International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 01-10-2020; Accepted: 15-10-2020; Published: 04-11-2020
www.medicalsciencejournal.com
Volume 6; Issue 11; 2020; Page No. 12-16

A comparative study of Labetalol and methyldopa in hypertensive disorder of pregnancy

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Abstract
Aim: To compare the efficacy and safety of Labetalol and methyldopa in hypertensive disorder of pregnancy.
Materials and Methods: This perspective randomized study was carried out in the department of Obstetrics and Gynecology, Kurji Holy Family Hospital, Patna, Bihar, India from November 2015 to November 2017. All the patients of blood pressure 150/100 mm of Hg above 20 weeks of gestations.
Results: We evaluated 100 patients. There was significant fall in mean arterial pressure [MAP] after treatment in both labetalol (98.51) and methyldopa (102.72) group but reduction was more in labetalol group. Mean gestational age in L group was 33.76 weeks and in M group was 34.21 weeks. So in prolongation of pregnancy and vaginal delivery labetalol came forward. They were less no. of caesarean section and reduced maternal and fetal morbidity.
Conclusion: Labetalol is more advantageous than methyldopa in terms of better and quicker control of blood pressure. The maternal and fetal morbidity was much lower in labetalol treated cases fetal outcome was much better and it showed fewer side effects.

Keywords: pregnancy, methyldopa, labetalol, methyldopa

Introduction
Hypertensive disorders seem to complicate approximately 10% of pregnancies and are important causes of maternal and fetal morbidity and mortality [1]. It is estimated that globally 6-8% of pregnancies are complicated by hypertension [3] It is said that preeclampsia and eclampsia contribute to the death of a women every 3 minutes worldwide [2, 4].Women with hypertensive disorder are at greater risk of abruptio placenta, CVA, Organ failure, DIC. Fetus is at greater risk of IUGR, prematurity, and IUD. Eclampsia is a severe form of associated with seizure and it occur in one in 16000 pregnancies. HELLP syndrome is a complication which includes the breakdown of RBC, changes in liver and low platelets. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing its progression to adverse outcomes for the mother and fetus [5, 6]. Methyldopa, labetalol and long acting nifedipine are acceptable oral antihypertensive agent if drug therapy is required in pregnant women with mild to moderate hypertension [7]. Labetalol is a selective α_1 blocker with nonselective β blocking action with some β_2 agonistic action [8]. It lowers blood pressure by reduction of systemic vascular resistance (via α blockade) without significant alteration in heart rate and cardiac output [9]. It has the advantage of rapid and smooth action. When administered orally it acts within 1-2 hours. Bishop score is also higher in patients receiving Labetalol [10]. It improves renal function. It stimulates pulmonary surfactant formation [11].

Methyldopa is a centrally actingα_2 agonist which lowers blood pressure by decreasing total peripheral vascular resistance with variable reduction in heart rate and cardiac output [12]. It is widely used in the treatment of hypertensive disorder of pregnancy. It takes 12-24 hours for adequate therapeutic response. In larger dose it can cause oliguria. It causes depression, dizziness, fatigue, nightmare, jaundice, hemolytic anaemia, orthostatic hypotension [13, 14]. Hence the present study was conducted with the aim to compare the efficacy and safety of Labetalol and methyldopa in hypertensive disorder of pregnancy.

Materials and Methods
Study Population: All the patients of blood pressure ≥ 150/100 mm of Hg above 20 weeks of gestation attending OPD or admitted in Obstetrics and Gynecology department at Kurji Holy Family Hospital during study period from November 2015 to November 2017.

Study Design
A prospective, randomized, comparative study.

Sample Size
After obtaining informed consent for Parti cipation in the study from the patienta total of 100 patients, fulfilling the predefined inclusion criteria were randomly assigned to treatment with either Labetalol or methyldopa. They were divided into two groups.
Group L: It comprised of 50 patients who were treated with Labetalol.
Group M: It comprised of 50 patients who were treated with Methyldopa.

Inclusion Criteria
1. All the patients of BP≥150/100 mm of Hg on two separate occasions 6 hours apart after 20 weeks of pregnancy till terms with or without proteinuria or oedema were included.
2. Primigravida as well as multigravida 3. Agree to participate in study

Exclusion Criteria

1. 1.All the cases of BP <150/100 mm of Hg
2. All the cases of BP ≥ 150/100 less than 20 weeks of pregnancy
3. Women with preexisting or concurrent medical disorder like diabetes mellitus, cardiac disease, renal disease, twin pregnancy, thyrotoxicois, chronic hypertension.
4. Known cases of bleeding disorder like Idiopathic thrombocytopenic purpura, thalessemia.

