COMPARISON OF ANTIHYPERTENSIVE EFFICACY OF LABETOLOL, NIFEDIPINE AND METHYL DOPA IN PREGNANCY INDUCED HYPERTENSION

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Summary

Pregnancy induced hypertension has attendant maternal and neonatal morbidity and mortality. The transition from mild to severe degree of pregnancy hypertension is rapid and unpredictable. Since the cause of Pregnancy induced hypertension is pregnancy, treatment is thus remains termination of pregnancy. But this can not be done in all cases due prematurity of foetus. The role of antihypertensive drugs is to control the high blood pressure and prolong the pregnancy till the reasonable period of maturity and to prevent complications in mother. In this study three class of antihypertensive drugs namely nifedipine, methyl dopa and labetolol were compared with respect to control of blood pressure. The blood pressure was monitored at 0, 6, 24, 48 and 72 hours of initiation of antihypertensive treatment. The blood pressure readings were analysed in three groups. It was found that all three drugs were effective in controlling hypertension, but labetolol had rapid on set and sustained action with low incidence of side effects.

Key words: Pregnancy induced hypertension, labetolol, methyl dopa, nifedipine.

Introduction

Pregnancy induced hypertension (PIH) are the commonest medical disorder in pregnancy, affecting 6 to 8% of all pregnancies. It is a disease of multiple organ system that is unique to pregnancy and often associated with maternal and neonatal mortality and morbidity.[1-3] The rise in blood pressure in cases of pregnancy induced hypertension occurs after 20 weeks of pregnancy.[4] Based on blood pressure pregnancy induced hypertension is classified as mild and severe. In mild pregnancy induced hypertension systole blood pressure is 140-169 mm of Hg and diastole blood pressure is 90-109 mm of Hg, in severe it is more than 170 mm of Hg systole blood pressure and 110 mm of Hg diastole blood pressure.[5] The transition from mild to severe variety is unpredictable, hence it is prudent to start antihypertensive drugs in mild variety it self. It is found that women whose blood pressures are in mild variety generally have maternal and foetal outcome as comparable to normotensive women.[6] Once the blood pressure falls in severe variety, the maternal and foetal outcome will be poor.

The aim of antihypertensive drug therapy is to prevent complications due to hypertension while prolonging pregnancy. Severe pregnancy induced hypertension definitely requires antihypertensive drugs to prevent complications like cardiovascular accident or target organ damage. But mild pregnancy induced hypertension there is no consensus regarding antihypertensive drugs therapy, but in view of unpredictable transition to severe variety, it is suggested to start drugs to keep blood pressure in mild variety.[7] The antihypertensive drugs recommended are nifedipine, methyl dopa and labetolol.[8,9] These three drugs belong to different class based on their mode of action. The present study was undertaken to compare these drugs with respect to control of blood pressure and side effects when used in the treatment of pregnancy induced hypertension.

Material and methods

The study group consists of 107 pregnant women with pregnancy induced hypertension, according to International Society for the Study of Hypertension in Pregnancy (ISSHP) and accomplice inclusion and exclusion criteria.

Inclusion criteria:
All pregnant patients with systolic blood pressure of more than 140 mm of Hg and a diastolic blood pressure of more than 90 mm of Hg on two occasions four hours apart after 20 weeks of gestation admitted in the Kempegowda Institute of Medical Sciences Hospital between July 2006-July 2008.

Exclusion criteria:

1) Severe PIH with imminent eclampsia
2) Heart diseases including ischemic heart disease.
2) Haematological disorders.
    a. Liver diseases.
    b. History of intolerance/hypersensitive to dihydropyridine/methyl dopa.

All the patients were inpatients. Ethical clearance from the Institutional Human Ethics committee of Kempegowda Institute of Medical Sciences Hospital, Bangalore was taken for the study. Informed consent was taken from patients. In labetolol group 31 randomly selected patients received labetolol 100 mg BID orally, in nifedipine group 40 randomly selected patients received Nifedipine orally in the dose 10mg TID, in methyl dopa group 36 randomly selected patients were given 250mg methyl dopa orally QID. Besides complete obstetric examination, detailed history was taken, with special attention to hemorrhagic disorders, thromboembolic episode, epilepsy, hepatic or renal disorder and drug intake. Blood samples were taken for estimating Hb%, total and differential white cell counts, blood sugar, blood urea, serum uric acid and total platelet count.Fetal kick count chart, ultrasound, fundoscopy, cardiotocography, and Doppler ultrasound were also done. Blood pressure was recorded using Mercury Sypganomanometer with patient in 15 degrees left lateral recumbent position.Korotkoff V sound was used for determining diastolic blood pressure.[10-12] Blood pressure was recorded at 0, 6, 24, 48 and 72 hours of initiation of antihypertensive treatment. Side and adverse effects of the drugs were also recorded.

