(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume2, Issue 2, Page No: 221-227
March-April 2019

To Study the Safety and Efficacy of Labetalol In Comparison To Methyldopa in Stage I Pregnancy Induced Hypertension

Dr. Murassa Shamshad[1], Dr Owais Ahmed wani[1], Dr. Saqiba Afzal[1], Dr Dawood Banday[1], Dr.Bilal Ahmed[1], Dr Asma Shah[1], Dr Suhail Malik[1], Dr.Arif[1], Dr Tajamul[1] , Dr . Mushtaq[1], Prof. Sonaullah Shah[2], Prof. Rafi Jan[2], Dr Omar Hafiz[3]
Senior resident[1] Professor[2] Associate Professor [3]
Postgraduate Department of Internal and pulmonary Medicine, SKIMS, Soura Srinagar

***Corresponding Author:**

Dr Owais Ahmed wani
Senior resident
Postgraduate Department of Internal and pulmonary Medicine, SKIMS, Soura Srinagar

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT

The present prospective study on the pharmacological therapy for pregnancy-induced hypertension (PIH) was conducted in a tertiary care hospital in north india between August 2012 to Jan 2014. A total of 100 previously normotensive consecutive pregnant women 20 to 36yrs of age presenting between 20 and 38 weeks of gestation and having mild to moderate PIH were studied.. The following conclusions were drawn:

1. Labetalol and methyldopa were almost equally effective in controlling maternal blood pressure and in reducing nonfatal adverse events in the mother and the fetus. However, there was a trend towards a lower rate of adverse maternal outcomes like proteinuria, severe hypertension, antenatal hospitalisation, and caesarean section with labetalol as compared to methyldopa. The fetal outcomes were comparable between the two study drugs except for some reduction in the admission rate to neonatal care units with labetalol compared to methyldopa.

2. Both labetalol and methyldopa were well tolerated with acceptable frequency of mostly minor non-limiting side effects; the incidence of side effects was slightly higher for methyldopa as compared to labetalol. Thus, elective pharmacological treatment of mild to moderate hypertension during pregnancy appears to be effective and safe and is associated with lower rate of maternal and fetalneonatal morbidity. Labetalol, a combined alpha and beta blocker, may be marginally superior to methyldopa in reducing maternal and neonatal morbidity..

Keywords: NIL

INTRODUCTION

Hypertension during pregnancy is an important medical-obstetric disorder that is frequently associated with adverse fetal and maternal outcome. Hypertension complicates 6-10% of all pregnancies,[1] although estimates as high 22% have been suggested.[2] As a group, hypertensive disorders represent the most significant complication of pregnancy, contributing greatly to maternal and perinatal morbidity and mortality throughout the world.3 Hypertensive disorders are responsible for about 17% of maternal deaths, making them the leading cause of maternal mortality, after thromboembolism and haemorrhage.[2,4,5] The adverse maternal consequences of hypertension during pregnancy include eclampsia, disseminated intravascular coagulation, hemolysis, elevated liver enzyme levels and a low platelet count (HELLP) syndrome, pulmonary edema, renal failure, cerebral

edema and haemorrhage, liver failure and antepartum haemorrhage.[1,6-9] The fetal complications of maternal hypertension are related to decrease in placental perfusion and may include intrauterine growth retardation, premature delivery, hypoxemia, acidosis and fetal and perinatal death.[7,10-12]

Hypertension in pregnancy is defined as systolic blood pressure (SBP) of 140 mmHg or higher and/or diastolic blood pressure (DBP) of 90 mmHg or higher on atleast 2 occasions, 6 or more hours apart.[1,4] Two groups of hypertensive pregnant patients can be recognisedthose with pre-existing hypertension and those who develop hypertension for the first time during pregnancy.[1,4,13]

