DISCUSSION
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High blood pressure in association with pregnancy has long been regarded as an ominous sign. Kaplan et al (1962) reviewed chronic renal diseases and hypertension associated with pregnancy and advised that therapeutic abortion should be carried out, if the blood pressure rises to 160/100mm Hg. Fiarly and Kincaid Smith (1968) concluded that morbidity and mortality rates (mainly relating to the foetus) were increased in the presence of hypertension.

Prevention and treatment of pregnancy induced hypertension have learned in the last 10 years. High blood pressure complicated approximately 10% of all pregnancies. Pre-eclampsia, the association of hypertension proteinuria and oedema, accounts for more than 50% of all the hypertensive disorders of pregnancy and is a major cause of foetal and maternal morbidity and mortality.

Hypertension in pregnancy treated as :-

1. Na restriction, bed rest.
2. Elucidation of some of the mechanisms responsible for blood pressure elevation in pregnancy has permitted therapy to be based on more rational principles.
3. Anti hypertensive therapy using sympathetic inhibition with either methyldopa or alpha and beta adrenoceptor blockage.
Vasodilation with hydralazine, calcium entry, blockers (nifedipine) intravenous labetalol or diazoxide is primarily used in severely hypertensive patients.

4. During long term antihypertensive therapy, treatment with pindolol yielded better foetal growth than therapy with atenolol.

Aim of this study was to evaluate the effect of nifedipine in pregnancy induced hypertension. Patients with pregnancy induced hypertension who were scheduled for emergency caesarean section procedures requiring general anaesthesia and spinal anaesthesia were selected for the study. Very few studies have been reported in which such drug and combination of drugs have been used for this purpose.

Numerous techniques and agents have been employed for this purpose but none was found to be 100% successful.

Beta blockers were also studied very extensively. Pry's Roberts et al (1969) reported that propanolol was effective in suppressing the cardiovascular response to tracheal and nasopharyngeal suction of secretion in tetanus patients.

Protocol (Prys-Roberts, 1973) given intravenously or orally was shown to be effective in suppressing the pressor responses to laryngoscopy and intubation. Metoprolol, a cardioselective beta blocker was
shown to be reducing arterial pressure during intubation and after extubation (Magnusson et al, 1986).

Sodium nitroprusside (Stoelting, 1979) intranasal nitroglycerine (Fassoulabi and Kanaris, 1973; Kolak et al, 1986), Isosorbide dinitrate (Hatano et al, 1989), trimetaphan (Saitoh et al, 1991) were all found to be reducing the magnitude of the rise in blood pressure but the associated tachycardia was not prevented.

Smith et al (1982) employed hydralazine and diazoxide in severe hypertension, but there were certain limitations associated with the use of these agents as they have to be administered parenterally and there is high incidence of side effects of the use of these agents at times it become extremely difficult to control hypertension in pregnancy with conventional antihypertensive drugs. Antihypertensive therapy utilizing sympathetic inhibition with either methyldopa or alpha and beta adrenoceptor blockade yield, and the most promising results vasodilation with hydralazine calcium entry blockers (nifedipine) intravenous labetalol or diazoxide is primarily used in severely hypertensive patients. The use of orally administered nifedipine in severely hypertensive women is associated with encouraging results.

It is clear that women with blood pressure levels greater than 170/110 mm Hg need antihypertensive therapy for maternal safety. It remains to be proven to
what extent foetal growth and welfare can be improved in women with diastolic pressure levels 85-110 mm Hg when adrenoceptor blocking agents and used for blood pressure control. Initial studies were suggestive of improved foetal growth, prevention of proteinemia and the respiratory distress syndrome but more long term controlled studies are required.

Chronic hypertension is treated with methyldopa and PHN is treated with atenolol. There is evidence that therapy is beneficial in terms of immediate pregnancy outcome and is not harmful to the child. Atenolol is currently being evaluated in combination with nifedipine to treat cases of early onset of severe pre-eclampsia and preliminary results and are encouraging prevention rather than cure should be the aim in managing hypertensive diseases during pregnancy. Early intervention can prevent serious problems later on (Rubin, 1990).

Of the calcium channel blocking agent nifedipine was found to be very effective in reducing the pressor response (Khan et al, 1987; 1989; Puri and Batra, 1988; Bholia and Abraham, 1990). Varapin was not as effective as nifedipine and also a significant prolongation of P-R interval was observed in some patients (Kolli et al, 1987; Rashid Khan et al, 1989). Diltiazem was reported to be unsuccessful in this respect (Chandralekha et al, 1990).

