ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFICACY OF METHYLDOPA VERSUS LABETALOL IN THE TREATMENT OF PREGNANCY INDUCED HYPERTENSION. A RANDOMIZED CONTROL TRIAL.

Surgery

Dr Javid Iqbal* MS, Lecturer, Department of Surgery, Government Medical College Jammu *Corresponding Author

Dr Vikar Hussain Qazi MD, Senior Resident, Department of Nephrology, Max Superspecility Hospital Saket, Delhi

Dr Munaza Aman MBBS, Post Graduate, Department of Microbiology, Government Medical College Jammu

Dr Yasmeen Kousar MBBS, DGO, Medical Officer, Government Medical College Jammu

ABSTRACT

Background: Hypertensive disorders complicating pregnancy are one of the common cause of maternal morbidity and mortality.

Aim and objectives: To compare the efficacy of treatment with methyldopa versus labetalol in women with pregnancy induced hypertension (PIH).

Material and Methods: A total of 100 patients presenting with PIH were enrolled in this study. After taking written informed consent from patients who fulfill inclusion criteria were randomly divided into two groups. Group I comprised of 50 patients who were given methyldopa and Group II comprised of 50 patients who were given labetalol. Methyldopa was begun at a dosage of 750 mg per day (250mg thrice daily) whereas, labetalol was started at a dosage of 300 mg per day (100 mg thrice daily). Fall in mean systolic and diastolic BP was noted. Side effects of both drugs were recorded in both groups. Aim was to reduce and maintain blood pressure below 140/90 mm Hg.

Results: Maximum number of patients were in the age group of 21-25 years. The mean gestational age at entry in group I was 33.6(SD=2.7) weeks and in group II was 33.7(SD=3.1) weeks. Labetalol caused more reduction in mean systolic and diastolic B.P. than methyldopa. In comparison to methyldopa, absolute fall seen in mean systolic B.P. with labetalol was statistically significant (p=0.01); while that seen in mean diastolic B.P. was also statistically significant (p=0.003). 14% of patients in Group I and 46% in Group II showed response within 24 hrs, while 60% of patients in Group I and 40% in Group II showed response in more than 24 hrs. This difference between two groups was statistically significant (p=0.001). Complete response was reported in 74% of patients in Group I and 86% in Group II. Failure of response was seen in 26% of patients in Group I and 14% in Group II. There was no statistically significant difference between two groups (p=0.1). Side effects were more in Group 1, the difference between the two groups considering frequency of side effects was statistically significant (p=0.01)

Conclusion: Labetalol has been found to be more advantageous than methyldopa in terms of better and quicker control of blood pressure with minimal side effects.

KEYWORDS

Methyldopa, Labetalol, pregnancy induced hypertension.

INTRODUCTION:

Hypertensive disorders complicating pregnancy are common and form one of the deadly triad, along with hemorrhage and infection that results in much of the maternal morbidity and mortality related to pregnancy. Upto 50,000 women die due to pre-eclampsia or eclampsia each year, mostly in developing countries.[1] Hypertension is diagnosed when blood pressure is 140/90 mm Hg or greater, using Korotkoff phase V to define diastolic blood pressure. A wide variety of drugs are being used effectively in the treatment of hypertension in pregnancy, which includes methyldopa, hydralazine, nifedipine, atenolol, labetalol etc.

Methyldopa is usually started at dosage of 250mg three or four times daily and then can be gradually increased up to maximum dose of 04gm/day. Several side effects have been described in association with methyldopa treatment like sedation, depression, postural hypotension, positive Coomb's test result, hemolytic anemia, hepatitis, fever and withdrawal hypertension.

Labetalol has been used in the treatment of PIH (pregnancy induced hypertension) and is a safe and efficient drug. It can be used for both oral and intravenous administration. Oral labetalol is usually started with 100mg twice or thrice daily and then can be gradually increased up to maximum dose of 2400mg /day. The working group (2000) recommends starting with a 20mg intravenous bolus. If not effective within 10 minutes, this is followed by 40mg, then 80mg every 10 minutes, but not to exceed a 220mg total dose. The main side effects of labetalol are fatigue, headache, postural hypotension, gastrointestinal symptoms (if it is used in high dose), and it can worsen bronchial asthma.[2]

The present study has been done to compare the efficacy of treatment with methyldopa versus labetalol in women with pregnancy induced hypertension (PIH).

