A RANDOMISED CONTROLLED TRIAL OF ORAL NIFEDIPINE VS INTRAVENOUS LABETALOL IN ACUTE CONTROL OF BLOOD PRESSURE IN HYPERTENSIVE EMERGENCIES OF PREGNANCY.

By

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DISSERTATION

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Under the Guidance of

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Declaration

I hereby declare that this dissertation entitled **"A RANDOMISED CONTROLLED TRIAL OF ORAL NIFEDIPINE VS INRAVENOUS LABETALOL IN ACUTE CONTROL OF BLOOD PRESSURE IN HYPERTENSIVE EMERGENCIES OF PREGNANCY "** is a bonafide and genuine research work carried out by me under the guidance of **Dr. M.K.SWAMY** Professor, Department of Obstetrics & Gynecology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.

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Dr. Bhushan Desai

Abbreviations

BP	: Blood Pressure
PIH	: Pregnancy Induced Hypertension
WHO	: World Health Organization
HELLP	: Hemolysis, Elevated liver enzymes and Low platelet count
NICU	: Neonatal Intensive Care Unit
RDS	: Respiratory Distress Syndrome
IUD	: Intra Uterine Death

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ABSTRACT

Objectives:

To compare the efficacy of oral nifedipine and IV labetalol in hypertensive emergencies of pregnancy, and their adverse effects

Methodology:

100 women with blood pressure greater than 160 mmHg systolic and/or 110 mmHg diastolic were randomized to oral nifedipine or IV labetalol. They were administered drugs until blood pressure was less than or equal to 150 mmHg systolic and 100 mmHg diastolic. The time required to reduce blood pressure to the target value, the number of doses required and the adverse effects were measured. The statistical level of significance was taken at $P < 0.05$.

Results:

The patients who came in the inclusion criteria were treated with either nifedipine or labetalol based on their randomization number. It was found that oral nifedipine required 22.55 (± 9.02) minutes where as, Inj. labetalol requires 38.43 (±17.93) minutes to control blood pressure. The P-value was <0.001. This indicates that the difference was highly significant. This study reveals that oral nifedipine acts much quicker than Inj labetalol to reduce blood pressure in hypertensive emergencies of pregnancy. It was also found that nifedipine requires fewer doses than labetalol to achieve the same goal. Oral nifedipine required one dose of 10 mg to reduce blood pressure where as Inj Labetalol required 2 doses, a total of 60 mg to reduce blood pressure to the target level. The p-value calculated was <0.001. Indicating the difference was highly significant. Patients were also monitored for any side effects that may arise from the drugs. The adverse effects noted were, hypotension, dizziness, sweating, flushing, nausea, vomiting, palpitations, headache and fetal tachycardia. Adverse effects observed were very few and of minor degree. There was no statistical difference noted in the adverse effects in both group.

Conclusion:

Both oral nifedipine and IV labetalol were ultimately effective in reaching the therapeutic goal, but nifedipine achieved the target blood pressure more rapidly and with fewer doses than labetalol. Both drugs demonstrated a similar adverse effects profile. Nifedipine is also cheaper, easier to store, easier to administer as it is given orally, where as IV labetalol is more expensive, needs to be stored at a lower temperature and needs slow IV administration. Thus the present study concludes that Nifedipine is the preferred drug in case of severe pre-eclampsia to control blood pressure as it is more efficacious and can be used in the peripheral centers due to cost effectiveness and its ease of administration and storage. Inj

labetalol still has a role in hypertensive emergencies in pregnancy, as it can be used in an unconscious or drowsy patient.

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

To compare the efficacy of oral nifedipine VS intravenous labetalol, in reducing the BP to systolic 150 mmHg and diastolic 100 mmHg or lower within the shortest interval of time.

SECONDARY OBJECTIVE:

To asses the adverse effects of the drugs along with the maternal and perinatal outcome.

INTRODUCTION

Hypertensive disorders are one of the most common medical disorders complicating pregnancy and form part of a deadly triad, along with hemorrhage and sepsis[1]. It contributes greatly to the maternal morbidity and mortality[1]. The incidence of hypertensive disorders ranges from 2-8% of all pregnancies and contributes to 9% of maternal mortality in Asia and 12% in India[2,3].

Approximately 70% of hypertensive disorders are due to gestational hypertension-preeclampsia[4]. The spectrum of hypertensive disease that can complicate pregnancy is broad, ranging from "white coat" hypertension to gestational hypertension, chronic hypertension and preeclampsia to chronic hypertension with superimposed preeclampsia. Particularly challenging, however, is hypertension in pregnancy that becomes severe enough to qualify as a hypertensive crisis, bringing immediate risk to both the mother and fetus[5].

The risk may evolve over days or just few hours and may present as worsening blood pressure that may culminate into hypertensive emergencies. Placental abruption and fetal distress are common with severe preeclampsia along with maternal complications like hypertensive encephalopathy and cerebrovascular accidents[5]. Aggressive blood pressure control, while fundamental, needs to be balanced against the risks to both mother and fetus of overcorrection and undercorrection

Overall, 10% to 15% of direct maternal deaths are associated with preeclampsia and eclampsia[6]. Where maternal mortality is high, most of deaths are attributable to eclampsia, rather than preeclampsia[6]. It has been estimated by the WHO that world wide approximately 45,000 women will die each year from hypertensive disorders of pregnancy[2]. How pregnancy incites or aggravates

hypertension is still not clear, despite decades of intensive research, preeclampsia remains amongst the most important unresolved problems of obstetrics.

The obstetrician should aim not just for the diagnosis, but also the prevention of complications of hypertensive disorders. Maternal complications due to very high blood pressure include eclampsia, cerebral hemorrhage, cortical blindness, cortical and tubular necrosis and abruption. All these complications are directly related to raised blood pressure. Hence quick and effective reduction of blood pressure can prevent many of the complications mentioned above.

There have been many drugs that have been described in control of preeclampsia; they include Hydralazine, Labetalol and Nifedipine. A few trials have been conducted on the above-mentioned drugs, but no single drug has been identified as being superior to the other. There is no consensus reached as yet on which antihypertensive is preferable to the others for improving outcome for women with very high blood pressure during pregnancy, and their babies. Until better evidence is available, the best choice of drug for an individual woman probably depends on the experience and familiarity of her clinician with a particular drug, and on what is known about adverse maternal and fetal side effects[7].

Inj. Hydralazine is the most commonly used drug in other developed countries in the world, but it is not available in the Indian market. Hence the aim of the present study is to compare the two most commonly used drugs in India i.e. oral nifedipine and I.V labetalol in terms of time taken to lower blood pressure, dosage required, adverse effects, the maternal and perinatal morbidity and mortality, cost effectiveness and ease of administration.

REVIEW OF LITERATURE

Hypertensive disorders are the most common medical complications of pregnancy, affecting 5% to 10% of all pregnancies. Approximately 70% of hypertensive disorders in pregnancy are due to gestational hypertension–preeclampsia. The spectrum of the disease ranges from mildly elevated blood pressures with minimal clinical significance to severe hypertension and multi-organ dysfunction. Understanding the disease process and its impact on pregnancy is of utmost importance, as hypertensive disorders remain a major cause of maternal and perinatal morbidity and mortality worldwide. Hence maternal blood pressure control is essential with expectant management or during delivery to control maternal complications. Medications can be given orally or intravenously as necessary to maintain blood pressure between 140 and 155 mm Hg systolic and 90 and 105 mm Hg diastolic. The most commonly used intravenous drugs for this purpose are labetalol and hydralazine. Care should be taken not to drop the blood pressure too rapidly so as to avoid reduced renal and placental perfusion and intrauterine hypoxia leading to sudden intra uterine death. Other drugs can include oral rapid-acting nifedipine[4].

According to the working group report on high blood pressure in pregnancy[8], the objective of treating acute severe hypertension is to prevent potential cerebrovascular and cardiovascular complications such as hypertensive encephalopathy, hemorrhage and congestive heart failure. Antihypertensive therapy is indicated when blood pressure is dangerously high or rises suddenly in women with preeclampsia. The most commonly used drugs such as hydralazine and parenteral labetalol have been shown to be effective for the treatment of acute severe hypertension in pregnancy. The use of oral nifedipine has been described in limited

number of studies. Nifedipine acts rapidly, causing significant reduction in blood pressure within 10 to 20 minutes of oral administration[8].

The royal college of obstetricians and gynecologists has provided guidelines for the management of severe preeclampsia/eclampsia 2006. The guidelines suggest that antihypertensive treatment should be started in women with a systolic blood pressure over 160 mmHg or a diastolic blood pressure over 110 mmHg. In women with other markers of potentially severe disease, treatment can be considered at lower degrees of hypertension. The drugs recommended for the acute management of severe hypertension are, labetalol (orally or intravenously), nifedipine, intravenous hydralazine. They recommend that nifedipine should be given orally not sublingually[9].

The society of obstetricians and gynecologists of Canada recommend that, blood pressure should be lowered to <160 mmHg systolic and <110 mmHg diastolic. Initial antihypertensive therapy should be with labetalol, nifedipine capsules or hydralazine. Nifedipine and $MgSO_4$ can be used at the same time[10]. Labetalol has the added advantage that it can be given initially orally in severe hypertension and then, if needed, intravenously[10]. There have been many studies where various antihypertensives mentioned above have been compared, some of the studies have been mentioned below.

In a comparative Trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy in 1987, sixty peripartum patients with diastolic blood pressures of 110 mmHg or higher were randomized to receive repeated injections of either labetalol or hydralazine until the diastolic blood pressure was

below 100 mmHg. Hydralazine lowered the mean arterial pressure more that labetalol did, but labetalol had a more rapid effect. There was considerable inter-patient variability in the dose of labetalol required to control blood pressure, which could not be predicted. The duration of action also varied in the labetalol group, with the shortest duration occurring in those patients who required the highest dosage for BP control. They concluded that labetalol appears to be a safe and effective alternative to hydralazine for treating hypertension in the peripartum period, but serious and rare side effects have not yet been quantified [11].

A randomized controlled trial was conducted in 1989, where 33 patients with severe hypertension were randomized to either nifedipine or hydralazine. In this study nifedipine had an earlier peak action in lowering diastolic blood pressure. However the difference in the mean fall in diastolic blood pressure levels were not statistically significant. For both drugs systolic blood pressure stabilized within 30 min with nifedipine having a quicker onset of action. In conclusion, this study suggests that nifedipine may be more effective than hydralazine in the acute lowering of very high blood pressure. It was concluded by the authors that further research is required on the use of nifedipine in pregnancy. Because of its ease of administration and the rapid onset of action nifedipine may be of value in reduction of blood pressure in acute hypertensive emergencies[12].

A randomized, double blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy was conducted in 1991, 50 women with blood pressure systolic greater than 170 mmHg and diastolic greater than 105 mmHg were randomized to either labetalol or nifedipine. It was concluded that both nifedipine and intravenous labetalol are effective in the management of acute hypertensive emergencies of pregnancy; however, nifedipine controls hypertension more rapidly.

In this study, nifedipine achieved the therapeutic blood pressure goal more rapidly and with fewer dosages than labetalol while demonstrating a similar side effect profile. The pharmacokinetics of nifedipine includes rapid onset, long action, oral bioavailability, and infrequent side effects. These characteristics theoretically make it and ideal agent for hypertensive emergencies in pregnancy. In fact, previous investigations have shown that nifedipine effectively lowers blood pressure without worsening already reduced utero-placental blood flow and without any significant fetal heart rate abnormality. These additional benefits are important characteristics expected of an ideal therapeutic agent for the treatment of hypertensive emergencies complicating pregnancy[13].

In 1995, a randomized prospective trial was conducted on, oral nifedipine therapy in the management of severe preeclampsia. In this study the efficacy of two drugs, nifedipine and hydralazine were compared. Good blood pressure control was achieved with both nifedipine and hydralazine throughout pregnancies with average pressure of 140/96 mmHg for nifedipine and 150/98 mmHg for hydralazine. Within the first 30 min, oral nifedipine and intravenous hydralazine lowered the average systolic/diastolic blood pressure by 19/17 and 26/28 mmHg. The fall in blood pressure values in their study was more drastic with hydralazine than with nifedipine. They concluded that nifedipine and hydralazine could both be used to effectively control blood pressure in severe preeclampsia. While hydralazine is administered intravenously and needs strict monitoring, nifedipine is more effective, easy to administer orally, less demanding on the hospital staff, convenient and more predictable[14].

