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Outcome of Labetalol and Methyldopa as Oral Antihypertensive Agent in the Treatment of Pregnancy Induced Hypertension

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Abstract

Background: In a developing country like Bangladesh pregnancy induced hypertension is an important medical problem and a major cause of maternal and perinatal mortality and morbidity. Antihypertensive drugs are often used to lower blood pressure and also help in reducing maternal and fetal complications. Objective: To compare the efficacy and safety of labetalol and methyldopa in management of pregnancy induced hypertension. Methods: A total of 100 patients having newly onset hypertension during pregnancy were taken and divided randomly into two groups. Group A was given labetalol and group B methyldopa. In both groupsmean blood pressure was measured on 1stday as pretreatment and at 48th hour and 8th day as post-treatment measurement, total dose of each drug require per day and side effects were recorded.Reduction in blood pressure, doseand side effects were compared. Results: Labetalol treated group of patients showed significant fall in mean blood pressure from 1st day to 48th hour and 1st day to 8th day.In patients treated with labetalol mean blood pressure on 1st day was 123.9 ± 17.11 mmHg and was controlled to 100.03 ± 6.38 mmHg on 48th hour and 94.13 ± 4.3 mmHg on day 8, while in methyldopa treated group on 1st day was 121.23 ± 13.597 mmHg which was reduced to 105.8 ± 6.53 mmHg on 48th hour and 97.96 ± 4.11 mmHg on day 8.The mean drug dosage required to control BP in group A was 380 ± 259.5 mg and in group B was 1540 ± 503.45 mg. Group A had less side effects. Conclusion: Labetalol is safe more efficacious and quicker control of blood pressure withless maternal adverse effects and thus advantageous over methyldopa.

Key words: Labetalol, Methyldopa, Hypertension, Pregnancy.

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Introduction

Hypertensive disorder is the most common medical problem encountered in pregnancy with a high perinatal and maternal mortality & morbidity.1 Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. Fetal mortality rate is thought to be on the order of 5,00,000 per annum.2 PIH is responsible for approximately 31% maternal mortality in developing countries of which 24.7% is due to eclampsia.3 Hypertension during pregnancy is defined as a diastolic blood pressure of ≥ 90 mm of Hg on two occasions >4 hours apart or a single reading of diastolic blood pressure >110 mm of Hg.4 The risk of developing severe hypertension is reduced to half by using antihypertensive medications.5 In PIH, first-line medicines are Methyldopa, Labetalol or oxprenolol; Second-line medicines are Hydralazine, Nifedipine, Prazosin. Medicines to avoid are ACE inhibitors and angiotensin-II receptor blockers, diuretics, beta blockers except labetalol and oxprenolol, calcium-channel blockers except nifedipine during pregnancy.6 α-methyldopa was most commonly used but it takes longer time to act and also less efficacious7 and has side-effects such as drowsiness, headache, nasal congestion, postural hypotension.8 The Recent United Kingdom (UK) guidelines from the National Institute of Health and Clinical Excellence (NICE) recommend oral Labetalol as the first line choice in the treatment of hypertension in pregnancy.9 Patients receiving labetalol complained of dyspnoea, no other side-effects were noticed.8 α-methyldopa has often been used as a control while comparing the effect of different drugs. Labetalol has also been successfully used for treatment of hypertensive disorder in pregnancy. As there is less evidence to establish in favour of labetalol as antihypertensive in pregnancy induced hypertension. So this study will compare the effect of labetalol versus methyldopa in PIH (pregnancy induced hypertension).

Materials and methods

The study was a prospective, comparative study conducted in the Department of Pharmacology and Therapeutics, Sher-E-Bangla Medical College, Barisal and in the department of Gynaecology and Obstetrics, Sher-E-Bangla Medical College Hospital, Barisal and Gazi Medical College Hospital, Khulna From 1st July 2015 to 30th June 2016. All the admitted patients of 20-40 weeks of gestation, Singleton pregnancy with New onset of hypertension without prior antihypertensive treatment were included in this study whereas patient with chronic hypertension, DM, CCF, Bronchial asthma, multiple pregnancy, APH and labour pain were excluded. Total 100 patients were enrolled in this study. All patients were selected consecutively after considering inclusion and exclusion criteria. An informed written consent was obtained from the patient. A questionnaire was prepared considering key variables like age, gestational age, blood pressure,Total dose of each drug require per day, adverse effects & investigations and the data was collected. According to the enrollment criteria one hundred patients were enrolled and divided into two groups, experimental group A and experimental group B. Group Aconsisted of 50 patients and received Tab labetalol (Labeta) 100mg/200 mg and Group B consisted of 50 patients and received Tab methyldopa (Sardopa) 250 mg. Before giving treatment, blood pressure, pulse rate, fetal heart rate, USG of gravid uterus for pregnancy profile and blood

sugar were examined.

