"A RANDOMISED PARALLEL-GROUP TRIAL FOR COMPARISON OF SAFETY AND EFFICACY OF ORAL NIFEDIPINE RETARD VERSUS INTRAVENOUS LABETALOL IN MANAGEMENT OF HYPERTENSIVE EMERGENCIES OF PREGNANCY"

BY

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BL.D.E. (DEEMED TO BE UNIVERSITY), VIJAYAPURA

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

OBSTETRICS AND GYNECOLOGY

Under the guidance of

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LIST OF ABBREVIATIONS

SBP	**Systolic blood pressure**
DBP	**Diastolic blood pressure**
PE	**Pre-eclampsia**
BP	**Blood pressure**
WHO	**World health organization**
NICU	**Neonatal intensive care unit**
ACOG	**American congress of obstetricians**
PLGE	**Placental growth factor**
TNF	**Tumor necrosing factor**
VEGF	**Vegetative growth factor**
PRES	**Posterior reversible encephalopathy syndrome**
RBF	**Renal blood failure**
GFR	**Glomerular filtration rate**

DIC	**Disseminated intravascular coagulation**
HELLP	**Haemolysis, elevated liver enzymes, low platelet count syndrome**
MAP	**Mean arterial pressure**
RFT	**Renal function test**
LFT	**Liver function test**
LDH	**Lactate dehydrogenase**
CTG	**Cardiotocography**
LV	**Left ventricular**
RV	**Right ventricular**
PIH	**Pregnancy-induced hypertension**

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ABSTRACT

Background:

Pre-eclampsia is a complication of pregnancy that is associated with substantial maternal and fetal morbidity and mortality. The disease presents with new-onset hypertension and often proteinuria in the mother, which can progress to multi-organ dysfunction, including hepatic, renal and cerebral disease, if the fetus and placenta are not delivered. Treating of severely increased blood pressure is widely recommended to reduce the risk for maternal complications. Regimens for the acute treatment of severe hypertension typically include intravenous medications. Although effective, these drugs require venous access and careful fetal monitoring and might not be feasible in busy or low resource environments.

Aims and objectives: To compare the safety and efficacy of oral Nifedipine retard to intravenous Labetalol in the management of hypertensive emergencies of pregnancy.

Methodology: A Randomized parallel group comparative study was conducted in Department of Obstetrics and Gynecology of Shri B.M Patil Medical College And Research Centre, Vijaypura. A total of 104 pregnant women with Hypertensive emergencies attending outpatient department were included and divided into 2 groups with 52 each in group A which was given IV labetalol and group B with oral Nifedipine retard 20mg. IV Labetalol group received 20mg initially followed by

escalating doses of 40m and 80mg up to maximum of 5 doses every 15min up to target blood pressure is reached. Group B received Oral Nifedipine retard (Extended release) 20mg initially followed by repeated doses of 20mg every 30 minutes maximum of 5 doses until desired target blood pressure was reached. (SBP <150 mm Hg and DBP between 80-100 mm Hg). During the study, vitals are monitored closely and the maternal blood pressures will be recorded at every 15 minutes to achieve target blood pressure. Then at every 30 minutes for the next 2 hours followed by hourly monitoring and recording any adverse effect of the drugs.

Results: The present study showed the maximum age group were in between 18-24 year of age. In this study mean of SBP enrollment of IV Labetalol and Oral Nifedipine retard was 169.42±13.197 and 163.48±5.363 respectively and Mean DBP of IV Labetalol and Oral Nifedipine retard was 112.69±7.440 and 112.60±5.154 respectively. Proteinuria and oedema were more in IV Labetalol than in Oral Nifedipine retard group. Mean dose of IV Labetalol and Oral Nifedipine was 70±42.565 and 33.17±13.137 respectively. A highly significant (p value 0.001) results with mean of total number of doses given in IV Labetalol and Oral Nifedipine was 2.06±.669 and 1.73±.630 were obtained respectively. Mean SBP after 15 min, 30 min, 45 min, 60 min, 75 min and 90 min in group A and group B was 155.10±13.172 and 158.54±5.301, 143.64±12.776 and 149.48±7.883, 141.67±16.967 and 148.47±6.601, 138±16.745 and 140.96±8.126, 136±11.256 and

138.40±6.066 and 132±13.246 and136±7.071 respectively. Results were found to be significant. Mean DBP after 15 min, 30 min, 45 min, 60 min, 75 min and 90 min was in group A and group B was 100.78±7.441 and 107.37±6.630, 92.73±8.174 and 98.63±7.659, 90.83±9.962 and 98.17±6.412, 86±6.783 and 90.56±5.938, 84±8.567 and 88.40±3.209 and 82 ±9.563 and 86±8.960 respectively. Results were found to be significant. Mean target SBP of IV Labetalol and Oral Nifedipine was 139.42±8.498 and 139.12±6.379 respectively. Mean target DBP of IV Labetalol and Oral Nifedipine was 89.42±6.076 and 89.52±4.672 respectively. Most of the patients 35(67.3%) of IV Labetalol and 30(57.5%) of Oral Nifedipine group B did not had any side effects. 7(13.4%) patients had Headache and 2(3.9%) patients had abdominal pain side effect in IV Labetalol and 12(23%) had tachycardia in Oral Nifedipine. Results were found to be significant (P value0.04) when comparing side effect in IV Labetalol and Oral Nifedipine.

Conclusion: The blood pressure can be effectively controlled with the use of Labetalol in the dosage used which was observed in cases of moderate to severe pregnancy- induced hypertension. IV labetalol is safe drug and effective drug in management of hypertension in pregnancy.

Keywords: SBP, DBP, Pre-eclampsia, eclampsia, proteinuria, edema, IV labetalol, Oral Nifedipine retard.

INTRODUCTION

While being pregnant is a wonderful and life-changing time for women, it may also bring with it a number of difficulties that need to be well watched over and managed. Almost ten percent of pregnant women suffer from hypertension, one of the most prevalent medical conditions while expecting. Some examples of hypertensive diseases during pregnancy such as hypertension and pre-existing hypertension, pre-eclampsia, eclampsia during gestation can occur with or without superimposed pre-eclampsia.(1)

An extreme rise in blood pressure (≥160/110 mmHg) accompanied by symptoms of damage to target organs are likely to be pulmonary edema, cardiac ischemia, Acute Renal Failure, neurologic disorders, aortic dissection and eclampsia; are referred to as a hypertensive emergency.(2)

With a reported prevalence of 5–10%, these disorders are amongst primary prevalent consequences of pregnancy. It appears that human hypertension originates de novo during pregnancy. Globally, these conditions are ranked contributors to neonates and mothers' morbidity, death reportedly associated to 22% perinatal deaths and 30% maternal deaths. Worldwide, World Health Organisation (WHO) estimated that hypertensive diseases during pregnancy would claim the lives of about 50,000 women annually.(3)

Among 3 lakh women from Asian, African and Latin Americans, according to WHO

in 2013, worldwide hospital study on maternity- newborn health revealed pre-eclampsia to be at an incidence of 2.5% while eclampsia to be0.3%.[4]

The two most crucial hospital treatments if pre-eclampsia is confirmed are blood pressure management and seizure control. The impacted organs must be identified by assessing the mother and fetus. It affects young, nulliparous women, and racial/ethnic factors, including genetics, impact occurrence. A few other risk factors are thrombophilias, obesity, and multiple fetal gestations.**[5]**

In addition to increasing the risk of a cardiovascular accident, severe PIH must be treated right away as a prevention measure for intracerebral haemorrhage followed by complications of hypertensive encephalopathy and organ damage of any other target organ. Severe PIH also pose high chances of complications for fetus, such as preterm, Low Birth Weight (LBW) babies, NICU admissions with fetal life loss.[6-8]Pregnancy-related hypertension illnesses since ages are related to posed increases in blood pressure, cardiovascular diseases in women, added to risks these cause to the pregnancy. [5,6]

Pre-eclampsia can only be treated with careful birth planning. The date of birth must be determined from gestational age, illness severity, delivery advantages, risks associated with conservative care. A single round of prenatal corticosteroids to hasten the maturity of the fetal lung when gestational age is less than 34 weeks [6]

Here it is one unique case since the mother and fetus are exposed to medications for short span, advantages to mother may not be immediately apparent, and the therapy is shorter. Below gestational age of 28 weeks, that is when the fetus is considered as severely immature, this is typically troublesome, even if the birth is the sole treatment and it results in the disorders disappearing.

Additionally, the pharmacokinetics and pharmacodynamics of the prescribed medications would be impacted differently by the pathophysiology of hypertension diseases during pregnancy. The National Institute for Health and Clinical Excellence (UK) suggests that labetalol whether oral or intravenous, intravenous hydralazine or oral nifedipine are first -line alternatives to hypertensive women in a critical care environment for inpatient treatment.[7,8]

Hydralazine, a peripheral vasodilator, has a hypotensive effect in five to twenty minutes. The maximum impact lasts for about 10- 80 minutes, its activity lasting around two to six hours. According to a meta-analysis, hydralazine is linked to an increased chances of maternal hypotension, placental abruption, maternal oliguria and caesarean sections having negative consequences on fetus heart rate when compared to otherwise used antihypertensive medications for maternal hypertension cases.[9]

Because it blocks beta adrenergic receptors non-selectively, labetalol cause a drop in blood pressure due to dose related effect without appreciably lowering heart rate. Intravenous labetalol starts to work after five minutes. The activity lasts from 45 minutes to six hours, with the peak impact happening between 10 and 15 minutes in. It is advisable to preload with fluids in order to prevent an abrupt drop in blood pressure.(10)

It is believed that high blood pressure during pregnancy can be controlled with intravenous labetalol. Its benefits include reduced maternal tachycardia, palpitations, and placental transfer; nevertheless, some trials have shown newborn hypotension and bradycardia, and it is not as economical as nifedipine.(11)

A calcium channel blocker is nifedipine. Its first effect signs appear thirty minutes after ingestion via oral route. After administration, the half-life of the pill is around 6 to 12 hours. Nifedipine's pharmacological effects might last for a maximum of twelve hours following pill ingestion.

Although nifedipine is inexpensive, it acts quickly, lasts a long time, and can be taken orally. However, when combined with magnesium sulphate, it can cause palpitations, transient neuromuscular weakness, abrupt hypotension in the mother and fetal distress as a result of placental hypoperfusion. Patients with liver impairment should also use caution when using nifedipine.(12)

In order to prevent potentially hazardous blood pressure swings or exacerbations during birth or anesthesia stays a standard practice in order to stabilise significant hypertension in mothers before delivery, either through induction of labor or by the caesarean section.

Therefore, plenty situations in late pregnancy with severe hypertension, prompt yet safe blood pressure management facilitates last treatment—delivery of fetus—to occur with the least amount of delay.

Keeping this in mind the present study has been undertaken to determine safety and efficacy of antihypertensive agents- nifedipine and labetalol in Acute Blood Pressure control in hypertensive emergencies of pregnancy.

AIMS AND OBJECTIVES OF THE STUDY

OBJECTIVES OF STUDY

1. **Aim of the study:** To compare the safety and efficacy of oral Nifedipine retard to intravenous Labetalol in the management of hypertensive emergencies of pregnancy.

PRIMARY OUTCOME

- The time and the dose of the drug required to achieve the targeted blood pressure.
- To know the safety and efficacy of the drug and route.

SECONDARY OUTCOME

- Total antihypertensives required to achieve target blood pressure and need for additional antihypertensive drug.
- Mode of delivery.
- Complications associated with drugs effects like hypotension, headache, tachycardia are to be analysed.
- Fetal outcome is analysed based on APGAR score of 5 minutes, neonatal intensive unit (NICU) admission (Respiratory distress/ Convulsions/ Sepsis) and Neonatal death.

PREECLAMPSIA

According to ACOG standards, hypertensive diseases during pregnancy are categorised as under: pre-existing hypertension with/ without superimposed preeclampsia, chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia. [8].

Classification of hypertension:

American Congress of Obstetricians and Gynecologists (ACOG) in 1972 classified pre- eclampsia and revised it in 2011.

There are now four categories into which the ACOG Task Force divides pregnancy hypertension:

I. **Hypertension during pregnancy**: Blood pressure readings more than 140/90 mm Hg on two or more occasions, recorded at four hour time interval post 20 weeks of gestation.

- Without Proteinuria
- Blood pressure stabilises before the 12-week postpartum period

  In 50% of instances, gestational hypertension advances to pre-eclampsia.

II. Pre-eclampsia and Eclampsia syndrome:

Blood pressure more than or equivalent to 140/90 mmHg measured twice, four hours interval, or blood pressure greater than or equivalent to 160/110 mmHg verified within 15 minutes of the 20-week gestation period with either proteinuria or maternal end organ failure is considered pre-eclampsia[13].

DIAGNOSTIC CRITERIA FOR PRE-ECLAMPSIA[19]

the diastolic blood pressure is 90 mm Hg is while systolic blood pressure is 140 mm Hg seen twice, four hours interval, with proteinuria.

Proteinuria

Any one of the below-

1) a more than 300 mg per 24hour urine collection (or extrapolated from timed collection), or

2) ratio of protein to creatine to be more than 0.3mg/dl, or

3)Dipstick reading of 2+ (used only when other methods not available)

The following two characteristics are discernible when proteinuria is absent:

- Increased liver enzyme levels
- Hematological issues such as hemolysis, disseminated intravascular coagulation, and thrombocytopenia (platelet count < 150,000/μL)
- Acute kidney damage (more than 1.1 mg/dl serum creatinine)
- a recent headache that is persistent
- Pulmonary edema
- Persistent epigastric discomfort
- Visual problems such blurring of vision
- Neurological dysfunction

Critical forms of pre-eclampsia may be complicated due to[13]

1) Renal

2) Cardiac

3) Pulmonary

4) Hepatic

5) Neurological Dysfunction

6) Hematologic Disturbances

7) Fetal Growth Restriction

8) Still Birth

9) Maternal Death.

Chronic hypertension can be defined as hypertension measured at pressure more than 140/90 mm Hg and diagnosed before the gestational age of 20 weeks or before conception. At least two measurements of hypertension, spaced at least four hours apart, should be recorded.

• A rise in blood pressure that continues for more than 12 weeks following birth.[19]

• When persistent hypertension appears to have no discernible underlying cause, essential hypertension is diagnosed.[19]

• Essential hypertension is diagnosed when chronic hypertension seems to have no apparent underlying cause[19].

Prolonged hypertension combined with pre-eclampsia on top: It is diagnosed when a pregnant woman with pre-existing chronic hypertension has the onset of one or more pre-eclampsia signs (e.g., increased liver enzymes, low platelets, proteinuria) after 20 weeks of pregnancy.[19]

According to the (NICE), hypertension is further classified into mild, moderate, and severe categories for treatment purposes.[20]

• Mild hypertension is said to be when the Systolic BP is 140–149 mm Hg and the Diastolic BP ranges between90–99 mm Hg.

• Moderate hypertension is when Systolic BP ranges 150–159 mm Hg while the Diastolic BP is 100–109 mm Hg.

• Severe hypertension is marked by a Systolic BP of 160 mm Hg or higher while a Diastolic BP of 110 mm Hg or higher.[(20)].

Eclampsia

Pre-eclampsia complicated with early onset of tonic-clonic seizures, focal or multifocal seizures or a state of coma[(13)].

Epidemiology:

It is a major cause of disease and mortality for mothers and perinatals, affecting from two to eight percent of pregnancies.[15]

Within the US, HDP accounted for 212 (7%) of the almost 3,000 pregnancy-related fatalities that occurred between 2011 and 2015.[15]

Pre-eclampsia (PE) is a disease of pregnancy that has marked influence on about 5-8% of pregnant women globally.[16]

A prime reason for maternal mortality, PE claims the lives of 50,000–60,000 people globally each year.[16]

It is associated with an increased risk of cardiovascular disease and diabetes mellitus in the offspring as well as the mother.

History:

Early on in the history of obstetrics, Francois Mauriceau published a treatise on pre-eclampsia in 1637[(17)]. He mentioned the elevated risk of seizures in primigravida and the high incidence of seizures in pre-eclampsia.[17]

Mauriceau proposed two possible causes for the onset of eclamptic seizures: intrauterine fetal demise or abberant blood flow.[17] Boissier de Sauvages postulated in the eighteenth century on the eclamptic convulsions which were attempts of nature to purge "morbid element" and recognized crucial difference between eclampsia and epilepsy based on latter's postpartum symptom remission. Preeclampsia was first identified by Robert Johns in 1843, with typical symptoms of headache, blurring of vision and edema among afflicted individuals. John Lever also discovered albumin in the urine of women having preeclampsia.

Researchers in 1960s' first identified the role of poor placental implantation in pre-eclampsia. In 1989, Roberts et al. proposed a theory based on the reduced perfusion

via placenta observed in pre-eclampsia and widespread endothelial dysfunction in mothers.[17]

Risk factors: (18)

Maternal factors	Couple related factors	Pregnancy related factors
Elderly primigravida Previous history of PIH Chronic hypertension Family history Nulliparity Renal diseases Maternal infections Autoimmune diseases Susceptibility genes Antiphospholipid syndrome Pregestational diabetes mellitus Thrombophilias	Primiparity New paternity Limited sperm exposure	Multi- fetal gestation Hydropic degeneration of placenta Hydrops- fetalis Chromosomal abnormalities-Trisomy13 Structural- congenital anomalies

High BMI prior to pregnancy		

DIAGNOSTIC CRITERIA FOR SEVERE PREECLAMPSIA[20]

Blood pressure criteria

≥160/110 mm Hg on two occasions for a minimum of 4 hours interval with any level of proteinuria.

Proteinuria (severe)

More than or equal to 5 g/24 hour Urine and protein: creatinine ratio greater than 0.3 in 24 hours.[16,17]

Dip stick reading showing +2

End-organ involvement

Hematologic dysfunction:

- Thrombocytopenia (platelets< 1 lakh/microlitre)

Hepatic dysfunction:

- Raised liver transaminases (two fold the normal or severe concentration)
- Right upper quadrant pain or Epigastric pain

Neurologic dysfunction:

- New onset headache not responding to medications
- Visual disturbances

Pulmonary dysfunction:

- pulmonary edema

Renal dysfunction:

- Oliguria
- Raised serum creatinine level

Fetal:

- Intrauterine growth restriction
- Oligohydramnios

	National Institute for Clinical Excellence (2010) (any of the features below in combination with hypertension and proteinuria)	American College of Obstetricians and Gynecologists (2013) (any of the below with known preeclampsia)	American Society of Hypertension (2008)
Symptoms	Headache Visual disturbance Vomiting Epigastric pain	Severe persistent right upper quadrant or epigastric pain Cerebral or visual disturbance	Headache Visual disturbance Abdominal pain
Signs	Papilloedema Clonus Liver tenderness	Pulmonary edema	Oliguria Early onset disease (<35 weeks) Nonreassuring fetal monitoring
Hypertension	Severe hypertension and proteinuria alone	Systolic BP >160 mmHg Diastolic BP >110 mmHg (on two occasions >4 h apart while on bed rest)	Diastolic >110 mmHg
Other maternal disorders	HELLP syndrome Platelets $<100\times10^9$/L AST or ALT >70	Platelets $<100\times10^9$/L Liver enzymes > twice normal concentration Progressive renal insufficiency	Elevated creatinine Nephrotic range proteinuria Elevated AST or LDH

(Adapted from ACOG Practice Bulletin No. 202 and ISSHP recommendations.*.**)**[20]

Pathogenesis of pre-eclampsia:

In preeclampsia, the **accurate etiopathogenesis is not known.**

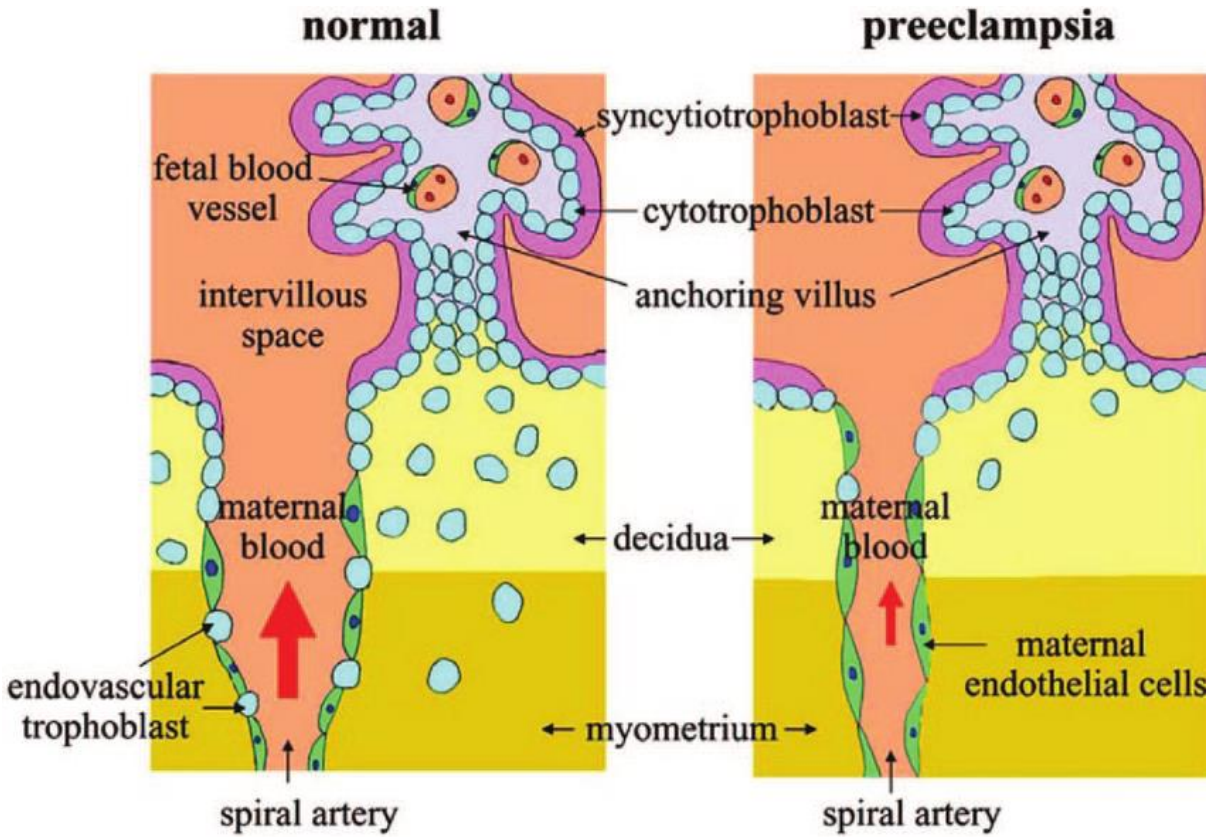
• **Abnormal invasion of trophoblasts of the uterine vessels:**

The flow of blood to the uterus rises dramatically during a normal pregnancy in order to support enough fetal development and proper intervillous gap refilling. To do this, spiral arteries undergo four separate remodelling processes, each of which is facilitated by trophoblastic invasion of the wall.
The invasion of the decidua comes first, followed by the migration of intra-arterial trophoblasts, then the invasion of the arteries intramurally when the middle (muscular) layer is destroyed and replaced with fibrin and connective tissue. The

endothelialization of arteries and other related maternal alterations are part of the final stage.

These capillaries can successfully supply the intervillous region with appropriate blood flow in order to maintain pregnancy when they show signs of a mean diameter that is noticeably larger than non-pregnant uterus in a women with relatively low resistance in the blood flow. The radial arteries' walls will have higher blood pressure as a result of the increased blood flow. This will lead to stress, which will then release nitric oxide from the endothelium, causing the uterine arteries to vasodilate generally. The middle of the placental bed experiences the greatest amount of spiral artery remodelling, which progressively diminishes towards the periphery.

The percentage of remodelled vasculature is significantly lower in pre-eclampsia, partically in the middle area of the placental bed. The process of artery atherosis produces outcomes that are strikingly similar to those of atheromatous plaque formation: the lumens of the arteries are invaded by macrophages rich in lipids, peri-vascular mononuclear inflammatory cell infiltrates and the vessel walls with fibrinoid necrosis, all of which lead to placental ischemia during pregnancy.



Courtesy: **Figure 1:** showing spiral artery of normal pregnancy and pre-eclampsia

Because of the metabolic stress experienced by the trophoblast cells' endoplasmic reticulum—structures that are ultimately in charge of cellular homeostasis and apoptosis which involves ischemic and reperfusion events as vicious cycles

Establishing intervillous area. This mechanism releases free radicals and nano molecules into the mother's bloodstream, which can lead to a widespread intravascular inflammatory response—a critical stage in the development of preeclampsia.[25], Due to severe oxidative stress, the breakdown of placental defense systems, and antioxidant enzymes,[28] Given that it includes both maternal genetic

predisposition and systemic inflammatory response, it may be said that such a process is immunomediated.[26,28,29]

The cellular death and the previously described oxidative stress would establish a disparity in between pro-angiogenic and anti-angiogenic factors, with predominating factors being the anti-angiogenic[29]. The antiangiogenic elements a typical of preeclampsia predominate and are associated with high concentrations of Vascular Endothelial Growth Factor(VEGFR-1) that block its angiogenic action and its soluble form, fms-like tyrosine kinase 1 (s Flt1). Additionally, decreased synthesis in placental growth factor (PLGF) is linked to these increased concentrations[29,30].

Lastly, despite its limitations, the cause of preeclampsia is partially understood to involve vasospasm, prostacyclin deficiency, and activation of platelets at levels higher than those seen in healthy pregnancies, both having vasodilatory effect, prevents aggregation of platelets. The placentas of women with preeclampsia, otherwise may produce more thromboxane A2, which dictates the preponderance of vasoconstriction and enhanced platelet aggregation[31].

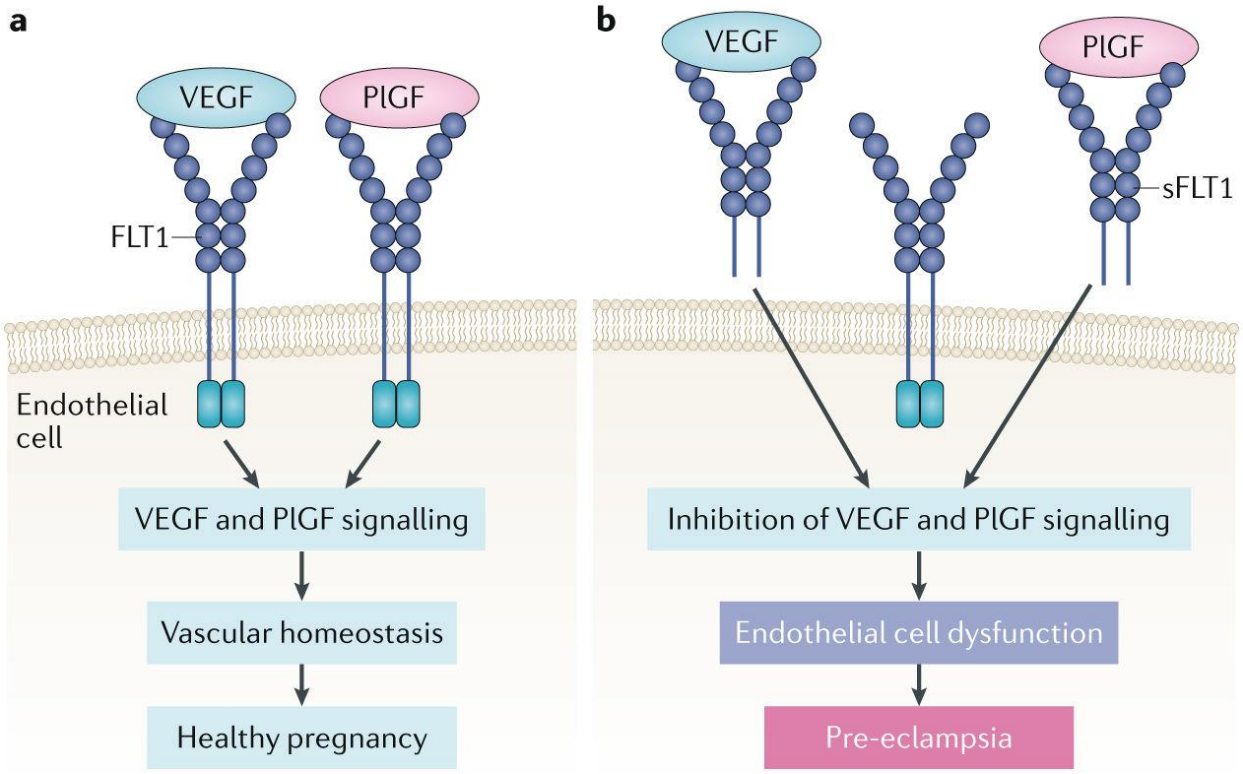
Thrombin mechanism linked to placental abruption in cases of disseminated intravascular coagulation[32]. Increased thrombin production is a feature of preeclampsia's more intense inflammatory response, which is already described as a factor that influences the deposit of fibrin in many organs and strengthens the clinical condition's systemic nature[33].

