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Intravenous Labetalol versus Intravenous Nitroglycerin versus Sublingual Nifedipine to Control Blood Pressure in Severe Pre-Eclampsia, Prospective Comparative Study: As A Review of Literature

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ABSTRACT

Background: Worldwide, hypertensive diseases of pregnancy cause around 60000 maternal and 500000 fetal fatalities annually, affecting between three percent and five percent of pregnancies. Pre-eclampsia (PE) and eclampsia are recognized to be the hypertension (HTN) conditions that pose the greatest health hazards to the expectant mother and the developing fetus.

Objective: This review compared the effects of sublingual nifedipine, Intravenous (IV) nitroglycerin, and IV labetalol on blood pressure (BP) management in patients with severe PE.

Methods: From January 2000 to June 2025, a thorough search was carried out in PubMed, Google Scholar, and Science Direct using the following keywords: PE, BP, Labetalol, Nitroglycerin, and Nifedipine. The reviewers also assessed the references to pertinent literature. Only the most recent or comprehensive study was considered. Oral presentations, dissertations, conference abstracts, and unpublished papers are a few examples of works that weren't considered important scientific study. Documents published in languages other than English were ignored as a result of lack of translation resources.

Conclusion: The following treatments were administered to women with severe PE: IV nitroglycerine, sublingual nifedipine, and a continuous infusion of labetalol. These treatments significantly decreased BP after administration compared to baseline, with the labetalol group experiencing a much greater reduction in mean arterial BP. The labetalol group achieved the desired BP considerably more quickly than the nitroglycerin and nifedipine groups respectively.

Key words: Pre-eclampsia, BP, Labetalol, Nitroglycerin, Nifedipine.

INTRODUCTION

Early in the gestational period, there are notable metabolic and hemodynamic changes that occur throughout pregnancy. Significant hemodynamic alterations include a rise in cardiac output in the first trimester, water and salt retention that causes the plasma volume to expand, peaking around week 30, and decreases in systemic BP and systemic vascular resistance [(1)].

The rise in the synthesis of vasodilating molecules, such as prostacyclin and nitric oxide (NO), and the decrease in sensitivity to norepinephrine and angiotensin are the causes of the approximately twenty five percent reduction in systemic vascular resistance [(2)].

Starting in the seventh week of pregnancy, the diastolic blood pressure (DBP) starts to drop. Between weeks 24 and 26, it drops by 10 mmHg, and by the third trimester, it is back to normal [(3)].

Some of the changes that might happen during pregnancy include these. According to many studies,

HTN affects seven percent and ten percent of pregnancies globally, making it the most common maternal complication [(4)].

It is linked to a high rate of morbidity and death for both the mother and the baby. According to estimates, 192% die each day from hypertensive problems during pregnancy, making HTN the second leading cause of direct maternal mortality globally (fourteen percent of all deaths) [(5)].

Two HTN diseases of pregnancy that are thought to be substantial contributors to maternal and perinatal morbidity and death are PE and eclampsia [(6)].

Pregnancy-related hypertensive disorders are divided into four groups by the NHLBI's National High BP Education Program: gestational HTN, chronic HTN, PE, and PE layered on top of preexisting HTN (Table 1) [(3)].

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Table (1): Classification of HTN in pregnancy [3]:

Chronic hypertension	1. Increased BP before week 20 (or known to exist before pregnancy. 2. Hypertension persist for more than 12 weeks after pregnancy.
Pre-eclampsia, Eclampsia	1. De-novo appearance of hypertension after mid pregnancy. 2. Proteinuria at least 300mg/ 24 hr.
Pre-eclampsia superimposed upon existing hypertension	1. New onset proteinuria.
Gestational hypertension	1. Transient hypertension appearing after mid pregnancy. 2. Confirmed by return to normal BP postpartum. 3. No proteinuria.

In pregnancy, HTN is defined as a diastolic pressure of 90 mmHg or higher or a systolic pressure of 140 mmHg or higher. A suitably sized cuff should be used to take the patient's BP in the upper arm while they are sitting. For at least a few minutes, the individual should be at rest. Another BP reading should be taken at least twenty minutes apart, or even on a different occasion, to corroborate the first one. It is not the shift in sounds that determines the diastolic measurement, but rather the cessation of sound [7].