In 2002, a study compared nifedipine and hydralazine as a first line agent to control hypertension in severe preeclampsia. 126 women were included in the trial. They were randomized to either nifedipine or hydralazine. 9.3% of the nifedipine patients required more than 3 doses in comparison with 19.7% in the hydralazine group to achieve effective blood pressure control. Fewer doses of nifedipine were required to achieve effective blood pressure control when compared with hydralazine. Patients receiving nifedipine achieved effective blood pressure control more quickly than those receiving hydralazine, although it did not differ statistically. Their study demonstrates that compared with hydralazine, nifedipine is effective for longer and requires fewer doses. It quickly achieves good blood pressure control in patients and the diuresis noted may impact on improvement in condition of these patients. It is safe for mother and fetus. In addition, it can be conveniently and easily administered. These properties make nifedipine, more appropriate for treatment of hypertension in severe preeclampsia when compared with hydralazine[15].

Another randomized clinical trial done in 2006, compared hydralazine and labetalol. 200 women were randomized to the study drugs. They found that the success rate obtained with labetalol was exactly the same as that of hydralazine. Both drugs fulfilled the criteria required of an antihypertensive drug for this purpose.[17].

Despite the various trials done, the present Cochrane review of 2006 has concluded that there is no clear evidence that one antihypertensive is preferable to the others for improving outcome for women with very high blood pressure during pregnancy, and their babies. Until better evidence is available, the best choice of drug for an individual woman probably depends on the experience and familiarity of her clinician with a particular drug, and on what is known about adverse maternal and fetal side effects[7]. On review of the literature on hypertensive emergencies and the

drugs for such urgencies we have come to the conclusion that quick and controlled reduction of blood pressure is of utmost importance. Very few drugs are actually used for hypertensive emergencies, which include Inj. hydralazine, Inj. labetalol and nifedipine.

There are numerous studies comparing various drugs mentioned above and most studies conclude that Inj. labetalol and nifedipine are more efficient and have lesser side effects than Inj. Hydralazine. Inj. hydralazine is not available in India; hence we need to evaluate the available drugs like Inj. labetalol and Nifedipine. Inj. labetalol is expensive, requires cold storage and requires slow IV infusion. Availability in peripheral centers is unlikely as storage is difficult. Nifedipine is cheap, easy to store and easy to administer and is particularly useful in the peripheral centers in India.

There are two guidelines suggesting that Inj labetalol and oral nifedipine can be used to control blood pressures in hypertensive emergencies of pregnancy. There has been one major international review, which has not reached a consensus regarding the drug of choice in hypertensive emergencies of pregnancy. There are a few randomized controlled trials comparing either nifedipine or labetalol to other antihypertensives, but there is only one randomized controlled trial comparing oral nifedipine to IV labetalol. Hence we need to compare these drugs to compare their efficacy in our setup.

Nifedipine:

Nifedipine is available as a capsule as well as a tablet.

Nifedipine belongs to a class of pharmacological agents, the calcium channel blockers. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, C17H18N2O6,

Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3. Nifedipine Capsules are formulated as soft gelatin capsules for oral and sublingual administration each containing 5 mg/10 mg nifedipine.

Mechanism of action

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without changing serum calcium concentrations.

Pharmacokinetics and metabolism

Nifedipine is rapidly and fully absorbed after oral administration. The drug is detectable in serum 10 minutes after oral administration, and reaches peak blood levels in approximately 30 minutes. Bioavailability is proportional to dose from 10 to

30 mg; half-life does not change significantly with dose. There is little difference in relative bioavailability when nifedipine capsules are given orally and either swallowed whole, bitten and swallowed, or bitten and held sublingually. However, biting through the capsule prior to swallowing does result in slightly earlier plasma concentrations (27 ng/mL 10 minutes after 10 mg) than if capsules are swallowed intact. It is highly bound by serum proteins. Nifedipine is extensively converted to inactive metabolites and approximately 80 percent of nifedipine and metabolites are eliminated via the kidneys. The half-life of nifedipine in plasma is approximately two hours. Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92–98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

Hemodynamics

Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. Nifedipine causes decreased peripheral vascular resistance and a fall in systolic and diastolic pressure, which is usually modest (5–10mm Hg systolic), but sometimes larger. There is usually a small increase in heart rate, a reflex response to vasodilation.

Pregnancy

Pregnancy Category C

Nifedipine has been shown to produce teratogenic findings in rats and rabbits,

including digital anomalies similar to those reported for phenytoin. On a mg/kg basis, all of the doses associated with the teratogenic, embryo-toxic or feto-toxic effects in animals were higher (3.5 to 42 times) than the maximum recommended human dose of 120 mg/day. On an mg/m2 basis, some doses were higher and some were lower than the maximum recommended human dose but all are within an order of magnitude of it. The doses associated with placento-toxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m2 basis.

Non-teratogenic Effects:

There are no adequate and well-controlled studies in pregnant women. Nifedipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dosage:

10mg is the initial dose give orally. Followed by 20 mg given every 20-30 minutes, until the total dose of 120 mg/day.

Adverse effects:

Nifedipine has frequent adverse effects but generally not serious and rarely require discontinuation of therapy or dose adjustment. Sudden hypotension is one of the greatly feared adverse effects of nifedipine. This is most commonly seen in sublingual use. Other adverse effects like peripheral edema**,** dizziness or lightheadedness**,** nausea**,** headache flushing, weakness**,** transient hypotension**,** palpitation, nasal and chest congestion, shortness of breath, diarrhea, constipation, cramps, inflammation, joint stiffness, muscle cramps, shakiness, nervousness are noted.

Labetalol Hydrochloride:

Labetalol hydrochloride injection is an adrenergic receptor-blocking agent that has both selective alpha 1-adrenergic and non-selective beta-adrenergic receptor blocking actions in a single substance.

Labetalol injection is a clear colorless to light yellow, aqueous, sterile, isotonic solution for intravenous injection.

Labetalol Hall combines both selective, competitive, alpha1-adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity in a single substance. In man, the ratios of alpha- to beta-blockade have been estimated to be approximately 1:3 and 1:7 following oral and IV administration, respectively.

Labetalol Hall produces dose-related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its alpha- and beta-blocking effects. Hemodynamic effects are variable, with small, nonsignificant changes in cardiac output seen in some studies but not others, and small decreases in total peripheral resistance. Elevated plasma renins are reduced.

Doses of Labetalol HCL that controlled hypertension did not affect renal function in mild to severely hypertensive patients with normal renal function.

Pharmacokinetics and Metabolism

Following IV infusion of Labetalol, the elimination half-life is about 5.5 hours and the total body clearance is approximately 33 mL/min/kg. The plasma half-life of Labetalol following oral administration is about 6 to 8 hours. In patients with

decreased hepatic or renal function, the elimination half-life of Labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased "first-pass" metabolism.

The metabolism of Labetalol is mainly through conjugation to glucuronide metabolites. The metabolites are present in plasma and are excreted in the urine and, via the bile, into the feces. Approximately 55% to 60% of a dose appears in the urine as conjugates or unchanged Labetalol within the first 24 hours of dosing.

Labetalol has been shown to cross the placental barrier in humans. Only negligible amounts of the drug crossed the blood-brain barrier in animal studies. Labetalol is approximately 50% protein bound. Neither hemodialysis nor peritoneal dialysis removes a significant amount of Labetalol HCL from the general circulation (<1%).

Pregnancy:

Pregnancy Category C

A teratology study performed with Labetalol in rabbits at IV doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with Labetalol HCL for hypertension during pregnancy.

Labor and Delivery

Labetalol HCL given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Dosage

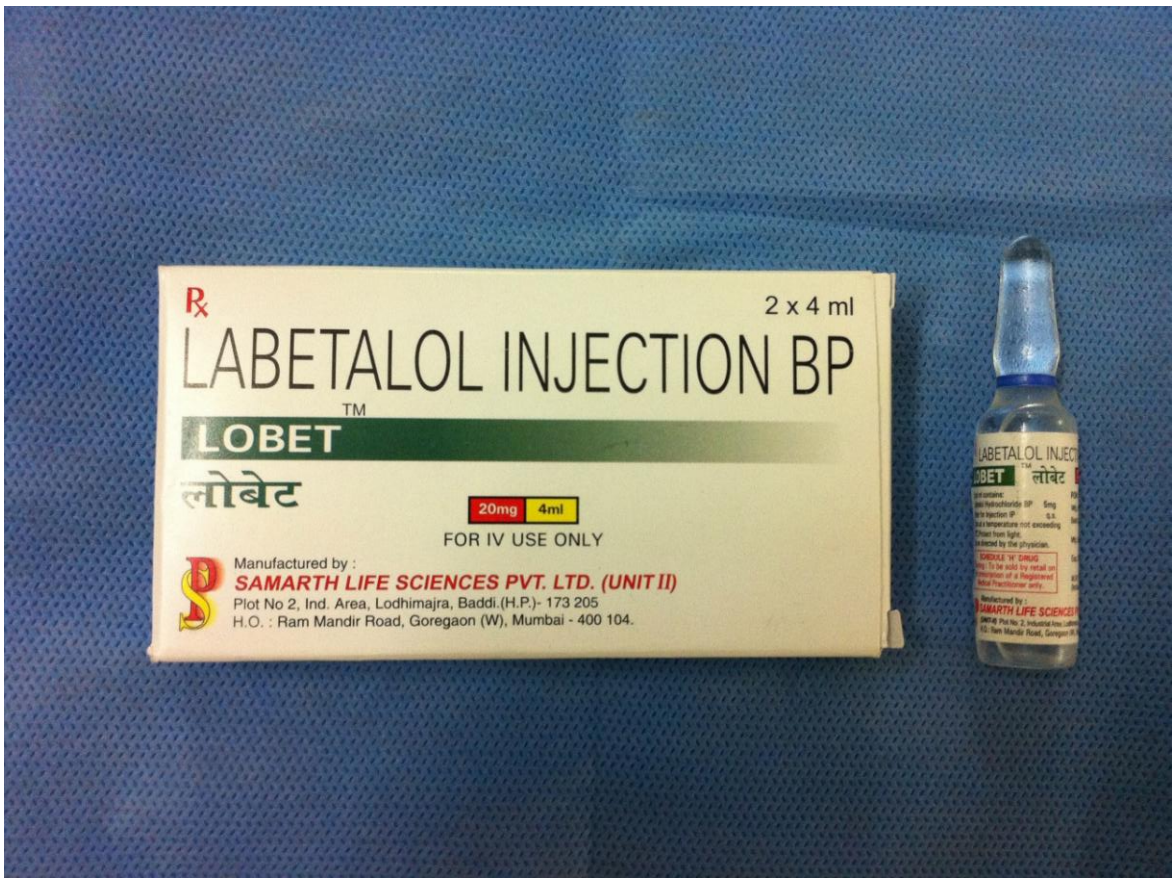
Initially, Labetalol hydrochloride injection should be given in a 20 mg dose by slow IV injection over a 2-minute period.

Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 or 80 mg can be given at 10-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg of Labetalol HCL has been injected. The maximum effect usually occurs within 5 minutes of each injection.

Adverse Reactions

Labetalol hydrochloride injection is usually well tolerated. Most adverse effects have been mild and transient. Symptomatic postural hypotension (incidence, 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving Labetalol hydrochloride injection. Moderate hypotension, Ventricular arrhythmia, dizziness tingling of the scalp, hypoesthesia (numbness) and vertigo Nausea, vomiting, dyspepsia and taste distortion and somnolence/yawning have been noted.

Nifedipine capsules 10 mg



Inj labetalol 20 mg/4 ml

MATERIALS AND METHODS

The study got ethical approval by institutional review board of Jawaharlal Nehru medical college, Belgaum, Karnataka, India on October 11th 2010.

Study Design: Randomized control trial.

