EVALUATION OF LABTALOL IN PREGNANCY INDUCED HYPERTENSION

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SUMMARY

A Prospective randomised, well controlled trial was conducted in Smt. Sucheta Kriplani Hospital, New Delhi on 50 pregnant patients of moderate or severe pregnancy induced hypertension between 28 and 37 weeks of gestation, who fulfilled the eligibility criteria of the study. They were divided into group I (study group) of 25 patients who were put on labetalol and group II (control group) of another 25 patients who received methyldopa. Both groups were given similar antenatal, intra-natal and perinatal care. No statistically significant difference was found in the percentage of responders to drugs, efficacy of blood pressure control, mean pregnancy prolongation, induced labor, Cesarian section rate, low birth weight and small for date babies or perinatal morbidity in both groups. No significant adverse effect of labetalol was observed in mother or neonates. Thus labetalol is effective and safe for use in pregnancy induced hypertension.

INTRODUCTION

In India, toxaemias of pregnancy still account for one of the three leading causes (hemorrhage, sepsis and toxaemia) of maternal mortality. Pregnancy induced hypertension (PIH) is responsible for high perinatal morbidity and mortality. The only definite treatment of PIH is termination of pregnancy. This, however, is often not desirable when fetus is too immature for extra-uterine survival. Anti-hypertensive drugs help in decreasing maternal morbidity and mortality in moderate and severe PIH but their effect on perinatal outcome is less clear. Although a number of anti-hypertensive drugs have been used there is no entirely satisfactory drug for use in hypertensive states of pregnancy. Labetalol is unique

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which combines alpha and beta adrenoceptor antagonistic properties. It effectively lowers B.P. and is of special interest to the obstetrician as it is found to have favourable effect on utero-placental blood supply and to have no adverse effect on the foetus as observed by some workers like Lunell et al (1982) and Joupilla et al (1986). Its safety and efficacy has been observed by several workers like Lammings et al (1979), Micheal (1979), Redman (1977) and Plouin et al (1988). Its effect on Indian patients however barring one or two studies, has not been carried out. The present study was undertaken on Indian patients to evaluate the efficacy of labetalol in moderate and severe PIH, to observe its effect on the foetus and to compare it with methyldopa.

MATERIAL AND METHODS

Fifty pregnant patients with known dates between 28 and 37 weeks of pregnancy having moderate or severe PIH and admitted to maternity wards of Smt. Sucheta Kriplani hospital between July 1989 and May 1990, were enrolled for study.

PIH was defined as a B.P. of atleast 140/100 mm of Hg. taken in left lateral position after 10 min. of rest on two or more occasions, 6 or more hours apart. Patients with or without proteinuria and or oedema were included in the study.

Patients with H/O contra-indications to beta-blockade, diabetes, hypertension were excluded from the study. Patients with hypertension before 20 wks of pregnancy, antepartum hemorrhage, intra-uterine fetal death, acute febrile illness, signs and symptoms of acute fulminant toxaemia in the present pregnancy or patients with less than 5 days of treatment were excluded from the study.

These patients were divided into two groups. Group I (study group) comprised of 25 patients who were put on labetalol (Normadate of Glaxo laboratories). These patients were started on 50 mg tablet t.d.s. after meals. An increment of 150 mg of drug was made every 24-48 hrs till response. A maximum of 900 mg dy of labetalol was given. If patients did not respond to this dose dihydrallazine was added in doses of 75 to 150 mg and SL Depin was given when indicated. Sedatives were added when required. If patient still did not respond, she was evaluated for termination of pregnancy. Group II (control group) also comprised of 25 patients who were started on methyldopa (Aldomet of Merind) 250 mg t.d.s. and dose was gradually stepped up every 24-48 hrs till response or a maximum of 2 gm dy. Antihypertensives and sedatives were added as in Group I when indicated. If patient still did not respond she was evaluated for termination of pregnancy.

Patients were considered responders when B.P. fell to <140 90 mm of Hg. Non-responders were patients who developed signs and symptoms of impending eclampsia while on treatment, patients where B.P. remained uncontrolled inspite of maximum dose of drug and who required addition of other antihypertensive drugs.

