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ORIGINAL ARTICLE

Comparison of Efficacy of Oral Nifedipine Versus Intravenous Labetalol in the Acute Management of Hypertensive Urgency of Pregnancy

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ABSTRACT

Objective: To compare the oral nifedipine efficacy with intravenous labetalol in hypertensiveurgency of pregnancy.

Methodology: A total of 220 patients with sudden arterial hypertension who were 18 to 38 years old and had singleton gestations over 24 weeks were enrolled in this study. Patients with multiple pregnancies, heart disease, asthma, last child birth>4 years old, and those allergic to nifedipine orlabetalol were excluded. The selected patients were randomly divided into two groups by balloting: Group A (oral nifedipine) and Group B (intravenous labetalol). For positive or negative results, variable results (efficacy) such as blood pressure control were observed within two hours of starting treatment.

Results: The mean age of women in group A was 24.24 ± 3.38 and in group B was 23.18 ± 4.05 years (p<0.0001). The mean gestational age in group A was 34.75 ± 3.11 weeks and in group B was 33.98 ± 3.87 weeks (p<0.0015). There was normalization of blood pressure within two hours in 93 (84.55%) patients in Group A while in Group B, it was seen in 77 (70.0%) patients. So, efficacy was 84.55% in group A (oral nifedipine) and 70.0% in group B (IV Labetalol) with p-value of 0.0003. The mean time for blood pressure control was 26.87 ± 9.22 and 45.54 ± 16.91 for oral nifedipine and IV labetalol group respectively with a p-value <0.0001.

Conclusion: Oral nifedipine can be used as a first-line antihypertensive drug for the emergency treatment of hypertensive urgency of pregnancy.

Keywords: Pregnancy-induced hypertension, blood pressure control, oral nifedipine, intravenous labetalol.

INTRODUCTION

Hypertension is the most common medical problem during pregnancy, affecting 2-3% of pregnancies. Hypertensive emergencies include multiple clinical manifestations, in which uncontrolled blood pressure can lead to threatening and progressive target organ dysfunction[1]. In this case, the blood pressure should be actively lowered within a few minutes to a few hours. Severe hypertension without acute target organ damage is called hypertensive urgency [2]. In developed and developing countries besides bleeding and infection, pregnancy-induced hypertension (PIH) is still the main cause of maternal death. Pregnancy induced hypertension, pre-eclampsia, and eclampsia are terms used to describe different stages of the same syndrome [3]. However, eclampsia and pre-eclampsia are rare before the 20th week of pregnancy. The causes of pregnancy-induced hypertension and pre-eclampsia are unclear.