Sample size: Sample size was calculated on the basis of a previous study where oral nifedipine required an average of 25 min ($\bar{x}_1$=25) to reduce blood pressure and IV labetalol required 43.6 min ($\bar{x}_2$=43.6) to reduce blood pressure[11]. Level of significance was taken as 5% (Z_α=1.96) and the power of test was taken as 80% (Z_β=0.84).

Formula used for calculation was,

$$N = \frac{(Z_\alpha + Z_\beta)^2 \ 2s^2}{D^2}$$

Where; Z_α=1.96, Z_β=0.84, $\bar{x}_1$=25, $\bar{x}_2$=43.6, D= $\bar{x}_1$ - $\bar{x}_2$ =12.6 and

$2s^2 = (13.6)^2 + (25.4)^2$

Sample size calculated was 40, 20 belonging to each group. Sample size was small; hence all women meeting the inclusion criteria, during the study period were enrolled in the study.

Inclusion criteria:

- Period of Gestation more than 20wks.
- All women with a systolic BP of more than 160 mmHg or more and/or diastolic BP of 110 mmHg or more.

Exclusion Criteria:

- Patient with cardiac disease
- Asthma
- Any antihypertensive drug taken 24 hours prior to enrollment.

Source for data collection:

All women admitted with a systolic BP of more than 160 mmHg or more and/or diastolic BP of 110 mmHg or more during pregnancy who came to the labor ward or OPD at K.L.E.S Dr. Prabhakar Kore Hospital and MRC were included in the trial. Patients who came to OPD and casualty were admitted to the labor room for further management.

Informed Consent: Women who presented to labor room of K.L.E.S Dr. Prabhakar Kore hospital & MRC, Belgaum were screened for enrollment in the study using inclusion and exclusion criteria. Informed consent was obtained, a signature or left had thumb impression from the consented subject was obtained after reading the informed consent document. For illiterate participants, the consent document was read out. The patient and the relatives were explained the relative risk s involved in the study. None of the participants were pressurized to enroll into the trial. No monitory benefit was offered to any of the participants enrolled in the study.

Randomization: Assignment of the participants to the two groups was done using computer generated randomized number chart (Annexure I)

Patients with even numbers were allotted to Nifedipine group and with odd numbers were allotted to the Labetalol group.

Method of data collection

Once the patient was randomized to a group, a proforma regarding the basic details of the patient was entered (annexure III).

Once the basic details were entered, the B.P was recorded again. A sphygmomanometer was used to record blood pressure manually. Blood pressure was checked in the right arm with the cuff covering at least 2/3 of the arm. Systolic pressure corresponded to the appearance of Korotkoff sounds and diastolic pressure corresponded to the disappearance of Korotkoff V sounds.

All patients were administered prophylactic Magnesium sulphate.

The patients were administered either nifedipine or labetalol based on the randomization. Patients randomized to the labetalol group were administered with 20mg (4ml) of Labetalol. Blood pressure was measured every 5 minutes. The second dose of 40mg (8ml) labetalol was given if the target blood pressure was not achieved within 20 minutes. If blood pressure was not controlled another dose of 80mg (16ml) was infused. This was repeated at 20 min interval for two more times till a maximum total dose of 300mg was administered. Inj labetalol was always infused at a slow rate over 2-5 minutes.

The patients belonging to the nifedipine group were given 10 mg of nifedipine capsules the first dose. The dosage was increase to 20 mg

after 20 min if BP was not brought under control. The 20 mg dose was repeated for 4 times till a maximum of 90 mg was administered. Nifedipine was never give sublingually.

The time required for blood pressure to reach the target value was noted. The number of doses required to achieve the target value was noted.

The blood pressure was measured every 5 minutes for 1 hour. Thereafter the blood pressure was monitored every 15 minutes for the following 3 hours. Blood pressure was monitored for a total of 4 hours.

Adverse effects if any were noted. The patient was followed up and any complications arising as a result of severe hypertension were noted. The mode of delivery, maternal and perinatal morbidity and mortality were noted. The neonates if admitted in NICU were followed up till discharge.

For every woman the following data was noted

- Number of doses administered
- Time needed to control blood pressure
- Adverse effects
- Maternal and perinatal outcome

The significance of these tests was calculated using various formulas. The significance was based on P-value. The following formulas were used to obtain P-value.

- To compare the duration of effectiveness of the drugs, students unpaired t test was used.
- For the number of doses Mann Whitney test
- For comparison of adverse effects test of proportions was used.

The outcome was noted as.

Primary outcome:

1. The time taken in minutes, by either drug to reduce the blood pressure.

Secondary outcome:

2. The number of drugs required and the adverse effects.

RESULTS

Age distribution:

	Nifedipine (n=49)	Labetalol (n=51)
Average age	24.4 ± 3.73	23.9 ± 3.8

Table No 1. Mean age of the patient in years.

The two groups in consideration were comparable with regards to age distribution.

The average age for the nifedipine group was 24 years 4 months. And for the labetalol group was 23 years 9 months.

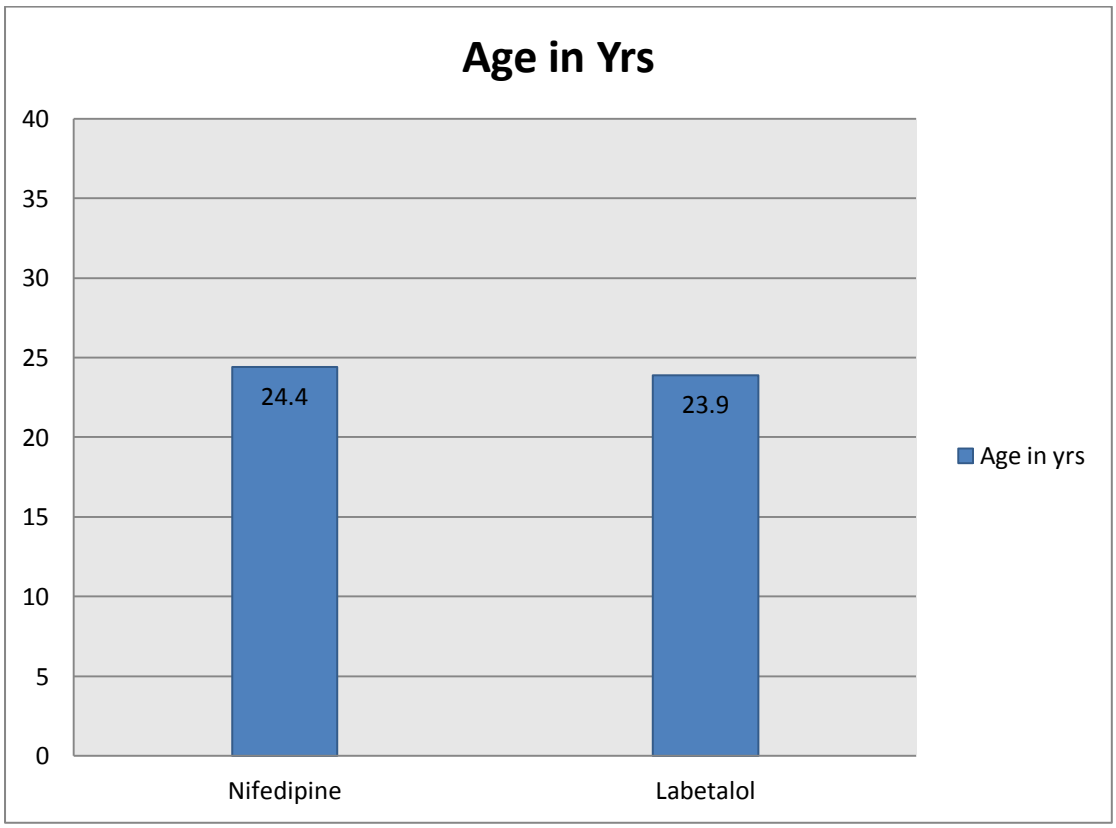


Chart No 1. Mean age of the patient in years.

Weight distribution:

	Nifedipine (n=49)	Labetalol (n=51)
Weight distribution	59.8 ± 6.42	56.9 ±7.5

Table No 2. Mean weight of the patient in kg.

The two groups were comparable in terms of weight distribution. The average weight in kilograms, for the nifedipine group was 59.8 kg and 56.9 kg for the labetalol group.

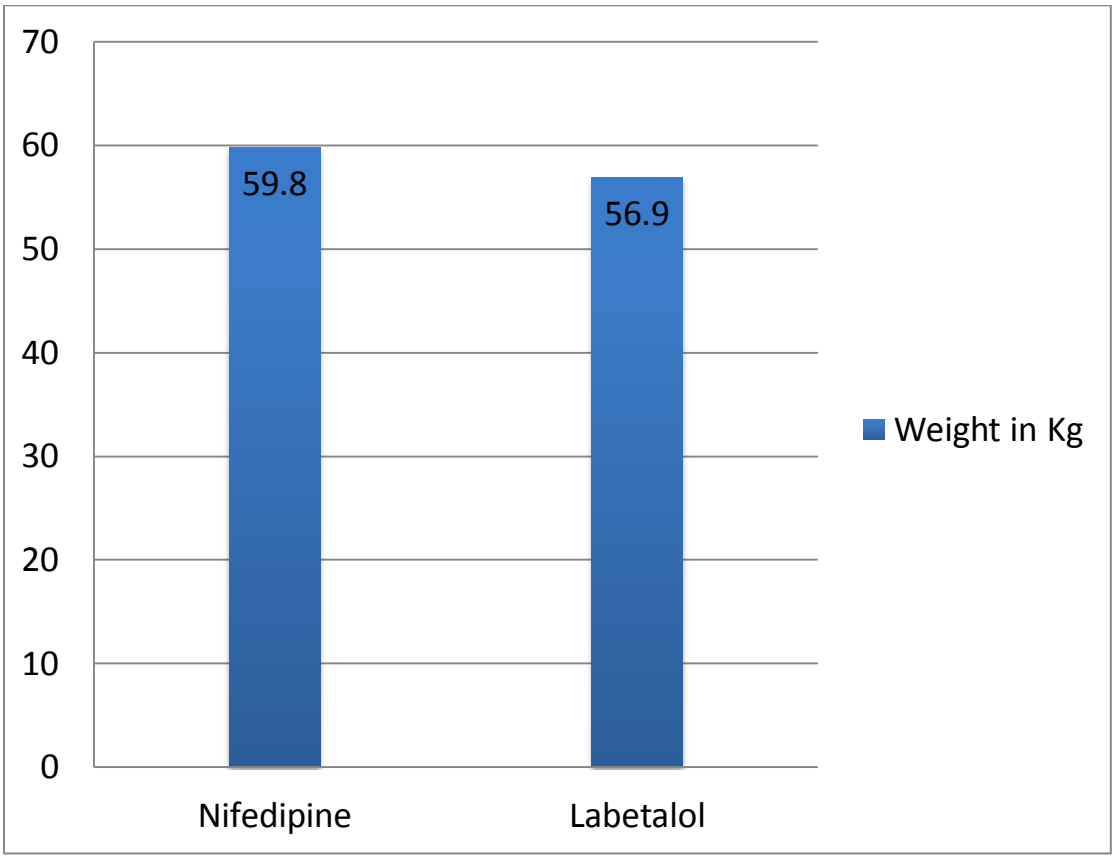


Chart No 2. Mean weight of the patient in kg.

Parity:

Parity	Nifedipine (n=49)	Percentage	Labetalol (n=51)	Percentage
1	27	55.1%	29	56.8%
2	7	14.2%	11	21.5%
3	13	24.4%	6	11.7%
>3	3	6.1%	5	9.8%

Table No.3 Parity

49 women were randomized to Nifedipine group and 51 to the Labetalol group. In the Nifedipine group 27 patients (55.1%) were primigravida, 7 patients (14.2%) were 2nd gravida, 12 patients (24.4%) were 3rd gravida and 3 patients were more than 3rd gravida. In the labetalol group, 29 patients (56.8%) were primigravida, 11 patients (21.5%) were 2nd gravida, 6 patients (11.7%) were 3rd gravida and 5 patients (9.8%) were greater than 3rd gravida.

