralazine can be used to treat hypertension associated with preeclampsia. However, it is limited by its side effects, including lower extremity swelling and reflex of tachycardia.[17] Consensus has not been reached regarding the management of PE without severe hypertension in patients who have chronic hypertension or CKD. For PE with severe hypertension (sustained systolic blood pressure of at least 160 mmHg or diastolic blood pressure of at least 110 mmHg), the use of antihypertensives is recommended.[2] Labetalol, nifedipine, or methyldopa are often recommended as first-line therapy. The recent studies have shown that the calcium channel blocker, nifedipine, in the rapid-onset of oral release form may also be considered first-line therapy.[18-24] The 2017 Committee Opinion by the American College of Obstetricians and Gynaecologists' Committee on Obstetric Practice recommends the use of oral-rapid onset nifedipine as first-line therapy, especially when IV access is not available. Inhibitors of the renin-angiotensin-aldosterone system such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists should be avoided. The recommended blood pressure target is between 120/80 mmHg and 160/105 mmHg. It is also known that antihypertensives do not prevent eclampsia. Although magnesium sulfate is not recommended as an antihypertensive agent, it has been used for many years for the prevention of seizures in preeclamptic women with severe symptoms and for managing recurrent seizures in eclampsia. A limited double-blind, placebo-controlled trial has shown that there is no significant difference in the occurrence of eclampsia between patients with

severe asymptomatic preeclampsia treated with magnesium sulfate and that given placebo.[25] The recommendations of the American College of Obstetricians and Gynaecologists' (ACOG) in 2013, stated that for women with preeclampsia with systolic blood pressure less than 160 mmHg and diastolic blood pressure less than 110 mmHg and no maternal symptoms, it is recommended that magnesium sulfate not be universally administered for the prevention of eclampsia. In other words, ACOG limits the use of magnesium sulfate for the prevention of eclampsia in patients with BP 160/110 or higher, or if blood pressure is less than 160/110, other severe symptoms that usually precede seizures occur. Studies have shown that magnesium sulfate is more effective for the prevention of recurrent seizures in eclampsia than other traditional anticonvulsants, including phenytoin and diazepam or lytic cocktails.[24-26] The mechanism of action of magnesium sulfate in preventing seizures is not fully understood but is thought to be due to its effects on the central nervous system, possibly due to its effects on n-methyl d-aspartate (NMDA) receptors, calcium channels, and acetylcholine. Although data are limited, concerns that the simultaneous use of magnesium sulfate and nifedipine will cause serious side effects, including hypotension and neuromuscular inhibition, are not supported by the available evidence.[27] A study that involving 108 antenatal women was diagnosed with severe preeclampsia, with two recorded high blood pressures of 150/100 mmHg in the postpartum period within the first 24 hours of delivery, was enrolled in this study. These patients were randomly assigned to two groups (Group A: furosemide 20 mg OD + nifedipine & Group B: nifedipine alone). The study found the use of additional antihypertensives to be significantly higher in women in group B (26.0% vs 8.0%, p = 0.017). The duration of hospital stays and postpartum and the use of antihypertensives at discharge were similar in the two groups.[28]

Table 2. Antihypertensive Drugs Commonly Used in Preeclampsia with Severe Symptoms

Drug	Indication	Dose
First Line		
Methyldopa	PE with severe symptoms Hypertension in pregnancy	0.5-3 g/day PO in 2 divided doses
Labetalol	PE with severe symptoms, usually IVformulation	Starting with 20 mg IV bolus May require double dose 10 minutes later
Hydralazine	PE with severe symptoms, usually IV formulation. Long acting nifedipine	5 mg IV slowly over 1 to 2 minutes 30-90 mg once daily. It can increased at 7 to 14-day intervals, up to a maximum dose of 120 mg daily
Nifedipine	PE with severe symptoms, immediate release of an oral formulation	Start with 10 mg PO May repeat 30 minutes later
Second Line		
Nicardipine	Severe acute-onset hypertension that is resistant when first-line fails	Give IV infusion of 3 to 9 mg/hour
Sodium Nitroprusside	Life-threatening acute hypertension associated with PE	Start with 0.24 g/kg/min. Can be titrated until maximum dose of 5 g/kg/min