In the present study sublingual nifedipine was used alone and in combination with diazepam each to
decrease the pulse rate and systolic & diastolic blood pressure. Use of any of the drugs or drug combination decrease significant reduction in systolic blood pressure and diastolic blood pressure, pulse rate following laryngoscopy and tracheal intubation.

Huysmans et al (1983) emphasized an advantage of a calcium antagonist in comparison to other vasodilators that it selectively increases cerebral and cardiac blood flow, as has been shown in human. Data of present study further suggest that a short term use of nifedipine does not appear to compromise neonatal outcome. Therefore, nifedipine appears to be safe and effective antihypertensive agent for short term use in acute obstetric hypertension because of ease of administration, rapid onset and long duration of action.

The results of this study showed that the blood pressure was significantly lowered after diazepam intramuscularly after sublingual administration of nifedipine in patients with pregnancy induced hypertension presenting for surgery. The peak effect occurred in 30 minutes.

The effect was sustained and the blood pressure remained stable throughout the period of anaesthesia. The blood pressure did not rise on. In fact, it remained well below the value with patient had presented. There was no significant change in pulse rate also. But Zusman et al (1987) reported a rise of 3.7 to 6.7% in pulse rate in
nifedipine treated patients during anaesthesia and operation. The finding of this study confirmed the observations reported by Zusman et al (1987) and Jain et al (1987).

Since nifedipine has also a coronary vasodilating action it may be useful in patients with coronary spasm (Reis et al, 1982). Thus nifedipine acquired a special usefulness in the perioperative period in hypertensive patients.

All patients who received nifedipine showed significant reduction in both systolic blood pressure and diastolic blood pressure. In patients who received diazepam showed adequate fall in blood pressure.

It is evident from this study that in all pregnant women having severe hypertension the response to diazepam and nifedipine was adequate. When nifedipine was administered to these patients a significant reduction in both systolic and diastolic blood pressure was observed. These results concus with the findings of earlier workers (Rubin et al, 1984) who in their uncontrolled study have shown the effectiveness of nifedipine in severe hypertension in pregnancy unresponsive to beta blockers. In the present study, nifedipine seemed to be better antihypertensive agent as all the patients who received nifedipine as initial therapy responded to it and patients who responded to diazepam no acute adverse effects on foetal outcome were observed with nifedipine.
Dulilzhy et al (1986) and Martenells et al (1986) showed that nifedipine when used alone was effective and safe in pregnancy. Constantine et al (1987) used slow release nifedipine with atenolol and alpha-methyldopa in 23 hypertensive females and found this combination useful.

A maximum fall in blood pressure was observed between 30 minutes and 3 hours after administration of nifedipine which was at variance to the results of other workers (Walkers and Redman, 1984) who observed the maximum fall between 20 to 30 minutes. With present knowledge it appeared very difficult to explain this variability in present.

At present no other anti-hypertensive drug is available in India which can be effective in lowering the blood pressure in hypertensive emergencies during pregnancy within 30 minutes. Nifedipine can lower the blood pressure within 20 to 30 minutes and has no adverse effect on foetus (Jain et al, 1987). Therefore, this drug can be useful addition to the armamentarium of antihypertensive drugs used in pregnancy.

Nifedipine exerts little or no effect on the blood pressure in normotensive subject (Stone et al, 1980). However, it is highly effective in the acute treatment of moderate to severe elevation of blood pressure where it produces a reliable reduction in systolic and diastolic pressures (Beer et al, 1981).
When nifedipine was administered orally or sublingually 90% of the drug is absorbed. The drug is detectable in the serum 3 minutes after the sublingual and 20 minutes after the oral administration effect in 30-60 minutes which lasts for 6-10 hours (Aobi et al, 1978; Kawajima et al, 1978). When given sublingually 10 mg nifedipine lowers blood pressure marking 15 minutes after its administration and the effect lasts for 90 minutes (Stone et al, 1980).

Schewitz (1971) observed hypertensive pregnant patients and showed contradictory results with sodium and water homeostasis. The use of diuretics may well have distorted some of the results where no increase or even depletion of sodium and water was reported. The accepted view at present is that hypertensive mothers have smaller increase in plasma volume, total exchangeable sodium and extracellular fluid than normal pregnant women (Chesley, 1972). These observations made it difficult to believe that sodium and water retention can be an important primary factor in the causation of pregnancy related hypertension.

Nifedipine reduces both systolic and diastolic blood pressure with a minimal amount of side effects including orthostasis (Spurrell et al, 1974). Nifedipine also induces a powerful basoreceptor mediated reflex beta-adrenergic response to affect its negative ionotropic action and thus enhancing ventricular performance
(Ellrodt et al, 1980). It suggests a state of tachycardia in the patients treated with nifedipine but in the present study the average pre-operative pulse rate was only 86.5±6.1. This did not cause any concern and the response at intubation was only a subdued like. Reported side effects of nifedipine are hypotension tachycardia and A.V. conduction blockage, none of which was present pre-operatively in the patients in this study.