Blood pressure values were expressed as mean ± standard error of mean (SEM).Control of blood pressure was assessed in each treatment group separately for systolic and diastolic blood pressure by statistical analysis using repeated measures one way ANOVA followed by Tukey-Kramer multiple comparison tests. $P < 0.05$ was considered as significant.

Results

The maternal age in the study was more in 20-35 years group. Most of the patients were primigravidas in three groups. Mild degree of pregnancy induced hypertension was common compared to severe degree (Table-1).

Table-1: Baseline characteristics of PIH patients

SL no.	characteristics of PIH patients	Labetolol group (n= 31) Number (%)	Nifedipine group (n=40) Number (%)	Methyl dopa group (n=36) Number (%)
1)	Maternal age			
	a)<20 yrs	0 (0)	2 (5)	2(6)
	b)20-35 yrs	31 (100)	37 (92.5)	33 (92)
	c)>35 yrs	0 (0)	1 (2.5)	1 (3)
2)	Parity			
	a)P_0	18 (58)	22 (55)	23 (64)
	b)P_1	11 (36)	16 (40)	8 (22)
	c)P_2	2 (6)	1 (2.5)	4 (11)
	d)P_3	0 (0)	1(2.5)	1 (3)
3)	Severity of PIH			
	a)Mild	14 (45)	25 (63)	28 (78)
	b)Severe	17 (55)	15 (37)	8 (22)

When effects of drugs were compared with respect to reduction in systolic blood pressure from base line values (0 hour), labetolol had rapid onset of action, as evidenced by significant reduction at 6 hours of treatment ($P<0.001$).Nifedipine also reduced systolic blood pressure at 6 hours of treatment but level of significance was less than labetolol ($P<0.005$), where as methyl dopa did not show significant effect at 6 hours (Table-2).At 24 hours of treatment period all the three drugs significantly reduced systolic blood pressure compared to base line values ($P<0.001$).Control of blood pressure towards normal values (less than 140 mm of Hg) was observed at 48 hours in labetolol group and at 72 hours in methyl dopa and Nifedipine groups. Significant progressive reduction in systolic blood pressure was seen every 24 hours in labetolol group ($P<0.001$) and 48 hours in Nifedipine group.

Whereas in methyl dopa group there was progressive reduction similar to labetolol group, but level of significance was less (P<0.005), progressive reduction was highly significant at 48 hours (P<0.001).

Table-2: Comparison of systolic blood pressure**.**

Treatment group.	Measurement of systolic blood pressure in mm of Hg during the treatment period at				
	0 hour	6 hours	24 hours	48 hours	72 hours
Labetolol group (n=31)	160.39± 2.501	153.87± 2.304***	146.06± 2.176$^{***,+++}$	138.39± 2.079$^{***,+++,▪▪▪}$	130.00± 1.606$^{***,+++,▪▪▪,●●●}$
Nifedipine group (n=40)	159.4± 2.416	153.10± 2.341*	148.45± 2.257***	142.85± 1.996$^{***,+++}$	138.90± 2.083$^{***,+++,▪▪▪}$
Methyldopa group (n=36)	154.56± 2.810	150.67± 2.519	145.00± 1.931$^{***,++}$	141.56± 1.576$^{***,+++}$	137.00± 1.750$^{***,+++,▪▪▪,●}$

All Values are in mean±SEM. One way ANOVA followed by Tukey-Kramer multiple comparison tests.

*-compare to zero hour.
+-compare to 6 hours.
▪-compare to 24 hours.
●-compare to 48 hours.

*, +, ▪, •P< 0.05
**, ++, ▪▪, ●● P< 0.01
***, +++, ▪▪▪, ●●● P< 0.001

Diastolic blood pressure rapidly reduced in labetolol group at 6 hours of initiation of treatment (P<0.001), whereas in methyl dopa group and Nifedipine group significant reduction observed at 24 hours (P<0.001) and at 48 hours (P<0.001) respectively compared to baseline values (Table-3).In labetolol group the reduction in diastolic blood pressure started at 6 hours and progressed significantly every 24 hours (P<0.001) to achieve normal values by the end of 48 hours. Further reduction was observed from 48 to 72 hours of treatment period (P<0.001).