Group A Patients received Tab. Labetalol. For Patient with diastolic BP 90-109 mmHg, the starting dose of labetalol was 100mg stat and 12hourly and with diastolic BP ≥ 110 mmHg the starting dose was 200 mg stat and 12 hourly. Depending upon the response to treatment, the dose of labetalol was doubled every 48 hours upto maximum 400mg 12 hourly to achieve diastolic blood pressure < 90 mmHg.Group B Received Tab. Methyldopa. For patient with diastolic BP 90-109 mmHg the starting dose of methyldopa was 250 mg stat and 6 hourly and with diastolic BP ≥ 110 mmHg the starting dose was 500mg stat and 6 hourly. Depending upon the response to treatment, the dose of methyldopa was doubled every 48 hours up to a maximum 2gm per day to achieve diastolic blood pressure < 90 mmHg. The patients were followed up (BP, pulse rate, fetal heart rate, dose of the drug, edema and maternal side effects) at 48th hour and 8th day after initiationof treatment.

All data were checked and edited after collection. Then the data were entered in the computer before analysis. Statistical analysis was done by applying paired 't' test for the difference in pre and post treatment values. For inter group analysis unpaired 't'-test and 'chi-square' test were applied. Pvalue <0.05 was taken as significant. Data analysis was done by computer aided statistical software SPSS and Data were presented in the form of tables and graphs.

Results

Among the participants the mean age in the labetalol treated group (A) was 26.16 ± 4.94 years and in the methyldopa treated group (B) was 24.54 ± 4.99 years and 't' value is 1.629; p > 0.05. In the labetalol treated group, the mean gestational age was34.9 ± 3.65 weeks and in the methyldopa treated group was35.78 ± 3.72 weeks and 't' value is 1.19; p > 0.05. Mean of MBP before treatment in labetalol and methyldopa treated group 123.9 ± 17.11 and 121.23 ± 13.59 respectively; p >0.05.The difference between the two groups was statistically not significant with regards to mean age of patient, gestational age, and mean blood pressure distribution.

Table 01: Comparison of demographic profile of patients

Variables	Mean ± Std. Deviation		't' value	*p* value
	Labetalol (G-A)	Methyldopa (G- B)		
Age of patient	26.16 ± 4.94	24.54 ± 4.99	1.629	NS
Gestational age	34.9 ± 3.65	35.78 ± 3.72	1.19	NS
Mean blood pressure before treatment	123.9 ± 17.11	121.23 ± 13.59	0.864	NS

* ***Unpaired 't'*** **– test was done to measure the difference between two groups.**

* **NS means not significant.**

In group A, the mean MBP prior to treatment was 123.9 ± 17.11mmHg that was reduced to 100.03 ± 6.389mmHg on the 48th hour of treatment. Reduction of MBP was statistically significant (p<0.001), compared to pretreatment value.In group B, the mean MBP prior to treatment was121.23 ± 13.597 mmHg and reduced to 105.8 ± 6.539 on the 48th hour of treatment. The reduction of MBP was statistically significant (p<0.001).

Table 02: Comparison ofpre and post treatment (at 48th hour) mean MBP with labetalol and methyldopa.

Group	Mean ± Std. Deviation		*'t'* value	*p*
	Pre-treatment mean BP(mmHg)	Post- treatment (at 48th hour) mean BP(mmHg)		
Labetalol (G - A)	123.9 ± 17.11	100.03 ± 6.389	13.449	<0.001
Methyldopa (G - B)	121.23 ± 13.597	105.8 ± 6.539	11.882	< 0.001

*** *Paired 't'* – test was done to measure the difference between two groups.**

In the labetalol treated group, the mean MBP prior to treatment was 123.9 ± 17.11 mmHg that was reduced to 94.13 ± 4.302 mmHg on the 8th day of treatment. Reduction of MBP was statistically significant (p<0.001). In the methyldopa treated group, the mean MBP prior to treatment was121.23 ± 13.597 mmHg and reduced to97.966 ± 4.115 on the 8th day of treatment. Reduction of MBP was statistically significant (p<0.001), compared to pretreatment average mean BP value.