Stone et al (1980) have evaluated the efficacy of a single oral or sublingual dose of nifedipine in preventing the rise in pulse and blood pressure induced by laryngoscopy and endotracheal intubation. Nifedipine exerts little or no effect on the blood pressure in normotensive subjects. When given sublingually 10 mg nifedipine lowers blood pressure markedly, 15 minutes after its administration and the effect lasts for 90 minutes.

Kawajuna et al (1978), Aobi et al, (1978) observed when nifedipine is administered orally or sublingually 90% of the drug is absorbed. The drug is detectable in the serum 3 minutes after the sublingual and 20 minutes after the oral administration on oral nifedipine (10 mg) exerts the peak haemodynamic effects in 30-60 minutes which lasts for 6-10 hours.

Smith et al (1982) in severe hypertension, hydralazine and diazoxide are employed but there are certain limitations associated with the use of these
agents as they have to be administered parenterally and there is high incidence of side effects the use of these agents at times it becomes extremely difficult to control hypertension in pregnancy with conventional antihypertensive drugs.

Reves et al (1982) oral nifedipine attenuated the pressure response only to a limited extent. It is likely that gastric absorption of nifedipine in the peri-operative period was erratic and effective blood levels were not achieved. Sublingual nifedipine proved to be significantly more effective in checking the rise in mean arterial pressure. But nifedipine did not check the rise in pulse rate. This was probably because nifedipine is devoid of any effect on the A.V. nodal conduction. But despite this drawback in nifedipine, the rate pressure product, which is an index of myocardial O₂ demand remains lower in nifedipine treated subjects.

Nifedipine is a calcium channel blocker. Its clinical use since 1973 had been found to be effective and safe in patients having moderate to severe essential hypertension (Murphy et al, 1983).

Nifedipine acts by blocking calcium entry to the smooth muscles. Thus interfere with excitation and contraction coupling given orally it was rapid onset of action and low incidence of serious side effects.

Nifedipine has been used in pregnancy for inhibition uterine contractions in preterm labour and prosta-
glandins induced termination of pregnancy where there was uterine hypotonus (Anderson et al, 1979). Its onset of action was not longer than 20 minutes. Hypotensive effect lasted at least 4 hours after 10 mg of nifedipine by mouth. No significant potentiation of the action of nifedipine with administration of other hypotensive agent was seen.

Nifedipine when combined with propanolol is highly effective because observed increase in heart rate with nifedipine is inhibited by propanolol probably by inhibiting the cardiovascular effects of the activity of the sympathetic nervous system.

Blood pressure is significantly after sublingual administration of nifedipine in patients with controlled hypertension. The effect is sustained and the blood pressure remains stable throughout the period of anaesthesia. The blood pressure does not rise to alarming level and even at the time of intubation or extubation. There is not significant change in pulse rate also. But Zusman et al (1987) reported a rise of 3.7 to 6.7% in pulse rate in nifedipine treated patients during anaesthesia and operation. The finding of present study confirm the observations reported by Zusman et al (1987) and Jain et al (1987).

Ahokas et al (1983) studied nifedipine (200 microgram/kg) effectively lowered mean arterial pressure 25% by decreasing total peripheral resistance 38% cardiac output was increased 15% blood flows to the splanchnic
region and the reproductive organs were increased after nifedipine administration. The increase in blood flow to the reproductive organs was the result of increased ovarian and uterine wall perfusion blood flow was not significantly altered, but resistance was decreased. Thus the use of nifedipine to lower maternal blood pressure in pregnancy complicated by extreme hypertension does not necessarily decrease uteroplacental blood flow.

The effect of nifedipine (Adalat Bayes Miles) a calcium channel blockers, which has a well established place in nonobstetric hypertension was compared with dihydralazine in 33 primigravidas with severe hypertension of pregnancy. Patients with a diastolic blood pressure greater than 110 mm Hg before or during administration were randomly assigned to treatment with either nifedipine or dihydralazine. Both drugs were found to be equally efficacious. Nifedipine, however, showed an earlier onset of action in lowering systolic blood pressure and had the advantage of oral administrations.

