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Labetalol in Comparison to Methyl Dopa in Treatment of Gestational Hypertension, A Randomized Trial

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Abstract

Objective: To evaluate the value and safety of labetalol in comparison to Alfa methyldopa in treatment of pregnant women with pregnancy-induced hypertension (PIH).

Methods: 264 patients with PIH were randomly distributed to take either methyldopa (group 1) labetalol (group 2). or Intake of medications with respect to Age, gravidity, Blood Pressure measurement, albumin in urine measurement Levels, Side Effects, dose of the drug, increasing duration of pregnancy, mode of delivery, Perinatal safety and APGAR scores were studied. The statistical level of significance was taken at $P<0.05$.

Results: A labetalol is very effective in controlling blood pressure and has earlier onset of action than methyldopa. Labetalol is very efficient in managing blood pressure, avoiding preeclampsia and eclampsia with statistically significant values in reducing Blood pressure in comparison to methyldopa with s P value less than 0.05 and increasing the length of pregnancy to reach fetal maturity. Labetalol has lower side effects than methyldopa. There is no difference in the 2 drugs as regard obstetric interference. Both drugs are safe for the neonate.

Conclusion: Labetalol is more safe, has lesser side effects on the mother and the neonate has a more rapid action in obtaining enough control of pressure with significant lengthening of the period of pregnancy if it is used in treatment of pregnancy complicated with hypertension.

Keywords: Labetalol; Methyldopa; Pregnancy; Preeclampsia; Hypertension

List of abbreviations: PE: Preeclampsia; PIH: Pregnancy Induced Hypertension; BP: Blood Pressure; GCP: Good Clinical Practice

Introduction

Hypertension is the most frequent disorder that happens in gestation [1]. Hypertensive problems comprise around ten percent of pregnancy and are one of the chief factors that can cause death to mothers and fetuses [2].

Hypertension is associated with an increase in the possibility of complications to mother, fetus and neonate as preterm delivery, chronic hypertension, intrauterine fetal growth retardation, perinatal death, acute renal failure, antepartum hemorrhage, postpartum bleeding and death of the mother [3-7].

Determining of the risk of developing hypertension in pregnancy can make control of elevated blood pressure more successful and effective. During this time the maternal and fetal state are followed with adjustment of hypertension by antihypertensive medications. The chance of having severe degree of hypertension is diminished to the half by taking antihypertensive agents [8].

A wide range of antihypertensive drugs are the reason of success of management of pregnancy induced hypertension [9-11].

Methyldopa was used on a large scale for management of hypertension during gestation due to its efficiency and safety for fetuses and pregnant ladies as an antihypertensive therapy with a drawback that it takes longer duration to work and also less effective as a hypotensive agent. However, it is still the most commonly utilized therapy for long term management of blood pressure during pregnancy. Methyldopa has a central action with its adrenergic antagonistic effect that causes activation of central alpha 2 receptors that leads to diminishing in sympathetic nerve stimulation causing arterial vasodilatation and so a decrease in Blood

Pressure. There are no available data that indicate any hazardous effect on the off springs in the Methyldopa treated patients. When methyldopa is given in high doses, the sedative and depressant effects of methyldopa are noted. Methyldopa should not be used if there is a risk of maternal depression where a beta-blocking drug or calcium channel blocker can be more appropriate. Labetalol has a better treating efficiency in controlling blood pressure when compared to other anti-hypertensive drugs [12].

Labetalol is a mixed alpha and beta-blocking medication and has the advantage over other beta blockers as it has an extra arteriolar vasodilating effect that helps to decrease peripheral vascular resistance with a slight or no decrease in cardiac output.

Advantage of labetalol is its availability in an injectable and oral form and the time to start its action is earlier than methyldopa [12].

However now, it is known that b-blockers cross the placental barrier and may cause a decrease in fetal heart rate.

Experimental evidence also suggests that β-blocking drugs decrease fetal affordability to hypoxic stress [12].

Patients and Methods

Study design

A Double blinded randomized controlled trial superiority with allocation ratio 1:1.