Group L (Study group)

1. Comprising of 50 patients who satisfied the eligibility criteria of the study were started on Labetalol 100 mg tablet t.d.s. orally after meal. Blood pressure was recorded every four hourly.
2. All those patients whose diastolic blood pressure fell to less than or equal to 90 mmHg were considered as responders and were maintained on this dose.
3. Those patients whose diastolic blood pressure continued to remain more than 90 mmHg but less than 100 mmHg after starting the drug, the dose was doubled after 48 hours.
4. If initial blood pressure did not fall at all or rose inspite of starting the drug, the dose was doubled in 24 hours. Dose of labetalol was increased by 300 mg/day till response.
5. Maximum dose of 1200 mg/day was given.

Group M (Control Group)

Patients in this group were started on Methyldopa. Initial dose of Methyldopa was 250 mg t.d.s. Blood pressure was recorded and response was judged as in Group L. Dose of Methyldopa was doubled as in Group L to 500 mg t.d.s. and increased to 500 mg Q.I.D.

Depending upon the response to drugs patients were divided into 2 groups.

Responders

Responders were all those patients whose blood pressure fell to □140/90 mmHg. They were allowed to go into spontaneous labor if fetal well-being was maintained.

Non-Responder

1. Patients who continued to have raised blood pressure even after taking maximum dose fixed for drug.
2. Patients who required other antihypertensive drug.
3. Patients who developed sign and symptoms of impending eclampsia while on treatment.

Termination of Pregnancy was done

1. If patient did not go into spontaneous labour till 40 weeks of gestation inspite of satisfactory control of blood pressure.
2. If patient showed clinical evidence of IUGR and baby shevidence of distress in utero.

Indications of Caesarean Section

1. Any other obstetric indication e.g. cephalopelvic disproportion, previous caesarean section, malpresentation.
2. Fetal distress.

Fetal Variables

1. Stillbirth or live birth
2. Preterm or term
3. Apgar score
4. Birth weight

Subsequent follow up

All patients, whose blood pressure remained high after delivery, were re-examined at 6 weeks and 12 weeks postpartum for any evidence of residual hypertension.

Statistical Analysis

Data was analysed using M S Excel, SPSS. The outcome variables in form of mean, standard deviation were assessed using student's t-test and Chi-square test. A p-value less than 0.05 were taken as statistically significant.

Result

1. Maximum number of patients (42%) in Labetalol group and (44%) in methyldopa group were of age between 20-24 year.
2. In comparison with multigravida, primigravida were prone to develop Hypertension in pregnancy with a higher incidence of (56%) in Labetalol group and also (56%) in Methyldopa group.
3. 3.These was significant fall in mean arterial pressure [MAP] after treatment in both labetalol(98.51) and methydopa(102.72) group but reduction was more in labetalol group.
4. Severity of the hypertension was attributed on the basis of diastolic blood pressure and the majority of women were presented with DBP between 100-109 mm Hg in both group. There were more patients who achieved DBP <90 mm Hg after treatment in labetalol (83.04) group in comparison to methyldopa (87.04) group.
5. Proteinuric cases were seen in both the groups. The percentage of post treatment persistent proteinuric cases were much lower in the labetalol group (8%) than methyldopa group (16%).
6. Majority of the cases presented with oedema at her first visit in both the group labetalol (78%) and methyldopa (68%).
7. Almost half of the patients in both groups achieved weight gain within the range of 0.5-0.7 kg over a week and among the other halves, few were achieved >0.75 or few were <0.5 mg over a week.
8. Serum uric Acid (> 4mg), decrease platelet count ($<10^5$/cmm) and increase serum creatinine (>1.2 mg) were also checked prior to commences the treatment in both groups.
9. It was noted that in both groups that, early hospitalization had carried a better fetal outcome, though majority of the cases were admitted between 33 to 36 weeks of gestation in both groups. Mean gestational age in L group was 33.76 weeks and in M group was 34.24 weeks.
10. During treatment the only maternal complication, imminent eclampsia was noted in both groups. It was 6% in L group and 20% in M group.
11. Maximum number of cases 84% in L group and 72% in M groupwere delivered at ≥37 weeks of gestation. So in prolongation of pregnancy labetalol will come forward.
12. To compare with methyldopa (52%), it was observed that in the labetalol group (60%), maximum number of deliveries were possible through vagina and minimum number of cases underwent caesarean section. They were less no. of caesarean section and reduced maternal and fetal morbidity and mortality in labetalol group in

comparison to methyldopa group.