Management of pregnant women with hypertension aims at opmitizing fetal and maternal outcome and may require consideration of several aspects unique to gestational cardiovascular physiology. The major goal of treatment is to prevent maternal complications, especially maternal cerebrovascular, renal, and cardiac complications, without compromising

uteroplacental perfusion and fetal circulation until and after the safe termination of the pregnancy. General measures like bed rest, dietary sodium restriction, cessation of smoking, and alleviation of anxiety are the primary nonpharmacological measures used.[14-16] Bed rest lowers BP, results in diuresis, and may reduce the incidence of premature labour. [16-17]

There is a general consensus that severe PIH, especially with pre-eclampsia or eclampsia, requires treatment with antihypertensive drugs although the most appropriate treatment and the threshold BP level for starting that treatment are not yet clearly known. Generally, a SBP ≥170 mmHg or a DBP ≥110 mm Hg is considered as indicative of a need for urgent BP control with pharmacological treatment.[1,20-24] Previous studies have demonstrated that treatment of DBP ≥110 mm Hg with medication decreases the incidence of maternal cerebral and cardiac events.[29] BP control, however, does not prevent or cure pre-eclampsia and the only definitive treatment of pre-eclampsia is the termination of pregnancy.[6,16,28-29]

Guidelines vary, with recommendations to treat ranging from thresholds of 140/90mmHg, 160/90 mmHg, and 150-160/100-110 mmHg in the Canada, Austarlia, and the United States,respectively.[1,13,20]. Some believe that antihypertensive drugs should be started at SBP of ≥140 mm Hg or a DBP of ≥90 mm Hg in women with gestational hypertension without proteinuria or pre-existing hypertension before 28 weeks gestation, those with gestational hypertension and proteinuria or symptoms at any time during the pregnancy, those with pre-existing hypertension and underlying conditions or target organ damage, and those with pre-existing hypertension and superimposed gestational hypertension. In the absence of proteinuria, drug treatment may be withheld unless BP is ≥150/95 mm Hg.[20]Such recommendations are based on the argument that with proper use antihypertensive medications, fetal distress attributed to placental hypoperfusion is rare and long term effects on the infant may be minimal. More commonly, however, the threshold for beginning antihypertensive therapy has been DBP of ≥100 mm Hg. The advocates of this strategy argue that treatment of mild hypertension (DBP <100 mm

Hg) has not been shown to produce significant maternal or fetal benefits and if pre-eclampsia has been ruled out by the absence of proteinuria, monitoring may be an appropriate option.[25-29] Thus it remains unclear whether drug therapy for mild to moderate hypertension during pregnancy is worthwile. The combination of oral antihypertensive drugs with bed rest and extensive antenatal fetal monitoring was reported in one study as prolonging gestation (but not beyond 37 weeks) in women with severe gestational hypertension with proteinuria. However, there was insufficient evidence on which to draw any reliable conclusion about the effectiveness of drug treatment in preventing preterm delivery.

Another controversial issue in the pharmacological management of PIH is the choice of an antihypertensive. Studies comparing different antihypertensive drugs in pregnant women have been largely inconclusive.[16] The small numbers of patients studied precludes any sound inferences about the comparative effects of different agents on maternal and paternal outcomes to be drawn from these studies, even when considered collectively in a metaanalysis.[16,30] Several antihypertensive drugs have demonstrated safety and effectiveness in PIH and sometimes, a combination of two or more drugs is needed to achieve effective BP control. Agents

Volume 2, Issue 2; March-April 2019; Page No. 221-227

from beta adrenoceptor blocker and central sympathetic antagonist classes of antihypertensive drugs have attracted particular attention because of their safety, efficacy, and prolonged experience of use by the physicians. Among these, two agents- labetalol and alpha methyldopa- have been demonstrated to be safe for use in the pregnant women and are commonly used for the management of various hypertensive disorders during

