



## PREGNANCY INDUCED HYPERTENSION; TO COMPARE EFFICACY OF METHYLDOPA AND LABETALOL IN MANAGEMENT

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**Article received on:**  
15/06/2016

**Accepted for publication:**  
07/09/2016

**Received after proof reading:**  
07/10/2016

**ABSTRACT...Introduction:** The hypertensive Disorders of pregnancy are major contributors to maternal and perinatal morbidity and mortality. The aim of hypertensive therapy is to prevent complications associated with hypertensive disorders of pregnancy. **Objective:** To compare efficacy of methyldopa and labetalol in management of pregnancy induced hypertension. **Study Design:** Randomized control trial. **Setting:** Punjab medical college and affiliated hospitals Faisalabad. **Methods:** Patient were be randomly assigned to either group A or Group by lottery method. Each group included 157 patients. In group A: labetalol was started at 100 mg three or four times a day and increased up to 1200 mg a day in divided doses. In group B: methyldopa was started at 250mg per day 3 to 4 divided doses and increased up to 500 mg in 3 to 4 divided doses. Blood pressure was recorded by sphygmomanometer. Blood pressure was recorded after 48 hours and then weekly till term on outpatient basis. **Results:** The treatment of methyldopa in group I was proved to successful in lowering the mean blood pressure and maintaining mean blood pressure within normal limits in 142 of 155 patients. It can be said it was successful in 91.61% cases. 8.39% cases progressed to severe hypertension or eclampsia because methyldopa was unsuccessful to prevent progress of disease. **Conclusion:** It is concluded that antihypertensive therapy such as methyldopa and labetalol are successful in lowering blood pressure in patient with pregnancy induced hypertension.

**Keywords:** Pregnancy induced hypertension, methyldopa, and labetalol

**Article Citation:** SharifN, Pregnancy induced hypertension; To compare efficacy of methyldopa and labetalol in management. Professional Med J 2016;23(10):1187-1193.  
**DOI:** 10.17957/TPMJ/16.3489

### INTRODUCTION

Pregnancy is a state which can induce hypertension in normotensive women.<sup>1</sup> Hypertension is one of the most common complications of pregnancy.<sup>2</sup> It complicates 12 to 22% of all pregnancies.<sup>3</sup> The spectrum of severity of hypertensive disorders of pregnancy is from mild to moderate disease being fairly substantial.<sup>4</sup> It is a major contributor to maternal, fetal and neonatal morbidity.<sup>5</sup> Early detection and appropriate management of hypertensive disorders of pregnancy may improve the outcome of both mother and fetus.<sup>6</sup>

The mild to moderate hypertension is acceptably diagnosed in the context of systolic blood pressure of 140 – 190 mm of Hg and a diastolic blood pressure of 90 -109 mm of Hg. Severe hypertension is labelled when systolic blood pressure is > 160 mm of Hg and diastolic blood pressure > 110 mm of Hg.<sup>7</sup>

The aim of antihypertensive therapy of pregnancy is lowering the Blood Pressure, while prolonging the course of pregnancy. The treatment of moderate hypertension in pregnancy is associated with a significantly reduction in severe hypertension.<sup>8</sup>

The agents suggested for management of hypertension in pregnancy include methyldopa, nifedipine and labetalol.<sup>9</sup> Various agents are associated with different side effects. Labetalol is being used worldwide as an effective hypertensive agent for many decades. Labetalol has the advantage that it can be given initially by mouth and then if needed intravenously by bolus or infusion. It is an alpha and beta adrenoceptor blocker and a frontline antihypertensive agent.<sup>10</sup> The other drug is methyldopa which is an extensively studied drug used for treatment of hypertension in pregnancy.

It is a centrally acting alpha 2 adrenoceptor agonist. Methyldopa has been proven safe in long term follow-up of the delivered babies<sup>11</sup>. However studies have suggested superior benefits of labetalol<sup>12</sup>. Both methyldopa and labetalol are easily available and are also cost effective.

The rationale of this study was to collect conclusive evidence in support of the effective drug in the treatment of pregnancy induced hypertension. Its use will reduce maternal and fetal complications of uncontrolled pregnancy induced hypertension. That is why this study is beneficial for both the patients and our department.

### OBJECTIVE

To compare efficacy of methyldopa and labetalol in management of pregnancy induced hypertension.

Main outcome measures of the study were:

- Treatment of moderate hypertension by achieving diastolic blood pressure during pregnancy <90 mm of Hg
- Preventing patient from progressing to severe hypertension (severe hypertension is blood pressure >170/110)
- 

The drug was considered efficacious when it fulfilled above criteria.

### MATERIAL AND METHODS

**Study Design** Randomised control trial

**Setting** Punjab medical college and affiliated hospitals, Faisalabad

### SUBJECT

The sample size was calculated by with 95% confidence level.