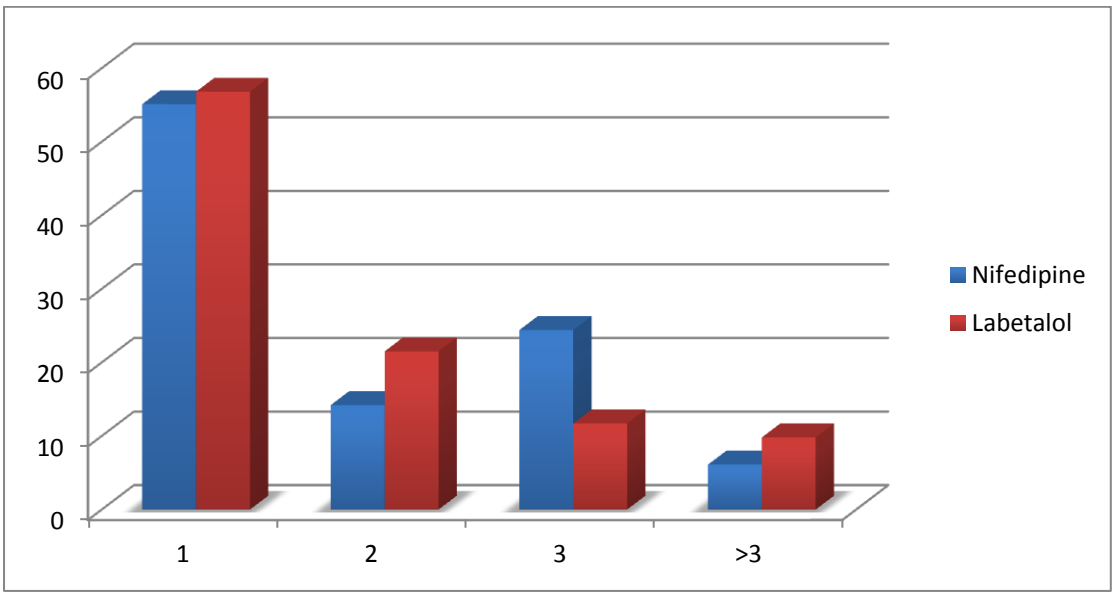


Chart No.3 Parity

Period of gestation:

	Nifedipine (n=49)	Labetalol (n-51)
Period of gestation	35 weeks 4 days	36 weeks 2 days

Table No.4. Mean period of gestation in weeks.

The average period of gestation in the two study groups were similar

The average gestational age for the nifedipine group was 35 weeks 4 days and average gestational age for labetalol was 36 weeks and 2 days.

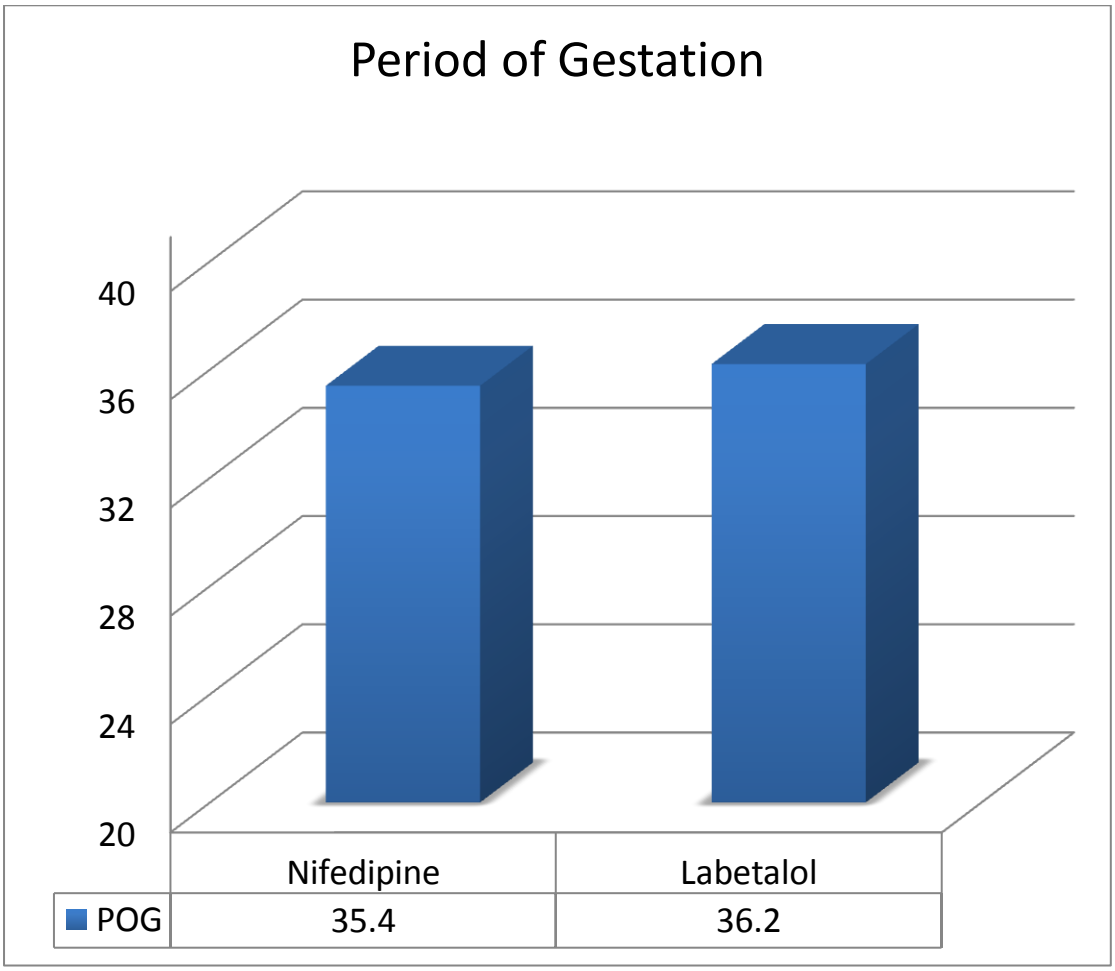


Chart No.4. Mean period of gestation in weeks.

Blood pressure at initiation of treatment:

	Nifedipine (n=49)	Labetalol (n=51)
Systolic	166.8 ± 6.47	167.5 ± 7.56
Diastolic	110.2 ± 5.27	110.8 ± 6.06

Table No.5 Blood pressure in mmHg.

The blood pressure before initiation of treatment was checked in both groups. In the Nifedipine group the mean systolic Blood pressure was 166.8 ± 6.47 mmHg and Diastolic blood pressure was 110.8 ± 6.06 mmHg. In the labetalol group systolic blood pressure was 167.5 ± 7.56 mmHg and diastolic blood pressure was 110.8 ± 6.06.

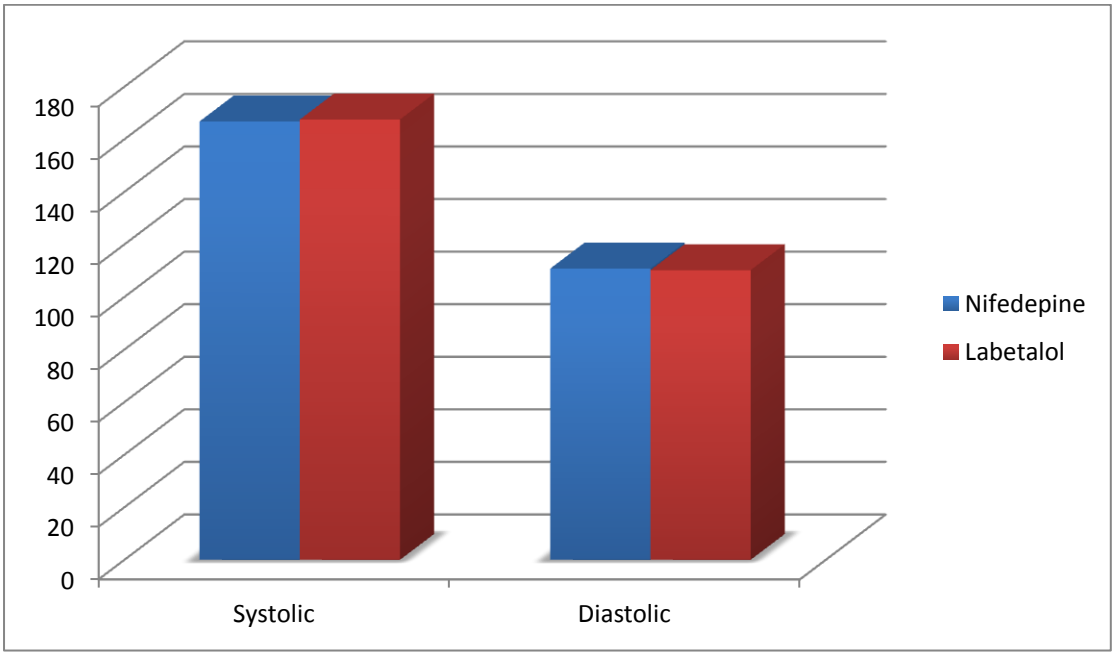


Chart No.5. Blood pressure in mmHg.

Time duration for the desired action:

	Nifedipine (n=49)	Labetalol (n=51)	P value
Duration for BP control	22.55 ± 9.02	38.43 ± 17.93	<0.0001

Table No.6. Time duration for action in minutes.

There was a significant difference in the time take to reduce the blood pressure to the target level. On an average the target blood pressure in the nifedipine group was achieved in 22.55 minutes with a standard deviation of 9.14 minutes and the time for achieving the target blood pressure in the labetalol group was 38.43 minutes with a standard deviation of 17.93 minutes. The test used to calculate the p-value in comparison was the STUDENT'S UNPAIRED T-test. The p-value obtained was <0.0001, which indicates that difference in the time between the two groups was very significant.

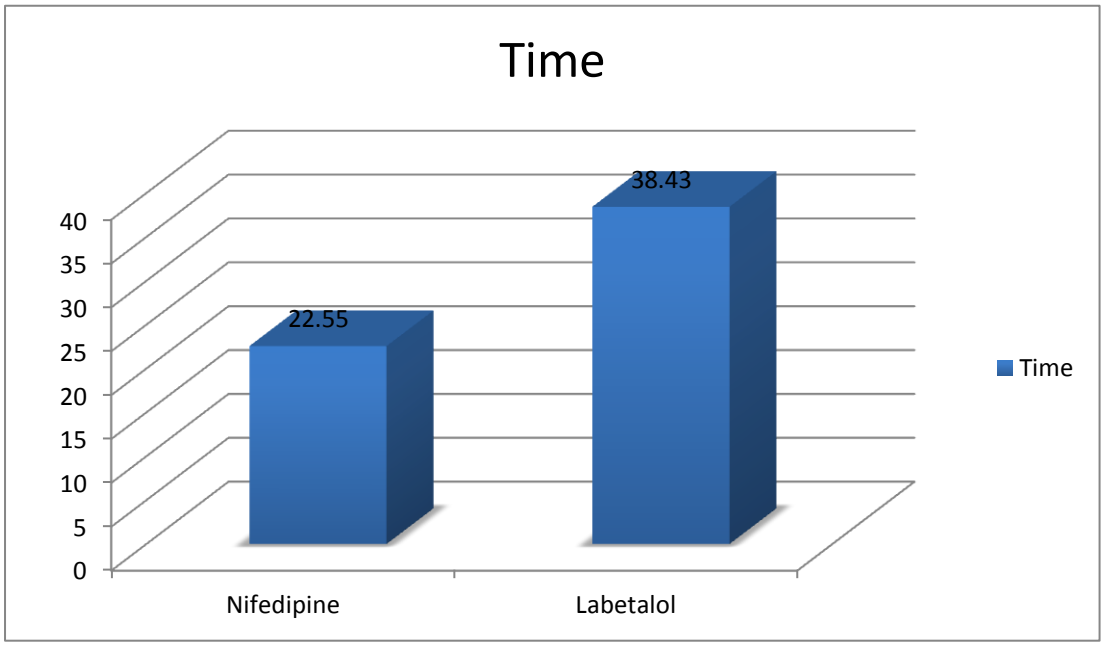


Chart No.6.Time duration for action in minutes.

