Comparison of the Efficacy of Nifedipine and Hydralazine in Hypertensive Crisis in Pregnancy

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Abstract- Intravenous hydralazine is a commonly administered arteriolar vasodilator that is effective for hypertensive emergencies associated with pregnancy. Oral nifedipine is an alternative in management of these patients. In this study the efficacy of nifedipine and hydralazine in pregnancy was compared in a group of Iranian patients. Fifty hypertensive pregnant women were enrolled in the study. A randomized clinical trial was performed, in which patients in two groups received intravenus hydralazine or oral nifedipine to achieve target blood pressure reduction. The primary outcomes measured were the time and doses required for desired blood pressure achievement. Secondary measures included urinary output and maternal and neonatal side effects. The time required for reduction in systolic and diastolic blood pressure was shorter for oral nifedipine group (24.0 ± 10.0 min) than intravenus Hydralazine group (34.8 ± 18.8 min) ($P \leq 0.016$). Less frequent doses were required with oral nifedipine (1.2 ± 0.5) compared to intravenus hydralazine (2.1 ± 1.0) ($P \leq 0.0005$). There were no episodes of hypotension after hydralazine and one after nifedipine. Nifedipine and hydralazine are safe and effective antihypertensive drugs, showing a controlled and comparable blood pressure reduction in women with hypertensive emergencies in pregnancy. Both drugs reduce episodes of persistent severe hypertension. Considering pharmacokinetic properties of nifedipine such as rapid onset and long duration of action, the good oral bioavailability and less frequent side effects, it looks more preferable in hypertension emergencies of pregnancy than hydralazine.

Introduction

Hypertensive disorders have been proven as one of the most common leading factors for complications of pregnancy which can even lead to maternal mortality (1-6). The maternal mortality from hypertensive disease has been studied for its attributing factors (UK series 1997-1999) (6) and it was known that intracerebral hemorrhage is the most commonly attributing factor (6). There is general agreement that rapid lowering of high blood pressure can reduce this maternal risk (1,7,8). There are three short acting antihypertensive agents known for this purpose worldwide, hydralazine, labetalol and short acting sublingual or oral nifedipine (1). Although no FDA recommendation has so far been released for these drugs in hypertension of pregnancy (9), but there are reports which have addressed the advantage of each drug. On the other hand different availabilities worldwide should be considered. Despite many advantages found for labetalol (10-14), hydralazine is known as the first line treatment for hypertension in pregnancy since years ago and it is easily available worldwide (9).

Intravenous hydralazine

Advantages: No significant crossing of placenta and reduction of placental blood flow, No lupus like syndromes for intravenous administration (9) and less neonatal bradycardia than labetalol (15). Disadvantages: Reflex tachycardia, headache, angina, flushing, nausea, vomiting (9), unpredictability of response and prolonged duration of action (9), more fetal distress (16,17), more

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severe hypertension than nifedipine (15), more maternal hypotension, and more cesarean sections, placental abruption, maternal oliguria, more adverse effects on fetal heart rate, lower Apgar scores at one minute and less than 7 scores at five minute, more maternal side effects. Some evidence does not support hydralazine as treatment of choice for severe hypertension in pregnancy (15).

Nifedipine

Advantages: Better urinary output than labetalol (18), rapid onset of action, long duration of action, few side effects in oral administration, no significant decrease in placental blood flow, and no significant adverse effect on fetal heart rate (19,20). Disadvantages: Uncertainty exists how safe short acting calcium channel blockers are for the mother (21). Severely hypertensive patients who are likely to undergo emergent caesarean section often have to receive magnesium sulfate (1). Concomitant prescription of nifedipine with magnesium sulfate has result in two case reports of transient neuromuscular weakness (22,23).

Labetalol

Advantages: Little placental transfer due to lipid solubility (9), less palpitation and less maternal tachycardia with labetalol than hydralazine (24). Disadvantages: Risk of neonatal bradycardia with parental labetalol (25), no significant differences was observed in the rates of maternal hypotension with intra venus hydralazine (24), neonatal hypotension and neonatal bradycardia is more frequent in labetalol than hydralazine (24).

According to the fact that the main question remains to clarify the best recommendation between Nifedipine and hydralazine, we therefore compared the efficacy and safety of oral nifedipine with intravenus hydralazine in a randomized clinical trial during hypertension crisis of pregnancy.

Materials and Methods

During a randomized clinical trial (RCT) study, pregnant women who admitted for labor to women Hospital (Tehran University of Medical Sciences), diagnosed with severe pre-eclampsia or chronic hypertension superimposed by pre-eclampsia with mean age of 37 (18-45) years and in gestational age of at least 24 weeks were candidates for inclusion in the study. Exclusion criteria for this study were patients who were diagnosed to have heart disease by a cardiologist; also

all patients with severe renal impairment and cerebrovascular accident were excluded. Data collection from participants were intra-partum and during 24 hours post partum. All participants were receiving prophylactic infusion magnesium sulfate continually to avoid convulsion. Hypertensive emergency was defined as measured sustained systolic blood pressure ≥ 170 mmHg or diastolic blood pressure ≥ 105 mmHg. Blood pressure measurements were repeated in intervals of 15 minutes as patients were in lateral decubitus position.

