



A Comparative Study of Perinatal Safety and Antihypertensive Efficacy of Methyldopa and Labetalol in Treatment of Hypertension in Pregnancy

Authors

Dr Sony Khedia¹, Dr Barkha Gurjar², Dr R.P. Rawat³

¹Assistant Prof. (Obg & Gynae) GMC Kota, ²GMC Kota, ³Sr. Prof Obg, GMC Kota

Introduction

Hypertensive disorders are the most common medical complications of pregnancy and are an important cause of maternal and perinatal morbidity worldwide¹. These include preeclampsia and eclampsia.

Gestational hypertension is defined as de novo rise in BP >140/90mmHg after mid pregnancy (20weeks) and distinguished from preeclampsia by the absence of proteinuria. Gestational hypertension is termed transient hypertension if preeclampsia does not develop and blood pressure has returned to normal by 12 weeks postpartum. It is considered mild when BP>140/90 mm Hg and severe when BP>160/110 mm Hg².

Pre-eclampsia is characterized by a rise of BP >140/90 mmHg after 20 weeks of gestation with proteinuria³. Proteinuria is described as 300 mg or more of urinary protein per 24 hours or persistent 30 mg/dl (1+dipstick) in random urine samples.

The cause of pregnancy induced hypertension (PIH) remains unknown; however placental dysfunction may initiate the systemic vasospasm, Ischemia and thrombosis that eventually damage maternal organs. Females with gestational hypertension have an increased responsiveness to a variety of endogenous substances (prostaglan-

dins, thromboxane) that can cause vasospasm and platelet aggregation⁴.

Risk factors for preeclampsia include extremes of maternal age, primigravida, multiple gestations, molar pregnancy, preexisting hypertension, diabetes mellitus, renal disease, prior history of preeclampsia and eclampsia, preexisting connective tissue disease, vascular disease and family history of preeclampsia or eclampsia.

There is very strong evidence to use antihypertensive agents in all forms of hypertension. The antihypertensive drugs in current use have good safety record with regard to both mother and baby⁵. Prompt effective treatment with variety of drugs can reduce the risk of both maternal and fetal death⁶.

Various drugs are used in gestational hypertension and preeclampsia. These include Alpha-methyl-Dopa, labetalol, nifedipine, etc. In our study we are focusing on alpha methyl-dopa and labetalol .

Aim and Objectives

Aim

To compare the antihypertensive efficacy and perinatal safety of alpha-methyldopa and labetalol in pregnancy induced hypertension.

Objectives

1. To compare the anti-hypertensive efficacy of labetalol and methyldopa.
2. To study the side effects and safety profile of the two drugs.
3. To study the effect of the two drugs on labour and fetal outcome.

Material and Method

This study was carried out in pregnancy induced hypertension patients attending antenatal clinic and those admitted in obstetric wards of J.K. LON Mother & Child Hospital and Associated Group Of Hospitals, Govt. Medical College Kota, (Rajasthan) to compare the efficacy and perinatal safety of Methyldopa and labetalol during period from July 2013 to Dec 2014. Patients were duly informed and consent was obtained before entry in the trial as per approval by Institutional ethical committee.

All pregnant hypertensive patients were screened in the above said period for conclusion in study.

Inclusion criteria for study included the following

1. A singleton pregnancy
2. Gestational age >20 weeks and
3. Blood pressure exceeding 140 and 90 mm of Hg, systolic and diastolic respectively.

Exclusion criteria included those with:

1. History of diabetes
2. Rhesus isoimmunization
3. Congestive heart failure
4. Cardiac shock
5. Asthma
6. Chronic hypertensive patients.

Hundred patients were screened and these patients were randomly divided into two groups of 50 patients each (Group A Group B). Group A received labetalol and group B received Methyldopa in appropriate doses.

Maternal and fetal status was evaluated clinically in reference to the following points:-

1. History

- History of presenting complaints

- History of antenatal visits
- Menstrual History
- Obstetric History
- Past History
- Family History
- Personal history

2. General physical examination

It was done meticulously to assess maternal condition and included:-

- Maternal pulse, Blood pressure, temperature and respiratory rate
- Pallor, icterus, cyanosis and pedal oedema
- Weight of patients

A meticulous blood pressure measurement is essential in screening patients with gestational hypertension.