Number of Doses required:

	Nifedipine (n=49)	Labetalol (n=51)	P-value
Number of drugs	1	2	<0.0001

Table No.7 Number of Doses required.

The number of drugs required for each group was calculated by the median. On an average the nifedipine group required 1 drug to bring about the desired action, the labetalol group required 2 drugs to bring about the same action. MANN-WHITNEY test was applied to calculate the p-value. The p-value of<0.0001 indicates that there was a significant difference in the number of drugs required to get the desired action.

Adverse effects:

	Nifedipine (n=49)	Labetalol (n=51)	P-value
Hypotension	0	0	0
Dizziness	0	1(1.9%)	0.32
Flushing/sweating	1(2.04%)	2(3.8%)	0.58

Table No.8A Adverse effects.

	Nifedipine (n=49)	Labetalol (n=51)	P-value
Nausea/vomiting	1(2.04%)	1(1.9%)	0.97
Palpitation	0	2(3.9%)	0.16
Headache	7(14.2%)	4(7.8%)	0.3
Fetal tachycardia	0	4(7.8%)	0.04

Table No.8B Adverse effects.

The various side effects that would arise from the study drugs were noted. There were no incidences of hypotension in either of the study groups. The patients in the nifedipine group had no dizziness but 1 in 51 individuals (1.9%) of the labetalol had dizziness. the p value was 0.3 which was not statistically significant.

1 patient (2.04%) of the nifedipine group (n=49) had sweating and flushing where as 2 patients (3.8%) in the labetalol group (n=51) had the same effects. The p-value being 0.58 shows, the difference was not statistically significant.

Similarly 1 (2.04%) patients in the nifedipine group and 1 patient (1.96%) in the labetalol group had complains of nausea and vomiting. The p-value was 0.97, which was not significant.

0 patients in the nifedipine group and 2 (3.9%) patients in the labetalol group had complains of palpitation. The p value was 0.16, hence not significant.

7 patients (14%) of 49 in the nifedipine group had complains of headache where as 4 patients (7.8%) patients in the labetalol group had headache. The p value was 0.3 hence the difference was not significant. Fetal tachycardia was noted in 4 (7.8%) patients in the labetalol group (n=51) alone. The p-value was 0.04 and the difference was insignificant.

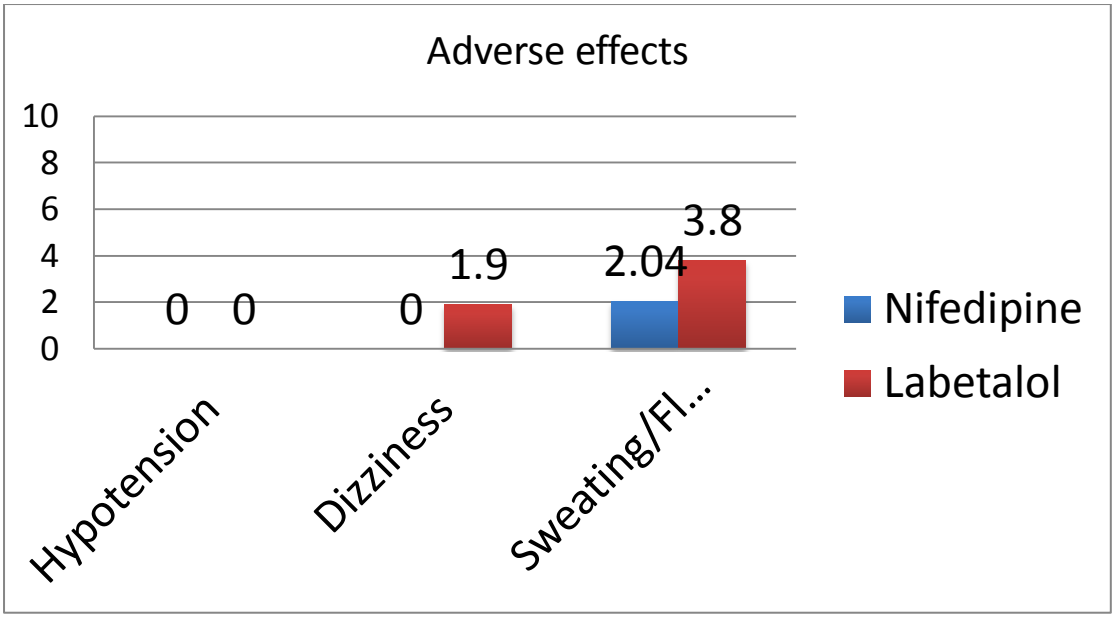


Chart No.7A Adverse effects.

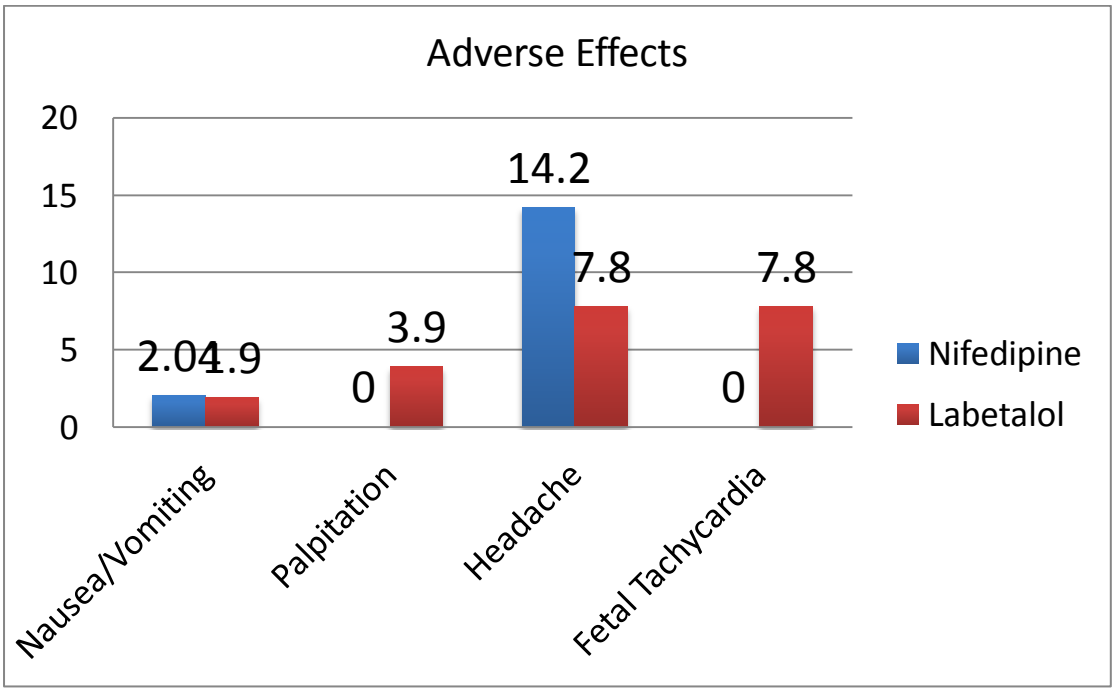


Chart No.7B Adverse effects.

Mode of delivery:

	Nifedipine (n=49)	Labetalol (n=51)	Percentage	
Cesarean section	23	50%	23	45.2%
Vaginal delivery	19	41.3%	27	52.9%
Instrumental delivery	4	8.7%	1	1.9%

Table No.9 Mode of delivery.

The modes of delivery in both groups were as follows. In the nifedipine group there were 23 (n=46, 50%) cesarean sections, 19 (n=46, 41.3%) vaginal deliveries and 1 instrumental delivery (n=46, 1.9%).

The number cesarean section in the labetalol group were 23 (n=51, 45.2%), there were 27(n=51, 52.9%) vaginal deliveries and 4 (n=51, 1.9%)instrumental deliveries.

The p-value did not reveal any significant difference in the two groups.

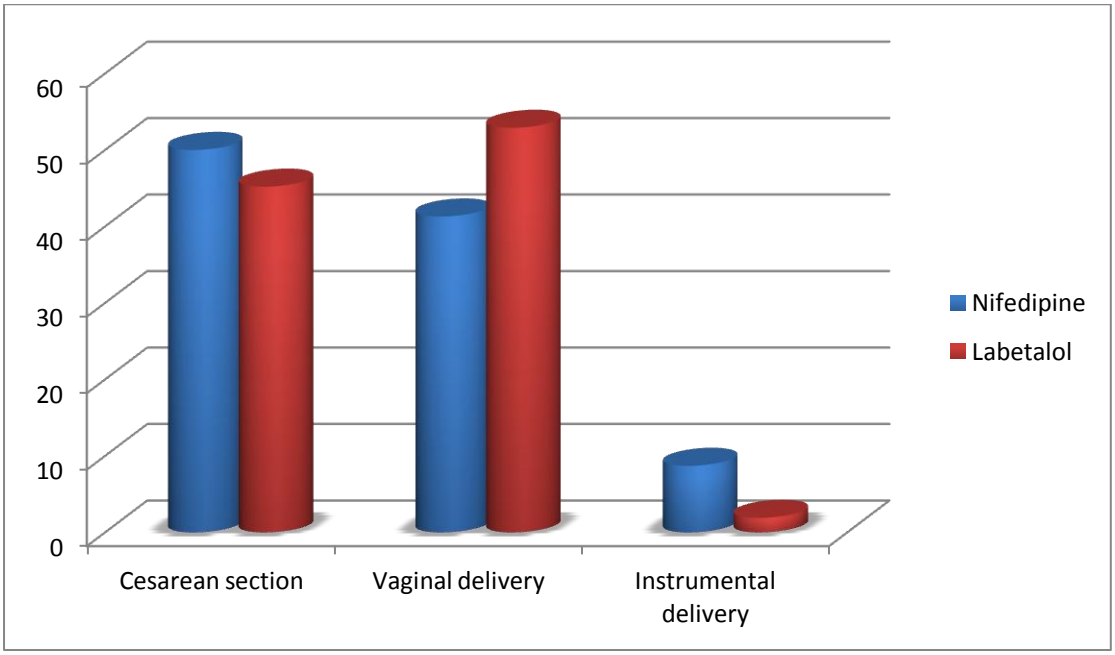


Chart No.8 Mode of deliver

Complications:

	Nifedipine	Labetalol	P-value
Eclampsia	2 (n=49) 4.08%	3 (n=51) 5.8%	0.42
Abruption	2 (n=47) 4.26%	2 (n=51) 3.9%	0.93
HELLP	0	1 (n=51) 1.96%	0.3

Table No.10A complications.

	Nifedipine	Labetalol	P-value
Renal failure	0	0	
Stroke	0	0	
Pulmonary edema	0	0	
Mortality	0	1 (n=51, 1.96%)	0.3

Table No.10B complications.

Complications arising due to severe preeclampsia in the two study groups were as follows. The complications were attributed to severe preeclampsia and were not related to the study drugs. Eclampsia recorded in this study occurred prior to admission. There were no incidences of eclampsia after therapy was started.

2 patients (n=49, 4.08%) in the nifedipine group and 3 patients (n=51, 5.8%) in the labetalol group had eclampsia.

2 patients (n=47, 4.26%) in the nifedipine group and 2 patients (n=51, 3.9%) in the labetalol group had abruption.

There were no incidences of HELLP in the nifedipine group where as one patient (1.96%) in the labetalol group was in HELLP syndrome.

There were no incidences of renal failure, stroke or pulmonary edema in either of the study groups. There was mortality in the labetalol study group.