• **Immunological factors**: The mother responds to the fetal trophoblast by mounting a sterile, low-grade inflammatory response since its believed to be an allo-antigen[4,19]. The reason may be syncytiotrophoblast microparticles (STMBs) found in the mother's blood stream. Nonetheless, it is recognized that elevated STMBs levels in circulation of mother are seen in 2nd and 3rdtrimester, but perfusion between uterus and fetus begins towards the end of 1sttrimester.21 Another inflammatory response is secondary while 2nd and 3rdtrimesterscaused by syncytiotrophoblast microparticles which are released into vascular system of the mother. During the 1st trimester, the primary inflammatory response results from interaction between decidual immune cells and trophoblasts.

• **Endothelial cell activation:**

Many series of actions are initiated in reaction to placental factors generated by ischemia, which ultimately result in endothelial cell damage. Leucocytes in the mother's circulation are very stimulated, which is the cause of this endothelial cell dysfunction. Tumour Necrosis Factor-alpha- (TNFa) and interleukins (IL) are cytokines causing oxidative stress by generating free radicals. The self-propagating lipid plaques damage endothelial cells, change synthesis of nitric oxide and disrupt the prostaglandin balance. Increased permeability manifests as oedema and proteinuria, microvascular coagulation manifests as thrombocytopenia, and

atherosis is produced by lipid-laden macrophages in response to this oxidative stress.



Courtesy: **Figure 2** Showing pathophysiology of pre-eclampsia[21]

The role of sFLT1 in endothelial dysfunction in pre-eclampsia.

a. By attaching to their receptors, Fms-Like Tyrosine Kinase 1 (FLT1) and others, vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) signal in the vasculature and preserve vascular homeostasis during a typical pregnancy.

b. The extra soluble FLT1 (sFLT1) is secreted in pre-eclampsia which binds to local and circulating VEGF and PlGF. It inhibits VEGF and PlGF signalling in the vasculature. This leads to dysfunction of Endothelial cell as a result of suppression includes decreased synthesis of prostacyclin and nitric oxide and release of pro-coagulant proteins.

• **Genetic influences:** The etiology of preeclampsia is multifaceted. There cannot be a single gene responsible for the inherited tendency. It most likely results from the interplay of several genes that are inherited from both the paternal and maternal sides. According to the genetic conflict theory, maternal genes are chosen to restrict transfer beyond an appropriate level by reducing blood pressure, whereas fetal genes are selected to increase blood pressure and promote the transfer of nutrients to the fetus.

Subtypes of Pre-Eclampsia – (based on the time of onset or recognition of disease)

1) Early- onset Pre -Eclampsia

- The clinical signs are observed prior to 33 weeks of gestation.
- A major cause of high maternal and fetal mortality and morbidity rates.[21]

2) Late-onset Pre-Eclampsia

– The clinical signs appearspost34 weeks of gestation.
- Constitutes the majority (>80%) of pre-eclamptics[21]

Pathological feature of early-onset Pre-Eclampsia

↓

Inadequate Spiral Artery Transformation

↓

Placental hypoperfusion

↓

Inadequate nutrient supply to the fetus.

↓

Signs of Fetal Growth Restriction (FGR).

Pathological feature in late-onset type,

↓

slightly altered diameter of spiral arteries,

↓

no signs of FGR(due to either no change or shallow modification of spiral arteries)

↓

hyperperfusion of the placenta in some cases[22-23]

The pathogenesis of Pre-eclampsia initiated during the 1st trimester much prior to apprarent clinical signs. The failure of trophoblasts to adopt an endothelial phenotype result in abnormal placentation[24]

impaired invasion of trophoblast

↓

incomplete remodeling of spiral artery

↓

ischemia of placenta

angiogenic markers increased (soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng).

↓

sFlt-1 binds and decreases Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor, major endothelial cell function mediators.

↓

maternal vasculature has endothelial dysfunction

(sEng is a cell surface co-receptor that binds and decreases TGF, which induces migration and endothelial cells proliferation)

↓

The downstream effects that are mediated to:[24, 25]

1) Create Endothelial Dysfunction

2) A Vasoconstrictive State

3) Oxidative Stress

4) Micro-Emboli

- Micro- embolileads to involvement of multiple organ systems which results in increased sympathetic nervous system causing PE.

Endothelial dysfunction

• causes immunologic abnormalities that give rise to preeclampsia

• Phenotype: T helper cells become more Th1 in nature, releasing proinflammatory cytokines like InterLukin-12 and InterLukin-18 more frequently and releasing less of former which causes apoptosis and less invasion of trophoblast.

• A higher number of CD19÷CD5þ B cells might aid in the synthesis of antiangiogenic factors

• Natural killer cells of uterus are distinct from peripheral natural killer cells; source of defective spiral artery remodelling.

• The trophoblast-produced vesicles known as syncytial knots have the potential to cause an inflammatory reaction in the placenta.

• The RNA-binding protein LIN28 influences the growth, invasion, differentiation, and metabolism of cells.

• LIN28A and LIN28B in preeclamptic conditions. The placenta experiences a drop in LIN28B levels through the promotion of inflammation and a reduction in trophoblast invasion and differentiation.

A dysregulation in Complement system and further rise in sFlt-1 are caused by elevated complement levels in preeclampsia.

lower levels of histocompatibility complex human leukocyte antigen-G and E levels in preeclamptic women, which is also suggestive of an immunological imbalance.

• A number of hereditary factors have been linked to pathophysiology of preeclampsia.

• Mutations in complement component 3 is linked to preeclampsia which might partially explain complement system dysregulation.

• A cardiac protein called as corin, in uterine tissue triggers Atrial natri-uretic Peptide; while mutations in corins associated to preeclampsia.

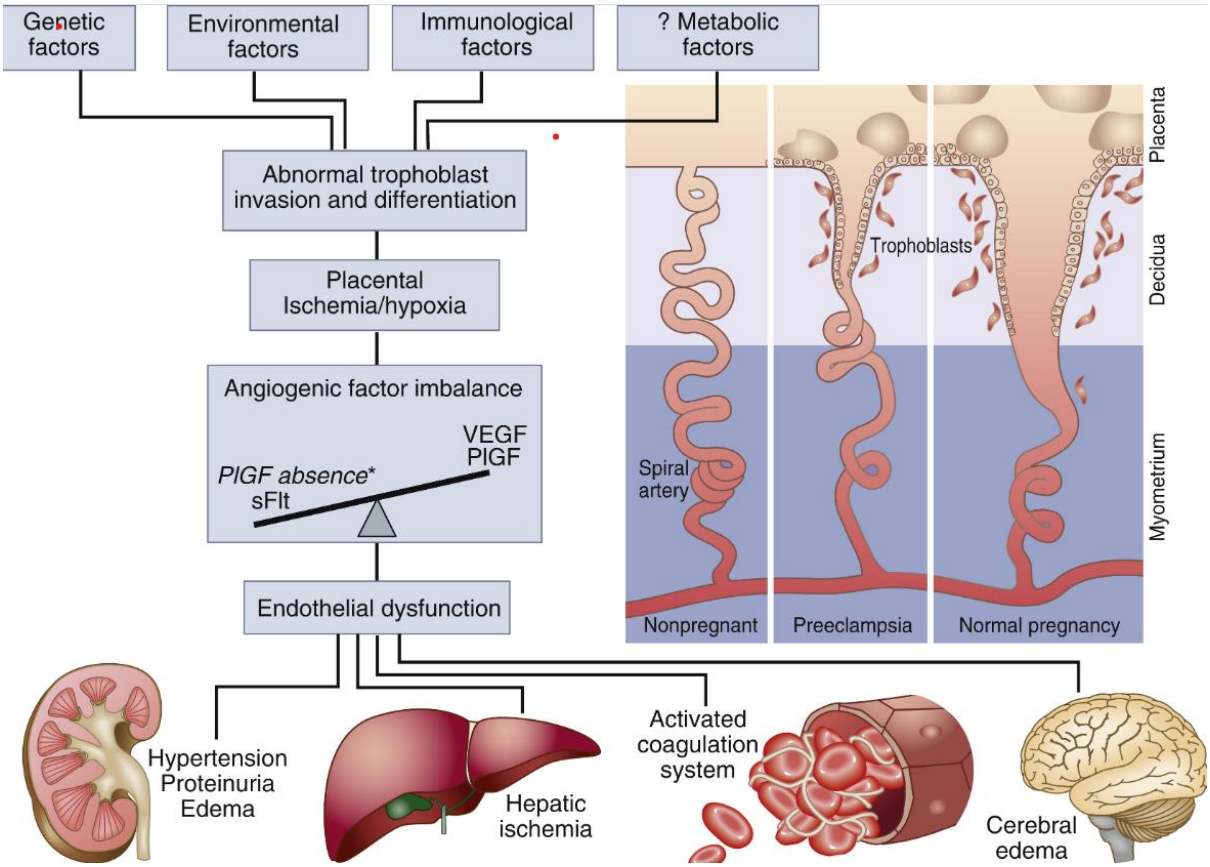
the chorionic villus samples of women with preeclampsia have been transcriptional profiled globally that suggests a genetic afflictions for pre-eclampsia.

• A disease of fatty acid metabolism also causes preeclampsia; long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency.[26-30]

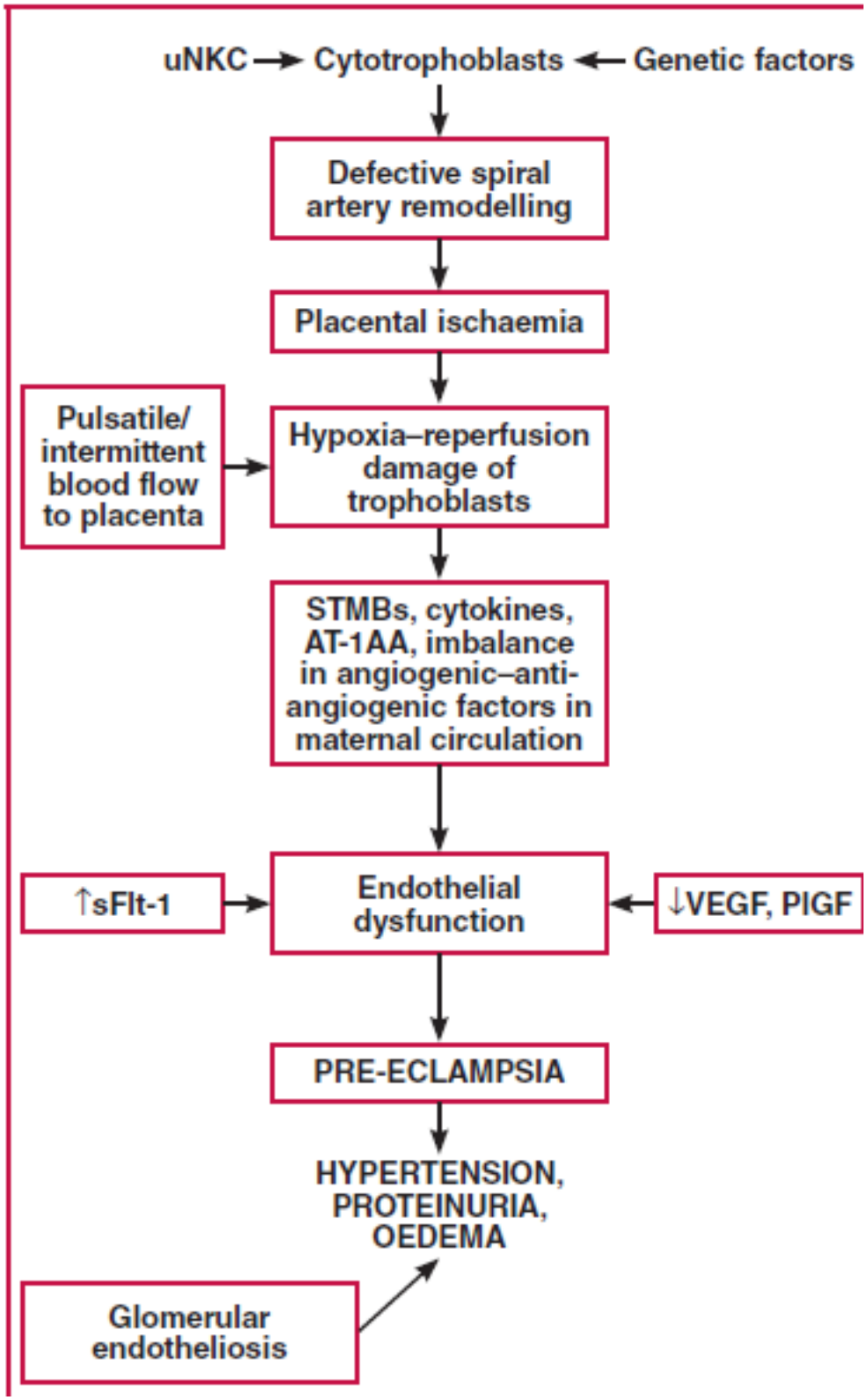
Maternal Inflammatory Response: • The etiology of PE involves both innate and adaptive immunological mechanisms. Th1 immunity predominates in PE, which is linked to endothelial dysfunction and an augmented inflammatory response in addition to impaired placentation. While InterLukin-10 titre was higher in late-onset PE than early-onset with plasma TNF-α, TNFR1, IL-1β and IL-12 levels and heat shock protein-70 are considerably raised among early-onset PE than in late-onset PE.

Maternal syndrome[31-33]

the hallmark of pathologic lesions of pre-eclampsia and eclampsia are broad endothelial lesions in several organ beds. the women had perivascular oedema (68.4%), hemorrhage(36.8%), hemosiderin(31.6%), small vessel thrombosis (10.5%), parenchymal necrosis (15.8%), liver lesions (72.2%) with peri-portal and portal necrosis and sinusoidal fibrin and 44.4% had hepatic arterial medial necrosis.



Courtesy **: Figure3** showing the factors affecting preeclampsia.)[34]



Courtesy: **Figure 4:** Aspects of pathophysiology of pre-eclampsia (ref)[34]

SIGNS OF PRE-ECLAMPSIA:

- Severe headache
- Disturbances in vision
- Confusion
- Hyperreflexia
- Epigastric or pain in right upper quadrant of abdominal (reflecting hepatic ischemia or capsular distention)
- Nausea and/or vomiting
- Dyspnea (reflecting pulmonary edema, acute respiratory distress syndrome [ARDS], or cardiac dysfunction secondary to increased afterload)
- Oliguria (reflecting decreased plasma volume or ischemic acute tubular necrosis)
- Stroke (rare cases)

Clinical features of Pre-Eclampsia: [35]

Clinical features	**Underlying abnormalities**	**Clinical consequences**
Hypertension	Increased SVR and afterload, Decreased CO, intravascular volumes,	Heart failure Pulmonary edema Renal dysfunction

	Activation of RAAS, ET-1, SNS AT1R down-regulated, placental hypoxia, and AT1R autoantibodies, Increased vasoconstrictors, decreased vasodilators Increased sFlt-1 and sEng, oxidative stress	Neurological injury
Proteinuria	Glomerular endotheliosis Disruption of filtration barrier Increased tubular permeability	Hypertension Ischemic Heart Disease, Stroke, Chronic kidney disease, End-stage renal disease
Renal dysfunction	Decreased RBF and GFR Glomerular endotheliosis Increased tissue factor expression,	Hypertension Chronic kidney disease End-stage renal disease

	Thrombotic microangiopathy	
Neurological abnormalities	Headache: loss of fenestrae on choroid plexus, periventricular edema, vasogenic edema in posterior cerebral circulation Visual disturbances: retinopathy, retinal detachment, cortical blindness, Central serous chorioretinopathy, hypertensive retinopathy, diabetic retinopathy	Seizures PRES Permanent blindness

Eclampsia	Unknown (potentially vasogenic or cytotoxic edema)	Permanent neurological dysfunction
Cardiac dysfunction	Increased SVR, afterload Concentric LV hypertrophy, LA enlargement Increased RVSP, increased LV filling pressures, LV diastolic dysfunction,	Heart failure Peripartum cardiomyopathy
Pulmonary edema	Increased vascular permeability Cardiac dysfunction Corticosteroids/tocolytics Iatrogenic volume overload	Acute hypoxemic respiratory failure
Hepatic dysfunction	Hepatic microcirculatory deterioration, hepatocellular injury	Liver failure, hepatic rupture

Hematologic dysfunction	Procoagulant state	Thrombocytopenia, DIC
Fetal growth restriction	Incomplete spiral artery remodeling Decidual vasculopathy Uterine and placental dysfunction	Fetal growth <10th percentile

COMPLICATIONS OF PREECLAMPSIA:

PREGNANCYINDUCED HYPERTENSION: [36-39]

Hypertensive complications in preeclampsia

1) AT1R forms a heterodimer with bradykinin receptor B2 to increase the pressor effects of angiotensin.
2) antibodies circulating against AT1R are produced through Placental hypoxia. These antibodies then activate endothelin-1, enhance vasoconstriction by increasing sensitivity to circulating Ang II, and increase placental synthesis of sflt1 and sEng.
3) Heme oxygenase-1 down-regulation lowers carbon monoxide production, which in turn raises sFlt-1 and sEng release even more.

4) Peripheral vascular resistance rises as a result of sFlt-1, raising blood pressure. Damage of Target organs such as heart failure, pulmonary edema, acute kidney injury and dysfunction, brain impairment, and cardiac stroke facilitated by hypertension in the context of preeclampsia.[36-39]

PROTEINURIA

A cause to proteinuria is high renal tubular permeability to the majority of large-molecular-weight proteins such as albumin, globulin, transferrin and haemoglobin.

Pathogenesis:

High circulating sFlt-1, decreased nitric oxide, both involved in mediating renal tubular injury. ↓

.

sFlt-1 inhibition of VEGF

↓

glomerular endothelial injury,(glomerular endotheliosis; pathognomonic for preeclampsia[41].

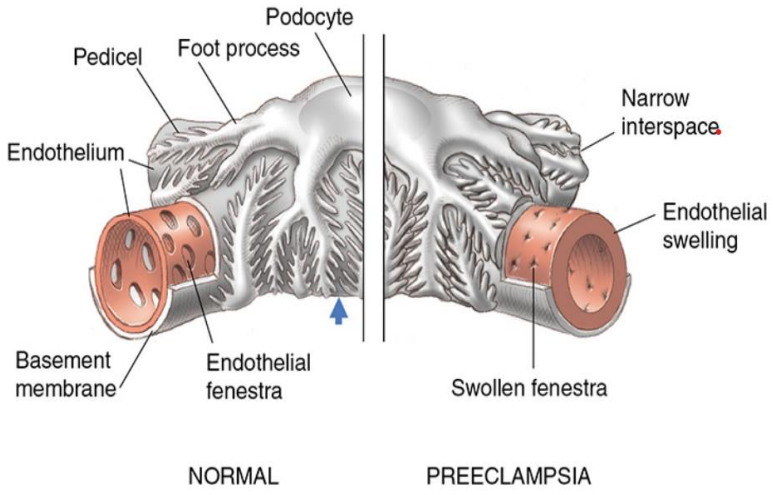
Glomerular endotheliosis:

1) Tubular casts, enlarged mesangial cells, subendothelial deposits of protein that are reabsorbed from the glomerular filtrate and endothelial cells that is swollen and vacuolated with fibrils are the characteristics of this.

2) An enlarged bloodless glomerulus with an obliterated capillary lumen (is not usually accompanied by inflated, bloodless glomerulus with a destroyed capillary lumen is present; unlike in thrombotic microangiopathy, this condition is typically not accompanied by noticeable capillary thrombi. prominent capillary thrombi as in thrombotic microangiopathy).

3) Elevated levels of sFlt-1 impede VEGF specific to podocytes, disrupting the glomerular filtration barrier and leads to development of fenestrae which exacerbate proteinuria.

4) An injury to the podocytes is caused by proteinuria. Nephrin, podocin, synaptopodin, and podocalyxin are slit diaphragm proteins that are essential for preserving the integrity of the glomerular barrier. These proteins are detected in the urine weeks before preeclampsia symptoms appear, suggesting that damage to these proteins causes additional proteinuria.[42-44]



courtesy : **Figure 5** showing glomerular capillaries of endotheliosis

RENAL DYSFUNCTION

When a serum creatinine doubles from baseline or rises over 1.1 mg/dl, it is considered renal failure in pre-eclampsia.

In preeclampsia, there is a remarkable reduction in renal blood flow and Glomerular Filtration rates(GFR).

Diffuse fibrin deposition, endothelial enlargement, podocyte loss and capillary space loss (glomerular endotheliosis) are clinical findings. In the context of glomerular endotheliosis, there is dysregulation of the glomerular filtration system. Expression of Tissue factor by endothelial cells and leukocytes is further stimulated by increased pro-inflammatory cytokines in preeclampsia. Prostaglandin and nitric oxide levels fall due to endothelial cells damage which then promote clotting and their anticoagulant properties are lost causing thrombotic microangiopathy in the kidneys.

Placental and renal failure are both exacerbated by elevated inflammatory cytokines, which are result of elevated toll-like-receptor 4. abnormalities in electrolytes: It happens when enhanced tubular calcium reabsorption causes a reduction in urine calcium. [45-47]

NEUROLOGICAL DYSFUNCTION

Preeclampsia can result in a variety of neurological issues.

1) **Headache**: Preeclampsia is linked to a number of main headache variations, such as tension type headache, migraine with or without aura. Thirty five percent of headaches during pregnancy are secondary headaches. The most prevalent cause of secondary headaches is HDPs, most often preeclampsia, which rises in frequency with increasing gestational age[48].Preeclampsia headache pathophysiology involves VEGF and TGF-b inhibition that causes fenestrae loss on choroid plexus, instability of endothelial cell and peri-ventricular edema. Seizures and posterior reversible encephalopathy syndrome, characterised by neurological abnormalities and vasogenic edema in posterior cerebral circulation distribution, may then result from these alterations[48].

2) Visual disturbances: headaches are linked to visual disturbances and get worse when blood pressure rises. Retinal detachment, cortical blindness, or retinopathy are possible causes of visual disruption in preeclampsia; these conditions usually go away after birth[49].

3)Hypertensive retinopathy is a disorder characterised by microvascular damage to the retina brought on by high blood pressure. It is caused by extreme vascular spasm when preeclampsia's angiogenic imbalance is present.[50]

4)Seizure: in the absence of other causes, new-onset tonic-clonic seizures, focal or multifocal seizures in the context. While progesterone increases the threshold for seizures, estrogen reduces it by inhibiting the production of gamma aminobutyric acid.[50]

5)Syndrome of posterior reversible encephalopathy (PRES)

6)hemorrhagic stroke. [50]

CARDIAC DYSFUNCTION:

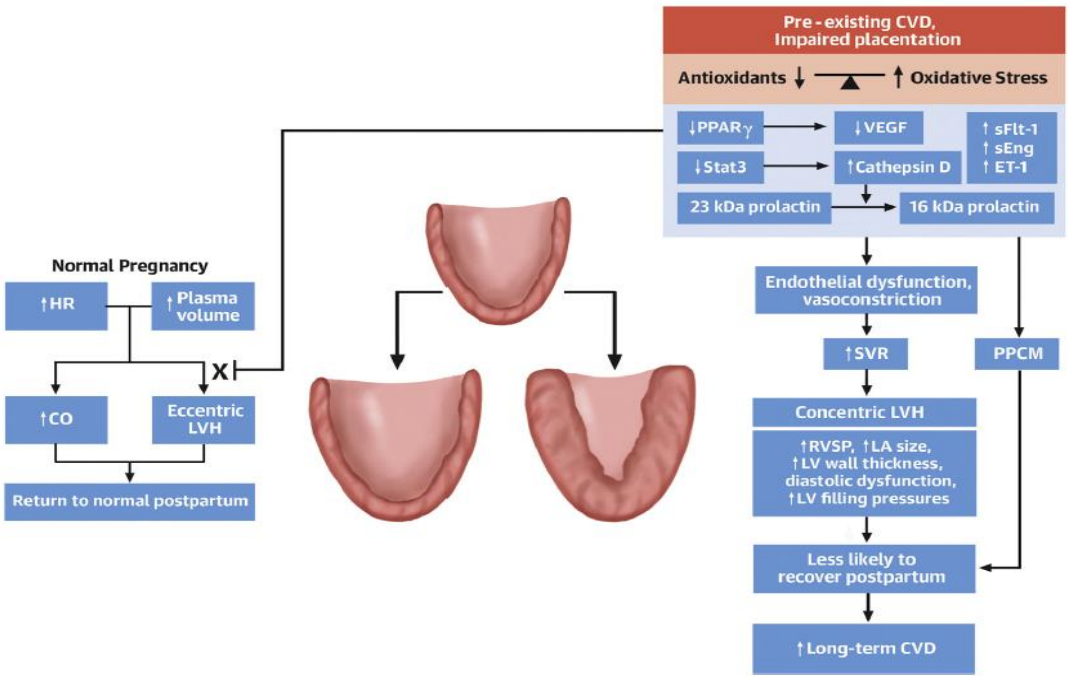
The deterioration of left ventricular remodelling in preeclampsia is caused by raised afterload from greater vascular resistance brought via poor placentation which causes mild-moderate isolated dysfunction in left ventricular diastole with concentric left ventricular hypertrophy. While concentric remodelling denotes an

aberrant response by cardiac system to elevated systemic vascular resistance observed pregnancy, eccentric remodelling represents a natural compensatory response. HDP raises the possibility of peripartum cardiomyopathy, a dangerous pregnancy-relatedcondition.

Peripartum cardiomyopathy is an exclusion diagnosis that is characterised by a diminished left ventricular ejection fraction (less than 45%) in last stages of pregnancy or while in initial postpartum months. Globally it affects 1 in 1,000 pregnancies and 1 in 3,000 live births in US.[51]

Pathogenesis:

- Because of the increased amounts of sFlt-1, peripartum cardiomyopathy is exacerbated by preeclampsia, upsetting the delicate sync between antioxidant capacity and oxidative stress.
- The transcriptional coactivator peroxisome proliferator-activated receptor G coactivator 1-a, which is crucial for biogenesis of mitochondria is observed in heart to perform angiogenesis by raising VEGF.
- A protein called Stat3 can mediate cardiomyocyte enlargement, stimulate myocardial angiogenesis, and upregulate antioxidant enzymes.
- Expression and activation of Stat3 is decreased in placentas of pre-eclampsia.[52, 53]



Courtesy: **figure 5**: Normal cardiac changes during pregnancy are disrupted by an angiogenic imbalance caused by preexisting CVD and the poor placentation that follows. The development of concentrated LVH and/or PPCM raises the likelihood of subsequent CVD problems. Cardio-vascular disease (CVD), endothelin (ET), Heart Rate, Left Atrial (LA), Left Ventricular (LV), Left Ventricular Hypertrophy (LVH), PPARg (peroxisome proliferator-activated receptor g coactivator), Peripartum Cardiomyopathy (PPCM), Right Ventricular Systolic Pressure (RVSP), soluble endoglin (sEng), Soluble Fms-Like Tyrosine Kinase (sFlt solublefms-like tyrosine kinase (Stat3), Systemic Vascular Resistance (SVR), and VEGF (vascular endothelial growth factor). (ref :[35])

PULMONARY EDEMA:

Reduced oncotic pressure and a relative intravascular volume depletion with a considerable amount of interstitial fluid are the results of hypoalbuminemia. Thus, pulmonary edema is far more common in preeclamptic women, especially in those with severe renal impairment. Because of this, all preeclamptic women need to have cautious fluid management, and pulmonary edema brought on by iatrogenic fluid excess is a factor in preeclamptic maternal death.

Fluid restriction is a typical technique for women who have severe preeclampsia. Large amounts of intravenous fluid are given to patients with preeclampsia, which can cause volume overload, especially when fluids are mobilised after delivery. Renal retention of salt and water can exacerbate the edema in these patients. Preeclampsia will have endothelial damage and pregnancy's lowered colloid osmotic pressure combine to cause increased vascular permeability. The pulmonary vasculature experiences an increase in hydrostatic forces when a dysfunction in diastole and an rise in vascular resistance are combined. [54, 55]

HEPATIC DYSFUNCTION:

Transaminases more than two folds in ranges of normal to chronic severe right upper quadrant or epigastric tenderness are indicative of hepatic dysfunction in preeclampsia.

Pathogenesis:

- Because aspartate amino-transferase is linked with periportal necrosis, it is often greater in preeclampsia than alanine aminotransferase.
- Since at least one case of alanine aminotransferase deficit in HDP diagnosis has been documented, alanine aminotransferase testing ought not be done in isolation.
- Hepatic synthetic function is altered and lactate dehydrogenase is elevated in preeclampsia, resulting in aberrations in fibrinogen, Prothrombin Time (PT) And Partial Thromboplastin Time (PTT).
- Hepatic microcirculatory degradation along with hepatocellular necrosis are brought on by endothelial dysfunction.
- Liver dysfunction and thrombocytopenia are also brought on by decreased production of endothelial nitric oxide synthase as a result of VEGF's antagonistic interaction with sFlt-1.
- • Hepatic rupture and liver failure are possible.[56, 57]

HEMATOLOGIC DISTURBANCE:

The following hematologic disorders are the most prevalent:

1) Thrombocytopenia.