Blood pressure measurement

Blood pressure measurements were taken with the patient in lateral position with the cuff placed on her right arm at the level of heart.

Blood pressure was recorded after making patient comfortable and ensuring that there was no severe exertion, eating, smoking or exposure to cold in at least the half an hour preceding the measurement.

All the tight clothing was removed from the arm. The cuff was fitted closely to the arm and centred the brachial artery.

The brachial artery was palpated with the fingers and the cuff rapidly inflated to about 30 mm Hg above the disappearance of the pulse, so that an auscultatory gap was not missed. The pressure was allowed to fall slowly with the stethoscope was placed over brachial artery. The stethoscope was held firmly and evenly, but not with excessive pressure over artery because this can cause the production of sounds below diastolic pressure.

Except for very high diastolic reading (110 mm Hg or more), all reading of 90 mm Hg or more should be confirmed after 6 hours. A regularly calibrated mercury sphygmomanometer, with appropriate sized cuff, is the instrument of choice

3. Systemic examination

Cardiovascular and respiratory systems will be examined in detail to rule out any medical disorder associated with pregnancy.

4. Obstetrical examination

Abdominal examination will be done with reference to-

- Any operative scar on the abdomen
- Symphysial-fundal height, to ascertain whether the height of uterus corresponding to the estimated gestational age.
- Abdominal girth at the level of umbilicus.
- Lie and presentation of foetus.
- Foetal heart sound, its rate, tone and rhythm were recorded.

This was followed by blood investigations, urinalysis, fundoscopy and ultrasonography (whenever possible).

In admitted patients, blood pressure measurement was done at 6 hours interval for 3 consecutive days or up to a period in which desirable blood pressure was attained. It was followed by 8 hourly blood pressure measurements. Doses were adjusted according to BP but not exceeding 800mg per day for labetalol and 2000mg per day for methyldopa. Known untoward side effects occurring during drug therapy were taken into account.

All patients in follow up were assessed for occurrence of unwanted symptoms, like alarming rise in BP, changes in body weight and proteinuria which was evaluated by means of dipstick test on a morning sample of mid stream urine. In patients

having more than a trace of proteinuria (30 mg/dl), measurement of 24 hours protein in urine was done. Blood was collected for urea, creatinine and uric acid weekly and for haemoglobin, hematocrit, platelet count, bleeding time, serum AST/ALT bimonthly and fundoscopy was done monthly.

Method of onset of labour (spontaneous or induced) and mode of delivery normal vaginal, forceps or by caesarean section was also taken into account. Any complication in the antepartum, intrapartum, and postpartum period was noted. Foetal outcome in terms of Apgar scoring and birth weight will be evaluated.

Birth weight of newborn was taken. Placental weight and ageing was done. Mothers and babies were followed at least till the third day after delivery.

Statistical analysis of the data was carried out using student's t-test. The level of significance was $P < 0.05$.

Observations and Results

At the completion of study, the number of patients in Group A and Group B were 47 & 46, respectively, as a total of 7 patients did not complete the study. Two patients (1 from each group) withdrew consent during the study while 5 patients (2 from Group A and 3 from Group B) were lost in follow up.

Thus a total of 94% in group A and 92% in Group B completed the study, collectively 93% patients complete the study.

Table 1: Demographic characteristics of patients

| | Group A (n=47) | Group B (n=46) | Combined (n=93) | P Value |
|--|-------------------|-------------------|--------------------|---------|
| Total number of patients | 47 | 46 | 93 | -- |
| Profile at booking | | | | |
| Mean Age (Years) | 23.21 | 20.51 | 22.58 | 0.24 |
| Mean weight (kg) | 62.17 | 57.58 | 58.17 | 0.62 |
| Mean arterial pressure | 115.13 | 114.32 | 114.42 | 0.73 |
| Mean gestational age at enrolment(weeks) | 29.64 | 29.84 | 29.61 | 0.94 |

Table 1 shows that mean age of group B (20.51) was slightly less than that of group A. Patients in group A had a slightly higher mean weight than group B. Above data also reveal that patients in

Group B had slightly lower mean arterial pressure than group A. Most of the patients presented around 29 weeks of gestation.