pregnancy.[4,31] Labetalol is a combined α- and β-blocker and has the advantage over other beta blockers due to its additional arteriolar vasodilatory action that helps to lower peripheral vascular resistance with little or no decrease in cardiac output. An important obstetric use of labetalol is for hypertensive emergencies in patient with severe pre-eclampsia and is replacing hydralazine for this purpose because it does not cause severe hypotension, headache and tachycardia and has no effect on uteroplacental blood flow.[31] The other commonly used antihypertensive in pregnancy - alpha methyldopa- is a centrallyacting adrenergic antagonist. Stimulation of the central α2 receptors with the agonist alpha methyldopa decreases sympathetic nerve activity resulting in a decrease in the adrenergic tone and arterial dilatation with reduction in BP. Because of the reduced or even absent venodilatation, cardiac output is largely unchanged and the incidence and severity of orthostatic hypotension is less. For oral use, methyldopa has a very long track record of safety and is the only agent whose effects have been studied in children exposed in utero. The two randomised controlled trials reporting a decrease in the rate of perinatal death with antihypertensive therapy involved the administration of methyldopa.[9,32]

Thus, as compared to severe forms of PIH, the therapeutic decisions for mild to moderate PIH are less clearly established. In particular, there is currently insufficient evidence to support or refute the routine use of antihypertensive medications for this form of hypertension. Such questions are difficult to answer in the answer in the absence of large sample trials to provide reliable estimates of the likely benefits and potential adverse effects of antihypertensive treatment for mild to moderate PIH.

Therefore one goal of the present study was to assess whether routine pharmacological treatment of mild to moderate PIH is effective in improving maternal and fetal outcomes.

Further, it is not clear which antihypertensive may be better than others although several potential choices are available. The choice of an antihypertensive during pregnancy is frequently empiric and is largely determined by the perceived urgency for BP control and the physician experience. Therefore, the second goal of this study was to compare the safety and efficacy of two commonly used antihypertensive agents – labetalol and methyldopa- for the management of mild to moderate PIH.

AIMS AND OBJECTIVE

The present study was conducted with the following specific aims:

1. To compare the antihypertensive effects and safety profile of labetalol and methyldopa in the management of mild to moderate PIH.

2. To compare the effects of labetalol and methyldopa on maternal and fetal outcome in mild to moderate PIH.

MATERIAL AND METHODS

I. SUBJECTS:

This prospective study was done in a tertiary care hospital in North India. A total of 100 subjects with PIH who first presented between 20 and 38 weeks of gestation, were recruited from August 2012 to January 2014. Informed consent was obtained from all the patients before enrolment. Patients were managed both as inpatients and outpatients. The initial attendance at the participating clinic was no later than 20 weeks gestation and all patients had to be normotensive prior to the 20 weeks of gestation.

Inclusion criteria

1. Physician-recorded SBP of 140-160 mmHg and/or 90-105 mm Hg in the office after 15 min rest on two occasions ≥24hrs apart without detectable proteinuria.
2. Conventional sphygmomanometer was used and phase V Koratokoff sounds were used for the DBP.1,4,29
3. Medical decision to rapidly control blood pressure
4. Acceptable cardiotocograph (CTG)

Volume 2, Issue 2; March-April 2019; Page No. 221-227

5. Maternal heart rate > or = 60 and 120 bpm

Exclusion criteria:

1. Underlying chronic hypertension with or without history of antihypertensivemedication.
2. Patients previously have given antihypertensive drugs in the current pregnancy.
3. Urinary tract infection.
4. Heart disease, diabetes, congestive heart failure, heart block, asthma, secondary hypertension including pheochromocytoma or hepatic, renal, or other medical disorders and in patients with allergy to labetalol.
5. Connective tissue disorders like systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease.
6. Depression or other psychiatric disorders.
7. Complication in the current pregnancy like RH isoimmunisation, multiple pregnancy, placenta previa, ultrasound documented congenital anomalies.

II. GENERAL EVALUATION

Detailed medical and obstetric history was obtained at the time of initial recruitment. Complete physical examination was also performed, including record of BP and relevant obstetric examination. Blood samples were drawn for routine haematological and biochemical tests and 12-lead resting electrocardiogram was taken. Urine was tested for the presence of protein. A timed (24 hour) urine collection was obtained for the quantification of proteinuria and the determination of creatinine clearance. A fetal ultrasonogram was performed to assess/confirm the gestational age and to look for fetal well being.