MATERIAL AND METHODS:

A total of 100 patients presenting with PIH were enrolled in this study, irrespective of age, parity and socioeconomic status. Eligibility criteria included a singleton pregnancy, systolic BP ≥ 150 mm Hg, diastolic BP≥95 mm Hg and gestational age from 20 weeks onwards till 38 weeks. Patients with history of metabolic disorders, diabetes, cardiovascular disease, respiratory disease, collagen disorder, Rhesus isoimmunisation and multiple gestation were not included in this study. Also patients with a history of hypertension antedating pregnancy, patients previously given antihypertensive drugs in the current pregnancy and those having B.P ≥ 170/110 mm Hg were excluded.

After taking written informed consent, eligible patients were randomly divided into two groups.

Group - I: patients who were given methyldopa.
Group - II: patients who were given labetalol.

If systolic blood pressure was ≥ 150mm Hg and diastolic pressure was ≥ 95 mm Hg as mentioned in the inclusion criteria, antihypertensive medication with either methyldopa or labetalol was started.

Methyldopa was begun at a dosage of 750 mg per day oral dose (250mg thrice daily) and was increased every 2-3 days, if needed, to control blood pressure. Maximum dose of 3000 mg per day was given. Whereas, labetalol was started at a dosage of 300 mg per day (100 mg thrice daily) and was increased every 2-3 days till response was obtained. Maximum oral dose required was 800 mg/day in this study. Aim was to reduce and maintain blood pressure below 140/90 mm Hg and these patients were considered responders. Non responders were those patients who developed signs and symptoms of impending eclampsia while on treatment, patients where blood pressure remained uncontrolled inspite of maximum dose of drug and who required

addition of other antihypertensive drugs for control of blood pressure. All patients with PIH remained inpatients until diastolic blood pressure of < 90 mm Hg was achieved and then followed weekly as outpatients. Side effects of these drugs were noted and the response of both these drugs was followed till the patients delivered. Delivery was expedited in non- responders or when the risk to the fetus or mother was greater, if pregnancy continued, labour was induced by either medical or surgical methods in those patients who responded to treatment but did not go into spontaneous labour by term gestation. Fall in mean systolic and diastolic BP was noted. Side effects of both drugs were recorded in both groups. Aim was to reduce and maintain blood pressure below 140/90 mm Hg.

RESULTS:

Out of 100 patients enrolled in this study, 50 patients were given methyldopa (Group 1) and 50 patients were given labetalol (Group II). Maximum number of patients were in the age group of 21-25 years, 44% in Group I and 40% in Group II as shown in Table 1.

Table 1: Age, parity and diastolic BP– wise distribution of patients

S. no.		Group-I		Group-II	
1.	***Age in years***	No. Of patients	%	No. Of patients	%
	16-20	5	10	4	8
	21-25	22	44	20	40
	26-30	19	38	18	36
	31-35	4	8	6	12
	Total	50	100	50	100
2.	***Parity***				
	P0	32	64	34	68
	P1	12	24	11	22
	P2 and above	6	12	5	10
	Total	50	100	50	100
3.	***Diastolic BP(in mm hg)***				
	96-100	10	20	7	14
	101-105	22	44	21	42
	106-109	18	36	22	44
	Total	50	100	50	100

64% of cases in Group I and 68% of cases in Group II were primigravidas. 24% of cases in Group I and 22% in Group II were para 1 and 12% of cases in Group I and 10% in Group II had a parity of two or more than two as shown in Table 1.

The mean gestational age at entry in Group I was 33.6(SD=2.7) weeks. The mean gestational age at entry in Group II was 33.7(SD=3.1) weeks. 44% of patients in Group I and 42% in Group II had diastolic blood pressure between 101-105 mmHg, while 36% of patients of Group I and 44% in Group II were having diastolic blood pressure between 106-109 mmHg. The mean diastolic pressure before treatment in Group I was 103.48(SD=3.35) mm Hg and in Group II was 104.12(SD=3.14) mm Hg. There was no statistically significant difference in the mean blood pressure between two groups before treatment (p>0.1) as shown in Table 2.

