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Research Paper

Labetalol Versus Methyldopa in The Management of Severe Pregnancy-Induced Hypertension

Medical Science

KEYWORDS : Pregnancy-induced hypertension, Labetalol, Methyldopa

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ABSTRACT

Objective: To assess the efficacy and safety of labetalol compared with methyldopa in the management of severe pregnancy-induced hypertension (PIH).

Methods: A prospective hospital based study was conducted in the Department of Obstetrics & Gynecology, M.M.Medical College & Hospital, MMU, Kumarhatti, Solan from Feburary 2015 to January 2016.

Seventy eight patients with severe PIH were allocated to receive either methyldopa (group A) or labetalol (group B). Administration of drugs with respect to Age, Gravid Status, Gestational Age, Blood Pressure Control, Time taken to Control Blood Pressure, Drug dosage, Additional Treatment, Side Effects, Perinatal safety and APGAR scores were studied. The statistical level of significance was taken at P<0.05.

Results: Group A and Group B were comparable with respect to age, gravidity, gestational age and pretreatment blood pressure. Both systolic and diastolic blood pressures in labetalol group were significantly lower compared to methyldopa group at 2 hrs ('p' < 0.01 & < 0.001), 4 hrs. ('p" < 0.001 & < 0.001) and 6 hrs (P < 0.05 & P < 0.01) after treatment. Labetalol was more effective, faster anti-hypertensive action and lesser side effects when compared to methyldopa. Perinatal outcome with labetalol is comparable to methyldopa. Conclusions: Present study showed that labetalol is more advantageous than methyldopa in terms of better and quicker control of blood pressure. Labetalol has comparatively less maternal side-effects with good prenatal outcome. The limiting factor in the use of labetalol is its higher cost.

INTRODUCTION

Hypertensive disorders seem to complicate approximately 10 per cent of pregnancies and are important causes of maternal and fetal morbidity and mortality[1]. Preeclampsia and eclampsia contribute to death of a woman every 3 minutes worldwide[2,3]. The disease accounts for 24% of all maternal deaths in India[4]. The benefits of acute pharmacological control of severe hypertension prior to and/or post delivery are generally accepted. Most of the drugs commonly used in the management of severe hypertension in pregnancy have significant maternal and/or neonatal adverse/side effects.

Methyldopa is the oldest drug used for PIH. It is effective and safe for both the mother and fetus. The main disadvantages are a delayed onset of action, drowsiness, depression, fluid retention and nasal congestion in mother. It may also give false positive coomb's test in 20% and may cause hemolytic anemia, systematic lupus erythematosus like syndrome and hepatic damage[5].

Labetalol is a rather unique substance in that, it has both selective, competitive alpha-1 and non selective, competitive beta adrenergic blocking actions. Labetalol has a quicker onset of action and does not result in reflex tachycardia[6]. In terms of fetal effects, blood pressure reduction with labetalol does not result in fetal distress[6,7]. As with all beta-blockers, labetalol has been associated with hypoglycemia, bradycardia and hypertension but neonatal outcome is uniformly good[6,8,9]. Labetalol has some interesting and potentially important non- antihypertensive effects that may be beneficial in Preeclampsia. Among these are antiplatelet aggregation action, a thromboxane reducing effect, and a fetal lung maturation accelerating influence[10,11,12].

This study was planned to assess and compare efficacy of methyldopa and labetalol in controlling blood pressure in patients with PIH and to study maternal and perinatal outcome in Indian population.

MATERIAL AND METHODS

A prospective hospital based study was conducted in the Department of Obstetrics & Gynecology, M.M.Medical College & Hospital, MMU, Kumarhatti, Solan from Feburary 2015 to January 2016.

Ethical committee approval was obtained. Written informed consent was obtained from all the patients.

Population being investigated: Pregnancy Induced Hypertensive women after 20 weeks of pregnancy coming to M.M.Medical College & Hospital, MMU, Kumarhatti, Solan on IPD basis from Feburary 2015 to January 2016.

Inclusion Criteria: Diagnosed PIH patients based on criteria-BP more than 160/110 mm Hg, proteinuria 2+ dipstick in midstream urine sample, and after 20 weeks of pregnancy till term.

