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A Randomized Controlled Trial on Use of Nimodipine in Mild P.I.H.

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Summary

This is a randomized prospective trial on 54 cases of mild pregnancy induced hypertension (P.I.H) treated with nimodipine, compared with 57 cases of mild P.I.H. treated with methyl dopa.
In non-proteinuric cases B.P. fell earlier and more with nimodipine (from M.A.P. 114.9 mm Hg to 106.9 mm Hg) after 2 weeks of treatment compared to methyl dopa (from 112.6 mm Hg to 107.3 mm Hg).
In proteinuric cases no significant difference was noted in both the groups. There was no significant difference between the groups regarding obstetric interventions or duration of stay in nursery.
Platelet count increased higher in nimodipine group than in methyldopa group (50% Vs 25%).

Introduction

Hypertension in pregnancy remains a major cause of maternal mortality throughout the world (Duley 1992). There is an increase in maternal morbidity associated with hypertension.

The value of antihypertensive treatment of hypertensive disorders in pregnancy is still being argued. Hutton et al (1992) found a postal survey among British consultants in 1991 that oral treatment of severe hypertension had become more common than 15 years earlier. Effects of antihypertensive drugs in mild PIH were studied in several randomized trials with effect on proteinuria, disease progressions and neonatal RDS, and the drugs were found to be effective (Rubin et al 1983), Pickles et al, 1989) though no change was found by some (Sibai et al, 1987, 1992). There is good evidence that early aggressive use is beneficial to both mother and the baby (Hutton et al 1992).

Serotonin has a role in the pathogenesis of pregnancy induced hypertension. Ketanserin, a type 2 serotonin antagonist, when used I.V. controls hypertension in pre-eclamptic women. Two group parallel study was carried out in N.R.S.M.C. & Hospital from January 2000 to December 2000 to evaluate the effectiveness of a new antihypertensive antiserotonin agent nimodipine in PIH, to find out any maternal biochemical changes before and after treatment, to find out any effect on platelets, find out any adverse effects on neonates. This drug was compared with the traditionally used agent L-methyl dopa.

Inclusion criteria for the study :-

1) first pregnancies
2) after 20 wks of gestation
3) not using any other antihypertensive agent
4) blood pressure 140/90 or more detected on two occasion more than 60 hour apart.

Exclusion Criteria :-

1) 2nd pregnancy onwards.
2) history of increased blood pressure before 20 wks of gestation.
3) history of intake of antihypertensive drug before.

One hundred eighteen women with hypertension in pregnancy but otherwise healthy and meeting the inclusion criteria were enrolled. The patients were randomized by number to treatment with tablets of oral nimodipine 30 mg 6 hourly or with tablets of αmethyl dopa 250 mg 6 hourly.

One hundred & eleven women were evaluated with 7 dropouts, 54 were randomized to treatment with nimodipine, 57 were randomized to methyldopa group. Proteinuria of >2+ was considered significant. All patients with significant proteinuria were admitted to an antenatal ward.

Blood samples for laboratory analysis (i.e. platelets in blood, serum uric acid, serum alanine aminotransferase, serum aspirate aminotransferase and serum creatinine) were taken before the start of the study, and after 1 wk and weekly thereafter.

Table I :
Demographic data on enrolment

Characteristics	Nimodipine (n=54)	Methyldopa (n=56)
Maternal age (Yr.)	26 (19-40)	27 (21 – 40)
Maternal wt. at first ANC	48.4	47.6
MAP at first ANC	92.3	94
Gestational age (wk)	34.2	34

(Values are mean)

Results

After 3 days of treatment MAP decreased significantly in the nimodipine group (from 114 ± 6 to 109 ± 7 mm Hg, p< 0.001) but not in the methyl dopa group (from 113 ± 5 to 112 ± 9 mm Hg p<0.28). After 2 wks of treatment MAP was lower in the group tested with nimodipine, but the difference was not significant. On enrolment 11 patients in the nimodipine group and five in the methyl dopa group had significant protenuria. In another 10 patients in the nimodipine group and 18 in the methyldopa group, significant protenuria developed during the time of study. The result indicates that nimodipine is effective in women with non proteinuric hypertension but does not prevent development of proteinuria.

