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Severe hypertension in pregnancy: Hydralazine or labetalol A randomized clinical trial

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for the HYLA treatment study

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Abstract

Objective: The objective was to compare the safety and efficacy of intravenous labetalol and intravenous hydralazine for acutely lowering blood pressure in pregnancy.
Study design: Two hundred women with severe hypertension in pregnancy were randomized to receive hydralazine (5 mg as a slow bolus dose given intravenously, and repeated every 20 min up to a maximum of five doses) or labetalol (20-mg intravenous bolus dose followed by 40 mg if not effective within 20 min, followed by 80 mg every 20 min up to a maximum dose of 300 mg). The primary end point was successful lowering of blood pressure and maternal hypotension.
Results: Women were similar with respect to characteristics at randomization. No significant differences were observed for maternal hypotension or persistent severe hypertension; only two patients in the hydralazine group presented with hypotension. Palpitations ($p = 0.01$) and maternal tachycardia ($p = 0.05$) occurred significantly more often in patients treated with hydralazine. The main neonatal outcomes were very similar per group; however, hypotension and bradycardia were significantly more frequent in the labetalol group. There were two neonatal deaths per antihypertensive drug group.
Conclusions: This randomized clinical trial shows that labetalol and hydralazine fulfill the criteria required for an antihypertensive drug to treat severe hypertension in pregnancy.

Keywords: Antihypertensive drugs; Hydralazine; Labetalol; Severe hypertension of pregnancy; Preeclampsia

1. Introduction

Hypertensive disease occurs in around 12–22% of pregnancies depending on the populations and definitions used [1]. Hypertension in pregnancy is the second-leading cause of morbidity and mortality in the United States [2], and is a major risk factor for fetal morbidity and mortality [2,3], particularly the severe hypertension of preeclampsia. Worldwide, preeclampsia and eclampsia probably account for more than 50,000 maternal deaths a year [4].

The most recent classification of hypertension in pregnancy recommended by the National High Blood Pressure Education Program [2] is as follows: (1) chronic hypertension (essential and secondary); (2) preeclampsia/eclampsia; (3) preeclampsia superimposed on chronic hypertension; and (4) gestational hypertension. The four groups have been associated with acute, severe hypertension. There is general consensus that maternal and fetal risks are decreased by antihypertensive treatment that acutely lowers severe hypertension [2,5]. According to this opinion, the control of acutely raised blood pressure has become obligatory for women with hypertensive disorders of pregnancy. The most commonly used threshold for

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treatment is a sustained diastolic blood pressure of 110 mmHg or higher [6], and the treatment of a sustained systolic blood pressure greater than or equal to 160 mmHg is recommended by the National High Blood Pressure Education Program [2].

For many years, hydralazine has been the antihypertensive of choice for women with severe hypertension in pregnancy [2,5]. However, its side effects are common and mimic symptoms of deteriorating preeclampsia. Furthermore, a meta-analysis of clinical trials [7] showed that hydralazine was associated with more maternal hypotension, cesarean section, placental abruption, maternal oliguria, adverse effects on fetal heart rate, and more low 1-min Apgar scores; however, these results are not robust enough to guide clinical practice [7].

Intravenous labetalol is also used to treat acute hypertension in pregnancy as a first- or second-line drug and has a better side effect profile, but specific concerns have been raised about the risk of neonatal bradycardia [8].

Short-acting oral or sublingual nifedipine is commonly used to control acute, severe hypertension in women with preeclampsia. However, uncertainty exists about how safe it is for the mother [9,10].

A recent systematic review [11] and a recent meta-analysis [7] of the available small, randomized controlled trials concluded that intravenous labetalol or oral nifedipine is as effective as, and has fewer side effects than, intravenous hydralazine for the treatment of severe hypertension in pregnancy. However, parenteral hydralazine and labetalol are the drugs most commonly used to control acute severe hypertension in women with preeclampsia [2,3,12]. Nifedipine is not currently approved for acute severe hypertension in pregnancy by the American College of Obstetricians and Gynecologists [1].

The purpose of this study was to compare the safety and efficacy of intravenous labetalol and intravenous hydralazine for acutely lowering blood pressure in pregnant patients using a randomized clinical trial.

2. Materials and methods

The Complejo Hospitalario ‘‘Arnulfo Arias Madrid’’ de la Caja de Seguro Social in Panama City, is a tertiary referral hospital for the Republic of Panama. Pregnancies with severe hypertension are hospitalized in this area. The study population was drawn from women admitted for hypertensive disorders in pregnancy with severe hypertension between December 1, 2003 and November 17, 2004. The study was initiated after approval by the institutional Research Committee and Teaching staff of the hospital. In addition each patient included in the study signed an informed consent form.

Entry criteria were (1) pregnancy more than or equal to 24 weeks with a live fetus and hypertensive disorders, (2) systolic blood pressure of at least 160 mmHg and/or diastolic blood pressure at least 110 mmHg, (3) no concurrent antihypertensive therapy or absolute contraindications for labetalol or hydralazine. Standard mercury sphygmomanometers with appropriately sized cuffs were used. The first and fifth Korotkoff sounds were recorded for systolic and diastolic blood pressure, respectively.

Enrolled patients were randomly allocated to one of the two therapeutic regimens. Randomization was performed according to a computer-generated list by means of sequentially numbered, opaque, sealed envelopes indicating their medication. One group of patients received hydralazine and the other group received labetalol (Table 1). The study was not blind, because of logistic and economic constraints. Patients were treated according to the usual routine at the hospital, with no interference by the research group. Success was defined as lowering the diastolic blood pressure to below 110 mmHg or the systolic blood pressure to below 160 mmHg with one dose (minimum) up to five consecutive doses (maximum) of the antihypertensive drug.

Persistent severe hypertension was diagnosed when the patient presented levels above 160 or 110 mmHg after administration of the maximum consecutive doses (five) of the antihypertensive drug. After this diagnosis the women received the other antihypertensive drug. All patients were treated with intravenous hydralazine or intravenous labetalol and pregnancy termination.

Severe preeclampsia was defined as elevated blood pressure (at least 140/90 mmHg) with proteinuria (a dipstick reading of 1+ or more) in association with one or more of the following: headache, visual disturbances, epigastric pain, oliguria, pulmonary edema, elevated liver aminotransferase levels, elevated creatinine level, hemolysis, thrombocytopenia, intrauterine growth restriction, or oligohydramnios. A blood pressure of 160/110 mmHg or higher with proteinuria in the absence of any of the other features was also classified as severe preeclampsia.

The diagnosis of chronic hypertension was based on either of the following findings: (1) a history of hypertension before pregnancy (pregestational chronic hypertension) and (2) persistent blood pressure elevations of at least 140/90 mmHg before the 20th week of gestation.

The diagnosis of superimposed preeclampsia was made with the following findings: (1) in women with pregestational hypertension and no proteinuria early in pregnancy (<20 weeks’ gestation): sudden increase in blood pressure in a woman whose hypertension had previously been well

Table 1
Treatment of acute, severe hypertension

Drug	Recommendations
Hydralazine	5 mg as a slow bolus dose given intravenously, and repeated every 20 min until the desired effect is achieved or up to a maximum of five doses
Labetalol	20 mg intravenous bolus dose followed by 40 mg if not effective within 20 min, followed by 80 mg every 20 min up to a maximum dose of 300 mg (five doses)