Methyldopa and labetalol both caused a statistically highly significant fall in mean blood pressure both systolic and diastolic (P<0.0001).

Table 2: Table showing the fall in mean blood pressure in Group I and II patients

Blood pressure	Pre-treatment BP on entry (mm Hg)	Post entry treatment BP before labor (mm Hg)	Absolute fall in BP. (mm hg)
Mean systolic B.P in group I	158.4 (4.35)	136.48(14.05)	22
Mean Diastolic BP in group I	103.48 (3.35)	88.92 (9.40)	14.5
Mean systolic B.P in group II	158.4 (4.68)	130.4(11.24)	28.2
Mean Diastolic BP in group II	104.12 (3.14)	83.76 (7.469)	20.4

Results show mean (SD), P<0.0001 for both groups.

Labetalol caused more reduction in mean systolic and diastolic B.P. than methyldopa. In comparison to methyldopa, absolute fall seen in mean systolic B.P. with labetalol was statistically significant (p=0.01); while that seen in mean diastolic B.P. was statistically highly significant (p=0.003). 14% of patients in Group I and 46% in Group II showed response within 24 hrs while 60% of patients in Group I and 40% in Group II showed response in more than 24hrs. This difference between two groups was statistically significant (p=0.001). Complete response was reported in 74% of patients in Group I and 86% in Group II. Failure of response was seen in 26% of patients in Group I and 14% in Group II. There was no statistically significant difference between two groups (p=0.1).

In Group I, 82% of patients and in Group II, 88% of patients were able to reach term. 18% of patients in Group I and 12% of patients in Group II could not reach term. They had either spontaneous onset of labour or had to be induced before term. There was no statistically significant difference between two groups (p=0.4). The mean gestational age at delivery was 37.64 (SD = 2.31) weeks in Group I and was 38.29 (SD-=2.11) weeks in Group II. No statistically significant difference was seen between the two groups (p=0.14).

Forty two percent patients in Group-I went into spontaneous labour and in 46%, labour was induced by medical or surgical methods. 12% of patients of Group I had elective LSCS before onset of labour. In Group II, 48% of patients went into spontaneous labour and in 38%, labour was induced. 14% of patients had elective LSCS before onset of labour. There was no significant difference in mode of labour in the two groups (p=0.7). 62% of patients in Group I had a normal vaginal delivery, 06% patients had instrumental delivery in the form of forceps or ventouse and 32% were delivered by LSCS. 70% of patients in Group II had a normal vaginal delivery, 4% had instrumental delivery and 26% were delivered by LSCS. There was no significance difference in mode of delivery in the two groups (p=0.6).

Table 3: Frequency of side effects of methyldopa and labetalol

Side effects	Group-I		Group-II	
	No. Of patients	%	No. Of patients	%
Headache	13	26	4	8
Drowsiness	4	8	3	6
Generalized weakness	1	2	2	4
Hypotension	1	2	1	2
Nausea / Vomiting	2	4	1	2
Nasal stuffiness	1	2	-	-
No side effects	28	56	39	78
Total	50	100	50	100

The difference between the two groups considering frequency of side effects was statistically significant (p=0.01) as shown in Table 3.

DISCUSSION

Antihypertensive therapy has an important role in management of PIH. However, close maternal and fetal monitoring during hypertensive treatment is mandatory and if signs of an impending maternal or fetal crises develop the pregnancy should be terminated. Methyldopa is being extensively used for the treatment of hypertension in pregnancy[3,4]. Methyldopa decreases blood pressure by acting centrally on alpha 2 receptors and by decreasing sympathetic nerve activity[5,6]. It takes 12-24 hours for adequate therapeutic response and large dose is required but it is helpful for long term control of blood pressure. Most of the drug is excreted via the kidneys[7].