Study Settings

was carried out in multicentres at Ain Shams University maternity hospital in collaboration with kasralainy maternity hospital and National research centre, Egypt and Aljazeerah hospital, Egypt.

Study duration

The study was conducted in the period from 5 January 2017 till 10 december 2017.

Eligibility criteria

Inclusion and exclusion criteria.

Inclusion criteria:
1. Pregnant women aged 22-40 years.
2. Gestational age between 24 and 34 weeks.
3. Blood pressure greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic or more after blood pressure measurement on 2 occasions with 4 hours apart in a previously normal blood pressure.
4. Patients were kept in house with regular follow up visits.

Exclusion Criteria:
1. Pregnant women with underlying chronic hypertension, history of antihypertensive medication before 20 week gestation and secondary hypertension.
2. Patients with molar pregnancies, multiple pregnancy, placenta previa.
3. Pregnant women with renal disease, hematological disease, heart disease.

Intervention

Randomized in to 2 groups. Group A will receive labetalol and group B will receive alpha methyldopa then measure BP.

Subjects

Study group: 264 women attending Ain Shams University maternity hospital. Patients were distributed in two groups randomly. After randomization group A received labetalol 100 mg tid and group B received methyldopa 250 mg tid as starting dose. Mean Arterial pressure (MAP) was calculated.

Patients were kept in house and they were asked to come for regular follow up in the antenatal clinic in a fixed visits where Patients were monitored in the antenatal clinic after 48hrs from taking the drug and dose was assessed to control BP When there was no fall in BP even after 48 hours of drug therapy, dose of the drug was doubled. Then monitored in the antenatal clinic weekly for two weeks. Then every 2 weeks till delivery.

Measurement of BP

Auscultatory measurement with the sphygmomanometer is the most widespread method for indirect BP determination, having a high concordance level with the direct intra-arterial method.

Guidelines include:
- Seat the woman for 5-10 minutes prior to BP measurement. In semi sitting or left lateral position.
- Cuff size adequate to the patient`s arm circumference and positioned 2-3 cm above the antecubital fossa.
- Positioning of the central portion of the rubber bladder on the brachial artery.
- Positioning of the upper limb at the heart level.

Outcomes

Primary outcome: Control of mean arterial BP in mmHg in women with pregnancy induced hypertensions within 6 months.

➢**Secondary outcome:**
• Need for adding antihypertensive drugs.
• Side effect of drug used:

➢**Side effect of labetalol:**
• More common: nausea.
• Less common.

➢Blurred vision or other changes in vision.
➢Confusion.
➢Dizziness, fainting, light headache when getting up from lying or sitting position.

➢**Side effect of alpha methyldopa:**
• More common :drowsiness, dryness of mouth, headache.
• Less common: fever shortly after taking the drug.

Observations

1. Fall in mean arterial BP with labetalol/methyldopa.
2. Time required controlling BP.
3. Average dose of drugs required to control BP.
4. Side effects of drugs.

Methods

Randomization: Randomization of cases was done by computer method. 264 women with pregnancy induced hypertension were enrolled in the study and were distributed in two groups:group A and group B. The randomization allocation was 1:1.The two groups are randomly selected.

Allocation and Concealment: 264 opaque envelopes were numbered serially and in each envelope the corresponding letter which donate the allocated group was put according to randomization table then all envelops were closed and put in one box. When the first patient arrives the first envelope was opened and the women were allocated according to the letter inside.

Blinding

1. Subjects
2. Investigator
3. Outcome assessor
4. Caregiver

Sample size: Sample Size Calculation

The required sample size has been calculated using the G*Power Software (Universität Düsseldorf, Germany).
The primary outcome measure is the proportion of patients with adequate control of blood pressure at 48 hours from starting treatment, defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. The secondary outcome measure is the proportion of patients that would undergo spontaneous onset of labor.
There is at present no adequate information regarding the expected difference in the outcome measures between labetalol and methyldopa in patients with gestational hypertension. So, the present study tries to target an effective size that would be clinically relevant.

The study was conducted after approval of the ethical committee of Ain Shams University Maternity Hospital. Patients signed an informed consent to participate in the study.