On admission a detailed history was taken and examination done. B.P. was taken as detailed above and mean arterial pressure (M.A.P) calculated by Burton's formula i.e.

$$\text{M.A.P.} = \text{Systolic B.P.} + 2\,(\text{Diastolic B.P.})$$

B.P. was checked 4 hourly till settled and then twice a day. Urine was examined daily for proteinuria. Patients were serially investigated by hemogram, KFT, LFT, retinal examination. Ultra-sonography. Daily fetal movement (DFMR) and non-stress test (NST) were done when indicated. Pregnancy was terminated if patients did not go into labour by 40 wks of gestation inspite of control of B.P., showed signs of fetal distress in utero or had intra-uterine growth retardation (IUGR). At birth, infant's Apgar score, birth weight, evidence of IUGR, gestational age or any other complication was noted. Cord blood was taken for estimating blood sugar and S. electrolytes. Placenta was grossly examined. Results were analysed statistically by student's 't' test and chi-square. All patients whose B.P. remained high were re-examined at 6 weeks post-partum.

OBSERVATIONS

Patients in both groups were equally matched as regards their demographic profile, obstetric status and initial B.P., proteinuria, and oedema at entry into the study. Seventy-two percent of patients responded to labetalol in Group I as against 64% who responded to methyldopa in Group II (Table I).

There was a significant and almost similar fall in mean systolic B.P. (SBP) and in the mean diastolic B.P. (DBP) in both groups, fall being greatest in first 24 hrs followed by more gradual and sustained fall over the next 7 days till B.P. fell to near normal levels (Fig. 1).

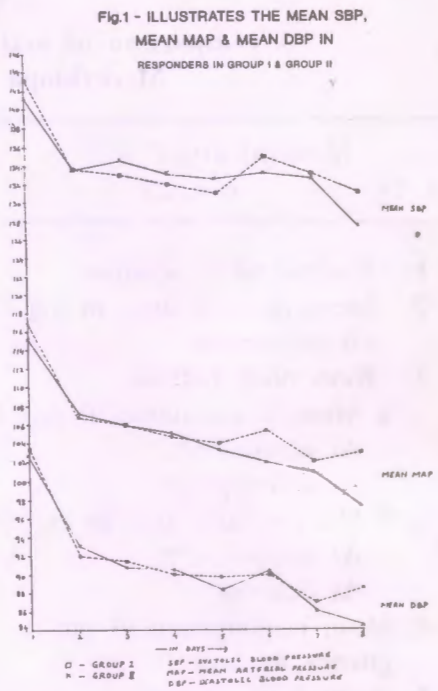

Fig. 1

Dose of labetalol for controlling B.P. in Group I ranged from 150 to 600 mg with a mean of 300 mg. Increasing the dose beyond 600 mg did not improve the response rate as none of the patients put on the next increment of 900 mg of labetalol responded to the drug. Patients in Group II required 750 to 2000 mg of methlydopa with a mean of 1300 mg for controlling their B.P. Patients in Group I demonstrated an insignificant rise in their s. creatinine as against a significant rise in Group II whereas s. uric acid showed no change in Group I as against insignificant rise in Group II (Table I). There was no stastistical difference in mean prolongation of pregnancy, induction of labor and LSCS rate in Group I & II

TABLE I
A comparison of maternal effects of Labetalol and Methyldopa in Gp I and Gp II

Maternal effect	Gp I n = 25	Gp II n = 25
1. Number of responders	18	16
2. Mean dose of drug in mg for responders.	300	1300
3. Biocemical indices		
a. Mean s. creatinine in mg %		
At admission*	1.02#	0.89$
At delivery	0.98	0.95
b. Mean s. uric acid in mg %		
At admission**	6.78#	6.44$
At delivery	6.76	6.84
4. Mean prolongation of pregnancy in days.	21.7	20.5
5. Number of patients		
a. Induced	7	6
b. LSCS	7	6
c. Forceps	0	2

* Standard deviation GpI = 0.22, GpII = 0.20
** —do— GpI = 1.73, GpII = 1.64
*** Lower segment cesarean section.
# P = 0.05 (NS), $ p = <0.05 (S)

(Table I). There was no statistical difference in mean birth weight, still-birth rate, neonatal deaths, small for date infants and neonatal complications in Group I & II (Table II).