13. Number or percentage of low birth weight, preterm, IUGR babies were less in labetalol treated group in comparison of methyldopa.
14. The mean dose required to control BP in labetalol group was 552.63 mg and in methyldopa group was 1093.75 mg.
15. The mean time required to control B.P. in labetalol group was 3.33 days and in methyldopa group was 3.62 days.
16. Among the side effects of antihypertensive drugs, dyspnea and headache, nausea seen in labetalol group but other side effects like postural hypotension, headache, drowsiness, nasal stiffness seen in methyldopa group.
17. All the patients were seen on their usual follow up in the OPD, but percentage of cases showed persistence of hypertension 6% in L group and 12% in M group, proteinuria 4% in both group.

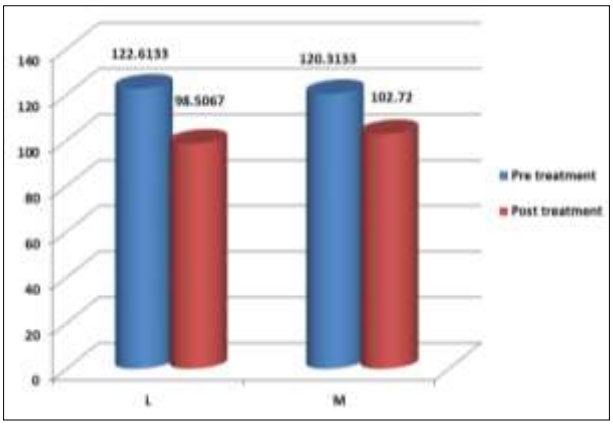

Fig 1: Mean Arterial Pressure

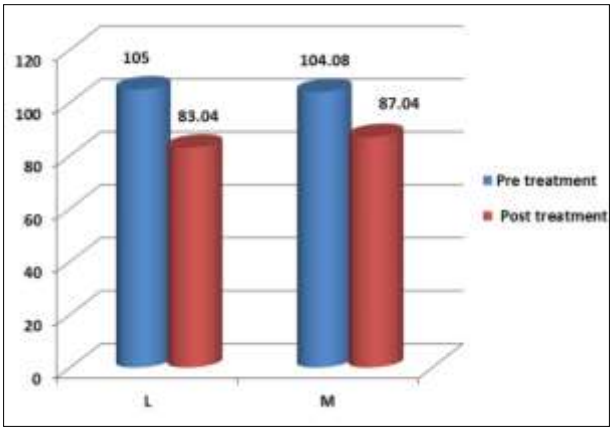

Fig 2: Diastolic Blood Pressure

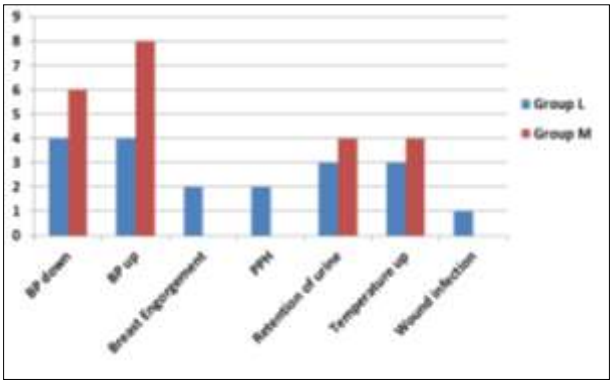