Results

	Methyldopa group		Labetalol group		P value
	Mean	SD	Mean	SD	
SBP baseline	152.11	7.25	152.30	6.76	0.820
SBP 48 h	124.64	9.37	119.27	8.63	< 0.001
SBP 1 week	119.55	8.61	115.26	8.64	< 0.001
SBP 3 weeks	118.64	9.47	112.23	7.85	< 0.001
SBP 5 weeks	115.48	8.92	112.33	10.63	0.010
SBP 7 weeks	117.03	9.09	104.33	9.45	< 0.001
SBP 9 weeks	117.28	8.66	105.62	8.48	< 0.001
SBP At delivery	114.29	9.11	100.70	6.05	< 0.001
DBP baseline	99.77	6.14	99.89	6.00	0.871
DBP 48 h	89.92	9.26	85.32	8.85	< 0.001
DBP 1 week	87.39	8.87	82.17	5.25	< 0.001
DBP 3 weeks	86.81	8.00	80.04	4.49	< 0.001
DBP 5 weeks	85.43	8.70	79.05	4.49	< 0.001
DBP 7 weeks	81.11	5.91	77.58	4.55	< 0.001
DBP 9 weeks	80.20	6.22	76.12	5.71	< 0.001
DBP At delivery	78.60	5.22	73.55	7.93	< 0.001
MABP baseline	117.04	4.78	117.19	4.70	0.802
MABP 48 h	101.48	6.36	96.63	7.10	< 0.001
MABP 1 week	98.10	6.85	93.19	4.05	< 0.001
MABP 3 weeks	97.31	6.43	90.66	3.66	< 0.001
MABP 5 weeks	95.35	6.37	90.04	4.79	< 0.001
MABP 7 weeks	92.97	5.04	86.41	4.24	< 0.001
MABP 9 weeks	92.44	4.94	85.86	4.69	< 0.001
MABP At delivery	90.38	4.64	82.51	5.49	< 0.001

Table 1: Shows a Comparison between group 1 methyldopa and group 2 labetalol group

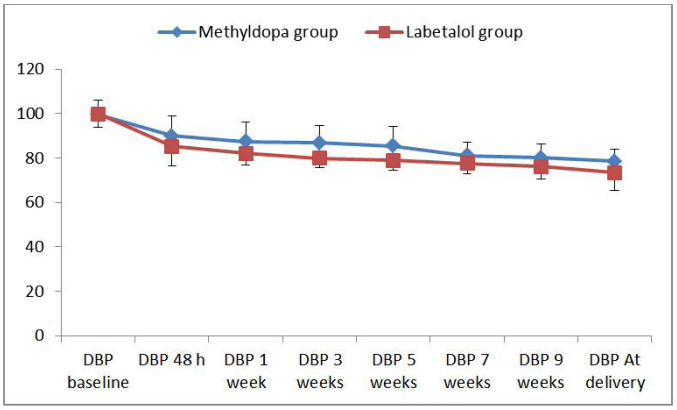

Figure 1: Shows a comparison between the 2 groups regarding Diastolic blood pressure measurements after treatment till delivery

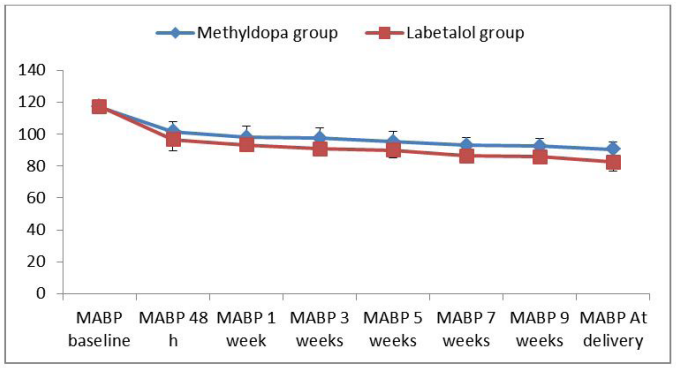

Figure 2: Shows a comparison between the 2 groups regarding mean arterial blood pressure measurements after treatment till delivery