However, many relevant factors are known [4]. Major risk factors for pre-eclampsia include diabetes mellitis, SLE, hereditary thrombophilias, APLS, multiple gestation,, previous or family history of pregnancy-induced hypertension, chronic hypertension, and chronic kidney disease. [5]. Like other developing countries, Pakistan has about 75% of the population in rural areas without basic medical services. The concept of prenatal monitoring is lacking. Even in Karachi, Pakistan's largest and most educated city, only 50% of women receive prenatal care and hospital delivery. These pregnancy disorders have made a significant contribution to maternal and newborn morbidity and mortality worldwide[6, 7]. In the Netherlands, these disorders are the main reason. Most hypertensive diseases occur after 36 weeks of pregnancy [7].Patients with sudden hypertension may experience severe headaches, shortness of breath or nosebleeds.[8]. In hypertensive emergencies, the clinical manifestations depend on damaged organs and other symptoms, such as headaches. Thorough assessment should be carried out to distinguish between urgencies and emergencies. Tell your doctor about any medications, including herbal and over-the-counter medications usage. In all patients previously diagnosed with hypertension, the treatment's compatibility should be evaluated, including the time of the last dose. The correct measurement technique should be used to confirm blood pressure in both arms. Physical examination is an important part of the diagnosis. The examination should include assessment for heart failure, myocardial infarction, aortic dissection, hypertensive encephalopathy, cerebrovascular accidents, renal failure, retinopathy, retinal hemorrhage, and papillary edema[9]. Laboratory examinations should include end-organ evaluation like renal function tests and liver function tests, urinalysis, complete blood count and serum uric acid levels. For maternal hypertension, childbirth is the only causal treatment. In case of pregnancies that are remote from term, if the mother and baby's risk is mild and acceptable, conservative treatment is recommended. On the other hand, there are different schools of thought about how to treat mild hypertension during pregnancy. When treating women with pregnancy-induced hypertension or mild pre-eclampsia who are at or beyond 37 weeks of gestation, there is little evidence to explain the role of induction of labor versus vigilant waiting. Management of such women by induction of labor saves the mother and baby from the adverse outcomes like abruptio placentae, eclampsia, HELLP syndrome and intrauterine hypoxia but is also associated with the hazards of induction like operative vaginal delivery and caesarean section which increases the mortality and morbidity of both the mother and the baby (10, 11). Severe maternal hypertension should be stabilized before delivery to avoid fluctuations or worsening of blood pressure during anesthesia and delivery[10]. Therefore, in many cases, rapid but safe blood pressure control can minimize the delay in delivery during the late third trimester of pregnancy[11].With the advent of antihypertensive drugs, emergency hypertension in hypertensive patients has decreased from 7% to approximately 1%[12].When developing a treatment plan, it is important to distinguish between urgency and emergency of hypertension. In these patients, the best treatment is to use oral medications to lower blood pressure for 24-48 hours[13].The consensus is that severe hypertension in pregnancy (defined as BP ≥160/110 mmHg) needs immediate treatment because these women have an increased risk of cerebral hemorrhage, and treatment reduces maternal death [14, 15]. People with hypertensive encephalopathy, hemorrhage or eclampsia need treatment with parenteral medication. Reduce the mean arterial pressure (2/3 diastolic blood pressure + 1/3 systolic blood pressure) by 25% in a few minutes or hours and lower the blood pressure to less than 160/100 mm Hg in the next few hours. It is important to avoid hypotension because the degree of self-regulation of placental blood flow has not been established, and sudden marked reduction in blood pressure can cause fetal hypoxia. In women with pre-eclampsia, consideration should be given to starting treatment with lower doses for severe acute hypertension because these patients may have reduced volume in the vascular compartment and an increased risk of hypotension.

METHODOLOGY

A randomized, controlled trial was conducted at the Bahawal Victoria Hospital, Bahawalpur in the Department of Obstetrics and Gynecology, between May 2019 and October 2019. The inclusion and exclusion criteria were as follows.

a. Inclusion Criteria:

- Patients 18-38 years of age.
- All patients with gestational age >24 weeks (assessed on Dating scan) and with severe hypertension with a systolic blood pressure of ≥160mmHg or a diastolic blood pressure of ≥110mmHg measured on two occasions at least 4 hours apart.
- Patients with a singleton pregnancy and upto para-4.

b. Exclusion Criteria:

- Patients with age <18 and >38 years.
- Patients with multiple pregnancies and para >4.
- Hypersensitivity to nifedipine or labetalol.
- H/o arrythmias, heart failure, and asthma.
- Non-pregnancy related hypertension.

Procedure for collection of data:

220 patients were selected after obtaining the approval of the local ethics committee. These patients were enrolled in the Obstetrics and Gynecology Department of Bahawal Victoria Hospital in Bahawalpur and met the inclusion/exclusion criteria. After clarifying the objectives, methods, reasonably expected benefits, and potential risks of the research, informed and written consent was obtained. The subjects were told that their participation was voluntary and they could withdraw their consent to participate at any time during the study period. They were also told that not participating will not affect their care. A senior gynecologist (with five years of post-research work experience) can provide patients and researchers with more detailed information if necessary.

After the patient agrees to participate in the study, a complete mixed leaf (half of the leaf contains the letter "A" and the other half of the leaf contains the letter "B") is provided to all patients with severe pregnancy-induced hypertension and allocated to the suitable group of people Basic tests have been performed, for example, blood count, spot blood glucose, complete urine test, renal function test and liver function test.