2) Disseminated intravascular coagulopathy, which results in intravascular coagulation and secondary fibrinolysis due to a disturbance of the clotting cascade.[58]

Platelets <100,000 in thrombocytopenia is probably caused due to rise in platelet activation, their aggregation and consumption. Essentially, there are two theories.

1) Due to the rise in fibrinogen and other clotting factors, fall in anticoagulants (Protein C and S), pregnancy is a procoagulant condition. A theory has been proposed that extracellular vesicles and soluble substances are released when syncytiotrophoblasts shed extracellular vasculature, increasing platelet activity and perhaps exacerbating systemic and placental microvascular ischemia.

2) It's also possible that there is aberraations in angiogenic factors, particularly sFlt-1 and sEng. Von Willebrand factor multimers is released which binds to platelets and causes excessive aggregation of platelets and formation of thrombus in microcirculation, is another theory that suggests abrupt vascular endothelial cascade activation which causes consumptive thrombocytopenia, anaemia hemolytic type and hepatic dysfunction.[59]

Disseminated intravascular coagulopathy:

It is seen in severe form of preeclampsia.

Severe preeclampsia accompanied by hemolysis, increased enzymes of liver and low platelet count (HELLP) syndrome is associated with DIC.

Pathophysiology:

consumption coagulopathy

↓

hepatic injury (decrease clotting factor production), and/or

↓

systemic maternal inflammatory response.

In order to help women with preeclampsia through this potentially fatal aspect of the condition, it is crucial to keep an eye out for hematopathological abnormalities.[60]

HELLP syndrome: The severe type of preeclampsia is characterised by increased enzymes of liver (AST.70 U/L, LDH.600 U/L), followed by thrombocytopenia (100,000/mm3) and hemolysis (abnormal peripheral blood smear and bilirubin 1.2 mg/dL).

FETAL GROWTH RESTRICTION/ FETAL IMPLICATIONS

The restriction in Fetal growth is defined as an estimated fetal weight less than the tenth percentile for gestational age which is brought about by uterine and placental malfunction in preeclampsia.[61]

Pathogenesis:

- Vascular insults from placenta such as placental infarcts, arise from incomplete pseudovasculogenesis caused by spiral arteries that do not form properly.
- Unfinished spiral arterial remodelling is the source of maternal radial artery atherosis that manifests as lipid-laden macrophages in lumen, fibrinoid necrosis in wall and mononuclear perivascular infiltration.
- As a result of these modifications Decidual vasculopathy characterised by vessel media hypertrophy, lack in changes of smooth muscle, loose, edematous endothelium, and increased expression of hypoxia-inducible transcription factor-1a.
- Hyaluronic acid and glycocalyx structural alterations are also seen. Moreover, sEng-induced inhibition of TGF-b impairs endothelial vasodilation.
- Placental ischemia and reduced diastolic placental flow on ultrasonography are the results of these alterations.[61, 62]

LABORATORY FINDINGS:

Renal function tests: Increased uric acid levels

Changes in Liver Function Test: mild elevation in serum transaminases, increased AST and ALT.

Hematologic Abnormalities: reduction in plasma volume causes an increase in hemoglobin and hematocrit, and the concentration of plasma fibrinogen rises gradually. Blood clotting in cases of severe eclampsia

Ophthalmic Assessment:

Fetal Growth Assessment: examination of uterine, umbilical(UA) and middle cerebral artery (MCA) Doppler.

The uterine artery Doppler is a screening technique that can indicate growth limitation and offer an evaluation of the utero-placental circulation. The integrity of the mother's supply line is indicated by a normal result, but an abnormal uterine Doppler is defined by an elevated Pulsatility Index (PI), systolic and diastolic (S/D) ratio and bilateral diastolic notching indicate an irregular blood flow obstruction in the placenta of the mother. Although it is used in the first assessment of women who may develop preeclampsia between weeks twenty and twenty-four, the uterine artery Doppler is not useful for follow-up of such studied individuals.

The artery in the umbilicus is an evaluation of placental-umbilical circulation is provided by Doppler. Unusual elevation of the umbilical artery pressure index (PI), diastolic flow absence and reversal in diastolic flow are signs of fetal side of the placental circulation blood flow resistance that get worse with time. Low PI indicates that there is a brain sparing effect, according to Doppler imaging of the middle cerebral artery flow. When hypoxia is present, the fetus tries to reroute blood flow from the peripheral to the brain and other important organs. When the MCA S/D ratio exceeds the UA S/D ratio (MCA/UA. 1.0), sometimes referred to cerebro-placental ratio (CP ratio), it indicates that placenta maintains sufficient reserves while fetus does not experience severe acidosis or hypoxemia. The placental insufficiency has gotten so bad that the fetus is boosting blood supply to brain and lowering blood flow to other organs (a phenomenon known as the "brain sparing effect") when the cerebroplacental ratio (MCA/UA ratio, 1.0) drops below 1. But for pregnancies under 34 weeks, this cervical redistribution (CP ratio, 1) does not suggest an early birth.

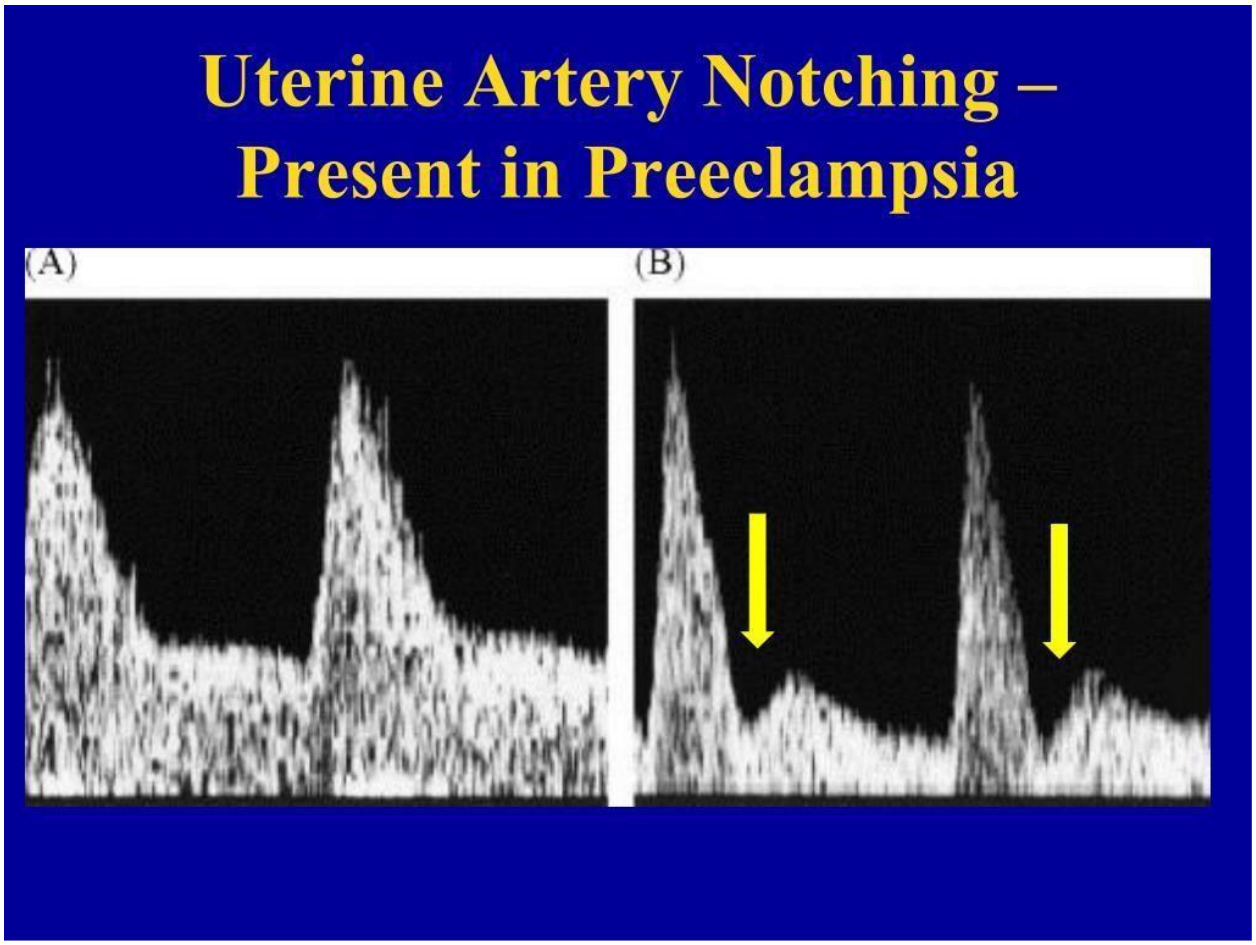


Figure 6: showing wave with notch d in uterine artery

MANAGEMENT:[63-68]

Screening for pre-eclampsia the high-risk pregnancies in the 1st trimester with low-dose of aspirin may lower its incidence by as much as 50% [41] and may enhance related fetal and mother outcomes.

Areas under investigation:

Provocative Pressor Tests

These tests evaluate the rise in blood pressure that occurs in response to an external stimulation. They take a lot of time and are laborious. All of these tests have sensitivity ranges of 55- 70% and specificities to around 85%.

These include:

Angiotensin Sensitivity Test

A screening test for preeclampsia patients can identify those at risk by measuring sensitivity towards angiotensin II. Patients with aberrant vascular reactivity may show symptoms weeks before the condition manifests itself. Regretfully, a higher chances of false positive and false negative finding sex is with this test, and it is labor expensive. Furthermore, there are no human-use formulations of angiotensin II available.

Roll-Over Test

Originally, this test reportedly was a non- invasive procedure performed at office that was highly predictive of the onset of preeclampsia and had a good connection with the angiotensin sensitivity test. When women are 28- 32 weeks pregnant and resting in left lateral decubitus position before rolling into supine posture, the hypertensive response is measured. However, if patients turn to supine position from lateral, their blood pressure rises by 20 mmHg or higher, indicating a positive test. Regretfully, the test has little clinical use and has low sensitivity and specificity.

Isometric Exercise Test (Hand Grip Test)

In this test a handball is squeezed while utilising the same idea.

Mean Blood Pressure in second trimester

Pre-eclampsia has traditionally been associated with Mean Arterial Pressure (MAP) $90 mmHg during the 2nd trimester of pregnancy (systolic 1 2 (diastolic)/3). Its poor positive predictive values and limited sensitivity are its drawbacks.

Urinary Calcium

Numerous research works have indicated a correlation between hypocalciuria and preeclampsia. Ti rule out diagnosis for pre- eclampsia, a urine calcium concentration 12 mg/dL or less in 24hour sample had a predictable positive and negative values 85 and 91%, respectively. On determining the accuracy of calcium/creatinine ratio among randomly selected urine samples appeared comparable to that of 24h collection. In normotensive pregnancy, the ratio is 0.44 6 0.32 and it is 0.20 6 0.18 in cases of chronic hypertension cases, whereas a significantly lower (0.03 6 0.03) in preeclampsia. It has been proposed that early onset and persistence of hypocalciuria during pregnancy is helpful in identification of preeclamptic women on early onset risk.

Fibronectin

Plasma fibronectin with elevated levels have glycoprotein as a high molecular weight which constitutes of connective tissue and basement membranes and plays a significant role in all cellular adhesions, are seen in preeclamptic patients. Studies show that elevated levels of endothelium-derived fibronectin in the plasma occur before pre-eclampsia clinical indications appear, which may help anticipate the condition.

Uterine Artery Doppler

Preeclampsia is hypothesised to be caused by inadequate invasion by trophoblasts in the mothers' spiral arteries leading to conversion of tight muscular vessels into large non-muscular channels without the need for maternal vasomotor regulation. At 22–24 weeks the uterine artery, Doppler velocimetry can be employed for identifying women at risk of developing preeclampsia. The early diastolic notching either unilateral or bilateral or a Pulsatility Index (PI) above 95th percentile indicate aberrant UA velocity waveform. Preeclampsia rates are linked to a six-fold rise during these pregnancies.[77]The sensitivity of abnormal UA Doppler for preeclampsia prediction ranges 20% to 60%. For women experiencing severe types of these problems require an early delivery that is before 32 weeks and hence, sensitivity rises80% to 90%. Uterine artery Doppler screening in 2nd trimester had greater predilection ratio as 6.61 and a negative likelihood ratio as 0.55, respectively.UA Doppler ultrasonography appears to be the best test now available

for the early diagnosis of placental-onset preeclampsia, although being far from ideal as a screening technique. The available data does not support the routine UA Doppler monitoring of all expectant mothers, although it could be useful screening tool in preeclampsia among women with high-risk to separate high-risk from low-risk women.

The Doppler examinations of uterine arteries at 11 to 13 weeks were conducted recently. It has been demonstrated that there is a rise in resistance to flow in pregnancies that lead to hypertensive diseases, with an especially noticeable increase cases of early preeclampsia. The detection rate is estimated in screening by combining uterine artery PI with derived a prior risk maternal factor was 35% for gestational hypertension, 45% for late preeclampsia, and 81% for early preeclampsia showing 10% false positive rate.

TESTS FOR PREDICTION OF PRE-ECLAMPSIA

Testing Related To	Examples
Placental perfusion-faulty trophoblastic invasion of spiral arterioles/increased vascular resistance	Roll over test, isometric handgrip or cold pressor test, angiotensin II sensitivity test, midtrimester mean arterial pressure, uterine artery Doppler, Nail bed arterial pressure stiffness test
Fetoplacental endocrine dysfunction	Increased HCG, AFP, estriol, placental protein 13 Low pregnancy associated plasma protein A (PAPPA), Low Inhibin A
Renal dysfunction	Serum uric acid, microalbuminuria, hypocalciuria
Endothelial dysfunction/ oxidative stress	Increased fibronectin, endothelin, C-reactive protein, hyperhomo-cysteine, antiphospholipid anti-bodies, plasminogen activator inhibitor (PAI), placental growth factor (PLGF), vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor-1 (sFlt-1), low platelet count
Others	Antithrombin III, free fetal DNA

PREVENTION:

1)**Aspirin** Since aspirin reduces the risk of preeclampsia in high-risk pregnant women after 12 weeks of gestation (recommended by American College of Obstetricians and Gynecologists and the United States Preventive Services Task Force).

By inhibiting cyclooxygenase-1 and cyclooxygenase-2, involved in prostaglandin generation and endothelial dysfunction. According to a recent Cochrane review, using aspirin as preventive measures can lower the incidence of preeclampsia 8% (Relative Risk: 0.82; 95% confidence interval: 0.77 - 0.88) based on data from 60 studies including 36,716 women.[69]

2) **Exercise**

It is suggested by International Society for Hypertension at pregnancy to be potential benefit and a low risk of side effects for the prevention of preeclampsia. The Society advises adhering to the 50-minute exercise regimen at least three days a week, since this has been linked to a decrease in weight growth and the incidence of HDP.[69]

3) **Calcium supplementation** Another method to lower the risk of preeclampsia, however this is more relevant to women in low- to middle-income nations or those who have nutritional deficiencies.

Vasoconstriction and elevated blood pressure may ensue from hypocalcemia's stimulation of parathyroid hormone or rennin production that might raise intracellular calcium in vascular smooth muscle. The supplementation of calcium can lessen contractility of smooth muscles and intracellular calcium by lowering parathyroid production. Similarly, taking supplements of calcium may lessen the

contractility of the uterine smooth muscle and maybe enhance the passage of blood into the placenta, so averting premature labor and delivery.[70, 71]

4)**Pravastatin** This has been suggested as an additional treatment to lower the preeclampsia risk and its effect is believed to be mediated via reversing angiogenic imbalance, enhancing endothelial function, and preventing oxidative and inflammatory damage.[72]

5) **Metformin** has been suggested as an option to lower preeclampsia risk with prospective use to prevent large gestational age fetuses among pregnant women who are obsess and without diabetes. Metformin was linked to 76% reduction in incidence although prime result was negative for reduced newborn birthweight.[72]

MANAGEMENT:

MANAGEMENT OF MILD PREECLAMPSIA:

Initial Evaluation

An evaluation of gestational age is the initial step in the care of women with moderate preeclampsia.

Gestational age more than equal to 37 weeks: the pre-eclampsia women with mild stages and are of 37 weeks or even above can deliver.

Gestational age between 24 and 36 weeks: early stages of clinical and laboratory findings, the patient with mild preeclampsia of 24 - 36 weeks are managed based on the mother and fetal condition. Evaluation of the fetus include a non-stress test (NST) and measures to determine the estimated fetal weight, Amniotic Fluid Index (AFI) and color doppler evaluation of uterine, umbilical and middle cerebral arteries.

The patient must stay in the hospital until delivery if they have any of the following conditions: raised hepatic enzymes, thrombocytopenia, oligohydramnios, restriction of fetal growth, elevated resistance in UA Doppler and proteinuria greater than 1g/ 24 hours. These conditions indicate that there is a high risk of complications. In-hospital care is also indicated by the occurrence of severe headaches, persistent visual problems, and significant epigastric or right upper quadrant discomfort. If the patient is untrustworthy and may not be able to adhere to outpatient therapy, this is another sign that they should receive in-hospital care. [73]

Antihypertensive Treatment:

	Atenolol	Captopril	Enalapril
Mechanism	Beta blocker	ACE inhibitor	ACE inhibitor
Pregnancy	Avoid in first and second trimester. Associated with fetal growth restriction and bradycardia, reduces uteroplacental blood flow	No – associated with severe fetal anomaly, fetal nephropathy, and intrauterine death	No – associated with severe fetal anomaly, fetal nephropathy, and intrauterine death
Breast-feeding	No known evidence of harm (NICE). Second line after labetalol	Manufacturers advise avoid; however recommended by SOGC. No known evidence of harm (NICE)	Not for preterm infants. No known evidence of harm (NICE) Particularly for women needing cardiac/renal protection
Postnatal	Yes	Yes	Yes
Side-effects	Risk of fetal growth restriction and bradycardia in pregnancy	Cough	Cough
Contraindications	Asthma		

Abbreviations: ACE, angiotensin-converting enzyme; CTG, cardiotocography; NICE, National Institute for Health and Care Excellence; SOGC, Society of Obstetricians and Gynecologists of Canada.

Labetalol is advised by NICE to be used as the first-line antihypertensive. If neither is suitable, methyldopa is the next best option. Commonly used and appropriate substitute is nifedipine. There is evidence that beta blockers are less successful in lowering hypertension in individuals of African descent who may have high renin levels, even when the patient is not pregnant. Oral dosages of 100–400 mg of labetalol should be administered every 8–12 hours.
No immediate need for antihypertensives if blood pressure is less than 150/100 mmHg unless there are indicators of a serious illness.
In women with severe preeclampsia, persistently high values >160/110 mm Hg are the most prevalent indication for delivery.[73]

2. **Hydralazine** (10 - 25mg bid) often employed to quickly decrease high blood pressure, reduces PVR by directly acting on the smooth muscles of the arteries.

In individuals with previously normal FHR tracing, the most common adverse effects are reduced uteroplacental perfusion and hyperdynamic circulation, which are indicated by late decelerations.

3**. Methyldopa** (250 – 500 mg tid or qid)

both peripheral and central antiadrenergic activity

Role of Glucocorticoids

Significantly lowers newborn problems such RDS, intraventricular hemorrhage, and mortality when betamethasone 12 mg is administered at two doses intramuscularly spaced at 24 hours interval if delivery is expected to occur before 34 weeks.

Delivery

When the women with pre-eclampsia has reached 37 weeks of gestation then we should induce the patient and deliver.

•Regular hourly monitoring of blood pressure.

• If there is a suspicion of fetal growth limitation, ongoing electronic fetal monitoring is done.

3rd stage of labor is managed by oxytocin or prostaglandins to prevent postpartum hemorrhage.

Acute management of pre-eclampsia

1) **Full physical examination** regarding possible pre-eclampsia issues ought to be done at admission and then on a frequent basis after that.

2) **Investigations**

Firstly, check CBC, and Urine routines.

LFT, RFTs and LDH and coagulation profiles including APTT, PT, fibrinogen.

3) **Blood pressure control**

The goal needs customization according to regulated blood pressure range of 90–100 diastolic and 140–150 systolic in a mother.

It is important to use caution when reducing blood pressure too much since this might have a detrimental effect on placental perfusion and lead to fetal impairment.[62]

It is noted that a BP more than equal to 170/110 mmHg requires a prompt treatment.

Use of magnesium sulphate

In conditions wherein premonitory signs of eclampsia are noted by an increased reflexes associated with clonus and/or severe headache, changes on vision or when severe pre-eclampsia with a DB/P >110 mmHg, proteinuria >300 mg/24 hours, abnormal titres of AST, ALT and LDH is diagnosed, prophylactic magnesium sulphate treatment should be initiated (thrombocytopenia <100x109/L).

As directed by protocol, magnesium sulphate was started and kept up as a maintenance infusion of serum. In the antepartum and intrapartum phases, magnesium concentrations should be monitored every six hours; the therapeutic level of magnesium sulphate is 1.7-3.5 mmol/L.

Prior to taking further anti-hypertensive medications into consideration, wait for the blood pressure to settle after magnesium sulphate delivery.[74]

Maintain diastolic B/P ≈ 90-100mmHg

Acute control of severe hypertension

Intravenous labetalol regarded as prime medication for the immediate treatment in severe pregnancy-related hypertension to eliminate the need for Hydralazine and is linked to a decreased frequency of negative side effects. The drug's availability as well as the physicians' knowledge and familiarity with it will determine how it is used.[74]

For female patients with congestive heart failure or asthma, hydralazine is still the recommended medication.[64, 65]

4) Fluid balance

An accurate assessment of fluid input/output is crucial for female patients with congestive heart failure or asthma, hydralazine is still the recommended medication.

Maintain a strict fluid balance chart: which is electronic. It is advised that a main line of intravenous line RINGER LACTATE be started via a multiflow adaptor into the IV site upon admission to the birth centre. A regulated infusion pump should be used to give intravenous fluids at a rate of no more than 75 mL per hour.[65]

5) Renal function

- the excretion of protein must be monitored by a full ward test of urine at every 24 hour interval.
- a random urinary protein/creatinine ratio may be considered.
- urinary catheter indwelling
- hourly measurement of urine output.

Inadequate Urine output of less than 20mL/h is considered with administration magnesium sulphate.

Management of oliguria with the administration of magnesium sulphate need to be interdisciplinary. Medical personnel should perform a fluid evaluation before giving out any additional fluids. AVOID PULMONARY EDEMA

 consider infusion of Hartmann's 250mL stat.

 prolonged oliguria demands obstetric and anesthetic consultation and insertion of a CVC may be considered.

 persistent oliguria might indicate for diuretic use following consultation with an obstetric/ anesthetic specialist.

 long lasting oliguria may need a transfer to a high dependency unit.

6) **Ongoing monitoring/ observations**

 ½ hourly blood pressure and pulse

 1 hourly respiratory rate

 1 hourly patellar reflexes

 1 hourly urine output measurement

If the diagnosis has been made regular testing for proteinuria is not considered.

 2 hourly temperature

 Continuous electronic fetal monitoring at antepartum and intrapartum from 26 weeks of gestation until clinical review/discussion by medical staff. The need to consider individualised management in regard to fetal monitoring between 24- 26 weeks gestation add link to CTG PPG.

7) **Pain Management**

If there are no contraindications and the patient's platelets are greater than 80 x 109/L, an epidural may be used to treat pain in addition to decreasing blood pressure.

8) **Fetal monitoring**

 continual electronic fetal monitoring in labor at Birth Centre.

A fetus on IUGR might not be tolerant of labor as a healthy, well-grown fetus, according to birth centre constant electronic fetal monitoring.

9) **Delivery**

Expedite the birth if any of the following:

 eclampsia (once stable)

 uncontrolled BP despite optimal treatment (when maximum dose of 3 anti-hypertensive medicines plus 2 or more BP readings 170/110 in 24 hours).

 HELLP syndrome diagnosis

 Abnormal renal function i.e, creatinine>90 and urea >10, neurological symptoms such as disturbances if vision and/or persistent frontal headache and eclampsia.

 abruption

 concerns regarding fetal well- being.

In cases of severe pre-eclampsia or when the fetus ≥37 weeks gestation, an expedited delivery is typically advised. Around boundaries of viability, efforts to postpone giving birth should be made at extremely early pregnancy.

Mode of delivery:

 depends on maternal and fetal factors (gestation, presentation)

 requires a multidisciplinary consultation

 If the fetus is less than 34 weeks gestation with stable maternal condition, consider to defer delivery for allowing time for administration of steroids.

 If labor induction is undertaken with oxytocin / ARM, an oxytocin infusion in a concentrated dose must be delivered via a syringe driver pump.

Second stage management:

 Although an operation is not always necessary to be called for if the lady exhibits signs of acute cerebral irritability, her blood pressure is not well managed, or her progress is not meeting expectations.

Third stage management:

 ought to be actively controlled: 10 international units of oxytocin IV bolus for stage three.

Postpartum

Immediate management

Within the first 24 hours following giving birth, the majority of women will begin to show indications of recovery; yet, a small percentage of women will continue to be unstable or worsen. Since most eclamptic seizures happen after delivery, intensive observation should last up to:

 stable BP

 occurrence of diuresis and normalized urine output.

 stable or improving blood investigations (CBC, Urine routine, RFT, LFT, LDH, coagulation profile)

Management of magnesium sulphate

• If clinically needed, discontinue use of magnesium sulphate no later than 24 hours after delivery.

• If there is no renal impairment or oliguria, postpartum magnesium levels can be clinically evaluated (reflexes, breathing rate) and serum levels should be measured every six hours, examine patellar reflexes every hour till the infusion is stopped.

Antenatal ward management

Indication for in-patient admission:

□ BP ≥ 150/100 mmHg on 2 occasions

□ maternal symptoms

□ concern for fetal well-being.

Antenatal ward admission

□ admission

□ 4/24 BP

□ daily ward urinalysis (if protein not previously confirmed as present)

□ CBC, U&Es, ALT and AST (alternate days)

□ 24 hour urine (creatinine clearance and protein) is only necessary if spot protein test is inconclusive/borderline.

□ **fetal assessment:**

□ growth - 2nd weekly

□ AFI, Doppler (initially on admission and repeat as indicated by fetal condition)

□ CTG: 2 -3 times weekly

 biophysical profile as required weekly

Antihypertensive therapy if blood pressure is more than 160/100 mmHg, keep it between 140-160/90-100 mmHg. Oral labetalol is typically the first-choice medication (take cautiously if you have asthma). Anti- hypertensive medication is ambiguous and may jeopardise placental perfusion when used in moderate pre-eclampsia instances. It must only be used in conjunction with other co-morbidities or disease indicators such as diabetes, renal illness, chronic hypertension or vascular disease. When blood pressure starts rising over 140/90 mmHg, senior colleagues should be consulted before starting antihypertensive medication. Closer monitoring is also necessary. Methyldopa is the first-choice drug for oral maintenance treatment. It is best to consider nifedipine of labetalol only after maximal dosage of methyldopa are administered.[65-68]

Medication	**Dose**	**Maximum dose in 24 hours**
Methyldopa	250mg-500mg 6-12 hourly	2g

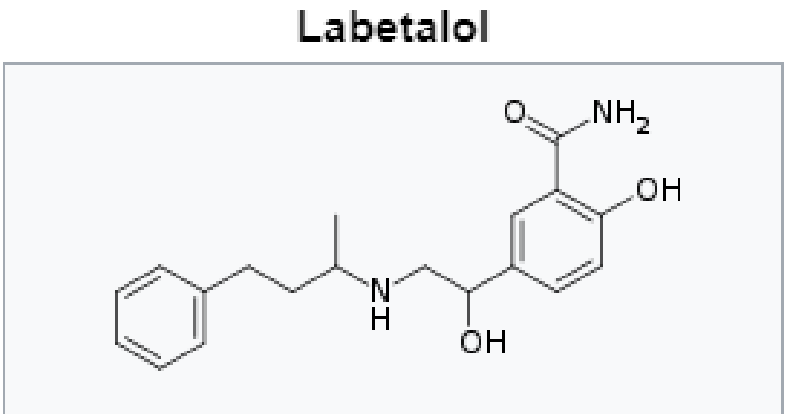
Labetalol (avoid in women with asthma)	100mg to 400mg 6-12 hourly	1600mg
Nifedipine SR	30mg-120mg daily	120mg
Prazosin	1-7mg eight hourly	21mg

Steroids if less than 34 weeks: 11.4mg intraperitoneal betamethasone (Celestone Chronodose), once day, separated by 24 hours.

A medical evaluation of the patient should be obtained prior to her transportation to the birth centre if her condition worsens (for example, her blood pressure becomes unmanageable or she exhibits symptoms of enhanced reflexes)[65-68]

Labetalol: In a single drug, labetalol exhibits non-selective, competitive beta-adrenergic (B1 and B2) blocking action as well as selective, competitive alpha1-adrenergic antagonistic activity.

After oral and intravenous (IV) treatment, the estimated activity ratios of alpha to beta-blockade are 1 to 3 and 1 to 7, respectively.



