Clinical Trial with Nimodipine in the management of P.I.H.

Alokendu Chatterjee, Joydev Mukherjee, Shankar Mitra, Srinjoy Saha
Dept. of Obst. & Gynaecology, N.R.S. Medical College, Calcutta.

Summary: The control of blood pressure has an important role in the management and prognosis of pregnancy induced hypertension (PIH). Serotonin being a mediator in the pathophysiology of P.I.H., the role of Nimodipine, an oral antiserotonin drug, may be logical. The aim of this study was to evaluate the effectiveness of Nimodipine in pregnancy induced hypertension. A collaborative study was carried out in a total of 101 cases of P.I.H., collected from four centres, namely, Calcutta, Mumbai, Allahabad, & Jamshedpur. The inclusion criteria included, hypertension either 140/90 or more, confirmed by two observations, 6 hours apart, after 20 weeks of gestation. A good response in terms of satisfactory reduction of blood pressure was observed in 70% of cases without any ill effects in the mother or the baby.

Introduction :

Hypertensive disorders in pregnancy cause substantial maternal & fetal mortality & morbidity throughout the world. The etiology of pregnancy induced hypertension is not yet definitely known but many theories have been suggested.

There may be release of a pressor substance from the uteroplacental complex, which could be serotonin (Hutter & Filshie 1993). A hyperserotonomic condition has been documented in pre-eclampsia-eclampsia by various workers with a central focus on blood platelets (Jelen. et al 1979: Gujarati et al 1994, Gujarati et at 1996). Placental ischaemia caused by defective trophoblastic invasion is the central event. Hypoxia of placental site may be followed by increased trophoblastic fragmentation and embolisation into the maternal venous circulation. As there is tissue damage, platelets will aggregate on to these fragments and serotonin will be released from these aggregates into maternal venous circulation. The serotonin acts on type two serotonin receptors in vascular smooth muscles leading to vasospasm, hypertension and Oligurea (Weiner 1987). Beneficial effects of Katanserin, a serotonin receptor antagonist, on hypertension in pre-eclampsia-eclampsia has been shown. (Weiner 1984).

We carried out a trial with Nimodipine, a Calcium channel blocker, which has been widely used in hypertension, cerebral ischaemia and migraine with an unique effect against cerebral arterial vasospasm. It combines antiserotonin properties with Case of oral administration and minimal side effects.

Setting:

A collaborative study was carried out in four centres spread over India. Nil Ratan Sircar Medical College, at Calcutta ; Nowrosjee Wadia Maternity Hospital at Mumbai ; Kamala Nehru Hospital at Allahabad and Tata Main Hospital at Jamshedpur.

Materials & Methods :

A total of 101 patients were studied. Patients selected were beyond 20 weeks of gestation and had blood pressure above 140/90 mm of Hg as confirmed independently by two different observers and measured twice at six hours apart. The patients received 30mg Tablets of Nimodipine twice daily for the first two days, followed by 30 mg thrice daily for the next two days. If Blood Pressure control was not satisfactory the dose was increased to 30 mg four times a day, If at the end of one week the response was not satisfactory, the investigator was allowed freedom to follow the conventional regimes of antihypertensive therapy.

Results:

The age of the patients recruited varied from 18-40 yrs with a mean of 26.14 yrs. The parity varied from 1-4 with a mean of 1.9.

Table –I. Shows that the mean systolic B.P. fell from 154

to 132 and the mean diastolic B.P. fell from 94 to 80 mm of Hg. The mean arterial pressure fell from 114 to 94 mm of Hg. The good response was worked out in 71 subjects, out of 101 (70.3%).

Table - I

Change of B.P.	Before treatment	After treatment
Mean Systolic	154	132
Mean Diastolic	94	80

Table II. Shows that there were no significant alterations in the biochemical parameters before & after treatment in respect of serum creatinine, glucose and S.G.P.T.