Fig 1: Distribution of cases according to age

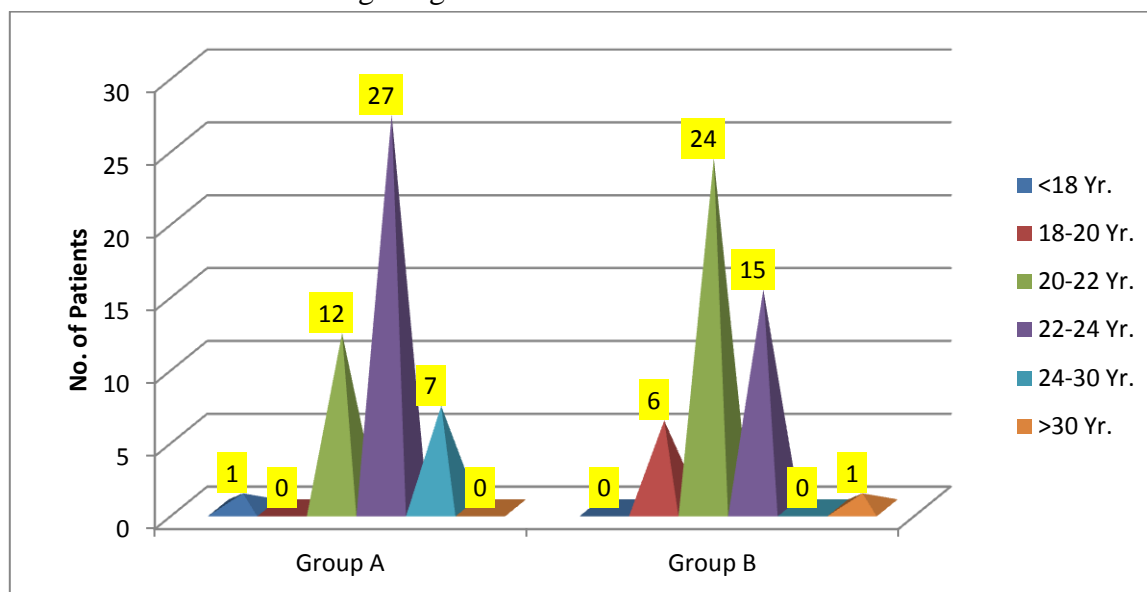


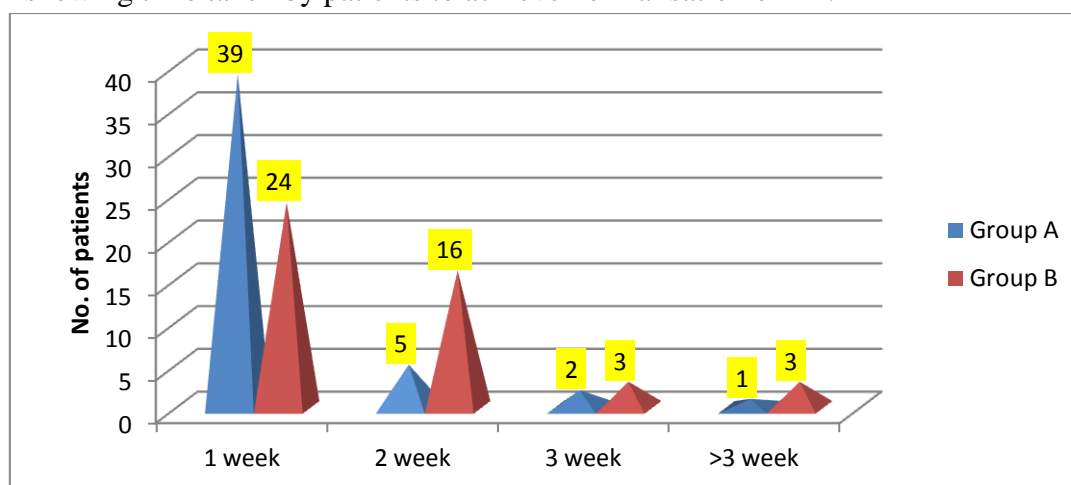
Fig 1 shows analytic data of age of patients. Most of the patients in group A and in Group B were in the range of 20-24 years.