Program details:

In Group A, each patient took the first 10 mg nifedipine tablet during the visit. If blood pressure is not controlled and systolic blood pressure>150 mmHg or diastolic blood pressure>100 mmHg, a second tablet given 15 minutes later. Dose repeated as needed for three additional treatment cycles to reduce blood pressure to the target range (≤150/100 mmHg). Once the target blood pressure is reached, the treatment is stopped. In Group B, each patient received labetalol intravenously in increasing doses of 20, 40, 80, 80, and 80 mg (5 doses at 15 minutes intervals) until the target blood pressure was reached (≤150/100mmHg). Treatmentstopped when the target blood pressure is reached.

All patients in the two groups were independently checked by the investigator for blood pressure, and the final blood pressure was recorded two hours after the start of treatment. If each group reaches the treatment goal (blood pressure ≤150/100 mmHg) within two hours after starting treatment, the treatment is considered effective; otherwise, it is marked as an unsucessful. Fetal monitoring also checked before, during and after the treatment using electronic fetal monitoring machine. All of these data are saved in a predefined form, which contains two parts; that is, the first part includes the biological data of the patient, and the second part contains the research variables.

Statistical Analysis:

All data were entered and analyzed using SPSS version 14.0. Age, gestational age and time to normal blood pressure are reported as mean ± standard deviation. The outcome variables are listed by frequency and percentage, such as a number of deliveries, dose, and efficacy of oral nifedipine and intravenous Labetalol. The chi-square test was used to analyze the comparison between the two groups in terms of the two schemes' effectiveness. A p-value of ≤0.05 is considered statistically significant. An effect modifier that normalizes blood pressure is needed by stratifying data according to age, gestational age, number of deliveries, number of doses, and time. After stratification, the chi-square test was used to observe its influence on the outcome variables. A p value ≤ 0.05 was considered significant.

RESULTS

Age range in this study was from 18 to 38 years with mean age of 23.91 ± 3.78 years. The mean age of women in group A was 24.24 ± 3.38 and in group B was 23.18 ± 4.05 years. Majority of the patients 117 (53.18%) were between 18 to 25

years of age as shown in Table **1**.

Gestational age was from 24 to 40 weeks with mean age of 34.42 ± 3.55 weeks. The mean gestational age in group A was 34.75 ± 3.11 weeks and in group B was 33.98 ± 3.87 weeks. Majority of the patients 79 (43.41%) were between 34 to 40 weeks of gestation as shown in Table **2**.

Stratification according to parity and time taken for normalization of blood pressure in both groups has shown in Table **3** & Table **4** respectively.

Table **5** has shown the stratification according to number of doses in both groups. There was normalization of blood pressure within two hours in 93 (84.55%) patients in Group A while in Group B, it was seen in 77 (70.0%) patients. So, efficacy was 84.55% in group A (oral nifedipine) and 70.0% in group B (Labetalol) with p-value of 0.0003 as shown in Figure **1**. Comparison of efficacy between two groups in terms of parity, gestational age and age of patients has shown in Table **6**.

Table 1. Distribution of Age in both groups (n=220).

Age (years)	Group A (n=110)		Group B (n=110)		Total (n=220)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-25	56	50.91	61	55.45	117	53.18
26-30	38	34.55	37	33.64	75	34.09
31-38	16	14.54	12	10.91	28	12.73
Mean ± SD	**24.24 ± 3.38**		**23.18 ± 4.05**		**23.91 ± 3.78**	

Table 2. Percentages of patients according to Gestational age in both groups.

Gestational Age (weeks)	Group A (n=110)		Group B (n=110)		Total (n=220)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
24-28 weeks	22	20.0	20	18.18	42	19.1
29-33 weeks	29	26.36	36	32.73	65	29.54
34-40 weeks	59	53.64	54	49.09	113	51.36
Mean ± SD	**34.75 ± 3.11**		**33.98 ± 3.87**		**34.42 ± 3.55**	

Table 3. Percentages of patients according to parity of pregnant women in both groups.

Parity	Group A (n=110)		Group B (n=110)		Total (n=220)	
	Frequency (No. of patients)	%age	Frequency (No. of patients)	%age	Frequency (No. of patients)	%age
1	59	53.64	61	55.45	120	54.55
2	18	16.36	23	20.91	41	18.64
3	27	24.55	21	19.09	48	21.82
4	06	5.45	05	4.55	11	5.0

Table 4. Percentages of patients according to the time taken for normalization of blood pressure.