		Methyldopa group		Labetalol group		P value
		Count	%	Count	%	
Gravidity	G1	29	22.0%	37	28.0%	0.451
	G2	42	31.8%	34	25.8%	
	G3	31	23.5%	36	27.3%	
	G4	30	22.7%	25	18.9%	
Parity	P0	29	22.0%	38	28.8%	0.263
	P1	49	37.1%	40	30.3%	
	P2	28	21.2%	35	26.5%	
	P3	26	19.7%	19	14.4%	
Number of abortions	nil	124	93.9%	123	93.2%	1
	one	5	3.8%	5	3.8%	
	two	3	2.3%	3	2.3%	
	three	0	.0%	1	.8%	
Proteinuria at delivery	yes	8	6.1%	1	.8%	0.036
	no	124	93.9%	131	99.2%	

Table 2: Comparison between the labetalol and methyldopa groups regarding age, parity, number of abortions and proteinuria

	Methyldopa group		P value
	Mean	SD	
SBP baseline	152.11	7.25	---
SBP 48 h	124.64	9.37	< 0.001
SBP 1 week	119.55	8.61	< 0.001
SBP 3 weeks	118.64	9.47	< 0.001
SBP 5 weeks	115.48	8.92	< 0.001
SBP 7 weeks	117.03	9.09	< 0.001
SBP 9 weeks	117.28	8.66	< 0.001
SBP At delivery	114.29	9.11	< 0.001

Table 3: Comparison between systolic blood pressure measurements starting before treatment (baseline) overtime till delivery in methyldopa group

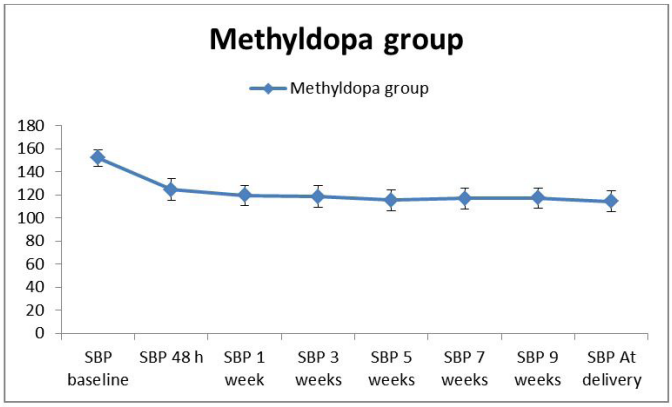

Figure 3: Comparison between systolic blood pressure measurements starting before treatment (baseline) overtime till delivery in methyldopa group

	Labetalol group		P value
	Mean	SD	
SBP baseline	152.30	6.76	---
SBP 48 h	119.27	8.63	< 0.001
SBP 1 week	115.26	8.64	< 0.001
SBP 3 weeks	112.23	7.85	< 0.001
SBP 5 weeks	112.33	10.63	< 0.001
SBP 7 weeks	104.33	9.45	< 0.001
SBP 9 weeks	105.62	8.48	< 0.001
SBP At delivery	100.70	6.05	< 0.001

Table 4: Comparison between systolic blood pressure measurements starting before treatment (baseline) overtime till delivery in labetalol group

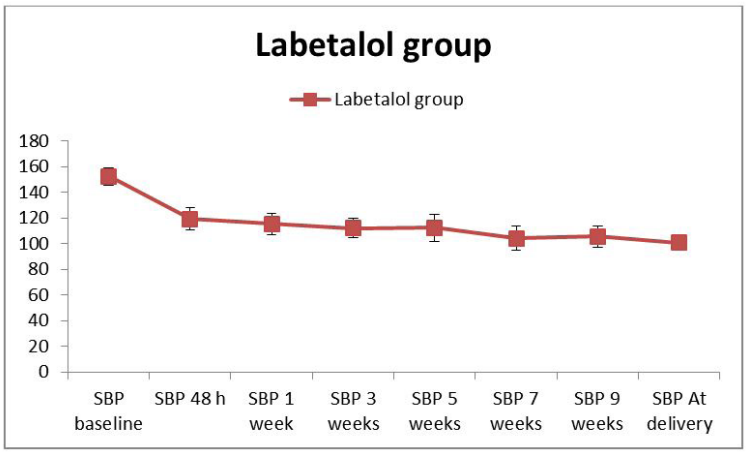

Figure 4: Comparison between systolic blood pressure measurements starting before treatment (baseline) overtime till delivery in labetalol group