Courtesy: **Figure 7:** Showing chemical structure of labetalol

Administration:

An initial dosage of 10-20 mg by IV line is choice for acute hypertension episodes (emergency) and subsequent bolus can be given at every 10 minutes until targeted systolic blood pressure is reached or up to a highest range of 300 mg every 24 hour period. 20 mg corresponds to around 0.25 mg/kg for a patient weighing 80 kgs. A continuous infusion can be opted, which may be start at 0.5 to 2 mg per minute and can be titrated up to10mg/min.

Metabolism:

Labetalol is metabolized by the liver and this results in an inactive glucuronide conjugate.

Onset of action:

The half-life of 5.5 hour for elimination and its duration of action up to 4 hours with onset of action 2-5 minutes, and a peak effect of 5- 15 minutes.

Hypertensive emergency:

For a pregnancy-related hypertensive emergency when SBP is 160 mm Hg or DBP is 110 mm Hg. The initial dose in first dosing strategy is 20 mg. It is appropriate to think about raising the dosage in every 10 minutes (increments of 20 - 40 mg, up to a maximum single dose of 80 mg, if blood pressure is even higher than threshold). In these cases, 300 mg is the maximum cumulative that is still advised.

Adverse effects: Labetalol is often found to be well tolerated overall. The side effects are minor and temporary mostly. Labetalol usage has been associated with flushing, headaches, high perspiration and dizziness.

If patients are permitted to change from sitting or supine position or tilted to a standing one, quite soon, it may result in symptomatic postural hypotension. This is particularly crucial in the post-operative phase when controlling a hypertensive patient on labetalol in ward, who would otherwise be able to walk too long. The likelihood of adverse effects appears to be dose-dependent after administering labetalol.

Like other beta-blockers, labetalol has adverse inotropic effects and can result in abrupt left ventricular failure when administered to individuals with compromised left ventricle function at dosages that are too high. In individuals with concomitant peripheral vascular disease, all beta-blockers have the potential to worsen intermittent claudication and the Raynaud phenomenon. the anesthesia providers in the peri-operative period must consider that a non-selective beta-blockers interacts with beta receptors causing bronchospasm in asthmatics or Chronic Obstructive Pulmonary Disease due to antagonism of beta receptors.

An abrupt stop in using beta-blockers may make you more sensitive to catecholamines. Palpitations, acute hypertensive crises, and tachyarrhythmias are possible side effects of this upregulation, albeit they are more frequent with long term usage.

Contraindications:

Patients with bronchial asthma, overt heart failure, greater than first degree heart block, cardiogenic shock, severe bradycardia and other disorders of sustained and severe hypotension should not take labetalol, and using it is strongly not advised in these cases. In patients with a history of hypersensitivity, it should be avoided to any part of the medication composition to prevent any kind of adverse response.

Monitoring:

For labetalol, drug monitoring is particularly not required. There is no need for monitoring because it is usually used to treat severe acute hypertension rather than chronic usage. It is also a safe medication with a wide safety margin; daily dosages up to 300 mg are allowed.

Oral Nifedipine:

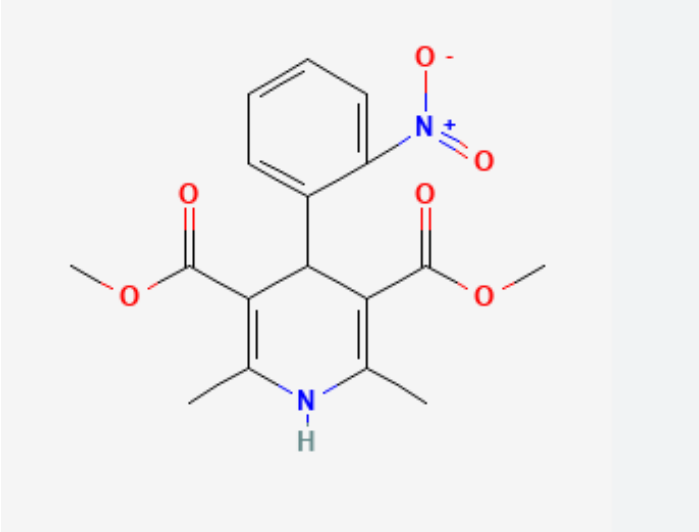
The first calcium channel blocker in the dihydro pyridine family was nifedipine.

When nifedipine was first created by Bayer in early 1970s, research revealed that a lowering of blood pressure from medication's which are short-acting formulations were successful but it also had serious adverse effect profile.

Long-acting, modified-release formulations that have lesser negative effects were created. Oral nifedipine is an inexpensive, efficient medication.

Controlling moderate to severe hypertension is advised, and treating hypertensive problems during pregnancy—more frequent in diabetic women —is one area in which it excels.

It is also licensed for treating angina.



Courtesy: figure 8: Chemical structure: Nifedipine

Pharmacology

Smooth muscle has voltage-gated L-type calcium channels, which are bound to and blocked by nifedipine. This causes relaxation by lowering intracellular calcium and calcium influx. Vasodilation is the main effect it has on the peripheral and coronary arteries. Peripheral vasodilation will lower blood pressure, whereas coronary vasodilation will help with angina.

Nifedipine inhibits the entry of extracellular calcium into myometrial cells, which results in non-specific smooth muscle relaxation and the potential tocolytic effect that is an inhibition of uterine contractions. This "off label" application has been successfully applied to stop preterm labor on a large scale.

Headache, flushing, and reflex tachycardia are among the side effects of nifedipine that are less common with modified-release formulations. Ankle edema is another

typical adverse effect of all calcium antagonists, which can be reduced from taking feasible lowest dose.

Safety and efficacy

Nifedipine has a long history of usage in the management of hypertension and angina. Only individuals receiving immediate-release nifedipine monotherapy had the effect, which was most likely caused by a sudden vasodilation coupled with activation of reflex sympathetic system.

Long standing randomized controlled trials using a long-acting formulations of nifedipine showed comparable efficacy and safety in diuretic patients with hypertension and also reduction in angina without any major adverse coronary events than in placebo with stable angina. A sizable number of diabetic patients participated in both trials.

Nifedipine use in pregnancy:

During pregnancy, it is suitable second-line medication for hypertension. On the recommendation of the makers, its short-acting sublingual version is taken off the market due to the previously mentioned negative impacts on Cardiovascular System. Preparations with modified release are more favourable side-effect profile and work well to reduce pregnancy-induced hypertension.

Palpitations, Flushing, headache and chest pain are the common side effects.

In a randomized controlled trial, 126 Sri Lankan women were asked to examine the efficacy of methyldopa and nifedipine in treating pregnancy-induced hypertension. The incidence of placental abruption, HELLP syndrome (Hemolysis, Elevated hepatic enzymes, Low Platelet count), eclampsia, caesarean section, maternal side effects, newborn weight, intrauterine mortality, or maturity at delivery did not change statistically significantly. According to an analysis of nifedipine's usage during pregnancy, the drug benefits decreasing maternal blood pressure, lowering cerebral hemorrhage risk and end-organ damage. Its side effects on fetus have not yet been determined.

Short-term effects of pregnancy-related nifedipine usage

According to a prospective cohort study, teratogenicity was not shown to be elevated in 78 women using nifedipine in 1st trimester of their pregnancy. Pregnant women with developed pre-eclampsia away from term were randomized to receive therapy with nifedipine plus bed rest, as opposed to bed rest alone, in a randomized controlled experiment. Nifedipine lowered blood pressure, but it had no impact on hospital stays or the health of unborn children.

Long-term outcomes of nifedipine use in pregnancy

Two studies examined a number of long-term consequences for offspring born to moms receiving nifedipine treatment for tocolysis during pregnancy. In order to control preterm labor, a Dutch study examined the prolonged term motor and

psychological consequences on fetus exposed to ritodrine or nifedipine in utero. There were no discernible prolonged changes between the two groups. Likewise, there was indiscernible variation in the developmental scores at 2 years of age between infants delivered from women randomly assigned to take ritodrine or nifedipine.

REVIEW OF LITERATURE

1. **Das S et al (2015)** did a hospital based comparative prospective randomized intervention on IV Labetalol with oral Nifedipine for hypertensive emergencies in pregnancy among pregnant woman with severe gestational hypertension were randomized for IV Labetalol injection in an escalating dose regimen of 20, 40, 80, 80 and 80 mg or Nifedipine 10mg tab orally up to 5 doses to achieve desire BP 150/90mm Hg. The authors concluded that both regimen are well tolerated and equally effective.[77]

2. **Kumari M et al (2020) conducted a** comparative randomized study reporting efficacy and safety of oral nifedipine and IV labetalol for severe hypertension treatment during pregnancy on 100 women received either incremental doses of

IV labetalol every 20 minutes, total 300 mg or 10 mg oral nifedipine every 20 minutes (up to 50 mg) for reducing BP to safer levels. It was found that a significantly less time to achieve target blood pressure in women who received oral nifedipine while those receiving nifedipine were found to have lesser doses to control BP. It was concluded that both drugs are equally effective for severe hypertension treatment during gestational period.[78]

3. **Thomas Easterling et al (2019)** conducted a randomized control trial to compare the efficacy and safety of three oral drugs namely labetalol, nifedipine retard and methyldopa for the management of severe hypertension in pregnancy among two public hospitals in Nagpur. Pregnant women aged at least 18 years who reached gestational age of at least twentyeight weeks were included who required pharmacological blood pressure control and randomly assigned to receive 10 mg oral nifedipine, 200 mg oral labetalol hourly or 1000 mg methyldopa in a single dose, without escalation. They discovered that when used alone, nifedipine retard use led to higher frequency of primary outcome attainment than other two drug use.[79]
4. **Raheem IA et al (2011)** in a double- blind randomized trial compared rapidity to control hypertensive emergencies of pregnancy with oral nifedipine with IV labetalol at hospital in Malaysia. Severe gestational hypertension patients with

≥160/110 mmHg required immediate treatment and randomized to receive 10 mg tablet, orally upto five doses of nifedipine and IV placebo saline injection or IV labetalol injection in escalating doses and a placebo tablet every 15 minutes to achieve target blood pressure (≤150/100 mmHg). The results showed that both were well tolerated and equally effective.[75]

5. **SK Biswas et al (2021)** compared efficacy of oral Nifedipine and IV labetalol to control hypertensive emergencies during pregnancy in a hospital on randomised pregnant women reportedly severe gestational hypertension (≥ 160/110 mm Hg) received either IV Labetalol injection in escalating dose regimen and Nifedipine (10 mg tab orally up to 5 doses) to aim target BP (150/90 mm Hg). The study found that both methods were effective and well-tolerated.[80]

6. **Juan Tamargo et al (2019)** in a randomized trial on severe pregnancy induced hypertension between 3 drugs namely; oral Labetalol, Methyldopa and Nifedipine retard. As separate drugs nifedipine and labetalol are best for reducing SBP/DBP to 120-150/ 70-100mm Hg than methyl dopa[81]

7. **Dr.Nivethana KB, Dr.SenthilPriya and Dr.Krupanidhi Karunanithi et al (2018)** did a study on 50 patients, of which 25 patients (group A) received oral

nifedipine while remaining 25(group B) received IV labetalol. Their study showed that the IV Labetalol had shown quick BP decline in shorter duration with minimal dosage comparative to other group.[82]

8. **Donel S et al (2023)** compared effectiveness of different drugs in decreasing BP during hypertensive crises among sixty patients with severe pre-eclampsia who were split evenly into three groups. Over the course of an hour, three doses of nifedipine, labetalol and hydralazine, were administered at 20-minute intervals. The researchers concluded that further doses of nifedipine are required to further drop blood pressure, even though single doses of the medicine are the most effective way to lower blood pressure.[83]

9. **Omkara Murthy K et al (2016)** conducted a study to determine intravenous labetalol on outcomes of maternal and perinatal BP in hypertensive crises on pregnant women whose blood pressure was greater than 160/110 mmHg. Intravenous labetalol injections were randomised administered to patients at interval of 15 minutes to reach aimed BP less than 150/100 mmHg. The results found that IV labetalol was safe and effective medication for treating hypertension in pregnancy.[84]

10. **Momina Zulfeen (2019)** in a review concluded that in controlling the BP, both IV labetalol and oral Nifedipine are effective. Also, due to its ease of using it orally and smooth dosing procedure oral Nifedipine may be a better substitute.[85]

11. **Shekhar S et al (2013**) in their research compared the efficacy of labetalol and oral nifedipine for acute blood pressure control in hypertensive emergencies of pregnancy with sustained increases in SBP 160 mm Hg or higher or DBP 110 mm Hg or higher. Women were randomized for IV labetalol or nifedipine of 10 mg tablet, up to five doses and IV placebo saline injection. The findings revealed that oral nifedipine was more effective in such patients.[86]

12. **S T Vermillion et al (1999**) in their study compared effectiveness of oral nifedipine and IV labetalol for treatment of hypertensive emergencies in pregnancy on 50 peri-partum patients with sustained SBP more than equal to 170 mm Hg or DBP more than equal to 105 mm Hg, the study's subjects received oral nifedipine (10 mg) and IV labetalol (20 mg). A therapeutic goal of SBP less than 160 mm Hg and a DBP less than 100 mm Hg was achieved and both drugs were effective and these treatments were repeated at successively increase in doses after every 20 minutes interval.[87]

MATERIALS AND METHODS

SOURCE OF DATA: This is a Randomized parallel group comparative study. All the pregnant women who fulfil the inclusion criteria will be studied. Informed and written consents will be taken in accordance with the Declaration of Helsinki once the patient is admitted.

SAMPLE SIZE: 104

INCLUSION CRITERIA

1. Pregnant women with hypertensive emergencies (Severe pre-eclampsia / Imminent eclampsia).
2. Maternal age above 18 years.
3. Gestational age > 28weeks.

EXCLUSION CRITERIA

1. Women with preexisting or concurrent medical disorders like diabetes mellitus, cardiac diseases, renal disease, thyrotoxicosis, hemophilia and chronic hypertension.
2. Women in active labor.
3. Received any other anti-hypertensive prior to admission.
4. Patients who have Intrauterine death at presentation.

5. Ecclampsia

STUDY PERIOD: September 2022 to April 2024.

METHODOLOGY:

All the pregnant women with gestational age >28 weeks with hypertensive emergencies after meeting inclusive criteria will be included in the study. Complete history, clinical evaluation with emphasis on full medical, surgical history, drug history and history of any drug allergies and Obstetric, gynecological, and menstrual history, general clinical examination and laboratory investigations will be noted.

These Cases are divided into 2 groups:

Group A: Will receive Intravenous Labetalol group 20mg initially followed by escalating doses of 40mg,80mg up to maximum of 5 doses every 15min up to target blood pressure is reached.

Group B: Will receive Oral Nifedipine retard (Extended release) 20mg initially followed by repeated doses of 20mg every 30 minutes maximum of 5 doses until the target blood pressure is reached. (SBP <150 mm Hg and DBP between 80-100 mm Hg)

During the study, vitals are monitored closely and the maternal blood pressures will be recorded at every 15 minutes till the target blood pressure is reached, then every

30 minutes for the next 2 hours then hourly for 24 hours. Any adverse events like hypotension, tachycardia, dizziness, headache, vomiting etc are documented.

Any need for additional anti hypertensives in each group will be noted.

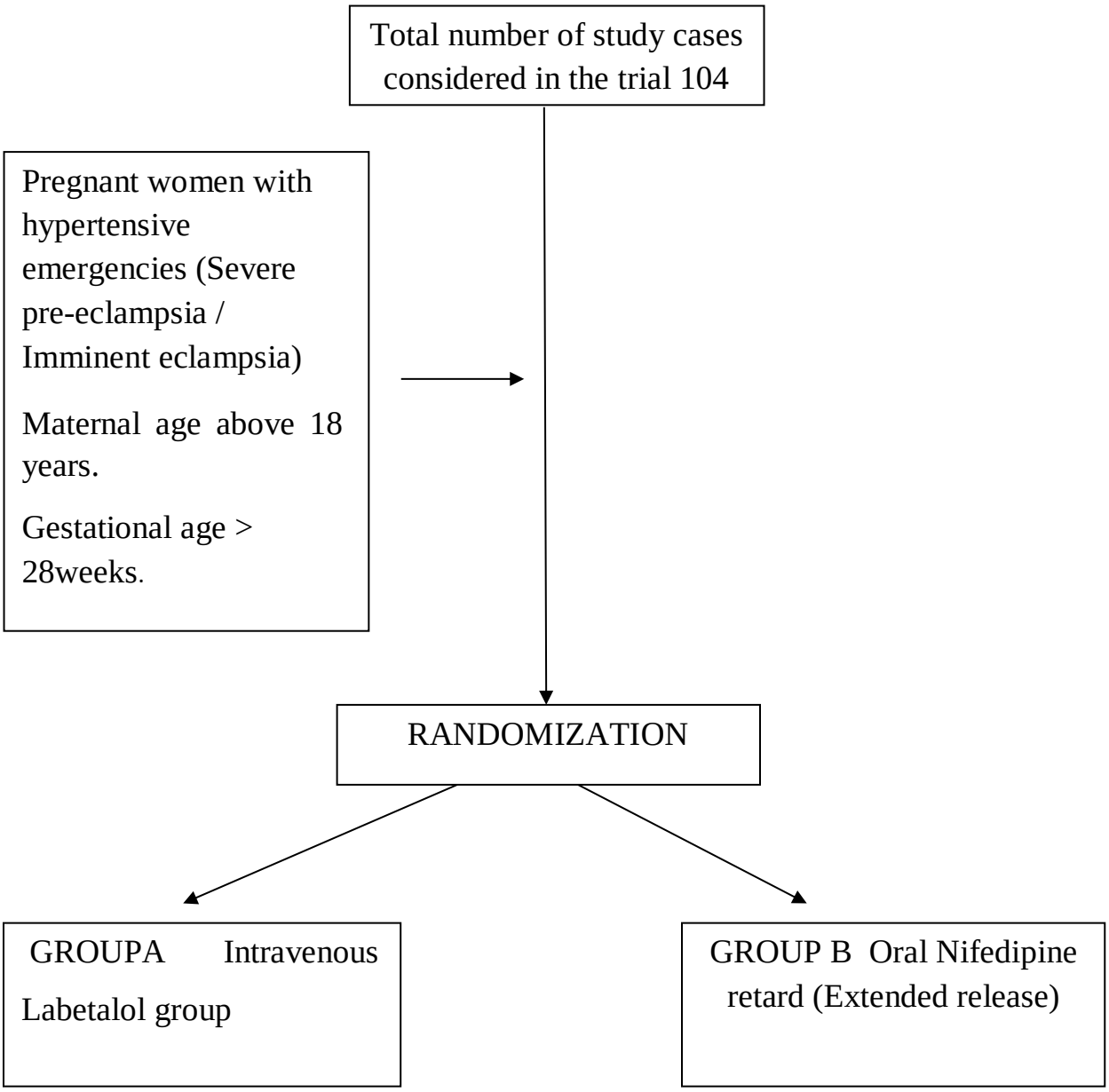
The continuation of the drugs in each group is considered based on the response of the patient, and the total dosage of each drug and the time taken by each drug to achieve the target blood pressure will be documented.

Sample size calculation

- The anticipated mean±SD of time required to achieve the target BP in women receiving nifedipine 37.6±23.3 minutes and for those receiving intravenous Labetalol 52±27.95 respectively[1]

The required minimum sample size is 52 for both group (i.e. a total sample size of 104 assuming equal group sizes) for power 80% and a level of significance 5%, effect size 0.559 for detecting a true difference in means between two groups. Sample size was calculated using G*power 3.1.9.7(1)

RESULTS



STATISTICAL ANALYSIS

- The data obtained will be entered in a Microsoft Excel sheet, and statistical analysis will be performed using statistical package for the social sciences (Version 20).
- Results will be presented as Mean±SD, counts and percentages and diagrams.
- For normally distributed continuous variables between two groups will be compared using Independent t test For not normally distributed variables Mann Whitney U test will be used. Categorical variables between two groups will be compared using Chi square test.
- $p<0.05$ will be considered statistically significant. All statistical tests will performed two tailed.

OBSERVATION AND RESULTS

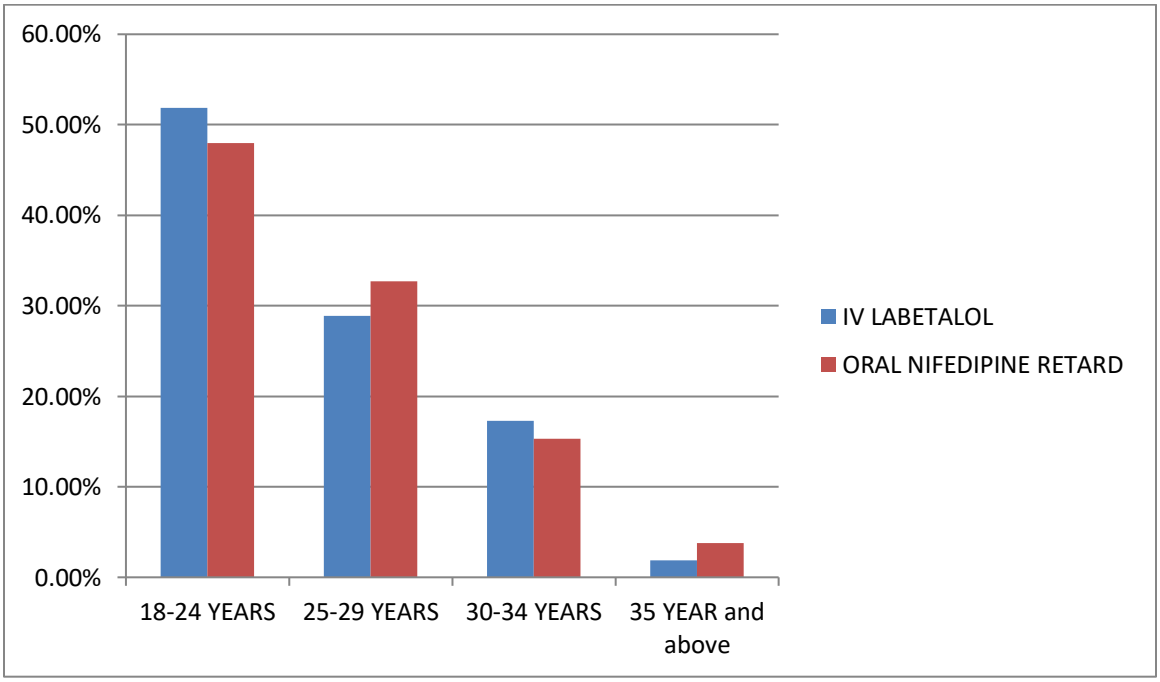
Table 1: Comparison of age between Group A (IV LABETALOL) and Group B (ORAL NIFEDIPINE RETARD)

AGE	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
18-24 years	27 51.9%	25 48.0%	42 40.3%	.16
25-29years	15 28.9%	17 32.7%	32 30.7%	
30-34 years	9 17.3%	8 15.3%	17 16.3%	
≥35 years	1 1.9%	2 3.8%	3 2.9%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, p>0.05 insignificant

Majority of the women belong to 18-24 years of age in IV Labetalol (51.9%) and (48.0%) in Oral Nifedipine group.

Figure 1: Bar diagram for comparison of age between Group A (IV LABETALOL) and Group B (ORAL NIFEDIPINE RETARD)



In IV LABETALOL group, 27(51.9%) women were 18-24 year of age, 15(28.9%) women were 25-29 years of age, 9(17.3%) were 30-34 years of age, and 1(1.9%) were above 35 years of age.

In ORAL NIFEDIPINE RETARD group, 25(48.0%) women were 18-24 year of age, 17(32.7%) women were 25-29 years of age, 8(15.3%) were from 30-34 year of age and 2(3.8%) were above 35 years of age.

The mean age (mean±SD) of patients in IV labetalol group and Oral Nifedipine group was 24.73±4.678 and 25.08±3.915

The distribution of mean age with Group was not statistically significant (p value 0.16).

Table 2: Comparison of gravida between Iv Labetalol and oral nifedipine group

GRAVIDA	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
PRIMIGRAVIDA	24 46.2%	29 55.8%	53 51.0%	.11
MULTIGRAVIDA	28 53.8%	23 44.2%	51 49.0%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, p>0.05 insignificant

In IV Labetalol group, 24(46.2%) patients were Primigravida and 28(53.8%) were Multigravidas. In Oral Nifedipine group, 29(55.8%) patients were Primigravida and 23(44.2%) were Multigravidas. Results were found to be insignificant (p value 0.11) on comparing gravida in both group using chi square test.

Figure 2: bar graph showing Comparison of gravida between Iv Labetalol and oral nifedipine group

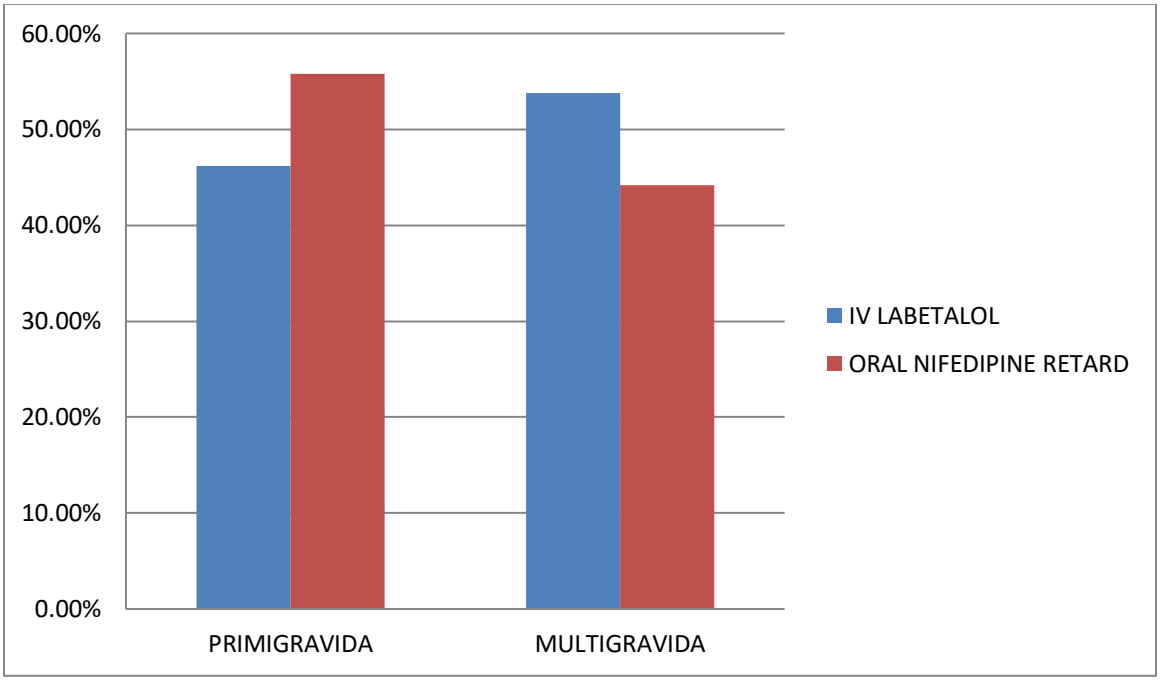
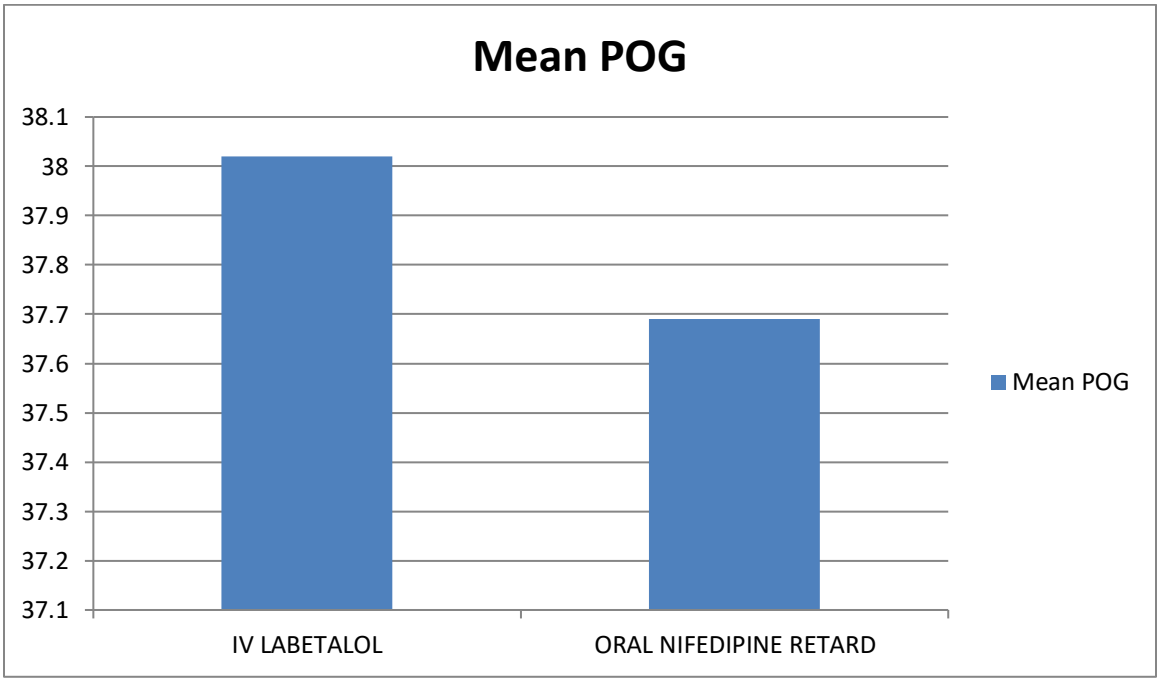


Table 3: Comparison of mean gestational age between IV Labetalol and Oral nifedipine

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	38.02	2.339	.327	.55
ORAL NIFEDIPINE	37.69	3.190		

Figure 3: **Bar graph showing Comparison of mean gestational age between IV Labetalol and Oral nifedipine**



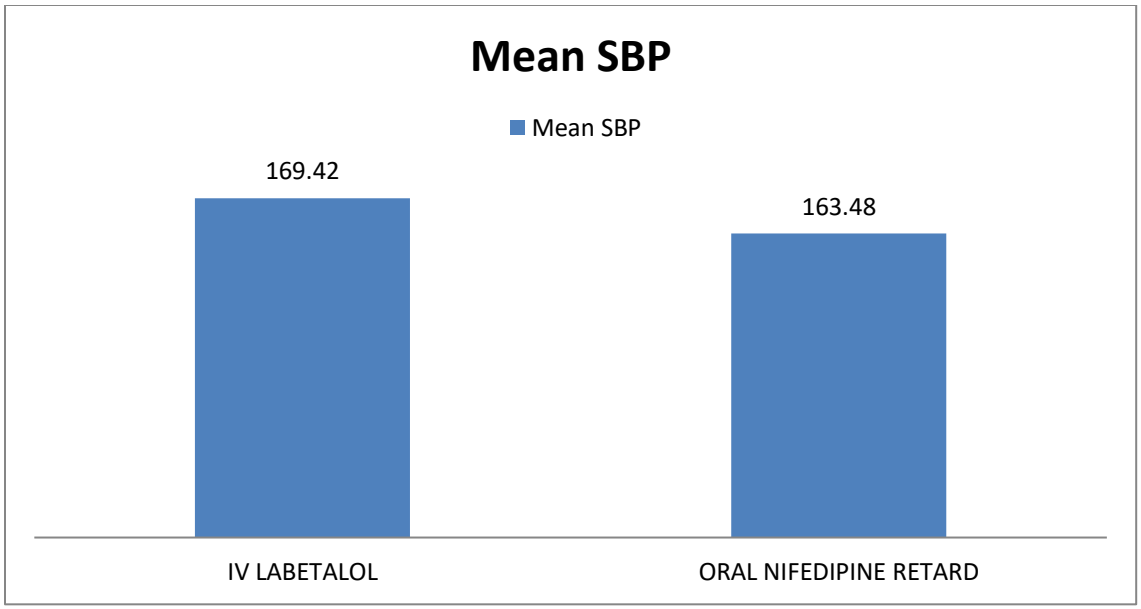
In IV Labetalol group, the mean gestational age of patients was 38.02±2.339. In Oral Nifedipine group, the mean gestational age of patients was 37.69±3.190. Results were found to be insignificant (p value 0.55) when comparing IV Labetalol and Oral Nifedipine retard with POG by using independent t test.