III. PHARMACOLOGICAL INTERVENTION

The patients were randomly allocated to one of the 2 treatment groups of 50 each. Patients in Group I received labetalol while those in Group II received Methyldopa in addition to the standard obstetric care.

Dosage and administration

Labetalol was started at a dose of 100 mg twice daily while methyldopa was started at a dose of 250 mg twice daily. The patients were called after 1 week. If the target BP level (<140/90 mm Hg but >110/70 mm Hg) was attained patient was maintained at the same dosage. If target level BP was not attained, doses were increased (at weekly intervals) in increments of 100 mg/d in case of labetalol and 250 mg/d in case of methyldopa until one of the following whichever first: target BP achieved, dose limiting side effects developed, or maximum dose (2400mg/d for labetalol, 2000mg/d for methyldopa) reached. Once the dosage was stabilised, the patients were followed at two-weekly intervals upto 32 weeks and weekly thereafter till delivery. The criterion for stopping treatment was the first recognition of side effects other than non-serious ones with either drug. If the patient was intolerant to the drug used or if the hypertension was refractory, other alternative treatment as appropriate was given. Treatment failure was defined as inability to attain satisfactory BP control (BP > 110/70mmHg but < 140/90 mmHg) despite maximally tolerated doses of labetalol or methyldopa.

IV. FOLLOW-UP

Patients were followed up for fetal and maternal well being with the progress of pregnancy as well as for the development of any unwanted drug effects. Haematological tests, biochemical assays, urinary protein determination, and measurement of creatinine clearance were repeated at monthly intervals upto 32 weeks and thereafter fortnightly upto delivery. A repeat fetal sonogram was performed at 37 weeks and whenever indicated. The number of days spent by the mother antenatally as an inpatient were recorded for eachwoman. The timing and management of delivery were adjusted to meet the needs of the individual patients. The perceived need for labour induction and the method of delivery was recorded. After delivery, maternal and neonatal examination was performed. Neonatal blood

sample was obtained from heel prick for measurement of blood glucose concentration from all infants. Birth weight (grams) and placental weight (grams) were recorded in every case. After delivery the drug was tapered off and the patient followed for 48 hrs.

V. OUTCOME MEASURES

Volume 2, Issue 2; March-April 2019; Page No. 221-227

The following end-points were recorded:

Maternal

1. Maternal death
2. Major maternal morbidity: eclampsia, accidental haemorrhage; disseminated intravascular coagulation; major systemic illness including cardiac (pulmonary edema, heart failure), hepatic (hepatitis or asymptomatic elevation of transaminases), renal (decrease in creatinine clearance to less than 100 ml/min, or vascular (stroke, other major vascular) complications.
3. Severe hypertension: SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg.
4. Severe pre-eclampsia: severe hypertension with proteinuria ≥ 2+ (or ≥ 2 g/24h) with or without other signs or symptoms.
5. Proteinuria: persistent or new proteinuria (1+ or more or ≥ 300 mg/24 h).
6. Delivery by caesarean section.
7. Caesarean section for severe uncontrolled PIH.
8. Antenatal hospital admission.
9. Composite maternal endpoint (one or more of the above adverse events)

Fetal

1. Fetal-neonatal death: intrauterine death, perinatal death (death in the first week of life)
2. Small for gestational age: low birth weight for gestational age, below the 10th percentile.
3. Preterm birth: all births before 37 completed weeks.
4. Apgar score at 1 min.
5. Admission to neonatal unit.
6. Composite fetal endpoint (one or more of the above adverse events)

OBSERVATION AND RESULTS

I. BASELINE SUBJECT CHARACTERISTICS

There was no difference in the age distribution between labetalol and methyldopa groups (p = 0.846). About 84% of the patients on methyldopa and 80% of patients in the labetalol group were under 30 year age. The baseline characteristics of subjects in the two treatment arms (labetalol and methyldopa) were similar. Mean age, parity status, maternal weight, history of previous PIH, BP level, blood counts and renal function parameters were similar between labetalol and methyldopa groups. Prior history of fetal growth retardation or fetal loss was present in almost similar percentage of patients between the different treatment arms. The ultrasonographic parameters were also comparable at baseline between labetalol and methyldopa groups with more than three-fourth of patients in each group having normal liquor and placenta. The baseline prevalence of small-for-gestational age fetus was also similar between the different treatment groups