P1 = 20% P2 = 10%

The sample size (n) = 157 patients in each group fulfilling the inclusion and exclusion criteria

### INCLUSION CRITERIA

All women with blood pressure after 20<sup>th</sup> week of gestation;

- Systolic 150 – 160 mm of Hg

- Diastolic 100 – 110 mm of Hg
- Known hypertensive on basis of history and clinical examination

### EXCLUSION CRITERIA

Following patients will be excluded from the study

- History of chronic / essential hypertension
- History of Diabetes mellitus
- History of cerebrovascular disease
- History of Chronic renal failure
- History of multiple pregnancy
- History of collagen disease

Exclusion will be on basis of history and examination

### METHODS

All inclusive Patients of the study were recruited from outpatients department or in the labour ward with pregnancy induced hypertension where clinical assessment of the patient was performed regarding inclusion and exclusion criteria.

Patients were randomly assigned to either group A or Group B by lottery method. Each group included 157 patients.

**In group A:** labetalol was usually started at 100 mg three or four times a day and then was increased up to 1200 mg a day in divided doses.

**In group B:** methyldopa was started at 250mg per day 3 to 4 divided doses and was increased up to 500 mg in 3 to 4 divided doses.

Blood pressure was recorded by sphygmomanometer. Blood pressure was recorded after 48 hours and then weekly till term on outpatient basis. Data was collected through specifically designed proforma. Successful lowering of blood pressure in terms of achieving desired blood pressure 140/90 was recorded.

Risks like maternal hypotension, flushing, nausea, vomiting and benefits like significant reduction of blood pressure, prevention of severe hypertension, side effects, reduced chances of abortion, low cost and control of blood pressure were explained to the patient.

The study was approved from the ethical committee.

**STATISTICAL DATA ANALYSIS**

Frequency and percentages of all categorical variables like efficacy of drug were recorded. Mean and standard deviation for all numerical variables was calculated including age gestational age, parity, gravidity, abortion, blood pressure at booking, 48 hrs, week 1,2,3,4 will be recorded. Chi-square test was used to compare blood pressure (normal, raised) at 48 hours, week 1,2,3,4 in both treatment groups. P-Value <0.05 was be considered significant.

**RESULTS**

In this study two groups were formed to method described. Group I was of 157 patients. The mean age was 27.30 years with standard deviation of ± 4.197. The mean gravidity was 3.0 with standard deviation of ± 1.616. Mean parity was 1.59 ± 0.607. The mean gestational age was 33.56 weeks with standard deviation of ± 2.450 as mentioned in table 1.

VARIABLE	NUMBER	MEAN	STANDARD DEVIATION
AGE (years)	157	27.30	±4.197
G (gravidity)	157	3.00	±1.616
P (parity)	157	1.59	±1.549
A (abortion)	157	0.39	±0.607
Gestational age (weeks)	157	33.56	±2.450

**TABLE NO 1: EPIDEMIOLOGICAL VARIABLES Group I (methyldopa)**

The subjects of group I were given methyldopa according to the protocol and blood pressure was recorded at booking , 48 hours , 1 week , 2 weeks , 3 weeks and 4 weeks. All patients were followed on out patient basis . Two patient were lost to follow up. The mean blood pressure at booking was 155.30/104.58 , at 48 hours 140.32 / 93.06 , at 1<sup>st</sup> week 134.76 / 90.99 , at 2<sup>nd</sup> week 132.54 / 90.14 , at 3<sup>rd</sup> week 131.26 / 89.55 and at 4<sup>th</sup> week 131.19 / 85.68 . This shows gradual reduction in blood pressure on antihypertensive

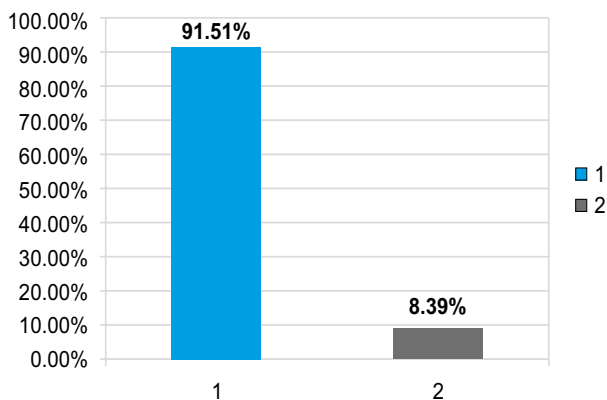
therapy in form of methyldopa. (Table 2)