Fig 3: Maternal Complication after Caesarean Section

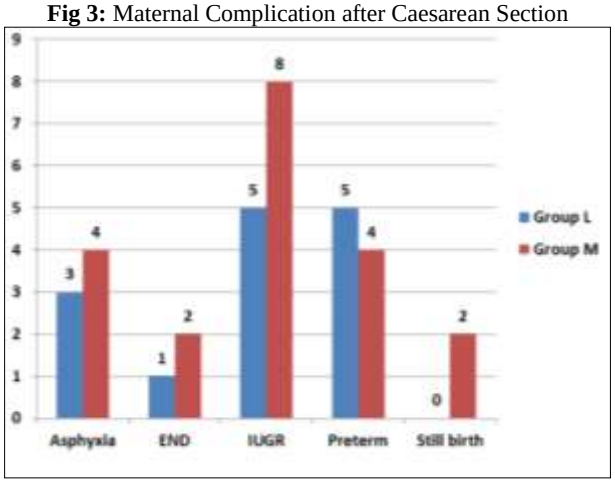

Fig 4: Fetal Outcome

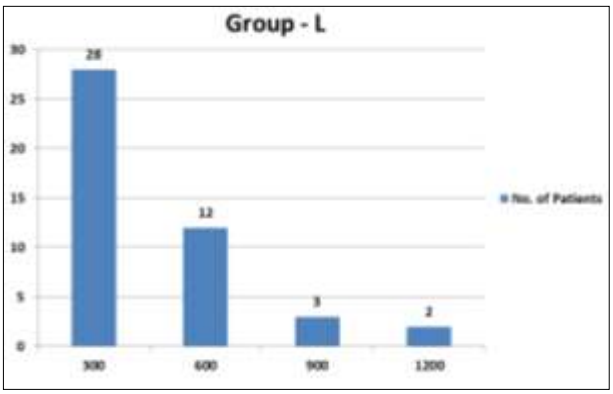

Fig 5A: Dose of Drug

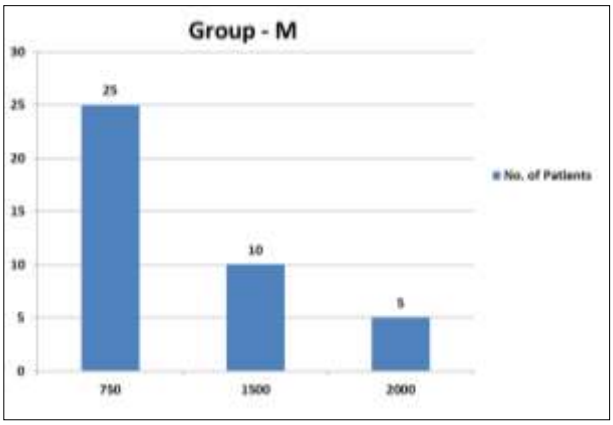

Fig 5B: Dose of Drug

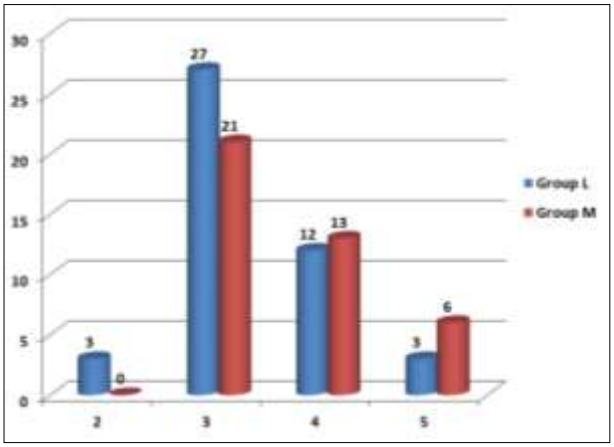

Fig 6: No. of Days to Control Blood Pressure

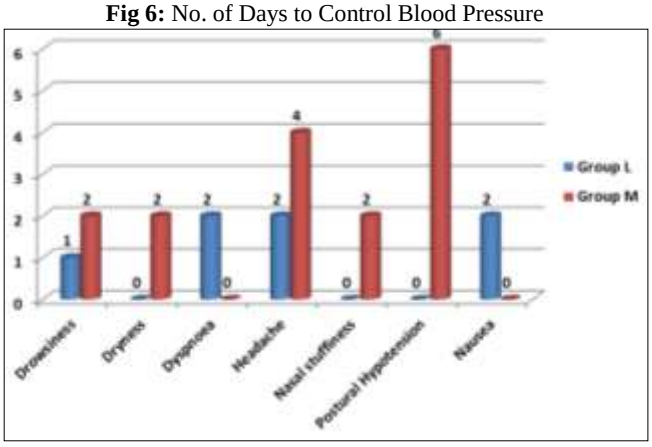

Fig 7: Side Effect of Drug

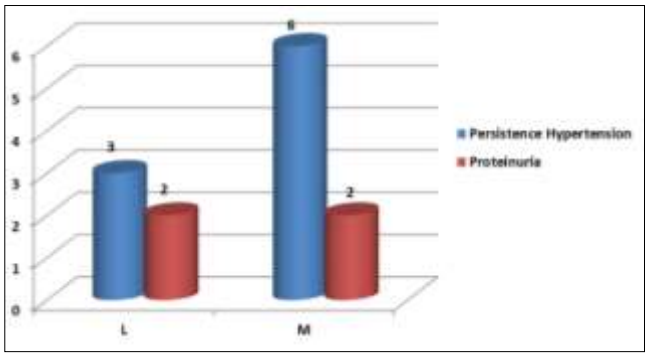

Fig 8: Status of Blood Pressure, Proteinuria 6 Week after Confinement

Discussion

The mean age in group L was 26.98 and mean age in group M was 26.28 years. The p value was >.05, indicating no significant difference between two groups. In comparison with multigravida, primigravida were prone to develop Hypertension in pregnancy with a higher incidence of 28 (56%) in labelatol group and also 28 (56%) in methyldopa groups. The p value was >.05 indicating no significant difference between two groups.