Table 2: Distribution of cases according to obstetric history

| | Group A (n=47) | | Group B (n=46) | | n | % | |
|----------------|-------------------|------|-------------------|------|----|------|------|
| | n(S.D.) | % | n(S.D.) | % | | | |
| Primi gravida | 25(4.4) | 53.2 | 30(4.7) | 65.2 | 55 | 59.1 | 0.70 |
| Second gravida | 7(2.3) | 14.9 | 3(1.7) | 6.5 | 10 | 10.8 | 0.63 |
| Multi gravida | 15(3.7) | 31.9 | 13(3.4) | 28.3 | 28 | 30.1 | 0.87 |

Table shows that in both groups, most of patients were primigravida. Second gravida patients were lesser in number in comparison to multigravida.

Fig 3: Graph showing time taken by patients to achieve normalisation of BP.



This Figure shows a statistically significant difference in number of patients achieving normalisation of BP in one week of treatment in

Group A. More number of patients on labetalol had a sooner control of elevated BP as compared to methyldopa.

Table 3: Side effects profile

| *Type of side effects | Frequency | |
|-----------------------|-------------------|-------------------|
| | Group A (n=47) | Group B (n=46) |
| Drowsiness | 0 | 9 (19.6) |
| Nausea | 4 (8.6) | 0 |
| Headache | 0 | 3 (6.5) |
| Nasal congestion | 0 | 3 (6.5) |
| Dyspnoea | 2 (4.3) | 0 |
| Postural hypotension | 0 | 1 (2.2) |
| Others | 2 (4.3) | 0 |

*Values show number of patients (percentage)

Side effects profile as shown in this table shows that the most common side effect in labetalol group was nausea while dyspnoea was also seen in a small percent (4.3). Drowsiness, headache and nasal congestion were common side effects in methyldopa group. Any major side effect leading to discontinuation of drug was not observed in either group.

Table 4: Drug effect on labour

| Effect on labour* | Group A (n=47) | Group B (n=46) |
|--|-------------------|-------------------|
| Method of induction* | | |
| Spontaneous onset | 19 (40.4) | 12 (26.1) |
| Induction | 28 (59.6) | 34 (73.9) |
| Mode of delivery* | | |
| Normal vaginal | 33 (70.2) | 30 (65.2) |
| Forceps | 4 (8.5) | 6 (13.1) |
| Total Caesareans (all indications) | 10 (21.3) | 10 (21.7) |

*Values are number of patients (percentage).

This table shows that more patients in group A had a spontaneous onset of labour with less need for induction as compared to group B. There were more normal deliveries in group A as compared to group B. Caesarean percentage were almost similar in the two groups.

Table 05: Distribution of cases according to birth weight of the baby

| Weight (gms)* | Group A (n=47) | Group B (n=46) | Total (n=93) |
|------------------|-------------------|-------------------|-----------------|
| <1500 gm | 0 | 1 (2.2) | 1 (1.1) |
| 1500-2000 gms | 0 | 0 | 0 |
| 2000-2500 gms | 4 (8.5) | 3 (6.5) | 7 (7.5) |
| 2500-3000 gms | 21 (44.7) | 27 (58.7) | 48 (51.6) |
| >3000 gms | 22 (46.8) | 15 (32.6) | 37 (39.8) |

*Values are no. of patients (percentage)

This table shows the distribution of cases according to baby weight. Only one patient had baby weight <1500 gm and that belonged to group B. Around 90% in both group A and group B had baby weight more than 2500 gms, more patients of group A had baby weight >3 kg.

Table 6: Drug therapy and foetal/neonatal outcome

| | Group A (n=47) | Group B (n=46) | P Value |
|---|-------------------|-------------------|------------|
| | Mean | Mean | |
| Apgar score at 1 min. | 7.36 | 7.09 | 0.66 |
| Apgar score at 5 min. | 8.51 | 8.47 | 0.69 |
| Admission to nursery in days | 3.67 | 4.43 | 0.27 |
| Birth weight (kg) | 2.93 | 2.84 | 0.33 |
| Placental weight (gms) | 494.5 | 484.13 | 0.44 |
| No. of babies born before 37 weeks (%) | 3 (6.4) | 3 (6.5) | -- |

This table shows the foetal outcome in the two groups. Birth weight, placental weight and Apgar score at 1 and 5 min were slightly higher in labetalol group but it was not statistically significant. There were 3 preterm deliveries in both groups.