BLOOD PRESSURE	NUMBER	MEAN	STANDARD DEVIATION
Booking systolic BP	157	155.30	±7.582
Booking diastolic BP	157	104.58	±5.313
Systolic BP at 48hrs	157	140.32	±10.82
Diastolic BP at 48hrs	157	93.06	±5.822
Systolic BP at 1 week	147	134.76	±8.467
Diastolic BP at 1 week	147	90.99	±5.753
Systolic BP at 2 week	138	132.54	±5.412
Diastolic BP at 2 week	139	90.14	±3.944
Systolic BP at 3 week	111	131.26	±6.341
Diastolic BP at 3 week	110	89.55	±2.837
Systolic BP at 4 week	84	131.19	±10.46
Diastolic BP at 4 week	88	85.68	±19.06

**TABLE NO 2: MEAN BLOOD PRESSURE Group I (methyldopa)**

The treatment of methyldopa in group I was proved to successful in lowering the mean blood pressure and maintaining mean blood pressure within normal limits in 142 of 155 patients. It can be said it was successful in 91.61% cases. 8.39%<sup>13</sup> cases progressed to severe hypertension or eclampsia because methyldopa was unsuccessful to prevent progress of disease. (Graph 1)

Group II was of 157 patients. The mean age was 26.89 years with standard deviation ± 4.82. The mean gravidity was 3.03 with standard deviation ± 1.64. Mean parity was 1.62 ± 0.61. The mean gestational age was 33.57 weeks with standard deviation of ± 2.43 as mentioned in Table 3.



**GRAPH 1: EFFECTIVE TREATMENT GROUP I (METHYLDOPA)**

VARIABLE	NUMBER	MEAN	STANDARD DEVIATION
AGE (years )	156	26.89	±4.82
G (gravidity)	156	3.03	±1.64
P (parity)	156	1.62	±1.58
A ( abortion)	156	0.38	±.61
Gestational age ( weeks )	156	33.57	±2.43

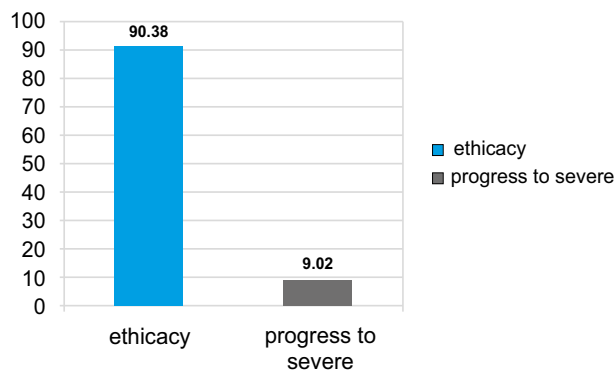
**TABLE NO 3: EPIDEMIOLOGICAL VARIABLES Group II (labetalol)**

The subjects of group II were given labetalol according to the protocol and blood pressure was recorded at booking , 48 hours , 1 week , 2 weeks , 3 weeks and 4 weeks. All patients were followed on out patient basis . Two patient were lost to follow up. The mean blood pressure at booking was 155.5/104.6 , at 48 hours 140.6 / 93.24 , at 1<sup>st</sup> week 135.3 / 93.24 , at 2<sup>nd</sup> week 132.6 / 90.14 , at 3<sup>rd</sup> week 131.3/ 89.54 and at 4<sup>th</sup> week 131.4 / 85.44 . This shows gradual reduction in blood pressure on antihypertensive therapy in form of methyldopa. (table 4)

The treatment of labetalol in group II was proved to successful in lowering the mean blood pressure and maintaining mean blood pressure within normal limits in 141 of 156 patients. It can be said it was successful in 90.38% cases. 9.62 %<sup>15</sup> cases progressed to severe hypertension or eclampsia because methyldopa was unsuccessful to prevent progress of disease. (Graph 2)

BLOOD PRESSURE	NUMBER	MEAN	STANDARD DEVIATION
Booking systolic BP	156	155.5	±7.78
Booking diastolic BP	156	104.6	±5.31
Systolic BP at 48hrs	156	140.6	±11
Diastolic BP at 48hrs	156	93.24	±6.19
Systolic BP at 1 week	148	135.3	±9.65
Diastolic BP at 1 week	148	91.52	±7.39
Systolic BP at 2 week	137	132.6	±5.43
Diastolic BP at 2 week	138	90.14	±3.96
Systolic BP at 3 week	110	131.3	±6.37
Diastolic BP at 3 week	109	89.54	±2.85
Systolic BP at 4 week	86	131.4	±10.3
Diastolic BP at 4 week	88	85.44	

**TABLE NO 4 :MEAN BLOOD PRESSURE Group II (labetalol)**



**GRAPH 2: EFFECTIVE TREATMENT Group II (labetalol)**

**Statistical analysis**

We used the analysis of variance test to compare the groups. First we applied the ANOVA in SBP and second in DBP. We concluded that the there was no difference in methyldopa group 1 & 2 in SBP because the p-value is 0.64 (non-significant). Secondly used the anova in DBP the p-value is 0.61(not significant) and conclude that the there is no difference in methyl dopa group 1 & 2. The overall result is non-significant.