Exclusion Criteria: Patients with the following diseases/conditions were excluded. Multifetal pregnancy, and women with preexisting or concurrent medical disorders like diabetes mellitus, cardiac diseases, bronchial asthma, renal disease, thyrotoxicosis, hemophilia, depression and chronic hypertension

attributable to hypertension during their pregnancy. Patients who had taken any antihypertensive drug within 48 hours of hospitalization were also excluded.

STUDY GROUPS: 78 patients were allotted to either of the groups:

Group A: Received Methyldopa 500 mg q.i.d. orally.

Group B: Received Labetalol 400 mg t.d.s. orally.

Tab. nifidipine 5-10 mg. was added if the B.P. control was not achieved by the drug under study or signs and symptoms of severity of the disease persisted or started increasing while on the drug under study. Other antihypertensive drugs were added as per the requirement of the individual patient and the standard regimen. if the B.P. control was not achieved by the second line antihypertensive drug. Target blood pressure was Systolic B.P. of <160 mm Hg and Diastolic B.P. of <100 mm Hg[13]. All patients were subjected to detailed history, general physical examination and systemic examination after taking informed consent. The antihypertensive drugs under study were evaluated in terms of

- Control of Blood Pressure
- Side effects of the drugs
- Perinatal outcome

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Statististical Analysis : The results thus obtained were subjected to standard

statistical analysis and analyzed using the Chi-square test.

A p value of less than 0.05 was considered statistically significant.

OBSERVATIONS:

The mean age of the patients in Group A was 23.1 ± 4.3 yrs and in group B was 23.0 ± 3.2 yrs (Table 1). In the present study, 53 patients were primigravidae, 30patients (62.5%) in methyldopa group and 23 patients (76.7%) in labetalol group. The difference between the two groups was statistically non significant with regards to mean age, period of gestation and parity distribution (Table 1, Table 2).

On comparing the two drugs, the systolic and diastolic blood pressures on admission in Group A and Group B were comparable (Table 3).

Both systolic and diastolic blood pressures in labetalol group are significantly lower compared to methyldopa group at 2 hrs. ('p' < 0.01 & < 0.001), 4 hrs. ('p" < 0.001 & < 0.001) and 6 hrs (P < 0.05 & P < 0.01) after treatment (Table 3).

Table 4 shows that labetalol took statistically significant less time to control blood pressure compared to methyldopa. (p value <0.01)

Table 5 shows that out of 48 patients in group A, only 22 (45.8%) cases achieved target BP with methyldopa alone. In 26 cases (54.1%) second line antihypertensive had to be given. In group B, 30 cases received oral labetalol as first line antihypertensive and BP was controlled in 27 (90%) cases. There is a statistically significant difference in between the two groups with respect to the number of patients whose blood pressure was controlled (p value,0.001)(table 5)

In the present study, most common side-effect observed was drowsiness. 7 patients in methyldopa grouop experienced this symptom. None of the patients labetalol group had this symptom. The other side observed in the methyldopa group headache, dry mouth, nasal stuffiness, nausea and low mood. Postural hypotension was observed in one patient in labetalol group and none in the methyldopa group(Table 6). The present study shows that methyldopa is associated with more side effects.

Regarding the prenatal outcome, no statistically significant difference was found in Apgar score at 1 min in either group None of the neonates had bradycardia. Hypoglycemia was observed in 1 case in group A, 2 cases in group B and 1 case in group C but there was no statistically significant difference.

Likewise there was no statistically significant difference in complications like jaundice, meconium aspiration syndrome, respiratory distress syndrome & peripheral circulatory failure in the three comparison groups.

DISCUSSION

Pregnancy induced hypertension affects young females, the mean age was 23.1 years in methyldopa group and 23.0 years in labetalol group. Maximum number of patients were primi gravidae, 30 patients (62.5%) in methyldopa group and 23 patients (76.7%) in labetalol group. Maximum number of patients were in the age group of 15 to 24 years in both the groups among the total 180 patients in the study conducted by Subhedar V et al[14]. Gravidity distribution in their study showed maximum patients of PIH as primigravidae in both the groups[14].