MAP in patients treated with Labetalol (L) group on admission was 122.61 while at the time of delivery reduced to 98.51. With Methyldopa (M) group, MAP on admission was 120.61 which reduced to 102.72. Reduction in MAP was statistically significant in both groups, since the p value was <0.001.DBP in the patients treated with labetalol (L) on admission was 105 while at the time of delivery reduced to 83.04. With methyldopa (M), DBP on admission was 104.08 and which reduced to 87.04. Reduction was statistically significant in both groups, since the p value <.001.post treatment persistent proteinuria cases were much less 8% in L group in comparison to 16% in M group.Oedema alone has no diagnostic or prognostic significance, in this present study the patients presented with Oedema were 78% in Labetalol (L) group and 68% in Methyldopa (M) group. The p value was >.05 indicating non-significant. Majority of the patients has antenatal record of wt. gain between 0.5-0.75 kg per week. Majority of patients with increased serum uric acid (>4 mg) were dealt in the Labetalol group (16%), in comparison with Methyldopa group (12%). Raised serum creatinine (>1.2 mg) in the labelatol and methyldopa groups were each of 8% of cases. 6% in labetalol and 8%in methyldopa cases were platelet count < 10^5. 64% in labetalol group and 68% in methyldopa groupwere admitted between 33-36 weeks, which comprised maximum admission.

The only maternal complication was imminent eclampsia, though it was only 3 (6%) labetalol group, where it was 5 (10%) in methyldopa group.maximum no. of the cases 42 (84%) in labetalol group and 36 (72%) in methyldopa group where delivered at or beyond 37 weeks. Majority of the patients were delivered by vaginally and it was prominent in labetalol group (60%), in comparison to methyldopa group (52%).

Compare with methyldopa in the labetalol group minimum number of cases underwent caesarean section. there were less no. of LSCS and reduced maternal and fetal morbidity and mortality in labetalol group comparison to methyldopa group.18 (36%) in the Labetalol group and 13 (26%) in Methyldopa group were rounded birth weight less than 2.5 kg.

In Labetalol group, Apgar score at 5 min of birth was 7-10 in 45 (90%), 0-6 in 5 (10%) babies and in Methyldopa group had Apgar score at 5 minutes of birth was 7-10 in 40 (80%), 0-6 in 10(20%) babies.

In the Labetalol group 3 babies showed asphyxia, 5 babies were preterm, 5 babies were IUGR and in methyldopa group 4 babies showed Asphysia, 4 babies were preterm, 8 babies were IUGR, 2 were still birth, 2 were END. Labetalol group showed better fetal outcome, and less fetal morbidity in comparison to methyldopa group.

The mean dose required to control BP in Labetalol (L) group was 552.63 mg. In the Methyldopa group the mean dose required to control BP was 1093.75 mg. the mean time required to control BP in Labetalol group was 3.33 days and in Methyldopa group was 3.62 days. The p value >0.05, which is statistically non-significant.

The persistent hypertensive case were reffered to cardiology OPD and in proteinuria disease, it was tried to rule out renal dysfunction or urinary tract infection.

Among the side effects of antihypertensive drugs, dyspnea and headache, nausea seen in labetalol group but other side effects like postural hypotension, headache, drowsiness, nasal stiffness seen in methyldopa group. All the patients were seen on their usual follow up in the OPD, but percentage of cases showed persistence of hypertensive and proteinuria were much less in labetalol group.

Conclusion

In this study we found that labetalol is more advantageous than methyldopa in terms of better and quicker control of blood pressure. It delays in appearance of premonitory signs and symptoms of preeclampsia, this allowing prolongation of pregnancy. The chances of spontaneous onset of labour were greater in labetalol group and it increases vaginal births. The maternal and foetal morbidity was much lower in labetalol treated cases, fetal outcome was much better and it showed fewer side effects.The present study clearly hints at the fact that, labetalol it currently a good single drug option for controlling hypertension and its complication during pregnancy.

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