Discussion

I have tried to compare the anti-hypertensive efficacy and perinatal safety of alpha methyldopa and labetalol in pregnancy induced hypertension, through this hospital based, randomized, prospective study.

The comparison between age, parity, social background and personal history and a thorough analysis of the different variables in the two treatment groups was done. Statistical analysis of the data was carried out using student's t test.

Both group (A&B) were well matched and there was no statistically significant difference in age between the two groups (23.2 years and 20.51 years in group A and B, respectively); weight (62.17 kg and 57.58 kg in group A and B respectively), mean arterial pressure at enrolment (115.13 and 114.32 mm Hg in group A and group B respectively). 53.2% and 65.2% patients in group A and group B respectively were

primigravida while 31.9% and 28.2% in the two groups constituted multigravida patients. A total of 15 patients (9 from group A and 6 from group B) gave history of previous hypertensive pregnancy but were normotensive postpartum and in the period between the two pregnancies and developed hypertension after 20 weeks in this pregnancy favoring a diagnosis of gestational hypertension. 9 patients, 3 in group A and 6 in group B were having history of previous small for date babies. A total of 13 patients (7 in group A and 6 in group B) had proteinuria on admission in the study.

On comparing my study with the study of 176 PIH patients done by Plouin et al.⁸ my patients presented late than theirs (25.8 weeks and 26.2 weeks in labetalol and methyldopa groups) but it was earlier than A.M. El-Qarmalawi et al.¹⁰ study. Mean age of PIH patients was 25.8 years and 24.7 years respectively for labetalol and placebo groups; gestational age at presentation was 34 weeks with 23.7% and 11% patients in the two groups giving a past history of hypertensive pregnancy in a study by Pickles et al.⁹. Number of smokers was also more in that study.

Mean arterial pressure decreased in both labetalol and methyldopa treated group (115.13 mmhg to 95.77 mmhg and 114.37 mmhg to 96.24 mmhg respectively) but 82.9% of patients in labetalol group achieved normalization of BP in the first week as compared to 52.2% in group B which is also statistically significant. Similar results with labetalol were seen by Mahmoud TZ et al. with 85% patients showing BP control in 1 week. Qarmalawi et al.⁹³ noted that 81.4% in group A had a significant fall in MAP to below 103.6 mmhg compared to 68% in group B.

Side effects observed in labetalol treated group include nausea (8.7%), dyspnoea (4.3%), flushing and mild tremulousness in one patient each while drowsiness (19.6%), headache (6.5%), nasal congestion (6.5%) and postural hypotension (2.2%) were those observed with methyldopa. Wallin J.D. et al.⁷ observed nausea with labetalol

and asthenia, somnolence and dry mouth with methyldopa.

Spontaneous onset of labour was found in 40.4% patients in labetalol group as compared to 26.2% in methyldopa group while the rest needed induction. Normal deliveries were observed in 70.2% patients, forceps in 8.5% and LSCS in 21.27% patients of labetalol group while in methyldopa group these were 65.2%, 13.1%, and 21.74% respectively. More patients with spontaneous onset of labour and higher Bishop Score with labetalol were noted by Qarmalawi et al.¹⁰ (54% with labetalol and 22.2% with methyldopa).

Mean Apgar scores at 1 min and 5 min were 7.36 and 8.51 in labetalol group and 7.09 and 8.47 in methyldopa group. 6 babies in labetalol group were admitted in nursery for average of 3.67 days as compared to 7 babies and 4.43 days in methyldopa group. Qarmalawi et al.¹⁰ observed that same number of babies in both group had Apgar score <5 at 1 min (as compared to 1 and 2 babies in both groups respectively in my study).

Conclusion

In this way, I observed that both labetalol and methyldopa are equally effective in control of BP but labetalol has quicker action. Labetalol decreases the incidence of proteinuria, increases the chance of spontaneous onset of labour and have good foetal outcome. Both the drugs are well tolerated by the subjects.

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