Table 4: **Comparison of mean SBP at the time of enrollment**

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	169.42	13.197	5.942	.003**
ORAL NIFEDIPINE	163.48	5.363		

Test used- independent t test, p< 0.01 highly significant

Graph 4: Bar graph showing Comparison of mean SBP at the time of enrollment



Mean SBP of IV Labetalol and Oral Nifedipine retard was 169.42±13.197 and 163.48±5.363 respectively. Results were found to be highly significant (p value 0.003) when comparing IV Labetalol and Oral Nifedipine retard with SBP by using independent t test.

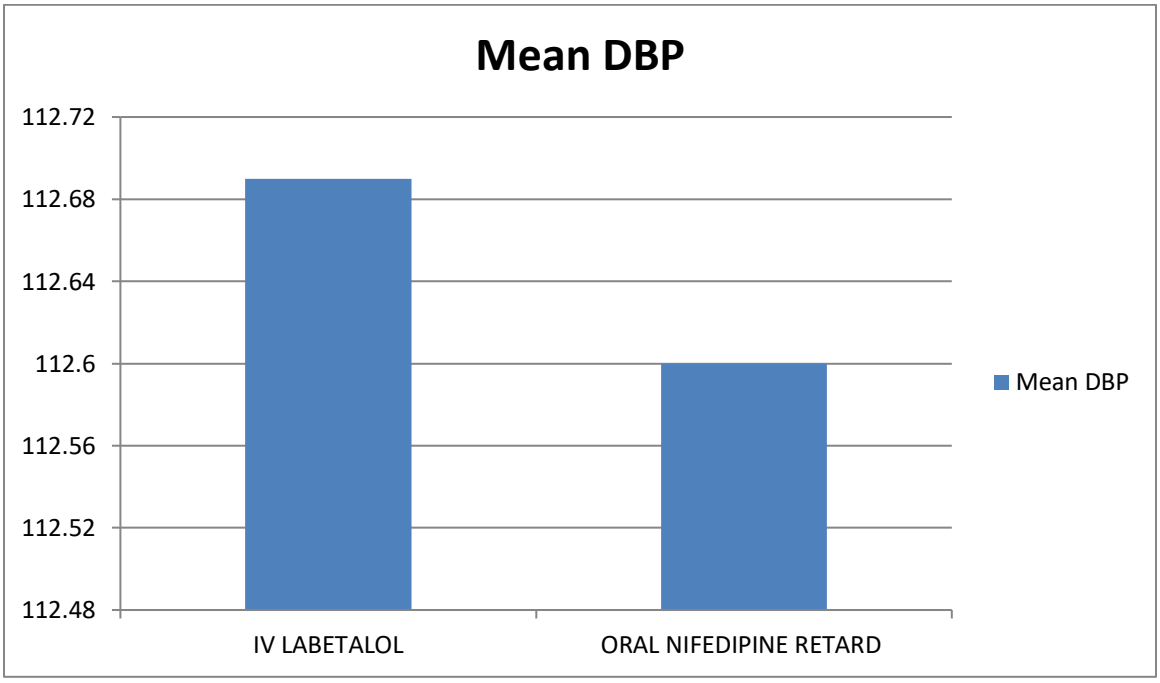
Table 5: **Comparison of mean DBP at the time of enrollment**

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	112.69	7.440	.096	.93

ORAL NIFEDIPINE	112.60	5.154		

Test used- independent t test, p>0.05 insignificant

Graph 5: Bar graph showing Comparison of mean DBP at the time of enrollment



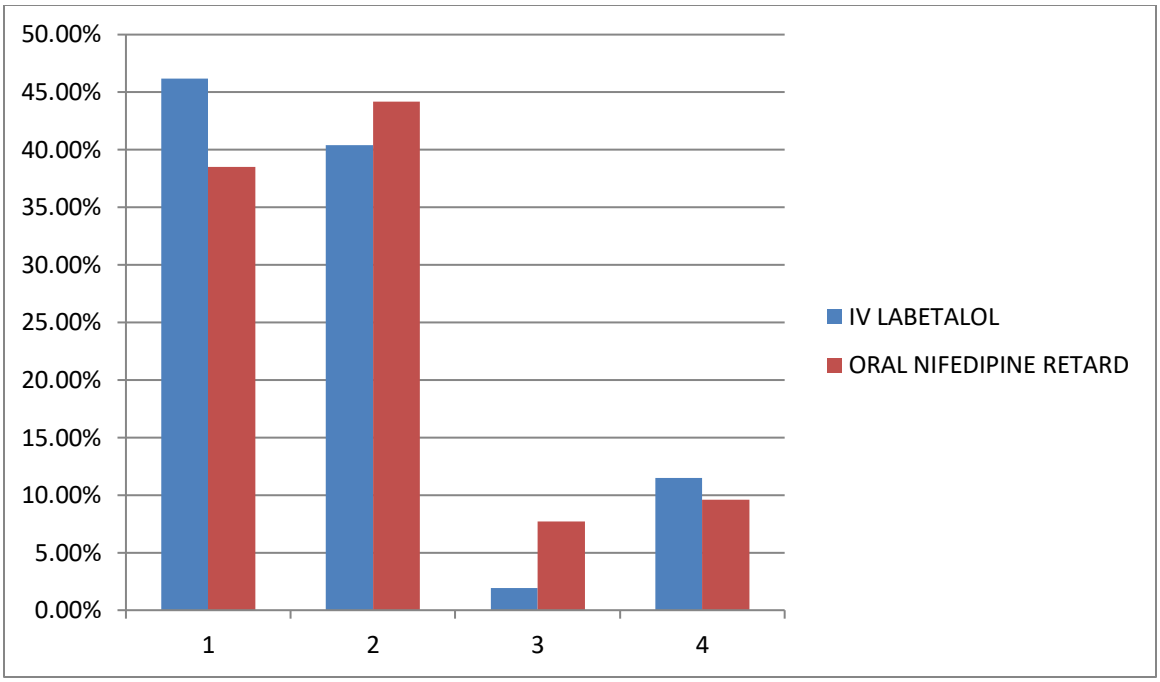
Mean DBP at the time of enrollment of IV Labetalol and Oral Nifedipine retard was 112.69±7.440 and 112.60±5.154 respectively. Results were found to be insignificant (p value 0.93) when comparing IV Labetalol and Oral Nifedipine retard with DBP by using independent t test.

Table 6: **Comparison of proteinuria in IV Labetalol and Oral Nifedipine group**

PROTEINURIA	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
1	24 46.2%	20 38.5%	44 42.3%	0.23
2	21 40.4%	23 44.2%	44 42.3%	
3	1 1.9%	4 7.7%	5 5.7%	
4	6 11.5%	5 9.6%	11 10.6%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, p>0.05 insignificant

Graph 6: **Bar graph showing Comparison of proteinuria in IV Labetalol and oral Nifedipine group**



In IV Labetalol Group, Proteinuria 1+ was observed in 24(46.2%) women, 2+ in 21(40.4%) women, 3+ in 1(1.9) women and 4+ in 6(11.5) of women.

In Oral Nifedipine retard group, Proteinuria 1+ was observed in 20(38.5%) women, 2+ in 23(44.2%) women, 3+ observed in 4(7.7%) women, 4+ seen in 5(9.6%) of women.

Most of the women were having proteinuria 1+ and 2+ in IV Labetalol and Oral Nifedipine retard group. Mean proteinuria of IV Labetalol and Oral Nifedipine retard was 1.73±.972 and 1.88±.922 respectively.

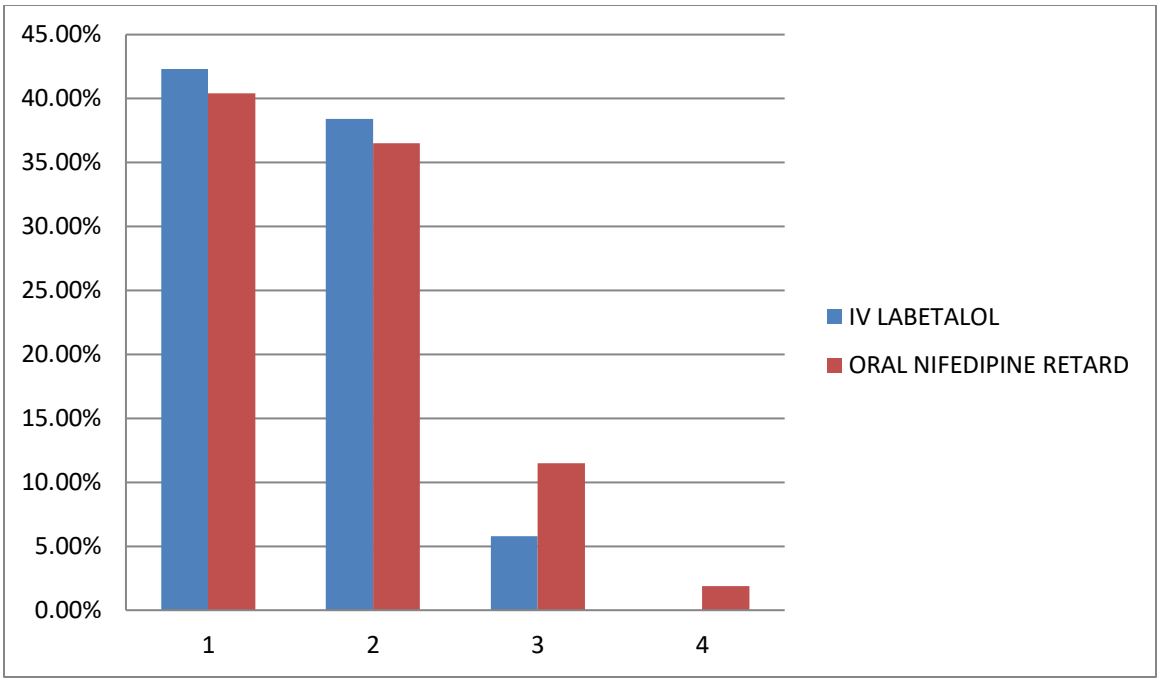
Results were found to be insignificant (p value 0.23) when comparing IV Labetalol and Oral Nifedipine retard with proteinuria by using independent t test.

Table 7: **Comparison of edema in IV Labetalol and Oral Nifedipine group**

Edema	IV LABETALOL	ORAL NIFEDIPINE	Total	P value
1	22 42.3%	21 40.4%	43 41.3%	0.35
2	27 51.8%	24 46.2%	51 49.0%	
3	3 5.8%	6 11.5%	9 8.7%	
4	0 0.0%	1 1.9%	1 1.0%	
Total	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, $p>0.05$ insignificant

Graph 7: Bar graph showing Comparison of edema in IV Labetalol and Oral Nifedipine group



Out of 52women in each group,22(42.3%) women of IV Labetalol and 21(40.4%) women of Oral Nifedipine had grade 1 edema and 20(38.4%) of IV Labetalol and 19(36.5%) of Oral Nifedipine had grade 2 edema. Results were found to be insignificant (p value 0.35) when comparing edema in both groups using chi square test.

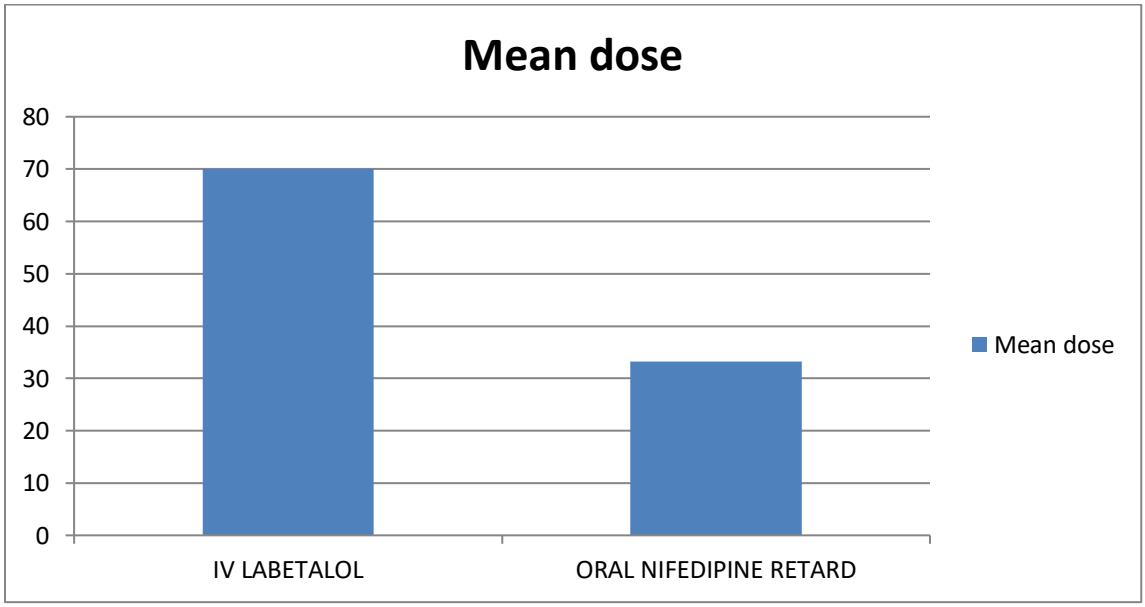
Table 8: **Comparison of mean dose given in IV Labetalol and oral nifedipine group**

DRUG	Mean	Std. Deviation	Mean diff	P value

IV LABETALOL	70.00	42.565	36.827	<0.001**
ORAL NIFEDIPINE	33.17	13.137		

Test used- independent t test, p< 0.001 highly significant

Graph 8: Bar graph showing Comparison of mean dose given in IV Labetalol and oral nifedipine group



Mean dose of IV Labetalol and Oral Nifedipine retard was 70±42.565 and 33.17±13.137 respectively. Results were found to be highly significant (p value

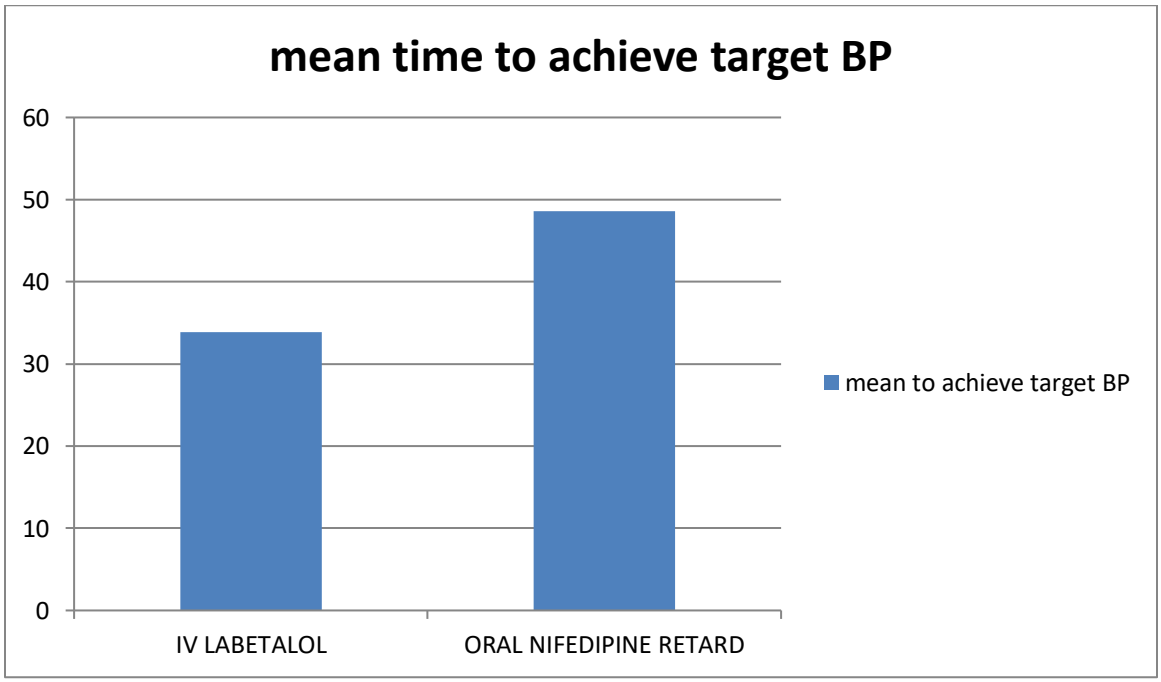
0.001) when comparing IV Labetalol and Oral Nifedipine retard with mean dose by using independent t test.

Table 9: **Comparison of mean of time (minutes required to achieve target BP)**

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	33.85	11.866	-14.712	<0.001**
ORAL NIFEDIPINE	48.56	17.358		

Test used- independent t test, p< 0.001 highly significant

Graph 9: Bar graph showing Comparison of mean of time (minutes required to achieve target BP)



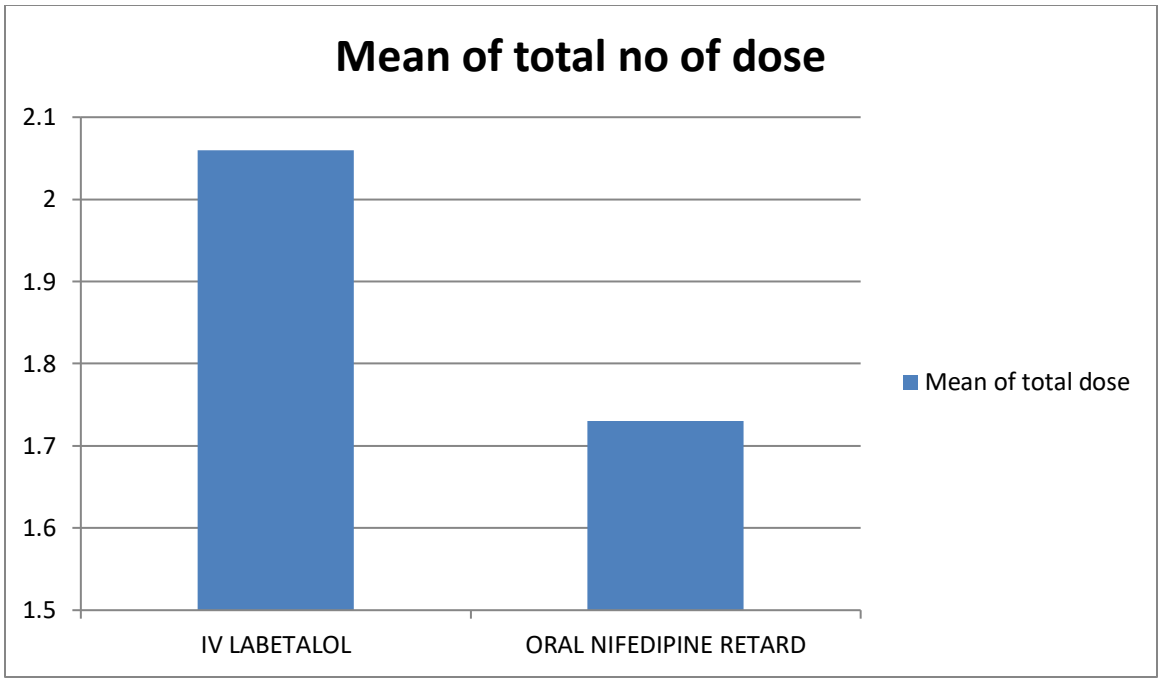
Mean time to achieve target BP of IV Labetalol and Oral Nifedipine was 33.85±11.866 and 48.56±17.358 respectively. Results were found to be highly significant (p value 0.001) when comparing IV Labetalol and Oral Nifedipine with time required to achieve target BP by using independent t test.

Table 10: **Comparison of mean number of doses required to achieve target BP**

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	2.06	.669	.327	.01*
ORAL NIFEDIPINE	1.73	.630		

Test used- independent t test, p≤0.05 significant

Graph 10: **Bar graph showing Comparison of mean number of doses required to achieve target BP**



Mean of total number of doses given in IV Labetalol and Oral Nifedipine retard was 2.06±.669 and 1.73±.630 respectively. Results were found to be significant (p value 0.01) when comparing IV Labetalol and Oral Nifedipine retard by using independent t test.

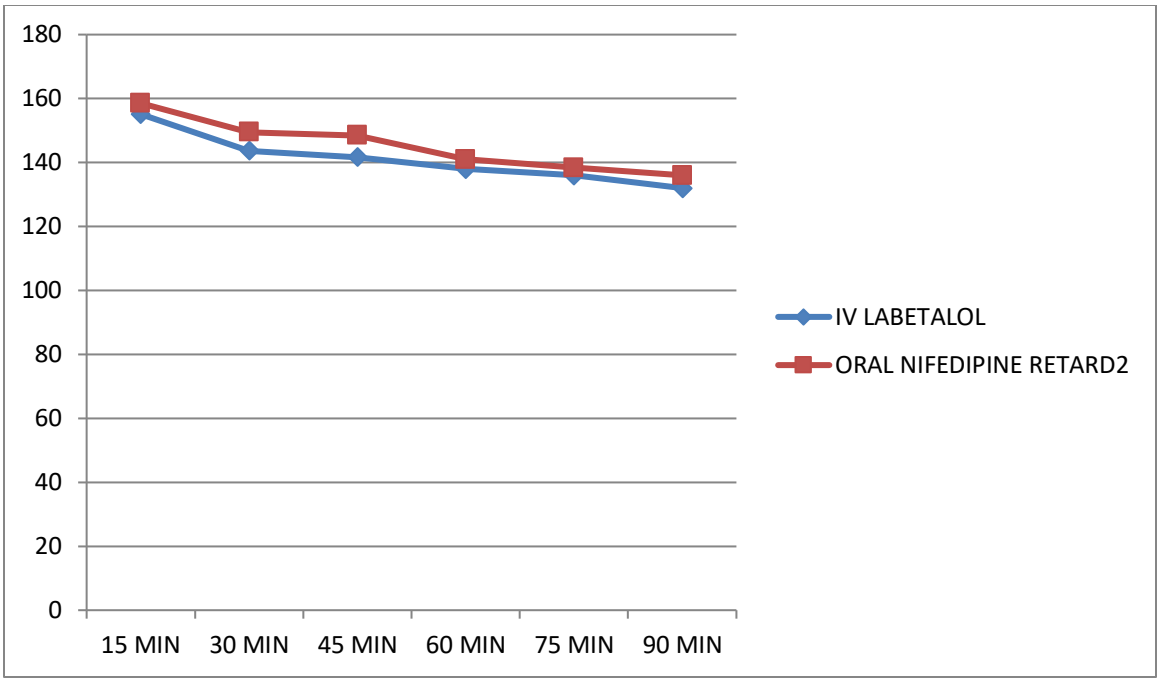
Table 11: Mean of SBP after 15min,30min 45min, 60min, 75min, 90min (GROUPA -IV Labetalol, GROUP B-Oral Nifedipine)

TIME	GROUP	Mean	Std. Deviation	Mean diff	P value

15 min	GROUP A	155.10	13.172	-3.440	.05*
	GROUP B	158.54	5.301		
30 min	GROUP A	143.64	12.776	-5.844	.007***
	GROUP B	149.48	7.883		
45 min	GROUP A	141.67	16.967	-6.800	.05*
	GROUP B	148.47	6.601		
60 min	GROUP A	138.00	16.745	-2.96	.06
	GROUP B	140.96	8.126		
75 min	GROUP A	136.00	11.256	-2.4	.05*
	GROUP B	138.40	6.066		
90 min	GROUP A	132.00	13.246	-4.000	.02*
	GROUP B	136.00	7.071		

Test used- independent t test, $p \leq 0.05$ significant

Graph 11: **Bar graph showing Mean of SBP after 15min,30min 45min, 60min, 75min, 90min (GROUPA -IV Labetalol, GROUP B-Oral Nifedipine)**



Mean SBP after 15 min, 30 min, 45 min, 60 min, 75 min and 90 min was in group A and group B was 155.10±13.172 and 158.54±5.301, 143.64±12.776 and 149.48±7.883, 141.67±16.967 and 148.47±6.601, 138±16.745 and 140.96±8.126, 136±11.256 and 138.40±6.066 and 132±13.246 and136±7.071 respectively. Results were found to be significant when comparing SBP after 15min, 30 min, 45 min, 75min and 90 min in group A and group B except at 60min.

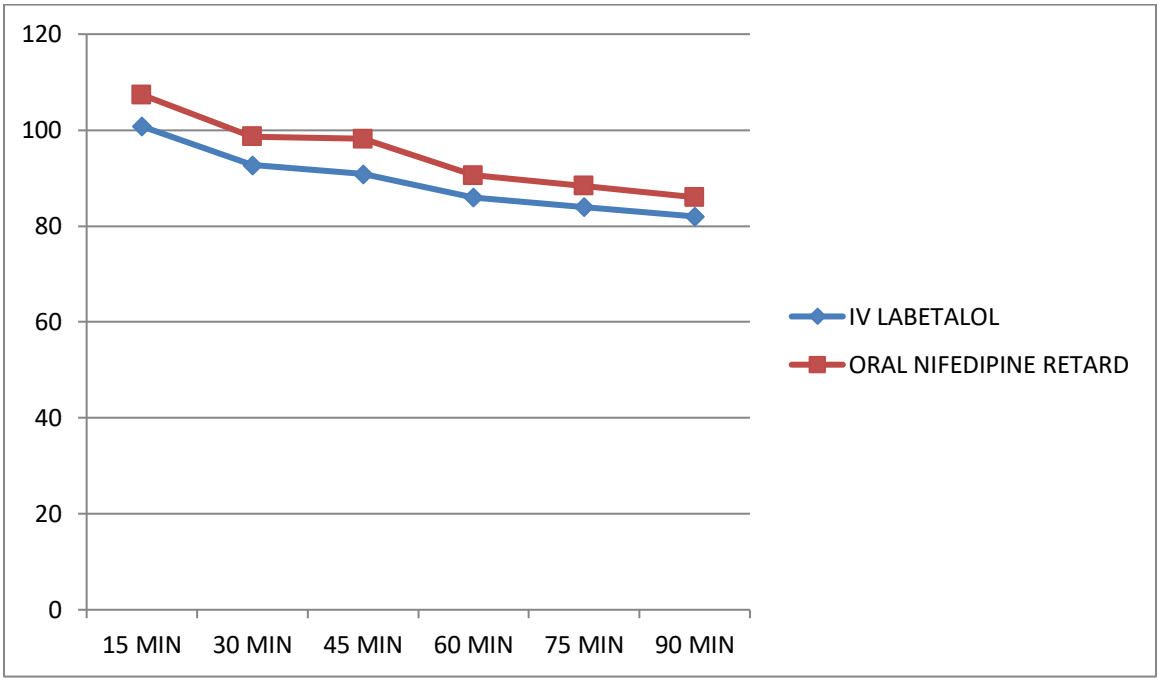
It was clear in graph SBP was maximum in group B after 15min, 30 min. 45 min, 60 min, 75 min and 90 min.

