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Original Research Article

## Comparison of maternal outcome in patients treated with methyldopa and labetalol in the management of hypertensive disorders of pregnancy

Harish K. M.<sup>1\*</sup>, Shwetha N.<sup>1</sup>, Dipankar Debnath<sup>2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Malabar Medical College, Calicut, Kerala, India

<sup>2</sup>Department of Obstetrics and Gynecology, Regional Institute of Medical Sciences, Imphal, Manipur, India

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**\*Correspondence:**

Dr. Harish KM,

E-mail: kmharish07@gmail.com

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### ABSTRACT

**Background:** To compare the maternal outcome in patients treated with methyldopa and labetalol in the management of moderate to severe hypertensive disorders of pregnancy (HDP).

**Methods:** The present study is Prospective parallel group comparative study on 200 out-patients and inpatients selected between January 2013 to December 2013 from OPD and antenatal ward of Obstetrics and Gynaecology department, of tertiary care teaching hospital, Regional Institute of Medical Sciences, Imphal. 100 patients each were distributed to methyldopa group and labetalol group respectively.

**Results:** There was statistically significant reduction in the mean systolic BP + Standard deviation / Diastolic BP + Standard deviation and Mean arterial pressure (MAP) in Labetalol group (from 156.84 + 5.75/100.20 + 6.02 mmHg and 119.08 + 4.07 to 133.76 + 3.50/85.14 + 3.98 mmHg and 101.35 + 2.94) compared to Methyldopa group (from 156.00 + 6.581/100.96 + 6.896mmHg and 119.30 + 4.86 to 137.20 + 2.36/89.02 + 2.38mmHg and 105.08 + 1.78). Risk of adverse effects was less in Labetalol group (12%) but complication during pregnancy was more in Methyldopa group (51%). Number of spontaneous onset of labour and vaginal mode of delivery was more in Labetalol group.

**Conclusions:** The present study shows that primiparity, residing in rural area, with low income group and overweight are at high risk of developing Hypertensive Disorders of Pregnancy. Labetalol is the better drug in controlling blood pressure with less adverse effects and maternal complication.

**Keywords:** Hypertensive disorders of pregnancy, Labetalol, Methyldopa

### INTRODUCTION

Hypertensive disorder of pregnancy is an idiopathic multisystem disorder of pregnancy characterised by proteinuric or non-proteinuric hypertension. Hypertension complicates 6-12% of all pregnancies.

Although the overwhelming majority of the affected will have successful pregnancy outcome, the condition can give rise to severe multisystem complication including cerebral haemorrhage hepatic and renal dysfunction and respiratory compromise.<sup>1</sup> Recent estimate indicates that over 63000 women die worldwide each year because of

Hypertensive disorders of pregnancy complications and 98% of these occurring in developing countries. Hypertensive disorders of pregnancy include two relatively benign conditions (chronic and gestational hypertension) and the more severe condition of pre-eclampsia and eclampsia. Pre-eclampsia/ eclampsia constitute 70% and chronic hypertension 30%. The incidence of eclampsia is one in 100 to 1 in 2000 pregnancies.<sup>2</sup>

The Working group classification of hypertensive disorders complicating pregnancy describes four types of hypertensive disease.<sup>3</sup>

- Gestational Hypertension.
- Pre-eclampsia.
- Eclampsia.
- Superimposed pre-eclampsia on chronic hypertension.
- Chronic Hypertension.

Hypertension in pregnancy is diagnosed empirically when appropriately taken blood pressure exceeds systolic 140 mmHg and diastolic 90 mmHg. In normal pregnancy systolic blood pressure changes little; however, diastolic pressure decreases by an average of 10 mmHg early in gestation (13 to 20 weeks) and rise again to pre-pregnancy level in third trimester.<sup>4</sup>

First line agents for moderate and severe hypertension are methyldopa and labetalol. The aim of antihypertensive therapy is to achieve blood pressure lower than 160/110 mm Hg but not lower than 130/90 mmHg without compromising uteroplacental blood flow and placental perfusion.<sup>5</sup>

Treating hypertension during pregnancy is a real challenge. Opinion differs as to which is the best antihypertensive agent during pregnancy. While the goal of treatment is to reduce maternal risk, agents selected must be efficacious.<sup>6</sup>

## METHODS

The present study is a hospital based prospective parallel group comparative study of patients in Obstetrics and Gynaecology department of tertiary care teaching hospital, Regional Institute of Medical Sciences, Imphal. Data collection will be over a period of one calendar year i.e. from January 2013 to December 2013.

