Research Article

A comparative evaluation of intravenous labetalol versus oral nifedipine for control of severe pregnancy-induced hypertension with low-dose regimen

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Received October 16, 2015. Accepted November 2, 2015

Abstract

Background: Hypertensive disorders complicate 5%–10% of all pregnancies and contribute greatly to maternal morbidity and mortality rates. Dangerous hypertension can cause cerebrovascular hemorrhage, hypertensive encephalopathy, and can trigger eclamptic convulsions. Blood pressure (BP) ≥160/110 mmHg in pregnancy requires prompt treatment. Both nifedipine and intravenous (IV) labetalol are effective antihypertensive agents belonging to different pharmacological classes and with different mechanisms of action. This study compares both the drugs.

Objective: To compare the efficacy and safety of oral nifedipine versus IV labetalol for control of BP in cases of severe pregnancy-induced hypertension (PIH) with low-dose regimen.

Materials and Methods: Pregnant women aged 18–40 years admitted in obstetrics and gynecology department with severe PIH, that is, BP ≥160/110 mmHg were included in this randomized prospective study. Simple randomization was done. A total of 30 patients in group A were given 5 mg oral nifedipine, to be repeated after half an hour if target BP of 150/100 mmHg was not achieved. A total of 30 patients in group B were given IV labetalol 20 mg initially followed by doses of 20, 20, 40, 40, and 80 mg every 20 min, if target BP was not achieved (maximum dose not to exceed 220 mg). The primary outcome variable was time necessary to achieve target BP. The secondary outcome variables were number of doses, cost of drug, need of crossover treatment, and adverse maternal and fetal side effects.

Result: Patients receiving oral nifedipine achieved the target BP in 43 ± 16.74 min as compared with 38.67 ± 19.43 min in labetalol group ($p = 0.3589$). This difference was not significant. No maternal or fetal side effects were observed in both the groups. Labetalol was the costlier drug.

Conclusion: Both regimens were equally effective in management of severe PIH with respect to time taken to achieve target BP. The adverse events in mother and baby were also less in view of the lower doses of the two agents used. Oral nifedipine was significantly less costly whereas IV labetalol was preferred in patients who were unable to take drug orally as in immediate postoperative patients and patients with altered sensorium.

KEY WORDS: Pregnancy-induced hypertension, labetalol, nifedipine

Access this article online	
Website: http://www.ijmsph.com	Quick Response Code:
DOI: 10.5455/ijmsph.2016.16102015178	

Introduction

Hypertensive disorders complicate 5%–10% of all pregnancies and contribute greatly to maternal morbidity and mortality rates.[1] Preeclampsia remains a leading cause of maternal and perinatal mortality and morbidity. Worldwide, every year, more than four million women develop preeclampsia and around 100,000 women experience eclamptic convulsions. Ninety percent of these cases occur in developing countries.[2]

Berg et al.[3] reported that half of these hypertension-related deaths were preventable. American College of Obstetricians and Gynecologists (ACOG) classifies preeclampsia into mild and severe, severe being blood pressure (BP) ≥160/110 mmHg with 3+ proteinuria and other associated complaints such as headache, visual disturbance, upper abdominal pain, oliguria, eclampsia, abnormal renal and liver function, intrauterine growth retardation, and pulmonary edema.[4]

Dangerous hypertension can cause cerebrovascular hemorrhage, hypertensive encephalopathy, and can trigger eclamptic convulsions. It seems likely that at least half of the serious hemorrhagic strokes associated with preeclampsia were in women with chronic hypertension.[5] Because of these factors, BP ≥160/110 mmHg in pregnancy requires prompt treatment. For years, parenteral hydralazine was the only drug available, later nifedipine and parenteral labetalol were introduced. Both nifedipine and intravenous (IV) labetalol are effective antihypertensive agents belonging to different pharmacological classes and with different mechanisms of action. Nifedipine is L-type calcium channel blocker and causes fall in BP by reducing peripheral vascular resistance. The mechanism of action in hypertension is inhibition of calcium influx into arterial smooth muscle cells. Nifedipine is more selective vasodilator and has less cardiac depressant effect. Oral short-acting nifedipine has been used in emergency management of severe hypertension. Labetalol is an adrenoceptor blocker having combined α_1- and β-blocking activity, thus useful in treating hypertensive emergencies by repeated IV bolus injection for rapid control.