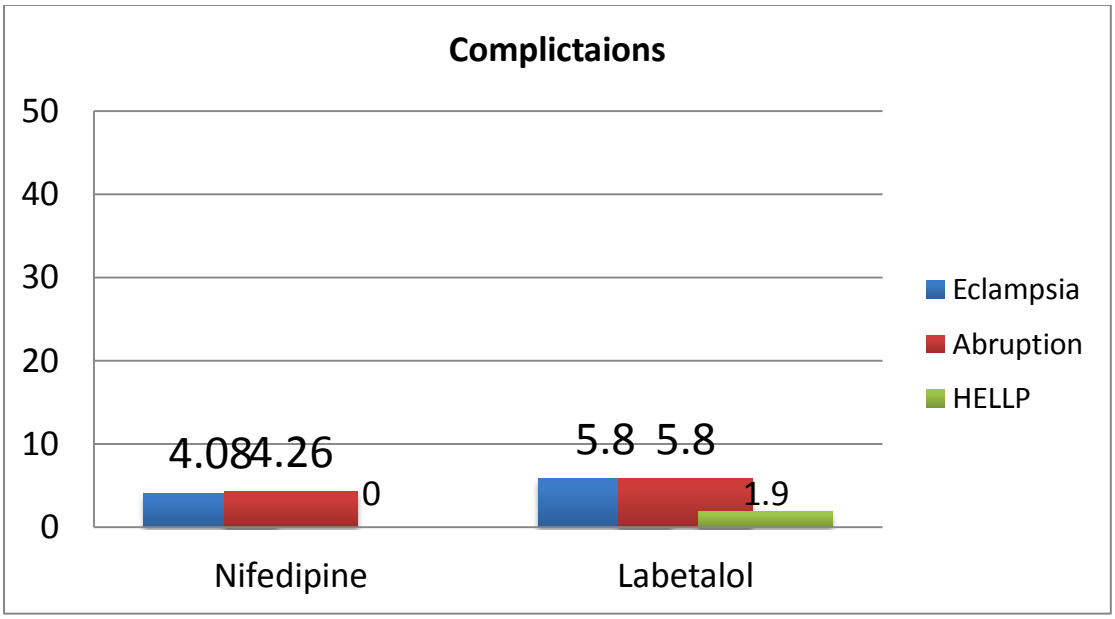


Chart No.9A complications.

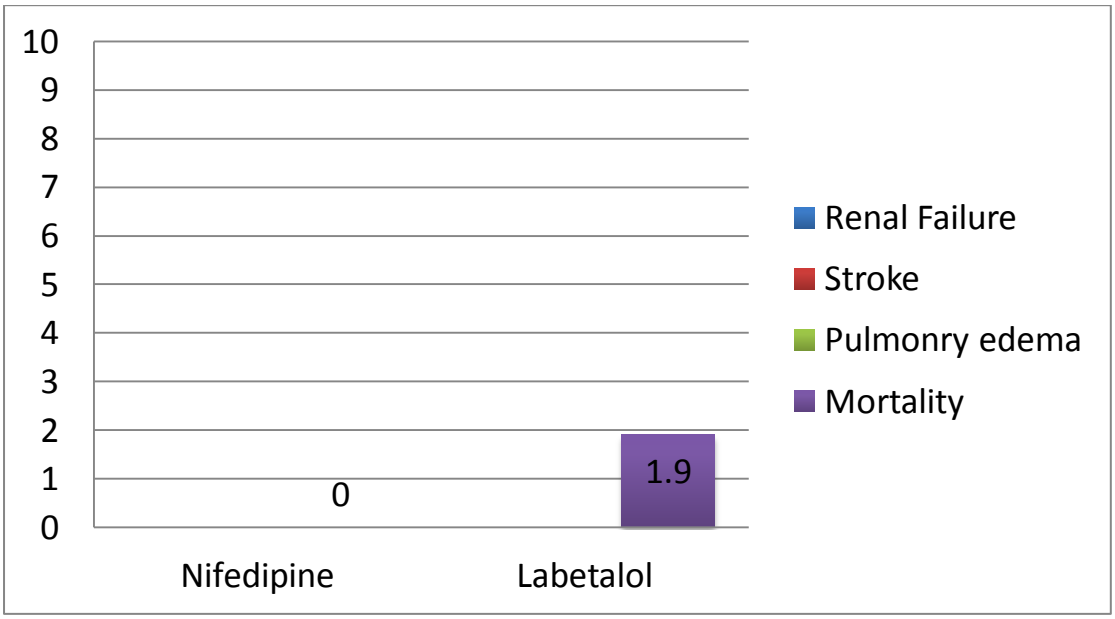


Chart No.9B complications.

Fetal weight:

	Nifedipine	Labetalol
Birth weight	2.16 ± 0.7	1.91 ± 0.85

Table No.11 Fetal weight in Kg.

The average fetal weight for the nifedipine group was 2.16 Kg and for the labetalol group was 1.91 kg.

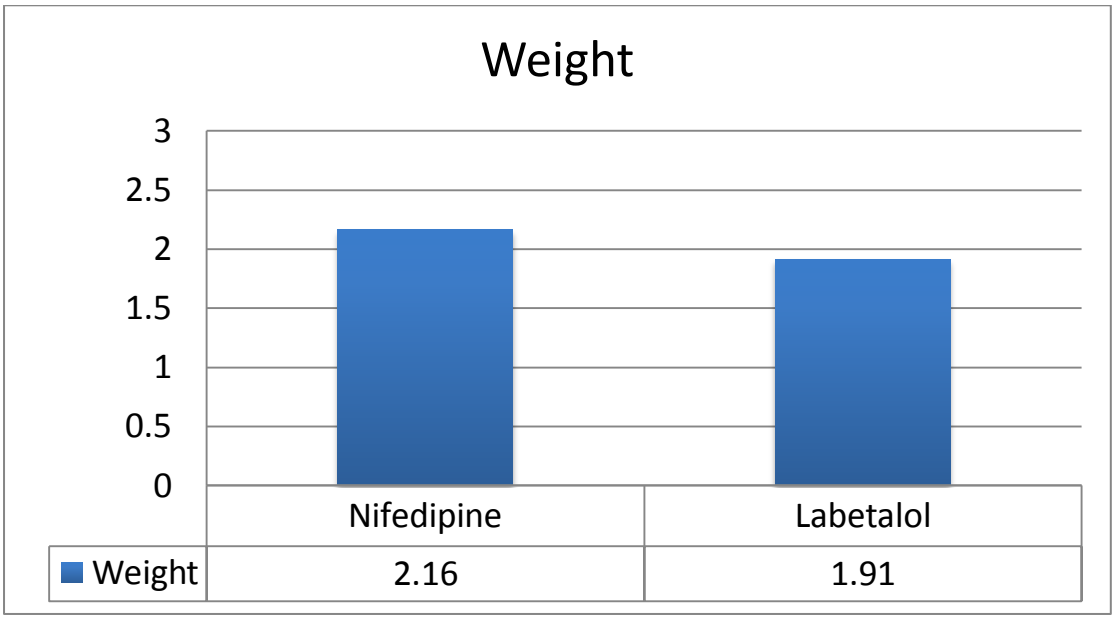


Chart No.10 Fetal weight in Kg.

Neonatal complications:

	Nifedipine n=40	Labetalol n=41	P-value
Preterm	13 (32.5%)	20 (46.5%)	0.19

Table12A. Preterm.

NICU admissions	9 (22.5%)	18 (41.8%)	0.05

Table12B. NICU admissions.

RDS	0	6(14.2%)	0.01(s)
Hyperbilirubinemia	13 (32.5%)	20 (46.5%)	0.19

Table No.12C Neonatal complications.

	Nifedipine	Labetalol	P-value
IUD	6 (15%)	10 (23.2%)	0.43
Neonatal mortality	3 (7.5%)	8 (18.6%)	0.13

Table No.12D Neonatal mortality.

There were 11(n=40, 32.5%) preterm deliveries in the nifedipine group and 20 (n=43, 46.5%) preterm deliveries in the labetalol group. The p-value derived was 0.15. The difference was not statistically significant.

9 (22.5%) babies in the nifedipine group and 17 (41.8%) babies in the labetalol group required NICU admission, p-value was 0.05. the difference was not significant.

6 (14.2%) babies in the labetalol group had respiratory distress syndrome (RDS) where as the nifedipine group had none. The p-Value was 0.01. The difference was statistically significant. The incidence of hyperbilirubinemia was 32.5% (13 patients) in the nifedipine group and 46.5% (20 patients) in the labetalol group. P-value was 0.19, which was not significant.

There were a total of 16 IUD s of which 6 (13%) belonged to the nifedipine group and 10(23.2%) belonged to the labetalol group. The p-value was 0.43.

The neonatal mortality for the nifedipine group was 3 (7.5%) and for the labetalol group was 8 (18.6%). The P-value was 0.13, which was not significant statistically.

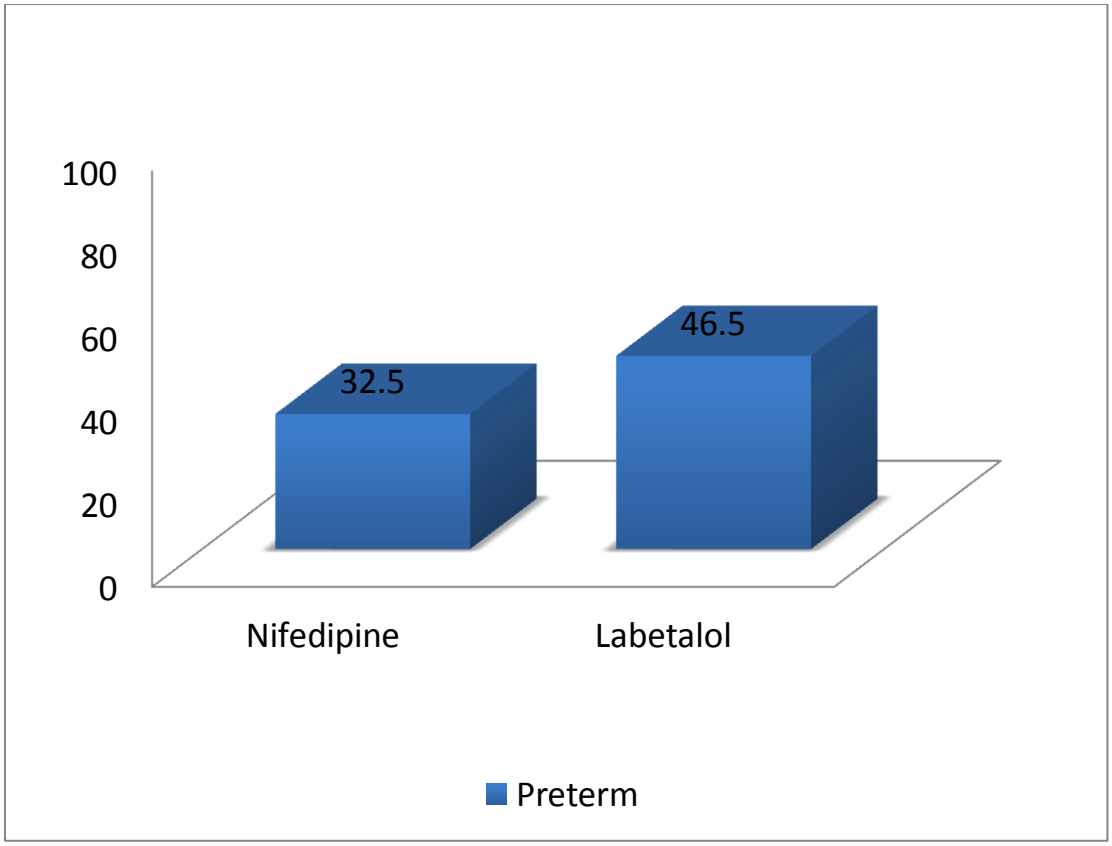


Chart No.11A Neonatal complications-preterm.