The pretreatment mean systolic blood pressure at in group A and group B was 170.54 ± 11.5 mmHg and 169.6 ± 13.3mm Hg respectively. The mean diastolic blood pressure in group A was 113.8 ± 6.8 mmHg and in group B was 112.4 ± 5.5 mm Hg respectively.

The diference between mean systolic BP and mean diastolic BP in methyldopa and labetalol groups at 2, 4 & 6 hours after therapy was statistically significant. Labetalol group was characterized by significantly lower systolic and diastolic blood pressures.

Labetalol treatment has been shown to effectively control hypertension during pregnancy[5,8,14,15] conducted a study to assess the efficacy and safety of labetalol compared with methyldopa in the management of pregnancy-induced hypertension One hundred four primigravidas with PIH were randomly allocated to receive either labetalol (group A) or methyldopa (group B).Target was to maintain a mean arterial blood pressure < or = 103.6 mmHg. Labetalol was found to be quicker and more efficient at controlling blood pressure. In the present study alls, the mean time taken to control blood pressure was significantly less in the labetalol group.

Lamming et al[8] treated nineteen pregnant patients whose mean arterial pressure (MAP) was persistently greater than or equal to 103.3 mmHg with labetalol or methyldopa. Significant fall (P less than 0.001) in BP only occurred in the group treated with labetalol, and daily BP control was better in this group.

In pregnant women with hypertension, the peak serum level of labetalol has been shown to occur within 20-60 minutes[16]. Labetalol takes an hour to have a significant effect[17]. The usual oral dose of methyldopa produces it's maximal anti hypertensive effect in 6-8 hours, and the effect can persist for up to 24 hours[18]. In our study, nifedipine had to be administered in 26 cases of methyldopa group during hypertensive crisis which explains antihypertensive action within 2-4 hours seen in this group in our study.

Drowsiness (14.58%), nasal stuffiness (8.33%), headache (6.25%), dry mouth (6.25%) and depression (2.08%) were the symptoms reported in decreasing frequency in methyldopa group.

Methyldopa regularly causes sedation. After a single dose this is of shorter duration than the hypotensive effect and it tends to decrease with continued medication. However a persistent lassitude and drowsiness particularly disturbing to individuals doing mental work represent the overall most important side effects. Dry mouth and nasal stuffiness may also be central in origin[19].

Labetalol were found to have less side effects compared to methyldopa as drowsiness, nasal stuffiness ,headache, dry mouth, low mood were not reported with labetalol.

In Group B (oral labetalol), one patient reported postural hypotension Labetalol interferes with the innervations of the α receptor and symptoms of postural hypotension might be expected to result. However, it is not often a problem with labetalol as the α inhibition is competitive at usual dosage levels. The increased endogenous sympathetic traffic partly overcomes the competitive block therefore a positive fall does not occur[20].

Our results are in accordance with Michael et al[12], who reported that labetalol did not cause significant side effects in pregnant patients, postural hypotension occurred in four patients, scalp tingling in two, and lethargy, headache, and generalized rash in one patient. It was not necessary to discontinue the drug because of side effects.

Redman et al, reported that the most common side effect with

labetalol has been the acute onset of tremulousness or shakiness which must be distinguished from impending eclampsia. In our study this side effect was not observed.

The mean apgar score at 1 minute in group A was 7.5 ± 2.6, while in group B and group C, it was 8.1±2.2 and 7.6±2.4.There was no statistically significant difference found in either of the comparison groups.

No difference existed in the mean Apgar scores in the babies in the methyldopa and labetalol treated groups in the study of Lamming et al[15] which is in accordance to our study.

None of the neonates had bradycardia. Hypoglycemia was observed in 1 case in group A (methyldopa group), 2 cases in group B (oral labetalol) & 1 case in C (oral+iv labetalol) but there was no statistically significant difference. Hypoglycemia was transient and clinically insignificant.

Labetalol does not cause clinically important sympathetic blockade in the mature newborn infant[22].It is in agreement with our study.

Treatment with beta-blockers during pregnancy has been associated with neonatal hypoglycemia[23]. Clinically significant fetal hypoglycemia does not usually occur during treatment with labetalol[14]. It is in agreement with our study.