Hypertensive disorders of pregnancy will be diagnosed when blood pressure measurement shows systolic BP of 140 mmHg and above or diastolic BP of 90 mmHg and above, measured on two occasion 6hours apart. The severity of hypertension in terms of systolic/diastolic pressure was classified as mild (140-149/90-99 mmHg), moderate (150-159/100-109 mmHg) or severe (>160/110mmHg). Blood pressure will be recorded using Mercury Sphygmomanometer with patient in 15 degrees left lateral recumbent position.

Steps involved in BP measurement using the auscultatory technique includes use of the correct-sized cuff, initial inflation of the cuff 20-30 mmHg above the palpable systolic BP, deflation at a rate of 2 mmHg per second, recording BP to the nearest 2 mmHg and use of Korotkoff phase V to indicate diastolic BP.

Cases of women with moderate to severe hypertensive disorder of pregnancy will be included in the study. Patients who are in labour, critically ill, presenting with eclampsia, HELLP syndrome, heart disease, liver disease

will be excluded from the study. Written consent from the patients will be taken before including in the study.

After clinical examination, patients with Hypertensive disorders of pregnancy will be offered with integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests.

Urine protein will be checked by automated reagent-strip reading device and patients are classified as proteinuric and non-proteinuric Hypertensive disorders of pregnancy.

The patient for the study will be selected randomly and using computer generated sequence of random numbers and distributed to either of the two-treatment arm - Labetalol or Methyldopa. Both proteinuric and non-proteinuric Hypertensive disorders of pregnancy patients are equally distributed into two treatment arms.

Patients with moderate Hypertensive disorders of pregnancy will be given either labetalol 200 mg or methyldopa 750 mg daily in divided doses. This dose will be doubled 3 days later if satisfactory BP control had not occurred. Maximum dose for labetalol is 1200mg/day and for methyldopa is 3gms/day.

BP control will be considered satisfactory if two of three consecutive readings of MAP were less than 105 mmHg. Patients with severe hypertension will be initially treated with intravenous labetalol to stabilize the blood pressure in the range of systolic 130-150mmHg and diastolic 85-100mmHg, there after patients will be equally distributed into two treatment arms.

Women with moderate gestational hypertension will be managed as outpatient with twice weekly BP monitoring. Severe gestational hypertensive patient and moderate to severe pre-eclampsia patients will be managed as in-patients with 4 times/day BP monitoring.

BP monitoring is done till the time of termination of pregnancy. The results are pooled to determine average systolic/diastolic and mean arterial pressure. Time and mode of termination of pregnancy will be done as per NICE clinical guidelines No. 107 and obstetric indication.<sup>7</sup>

Following parameters will be documented during the time of the study:

- Blood pressure (systolic/diastolic and mean arterial pressure) before commencement of anti-hypertensive treatment.
- Socio-demographic profile of patients such as marital status, educational status, occupation, religion and habitant.
- Characteristic of patients under study such as Age, BMI, Parity and Period of gestation.

Types of outcome measured are

- Average blood pressure during anti-hypertensive therapy
- Adverse effects of labetalol and methyldopa.
- Progression to pre-eclampsia and eclampsia, Obstetric and systemic complication.
- Mode of onset of labour and mode of delivery.

Statistical calculation is done by paired and unpaired t-test, chi-square test using SPSS software version 16. Results of blood pressure will be expressed as mean + standard deviation. The significance of differences between means will be determined using student's t test (BPs). P <0.05 will be considered as significant.

**RESULTS**

Present study shows that 200 patients were detected to have moderate (150/100 to 159/109 mmHg) to severe (160/110 mmHg and above) hypertensive disorder of pregnancy, among these 180 had non-proteinuric and 20 had proteinuric hypertension. 100 each (90 non-proteinuric and 10 proteinuric Hypertensive disorders of pregnancy) were distributed randomly using computer generated sequence of random numbers to either of the two-treatment arms labetalol or methyldopa. Table 1 shows socio-demographic profile of patients. Majority of the patients with Hypertensive disorders of pregnancy in present study were married (99%), house wife (87%) by occupation, studied up to graduation (49%), Hindu (45%) by religion, residing in rural (70%) area and belong to medium income (72%) group.

**Table 1: Socio-demographic profile.**

Socio-demographic profile	No.	%	
Marital status	Unmarried	2	1
	Married	198	99
	Total	200	100
Educational status	Illiterate	02	1
	Undermetric	18	9
	Metric	38	19
	Intermediate	44	22
	Graduate	98	49
Total	200	100	
Occupation	Unemployed	2	1
	Student	24	12
	Housewife	174	87
	Total	200	100
Religion	Hindu	90	45
	Muslim	86	43
	Christian	24	12
	Total	200	100
Habitant	Urban	60	30
	Rural	140	70
	Total	200	100
Socioeconomic state	Low	56	28
	Medium	144	72
	Total	200	100

Table 2 indicates that more number of patients were in the age group between 20 to 24 yrs (64%) and overweight patients were 60%.