Table 12: Mean of DBP after 15min,30min 45min, 60min, 75min, 90min (GROUPA -IV Labetalol, GROUP B-Oral Nifedipine)

TIME	GROUP	Mean	Std. Deviation	Mean diff	P value
15 min	GROUP A	100.78	7.441	-6.581	<0.001***
	GROUP B	107.37	6.630		
30 min	GROUP A	92.73	8.174	-5.097	<0.001***
	GROUP B	98.63	7.659		
45 min	GROUP A	90.83	9.962	-7.333	.007**
	GROUP B	98.17	6.412		
60 min	GROUP A	86.00	6.783	-4.56	.05*
	GROUP B	90.56	5.938		
75 min	GROUP A	84.00	8.567	-4.4	.05*
	GROUP B	88.40	3.209		
90 min	GROUP A	82.00	9.563	-4.00	.05*
	GROUP B	86.00	8.690		

Test used- independent t test, $p \leq 0.05$ significant

Graph 12: Bar graph showing Mean of DBP after 15min,30min 45min, 60min, 75min, 90min (GROUPA -IV Labetalol, GROUP B-Oral Nifedipine)



Mean DBP after 15 min, 30 min, 45 min, 60 min, 75 min and 90 min was in group A and group B was 100.78±7.441 and 107.37±6.630, 92.73±8.174 and 98.63±7.659, 90.83±9.962 and 98.17±6.412, 86±6.783 and 90.56±5.938, 84±8.567 and 88.40±3.209 and 82 ±9.563 and 86±8.960 respectively. Results were found to be significant when comparing DBP after 15min, 30 min, 45 min, 60min, 75min in group A and group B.

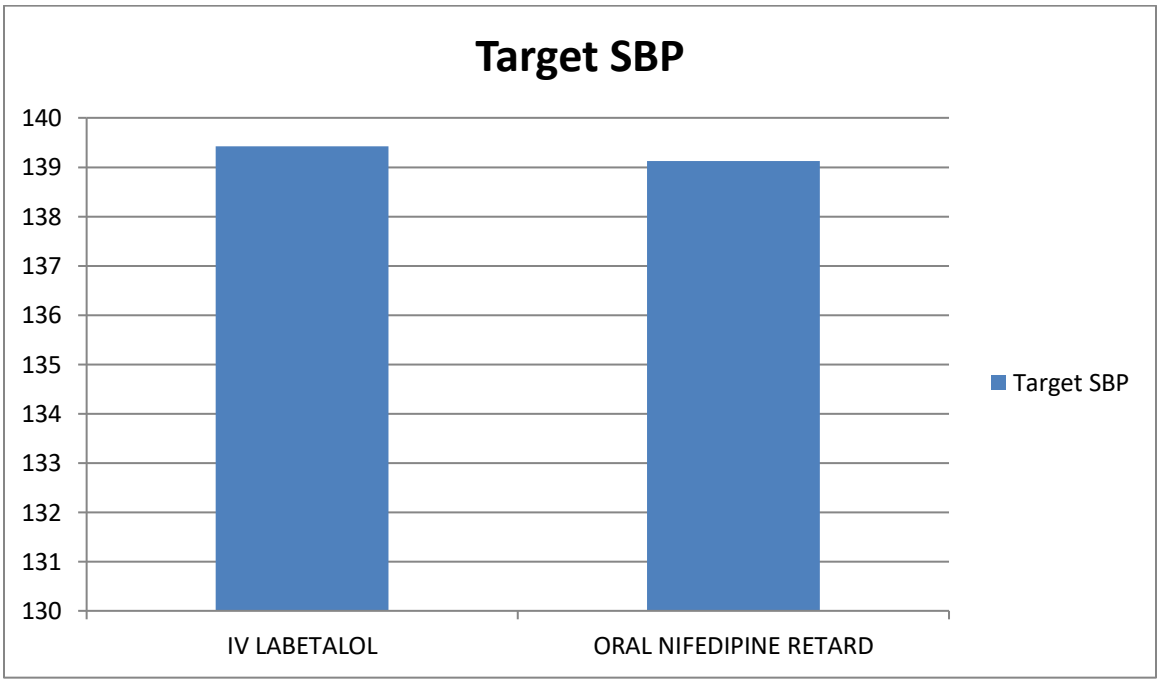
It was clear in graph DBP was maximum in group B after 15min, 30 min and 45 min, 60 min, 75 min and 90 min.

Table 13: Comparison of mean of target SBP reached in IV Labetalol and Oral nifedipine

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	139.42	8.498	.308	.83
ORAL NIFEDIPINE	139.12	6.379		

Test used- independent t test, p>0.05 insignificant

Figure 13: **Bar graph showing Comparison of mean of target SBP reached in IV Labetalol and Oral nifedipine**



Mean target SBP of IV Labetalol and Oral Nifedipine retard was 139.42±8.498 and 139.12±6.379 respectively. Results were found to be insignificant (p value 0.83) when comparing target SBP in IV Labetalol and Oral Nifedipine retard by using independent t test.

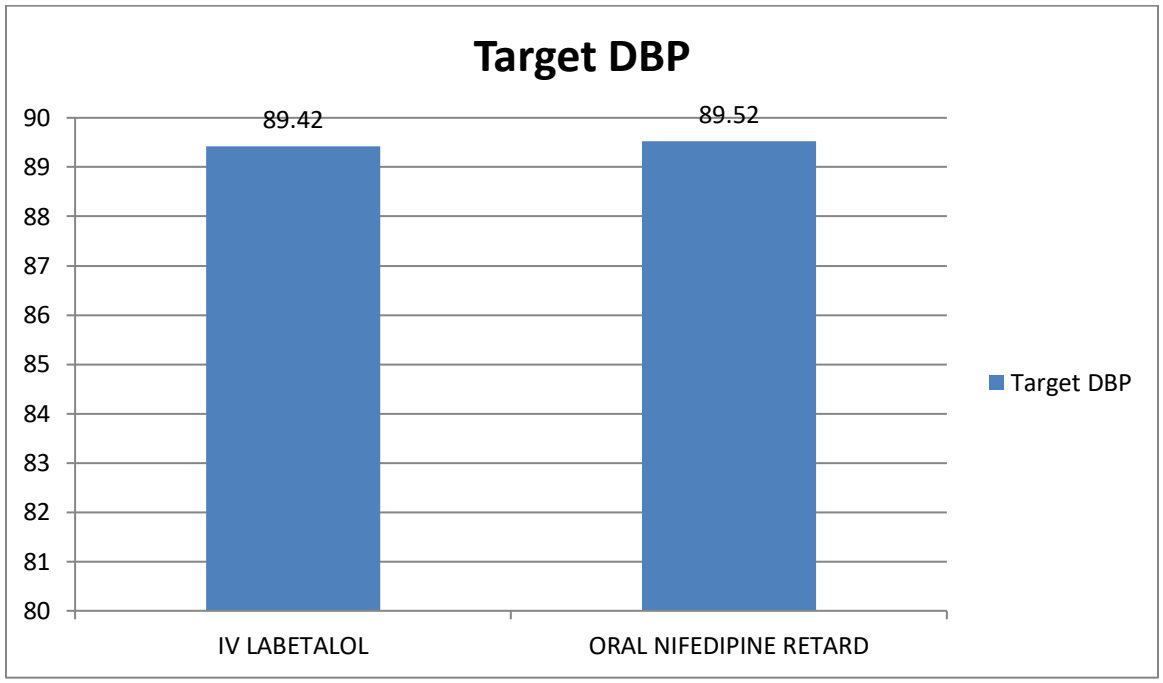
Table 14: **Comparison of mean of target DBP reached in IV Labetalol and Oral nifedipine**

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	89.42	6.076	-.096	.92
ORAL NIFEDIPINE	89.52	4.672		

Test used- independent t test, p>0.05 insignificant

Mean target DBP of IV Labetalol and Oral Nifedipine was 89.42±6.076 and 89.52±4.672 respectively. Results were found to be insignificant when comparing target DBP in IV Labetalol and Oral Nifedipine by using independent t test.

Graph 14: Bar graph showing Comparison of mean of target DBP reached in IV Labetalol and Oral Nifedipine



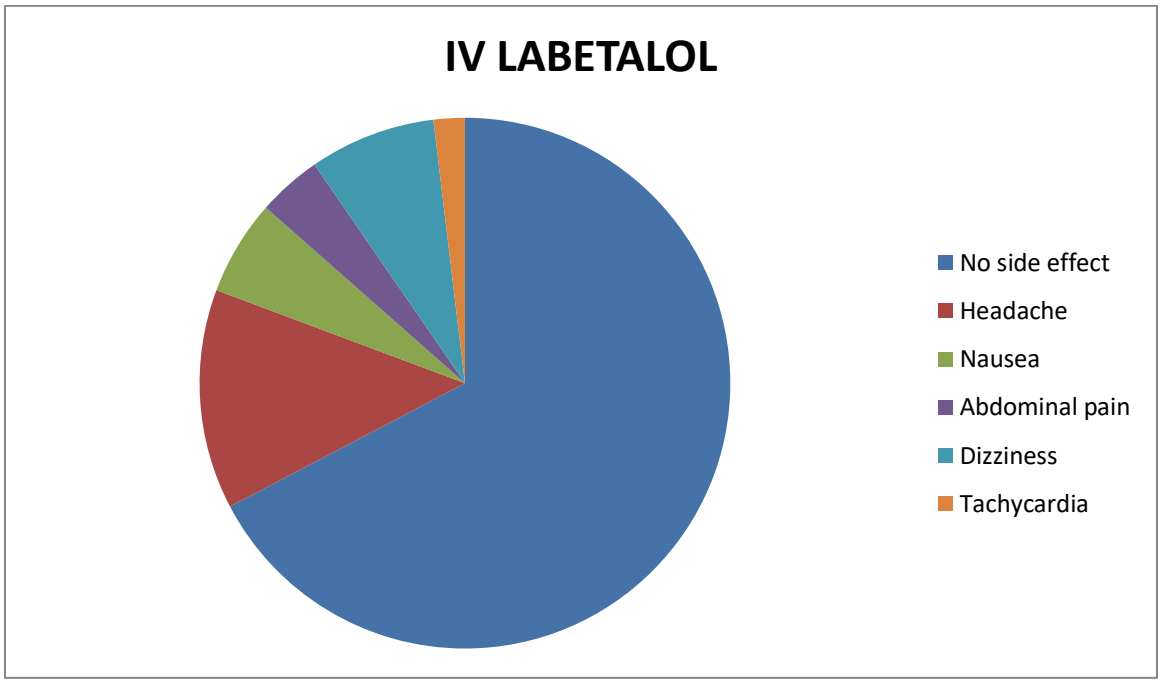
Mean target DBP of IV Labetalol and Oral Nifedipine was 89.42±6.076 and 89.52±4.672 respectively. Results were found to be insignificant when comparing target DBP in IV Labetalol and Oral Nifedipine by using independent t test.

Table 15: Comparison of side effects in IV Labetalol and oral nifedipine group

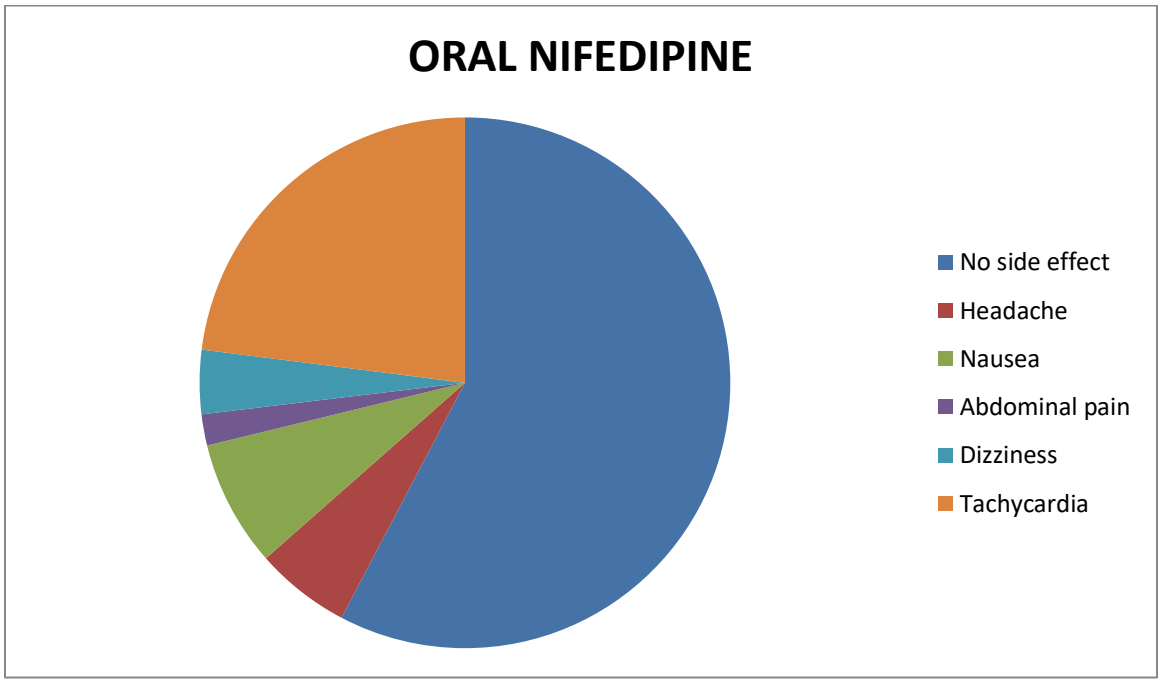
Side effects	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
No side effect	35 67.3%	30 57.7%	65 62.5%	.04*
Headache	7 13.4%	3 5.8%	10 9.6%	
Nausea	3 5.8%	4 7.7%	7 6.7%	
Abdominal pain	2 3.9%	1 1.9%	3 2.9%	
Dizziness	4 7.7%	2 3.9%	6 5.7%	
Tachycardia	1 1.9%	12 23.0%	13 12.5%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, $p<0.05$ significant

Graph 15(a): Graph showingside effects in IV Labetalol group



Graph 15(b): Graph showing side effects in Oral nifedipine group



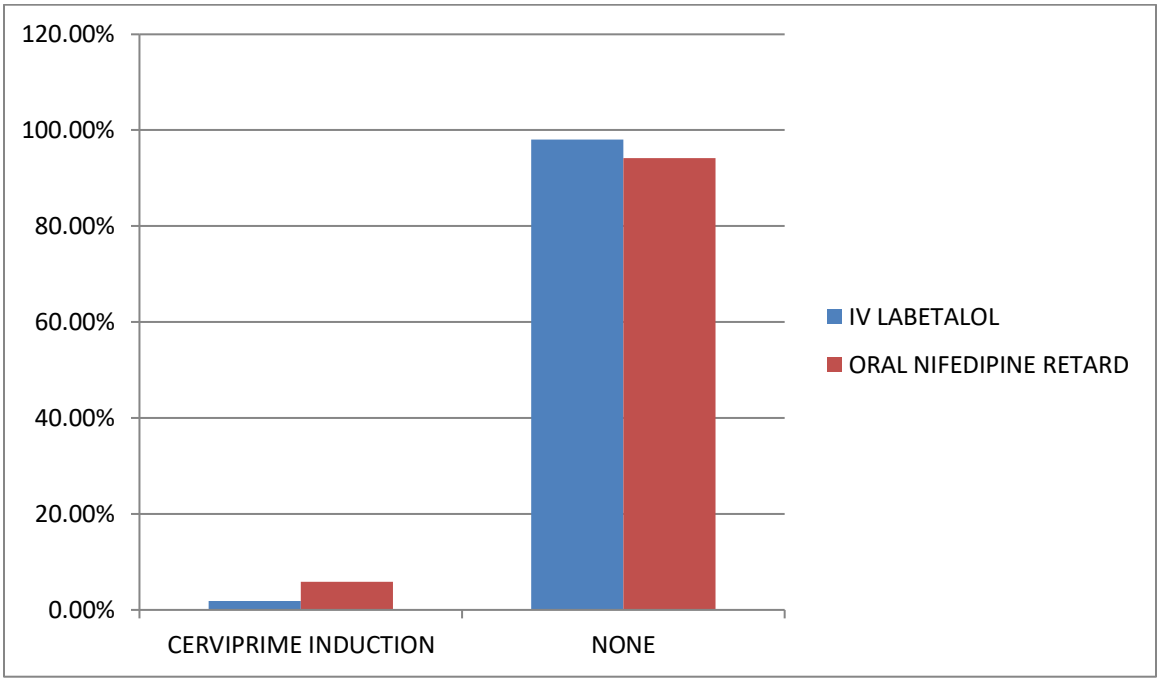
Most of the patients 35(67.3%) of IV Labetalol and 30(57.5%) of Oral Nifedipine group B did not had any side effects. 7(13.4%) patients had Headache and 2(3.9%) patients had abdominal pain side effect in IV Labetalol and 12(23%) having tachycardia side effect in Oral Nifedipine. Results were found to be significant (P value0.04) when comparing side effect in IV Labetalol and Oral Nifedipine.

Table 16: **Comparison of Induction in IV Labetalol and oral Nifedipine**

INDUCTION	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
CERVIPRIME INDUCTION	1 1.9%	3 5.8%	4 3.8%	.308
NONE	51 98.1%	49 94.2%	100 96.2%	
TOTAL	52 100%	52 100%	104 100%	

Test used- chi square, p>0.05 insignificant

Graph 16: Comparison of Induction in IV Labetalol and oral Nifedipine



Cerviprime induction was done in 1(1.9%) in IV Labetalol and 3(5.8%) in Oral Nifedipine group. Results were found to be insignificant when comparing induction in IV Labetalol and Oral Nifedipine.

Table 17: **Comparison of mode of delivery in IV Labetalol and Oral nifedipine group**

DELIVERY	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
Preterm vaginal delivery	4 7.7%	3 5.8%	7 6.7%	.361
Full term vaginal delivery	7 13.5%	6 11.5%	13 12.5%	
Preterm emergency LSCS	5 9.6%	12 23.1%	17 16.3%	
Full term emergency LSCS	35 67.3%	31 59.6%	66 63.5%	
Ventouse	1 1.9%	0 0.0%	1 1.0%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, p>0.05 insignificant

Majority of the patients underwent cessarean section 40(76.9%) in IV Labetalol and 43(82.7%) in Oral Nifedipine group.

Maximum number of patients who underwent full term emergency LSCS in both IV Labetalol and Oral Nifedipine retard i.e. 35(67.3%) and 31(59.6%). Results were found to be insignificant (p value 0.361) when comparing delivery in IV Labetalol and Oral Nifedipine group.

Graph 17: **Bar graph showing Comparison of mode of delivery in IV Labetalol and Oral nifedipine group**

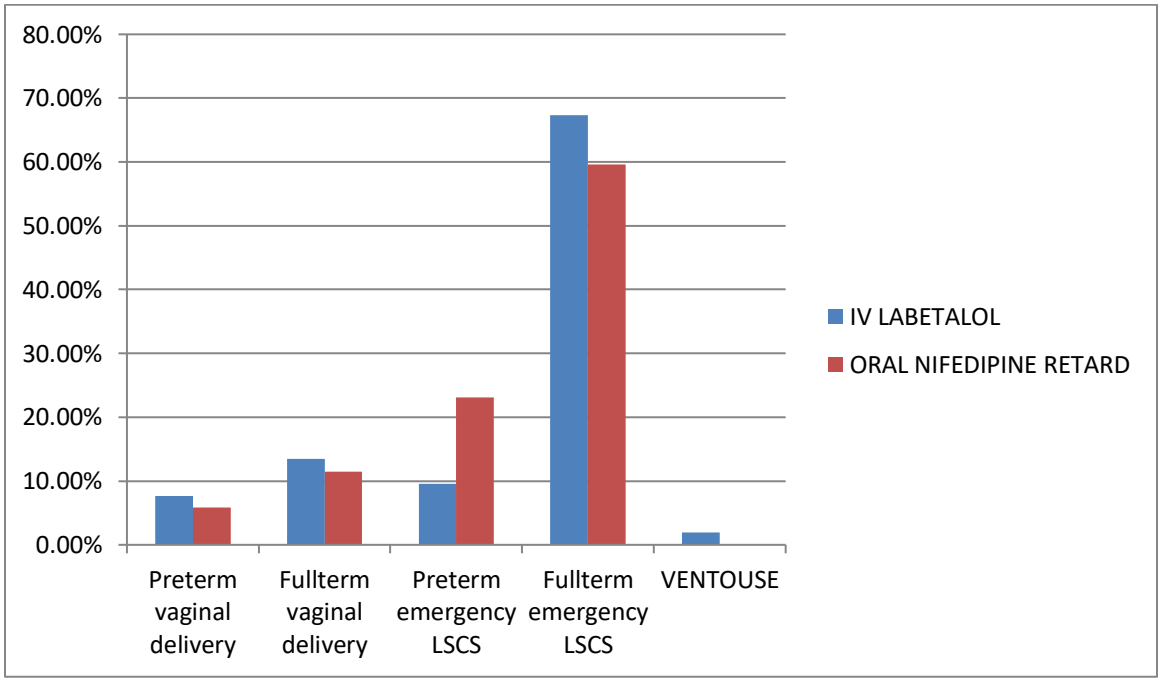


Table 18: Mean birth weight of IV Labetalol and Oral Nifedipine group

DRUG	Mean	Std. Deviation	Mean diff	P value
IV LABETALOL	2.4769	.74692	-.08327	.53
ORAL NIFEDIPINE	2.5602	.61273		

Test used- independent t test, p>0.05 insignificant

Mean birth weight of IV Labetalol and Oral Nifedipine was 2.4769±.74692 and 2.5602±.61273 respectively. Results were found to be insignificant (p value 0.53) when comparing mean birth weight in IV Labetalol and Oral Nifedipine by using independent t test

Graph 18: Bar graph showing Mean birth weight of IV Labetalol and Oral Nifedipine group

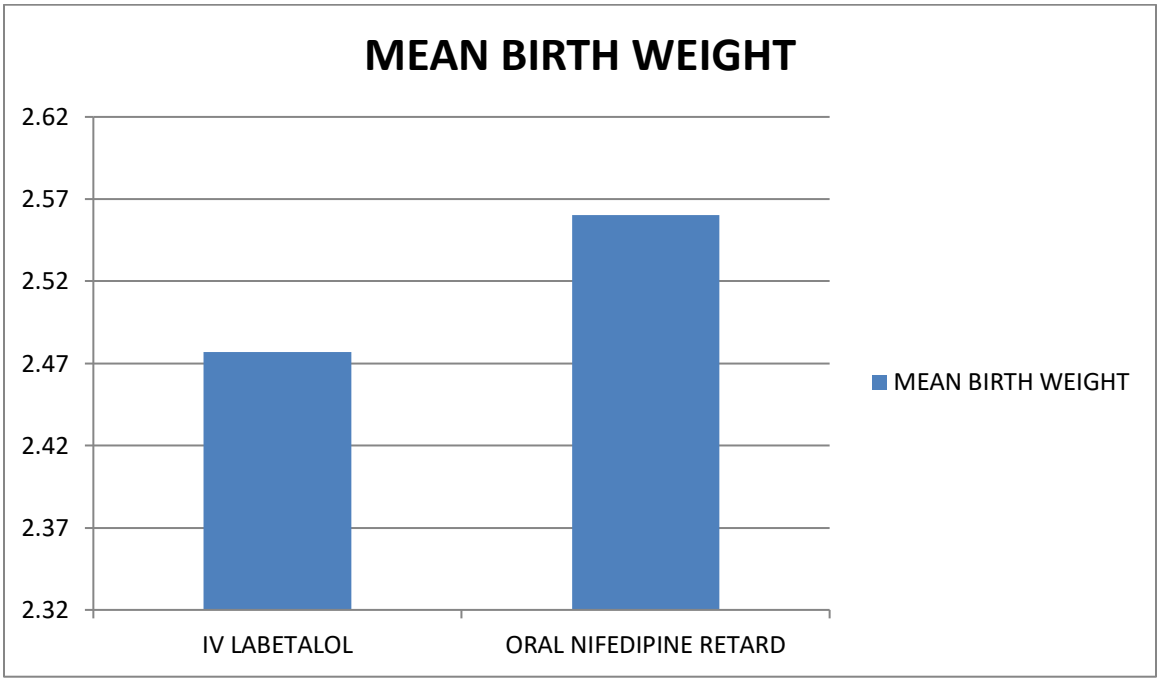


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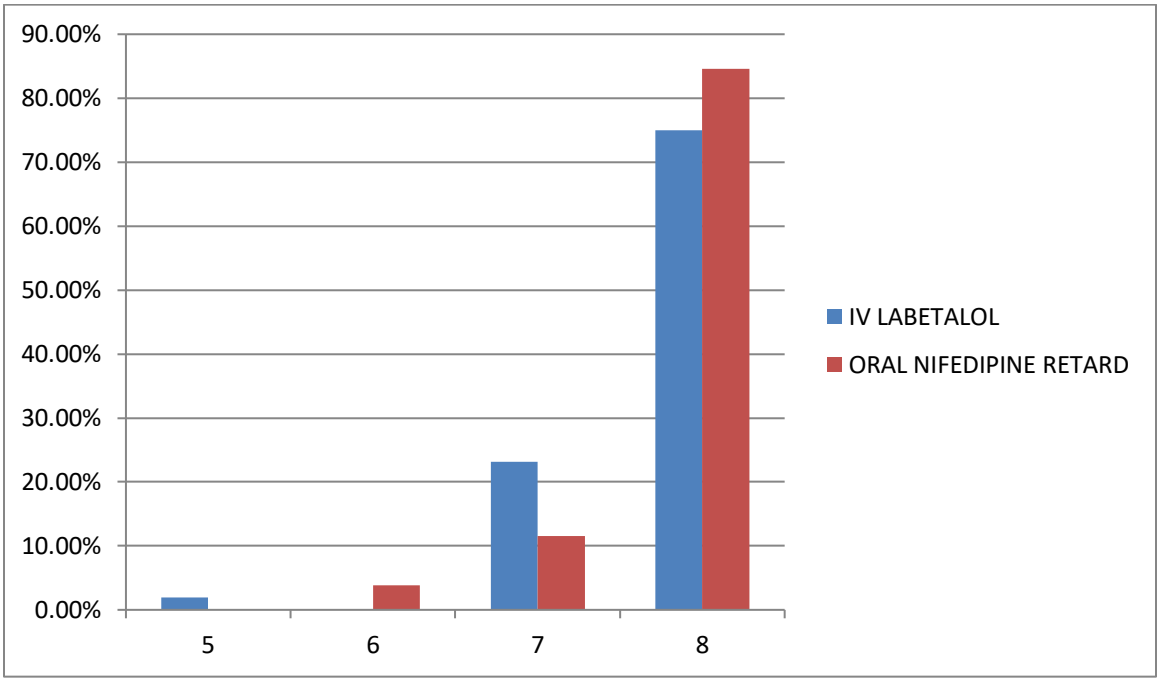
Table 19: Comparison of Apgar score at 1min in IV Labetalol and Oral Nifedipine group

APGAR 1 MIN	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
5	1 1.9%	0 0.0%	1 1.0%	.15

6	0 0.0%	2 3.8%	2 1.9%	
7	12 23.1%	6 11.5%	18 17.3%	
8	39 75.0%	44 84.6%	83 79.8%	
TOTAL	52 100.0%	52 100.0%	104 100.0 %	

Test used- chi square, p>0.05 insignificant

Graph 19: Bar graph showing Comparison of Apgar score at 1min in IV Labetalol and Oral Nifedipine group



APGAR score at 1min was 8 in 39(75%) in IV Labetalol and 44(84.6%) in Oral Nifedipine group. Number of newborns having APGAR score at 1 min- 8 was seen more in Oral Nifedipine than compared to IV Labetalol group. Results were found to be insignificant (p value 0.15) on comparing APGAR 1 min in IV Labetalol and Oral Nifedipine.