Time	Group A (n=110)		Group B (n=110)		Total (n=220)	
	Frequency (No. of patients)	**%age**	**Frequency** (No. of patients)	**%age**	**Frequency** (No. of patients)	**%age**
0-30 minutes	64	58.18	17	15.45	81	36.82
31-60 minutes	18	16.36	47	42.73	65	29.55
61-120 minutes	11	10.0	13	11.82	24	10.91
>120 minutes	17	15.45	33	30.0	50	22.73
Mean ± SD	**26.87 ± 9.22**		**45.54 ± 16.91**		**40.33 ± 17.31**	

P-value<0.0001, which is statistically significant.

Table 5 %age of patients according to a number of doses.

No. of Doses	Group A (n=110)		Group B (n=110)		Total (n=220)	
	Frequency	%age	Frequency	%age	Frequency	%age
< 3 doses	87	79.09	71	64.55	158	71.82
> 3 doses	23	20.91	39	35.45	62	28.18

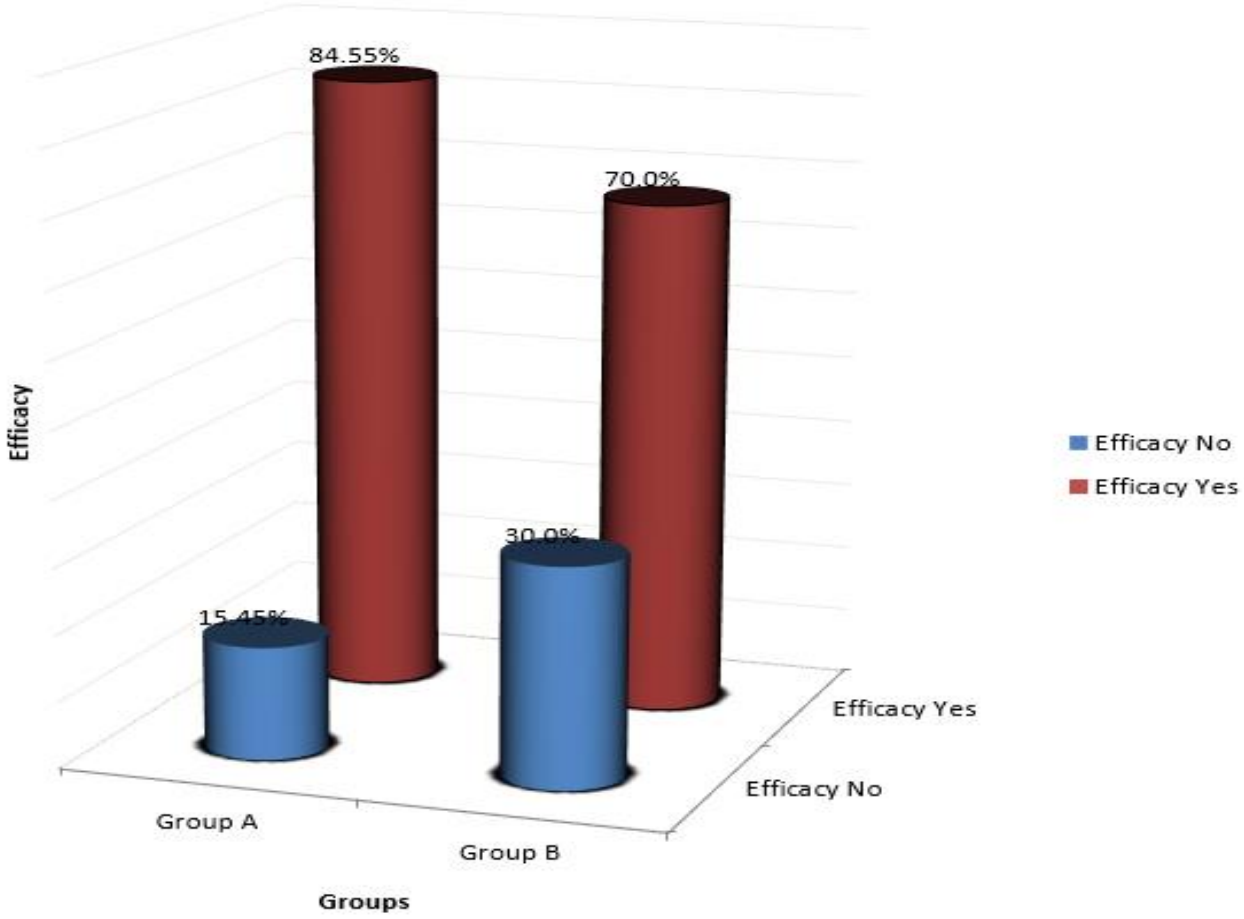

Figure 1. Efficacy of both Groups (n=220).

Table 6. Comparison between the effectiveness of both groups rendering to parity, age, and gestational age.

Parity	Group A (n=110)		Group B (n=110)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
1	53 (89.83%)	06 (10.17%)	46 (75.41%)	15 (24.59%)	**0.0377**
2	14 (77.78%)	04 (22.22%)	15 (65.22%)	08 (34.78%)	**0.3804**
3	21(77.78%)	06 (22.22%)	15 (71.43%)	06 (28.57%)	**0.6143**
4	05 (83.33%)	01 (16.67%)	01 (20.0%)	04 (80.0%)	**0.0357**
Age of patients					
18-25 years	51 (91.07%)	05 (8.93%)	47 (77.05%)	14 (22.95%)	**0.0399**
26-30 years	30 (78.95%)	08 (21.05%)	26 (68.42%)	12 (31.58%)	**0.2974**
31-38 years	12 (75.0%)	04 (25.0%)	05 (41.67%)	07 (58.33%)	**0.0739**
Gestational Age					
24-28 weeks	18 (81.82%)	04 (18.18%)	11 (55.0%)	09 (45.0%)	**0.0604**
29-33 weeks	25 (86.21%)	04(13.79%)	23(63.89%)	13 (36.11%)	**0.0418**
34-40 weeks	50 (84.75%)	09 (15.25%)	43 (79.63%)	11 (20.37%)	**0.477**

DISCUSSION