Majority of patients were Primiparous (48%) and between 33 to 37weeks of pregnancy (85%).

**Table 2: Characteristics of patients.**

Characteristics of patients	N0	%	
Age	<19 years	4	2
	20-24 years	128	64
	25-29years	20	10
	30 years and above	28	14
	Total	200	100
BMI in kg/m <sup>2</sup>	<18	8	4
	18-24.9	88	44
	25-29.9	98	49
	>30	6	3
	Total	200	100
Parity	P <sub>0+0</sub>	96	48
	P <sub>1+0</sub>	68	34
	P <sub>2</sub> and above	36	18
	Total	200	100
Period of gestation	28-32 weeks	20	10
	33-37 weeks	170	85
	38-40 weeks	10	5
	Total	200	100

Table 3 shows that there is no statistically significant difference between labetalol and methyldopa in systolic BP (with p value 0.337), diastolic BP (p value 0.403) and MAP (p value 0.729) before the commencement of treatment.

There was statistically significant reduction in the mean systolic BP + Standard deviation / Diastolic BP + Standard deviation in Labetalol group (from 156.84 + 5.75/100.20 + 6.02 mmHg to 133.76 ± 3.50/85.14 ± 3.98 mmHg) compared to Methyldopa group (from 156.00 + 6.581/100.96 + 6.89mmHg to 137.20+2.36/89.02 + 2.38mmHg). Mean arterial pressure (MAP) reduction was more in Labetalol group (from 119.08 + 4.07 to 101.35+2.94) than Methyldopa group (from 119.30 + 4.86 to 105.08 + 1.78).

Table 4 shows that risk of adverse effects due to drugs were more in patients who received Methyldopa (18%) in relation to the patients who received Labetalol (12%). Minor side effects were common in labetalol group. Even though adverse effects were more in the methyldopa group, p value is 0.322 shows no statistical significant difference.

Table 5 shows that 57% in labetalol group and 49% in methyldopa group had no complications. Among 90 patients in each group who had non-proteinuric hypertension, 26 patients in methyldopa group and 22 patients in labetalol group progressed to proteinuric

Hypertensive disorders of pregnancy. Obstetric and systemic complications were 28% and 3% respectively in labetalol group where as 33% and 5% respectively in

Methyldopa group. Increase in risk of pregnancy complication in methyldopa group is statistically not significant with p value 0.322.

**Table 3: Evaluation of Blood pressure.**

Blood Pressure	Before treatment	During treatment	P value
<b>Systolic BP mmHg</b>			
Labetalol Group	156.84 ± 5.75	133.76 ± 3.50	<0.001
Methyldopa Group	156.00 ± 6.58	137.20 ± 2.36	<0.001
P value	0.337	0.001	-
<b>Diastolic BP mmHg</b>			
Labetalol Group	100.20 ± 6.02	85.14 ± 3.98	<0.001
Methyldopa Group	100.96 ± 6.89	89.02 ± 2.38	<0.001
P value	0.4037	0.0001	-
<b>MAP Rx</b>			
Labetalol Group	119.08 ± 4.07	101.35 ± 2.94	<0.001
Methyldopa Group	119.30 ± 4.86	105.08 ± 1.78	<0.001
P value	0.7290	0.0001	-

**Table 4: Adverse effects of drug on patients.**

Adverse effects	Labetalol Group (n=100)		Methyldopa Group (n=100)		P value
	No	%	No	%	
Nil	88	88.0	82	82.0	0.322
Present	12	12.0	18	18.0	
Minor side effects of Labetalol, Fatigue, insomnia, bad dreams	10	10			
Serious side effects of Labetalol Bronchospasm, blunted response to hypoglycemia	2	2			
Adverse effects of methyldopa: Postural hypotension, Sedation, depression, Abnormal LFT, Salt and water retention			18	18	

**Table 5: Pregnancy Complications.**

Complications	Labetalol Group (n=100)		Methyldopa Group (n=100)		P value
	No	%	No	%	
No Complication	57	57%	49	49%	P=0.322
Present	43	43%	51	51%	
Progression of non proteinuric Hypertensive Disorders of Pregnancy to: Preeclampsia Eclampsia	22	22%	26	26%	
Obstetric Complications: Placental Abruption Preterm labour PPH	28	28%	33%	33%	
Systemic complications: Hepatic complication (HELLP Syndrome) Renal complication Cerebro-vascular accident	3	3%	5	5%	
Maternal Mortality	0	0%	0	0%	