The BP standards used to diagnose PE are still up for debate. A quick increase in BP of 30 mmHg systolic or 15 mmHg diastolic should be enough to diagnose PE, according to several specialists in this specialty of medicine. Women who just experienced this alteration, according to the 2000 working group's current recommendations, are not yet preeclamptic but do need to be closely monitored, particularly if proteinuria and hyperuricemia are present [8].

PE with and without severe features

PE is a multisystemic illness that manifests as HTN in a previously normotensive woman after twenty weeks of pregnancy, either with proteinuria present or without it, along with symptoms or indicators of target organ damage [7]. PE is usually linked to proteinuria and new-onset HTN, which usually happens after 20 weeks of pregnancy. A 24-hour urine collection of 300 mg or more, a protein to creatinine ratio of 0.3 mg/dL or higher, or a dipstick reading of 2+ in the absence of quantitative techniques are the three criteria that ACOG uses to characterize proteinuria [7].

PATHOPHYSIOLOGY

Despite much research, the pathophysiology of PE is still unknown. PE is primarily regarded as a vascular condition, and its development is assumed to be influenced by a number of important characteristics. The most likely reasons of this condition are an improper deep placentation and a failure of trophoblast invasion, which results in a failed transformation of the uterine spiral arteries [9]. Additionally, two crucial processes in placental development—trophoblast invasion and vascular growth—can be controlled by decidual natural killer (NK) cells [10].

Some of the reasons of PE, which results in a high-flow and high-pressure condition, include aberrant expression of NK cell surface antigens and a breakdown in the control of NK cell cytotoxicity and cytokines or angiogenic factors. Because of the vasoconstriction of the maternal arteries, there is a significant risk of ischemia-reperfusion damage of the placenta. This will result in the production of reactive oxygen radicals and further endothelial dysfunction. Therefore, the overproduction of certain mediators by the damaged endothelium cells may be linked to PE [4].

Women who are pre-eclamptic have lower levels of prostacyclin (PGI2), another powerful vasodilator. Reactive oxygen species (ROS)-induced suppression of PGI2 synthesis and compromised endothelial Ca^{2+} signaling may be the cause of this [4].

Thrombocytopenia has also been linked to PE. Indeed, a number of characteristics, such as larger platelets and shorter lifespans, elevated maternal plasma levels of platelet factor 4 and β thromboglobulin, increased platelet production of thromboxane B2, and thrombi formation in the microcirculation of multiple target organs, have demonstrated the role of platelet activation in PE [11].

Consequences of HTN in pregnancy

Globally, one of the leading causes of maternal morbidity and death during pregnancy is HTN. It should come as no surprise that a number of factors influence the outcome of HTN during pregnancy. These include (but are not restricted to) the severity of the

illness, the existence of concomitant diseases, and the gestational age upon start. Short-term and long-term problems are the two categories of adverse outcomes associated with HTN during pregnancy [12].

- **Short-term complications**

  1. Maternal: The main negative consequences include damage to the CNS, including seizures (eclampsia), hemorrhagic and ischemic strokes, hepatic damage ranging from elevated transaminase, the so-called "HELLP syndrome" (low platelets, elevated liver enzymes, and hemolysis), hepatic failure, renal dysfunction, and a higher incidence of preterm delivery, Cesarean delivery, and abruptio placentae [7].

  2. Fetal: Induced labor, fetal growth limitation, newborn respiratory problems, and more frequent admissions to the neonatal intensive care unit are all consequences of PE-eclampsia. Even the most severe types of HTN during pregnancy only slightly raise the chance of fetal or perinatal mortality [13].

- **Long-Term Complication:**

  Premature babies that are tiny may stay in neonatal critical care units for extended periods of time and frequently endure developmental difficulties. The risk of PE in later pregnancies and a number of long-term maternal health hazards are examples of remote consequences [14].