Nifedipine is an antagonist of calcium influx through slow channel of the cell membrane. Its hypotensive action is mainly due to dilatation of the arterial resistance vessels. Dose and route of administration of the drug used in this study were same as that used by Puri and Batra (1988) and Khan et al (1987). Nifedipine prevented the rise in mean arterial pressure significantly.
The rise in mean arterial pressure from the basal to the maximum recorded value in the control group was 43.3% of the basal and in the nifedipine group 21.74% compared with buprenorphine nifedipine produced a significantly higher reduction in maximum rise in mean arterial pressure (p ≤0.05). Three minutes after intubation the mean arterial pressure was significantly lower than that of control, lignocaine or buprenorphine groups (p ≤0.05). The increase in rate pressure product in the nifedipine group was also lesser than in the buprenorphine one, but the difference was insignificant.

In the present study, nifedipine effectively lowered the blood pressure. Its onset of action was prompt, not longer than 20 minutes in most instances, but the spontaneous subsidence of spiker of high blood pressure is often observed. For this reason the entry criteria specified that the hypertension should be sustained over at least 20 minutes. The hypotensive effect lasted at least 4 hour after 10 mg of nifedipine by mouth. No significant potentiation of the action of nifedipine with concurrent administration of other hypotensive agents was seen contrary to the effects described in non pregnant patients (Gudzzi et al, 1980).

No serious side effects were observed with nifedipine, mild to moderate headache and palpitation could not be specifically correlated with use of
nifedipine alone as former should be a manifestation of severe PIH / or eclampsia and later could result from magnesium sulfate therapy as well. Most of the other side effects like insignificant rise in pulse rate and occurrence of flushing are expected consequence of the vasodilatation effect of nifedipine by which it exerts antihypertensive action (Huysmans et al, 1983).

The three drug combination used were lignocaine+ buprenorphine, lignocaine + nifedipine and buprenorphine+ nifedipine. A combined effect of each of the individual drugs were expected with this technique. But in fact the study failed to demonstrate any such additive effects. There was no significant difference in the mean heart rate values. The degree of reduction in maximum rise in mean arterial pressure with the drug combination stool close to the effect of that particular individual drug of the combination which showed a better effect than the other when used alone.

All 90 patients who received either diazepam or nifedipine or diazepam nifedipine combination showed significant reduction in both systolic and diastolic blood pressure. There was a significant decrease in pulse rate in all groups after atropine, diazepam nifedipine premedication.

Mean basal pulse rate of any group were not significantly different. Following laryngoscopy and intubation pulse rate decreased very significantly in
all groups reaching a maximum reduction at 30 minutes after premedicant and decreased gradually over the next 15 minutes. Pulse rate decreased after diazepam premedication intramuscularly in general anaesthesia was 93±7 minutes but in spinal analgesia the pulse rate was 95±4 minutes.

The maximum decrease in pulse rate who received nifedipine sublingually with general anaesthesia and spinal anaesthesia was 88±9/minute and 94±8/minute respectively.

The maximum decrease in pulse rate who received diazepam and nifedipine combination in general anaesthesia was 98±8/min.

Mean systolic blood pressure maximally decrease after diazepam in general anaesthesia and spinal analgesia was 121.68±4.095 mm Hg just after intubation, 120.4±4.2 after 45 minutes.

Maximum decrease in mean systolic blood pressure after nifedipine in general and spinal anaesthesia was 122.68±4.8 after 20 minutes and 123.4±4.8 after 20 minutes.

Maximum decrease in mean systolic blood pressure after diazepam + nifedipine combination in general anaesthesia was 110.4±33.4 mmHg.

Maximum decrease in mean diastolic blood pressure after diazepam in general and spinal anaesthesia was 79.6±2.15 after 20 minutes and 79.8±2.14 after 30 minutes.
Maximum decrease in mean diastolic blood pressure after nifedipine in general and spinal anaesthesia was 80.1±2.2 and 80.4±2.2 respectively after 20 minutes.

Maximum decrease in mean diastolic blood pressure after diazepam + nifedipine combination in general anaesthesia was 84.82±4.1 after 30 minutes of diazepam+nifedipine. There was no significant decrease in mean arterial blood pressure (p > 0.05) in all groups.

No complication like hypotension or bradycardia were noted in any of the patients during the subsequent period of anaesthesia. This is especially important with the view that volatile anaesthetic agents can potentiate the effect of calcium channel blockers.

This study shows that both diazepam and nifedipine are effective in decreasing the pulse rate in group Ia and IIa, systolic blood pressure and diastolic blood pressure and nifedipine provides a statistically better response than diazepam.

When diazepam was used in combination of nifedipine no added advantage or a better effect could be demonstrated. A safe agent or technique that can prevent the increase in pulse rate, systolic blood pressure, diastolic blood pressure is yet to be found out and more researches have to be carried out in this regard.