Nifedipine given sublingual is no longer recommended. Oral nifedipine 10 mg is administered and repeated every half hour if necessary, whereas IV labetalol can be administered in incremental doses. ACOG (2002) recommends a starting dose of 20 mg IV bolus. If not effective within 10 min this is followed by 40 mg, then 80 mg every 10 min but not to exceed 220 mg total dose per episode.[4]

The primary objective of our study was to compare the effectiveness in relation with time taken to achieve target BP after using IV labetalol or oral nifedipine in severe pregnancy-induced hypertension (PIH) preferably by using a low-dose regimen. In addition, tolerability and safety profile of agents, number of doses required, and total cost for controlling BP were also noted.

Materials and Methods

In this comparative prospective randomized study, all admitted patients aged 18 to 40 years with severe PIH with BP ≥160/110 mmHg during the 6-month study between March 2015 and August 2015 were included. Ethics committee approval was taken, and written informed consent was taken from participants. Enrolment occurred in antepartum, intrapartum, and within 7 days of postpartum period.

Severe PIH was diagnosed when a sustained systolic BP ≥160 mmHg and diastolic BP ≥110 mmHg, on repeated measurements at 5 min apart, were observed.

A total of 60 patients were recruited. Study subjects were divided in two groups, group A (n = 30) was given oral nifedipine 5 mg orally. These were the patients who were in a position to take anything orally. The dose was repeated every half hour if target BP ≤150/100 mmHg was not achieved (maximum dose: 20 mg). Group B (n = 30) included patients who were not in a position of taking anything orally, for example, postoperative or unconscious patients. Those were given IV labetalol 20 mg initially followed by 20, 20, 40, 40, and 80 mg every 20 min until the target BP ≤150/100 mmHg was achieved. Crossover treatment was allowed if maximum dosage was unable to achieve the goal.

Exclusion criteria were known cases of heart disease, bronchial asthma, and severe liver and kidney diseases.

Primary outcome variable was the time taken to achieve target BP. Secondary outcome variables were number of doses, cost of drug, need for crossover treatment, adverse maternal and fetal side effects. Maternal side effects included headache, oliguria, and so on. Poor baby outcome was analyzed by low Apgar score, presence of meconium, and admission to neonatal intensive-care unit.

All these data were analyzed by either the unpaired t test or the chi-square test.

Result

Table 1 shows distribution of age, maternal weight, and parity among the study subjects. It may be observed that both the groups were adequately matched.

Initial values of systolic BP in both groups were quite similar (p value not significant: p = 0.4983) (166.20 ± 11.85 mmHg in nifedipine group vs. 168.13 ± 10.01 mmHg in labetalol group). The initial diastolic BP values between the two groups showed variations (p value significant, i.e., 0.0159); the values being higher in labetalol group (112.07 ± 6.14 mmHg in nifedipine group vs. 115.40 ± 3.53 mmHg in labetalol group).

Significantly, the overall cost of treatment in labetalol group (Rs. 373.33 ± 172.07) was much higher as compared with nifedipine group (Rs. 1.67 ± 0.61) ($p < 0.0001$).

It was observed that in patients of nifedipine group, the target BP (150/100 mmHg) was achieved a little bit later, that is, in 43 ± 16.74 min as compared with labetalol group (38.67 ± 19.43 min). However, the difference was not much significant, As far as the number of repeat doses were concerned, the nifedipine group required an average of 1.67 ± 0.61 doses as compared with IV labetalol group, which required an average of 1.77 ± 0.63, which again was not significant (p = 0.534).