	Methyldopa group		P value
	Mean	SD	
DBP baseline	99.77	6.14	---
DBP 48 h	89.92	9.26	< 0.001
DBP 1 week	87.39	8.87	< 0.001
DBP 3 weeks	86.81	8.00	< 0.001
DBP 5 weeks	85.43	8.70	< 0.001
DBP 7 weeks	81.11	5.91	< 0.001
DBP 9 weeks	80.20	6.22	< 0.001
DBP At delivery	78.60	5.22	< 0.001

Table 5: Comparison between diastolic blood pressure measurements starting before treatment (baseline) overtime till delivery in methyldopa group

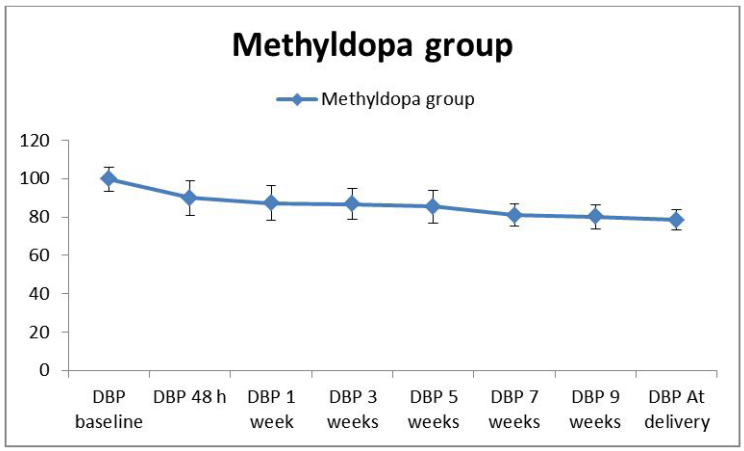

Figure 5: Comparison between diastolic blood pressure measurements starting before treatment (baseline) overtime till delivery in methyldopa group

	Labetalol group		P value
	Mean	SD	
DBP baseline	99.89	6.00	---
DBP 48 h	85.32	8.85	< 0.001
DBP 1 week	82.17	5.25	< 0.001
DBP 3 weeks	80.04	4.49	< 0.001
DBP 5 weeks	79.05	4.49	< 0.001
DBP 7 weeks	77.58	4.55	< 0.001
DBP 9 weeks	76.12	5.71	< 0.001
DBP At delivery	73.55	7.93	< 0.001

Table 6: Comparison between diastolic blood pressure measurements starting before treatment (baseline) overtime till delivery in labetalol group

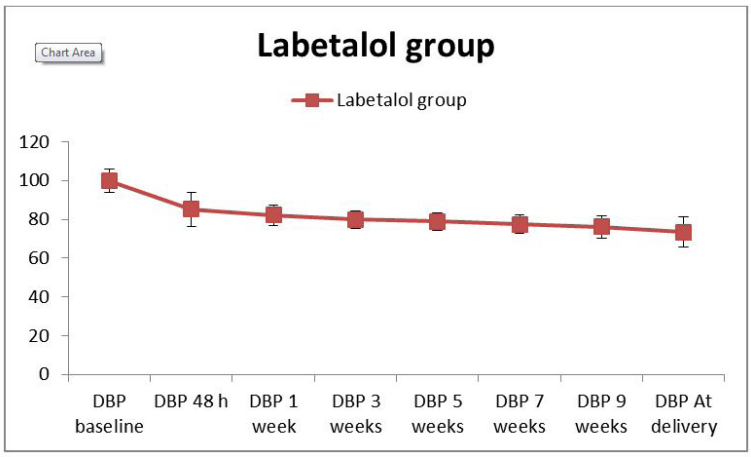

Figure 6: Comparison between diastolic blood pressure measurements starting before treatment (baseline) overtime till delivery in labetalol group