During labour, women receiving methyl dopa needed additional antihypertensive in 14 (29%) cases. Patients treated with nimodipine needed additional antihypertensive in 9 (22%) cases. There were no significant differences in serum creatinine or liver enzymes levels in both the groups on enrolment or during the study. But the platelet count increases in 27 (50%) cases in nimodipine group compared with 14 (25%) cases in methyldopa group. High uric acid levels in proteinuric patients become more pronounced during the treatment period.

In non-proteinuric women the serum urate level increased slightly in the methyldopa group but not in the nimodipine group of the proteinuric patients

Labour was induced in 9 (76%) patients in nimodipine group and 6 (55%) patients in methyl dopa group.

Fetal Outcome : In the current study there was no difference between the groups in the incidence of spontaneous labour. There was no perinatal death. The mean birth weight was higher, although not significantly so, in the nimodipine group. This emphasizes that

Table II: Maternal MAP before and during treatment

Treatment	Type of hypertension	Before Treatment		Days in Study		
				3	7	14
Nimodipine	Non proteinuric	114 (n=22) (p=0.12)	P<0.0001	106.6 (n=22) P=0.05	107.3 (n=19) P 0.07	106.9 (n 18) p 0.005
Methyl dopa	Non proteinuric	112.6 (n=39)	P<0.023	109.9 (n=39)	110.7 (n=37)	112.8 (n 29)
Nimodipine	Proteinuric	112.8 (n=32)	P<0.035	110.2 (n=32) P=0.01	112.0 (n=27) P-0.61	112.5 (m=16) P -0.62
Methyl dopa	Proteinuric	115.2 (n=17)	P<0.44	116.6 (n=17)	113.2 (n 12)	114.2 (n 7)

(Values are in mm of Hg)

Table III
Symptoms before and after 1 week of Treatment

Symptoms	Nimodipine				Methyldopa			
	Before Treatment (n=37)		After 1 week of Treatment		Before Treatment (n-37)		After 1 week of Treatment	
	No	%	No	%	No	%	No	%
Headache	16	30	14	26	18	31	15	26
Oedema	21	38	16	29	20	35	16	29
Nausea	6	11	3	6	9	16	7	13
Heartburn	7	13	4	7	10	18	8	14

perinatal outcome is good is women with mild P.I. H. even in the presence of proteinuria.

There was no significant difference between the groups regarding obstetric interventions or duration of stay in nursery.

In proteinuric group no significant difference is noted in both the groups. In the non-proteinuric group, the mean gestational age at delivery in nimodipine group was 38.2 ± 1.3 weeks. It is marginally higher than that in methldopa group (38.0 ± 1.5 weeks)

In the proteinuric group, the mean gestational age at delivery was almost similar in both the groups (36.4 ± 2.6 weeks).

Rate of induced labour was 33% in non proteinuric group treated with nimodipine compared to 41% with methyl dopa. In proteinuric group the rate was 76% with nimodipine and 55% with methyl dopa.

Conclusion

In this study of women with hypertensive disorders of pregnancy nimodipine effectively reduced the maternal MAP in non-proteinuric women. However, women with proteinuric hypertension at the start of investigation or in whom proteinuria later developed did not respond to the drug. Serum uric acid levels did not increase in non proteinuric group and the platelet counts increased in 50% of patients with nimodipine. No serious side effects on mother was noticed and the fetal outcome was also good. An initial multicentric trial on nimodipine (Chatterjee et al 1999) showed 73% success rate. Thus if antihypertensive therapy is indicated nimodipine can be an alternative form of drug treatment.

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