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Original Article

Hydralazine vs labetalol for the treatment of severe hypertensive disorders of pregnancy. A randomized, controlled trial

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SYNOPSIS

Hydralazine and labetalol for intravenous use are equally effective in the management of hypertensive crisis in pregnant patients (24 weeks or more) with severe hypertensive disorders of pregnancy, showing a similar frequency of adverse effects in both groups.

Introduction

Hypertensive disorders of pregnancy (HDP) are one of the most common medical complications of pregnancy and according to multiple reports affect 10–15% of all pregnancies, being a major cause of maternal, fetal and neonatal morbidity and mortality [1–2]. Around the world this group of disorders comprise one of the four leading causes of maternal death and our country is no exception.

Treatment of hypertensive crisis associated with HDP remains under investigation. There are many studies and meta-analysis on the subject, but there is no definitive consensus or recommendations of great power regarding which is the best antihypertensive to achieve short-term success in controlling a hypertensive crisis, without affecting the wellbeing of the mother and the fetus. Modern evidence indicates that the mismanagement of HDP can lead to serious maternal and fetal/neonatal complications, hence the importance of adequate control of hypertensive crisis in our obstetric population [3].

Hydralazine and labetalol are the two intravenous antihypertensive drugs most frequently used for hypertensive crisis management in the obstetric population. The purpose of our research was to compare both in regard to efficacy in controlling blood pressure, frequency of adverse reactions in pregnant patients (gestational age of 24 weeks or more) and rate of persistent hypertension during pregnancy and the first 24 hours postpartum.

Materials and methods

We conducted a prospective, randomized, controlled trial between July 2012 and May 2013. Women with pregnancies of 24 or more weeks of gestation who were admitted to the hospital with the diagnosis of a hypertensive crisis were eligible for the study. Once the purpose of the study was explained to the patient, written informed consent was obtained by one of the investigators. Inclusion criteria were: (1) patients with systolic blood pressure (SBP) $\geqslant$ 160 and/or diastolic blood pressure

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(DBP) ⩾ 110 mmHg, (2) single or multiple pregnancy, (3) gestational age ⩾ 24 weeks, (4) no contraindication to the use of hydralazine or labetalol. Patients were in stable condition (no evidence of maternal hemodynamic instability) before randomization and their management afterward followed the standards accepted in our country and established in the national guidelines for the management of any patient with a HDP.

For the sample size calculation we decided to use the meta-analysis done by Magee et al. They found a rate of persistent severe hypertension of 3.8% in the hydralazine group and 13.5% in the labetalol group. With an α error rate of 5% and a power of 80%, the calculated sample size was 258 (129 per group). A total of 284 patients (142 per group) were deemed necessary to account for drop-outs or other problems during follow-up.

The randomization protocol required a designated member of the staff to open a sealed, opaque envelope containing a computer generated code randomizing the patient into one of the two groups. The hydralazine group received 5 mg as an initial IV bolus in not less than five minutes. After 15 min, blood pressure was measured and if SBP persisted ⩾160 mmHg or/and if DBP ⩾110 mmHg, the procedure was repeated up to a maximum of three doses. The labetalol group received 20 mg as the initial IV bolus in not less than 10 min. As before, after 15 min the blood pressure was measured and if SBP persisted ⩾160 mmHg or/and if DBP ⩾110 mmHg, the dose was doubled (40 mg). If no control of the blood pressure occurred with this second IV bolus, the next dose was of 80 mg and it could be repeated two more times (up to a maximum of 300 mg). Regardless of the group, all patients were questioned about the presence or absence of adverse reactions related to the use of the medication with each dose.

Our protocol established that if the maximum dose was reached without an adequate control of the blood pressure (SBP < 160 mmHg or DBP < 110 mmHg), a second antihypertensive was used. In our case, oral nifedipine (10 mg) every 15 min until control of the crisis (up to a maximum of five doses). Afterward, antihypertensive management was at the discretion of the treating physician. However, we recommended using the same scheme that was successful previously. All new episodes of hypertensive crisis were recorded for the remaining of the pregnancy 24 hours postpartum.

The primary outcome was efficacy of the medication, described as the minimum number of doses required to obtain an adequate control of the blood pressure (SBP ⩽ 159 mmHg and/or DBP ⩽ 109 mmHg). Secondary outcomes were the rate of persistent hypertension (need to use a second antihypertensive drug) and adverse effects related to the use of the drug.

Statistical analysis was performed using EpiInfo version 7.0 (Centers for Disease Control and Prevention, Atlanta GA). Differences in continuous variables were analyzed using the Mann–Whitney *U* test and non-continuous variables were analyzed using the chi-square test. Statistical significance was set at $p < 0.05$. The study was approved by the National Bioethics Committee for Research (Approval Number: 975/CNBI/ICGES/2012) and registered in a public database (ClinicalTrials.gov – NCT01538875).

Results

A total of 280 patients were screened, but 19 were excluded from the study (11 patients were lost in the follow-up, 3 patients did not fulfill the inclusion criteria, in 3 patients the protocol was breached due to lack of the randomized medication or clinical condition and 2 patients declined to participate). Therefore, our sample was made of 261 patients (Hydralazine: 130/Labetalol: 131) fulfilling our initial calculations (Fig. 1).

Patients in both groups were similar with respect to age, parity, baseline SBP, DBP and MBP (Table 1) and in frequency of the specific HDP per group (Table 2). In the analysis of the primary outcome (antihypertensive efficacy), we found no statistical differences in SBP, DBP and MBP between the hydralazine and labetalol groups (Table 3).

One of the secondary outcomes was the presence of persistent hypertension. The analysis of the data showed a total of 6 cases (4.6%) in the hydralazine group and 2 cases (1.5%) in the labetalol group ($p = 0.085$). Although this difference was not statistically significant, we did observe a trend of persistent hypertension with the use of hydralazine (Table 4). There was no significant difference regarding the number of doses of nifedipine required to control persistent hypertension ($p = 0.24$) and no patient required the maximum dose. Similarly, we observed no significant difference between the groups in terms of presence of new episodes of hypertensive crisis during pregnancy ($p = 0.30$) or the first 24 h postpartum ($p = 0.40$).

The other secondary outcome, frequency of adverse reactions, showed no statistically significant difference between groups. Symptoms evaluated included headaches, visual symptoms, epigastric pain, palpitations, nausea, vomiting and flushing (Table 5).

Discussion

Our investigation established that the intravenous use of hydralazine and labetalol was equally effective for the control of the hypertensive crisis in patients with HDP. Also, there was no difference in the number of cases of persistent hypertension or maternal side effects, regardless of the group.

The meta-analysis of Magee et al. [4] evaluated [5] clinical randomized trials that compared hydralazine and labetalol for the treatment of severe HDP. They reported that the use of hydralazine was associated with less persistent hypertension and non-use of other antihypertensive agents for the control of hypertensive crisis. However, the use of hydralazine in continuous infusion was associated with more episodes of hypotension than labetalol and was associated with higher maternal adverse effects (headache, palpitations, tachycardia, and flushing); in our study, on the other hand, there were no cases of hypotension in any of the two study groups. Moreover, the samples of the 5 mentioned studies were small: Ashe et al. (20 patients), Bhorat et al. (34 patients), Garden et al. (6 patients), Harper and Murnaghan (30 patients) and Mabie et al. (60 patients). They concluded that the results are not strong enough to give a guideline on the use of antihypertensive