About 70% of hypertensive diseases are caused by pregnancy-induced hypertension and pre-eclampsia111. The range of hypertensive diseases that may complicate pregnancy is very wide, from "white coat" hypertension to pregnancy-induced hypertension, chronic hypertension, and pre-eclampsia to chronic hypertension combined with preeclampsia. Hypertension is particularly difficult to manage during pregnancy, especially when it becomes so severe, it can be classified as a hypertension crisis, posing a direct risk to the mother and fetus[16]. Overall, 10-15% of direct maternal deaths are related to pre-eclampsia and eclampsia[17]. When maternal mortality is high, most deaths are caused by eclampsia rather than pre-eclampsia[17]. The World Health Organization estimates that 45,000 women worldwide die of hypertension in pregnancyeveryyear114. Severe pre-eclampsia/eclampsia with a blood pressure of ≥160/110 mmHg is associated with an increased risk of complications such as hypertensive encephalopathy, intracranial hemorrhage, and eclampsia. The blood pressure must be lowered below 150/100 mmHg to reduce complications. The first-line antihypertensive drugs recommended for acute blood pressure control in severe pre-eclampsia are intravenous hydralazine, oral or intravenous labetalol, and oral nifedipine[18, 19]. Nifedipine is the most commonly used antihypertensive drug in Pakistan. It is used to control blood pressure in severe hypertension, because of its easy availability, quick onset, simple oral administration, and satisfactory blood pressure reduction. However, in some countries (such as Australia), it is banned due to sudden and unpredictable drops in blood pressure and cardiac side effects. The interaction between nifedipine and magnesium sulfate may be related to severe muscle weakness and hypotension. Both nifedipine and magnesium sulfate have relaxant effect on the uterine contractions and may increase the overall time span of labor[20].This randomized controlled trial compared oral nifedipine and intravenous labetalol efficacy in the acute treatment of hypertensive urgency during pregnancy. The average age of patients in the nifedipine group was 24.24±3.38 years, and the average age of