	Methyldopa group		P value
	Mean	SD	
MABP baseline	117.04	4.78	---
MABP 48 h	101.48	6.36	< 0.001
MABP 1 week	98.10	6.85	< 0.001
MABP 3 weeks	97.31	6.43	< 0.001
MABP 5 weeks	95.35	6.37	< 0.001
MABP 7 weeks	92.97	5.04	< 0.001
MABP 9 weeks	92.44	4.94	< 0.001
MABP At delivery	90.38	4.64	< 0.001

Table 7: Comparison between mean arterial blood pressure measurements starting before treatment (baseline) overtime till delivery in methyldopa group

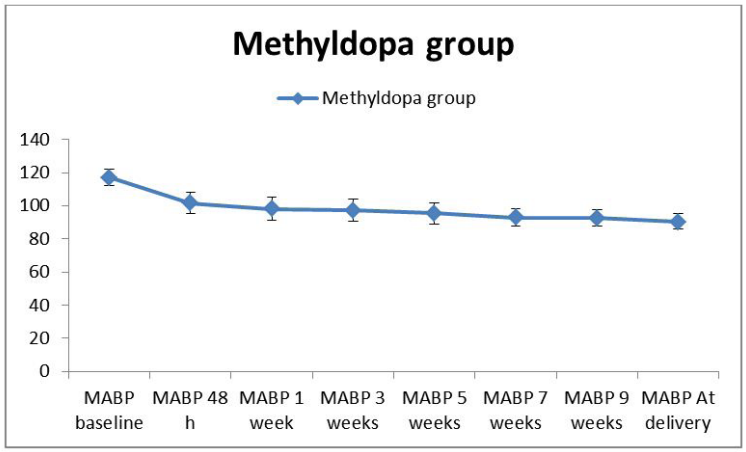

Figure 7: Comparison between mean blood pressure measurements starting before treatment (baseline) overtime till delivery in methyldopa group

	Labetalol group		P value
	Mean	SD	
MABP baseline	117.19	4.70	---
MABP 48 h	96.63	7.10	< 0.001
MABP 1 week	93.19	4.05	< 0.001
MABP 3 weeks	90.66	3.66	< 0.001
MABP 5 weeks	90.04	4.79	< 0.001
MABP 7 weeks	86.41	4.24	< 0.001
MABP 9 weeks	85.86	4.69	< 0.001
MABP At delivery	82.51	5.49	< 0.001

Table 8: Comparison between mean arterial blood pressure measurements starting before treatment (baseline) overtime till delivery in labetalol group

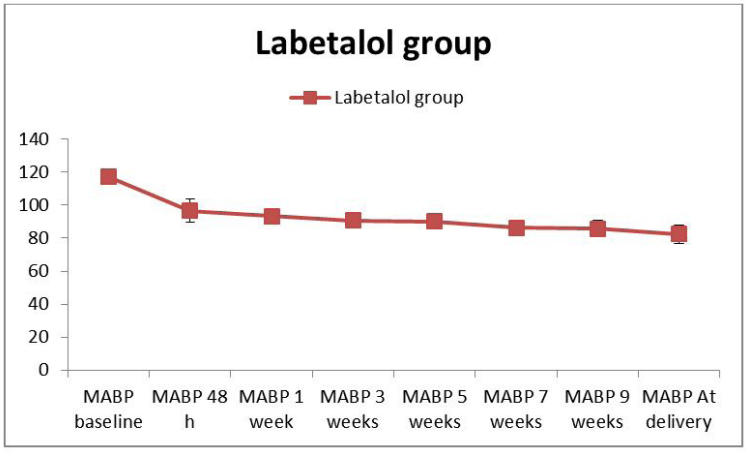

Figure 8: Comparison between mean arterial blood pressure measurements starting before treatment (baseline) overtime till delivery in labetalol group

Discussion

PIH is a major cause of fetal and maternal morbidity and mortality and protection from its development is not always possible as its pathology is not completely predictable .Various medications are used in controlling hypertensive abnormalities during pregnancy [13].