The Research Committee of Tehran Medical University approved the study. All participants provided written informed consent. The enrolled patients were randomly prescribed with oral Nifedipine as 10 mg capsules (Zahravi, Iran) or intravenous hydralazine (Apresoline, 5-10 mg). Nifedipine was administered initially with doses of 10 mg then 20 mg with intervals of 20 min up to maximum of 5 doses or when desired blood pressure (150/90-100) was achieved. Hydralazine was intravenously administered initially in 5 mg and repeated in 10 mg doses, up to maximum of 5 injections in intervals of 20 min. Intravenous hydration were all set at rate of 125 mg/h.

After administration of the first dose, blood pressure and maternal heart rate were measured in intervals of 5 min for up to 20 minutes patients; then in intervals of 30 minutes.

Continuous external fetal heart rate monitoring was also performed. Also urinary output volume was collected and measured in 1, 2, 6, 12, 18 and 24 hours using an indwelling Foley catheter. Side effects on mother (headache, hypotension, flushing, and nausea) or abnormalities of fetal heart rate and neonatal 5 minutes Apgar score were recorded.

This study was intended to determine the time (minutes) required achieving the desired systolic blood pressure (less than 150 mmHg) and diastolic blood pressure (between 90 to 100 mmHg) after hydralazine or nifedipine administration. Frequency of doses necessary for achieving the desired blood pressure as well as urinary output, maternal side effects, side effects on fetal heart rate, neonatal Apgar score, and repeated doses during first 24 hours post partum were also determined in the study.

The primary endpoint with respect to efficacy of nifedipine and hydralazine in the study was time and doses to achieve the desired blood pressure. Secondary outcomes were urinary output, and maternal and neonatal side effects.

To detect a 40% difference in the time interval required to achieve the therapeutic blood pressure, with

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α=0.05 and β=0.2, it was determined that 25 patients would be required in each group. We dispensed either nifedipine or hydralazine according to a random number table. It was not possible for us to blind the study, because there was no placebo group due to ethical considerations.

Data were analyzed using SPSS software. Independent t-test was applied to compare between quantities of two treatment groups and chi-square and Fisher exact test were used to compare qualitative variables. Probability values less than 0.05 were considered significant. Quantitative variables have been indicated in mean ± SD.

Results

Fifty patients were randomly grouped in two for nifedipine or hydralazine treatments. Groups were similar for maternal age, weight, gestational age, gravidity, diastolic blood pressure, systolic blood pressure and history of pregnancy induced hypertension (Table1).

Patients prescribed by oral nifedipine achieved the desired blood pressure in 24.0±10.0 minutes, compared with 34.8±18.8 minutes for intravenus hydralazine (*P*≤0.016). Also nifedipine group needed fewer doses to achieve the goal blood pressure 1-3 doses (1.2±0.5) compare 1-5 (2.1±1) in hydralazine group. Nifedipine treatment was associated with significantly more increase in urinary output in 1, 2, 6, 12, 18 and 24 hours after treatment (Figure 1 and Table 2). We detected hypertensive crisis within the first 24 hours after achieving desired blood pressure in 20% of nifedipine treated group and 44% of hydralazine treated patients. The adverse effects of nifedipine and hydralazine on mother and infant are shown in table 3. In nifedipine group 1 case and in the hydralazine group 3 cases had fetal heart rate (FHR) abnormality, but no significant difference was detected when the two groups were compared (*P*=0.609). We did not observe Apgar score less than 7 in 5 min in none of groups. Only one patient in the study developed hypotension (systolic blood pressure <10) after receiving nifedipine. Two cases developed headache after nifedipine administration. In the hydralazine group one case had headache, one case developed flushing and one case had nausea (*P*=1.0). All patients needed termination pregnancy.

Table 1. Demographic data of patient groups.

Variable	Nifedipine Mean ± SD (n=25)	Hydralazine Mean ± SD (n=25)	*P* value
Maternal age (years)*	29.4±5.8	29.6±6	0.943
Maternal weight (kg)*	77.2±11.5	81.5±11.9	0.198
Gestational age (weeks) *	35.6±2.5	34.2±3.3	0.103
Gravidity *	2.6±2.0	2.64±1.6	0.938
Diastolic blood pressure (mmHg)*	109.4±5.3	111.4±6.2	0.226
Systolic blood pressure (mmHg)*	166.8±9.9	169.2±16.1	0.527
History of pregnancy induced Hypertension [†]	1	0	1.0

* Independent t-test [†]Fisher exact test

Table 2. Efficacy parameters of nifedipine and hydralazine in controlling of blood pressure