II. EFFECTS ON MATERNAL PARAMETERS

Overall, there was no difference in change in maternal parameters between labetalol and methyldopa. However, the decrease in heart rate with methyldopa was not significant. Further, as compared to labetalol group, the increase in haemoglobin was modest in the methyldopa group . There was no significant difference with respect to change

in liver function parameters, serum uric acid level, or creatinine clearance between labetalol and methyldopa

III. EFFECTS ON FETAL PARAMETERS

There was a trend towards lower prevalence of abnormalities in liquor (16% vs. 28%; *P* = 0.121) and placenta (16% vs. 30%; *P* = 0.275) in labetalol group as compared to methyldopa group, but the differences were not statistically significant. Further, about 16% and 26% of patients on labetalol and methyldopa, respectively, showed evidence of IUGR (*P* = 0.220). No patient in any of the study groups had any overt fetal malformation .

Birth parameters of the neonate were comparable between labetalol and methyldopa groups.The duration of pregnancy, birth weight, and 1 min Apgar score tended to be higher on labetalol than methyldopa but the difference was not statistically significant in any of these parameters . There was no difference in the neonatal blood glucose level and placental weight between various study groups.

IV. MEASURES OF MATERNAL OUTCOME

Volume 2, Issue 2; March-April 2019; Page No. 221-227

With regard to comparison between the two treatment arms, labetalol was associated with a trend towards lower rate of adverse maternal events as compared to methyldopa (P = 0.067). Labetalol seemed to reduce the frequency of proteinuria (P = 0.790) and the need for hospitalisation before term in the mother (P =0.148) to a greater extent than methyldopa. Labetalol also was associated with slightly lower incidence of severe hypertension (P = 0.318) and reduced need for abdominal delivery (P = 0.052) as compared to methyldopa. However, there was no significant difference in the rate of occurrence of major morbid events in the mother.

DISCUSSION

Our findings largely confirm the earlier observation that routine antihypertensive treatment of non-severe forms of PIH does not lead to reduction in maternal or perinatal mortality rates. The results of the present study indicate that the elective pharmacological treatment of mild to moderate hypertension during pregnancy is safe and is associated with lower rates of maternal and fetal-neonatal morbidity. Labetalol, a combined alpha and beta blocker, seemed to be marginally superior to methyldopa in reducing maternal and neonatal morbidity. The occurrence of adverse effects was slightly greater in case of methyldopa, although the difference did not reach the level of statistical significance.