Likewise complications like jaundice, meconium aspiration syndrome, respiratory distress syndrome & peripheral circulatory failure occurred at comparable rates in the two study groups.

NICU admission & neonatal mortality rate was similar in the two comparison groups. Cochrane database systemic review 2003 reported that there is no statistically significant difference in methyldopa and beta blocker group regarding the incidence of admission to special care unit.

CONCLUSION

Present study showed that labetalol is more advantageous than methyldopa in terms of better and quicker control of blood pressure. Labetalol has comparatively less maternal side-effects with good prenatal outcome. The limiting factor in the use of labetalol is its higher cost.

Competing interests: There are no competing interests to declare

Table 1
BASELINE PARAMETERS OF THE STUDY GROUPS

	Gp A (Methyldopa) (n = 48)	Gp B (Labetalol)(n = 30)	P value
Age (years) Mean ± SD	23.1 ± 4.3	23.0 ± 3.2	NS
Period of gestation (weeks) (mean ± SD)	36.7 ± 3.9	36.7 ± 3.8	NS

Table 2
DISTRIBUTION OF PARITY IN THE STUDY GROUPS

Parity	Gp (Methyldopa) (n = 48)	Gp B (Labetalol) (n = 30)	**P value**
Primi	30	23	NS
G2	7	4	
G3	3	1	
G4	6	1	
G5	2	1	

Table 3
COMPARISON OF BLOOD PRESSURES OF STUDY GROUPS

	Gp A (Methyldopa) (n = 48)	Gp B (Labetalol) (n = 30)	**P value**
Pretreatment Systolic B.P. Diastolic B.P.	 170.54 ± 11.5 113.8 ± 6.8	 169.6 ± 13.3 112.4 ± 5.5	 N.S. N.S.
2 hrs after treatment Systolic B.P. Diastolic B.P.	 162.4 ± 13.0 106.4 ± 8.9	 153.1 ± 12.9 97.1 ± 7.6	 P < 0.01 P < 0.001
4 hrs after treatment Systolic B.P. Diastolic B.P.	 159.4 ± 19.7 105.6 ± 8.7	 144.3 ± 14.9 95.4 ± 8.0	 P < 0.001 P < 0.001
6 hrs after treatment Systolic B.P. Diastolic B.P.	 157.7 ± 15.7 105.6 ± 8.7	 150.8 ± 10.8 94.2 ± 6.7	 P < 0.05 P < 0.01

Table 4
MEAN TIME TAKEN TO CONTROL BLOOD PRESSURE

	Gp A (Methyldopa) (n = 22)	Gp B (Labetalol) (n = 27)	P value
Mean ±SD(Min)	272 ±127.80	130.55±115.6	<0.01

Table 5
BLOOD PRESSURE CONTROL ACHIEVED WITH 1ST LINE ANTIHYPERTENSIVE DRUGS

	Gp A (Methyldopa) (n = 48)	Gp B (Labetalol) (n = 30)	P value
B.P. Controlled	22	27	<0.001
B.P. Uncontrolled	26	3	

Table 6
COMPARISON OF SIDE EFFECTS OF DRUGS

	Gp A (Methyldopa) (n = 48)		Gp B (Labetalol) (n = 30)	
	No.	%	No.	%
Drowsiness	7	14.58	-	-
Headache	3	6.25	-	-
Dry Mouth	3	6.25	-	-
Nasal Stuffiness	4	8.33	-	-
Nausea	2	4.17	-	-
Postural Hypotension	-	-	1	3.33
Low mood	1	2.08	-	-

Table 7
COMPARISON OF PERINATAL OUTCOME IN STUDY GROUPS

Perinatal outcome	Gp A (Methyldopa) (n = 45)	Gp B (Labetalol) (n = 29)	P value
1 minute Apgar Score(Mean ± S.D.)	7.6 ± 2.6	8.1 ± 2.2	N.S.
Hypoglycemia	1	2	
Jaundice	4	2	
Meconium Aspiration Syndrome	5	1	
Respiratory Distress Syndrome	3	4	
Peripheral Circulatory Failure	1	1	

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