In nifedipine group significant reduction in diastolic blood pressure was observed after 48 hours of treatment (P<0.001), and progressed towards normal values at 72 hours. The reduction in blood pressure between 48 to 72 hours was not significant. In methyl dopa group significant reduction in diastolic blood pressure was observed from 24 hours of treatment (P<0.001) onwards and progressed further at 48 hours (P<0.001), but control was achieved at 72 hours (P<0.001) of treatment. From Table-3 it is evident that labetolol has rapid onset of action (6 hours) and faster control over diastolic blood pressure compared to methyl dopa and Nifedipine.

Table-3: Comparison of diastolic blood pressure

Treatment group	Measurement of Diastolic BP in mm of Hg during treatment period at				
	0 hour	6 hours	24 hours	48 hours	72 hours
Labetolol group n=31	106.6± 1.719	100.52± 1.487***	95.484± 1.097$^{***,+++}$	89.80± 0.876$^{***,+++,▪▪▪}$	85.48± 0.869$^{***,+++,▪▪▪,●●}$
Nifedipine group n=40	103.7± 3.005	103.05± 1.376	98.55± 1.069	94.60± 1.101$^{***,+++}$	91.50± 0.890$^{***,+++,▪▪}$
Methyl dopa group n=36	101.5± 1.568	99.722± 1.383	95.6± 1.254$^{***,+++}$	92.72± 1.096$^{***,+++,▪▪}$	89.69± 1.186$^{***,+++,▪▪▪,●●}$

All Values are in mean±SEM. One way ANOVA followed by Tukey-Kramer multiple comparison tests.

*-compare to zero hour.
+-compare to 6 hours.
▪-compare to 24 hours.
●-compare to 48 hours.

*, +, ▪, • P< 0.05
**, ++, ▪▪, ●● P< 0.01
***, +++, ▪▪▪, ●●● P< 0.001

Table 4: Side effects of Labetolol, Nifedipine and Methyl dopa group recorded during the treatment.

Side effects observed	Labetolol group (n=31)		Nifedipine group (n=40)		Methyl dopa group (n=36)	
	Number of patients	%	Number of patients	%	Number of patients	%
Headache	05	16	30	75	13	36
Palpitation	Nil	-	05	13	03	08
Dizziness	04	12	Nil	-	05	14
Giddiness	Nil	-	Nil	-	02	06
Weakness	05	16	01	03	02	06
Insomnia	Nil	-	03	08	01	03
Flushing	01	03	Nil	-	Nil	-
Tremors	Nil	-	Nil	-	01	03
None	16	52	01	03	09	25

The common side effect was headache in all groups. There were minimal side effects in labetolol group as 52% of patients did not have any side effects. Headache was frequently observed side effects in nifedipine group (Table-4).Even though there was diverse side effects in methyl dopa group, 25% of patients did not have side effects.

Discussion

In this study the efficacy of labetolol, Nifedipine and methyldopa in controlling blood pressure in patients with pregnancy induced hypertension were studied. These drugs have different mode of action, nifedipine is calcium channel blocker, methyl dopa is centrally acting drug which inhibits sympathetic outflow and labetolol is non cardio selective beta blocker. The pathophysiology of pregnancy induced hypertension is centred on vasospasm due to various factors like increased pressor response, vasoactive agents, endothelial damage, inflammatory response, genetic predisposition and immunological factors.Inspite of these varied pathophysiology and different mode of action of nifedipine methyl dopa and labetolol, all the three drugs were effective in controlling the pregnancy induced hypertension with minimal side effects.[13-15] These studies were with use of either nifedipine or methyldopa or labetolol separately as individual study on various aspects of hypertension in pregnancy ,but not comparative with respect to efficacy.

In the present study patients were randomly treated with nifedipine or methyldopa or labetolol simultaneously, efficacy was assessed based on control of blood pressure up to 72 hours. It was found that nifedipine; methyldopa and labetolol were equally effective in controlling mild to moderate blood pressure in pregnancy. Labetolol had faster onset and sustained action. Rapid onset of Labetolol may be due to faster absorption. Labetolol reduces peripheral resistance without reduction of cardiac output and pulse rate, hence minimal side effects.[16] Therapeutic goal was achieved in all the groups by 24 hours of initiation of therapy. When we consider undesirable side effects between the groups, they were found to be minimal and well tolerated. Also there were no incidences of adverse effect.

As this study was to access the efficacy of the drugs to control blood pressure in pregnancy, a long term study for the effects of these antihypertensive drugs on the both mother and new born is desired.[17]

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