Table 03: Comparison of pre and post treatment (at 8th day) mean MBP with labetalol and methyldopa.

Group	Mean ± Std. Deviation		*'t'* value	*p*
	Pre-treatment mean BP(mmHg)	Post- treatment (at 8th day) mean BP(mmHg)		
Labetalol (G - A)	123.9 ± 17.11	94.13 ± 4.302	14.479	<0.001
Methyldopa (G - B)	121.23 ± 13.597	97.966 ± 4.115	15.461	< 0.001

*** *Paired 't'* – test was done to measure the difference between two groups.**

Comparison of mean MBP at 48th hour and 8th day of treatment with labetalol and methyldopa, Labetalol decreases BP more compared to methyldopa and in every situationthe difference was statistically significant (p <0.001).

Table 04: Comparison of mean MBP at 48th hour and 8th day of treatment with labetalol and methyldopa.

Variables	Labetalol (G - A)	Methyldopa (G - B)	*'t'* value	*p*
Mean BP(mm Hg) at 48^{th} hour	100.03 ± 6.389	105.8 ± 6.539	4.263	< 0.001
Mean BP (mm Hg) at 8^{th} day	94.13 ± 4.302	97.966 ± 4.115	4.566	<0.001

* ***Unpaired 't'*** **– test was done to measure the difference between two groups.**

Mean total dose of drugs per day required to control BP by labetalol and methyldopa was 380 ± 259.51 mg and 1540 ± 503.45 mg respectively.

Table 05: Mean drugs dosage received by the patients.

Group	N	Mean ± SD (mg)
Labetalol (G - A)	50	380 ± 259.51
Methyldopa (G - B)	50	1540 ± 503.45

In group A, patients developed drowsiness, headache, nasal congestion, postural hypotension and dyspnoea were 0 (0%), 1 (2%), 1 (2%), 1 (2%) and 2 (4%) and with methyldopa were 12 (24%), 9 (18%), 7 (14%), 3 (6%) and 0 (0%) respectively. On comparison methyldopa significantly causes more drowsiness, headache and nasal congestion and the incidence of Postural hypotension and dysponea in both group were not significantly different.

Table 06: Comparison of adverse effects of labetalol and methyldopa.

Adverse effects	Labetalol (n =50) No of patient	Percentage	Methyldopa (n = 50) No of patient	percentage	χ^2	p
Drowsiness	0	0	12	24	13.636	<0.001
Headache	1	2	9	18	7.11	<0.01
Nasal congestion	1	2	7	14	4.892	<0.05
Postural hypotension	1	2	3	6	1.04	NS
Dysponea	2	4	0	0	2.04	NS

* **X2 – test was doneto measure the difference between two groups.**
* **< 0.001 means significant.**
* **<0.01 means significant.**
* **<0.05 means significant.**
* **NS means not significant**

Discussion

In this study all patients were aged between 18 – 40 years. The mean age was 26.16 years inlabetalol treated group (A), and 24.54 years in methyldopa treated group (B). A clinical trial by Janyanthy et al.10 showed that, the mean age of patients in labetalol group was 26.42 years and in methyldopa group was 26.4 years that correlates with the result of our study. Similar result was obtained from the study done by El-Qarmalawi et al.8, Dharwadkar et al.7 and Anagha et al.11

Almost all cases were diagnosed in third trimester of pregnancy. Most patients were between 32 -36 weeks of gestation. The mean gestational age was 34.9 weeks in group A and 35.78 weeks in group B. The result of both groups correlates with Janyanthy et al.10; El-Qarmalawi et al8 and Verma et al.12

According to this study, the mean pretreatment mean blood pressure in group A was 123.9 mmHg and in group B, that was 121.23 mmHg. The difference between the two groups was statistically not significant. A study by Verma et al.12 had shown that in methyldopa treated group the mean pre-treatment average mean BP was 118.51mmHg and in labetalol treated group 117.74 mmHg. According to Anagha et al11 on admission MAP in group A was 109.49 & group B was 109.86 mmHg. The difference in the mean pre- treatment MBP were probably due to race, geographical location, nutritional status as well as selection criteria like outpatient treatment or indoor admitted patient