patients in the IV-labetalol group was 23.18±4.05 years. The majority (53.18%) of the 117 patients in the two groups were between 18 and 25 years old. These results are very similar to the study of Desai B *et al*. [21], in which the average age of the oral nifedipine and IV-labetalol groups was 24.4 years and 23.9 years, respectively. In their study, Dhali B *et al*. [22] showed that the average age of the nifedipine group was 23.7 years, and the average age of the IV-labetalol group was 24.3 years. Dhali B *et al*. [22] and Desai B *et al*. [21] showed in their study that most patients suffer from the primary disease, namely 81% and 56%, respectively. These results are similar to our study, which showed a higher risk of first-time maternal hypertension, which is 54.55%. The average gestational age of the nifedipine group was 34.75±3.11 weeks, the average gestational age of the IV-labetalol group was 33.98±3.87 weeks, and Desai B *et al*. [21] found that the average gestational age of the oral group was 35.4 week. The IV-labetalol group was 33.98±3.87 weeks. 36.2 weeks later, Labellore's group IV.Many studies have shown that nifedipine and labetalol can be successfully used to treat hypertension crisis. This study shows that oral nifedipine lowers blood pressure much faster than intravenous labetalol. In this study, the average blood pressure control time of oral nifedipine and intravenous labetalol groups were 26.87±9.22 and 45.54±16.91, respectively, with a p value of <0.0001. Raheem IA *et al*. [23] also found that oral nifedipine duration was shorter, that is, 30 minutes, while the duration of intravenous labetalol was 45 minutes. Desai B *et al*. [21] and Dhali B *et al*. [22] also found that oral nifedipine lowered blood pressure much faster than labetalol. Vermillion ST [24], compared the efficacy of oral nifedipine and intravenous labetalol, and found that both drugs are effective in treating urgency of hypertension during pregnancy. Nifedipine can control high blood pressure faster and is related to a large increase in urine output. Many previous randomized trials also showed that the dose required to reach the target blood pressure in the nifedipine group was significantly less than that of the labetalol group and similar results were obtained in this study. This study showed that the blood pressure of 93 patients (84.55%) in Group A returned to normal within 2 hours, while the blood pressure of 77 patients (70.0%) in Group B returned to normal. Therefore, Group A (oral nifedipine) efficacy was 84.55%, and the p-value of 70.0% in Group B (labetalol IV) was 0.0003. The study by Dhala B *et al*. also showed that nifedipine has a better effect, achieves the goal of blood pressure treatment, and requires less dose than labetalol. Because nifedipine has a fast onset of action, high oral bioavailability, long-term effects, liver metabolism> 90%, urinary excretion, and few side effects, it may have pharmacokinetic properties as an excellent drug for severe hypertension in pregnancy [22].In the study of Vermilion ST *et al*. [24], the efficacy of nifedipine is better than that of intravenous labetalol due to the lower dose, faster action, and higher average value. Previous studies have shown that nifedipine can effectively lower blood pressure without significantly reducing blood flow to the uterus and placenta, and there is no obvious arrhythmia[25]. These additional benefits of nifedipine also confirm that it is a better choice for treating patients with severe PIH. The safety of nifedipine in pregnant women has also been demonstrated in other recent studies on hypertension treatment in pregnancy[26]. Magee reports that the combined use of nifedipine and magnesium sulfate does not increase the risk of serious magnesium-related effects [26].Considering the pharmacokinetics of nifedipine, such as fast onset, long action, good oral bioavailability, and fewer side effects, it seems that in the emergency of pregnancy-induced hypertension, antihypertensive therapy appears to be superior to other drugs.

CONCLUSION

Nifedipine orally is related to fast action and better aiming towards the required blood pressure. Also, oral nifedipine has been found to be more effective in young women with first pregnancy. Therefore, we recommend oral nifedipine as a first-line antihypertensive drug for the emergency treatment of hypertensive urgency of pregnancy to reduce the ovarall mortality and the morbidity of the mothers and the newborn.

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