In a Study made by Verma *et al*. denoted that adverse outcome was evidently less in the labetalol treated pregnant women compared to the methyldopa group [10].

In a study made by El-Qarmalawi *et al*. patients received methyldopa experienced side-effects as drowsiness (22.2%), headache (14.8%), nasal congestion (7.4%), and postural hypotension (5.6%). While 96 pregnant ladies in labetalol group complained from dyspnea, no other side-effects were documented [14].

In the present study, there is a decrease in the systolic blood pressure readings starting from a baseline which was the blood pressure before intake of the antihypertensive treatment and the measurements after 48 hours, 1, 3, 5, 7, 9 weeks after drug intake and at time of delivery in the methyldopa and labetalol group.

Verma *et al*. made a study and mentioned the age distribution which showed maximum patients between 19-24 years in both groups (64.44% in methyldopa group and 57.77% in labetalol group) and there was no significant difference in age distribution in both groups [13].

In the present study, there was a decrease in the diastolic blood pressure readings starting from a baseline which was the blood pressure before intake of the antihypertensive treatment and the measurements after 48 hours, 1, 3, 5, 7, 9 weeks after drug intake and at time of delivery in the methyldopa and labetalol group.

Most common age group is in contrast to the data obtained from a large database study indicate a linear relationship between age and incidence of PIH [15].

In the present study, there was a decrease in the mean arterial blood pressure readings starting from a baseline which was the blood pressure before intake of the antihypertensive treatment and the measurements after 48 hours, 1, 3, 5, 7, 9 weeks after drug intake and at time of delivery in the methyldopa and labetalol group.

In a study made by Dharwadkar MN *et al*. about 32.5 percent of the pregnant ladies in Methyldopa group and 37.5% in Labetalol group were primigravidae. The rest of the patients were multigravidae. However the percentage of primigravidae is greater in most other studies where the prevalence of primigravidae was 50% or above [16,17,22].

In the present study, our results show a statistically significant difference in control of blood pressure with values of systolic, diastolic and mean arterial blood pressure measurements are less in labetalol group than in methyldopa group after 48 hours, 1, 3, 5, 7, 9 weeks post drug therapy and at time of delivery with P value < 0.001 indicating a better control of blood pressure.

Labetalol is an effective antihypertensive drug which decreases both systolic and diastolic BP in pregnancy induced hypertension. About 55% of the methyldopa group received nifedepine and phenobarbitonewhere as only 22.5% of labetalol group received injections of labetalol and phenobarbitone showed that methyl dopa requires additional drugs to decrease BP than labetalol [18].

In a previous study demonstrated that labetalol is an efficient drug in decreasing blood pressure of the patients and then maintain optimal BP levels [22].

Similarly, Cruickshank *et al*. study revealed that Labetalol controlled the blood pressure in 45 of the 51 treated women (88%) within 24 hrs [19,20].

Marked decrease of both systolic and diastolic pressure within 24 and 48 hours from the onset of using methyldopa was observed by Hans and Kopelman [21].

Also in the present study, there was a considerable difference in pregnant women who developed proteinuria after the same dose of treatment by both drugs, as in the group of women received methyldopa there was 8 ladies developed proteinuria checked at time of delivery while in labetalol there was only one lady who had proteinuria at time of delivery with P value of 0.036 ,indicate a statistically significant value that denotes better control of arterial blood pressure and prevention of progression to preeclampsia with labetalol than with methyldopa treatment.

Future researches can be made on a larger number of pregnant women to compare various drugs used in treatment of hypertension.

Conclusion

The present study confirms that labetalol is an effective and safe drug for use and is more rapid in achieving adequate control of blood pressure in PIH. With a low chance of fetomaternal side-effects and this makes it appropriate to be used in PIH. Labetalol gives good control of blood pressure than methyldopa and decreases the liability for proteinuria and for progression to preeclampsia.

Labetalol has the advantage of decreasing peripheral vascular resistance with no decrease in cardiac output of the mother and heart rate and so better uteroplacental perfusion than methyldopa.

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