## DISCUSSION

The importance of this study is evident from the magnitude and sheer impact of pregnancy induced hypertension. International studies state that approximately 6-10 % of pregnant women suffer from pregnancy induced hypertension. (1,2).local studies support these figure by showing that about 1/5<sup>th</sup> of pregnancies suffer form of hypertension.<sup>3</sup>

This study suggests that pregnancy induced hypertension can be successfully treated with oral hypertensive agents such as methyldopa and labetalol. These both agents were compared in terms of efficacy and ability to prevent severe hypertension. This study shows that both agents, methyldopa and labetalol had efficacy of 91.61% and 90.38% in lowering blood pressure .There was no significant statistical significant in there efficacy as proven by Chi-square test with  $P > 0.5$ . These figures are supported by meta-analysis by Magee L and Duley L. This meta-analysis of thirteen trials compared beta-blockers with methyldopa . Beta-blockers appear to be no more effective and probably equally as safe. It is unusual for women to change drugs due to side effects.<sup>4</sup>

The efficacy of labetalol in study by Mahmoud shows efficacy of labetalol in controlling blood pressure in 85% patients on this drug.<sup>6</sup> In This study the efficacy of drug was determined when it achieved a safer target blood pressure which was comparable to the safe range of blood pressure 140 to 155/90 to 105 mm of Hg mentioned in study by Podymow and August.<sup>5</sup>

In both groups of this study the mean blood pressure at booking was 155/104 which was comparable with study of Mahmoud , Bjornsson and Calder.<sup>6</sup> In this study in both groups majority of cases were successfully treated and prevented from progressing to severe hypertension and eclampsia. In group 1, 8.39 % progressed to severe hypertension and in group II 9.63% progressed. Study by mahmoud had 18.5% cases progressing to severe hypertension.<sup>7</sup>

In another meta-analysis , patients treated with labetalol was unsuccessful in 8% cases progressing to severe hypertension and in patients on methyldopa 10% cases progressed to severe hypertension which is almost similar to the findings of our study.<sup>8</sup> Our study has results which are comparable by various national and international studies with almost similar results which is suggestive that both methyldopa and labetalol are successful antihypertensive agents used during pregnancy induced hypertension and have good safety profile. Both do not have significant difference in there efficacy and ability to prevent patient's progress to severe hypertension.

## CONCLUSION

It is concluded that antihypertensive therapy such as methyldopa and labetalol are successful in lowering blood pressure in patient with pregnancy induced hypertension. This study shows that methyldopa and labetalol were successful in lowering blood pressure in 91.61% and 90.38% cases. In group I 8.39% cases progressed to severe hypertension and in group II 9.69% progressed to severe hypertension. The mean blood pressure reduction in group I (methyldopa) was 16.44% reduction in systolic blood pressure and 17.14 % reduction in mean diastolic blood pressure . The mean blood pressure reduction in group II (labetalol) was 15.84% reduction in systolic blood pressure and 18.40 % reduction in mean diastolic blood pressure.

The data was analysed and variables of both groups were subjected to chi-square test which concluded that there was no significant difference in the efficacy of both groups in terms of blood pressure control and preventing the disease to progress to severe hypertension.

Our conclusion is a null hypothesis which concludes that both drugs labetalol and methyldopa have proved to be efficient in preventing progress of disease and controlling pregnancy induced hypertension. No significant difference was found. Further studies are recommended to assess the safety profile of both



drugs.

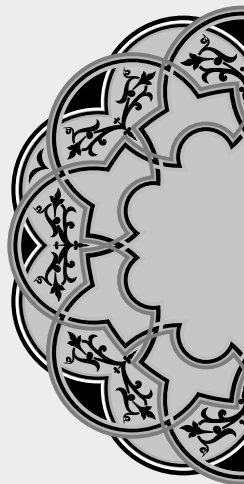
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## PREVIOUS RELATED STUDY

Noreen Akmal, Gul-e-Raana **WOMEN WITH PREGNANCY INDUCED HYPERTENSION; EPIDEMIOLOGICAL DIFFERENCES BETWEEN NORMOTENSIVE PREGNANT WOMEN (Original)** Prof Med Jour 13(2) 310-312 Apr, May, Jun, 2006.



*“Better to die standing  
than  
live on your knees.”*

Ernesto Che Guevara

**AUTHORSHIP AND CONTRIBUTION DECLARATION**

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2	Dr. Irum Usman		
3	Dr. Tasneem Azhar		