In group A, the mean MBP prior to treatment was 123.9 ± 17.11mmHg that was reduced to 100.03 ± 6.389 mmHg on the 48th hour of treatment. Reduction of MBP was statistically significant ($p<0.001$), compared to pretreatment value. In group B, the mean MBP prior to treatment was121.23 ± 13.597 mmHg and reduced to 105.8 ± 6.539 on the 48th hour of treatment. The reduction of MBP was statistically significant ($p<0.001$). On comparing labetalol and methyldopa groups the mean difference in mean blood pressure at 48th hours of treatment were statistically highly significant. So labetalol is rapid acting and highly effective than methyldopa. According to a study by Dharwadkar et al.7, labetalol was superior to methyldopa on reduction of BP at 48th hours of treatment. Similar result also obtained by Bharti and Chhikara.13

In the labetalol treated group, the mean MBP prior to treatment was 123.9 ± 17.11 mmHg that was reduced to 94.13 ± 4.302 mmHg on the 8th day of treatment. Reduction of MBP was statistically significant ($p<0.001$). In the methyldopa treated group, the mean MBP prior to treatment was 121.23 ± 13.597 mmHg and reduced to 97.966 ± 4.115 on the 8th day of treatment. Reduction of MBP was statistically highly significant ($p<0.001$). At 8th day of treatment Labetalol significantly reduces MBP than methyldopa. So labetalol is highly effective than methyldopa and causes sustain control of BP. The studies done by Subhedar et al.5; El-Qarmalawi et al.7 and Anaghaet al.11 showed that labetalol significantly

decreased mean blood pressure compared with methyldopa that is similar to this study, but another study shown that labetalol and methyldopa decrease mean blood pressure approximately equally, i.e. no one is superior.12 This study shows that the mean dose required to control BP by labetalol and methyldopa was 380 ± 259.51 mg and 1540 ± 503.45 mg respectively. In labetalol group, 31 patients (62%) required a dose of 200 mg/day, 6 patients (12%) required 400 mg/day and remaining 13 patients (26%) required 800 mg/day to achieve optimal BP control. In methyldopa group out of 50 patients, 23 patients (46%) required a dose of 1000 mg/day, 24 patients (48%) required 2000 mg/day to achieve optimal BP control. The rest 3 patients (6%) were remained uncontrolled. A study by Subhedar et al.5 showed that the mean dose required to control B.P in group A (methyldopa) was 1111.11mg. In group B (labetalol) the mean dose required was 382.22 mg. Here the mean dose of labetalol corresponds to this study but methyldopa differs, so need further study.

In this study, maternal adverse effects seen with both drugs are of known types. The frequency of occurrence of drowsiness, headache and nasal congestion were significantly less in labetalol group compared to methyldopa and postural hypotension and dysponea were similar in both groups. In labetalol treated group, headache was experienced by one (2%) patient in respect to 9 (18%) in methyldopa treated groups. No patient developed drowsiness with the treatment of labetalol compared to 12 (24%) with methyldopa. In labetalol treated group, only one patient (2%) had nasal congestion while it was 7 patients (14%) for methyldopa group. One (2%) patients developed Postural hypotension with the treatment of labetalol compared to 3 (6%) with methyldopa. In labetalol treated group, 2 (4%) patients had dysponea but in case of methyldopa no patient developed dysponea. This observations had similarity with previous study conducted by EI-Qarmalawi et al.8 and Verma et al.12 Subhedar et al.5 said that most common maternal side-effect observed was headache that was equal in both groups which is dissimilar to my study.

Conclusion

Present study showed that labetalol is a bit advantageous than methyldopa in terms of better and quicker control of blood pressure. In methyldopa treated group BP of 3 (6%) patients remain uncontrolled that is dangerous for both maternal and fetal outcome. Labetalol had less maternal adverse effect compared to methyldopa but fetal outcome was not observed in this study. This study is just a step in this long way. The result of this study will help the future researchers to identify the suitable antihypertensive in management of pregnancy induced hypertension for our country. Therefore, labetalol can be considered positively in the treatment of pregnancy induced hypertension.

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