Table 20: **Comparison of Apgar score at 5min in IV Labetalol and Oral Nifedipine group**

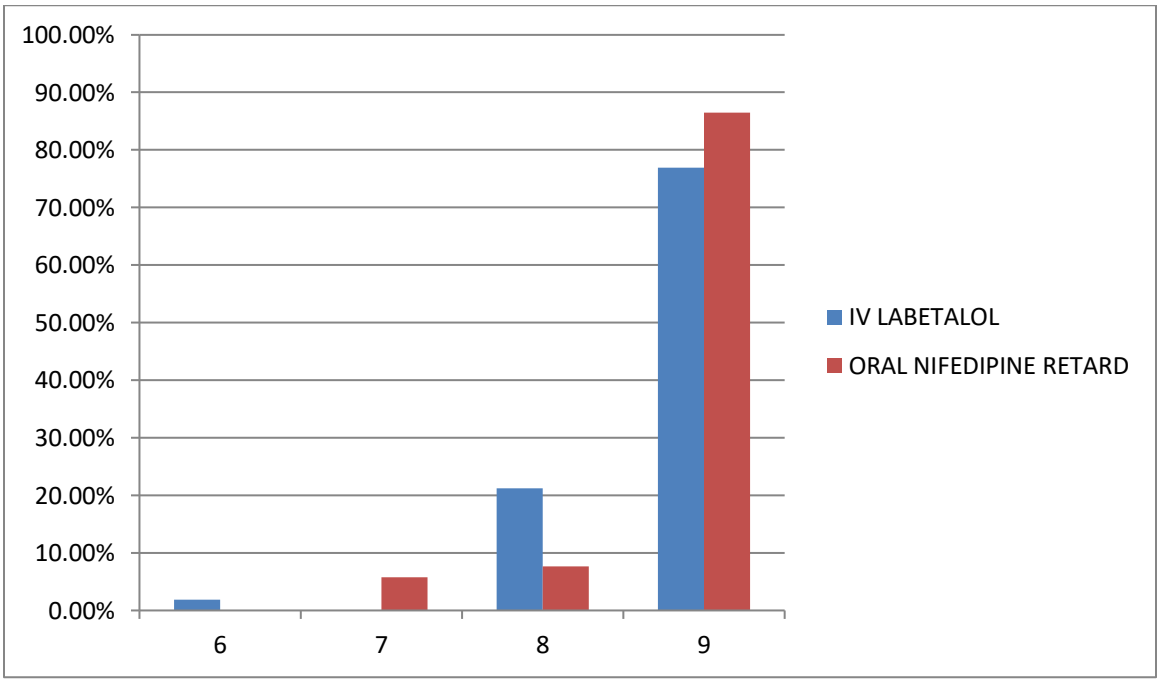
APGAR score at 5 min was 9 in 40(76.9%) in IV Labetalol and 45(86.5%) in Oral Nifedipine. APGAR score at 5 min was 8 more in Oral Nifedipine in compare to IV Labetalol. Results were found to be significant (p value 0.05) on comparing APGAR 5 min in IV Labetalol and Oral Nifedipine.

APGAR 5 MIN	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
6	1 1.9%	0 0.0%	1 1.0%	.05*
7	0 0.0%	3 5.8%	3 2.9%	

8	11 21.2%	4 7.7%	15 14.4%	
9	40 76.9%	45 86.5%	85 81.7%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, $p \leq 0.05$ significant

Graph 20: Bar graph showing Comparison of Apgar score at 5min in IV Labetalol and Oral Nifedipine group



APGAR score at 5 min was 9 in 40(76.9%) in IV Labetalol and 45(86.5%) in Oral Nifedipine. APGAR score at 5 min was 8 more in Oral Nifedipine in compare to IV Labetalol. Results were found to be significant (p value 0.05) on comparing APGAR 5 min in IV Labetalol and Oral Nifedipine

Table 21: **Comparison of MgSO4 given in IV Labetalol and Oral Nifedipine**

MGSO4	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
PRITCHARD REGIMEN	7 13.5%	1 1.9%	8 7.7%	.17
LOADING DOSE	6 11.5%	6 11.5%	12 11.5%	
NONE	39 75.0%	45 86.5%	84 80.8%	
TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, p>0.05 insignificant

Among total 52(100%), loading dose of MgSO4 was given in 6(11.5%) patients in IV Labetalol. Among total 52(100%), loading dose was 6(11.5%) of MGSO4 in Oral Nifedipine. Results were found to be insignificant (p value 0.17) when comparing fetal MGSO4 in IV Labetalol and Oral Nifedipine.

Graph 21: **Bar graph showing Comparison of MgSO4 given in IV Labetalol and Oral Nifedipine**

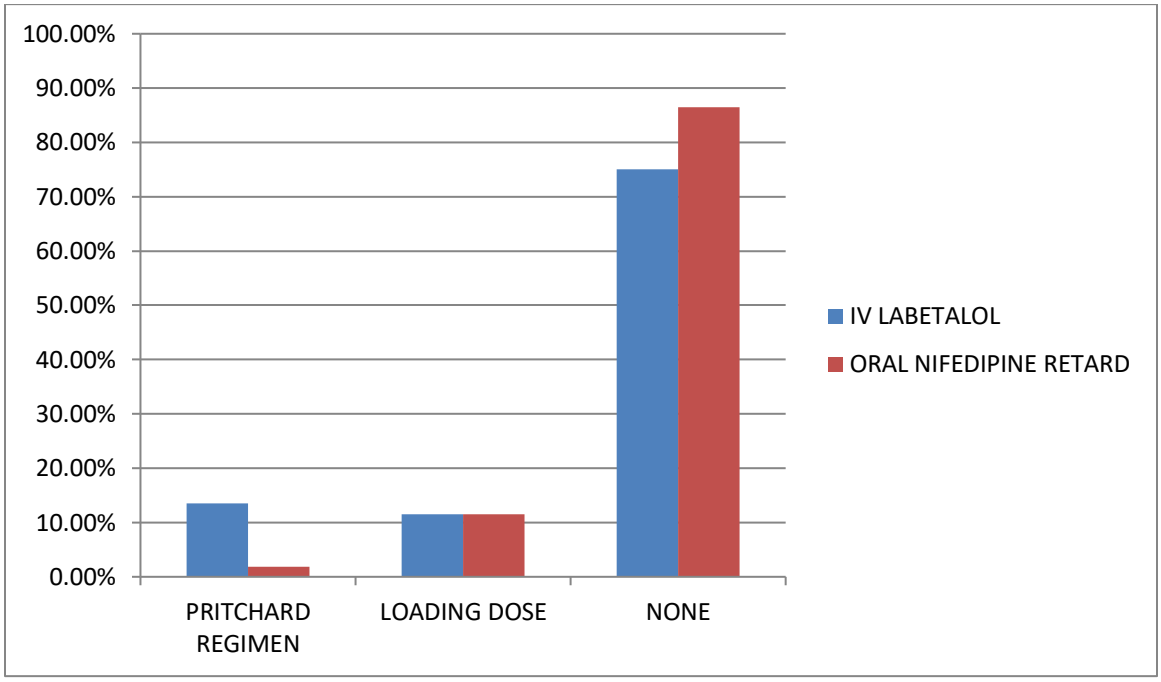


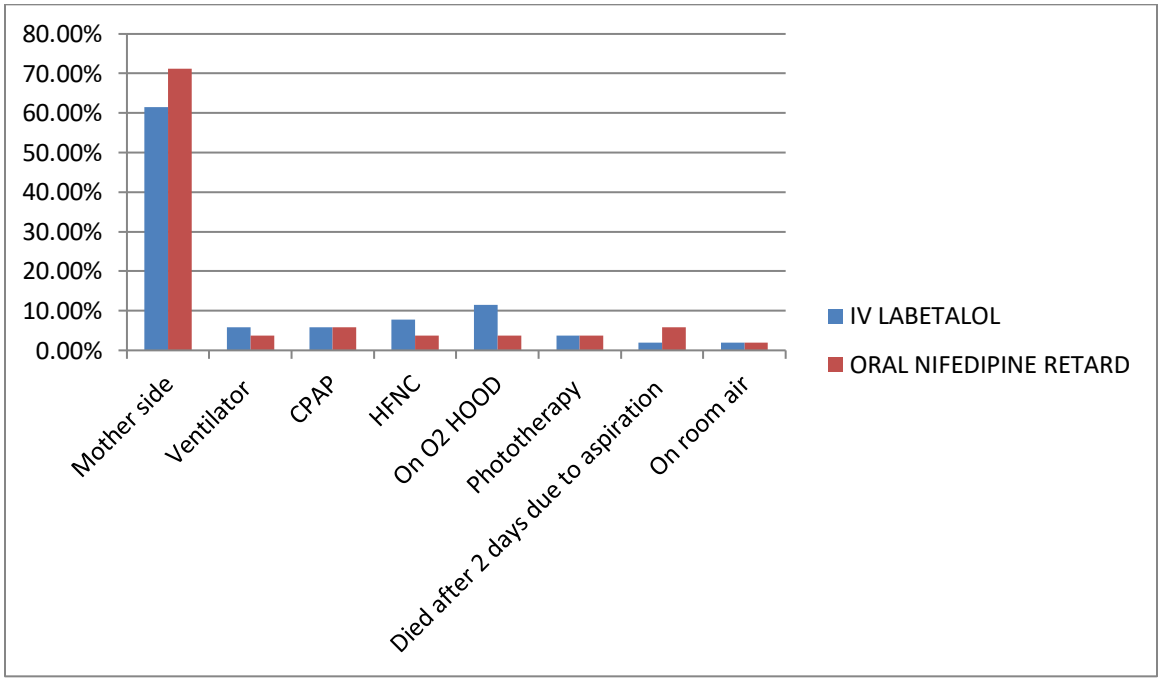
Table 22: Comparison of fetal outcome in IV Labetalol and Oral nifedipine

FETAL OUTCOME	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
MOTHER SIDE	32 61.5%	37 71.2%	69 66.3%	.37
VENTILATOR	3 5.8%	2 3.8%	5 4.8%	
CPAP	3 5.8%	3 5.8%	6 5.7%	
HFNC	4 7.7%	2 3.8%	6 5.7%	
On O2 HOOD	6 11.5%	2 3.8%	8 7.6%	
PHOTOTHERAPY	2 3.8%	2 3.8%	4 3.8%	
DIED after 2 days	1 1.9%	3 5.8%	4 3.8%	
ROOM AIR	1 1.9%	1 1.9%	2 1.9%	

TOTAL	52 100.0%	52 100.0%	104 100.0 %	

Test used- chi square, p>0.05 insignificant

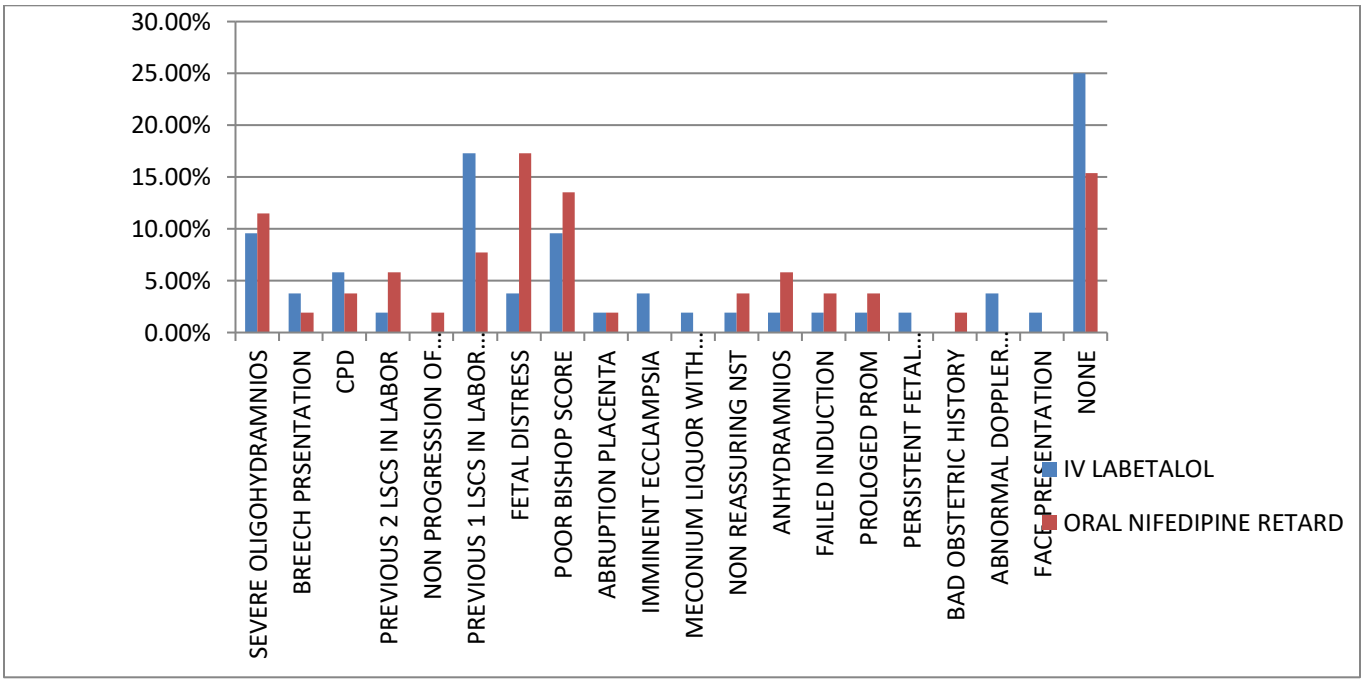
Graph 22: Bar graph showing Comparison of fetal outcome in IV Labetalol and Oral nifedipine



Most of the newborns were mother side i.e 31(59.6%) in IV Labetalol and 37(71.2%) in Oral Nifedipine. Results were found to be insignificant (p value0.37) when comparing fetal outcome in IV Labetalol and Oral Nifedipine.

Graph 23: Comparison of Indication of LSCS in IV Labetalol and Oral Nifedipine

Test used- chi square, p>0.05 insignificant



Results were found to be insignificant when comparing indication of LSCS in IV Labetalol and Oral Nifedipine.

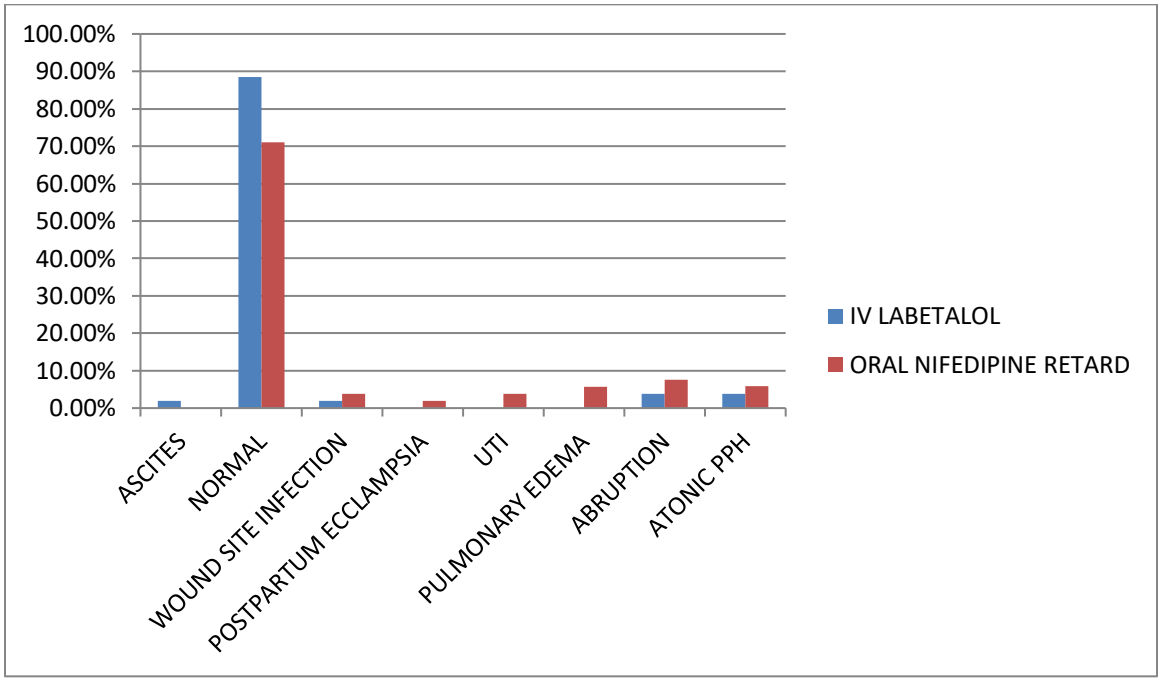
Table 23: **Comparison of maternal morbidity in IV Labetalol and Oral Nifedipine**

MATERNAL MORBIDITY	IV LABETALOL	ORAL NIFEDIPINE	TOTAL	P value
ATONIC PPH	3 5.7%	3 5.8%	6 4.8%	.09
ABRUPTION	2 3.8%	4 7.6%	6 5.7%	
WOUND SITE INFECTION	1 1.9%	2 3.8%	3 2.9%	
POSTPARTUM ECCLAMPSIA	0 0.0%	1 1.9%	1 1.0%	
UTI	0 0.0%	2 3.8%	2 1.9%	
PULMONARY EDEMA	0 0.0%	3 5.7%	3 2.9%	
NORMAL	46 88.4%	37 71.1%	83 79.8%	

TOTAL	52 100.0%	52 100.0%	104 100.0%	

Test used- chi square, p>0.05 insignificant

Graph 23: Bar graph showing Comparison of maternal morbidity in IV Labetalol and Oral Nifedipine



Among 52 women in each group, 46(88.4%) in IV Labetalol and 37(71.1%) in Oral Nifedipine had good maternal outcome. Important intraoperative findings like Atonic PPH, Abruption placenta observed in both the groups were compared. Maternal complications like Pulmonary edema, wound site infection, Postpartum

eclampsia, urinary tract infection seen in both the groups were compared. Results were found to be insignificant (p value0.09) when comparing maternal outcome in IV Labetalol and Oral Nifedipine retard groups.

DISCUSSION:

Management primarily aims at reduction of cardiovascular or cerebrovascular risks. There is no consensus on relative efficacy and safety of medications to treat severe hypertension in pregnancy. Recently a Cochrane review found insufficient data to recommend a specific drug and concluded that the choice of antihypertensive should be guided by clinicians' experience and familiarity with the drug, known adverse effects and women's experiences.

Thus, present study has done the comparative evaluation of medications that administered intravenously labetalol and oral Nifedipine Retard (20mg). This is the first study to address the comparison of oral nifedipine retard 20mg and intravenous labetalol.

In this study, 104 pregnant women of gestational period more than 28weeks were enrolled and grouped into group A and group B.

Group A (IV labetalol): Received Intravenous Labetalol group 20mg initially followed by escalating doses of 40mg,80mg up to maximum of 5 doses every 15min up to target blood pressure is reached.

Group B (oral Nifedipine retard): Received Oral Nifedipine retard (Extended release) 20mg initially followed by repeated doses of 20mg every 30 minutes maximum of 5 doses until desired BP is achieved. (SBP <150 mm Hg and DBP between 80-100 mm Hg).

The observations were made on mean age group, mean time to reach target blood pressure, side effects of the drugs, maternal outcome, fetal outcome, mode of delivery, MgSo4 level.

AGE

In our study age comparison has no significance among both the groups. Similar results were noted in other studies. All the patients were aged between 19-35 yrs. A study done by Riffat Sarwar et al[88] found that Group A has a mean age 27.96±4.79 and for Group B was 27.48±4.76. Swapan Das et al[77] also found the mean age in both the group was 25.4 years and our study has similar finding with the previous study.

Studies	**Mean Age**

	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
Swapan das et al[77]	25.4 years	25.4 years
Sarwar R et al[88]	27.96±4.79	27.48±4.76
Our study	24.73±4.678	25.08±3.915

In this study, (table 3, fig 3) shows the gestational age at presentation in each group. Most patients with pre-eclampsia belonged to 38-40 weeks of gestational age and mean POG of group A and group B was 38.02±2.339 and 37.69±3.190 respectively.

Comparison of mean SBP at the time of enrollment

In our study, the mean systolic blood pressure at the time of enrollment in Group A was169.42±13.197 and in Group B was 163.48±5.363mm of Hg.

This was similar to the study done by SK Biswas(2021)[80], Faridpur medical college where the mean SBP at the time of enrollment was 186.2 ± 12 mm Hg in Group A and 175 ± 12 mmHg in Group B. In Swapan das et.al(2015)[77] study which was done in Bankura Sammilani Medical College West Bengal ,mean systolic BP was 186.2 ± 12 m of Hg in group A and 175 ± 12 mm of Hg in the Group B.

Studies	**Mean SBP at time of enrollment**	
	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
Swapan das et al[77]	186.2 ± 12 mm Hg	175 ± 12 mmHg
SK Biswas et al[80]	171.08±8.1mmHg	171.8±8.4mm of Hg
Our study	169.42±13.197 mm Hg	163.48±5.363 mm of Hg

Comparison of mean DBP at the time of enrollment

In our study mean diastolic BP was 112.69 mm Hg in Group A and in Group B was 112.60 mm Hg. Raheem et.al showed that the mean diastolic BP was 108 (100-112) mm of Hg in Group A and 110 (110-116) mm of Hg in Group B with a P value of 0.012. Swapan das et al[77] showed that mean diastolic BP was 118.11 ± 8 mm of Hg in the group A and 112 ± 8 mm of Hg in the Nifedipine group with the 'P value was 0.745. Hence our study is in accordance with these previous studies.

Studies	**Mean DBP**

	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
Swapan das et al[77]	118.11 ± 8 mm of Hg	112 ± 8 mm of Hg
Raheem et.al[75]	108 (100-112) mm of Hg	110 (110-116) mm of Hg
Our study	112.69 mm of Hg	112.60 mm of Hg

Comparison of total dosage given in both the groups

In our study mean of total dosage given to the participants showed that IV labetalol group 70.00 and in Nifedipine retard group 33.17with the p-value of less than 0.001 which is significant. This presented that as we are giving IV Labetalol in escalating doses of 20mg, 40mg, 80mg, there is increased dosage in IV Labetalol group than Oral nifedipine where we give the same dose 20mg every 30minutes. IV labetalol had reduced BP with less doses in comparison with the Nifedipine retard.

Mean number of doses given in both the groups to reach target BP

In our study we found that mean number of doses were less in IV labetalol (1.73) in comparison with the oral Nifedipine retard (2.06) and this was statistically significant. As per Raheem et al[75] study, average number of total antihypertensive

doses to achieve BP≤150/100 mm of Hg were 3 in IV Labetalol group and 2 in Oral Nifedipine group, where as a study conducted by Monika et al[78] mean dosage required to achieve target blood pressure was 2.6±1.2 in Group A and 1.8±1.1 in Group B.

Studies	**Doses**	
	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
a randomized trial by Raheem et.al (2011) university of malaysia[75]	3(2-4)	2 (1.5-4.5)
Our study	1.73±.630	2.06±.669
A randomized controlled trial by Kumari M et al (2020), jodhpur[78]	2.6±1.2	1.8±1.1

In our study, additional hypertensive added to reach target BP in Group A was 4(7.6%) and 2(3.8%) in Group B. This shows that IV labetalol is having more failure rate than oral nifedipine retard in attaining target blood pressure.

Whereas In Swapan et al[77] study 12% and 14% in IV Labetalol group and Oral Nifedipine group were not controlled by 5 doses of either drug and required cross over treatment.

Comparison of Time required to achieve target BP

In our study the mean time required to achieve target BP were 33.85 for IV labetalol and 48.56 for oral Nifedipine retard with p value . This showed that IV labetalol took less time to achieve target BP than oral nifedipine retard.

This contradicts the other studies since the IV labetalol is the first line drug of choice according to NICE guidelines. Even though oral nifedipine has many advantages over IV labetalol but it reduces the BP quickly and not much side effects and this drug is used from ancient times since it is better tolerated than any other antihypertensive drugs. There are many studies which showed IV labetalol as drug of anti-hypertensive emergency at pregnancy.

Studies	**Mean time to achieve target BP**	
	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
Swapan das et al[77]	47.2 ± 13.5 mins	45.6 ± 14.5 mins
Raheem et.al[75]	45 mins (IQR 30-60 min)	30 mins (interquartile range 22.5 to 67.5 mins)

SK Biswas et al[80]	30.33 ± 10.44 mins	25.63 ±10.12mins
Kumari M et al[78]	52.0+_27.95 mins	37.6+-23.3 min
Dhali B et al[76]	48.4±23.5 minutes	28.2±11.7 minutes
Our study	33.85 min	48.56 min

Comparison of side effects in both the groups

In our study we observed that (table 15, fig 15) most of the patients 35(67.3%) of IV labetalol group and 30(57.5%) of oral nifedipine retard group did not had any side effects. 7(13.4%) patients had Headache and 2(3.9%) patients had abdominal pain side effect in IV labetalol group, and 12(23%) having tachycardia side effect in oral nifedipine retard group. There was a study conducted by monika k et al[78] also found that nifedipine showed tachycardia as side effect during the treatment and there were no such side effects in IV labetalol group in our study. In a study done by swapan das et al[77] and Raheem et al did not presented any side effects of both drugs and our study is in agreement with the previous studies.

Studies	**Side effects**

	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
Shekhar et al[86]	Headache, dizziness, vomiting	Refractory hypotension and uterine atony
Magee LA et al[89]	Headache, nausea, vomiting	refractory hypotension and uterine atony
Kumari M et al[78]	Headache, nausea, vomiting	Tachycardia
Swapan das et al[77]	Headache	Postural hypotension
Our study	Headache, nausea, vomiting	Tachycardia

In this study, (table 16, fig 16)Cerviprime induction was 1(1.9%) in group A(IV labetalol) and 3(5.8%) in group B(oral nifedipine retard).

Studies	**Induction**

	Group A (IV Labetalol)	**Group B (Oral nifedipine)**
Swapan das et al[77]	More of spontaneous delivery	32%
Raheem AI et al[75]	More of spontaneous delivery	28%
Our study	1(1.9%)	3(5.8%)

IV labetalol shows spontaneous delivery in comparison to oral nifedipine. Hence it required less induction and our study is in accordance with the previous studies. In Swapan das et al (77) Spontaneous vaginal delivery was more in the Labetalol group i.e 28% when compared to the Nifedipine i.e 14%.

Comparison of cessarean sections of both groups

In our studygroup A(IV labetalol) shows 40(76.9) of caesarean sections whereas in group B(oral nifedipine retard) 43(82.7%) underwent caesarean section. In this study maximum patients showed full term emergency.

In Swapan das et al[77] Spontaneous vaginal delivery was more in the Labetalol group i.e 28% when compared to the Nifedipine i.e 14%.

In this study (table 18, fig 18) shows Mean birth weight of group A(IV labetalol) and group B (oral Nifedipine retard)was 2.4769±.74692 and 2.5602±.61273 respectively. In the study of Raheem et.al the average birth weight in both the group were 2.9 kg with an interquartile range of 2.2 – 3.1 kg in the Nifedipine group and 2.7 – 3.2 kg in the Labetalol group. there was no affect on the birth weight of the neonates during the treatment in our study. This is in agreement with the previous studies.

Our study was accordance to Swapan das et al where Mean birth weight was 2.48 ± 0.54 kg in the Labetalol group and 2.43 ± 0.59 kg in the Nifedipine group, which was statistically not significant.

In this study, Among total 52(100%), 23(44.2%) admitted in NICU of group A(IV labetalol). Among total 52(100%), 13(25%) admitted in NICU of group B(oral nifedipine retard) results were found to be significant when comparing NICU admission in group A(IV labetalol) and group B(oral nifedipine retard) of which 1(1.9%) of Group A and 3(5.8%) of Group B was dead after 2 days of admission.

In this study (table 23, fig 23) shows Distribution of MGSO4 among total 52(100%), loading dose was 6(11.5%) of MGSO4 in group A(IV labetalol). Among total 52(100%), loading dose was 6(11.5%) of MGSO4 in group B(oral nifedipine retard). In this study, antihypertensive prior to admissions were given. In IV labetalol group, 42(80.2%) did not receive antihypertensive prior to admission in IV labetalol group and in nifedipine retard group 45(86.5%) did not receive antihypertensive prior to admission.

In this study there was no maternal ICU admission in both the groups.

In this study,(table 29, fig 29) distribution of intra op finding. In this we found that Meconium stained liquor intra op finding maximum in group A(IV labetalol) and group B (oral nifedipine retard)i.e. 11(21.2%) and 14(26.9%). In group A(IV In this study Distribution of maternal outcome shows that 46(88.4%) in group A(IV labetalol) and 37(71.1%) in group B(oral nifedipine retard) having normal maternal outcome. Postpartum eclampsia was seen in 1(1.9%) patients in group B(oral nifedipine retard). Results were found to be insignificant when comparing maternal outcome in group A (IV labetalol) and group B(oral nifedipine retard).

Blood and blood products was received in 7(13.5%) in group A(IV labetalol) and 5(9.6%) patients in group B(oral nifedipine retard).

In the present study, we found that IV labetalol was efficient in reducing BP in comparison to oral nifedipine retard 20mg. the IV labetalol took less time to achieve the target BP with less dose and the mean of the SBP and DBP at different interval was constantly reducing in comparison with the oral nifedipine retard and the results were statistically significant.