DISCUSSION

A randomised, well controlled prospective study was conducted on 50 pregnant patients of PIH who fulfilled the eligibility criteria of study. Patients of Group I were given labetalol while patients of Group II received methyldopa. There was no statistical difference in the percentage of patients showing satisfactory control of B.P. produced by labetalol (72%) and methyldopa (64%). Lamming et al (1979) and Redman (1977) observed B.P. control to be similar under similar conditions with both drugs as observed in the present study while Plouin et at (1988) observed that

TABLE II
Perinatal outcome in two groups

Perinatal outcome	Gp I n = 25	Gp II n = 25
1. Still-births		
Ante-natal	1	0
Intra-natal	0	0
2. Neonatal deaths	1	0
3. Mean birth weight in gms*	2422	2470
4. Low birth weight neonates	11	12
5. Small for dates neonates	2	1
6. Neonatal complications		
Apgar score <7	1	2
Septicaemia	2	0
Jaundice	4	3
Aspiration pneumonia	0	1
Admission to intensive care nursery	7	6

*P> 0.05

B.P. control was more satisfactorily achieved with labetalol as compared to methyldopa.

B.P. was controlled with labetalol in higher percentage of patients 36% as against 20% for methyldopa within 24 hrs, although by third day B.P. control was equal in both groups. This effect of labetalol is highly desirable in pregnant women where earlier response is required in the interest of mother and her foetus. In contrast to the results of the present study however, Lamming et al (1979), in their study comparing the effect of above drugs on similar groups of patients noticed that both drugs effectively controlled B.P. at the same time and by fourth day only. In the present study B.P. control in Group I was effected by a mean dose of 300 mg and a maximum dose 600 mg of labetalol. In a similar study Micheal (1979) required 600 mg or less of labetalol for control of B.P. in 84% of his cases. The patients who failed to respond might have already had pathological damage to alpha adrenoceptors in resistance vessels thereby impairing their responsiveness to further increase in drug dose of labetalol. In Group II mean dose methyldopa for B.P. control was 1.3 Gm and maximum of 2 Gm dy.

Labetalol seemed to have no adverse effect on kidney funtions as judged by

an insignificant fall in mean overall s. creatinine and of s. uric acid whereas methyldopa appeared to have an adverse effect on kidney functions as observed by significant rise in s. creatinine and s. uric acid levels (Table I). This property of labetalol is highly desirable in pregnant women with PIH where the disease process itself may have already demaged the kidneys and further iatrogenic damage is undesirable. Sibai et al (1987) however, observed deterioration in kidney functions with labetalol. There was no significant difference in patients on labetalol and methyldopa as regards their mean pregnancy prolongation, mean gestation at delivery, Bishop's score at delivery, induced labour and cesarean section (C.S.) rate as was the experience of Plouin et al (1988) in a similar study. The obstetrician's main concern of use of anti hypertensive drugs in PIH is the potential for increasing the risk of adverse perinatal outcome. In the present study no significant difference was observed in mean birth weights, the number of LBW and SFD of infants born to patients on both the above drugs. These results are in agreement with those of several workers like Lammings et al (1979), Redman (1977) and Plouin et al (1988). The mean birth weight of infants was on the lower side of normal and the number of LBW infants was also high in both groups although not statistically significantly different, perhaps due to the effect of the disease process itself on the utero-placental blood flow, which could not perhaps be reversed by the antihypertensive properties of either drug. The number of SFD infants however, was small in both groups (Table II). It is the SFD infants who are at high risk of ante-natal, intra-natal and post-natal complications. In the present study no statistical difference, however, was observed in Apgar score at birth, number of neonates admitted to intensive care unit, incidence of jaundice, septicaemia and neonatal complications in two groups.

The safety of methyldopa in pregnancy has been established for several years. In the present study labetalol was observed to be free of any major side effect as was the experience of several workers like Micheal (1979) and Plouin et al (1988). Minor side effects like dyspnoea, headache and dizziness were observed infrequently with labetalol. In the present study no adverse effect was noticed in neonates heart rate, respiratory rate or B.P. with both drugs. Macpherson et al (1986) also observed that labetalol was a safe drug for term neonate and it did not cause clinically important sympathetic blockade in it.

Thus to conclude labetalol is an effective antihypertensive in PIH and is safe for both the mother and her fetus. When compared to time tested drug methyldopa, it is equally efficacious in its B.P. lowering effect, has similiar perinatal outcome and minimal adverse maternal and fetal side effects. Labetalol further has no adverse effect on the kidneys.

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