Labetalol lowers the blood pressure by blocking peripheral arteriolar α-1 adrenergic receptors, thus reducing peripheral resistance. Concurrent beta- blockade protects the heart from the reflex sympathetic drive normally produced by peripheral vasodilators so the reduction in blood pressure is achieved without cardiac stimulation. Conversely, this increased reflex activity modulates the beta-blocking effect of the drug on the heart so that the heart rate and cardiac output are not significantly reduced[8,9]. It has got extensive first pass hepatic metabolism. Its plasma half-life is 6-8 hours and peak plasma levels occur within 1-2 hours after administration. It does not decrease placental perfusion, despite a significant reduction in maternal blood pressure[10]. Several possible advantages over other antihypertensive agents used in the management of hypertension in pregnancy have been suggested: Firstly, labetalol may exert a direct beneficial action on the maturation of fetal lungs[11], Secondly, it appears to have no

deleterious effect on uteroplacental blood flow[10,12]. Labetalol may also diminish the amount of proteinuria in women who have already developed proteinuric preeclampsia before commencement of therapy.

In the present study, maximum no. of patients were in the age group of 21-25 years in both groups i.e., 44% in Group I and 40% in Group II which is similar to study by Subhedar et al[13]. Gravidity distribution showed maximum patients of PIH were primigravidas in both the groups which is similar to study by Subhedar et al[11]. Maximum no. of patients in both the groups were from rural background which is similar to study by Mohan et al[14]. In the present study, labetalol caused statistically more reduction in both mean systolic blood pressure (p=0.01) and in mean diastolic blood pressure (p=0.01) than methyldopa which is similar to study by Subhedar et al[13] who found significant fall in mean arterial pressure in patients receiving labetalol as compared to methyldopa. Similar finding was observed by Dharwadkar et al[15] who found significant fall of blood pressure in labetalol group as compared to methyldopa group. Lamming et al[16] also found a significant fall in mean arterial pressure in both labetalol and methyldopa groups but labetalol lowered the mean arterial pressure significantly more than methyldopa (p<0.001). In the present study, patients on labetalol showed response within 24 hrs of treatment in significantly more number of patients as compared to methyldopa (p=0.001).This is similar to study by Subhedar et al[13] who also found significantly earlier control of blood pressure than methyldopa. Similar finding was observed by Roychoudhary et al[17]. In the present study, blood pressure control in methyldopa group was affected by a mean dose of 1346mg (SD=665.6) (range=750-3000) and in labetalol group mean dose was 351mg (SD=72.03) (range=300-800 mg). Our observations are similar to Subhedar et al[13] who found mean dose required to control blood pressure in methyldopa group was 1111.11mg and mean dose required to control blood pressure in labetalol group was 382.22mg. Gupta et al[16] found blood pressure control with mean dose of 1300 mg in methyldopa group (range=750-2000mg) and in labetalol group mean dose was 300 mg (range=150-600mg). In the current study, no statistically significant difference was reported in the mode of labour between the two groups (p=0.71). However, Subhedar et al[13]found rate of spontaneous labour was statistically more in patients with labetalol. Lamming et al[16] and El-Qarmalawi et al[19]also found higher incidence of spontaneous labour in labetalol group. There was statistically no significant difference in the mean gestational age at delivery in between the two groups (p=0.14). Lamming GD et al[16] and Pickels et al[20] also observed statistically no significant difference in the mean gestational age at delivery. No statistically significant difference was reported in the mode of delivery between two groups (p=0.68). Similar observation was reported by various authors Gupta et al[18], Pickles CJ et al[21] and Cruickshank et al[22]. Lower segment caesarean section for impending eclampsia was done in 10% of patients in methyldopa group and in 6% patients in labetalol group. Thus, more patients in methyldopa group needed caesarean section due to uncontrolled blood pressure. Similar observation was also made by El Qarmalawi et al[19] who reported caesarean section for PIH in 2% of patients in labetalol group and in 5.6% of patients in methyldopa group. Sibai et al[23] also found that the use of labetalol in preeclampsia reduce the incidence of early delivery for severe hypertension.

CONCLUSION:

Labetalol has been found to be more advantageous than methyldopa in terms of better and quicker control of blood pressure with minimal side effects.