In a study done by Omkar murthy K et al[84] showed that mean systolic blood pressure before treatment was 172.10mmhg and diastolic blood pressure was 114.27 and after labetalol infusion systolic blood pressure was 137.07mmhg and diastolic blood pressure was 89.37mmhg and the Target blood pressure of <150/100mmhg and thus the target blood pressure of keeping blood pressure between 140 to 155mmhg and diastolic blood pressure between 90 and 105mmhg in severe preeclampsia. Thus our study was according to Sibai's suggestions. Our study is in accordance with the previous studies. (75-84)

In a Kuwaiti trial involving 104 primigravida with mild-moderate PIH, the investigators compared alpha-dopa with labetalol for antihypertensive management, and concluded that labetalol is quicker, more efficient and better tolerated.[90]

Labetalol is a non-selective beta-blocker and a post-synaptic alpha-1 blocking agent. Intravenous Labetalol is also used for treatment of severe hypertension in pregnancy as a first line drug and has a better side effect profile but specific concerns have been raised about the risk of neonatal bradycardia.

A fall in blood pressure observed in patients with hypertension due to the actions of labetalol on both α-1 and β receptors contribute to. α 1 receptor blockade leads to relaxation of arterial smooth muscle and vasodilation, particularly in the upright position and contributes to a fall in blood pressure, by blocking reflex sympathetic stimulation of the heart. In addition, the intrinsic sympathomimetic activity of labetalol at β2 receptors may contribute to vasodilation.

The National Guideline Clearinghouse on treatment of pregnancy related hypertensive disorders has recommended labetalol to be used as initial antihypertensive therapy.

Since this is the first study to address the comparison between the IV labetalol and oral nifedipine retard 20mg, there have been no other studies comparing both drugs. Even though the oral nifedipine was proved as efficient drug in reducing hypertension in preeclampsia in many studies but from our study it is clear that IV labetalol is efficient drug in reducing BP. Even WHO essential list of drugs has ot listed nifedipine for treating severe hypertension during pregnancy. Hence from this study, proved that IV labetalol is the drug of choice in reducing SBP and DBP during eclampsia.[75]

Conclusion:

Hypertensive emergencies in pregnancy represent a serious complication in obstetrics. Managing hypertension in this context is particularly challenging, as a rapid decrease in blood pressure can lead to uteroplacental insufficiency, potentially resulting in intrauterine fetal demise. Conversely, sustained severe hypertension can negatively impact both maternal and fetal health.

Our trial's findings indicate that an intravenous labetalol regimen is the most effective option for quickly reducing blood pressure during hypertensive emergencies, such as severe preeclampsia. While IV labetalol effectively maintains lower blood pressure in a short timeframe, oral nifedipine retard is also effective and well-tolerated for rapid blood pressure control in severe hypertension, with minimal side effects reported in our study.

SUMMARY:

One pregnancy problem that is linked to significant morbidity and death in both the mother and the fetus is pre-eclampsia. If the fetus and placenta are not delivered, the illness can advance to multi-organ failure, including liver, renal, and brain disease. The sickness first manifests as new-onset hypertension and often proteinuria in the mother. It is generally advised to treat significantly elevated blood pressure in order to lower the risk of problems for expectant mothers. Intravenous drug regimens are

commonly used in the immediate treatment of severe hypertension. These medications work well, but they need venous access and close fetal monitoring, which may not be possible in busy or low-resource settings. Thus the study was done with an objective to compare the safety and efficacy of oral Nifedipine retard to intravenous Labetalol in the management of hypertensive emergencies of pregnancy. It is a Randomized parallel group comparative study and it is conducted in the Department of obstetrics and gynecology of BLDE (deemed to be university) Shri B.M Patil medical college and research centre, vijayapura. A total of 104 pregnant women with Hypertensive emergencies attending outpatient department were selected for the study and they were divided into 2 groups of 52 each in which group A was given IV labetalol and group B was given Oral Nifedipine retard 20mg. Intravenous Labetalol group received 20mg initially followed by escalating doses of 40mg, 80mg up to maximum of 5 doses every 15min up to target blood pressure is reached. Group B received Oral Nifedipine retard (Extended release) 20mg initially followed by repeated doses of 20mg every 30 minutes maximum of 5 doses until the target blood pressure is reached. (SBP <150 mm Hg and DBP between 80-100 mm Hg). During the study, vitals are monitored closely and the maternal blood pressures will be recorded at every 15 minutes till the target blood pressure is reached, then every 30 minutes for the next 2 hours then hourly for 24 hours and any adverse effect of the drugs were noted.

In the present study, maximum age group were18-24 year of age. In this study mean of SBP at the time of enrollment of IV Labetalol and Oral Nifedipine retard was 169.42±13.197 and 163.48±5.363 respectively and Mean DBP of IV Labetalol and Oral Nifedipine retard was 112.69±7.440 and 112.60±5.154 respectively. IV labetalol group presented with more proteinuria and oedema. Mean dose of IV Labetalol and Oral Nifedipine was 70±42.565 and 33.17±13.137 respectively. Results were found to be highly significant (p value 0.001) and mean of total number of doses given in IV Labetalol and Oral Nifedipine was 2.06±.669 and 1.73±.630 respectively. Mean SBP after 15 min, 30 min, 45 min, 60 min, 75 min and 90 min was in group A and group B was 155.10±13.172 and 158.54±5.301, 143.64±12.776 and 149.48±7.883, 141.67±16.967 and 148.47±6.601, 138±16.745 and 140.96±8.126, 136±11.256 and 138.40±6.066 and 132±13.246 and136±7.071 respectively. Results were found to be significant. Mean DBP after 15 min, 30 min, 45 min, 60 min, 75 min and 90 min was in group A and group B was 100.78±7.441 and 107.37±6.630, 92.73±8.174 and 98.63±7.659, 90.83±9.962 and 98.17±6.412, 86±6.783 and 90.56±5.938, 84±8.567 and 88.40±3.209 and 82 ±9.563 and 86±8.960 respectively. Results were found to be significant. Mean target SBP of IV Labetalol and Oral Nifedipine was 139.42±8.498 and 139.12±6.379 respectively. Mean target DBP of IV Labetalol and Oral Nifedipine was 89.42±6.076 and 89.52±4.672 respectively. Most of the patients 35(67.3%) of IV Labetalol and 30(57.5%) of Oral

Nifedipine group B did not had any side effects. 7(13.4%) patients had Headache and 2(3.9%) patients had abdominal pain side effect in IV Labetalol and 12(23%) having tachycardia side effect in Oral Nifedipine. Results were found to be significant (P value0.04) when comparing side effect in IV Labetalol and Oral Nifedipine. No additional hypertensive drugs were given. In cases of moderate to severe pregnancy-induced hypertension, the administration of Labetalol at the prescribed dosage was seen to effectively manage blood pressure. Intravenous labetalol is a safe and efficient medication for treating pregnancy-related hypertension.

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ANNEXURES

Annexure 1: CONSENT FORM

CONSENT FORM

B .L.D.E. (DEEMED TO BE UNIVERSITY) SHRI B.M.PATIL MEDICAL COLLEGEHOSPITAL AND RESEARCH CENTER, VIJAYAPURA-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned, _____, D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that **Dr.SUDEEPTHI CHETHY** of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases. Further Dr SUDEEPTHI CHETHY informed me that she is conducting dissertation/research titled **" A RANDOMISED PARALLELGROUP TRIAL FOR COMPARISON OF SAFETY AND EFFICACY OF ORALNEFIDIPINE RETARD VERSUS INTRAVENOUS LABETALOL INMANAGEMENT OF HYPERTENSIVE EMERGENCIES OF PREGNANCY" .**Under the guidance of **Dr ARUNA M BIRADAR** requesting my participation in the study.

Apart from routine treatment procedure, the postdelivery follow-up observations will be utilized for the study as reference data. The doctor has also informed me that during the conduct of this procedure like adverse effects may be encountered. Among the above complications, most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances, it may prove fatal despite the anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study would help in the evaluation of the results of the study which is a useful reference to the treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made photographs video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes. The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during treatment/study related to diagnosis, the procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged. After understanding the nature of

dissertation or research, diagnosis made, mode of treatment, I the undersigned Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient: Signature of doctor:

Date:

Place:

ANNEXURE 2: PROFORMA

PROFORMA

A Randomized parallel group trial for comparison of Safety and Efficacy of oral Nifedipine retard versus intravenous Labetalol in Hypertensive Emergencies of pregnancy:

A Randomized parallel group comparative Clinical Study at a Tertiary Care Hospital

NAME: AGE: I.P No.:	
DATE OF ADMISSION :	DATE OF DISCHARGE:
ADDRESS AND PHONE NUMBER :	
DEMOGRAPHY: RURAL	URBAN

CHIEF COMPLAINTS:

HISTORY OF PRESENT PREGNANCY:

MARITAL HISTORY: ML: NCM/ CM

OBSTETRIC HISTORY: G: P: L: A: D:

LMP:

EDD:

POG:

PAST HISTORY:

FAMILY HISTORY:

MEDICAL HISTORY:

TREATMENT HISTORY :

DURATION:

ANY PROCEDURE :

PERSONAL HISTORY

GENERAL PHYSICAL EXAMINATION:

PULSE: BLOOD PRESSURE: RESPIRATORY RATE:

TEMPERATURE: BSUA:

HEIGHT: WEIGHT:

PALLOR:

ICTERUS: THYROID:

CYANOSIS: SPINE:

CLUBBING : BREAST:

LYMPHADENOPATHY:

EDEMA:

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM:

PER ABDOMEN:

PER VAGINA:

DIAGNOSIS:

INVESTIGATIONS :

Complete hemogram:

Coagulation profile: APTT (T) : PT (T):

APTT (C): PT (C): INR:

LFT:

RFT: Sr.Urea : Sr.Creatinine: Sr.uric acid:

Sr. sodium: Sr. potassium: Sr.chloride:

Sr.Calcium Sr. Phosphorus

HIV: REACTIVE ☐ NON REACTIVE ☐

HBSAG: REACTIVE ☐ NON REACTIVE ☐

FUNDOSCOPY:

STUDY PARAMETERS:

ORAL NIFEDIFINE RETARD	1ST DOSE	2ND DOSE	3RD DOSE	4TH DOSE	5TH DOSE
BP					
TIME					

INTRAVENOUS LABETALOL	1ST DOSE	2ND DOSE	3RD DOSE	4TH DOSE	5TH DOSE

BP					
TIME					

Number of doses given:

Time and dosage for targeted BP : Time: Dose: Drug:

Any other drug added :

Headache yes ☐ no ☐ nausea: yes ☐ no ☐

Oedema : yes ☐ no ☐ Abdominal pain: yes ☐ no ☐

Constipation :yes ☐ no ☐ Tachycardia : yes ☐ no ☐

Feeling unwell: yes ☐ no ☐ Visual disturbances: yes ☐ no ☐

Allergic reaction: yes ☐ no ☐ Muscle cramps: yes ☐ no ☐

Anxiety : yes ☐ no ☐ Hypotension: yes ☐ no ☐

MODE OF DELIVERY:

VAGINAL DELIVERY - PRETERM ☐ FULL TERM ☐

LSCS : EMERGENCY -PRETERM ☐ FULLTERM ☐

ELECTIVE - PRETERM ☐ FULLTERM ☐

INDICATION OF LSCS: **INTRA OP FINDINGS:**

DATE OF DELIVERY:

FETAL OUTCOME:

DATE OF BIRTH:

TIME OF BIRTH:

SEX:

BIRTH WEIGHT:

APGAR SCORE: 1min - ; 5min-

NICU ADMISSION: YES ☐ NO ☐

IF YESINDICATION:

DURATION OF STAY:

DATE OF DISCHARGE:

MATERNAL OUTCOME:

SICU ADMISSION: YES ☐ NO ☐

IF YES -DURATION

VENTILATOR SUPPORT: Y ☐ NO ☐

IF YES – DURATION

INOTROPIC SUPPORT: YES ☐ NO ☐

IF YES- DRUGS USED : DURATION :

OXYGEN SUPPORT:YES ☐ NO ☐

IF YES DURATION:

TOTAL DURATION OF HOSPITAL STAY :

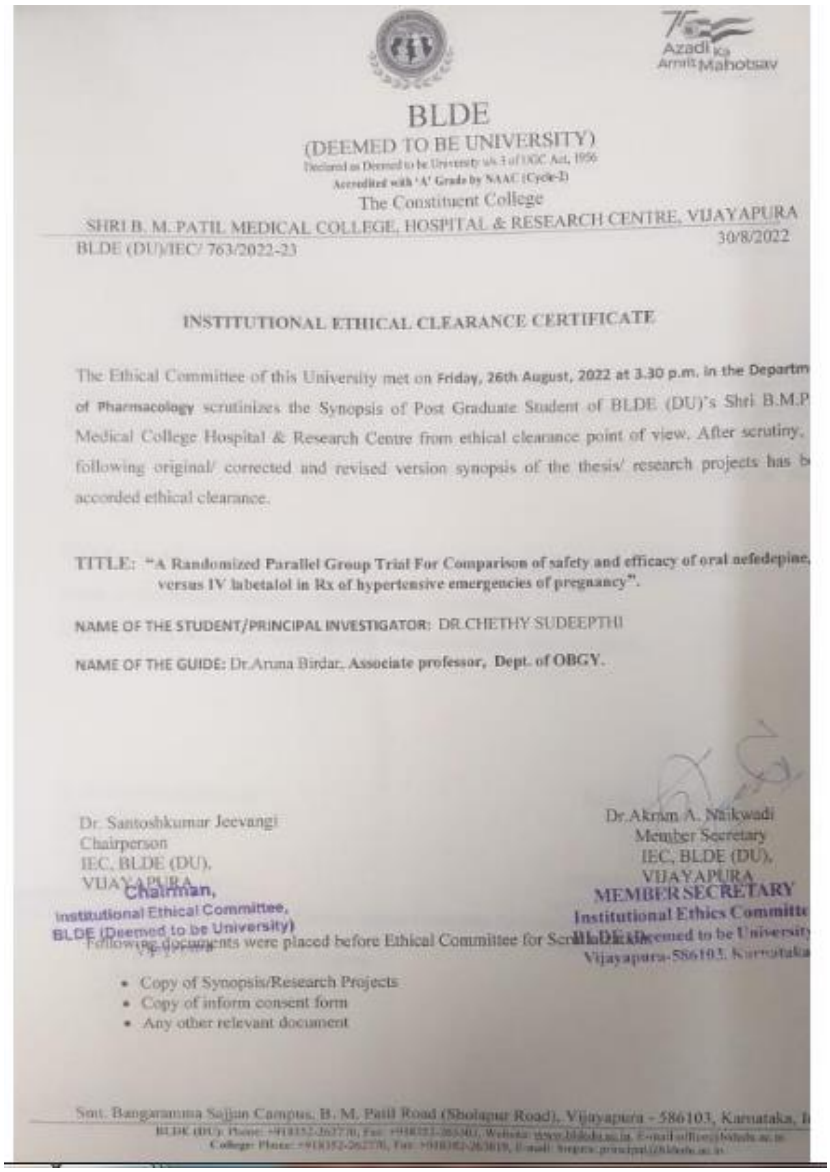
DATE OF DISCHARGE:

REMARKS:

IMPROVED / DEATH / DISCHARGE AGAINST MEDICAL ADVICE

IF DEATH -CAUSE OF DEATH

Annexure 3: ETHICAL CLEARANCE CERTIFICATE



Azadi Ka Amrit Mahotsav

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 763/2022-23 30/8/2022

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Friday, 26th August, 2022 at 3.30 p.m. in the Departm of Pharmacology** scrutinizes the Synopsis of Post Graduate Student of BLDE (DU)'s Shri B.M.P Medical College Hospital & Research Centre from ethical clearance point of view. After scrutiny, following original/ corrected and revised version synopsis of the thesis/ research projects has b accorded ethical clearance.

TITLE: **"A Randomized Parallel Group Trial For Comparison of safety and efficacy of oral nefedepine, versus IV labetalol in Rx of hypertensive emergencies of pregnancy".**

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.CHETHY SUDEEPTHI

NAME OF THE GUIDE: Dr.Aruna Birdar, **Associate professor, Dept. of OBGY.**

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committe
BLDE (Deemed to be University
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutiny:

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, I

MASTER CHART

			POG/WEE			PROTEIN						SBP AFTER				SBP AFTER													
Column2	AGE	P NUM	GRAVIDA	K	SBP	DBP	URIA	EDEMA	DRUG	DOSE	TIME (MIN TO ACHIEVE TARGET BP	TOTAL DOSES	SBP AFTER 15MIN	SBP AFTER 30MIN	SBP AFTER 45MIN	SBP AFTER 60MIN	75MIN2	SBP FOR 90MIN	SBP AFTER 15M	SBP AFTER 30MIN	SBP AFTER 45MIN	SBP AFTER 60MIN	SBP AFTER 75MIN	SBP AFTER 90MIN	TARGET SBP	TARGET DBP			
KAVERI	18	78009 PRIM	36	160	110	1	1	0	A	20	15	1	140						90						150	90			
KAMALABAI	33	91624 PRIM	37	170	120	3	1	B	40	60	2	170	160	150	140				108	104	95	90			140	90			
NIKITA	22	11890 G2	33	160	100	4	2	A	60	30	2	140	130						90	80					130	80			
NAZAMEEN	26	86646 PRIM	41	170	100	4	0	A	60	30	2	150	140						100	90					140	90			
JAYASREE	21	117800 PRIM	40	160	110	1	4	B	20	60	2	156	150	155	140				104	100	96	90			140	90			
NEELAMMA P	35	87574 G3	39	160	120	1	2	A	60	30	2	150	130						90	80					130	80			
ARTI PARASU	28	110509 G3	39	160	110	3	3	B	40	60	2	156	140						102	90					140	90			
SUNANDA	32	119022 G3	40	160	110	1	2	B	40	60	1	156	140						105	90					140	90			
RESHMA SAN	23	67729 G3	38	180	100	1	2	A	60	30	2	150	130						100	90					140	90			
PAVITRA	23	142456 PRIM	36	170	110	2	0	B	40	45	1	160	155	140					110	100	90				140	90			
SAVITA NINGA	24	111936 PRIM	40	160	100	1	0	A	20	15	1	140							90						140	90			
VIJAYALAXMI	27	143878 PRIM	37	170	110	4	0	B	40	45	2	160	150	140					112	90					140	90			
SHANTAMMA	38	110458 G2	38	160	110	4	1	A	60	30	2	150	130						100	90					130	90			
RAJASHREE	27	142450 G3	41	180	120	3	0	B	60	75	3	170	165	160	152	140			120	110	105	100	95		130	80			
MAHADEVI	32	134273 G2	41	200	120	2	0	A	140	45	3	180	160	150					110	100	90				150	90			
SHILPA GANGA	22	158394 PRIM	40	180	130	1	2	B	60	90	3	172	165	162	160	152	140		120	118	114	100	95	90	140	90			
NINGAMMA	20	125583 G2	39	160	110	2	0	A	60	30	2	150	140						100	90					140	90			
ARTI SHRISHAIL	21	165982 G4	38	160	100	2	1	B	40	60	2	155	140						100	90					140	80			
SATAKKA	20	153809 G2	37	170	110	4	0	A	60	30	2	150	140						100	90					140	90			
PRITI KASHINA	25	172239 PRIM	38	160	110	2	0	B	40	60	2	154	150	147	134				116	110	100	95			130	95			
BASAMMA	27	113932 GS	31	160	110	4	1	A	20	25	1	140	130						90	80					130	80			
GANGABAI	30	178223 G5	37	160	110	1	0	B	20	30	1	158	152	145					110	100	95	90			140	90			
SAVITA IRANNA	32	175574 G3	33	160	110	2	0	A	20	15	1	140							100						140	100			
PRABHAVATI	22	185209 PRIM	38	180	110	2	2	A	60	15	2	160	150						90						140	90			
SUREKHA	24	191404 PRIM	39	160	110	1	2	B	20	30	1	156	144						90	90					140	80			
KAVERI MAHAN	20	188038 PRIM	39	160	110	2	0	A	20	15	1	140							100						140	100			
MALLAMMA	25	191650 G3	39	160	110	1	0	A	20	15	1	140							90						140	90			
KAJAL	22	203871 G2	39	170	120	0	2	A	60	40	2	150							100	90					140	90			
GEETANJALI S	24	205226 G2	40	166	114	2	2	B	20	30	1	158	150						100	90					140	90			
NEELAMMA	30	206285 PRIM	40	160	110	2	2	B	20	30	1	155	150						106	100					150	100			
RESHMA	19	213834 G2	36	160	110	2	3	A	20	15	1	150							90						150	90			
FAKRUNISSA	26	213035 PRIM	40	200	130	2	2	A	140	45	3	180	160	150					110	100	90				150	90			
SHAKIRABI	29	12833 GS	33	160	120	1	3	A	20	15	1	140							90						140	90			
PARVATI	25	232339 G3	40	166	118	2	0	B	45	60	2	160	156	151	140				114	110	100	90			140	90			
LAXMI BASAPP	28	229436 GS	40	180	120	2	0	A	60	30	2	160	150						110	100					150	90			
AFRIN	19	223263 PRIM	37	160	110	2	2	B	20	30	2	156	151	148	140				105	100	96	90			140	90			
P MAHANANDA	32	226899 PRIM	41	160	110	2	2	B	20	30	1	155	150						105	90					150	90			
PRIMA YANAPA	28	233070 G4	39	180	110	1	1	A	140	45	3	160	150	140					100	90	90				150	90			
BHAGYASREE M	20	234804 PRIM	40	160	110	1	0	B	20	30	1	156	144						106	100					140	90			
PRIYANKA	22	114433 PRIM	39	180	120	1	0	A	140	45	3	160	150	130					110	100	80				120	70			
GEETA VINYAK	26	221132 PRIM	36	170	130	1	0	A	60	30	2	150	130						100	80					130	80			
BHAGYASREE	20	229437 PRIM	31	160	110	1	0	B	20	30	1	154	140						100	90					140	90			
BHUVANESHWA RI	20	233487 PRIM	39	160	110	2	0	B	20	30	1	154	145						90	90					140	90			
SAVITRI IRAYYA	28	221539 G2	36	160	110	1	0	B	20	45	2	158	150	140					110	100	90				150	90			
HASEENA BEGUM	20	168592 PRIM	35	160	110	2	3	A	60	30	2	160	140						100	90					130	90			
NAGAMMA	23	243875 G2	40	160	120	2	0	A	140	45	3	160	150	130					100	100	90				130	90			
MALANBEE	30	245766 G4	37	160	110	2	0	B	20	30	1	152	140						105	90					140	90			
VIJAYALAKSHMI	24	253488 G3	36	164	114	1	0	B	20	30	2	158	152	148	140				108	100	97	90			140	90			
RAJAMMA	25	218932 PRIM	30	166	110	2	2	B	20	30	2	156	151	146	140				106	100	96	90			140	90			
SHIVANI	19	195238 PRIM	38	160	110	1	2	A	60	30	2	150	140						100	90					140	90			
INAMBU	23	253470 G2	40	170	110	2	1	A	60	30	2	160	150						100	90					150	90			
KAVERI	21	254126 PRIM	37	160	110	2	0	B	40	60	2	158	156	150	140				100	106	100	90			150	90			
SAKINA	25	255567 PRIM	41	170	120	2	0	A	140	45	3	160	150	140					100	90	90				150	100			
BIBIFATIMA	26	258429 PRIM	38	160	110	1	2	A	60	40	2	150	140						100	90					140	90			
NASARIN	27	266039 G3	39	168	117	1	1	B	40	45	2	165	160	140					107	100	90				140	90			
BHAGYASREE	22	262996 PRIM	39	160	110	1	2	A	60	40	2	150	130						100	90					130	90			
ISRAT RIYAZ	21	268441 PRIM	39	160	110	2	1	B	20	30	2	150	140						107	100	106	90			140	90			
PREETI YALLAPPA	21	248725 PRIM	39	160	110	1	0	A	140	45	3	150	150	130					100	100	90				130	90			
DEEPA	22	268352 PRIM	38	170	110	1	2	A	60	40	2	160	150						100	100					150	100			
VARSHALI P BAGALI	30	275933 G3	41	160	110	2	3	B	40	60	1	154	140						100	90					130	90			
RUKSANABANU	20	286568 PRIM	38	168	114	1	2	B	40	60	2	162	150	150	130				108	100	106	90			130	90			
FATIMA	34	270676 PRIM	40	230	140	2	2	A	220	80	4	220	200	190	170	160	160		130	120	120	110	110	100	160	100			
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CHAITRA	26	289508 G2	41	174	110	1	1	B	20	30	2	170	160	156	150				114	110	106	100			150	100			
SAVITRI DEVENDER	29	272953 G2	38	170	120	1	2	A	60	40	2	160	150						100	100					150	100			
LAXMVVA	24	271995 PRIM	37	170	110	1	0	A	60	40	2	160	140						100	90					140	90			
VIJAYALAXMI																													
GURUMURTI	28	275058 G2	40	160	110	1	1	A	20	20	1		140							90					140	90			
BASAMMA	28	289536 G4	35	172	128	1	3	B	60	75	3	168	162	160	152	150			120	118	105	100	90		140	90			
RAJESHWARI	26	276133 G4	38	160	110	1	1	A	60	40	2	150	140	130					100	100	90				130	80			
SAVITRI	28	292115 PRIM	38	160	110	2	3	B	20	30	1	158	150						108	100					150	100			
AISHWARYA	21	298643 PRIM	35	160	112	2	0	B	20	30	1	154	140						105	90					140	90			
DANAMMA	21	285241 PRIM	37	180	110	2	1	A	140	45	3	160	150	130					110	100	80				140	80			
SARASWATI	20	282785 G2	40	160	110	1	0	A	60	40	2	150	140						100	90					130	90			
KARISHMA	23	293395 G2	23	164	114	2	3	B	40	60	2	156	150	140	130				115	100	96	90			140	90			
GURUBAI	19	339129 PRIM	41	160	112	1	0	B	40	40	2	158	150	140	140				110	100	96	90			140	90			
LAXMI TIPPANNA	32	289538 G4	33	170	110	1	0	A	60	40	2	150	130						100	80					130	80			
ROHINI	24	314242 PRIM	40	160	110	2	1	B	40	60	2	150	140						100	90					140	90			
TULAJABAI	23	295556 G2	41	160	110	1	0	A	60	40	3	170	160	140					110	100	90				140	90			
PALLAVI	22	316695 PRIM	36	160	110	1	0	B	40	60	2	150	130						100	90					130	90			
BHAGYASHRI	21	43783 PRIM	39	180	110	2	0	A	60	40	2	160	140						110	90					140	90			
PRIYA SURESH	23	345640 PRIM	41	160	110	2	0	B	20	40	1	157	140						107	90					140	90			
MALASHRI	30	376689 PRIM	35	180	120	2	2	A	140	45	3	170	160	140					110	110	90				140	90			
SUNANDA	24	408917 PRIM	39	160	110	2	0	B	40	60	2	158	150	140	130				110	100	90	80			130	80			
VIDYA MITHUN	21	44399 PRIM	38	160	110	2	1	A	60	30	2	150	130						100	90					130	90			
JAYASHRI ARJUN	22	314410 G2	39	180	120	1	2	A	60	30	2	160	150						110	100					150	100			
ANUPAMA	30	335022 G4	39	180	110	1	1	A	60	30	2	160	140						100	90					140	90			
MEGHA	34	227449 PRIM	36	170	118	2	1	B	40	60	2	160	150	140	130				110	100	90	80			130	80			
TRIVENI	32	6044 PRIM	35	160	110	3	0	B	20	30	1	158	140						108	90					140	90			
VIJAYALAKSHMI LAXMI	27	46190 G3	37	170	110	1	1	A	60	40	2	150	140						100	90					140	90			
JAMADAR	24	15707 PRIM	37	160	110	4	3	B	40	60	2	156	150	148	130				114	100	90	80			130	80			
SHABANA	20	340063 PRIM	39	170	110	4	1	A	60	30	2	160	150						100	90					150	90			
MALLAMMA	22	335509 PRIM	37	160	110	2	0	A	60	40	2	150	140						100	90					140	90			
SHAKUNTALA	25	398904 G4	41	170	120	1	2	B	40	60	2	168	159	151	138				118	100	90	80			130	80			
SHARADABAI	27	38799 G2	37	160	110	1	0	B	40	60	2	158	152	148	140				112	100	96	90			140	90			
GEETA BALAPPA	29	363401 G2	40	170	110	2	1	A	60	30	2	160	140						110	100					150	90			
SHOBHA SHILPA	26	49038 G4	39	160	116	1	0	B	20	30	1	157	140						100	90					140	90			
RENNAPPA	21	363239 G2	41	170	110	2	0	A	60	40	2	150	130						100	80					130	80			
MAHANANDA	22	43427 G2	39	168	124	1	2	B	60	90	3	166	160	152	150	140	130		118	110	106	100	97	90	130	90			
RESHMA REVU	23	26593 G3	33	160	110	4	2	B	40	60	2	158	156	150	140				110	100	106	90			140	90			
SHRUTI	20	15463 PRIM	37	160	110	4	1	B	20	30	1	158	140						100	90					140	90			
RESHMA NANDYAL	28	84844 G4	38	170	118	2	1	B	60	75	3	167	160	157	152	140			110	105	98	90	90		140	90			
ATIYA	25	164089 G2	39	165	116	2	1	B	40	60	2	162	158	152	146				107	108	102	90			144	90			
BORAMMA	25	134474 PRIM	36	160	110	4	2	B	40	60	2	157	150	148	140				108	100	98	90			140	90			

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