No patient required crossover therapy. No maternal or fetal side effects were seen in either group.

Discussion

Hypertension affects up to 10% of pregnant women in the United States. A consensus panel has issued guidelines for the management of hypertension in pregnancy (National High

Table 1: Age, maternal weight, and parity distribution

Variables	Nifedipine	Labetalol	*t*-Value	*p*-Value
Age (mean ± SD)	25.43 ± 3.48	26.03 ± 4.99	0.5402	0.5911
Maternal weight (mean ± SD)	52.17 ± 15.38	55.03 ± 13.89	0.7559	0.4528
Parity				
0	8	3		
1	15	13		
2	5	3		
3	2	11		

SD, standard deviation.

Blood Pressure Education Program Working Group 2000). The panel recommended initiation of drug therapy in women with a diastolic BP > 105 mmHg or a systolic BP > 160 mmHg.[6]

Preeclampsia generally presents after 20 weeks of gestation as a new onset hypertension with proteinuria (>300 mg of urinary protein/24 h).[6] Preeclampsia is thought to involve placental-derived factors that affect vascular integrity and endothelial function in mother, thus causing peripheral edema, renal and hepatic dysfunction, and in severe cases, seizures.[7] It may be assumed that in PIH, antihypertensive with reasonable evidence of safety (Category C) may be used, including the combination α_1-selective, β-nonselective adrenergic antagonist labetalol, and the Ca^{2+} channel blocker nifedipine.[6] A rapid control of BP in patients of PIH is of utmost importance so that complications of eclampsia can be prevented.

Pathophysiology of preeclampsia is not well understood, though in 1972, Brosens et al.[8] reported for the first time that preeclampsia was associated with maternal uterine spiral arteries that lacked the expected physiological change.

The remodeling of uterine spiral arteries from the nonpregnant state to the highly dilated thin-walled vessels of pregnancy is vital for a normal pregnancy development and in supplying nutrients to the placenta and the growing fetus. In pregnancy, the spiral arteries penetrate the inner part of the myometrium as well as endometrium; the latter is transformed into a "decidua" destined to fall off at the end of pregnancy. The failed vascular remodeling affected not only the myometrial part of the artery but also the decidual portions of some of the spiral arteries in preeclampsia. In preeclampsia, oxidative stress is believed to ensue partly because of the higher blood flow velocity into the intervillous space owing to spiral artery, which could damage the villous surface architecture and mediate the release of trophoblast microparticles into maternal circulation and, thus, induce inflammation and generalized endothelial dysfunction. In addition, the nontransformed spiral arteries have retained smooth muscle cells, which also increase the risk of spontaneous vasoconstriction and intermittent perfusion of intervillous space, generating ischemia–reperfusion injury. Such disturbed perfusion is believed to lead a chronic placental oxidative stress response.[2] Interestingly, the literature is silent about whether the two drugs namely nifedipine and labetalol actually modify the above noted failed vascular remodeling, physiological changes, and chronic oxidative stress response.

Both nifedipine and labetalol are being successfully deployed to control PIH and both these drugs belong to different classes and act by different mechanisms of action to cause reduction in BP. Nifedipine, a clinically useful L-type voltage-gated calcium channel blocker, having oral bioavailability of 45%–70% and half-life of 4 h, is the prototype of dihydropyridine family of calcium channel blockers and is the most extensively studied drug of this group.[9] Labetalol is brought into limelight owing to its combined adrenoceptor-blocking property along with the availability of IV formulation for use in hypertensive emergencies. Labetalol is an equimolar mixture of four stereoisomers. One isomer is an α_1 antagonist, another is a nonselective β antagonist with partial agonist activity, and the other two isomers are inactive. Because of its α_1 adrenergic receptor-blocking activity, IV labetalol can reduce BP rapidly, thus very useful in the treatment of hypertensive emergencies.[10]