	Nifedipine (mean ± SD)	Hydralazine (mean ± SD)	*P* value
Needed time to achieve goal blood pressure (min)[*]	24.0 ± 10.0	34.8 ± 18.8	0.016
Required frequency of doses to achieve goal blood pressure[*]	1.2 ± 0.5	2.1 ± 1.0	< 0.0005
Number of patients necessary for re-treatment during 24 hrs from first dose•	5	11	0.069
Number of patients necessary for re-treatment after 24hrs from first dose[†]	0	1	1.0

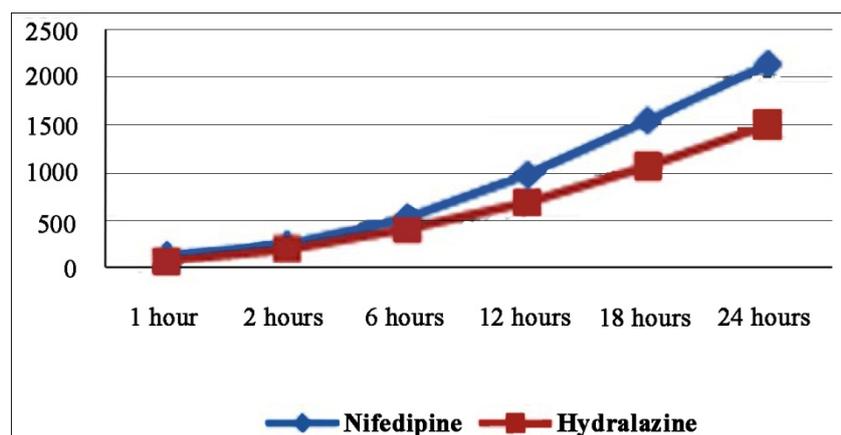* Independent t-test, •Chi square test,[†] Fisher exact test

Figure 1. Cumulative urine output after administration of drugs.

Table 3. Adverse maternal and infant outcomes

	Side effects	Nifedipine (N)	Hydralazine (N)	*P* value
Maternal	Headache [†]	2	1	1.0
	Hypotension[†]	1	0	1.0
	Flushing [†]	0	1	1.0
	Nausea [†]	0	1	1.0
Neonate	Abnormalities of FHR[†]	1	3	0.609
	5-min Apgar Score (mean ± SD) *	8.7 ± 0.8	8.5 ± 0.8	0.313

(No Apgar score less than 7 in 5-min was recorded) [†] Fisher exact test* independent t-test, N=number, FHR: fetal heart rate.

Discussion

This study shows that the time to achieve desired blood pressure was shorter for nifedipine compared to hydralazine. Also fewer doses of nifedipine were required for goal blood pressure achievement than hydralazine and urine outputs were higher for those patients prescribed nifedipine. The study of Aali and Nejad (25) also indicated better efficacy for nifedipine than hydralazine, because of fewer doses, more rapid effect and greater mean urinary output for nifedipine treated group. Similar to our findings, the study of Fenakel *et al.* (16) showed greater efficacy of nifedipine than hydralazine to achieve desired blood pressure in severe pre-eclampsia according to greater proportion of patients effectively controlled for blood pressure, furthermore they showed less fetal distress and less average of days spent in neonatal intensive care unit (NICU) for nifedipine (16). Also similar to our findings, the study of Kwawukume and Ghosh (26) has revealed better efficacy for nifedipine in controlling blood pressure in severe pre-eclampsia than hydralazine because of greater proportion of effectively controlled

patients. In our study no significant abnormality of FHR was detected. Dimitrios *et al.* also showed no adverse fetal side effects after administration of nifedipine for obstetric indication (27). In our study over shoot hypotension (systolic blood pressure<10) occurred in one patients receiving oral nifedipine, which was corrected within 5 min with intravenous fluids therapy, and did not lead to any fetal heart rate abnormalities. The same has been experienced in the study of Vermillion *et al.* when they compared oral nifedipine with intravenous labetalol (17). But no hypotension was developed for pre-eclamptic pregnant patients receiving sublingual nifedipine in another study (25). Hypertensive crisis was detected for pre-eclamptic pregnant patients receiving nifedipine in our study as in both above mentioned studies, but in different proportion of patients. We detected hypertensive crisis within first 24 hours of initial dose of oral nifedipine in 20% of patients, but it was detected for 60% of patients after sublingual nifedipine in the study of Aali and Nejad (25) and 12% in the study of Vermillion *et al.* (17). The safety of use nifedipine in pregnancy has been shown in several study recently and approved for the

treatment of hypertension in pregnancy (27-32). Montan also reported that although hydralazine has for many years been regarded as the first drug of choice for treatment of severe hypertension in pregnancy. Recent findings indicate that the calcium antagonist nifedipine might be a better alternative (33). Magee reported that use of nifedipine and magnesium sulfate together does not increase the risk of serious magnesium-related effects (29).

Considering pharmacokinetic properties of nifedipine such as rapid onset, long duration of action, good oral bioavailability and less frequent side effects, it looks more preferable anti-hypertensive therapy in hypertension emergences of pregnancy compared to the other drugs. More investigations are necessary to demonstrate urinary output, hypertensive crisis and less adverse effects as definite advantage for either medicine.

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