REFERENCES

1. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183:S1-S2.
2. Emery SP. Hypertensive disorders of pregnancy: overdiagnosis is appropriate. Cleveland Clin J Med 2005;72(4):345-352.
3. Seely EW, Lindheimer MD. Pathophysiology of pre-eclampsia. In: Izzi JL Jr. BlackHR, eds. Hypertension Primer, 3rd ed. Dallas: American Heart Association; 2003:160-163.
4. American College of Obstetrician and Gynecologists. Technical Bulletin. No. 219. Hypertension in Pregnancy. Int J Gynecol Obstet. 1996;53: 175-183.
5. Moodley J. Maternal deaths associated with hypertensive disorders of pregnancy: a population-based study. Hypertens Pregnancy 2004;23(3):247-256.
6. Garovic VD. Hypertension in Pregnancy: Diagnosis and treatment. Mayo Clin Proc 2000;75:1071-1076.
7. Solomon CG, Seely EW. Hypertension in Pregnancy. Endocrinol Metabol Clin North America 2006;35(1):157-171.
8. Perloff D. Hypertension and Pregnancy-related hypertension. Clin Cardiol 1998;16:79-101
9. Sibai BM, Anderson GD. Pregnancy outcome of intensive therapy in severe hypertension in first trimester. Obstet Gynecol 1986;67:517-522.57
10. Roberts CL, Algert CS, Morris JM, et al. Hypertensive disorders in pregnancy : a population-based study. Med J Austral 2005;182(7):332-335.
11. Sibai BM. Diagnosis and management of chronic hypertension in pregnancy. Obstet
12. Gynecol 1991;78:451-461.
13. Wallenburg HC, Visser W. Pregnancy-induced hypertensive disorders. Curr Opin
14. Obstet Gynecol 1994;6:19-29.
15. Brown MA, Haue WM, Higgins J, et al. The detection, investigation, and management of hypertension in pregnancy: full consensus statement. Aus N Z J Obstet Gynaecol 2000;40:139-155.
16. Gulloti D, Gulloti A, Schillaci L, et al. Management of uncomplicated arterial hypertension in pregnancy. Minerva Medica 2006;97(1):95-105.
17. Podymow, August T, Umans P, et al. Antihypertensive therapy in pregnancy. Semin Nephrol 2004;24(6):616-625.
18. Magee LA, Ornstein MP, von Dadelszen P. Management of hypertension in pregnancy. Br Med J 1999;318:1332-1336.
19. Goldenberg RL, Cliver SP, Bronstein J, et al. Bed rest in pregnancy. Obstet Gynecol 1994;84:131-136.
20. Gilstrap LC III, Cunningham FG, Whalley PE. Management of pregnancy-induced hypertension in the nulliparous patient remote from term. Semin Perinatol 1978;2:73-81.
21. Sibai BM, Gonzalez AR, Mabie WC, et al. A comparison of labetalol plus hospitalization versus hospitalization alone in the

Volume 2, Issue 2; March-April 2019; Page No. 221-227

management of pre-eclampsia remote from term. Obstet Gynecol 1987;70:323-327.
22. Rey E, LeLorier J, Burgess E, et al. Report of the Canadian Hypertension Society
23. Consensus Conference:3. Pharmacological treatment of hypertensive disorders in pregnancy. Can Med Assoc J 1997;157(9):1245-1254. 60
24. Tuffnell DJ, Lilford RJ, Buchan PC, et al. Randomised controlled trial of day care for hypertension in pregnancy. Lancet 1992;339:224-227.
25. Matthews DD, Agarwal V, Shuttleworth TP. A randomised controlled trial of complete bed rest versus ambulation in the management of proteinuric hypertension during pregnancy. Br J Obstet Gynaecol 1982;89:128-131.
26. Rothberg AD, Shuenyane E, Sefuba M. Psychosocial support for mothers with pregnancy- related hypertension: effect on birthweight. Pediatr Rev Commun1991;6:13-20.
27. Mabie WC. Management of acute severe hypertension and encephalopathy. Clin Obstet Gynecol 1999;42:519-531.
28. Linton DM, Anthony J. Critical care management of severe pre-eclampsia. Intensive Care Med 1997;23:248-255.
29. Khedun SM, Moodley J, Naicker T, et al. Drug management of hypertensive disorders of pregnancy. Pharmacol Ther 1997;74:221-258.
30. Magee LA. Treating hypertension in women of child-bearing age and during pregnancy. Drug Saf 2001;24:457-474.
31. Management of pre-eclampsia. American College of Obstetricians and Gynecologists: Technical Bulletin Number 91; 1986.
32. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. Heart 2004;90:1499-1504.61
33. Abalos E, Duley L, Steyn DW, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev.2001;(2):CD002252.
34. Lamming GD, Broughton Pipkin F, Symonds EM. Comparison of the alpha and beta blocking drug, labetalol, and methyldopa in the treatment of moderate and severe pregnancy-induced hypertension. Clin Exp Hypertens. 1980;2(5):865-895.
35. Rochat RW, Koonin LM, Atarsh JF. The Maternal Mortality Collaborative. Maternal Mortality in the United States: Report from the Maternal Mortality Collaborative. Obstet Gynecol 1988;72:91-97.

Volume 2, Issue 2; March-April 2019; Page No. 221-227