Table II

Biochemical changes	Before treatment	After treatment
Mean Serum Creatinine	1.12	1.11
Mean Blood Glucose	84.59	80.24
MEAN S.G.P.T.	39.4	40.2

Table III. Shows the changes in platelet count before and after therapy. In those patients with relatively lower platelet counts before therapy, the mean values improved from 1.4. to 1.8 ; there was no significent alteration in the majority of patients who had normal counts before treatment.

Perinatal Outcome :- 64 infants were born at the times of reporting : mean birth weight was 2.7 kg. There was no neonatal death.

Table – III

Platelet Count Lakhs/mm^3

No.of Patients	Before treatment	After treatment
	Mean	Mean
92	2.8	2.9
09	1.4	1.8

Discussion:

Calcium channel blockers act by blocking Ca-influx into smooth muscle cells, so interfering with excitation-contraction coupling and producing vasodilation. Considering the role of serotonin in pre-eclampsia with its vasospastic pathology, it is conceivable that any agent that combines both the anti-serotonin & vasodilator Calcium channel blocking actions would perhaps be more useful than other drugs employed in pregnancy induced hypertension. Nimodipine a second generation dihydropyridine, is a more potent cerebral vasodilator (Alborch et al 1992) and may be effective also in preventing seizures like magnesium sulfate. Belfort et al (1996) described the use of Nimodipine, given by infusion to lower blood pressure in pre-eclampsia. Our study demonstrates the favourable response of oral Nimodipine in pre-eclampsia.

Ketanserin, another serotonergic receptor antagonist has been reported useful to lower blood pressure and ameliorated the platelet count (Spitz et al 1993). The mean systolic blood pressure decreased from 157 to 132 mm Hg & the diastolic from 99 to 87, while the platelet count increased from 38.5 thousand to 1.3 lakhs. Our study demonstrated a 70% response in terms of blood pressure improvement together with slight improvement in platelet count in the more severe cases.

This being a preliminary report, no attempt is made to draw a final conclusion. There are good grounds for considering larger trials of Nimodipine in pregnancy induced hypertension in future.

Acknowledgement :

We are grateful to superintendent N.R.S. Medical College Hospital for allowing us to conduct the trial in this hospital. This trial was conducted in 4 Centres in India, Calcutta, Mumbai, Allahabad, & Jamshedpur by .

At Calcutta :- Dr. K.M. Gun, Dr Alokendu Chattarjee, Dr. Shankar Mitra, Dr. Joydev Mukherjee.
At Mumbai :- Dr. Usha Krishna, Dr. Duru Shah, Dr Kumud Ingle.
At Allahabad :- Dr. Raj Baveja.
At Jamshedpur :- Dr. S.B. Ram, Dr. M. Kabiraj, Dr.P.R Handa, Dr. S. Sen, & Prof. S. Dasgupta.

The entire team is very grateful to CONTECH DEVICES PVT.LTD. & particularly to Mr.Satyaki Dev, the

Managing Director, for generously supporting this trial & showing a great interest in the scientific research.

References :

1. Alborch E, Salom JB, Perales A. J. Eur J. Pharmacol 229: 83 1992
2. Balfort MA, Taskin O, Buhur A, Seade G, Yalcinoglu A. Am J. Obst Gyn.174 : 451,1996.
3. Gujarati VR, Goyal A, Gaur SPS, Singh N, Shanker K, Life Science. 55:327,1994.
4. Gujarati VR, Shankar K, Vrat S, Chandravati MS, Parmar SS Am J. Obst Gyn, 175:1543,1996.
5. Hutter C, Filshie G.M, Contemp. Rev. Obstet Gyne, 199-October'1993.
6. Jelen I, Fenamaparir L, Crawford TBB, Br. J Obst Gyn, 86: 468,1979.
7. Weiner CP, Socol MI, Vaisrub N. Am.J Obst Gyn, 149: 496-1984.
8. Weiner CP. Am J. Obst Gyn 156: 885-1987
9. Spitz B. Witters. K. Hanssens M. Van Assche FA, Keith J.C; Hypertension in Pregnancy 12,183 1993