REFERENCES

1. Roberts JM, Villar J, Arulkumaran S. Preventing and treating eclamptic seizures. BMJ 2002;325:609-610.
2. Kanto JH. Current status of labetalol, the first alpha beta-blocking agent. Int. J Clin Pharmacol Ther Toxicol 1985; 23(11);617-628.
3. Leather HM,Baker P et al. A controlled trial of anti- hypertensive agents in hypertension in pregnancy.lancet,1968;2:488.
4. Redman CWG, Beilin LJ, Bonnar J and Ounsted MK. Fetal outcome in trial of antihypertensive treatment in pregnancy.Lancetii;1976:753-756.
5. Molvi SN, Mir S, Rana VS, Jabeen F, Malik AR. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Archives of gynecology and obstetrics 2012; 285(6):1553-62.
6. Easterling TR, Pharmacological Management of Hypertension in Pregnancy Semin Perinatol. 2014 Dec; 38(8): 487–95.
7. Togarikar SM. Efficacy of methyldopa versus nifedipine in mild and severe pregnancy induced hypertension. Int J Reprod Contracept Obstet Gynecol 2017; 6:4544-48.
8. Edwards RC, Raftary EP. Hemodynamic effects of long-term oral labetalol.Br J Clin Pharmacol 1976;3(Suppl) : 733.
9. Mac Carthry E P, Blomfield SS. Labetalol: A review of its Pharmacology, Pharmacokinetics, Clinical uses and adverse effects. Pharmacotherapy, 1983;3:193.
10. Nylund L, Lunell NO et al. Labetalol for the treatment of hypertension in pregnancy:Pharmacokinetics and effects on the uteroplacental blood flow. Acta Obstet Gynecol Scand Suppl(1984);118:71-73.
11. Michael CA. early fatel ling maturation associated with labetalol therapy. Singapore J Obstet Gynaecol 1980;11:43-47.
12. Lunell NO, Fredholm B et al. Labetalol, a combined alpha and beta-blocker in hypertension of preganancy. Acta Med Scand 1982 ;(Suppl) 665:43-147.
13. Subhedar V, Inamdar S, Hariharan C, Subhedar S. Comparison of efficacy of labetalol and methyldopa in patients with pregnancy- induced hypertension. Int J Reprod contracept Obstet Gynecol 2013; 2(1):27-34.
14. Mohan P. Gupta N, Singh P et al. Pregnancy induced hypertension- A clinical epidemiological study. Abstracts from the Third international Scientific meeting of the Royal college of Obstetricians and Gynaecologists(1996).
15. Dharwadkar MN, Kanakamma MK, Dharwadkar SN et al. Study of Methyl Dopa versus Labetalol in management of preeclampsia and Gestational Hypertension. Gynecol Obstet(Sunnyvale) 2014;4(9):1-7.
16. Lamming GD, Broughton PF, Symonds E.M. Comparison of the alpha and beta blocking drug, labetalol and methyldopa in the treatment of moderate and severe preganancy induced hypertension. Clin Exp Hypertens1980;2(5):865-895.
17. Roychoudhury B, Sanyal P, Chowdhury B, Oswal K. Comparative study of efficacy of methyldopa vs labetalol in the management of pregnancy induced hypertension in respect to maternal and perinatal outcome. Glob J Med pub health 2015;4(4);1-1-6.
18. Gupta M, Gupta U, Kumar S. Evaluation of labetalol in pregnancy induced hypertension. J Obstet Gynaecol India 1995;45(3): 349-355.
19. EL-Qarmalawi AM. Morsy AH et al. Labetalol versus methyldopa in the treatment of pregnancy induced hypertension. Int. J. Gynaecol Obstet 1995 May; 49 (2):125-30.
20. Pickles CJ, Symonds EM, Broughton PE. The fetal outcome in a randomized double blind controlled trial of labetalol versus placebo in pregnancy induced hypertension. Br J Obstet Gynaecol 1992;99:964-968.
21. Pickles CJ, Symonds EM, Broughton PE. The fetal outcome in a randomized double blind controlled trial of labetalol versus placebo in pregnancy induced hypertension. Br J Obstet Gynaecol 1989;96:38-43.
22. Cruickshank DJ, Robertson AA et al. Does labetalol influence the development of proteinuria in pregnancy induced hypertension: A randomized controlled study. Eur J Obstet Gynecol Rep Biology 1992;45:47-51.
23 Sibai BM, Gonzalez AR et al. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstet Gynaecol 1987;70:323-327.