**Table 6: Pregnancy Outcome.**

	Labetalol Group		Methyldopa Group		P value
	No	%	No	%	
<b>Mode of onset of labour</b>					
Induced	36	36%	43	43%	0.252
Spontaneous	39	39%	31	31%	
Total	75	75%	74	74%	
<b>Mode of Delivery</b>					
Vaginal	52	52%	51	51%	0.999
LSCS	48	48%	49	49%	
Total	100	100.0	100	100.0	

Table 6 shows that 25% of patients in Labetalol group and 26% of patients in Methyldopa group were planned for elective caesarean section, and among remaining 75% of patients in Labetalol group, 39% went into spontaneous labour and in 36% labour was induced. In Methyldopa group among 74% of patients, 31% went into spontaneous labour and in 43% labour was induced. Mode of onset of labour does not have statistically significant difference between two groups.

Mode of delivery shows that 48% of patients in Labetalol Group and 49% of patients in Methyldopa Group underwent Caesarean section, were as vaginal delivery was 52% in labetalol group and 51% in methyldopa group, without statistical significance difference between two groups.

## DISCUSSION

Hypertensive disorders of pregnancy may complicate about 3–10% of all pregnancies with variable incidence among different hospitals and countries.<sup>8</sup>

It is one of the major causes of maternal morbidity and mortality leading to 10–15% of maternal deaths, especially in developing world.<sup>9</sup>

One of the main objectives in treating women with Hypertensive disorders of pregnancy with antihypertensive drugs is to prevent or delay progression to pre-eclampsia and other complication. Antihypertensive therapy is indicated for maternal benefit and also permits prolongation of the pregnancy and thereby improves fetal maturity.<sup>10</sup>

The first line drugs that can be used in Hypertensive disorders of pregnancy are Labetalol and Methyldopa.

The observations of present study shows that majority of the patients were Hindu (45%) by religion, residing in rural area (70%) and belong to medium socioeconomic state (72%). Most of the patients studied up to graduation (49%) and were married (99%) and house wife (87%). Hence, the patients residing in rural area with low income

are predisposed to Hypertensive disorders of pregnancy in the present study.

Majority of patients in present study, between 20 to 24yrs (64%), primiparous (48%), between 33 to 37wks of gestation (85%) and overweight (49%) are at higher risk of developing Hypertensive disorders of pregnancy.

Risk of HDP decreases as the age and parity increases, were as risk increases with increased BMI and period of gestation. Increased risk of HDP in primiparity and young age group in present study is similar to findings of Sudarshan et al.<sup>11</sup>

Risk of Hypertensive disorders of pregnancy is maximum between 33-37 weeks of period of gestation and 49% of women had increased BMI i.e. >25Kgs/m<sup>2</sup>. In the present study, increased risk of Hypertensive disorders of pregnancy is observed in groups with BMI >25-30 Kgs/m<sup>2</sup> and >30 Kgs/m<sup>2</sup>.

Significant reduction in systolic and diastolic BP with p value <0.001 after treatment is found in Labetalol group compared to Methyldopa group. This shows that labetalol is better drug in controlling BP in the present study.

Labetalol had less adverse effects with only 12% (out of 100 patients) of patients complaining of Fatigue, insomnia and bad dreams, whereas 18% of patients in Methyldopa group had various adverse effects of drug. This shows that labetalol is more compatible with better tolerance with less adverse effects in pregnancy.

Complications during pregnancy in patients treated with labetalol and methyldopa is documented. Some of the complications used to overlap in single patient. The overall rate of pregnancy complication due to Hypertensive disorders of pregnancy is less in labetalol group (43%) in comparison to methyldopa group (51%). Progression of Gestational Hypertension to preeclampsia/eclampsia is more in methyldopa group (26%) than in labetalol group (22%). Obstetric and systemic complications during pregnancy were less in labetalol group whereas it is more in Methyldopa group (51%). No maternal mortality was seen in either group.

Excluding the patients who were planned for elective caesarean section in both the groups, the need for 'induction of labour' (36%) is less and 'spontaneous mode of onset of labour' (39%) is more in Labetalol group. Also, labetalol group had more number of vaginal deliveries (52%) and less number of caesarean section (48%). Even though in Methyldopa group majority needed induction of labour (43%) and increased rate of caesarean section (49%) the difference is not statistically significant with Labetalol group.

## CONCLUSION

The present study shows that primiparity, residing in rural area with low income group and overweight patients are at high risk of developing Hypertensive disorders of pregnancy.

Even though Labetalol is a better drug in controlling blood pressure with statistically significant difference, the lesser "adverse effects and maternal complication" is not significant statistically when compared with methyldopa. Also, spontaneous onset of labour and vaginal mode of delivery is more in patients taking labetalol, it does not have statistical significant difference with patients taking methyldopa.

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