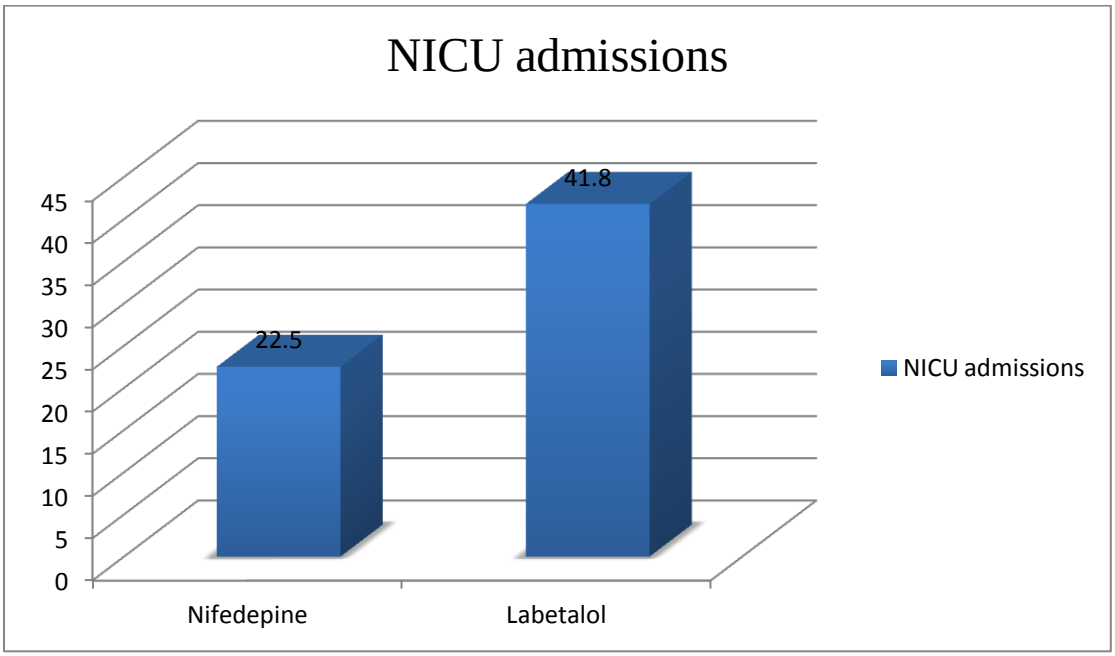


Chart No.11B Neonatal complications-NICU admissions.

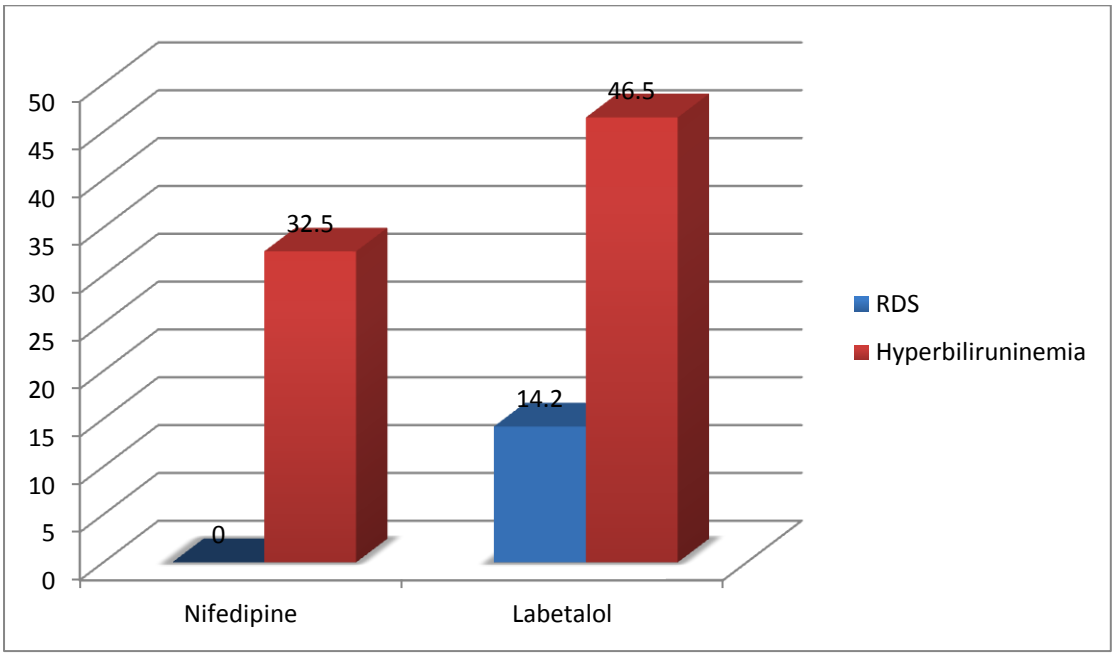


Chart No.11C Neonatal complications.

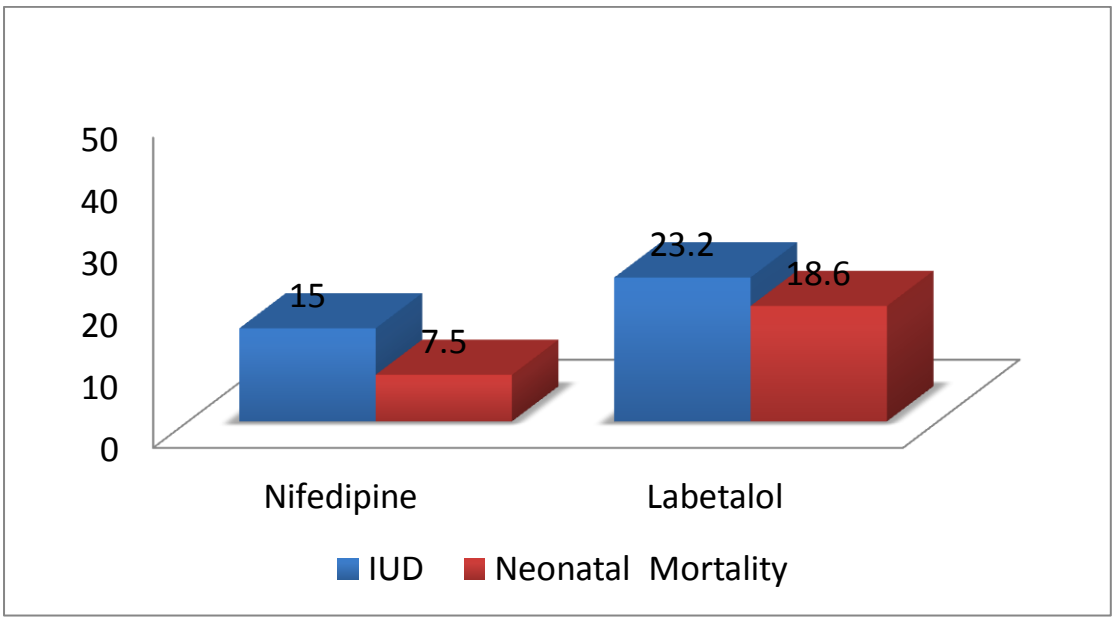


Chart No.11D Neonatal Mortality.

DISCUSSION

This randomized controlled study, compares the efficacy of two anti-hypertensive drugs, oral nifedipine and I.V labetalol.100 patients were included in the trial of which, 49 were randomized to nifedipine and 51 were randomized to labetalol.

Of the 49 patients who were randomized one patient went against medical advice. 2 patients enrolled were post partum.

Both groups were similar in terms of age, weight and period of gestation. The average age of a subject in the nifedipine group was 24 years and 5 months and the average age in the labetalol group was 23 years 10 months. The average weight of an individual in the nifedipine group was 59.8 kg (± 6.4). There was similar distribution of weight in the labetalol group with an average weight of 56.9 Kg (±7.5). The mean period of gestation in both groups was similar. The average gestational age in the nifedipine group was 35 weeks 4 days and 36 weeks 2 days in the labetalol group.

Time taken to control blood pressure:

Many studies have shown that both nifedipine and labetalol can be used successfully in treating hypertensive crisis. The present study reveals that oral nifedipine reduces the blood pressure at a significantly faster rate than Inj labetalol. The average duration to control blood pressure in the nifedipine group was 22.55 minutes with SD of 9.63 where as labetalol takes about 38.43 minutes with SD of 17.93. This indicates that both nifedipine and labetalol can be used to lower blood pressure but nifedipine does so, at a significantly faster rate. The p-Value was < 0.0001, calculated using students unpaired T test. The difference is statistically significant. This result is echoed by one of the randomized controlled study

comparing the two drugs. They had similar results where in nifedipine reduced blood pressure in a significantly shorter duration when compared to the labetalol group[13].

Number of doses required:

The mean for the dosage required to reduce blood pressure was 1.24 ± 0.56 for the nifedipine group and 2.13 ± 0.85 for the labetalol group. The nifedipine group requires 1 dose to reduce the blood pressure, where as the labetalol group requires 2 doses to achieve the same effect. P-value is calculated using the Mann-Whitney test. P-value obtained was <0.0001. This indicates that the test is highly significant. A randomized controlled trial done on the same drugs had similar results where a significantly smaller dose was required by Nifedipine to control blood pressure[11].

Adverse effects:

There are various side effects that may arise due to the drugs. The most common adverse effects were looked for. They included hypotension, dizziness, flushing, nausea, vomiting, palpitation, headache, and fetal tachycardia. Test of proportions was used to compare the results. There were no incidences of hypotension in either of the study group. 1 (1.9%) patient in the labetalol group had dizziness but there were no incidence of such complains in the nifedipine group. 1 patient (2.04%) belonging to the nifedipine group had sweating and 2 patients (3.8%) in the labetalol group had flushing and sweating. P-value was 0.58. The difference was not statistically significant. 1 patient (2.04%) in the nifedipine group and 1 patient (1.9%) in the labetalol group had complains of vomiting. The p-value was 0.97, hence not statistically significant.

2 patients (3.9%) patients in the labetalol group had palpitations where as no patients in the nifedipine had similar complains. The p-value obtained was 0.16 that was statistically not significant. The occurrence of headache was higher than other adverse effects. 7 patients (14.2%) in the nifedipine group and 4 patients (7.8%) in the labetalol group had headache. The P-value was 0.3. The difference is not significant. Since High blood pressure can present with headache, it is difficult to attribute it to the adverse effects of any of the drugs. 4 patients (7.8%) in the labetalol group had fetal tachycardia. There was no incidence of fetal tachycardia in nifedipine group. The p-value was 0.04. The difference was not statistically significant. Similar studies also indicate that the side effects of the above mentioned were rare and of a very minor degree.

Complications due to High Blood pressure:

Complications arising due to severe preeclampsia in the two study groups were as follows. The complications were attributed to severe preeclampsia and were not related to the study drugs. Eclampsia recorded in this study occurred prior to admission. There were no incidences of eclampsia after therapy was started. 2 patients (4.08%) in the nifedipine group and 3 patients (5.8%) in the labetalol group had eclampsia. P-value was 0.42, which was not significant.2 patients (4.26%) in the nifedipine group and 2 patients (3.9%) in the labetalol group had abruption. The difference was not significant as the p-value obtained was 0.93. There were no incidences of HELLP in the nifedipine group where as one patient (1.96%) in the labetalol group was in HELLP syndrome. The p-value was 0.3. There were no incidences of renal failure, stroke or pulmonary edema in either of the study groups.

There was mortality in the labetalol study group. The mortality was attributed to magnesium toxicity and its complications. There was no statistically significant difference in the two study groups regarding the complications. The complications.

Fetal weight:

The average fetal weight in the nifedipine group was 2.16 ± 0.7 kg and 1.91 ± 0.85 kg in the labetalol group.

Neonatal complications:

There were 11(32.5%) preterm deliveries in the nifedipine group and 20 (46.5%) preterm deliveries in the labetalol group. The p-value derived was 0.15. The difference was not statistically significant. 9 (22.5%) babies in the nifedipine group and 17 (41.8%) babies in the labetalol group required NICU admission, p-value was 0.05. The difference was not significant. 6 (14.2%) babies in the labetalol group had respiratory distress syndrome (RDS) where as the nifedipine group had none. The p-Value was 0.01. The difference was statistically significant. The incidence of hyperbilirubinemia was 32.5% (13 patients) in the nifedipine group and 46.5% (20 patients) in the labetalol group. P-value was 0.19, which was not significant. There were a total of 16 IUD s of which 6 (13%) belonged to the nifedipine group and 10 (23.2%) belonged to the labetalol group. The p-value was 0.43.The neonatal mortality for the nifedipine group was 3 (7.5%) and for the labetalol group was 8 (18.6%). The P-value was 0.13, which was not significant statistically. The higher incidence of RDS in the labetalol group can be explained by the higher incidence of preterm deliveries in the labetalol group.