Control of BP is an important modifiable change in patients of PIH so that complications such as eclampsia are prevented. RCOG recommends a 10-mg initial oral dose of nifedipine to be repeated every 30 min, if necessary.[11] In variance, a smaller starting dose in our study was used, thus, a smaller starting dose of 5 mg was to be repeated every half an hour till maximum dose of 20 mg of nifedipine. For labetalol, ACOG (2002) recommends starting dose of a 20 mg IV bolus. If not effective within 10 min, this is followed by 40 mg, then 80 mg every 10 min, not to exceed maximum dose of 220 mg total dose.[4] Our study used a wider time interval, and the initial dose of 20 mg was followed by 20, 20, 40, 40, and 80 mg every 20 min, not to exceed 220 mg total dose The explanation for smaller doses in this study has been in view of smaller stature, built, and weight of individual as well as majority of subjects were having anemia and hypoproteinemia. Moreover, PIH itself causes marked proteinuria. All these factors necessitated a reduced dosage administration. This holds true for both agents.

Randomized trials[12] that compared nifedipine and IV labetalol found neither one superior to other. In a recent study, Raheem et al.[13] showed that both these agents were equally effective while some other studies[14] reported that nifedipine controls hypertension more rapidly. Shekhar et al.[15] concluded that oral nifedipine lowers BP more quickly than IV labetalol during hypertensive emergency in pregnancy. Median time taken to achieve target BP of 150 mmHg systolic and

100 mmHg diastolic was 40 min for nifedipine and 60 min for injection labetalol, respectively. In our study, patients who were given nifedipine achieved target BP in 43.0 ± 16.74 min as compared with 38.67 ± 19.43 min in the IV labetalol group, though the difference was not significant. Thus, our observations are in variance to those of Shekhar et al.[15] This could be because of a lower initial dose used in our study.

In our study, no maternal or fetal adverse events of drugs were observed. This clearly suggested that both drugs were well tolerated and were fairly safe in controlling PIH. Concurring views were expressed by CLIP working group[14] who observed no difference in adverse maternal outcomes in both the groups. Study by Dhali et al.[16] showed significant increase in urinary output in nifedipine group.

Earlier studies have reported no adverse outcomes in fetus. This is in line with our study.

Data with respect to comparative cost of these agents are not available in any literature. Our study showed that IV labetalol therapy was definitely costlier than nifedipine for achieving the target BP. Cost of therapy is a prime consideration for the management of emergencies. Shi et al.[17] concluded that oral nifedipine could be an alternative to IV labetalol for lowering BP during hypertensive emergencies in pregnancy. Oral nifedipine is also preferable because of its ease of administration, low cost, and a flat-dosing regimen. Both groups required almost same number of repeat doses.

An interesting observation of study was that low-dose regimen of both these agents is quite effective in achieving target BP and of course, these cause lesser adverse effects as compared to standard regimen.

Therefore, this study clearly states that nifedipine is better than labetalol cost wise by having same effectiveness. This is in fact achieved by using low-dose regimen in both groups leading to decreased side effects.

But this study is limited by sample size; hence, in future large-scale studies have to be conducted regarding the use of such low-dose regimen.

Conclusion

Both oral nifedipine and IV labetalol are equally effective in controlling BP. Both drugs showed no adverse events in mother and baby. But nifedipine is cheaper and convenient to administer; therefore, it is of importance in low-resource settings. IV labetalol is important in patients who are unable to take medicine orally. Our study also showed that even low doses of both agents are quite effective. This study provides a good base for further large-scale prospective studies to be conducted in the future regarding the use of such cost-effective low-dose regimens.

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How to cite this article: Mukherjee S, Khan S, Jain U, Misra A, Sana, Poonam. A comparative evaluation of intravenous labetalol versus oral nifedipine for control of severe pregnancy-induced hypertension with low-dose regimen. Int J Med Sci Public Health 2016;5:1183-1186

Source of Support: Nil, **Conflict of Interest:** None declared.