IV: intravenous, PO: orally, PE: preeclampsia (Odig. Use of Antihypertensive Drugs During Preeclampsia. Frontiers in Cardiovascular Medicine. 2018)

PREECLAMPSIA PREVENTION

Prevention of preeclampsia is divided into three, namely primary, secondary, or tertiary.[6] Primary prevention involves avoiding pregnancy in women at high risk for PE, modifying lifestyle, or increasing nutritional intake in the entire population to reduce disease incidence. Therefore, probably most cases of PE cannot be prevented.[29] It is known that the risk of preeclampsia is higher in women with pre-existing obesity, dyslipidemia (especially hypertriglyceridemia and hypercholesterolemia), uncontrolled diabetes mellitus, obstructive sleep apnea (chronic hypoxemia).[30,31] Therefore, weight loss, correction of Abnormal lipid profile, tight control of blood sugar, and surgical treatment of sleep apnea should be applied in high-risk patients. Adding low molecular weight heparin to aspirin shows a modest beneficial preventive effect but may prove to be more effective when combined with other preventive methods.[32] Recent studies have shown that l-arginine or isosorbide mononitrate (both of which increase endothelial nitric oxide production) will decrease the incidence of preeclampsia and improve intrauterine growth and fetal growth outcome. Therefore, increased nitric oxide production should be part of the prevention protocol.[33] Even in patients without pre-existing dyslipidemia, statins should be included in the prevention protocol because of their known positive effects in inducing the HO pathway and in reducing the risk of preeclampsia.[34] A study of aspirin showed a positive impact on the prevention of preeclampsia. The odds ratio in the aspirin group for preeclampsia was 0.24 (95% CI, 0.09-0.65) for 90% adherence and 0.59 (95% CI, 0.23-1.53) for <90% adherence. Adherence was positively associated with a family history of preeclampsia and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian race, and a history of preeclampsia in a previous pregnancy. The study concluded that the good effects must be balanced with drug use compliance.[35] In another study on pregnancies at high risk of preeclampsia, aspirin administration reduced the length of stay in the neonatal intensive care unit by approximately 70%. This decrease can be attributed to a decrease in the birth rate at <32 weeks' gestation, mainly due to the prevention of early preeclampsia. These findings have implications for short and long-term health care costs and infant survival and disability.[36] In the trial, there were 1620 participants and 1571 neonates born alive. The total length of stay in neonatal intensive care was substantially longer in the placebo group than in the aspirin group (1696 vs 531 days). This is a reflection of the significantly shorter mean length of stay in infants admitted to the neonatal intensive care unit from aspirin than in the placebo group (11.1 vs 31.4 days), a reduction of 20.3 days (95% CI, 7.0–38.6; P = .008).[37] A recent study found a positive effect of taking heparin with aspirin. Aspirin combined with LMWH can effectively improve clinical efficacy, coagulation function, renal function, and blood pressure levels, and the combination can reduce

adverse pregnancy outcomes in patients with severe preeclampsia. After treatment, the total effective rate was 94.44% in the study group and 76.00% in the control group. The comparison revealed that the total effective rate of patients in the study group after treatment was significantly higher than in the control, and the difference was statistically significant ($P < 0.05$).[38]

CONCLUSION

Many factors complicate the prevention of PE cases. Most are associated with unknown etiology, the low predictive value of current screening tests, and multiple disease presentations. Interventions that define a small reduction in risk mean that a large number of women need to be treated to prevent a single case. For now, the definitive treatment remains delivery and expulsion of the placenta. No effective prophylaxis for PE is officially recommended at this time. However, given that PE is considered a global health problem, with relatively high maternal and infant morbidity and mortality rates in many countries, prophylaxis interventions with little or moderate benefit may be beneficial.

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