Table: comparing the present results to vermillion et al.

	Vermillion et al		Present study	
Drugs	Nifedipine	Labetalol	Nifedipine	Labetalol
Duration for BP control	25.0±13.6 mins	43.6±25.4 mins	22.6±9.14 mins	38.4±17.9 mins
No of drugs required	1.5±0.5	2.5±1.5	1	2
Headache	16%	20%	14.2%	7.8%
Flushing	8%	8%	2.04%	3.8%
Nausea	8%	8%	2.04%	1.9%

Strengths of the study:

There have been many studies comparing antihypertensive drugs, but there was only one study conducted in the early 1990's comparing these two specific drugs. This study is important, as Nifedipine and Inj labetalol are the only two drugs available in India that have been recommended for use in hypertensive emergencies in pregnancy.

The present study was a randomized controlled trial. Hence there was no bias in selecting patients to a particular study group.

Both groups were similar in most aspects, in terms of age, weight and period of gestation, parity and blood pressure.

None of the previous studies on antihypertensives measure the time required to reduce blood pressure and the dosage required. Since we have measured the time interval for action, dosage the adverse effects and the maternal and perinatal outcome we can very well conclude that nifedipine was a superior drug in treatment for hypertensive emergencies in pregnancy.

Drawbacks of the study:

The present study is an unblinded study. The study would have been more conclusive if there was blinding. There may be some amount of inter-observer variability as the Blood pressure was manually checked for each patient. Occasionally difficulty was encountered in measured the Blood pressure at the frequent interval of 5 minutes. The present study may also be criticized as there are some recommendations that Inj. labetalol dose should be repeated every 10 minutes.

CONCLUSION

In the present study, both oral nifedipine and IV labetalol were ultimately effective in reaching the therapeutic goal, but nifedipine achieved the target blood pressure more rapidly and with fewer doses than labetalol.

Both drugs demonstrated a similar adverse effects profile.

Nifedipine is also cheaper, easier to store, easier to administer as it is given orally, where as IV labetalol is more expensive, needs to be stored at a lower temperature and needs slow IV administration.

Thus the present study concludes that Nifedipine is the preferred drug in case of severe pre-eclampsia to control blood pressure as it is more efficacious and can be used in the peripheral centers due to cost effectiveness and its ease of administration and storage.

Inj labetalol still has a role in hypertensive emergencies in pregnancy, as it can be used in an unconscious or drowsy patient.

SUMMARY

The present study is a randomized controlled trial where in two antihypertensives; oral nifedipine and IV labetalol were compared. The study compared the efficacy of the two drugs in controlling acute hypertensive emergencies of pregnancy.

Patients with systolic blood pressure of 160 mmHg or more and/or diastolic blood pressure of 110 mmHg or more were treated with either oral Nifedipine or IV labetalol. The primary objective of the study was to calculate the time required to reduce the blood pressure to the target level of 150 mmHg systolic or less and 100 mmHg diastolic or less. The secondary out come was to calculate the number of doses required to achieve the target blood pressure and the adverse effects of the drugs.

100 consenting women were enrolled in the study. They were randomized to the nifedipine group and the labetalol group using a computer generated randomization chart.

The patients who came in the inclusion criteria were treated with either nifedipine or labetalol based on their randomization number. It was found that oral nifedipine required 22.55 (± 9.02) minutes where as, Inj labetalol requires 38.43 (±17.93) minutes to control blood pressure. The P-value was <0.001. This indicates that the difference was highly significant. This study reveals that oral nifedipine acts much quicker than Inj labetalol to reduce blood pressure in hypertensive emergencies of pregnancy. It was also found that nifedipine requires fewer doses than labetalol to achieve the same goal. Oral nifedipine required one dose of 10 mg to reduce blood pressure where as Inj Labetalol required 2 doses, a total of 60 mg to reduce blood

pressure to the target level. The p-value calculated was <0.001. Indicating the difference was highly significant.

Patients were also monitored for any side effects that may arise from the drugs. The adverse effects noted were, hypotension, dizziness, sweating, flushing, nausea, vomiting, palpitations, headache and fetal tachycardia. Adverse effects observed were very few and of minor degree. There was no statistical difference noted in the adverse effects in both group.

Complications arising from the raised Blood pressure such as, eclampsia, abruption, HELLP, stroke, renal failure, cerebrovascular accidents were noted. The complications that were noted were not attributable to the drugs. These complications were due to High blood pressure secondary to preeclampsia.

Perinatal morbidity and mortality was also noted. It was found that there was a statistically significant difference in occurrence of RDS in the labetalol group. This was attributed to the extreme preterm patients in the labetalol group. There was no statistical difference in the perinatal mortality or morbidity.

This study proved that nifedipine is the choice of drug in cases of hypertensive emergencies of pregnancy. Nifedipine acts faster, at a lesser dose and has equal side effects to that of labetalol. Nifedipine has the added advantage of being easily available, cheap and easy to administer.

Labetalol has an advantage that it can be given intravenously when the patient is unconscious or incapable of taking oral nifedipine, as seen following an eclamptic seizure.

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ANNEXURE

Annexure 1

Randomization chart

P01=**46**, p02=**26**, p03=**14**, p04=**63**, p05=**76**, p06=**51**, p07=**34**, p08=**36**, p09=**17**, p10=**44**, p11=**97**, p12=**49**, p13=**53**, p14=**99**, p15=**79**, p16=**16**, p17=**8**, p18=**27**, p19=**47**, p20=**31**, p21=**32**, p22=**91**, p23=**72**, p24=**33**, p25=**22**, p26=**89**, p27=**65**, p28=**41**, p29=**95**, p30=**43**, p31=**56**, p32=**2**, p33=**42**, p34=**1**, p35=**62**, p36=**82**, p37=**37**, p38=**75**, p39=**10**, p40=**66**, p41=**70**, p42=**94**, p43=**80**, p44=**28**, p45=**4**, p46=**74**, p47=**5**, p48=**48**, p49=**60**, p50=**12**, p51=**73**, p52=**38**, p53=**30**, p54=**13**, p55=**40**, p56=**59**, p57=**78**, p58=**64**, p59=**39**, p60=**11**, p61=**68**, p62=**83**, p63=**84**, p64=**88**, p65=**6**, p66=**86**, p67=**58**, p68=**85**, p69=**100**, p70=**57**, p71=**50**, p72=**21**, p73=**69**, p74=**18**, p75=**7**, p76=**92**, p77=**54**, p78=**90**, p79=**96**, p80=**55**, p81=**35**, p82=**87**, p83=**19**, p84=**61**, p85=**3**, p86=**9**, p87=**71**, p88=**24**, p89=**29**, p90=**45**, p91=**52**, p92=**23**, p93=**81**, p94=**67**, p95=**93**, p96=**77**, p97=**20**, p98=**15**, p99=**98**, p100=**25**

- Even no= nifedipine.
- Odd no = labetalol.

Exclusion criteria

1. Less than 20 weeks
2. Asthmatics
3. H/o cardiac illness
4. Exposure to antihypertensives within 24 hours
5. BP <160 /110.

Annexure 2

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

STUDY: RANDOMISED CONTROL TRIAL OF ORAL NIFEDIPINE VS IV LABETALOL IN ACUTE CONTROL OF BLOOD PRESSURE IN HYPERTENSIVE EMERGENCIES OF PREGNANCY.

Principal Investigator: Dr.Bhushan Desai; Postgraduate Student

Guide **:** Dr.M.K.Swamy Prof and HOU

We request you to be a participant in above said research to be conducted at KLE'S Hospital from Sep 2009 to Sep 2010 conducted by DR BHUSHAN DESAI. Postgraduate student in the Dept. Of obstetrics and gynecology at J.N. Medical College, Belgaum. Ph. No 9844869960

Your participation in this study is your voluntary decision whether or not to participate will not affect your current or future relationship with the KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre.

Procedure Involved:

If you agree in this research we would subject you to either of the two study drugs and measure the efficiency of the drugs to control blood pressure. The out come will be measured by regular blood pressure monitoring.

Risk and benefits:

There are no additional risks involved in this procedure, as they are getting the same conventional treatment that they would receive, if they were not part of the trial. If

any complications arise during the procedure then the patients will be treated with best of our knowledge. There will be no compensation or payment for such medical treatment.

If you attain any complication during the procedure you may contact Dr.M.K.Swamy professor and head of unit Ph. no 9448479147 and Dr.Bhushan Desai postgraduate in the Dept. of obstetrics and gynecology.

During the course of study you will be informed of any significant new findings such as changes in risks and benefits resulting from participation in the research.

Privacy and Confidentiality:

The only people who will know that you are a research participant are members of the research team. No information about you or provided by you, during the research will be disclosed to others without your written consent. When the results of the research are published or discussed the conferences, no information will be disclosed that would reveal your identity. Any information obtained in connections with this study and that can be identified with you remain confidential and will be disclosed only with your permission.

Voluntary participation:

Your participation in this study will help us identify a superior drug amongst the two that will help us treat the future patients with the same drug. You are free to discontinue the participation in the study at any time for any reasons and you will not be paid any reimbursement for participation in the research.

If you have any questions about your rights or research as research participant you may contact Dr. V.D.Patil, Principal JNMC, Belgaum.Ph. No 08312473777. You will be given a copy of this form for your information and to keep for your records.

Statement of Consent:

To voluntarily agree to take part in this study I must sign on the line below: If you chose to take part in this study I may withdraw at any time I am not giving up any of my legal rights, by signing this form. My signature below indicates that I have read or have read to me this entire consent form including the risks and benefits and had all questions answered, I will be given a copy of this consent form.

Signature of the Subject:

Name: Date:

Signature of the authorized representative:

Name: Date:

Relation to the Subject:

Signature of the witness:

Name: Date:

Signature of the investigator:

Name: Date:

Annexure 3

PROFORMA

STUDY: RANDOMISED CONTROL TRIAL OF ORAL NIFEDIPINE VS IV LABETALOL IN ACUTE CONTROL OF BLOOD PRESSURE IN HYPERTENSIVE EMERGENCIES OF PREGNANCY.

IDENTIFICATION

Sr no:

Randomization no:_____ Date:

Name:_____ I.P.No:

Age:_____ Wt:

Address:

INFORMED CONSENT

Was the consent given Y N

INCLUSION CRITERIA

History of any cardiac illness Y N

History of asthma Y N

History of exposure to antihypertensives within 24hrs Y N

ELIGIBILITY

Is the woman eligible? Y N

OBH

Gravida para abortion living

LMP: / / EDD: / /

POG:

VITALS ON ADMISSION

PR: BP:

VITALS BEFORE STARTING TREATMENT

PR: BP:

Patient put on prophylactic magnesium sulphate: Y N

Time of initiation of treatment

Time from 00:00 hrs	Blood Pressure	PR	U/O (if catheterized)
00:00			
00:05			
00:10			
00:15			
00:20			
00:25			
00:30			
00:35			
00:40			
00:45			
00:50			
00:55			
01:00			
01:15			
01:30			
01:45			
02:00			
02:15			
02:30			
02:45			
03:00			
03:15			
03:30			
03:45			
04:00			

Number of drugs required for achievement of target BP:

ADVERSE EFFECTS

1. Hypotension: Y N

   Minimum BP:

2. Dizziness Y N
3. Sweating, flushing Y N
4. Nausea, vomiting Y N
5. Palpitations Y N
6. Headache Y N
7. Fetal tachycardia Y N

MATERNAL OUTCOME:

Period of gestation

Mode of delivery normal/ instrumental/ cesarean

Eclampsia Y N

Abruption Y N

HELLP Y N

Renal Failure Y N

Cerebro-vascular accident Y N

Pulmonary edema/ left ventricular failure	Y	N
Mortality	Y	N
Others (pls mention)		

PERINATAL OUTCOME:

Gestational age		
Weight		
APGAR		
1min		
5min		
NICU Admission	Y	N
RDS	Y	N
Hyperbilirubinemia	Y	N
Preterm	Y	N
IUD	Y	N
Neonatal mortality	Y	N