  1. Risk of recurrence: Depending on the intensity and timing of the acute episode, there is a variable risk of recurring PE in later pregnancies. The incidence of recurrent PE in subsequent pregnancies is expected to be considerable for women who experience severe, early PE during their first pregnancy (25–65%) [14].

  2. Cardiovascular complications: The risk of developing HTN, IHD, stroke, type II diabetes, and venous thromboembolism is much higher for women with a history of PE than for those without. In women with PE, peripartum cardiomyopathy is more likely to develop [15].

  3. Renal disease: Although the absolute risk seems to be minimal, women with a history of PE are also more likely to develop ESRD.

  4. Cancer: In general, prolonged postpartum periods were observed to either diminish or eliminate the elevated risk of cancer in women with PE. The potential involvement of the immune system in the pathophysiology of the illness may help to explain this "protective" impact of PE. Although they are somewhat protected against cancer, women with sensitive immune systems may be more susceptible to PE [7].

Diagnosis of PE: Meeting the distinctive clinical characteristics listed above that characterize PE is a major factor in the diagnosis of PE. This section examines many techniques that have been suggested to properly diagnose and/or forecast the onset of PE [3].

- **Clinical assessment:** The development of SBP ≥ 140 or DBP ≥ 90, as well as proteinuria of 0.3 grams or more in a 24-hour urine test after 20 weeks of gestation in a woman who was previously normotensive, are the characteristic symptoms of PE [14].
- **Laboratory tests: Proteinuria**: Even if proteinuria is not present, PE should be suspected in any pregnant woman with HTN and distinctive signs or symptoms, even if proteinuria is typically regarded as an important component of PE [16].
- **Kidney function**: Even while the plasma creatinine level is either normal or very slightly higher (1.0-1.5mg/dL, 88-133mmol/L), this might indicate a 30–40% drop in GFR compared to pregnant normotensive controls [17].
- **Serum uric acid*:*** Hyperuricemia was allegedly one of the first symptoms of PE to be documented.
- **Urinary calcium excretion:** There have been reports linking PE to hypocalciuria. Numerous investigations aimed at assessing urine calcium excretion have demonstrated that this criterion has no predictive value in the diagnosis of PE, albeit the processes behind this shift are unclear [3].
- **Doppler US of the uterine arteries:** After twenty four weeks of pregnancy, the incidence of PE is more than six times higher in pregnancies with an abnormal uterine Doppler (high pulsatility index and/or early diastolic notch) [18].

PHARMACOLOGICAL THERAPY OF PE

Low-dose aspirin is presently the only known effective therapy for PE prevention. According to certain international standards, such as the WHO's, a dosage of 75–100 mg of aspirin should be provided between 12 weeks of pregnancy and birth [19].

1. **Sympathetic nervous system inhibitors that included centrally and peripherally acting agents [20]:**

- **Centrally acting agents:** One of the medications most frequently used to manage HTN during pregnancy is methyldopa. Methyldopa and clonidine, a selective alpha-2 agonist, function similarly and are equivalent in terms of safety and effectiveness. For multidrug management of resistant HTN, it is mostly utilized as a third-line therapy during pregnancy.
- **Peripherally acting agents:** Pregnancy has seen a large usage of beta-blockers, such as labetalol and atenolol.

2. **Diuretics:** Diuretics are first-line medications for the therapy of essential HTN before conception. Due to their apparent safety, they can be used either by alone or in conjunction with other medications throughout pregnancy, particularly in women who are more prone to develop salt-responsive HTN [18].

3. **Direct vasodilator:** such as sodium nitroprusside, hydralazine, and isosorbide dinitrates. Through an as-yet-unidentified mechanism, hydralazine preferentially relaxes the smooth muscle of the arteries. Severe HTN or the need of a third-line medication to treat refractory HTN are the most crucial indicators. It can be administered intramuscularly, IV, or orally [(20)].
4. **Serotonin receptor blockers:** S1 receptors promote serotonin-induced vasodilation, which is followed by the production of prostacyclin and NO. The non-pregnant population has utilized ketanserin, a selective S2 receptor-blocking medication.
5. **ACE-I and ARB:** In the second and third trimesters, ACE-I and ARB are contraindicated due to significant toxicity resulting from decreased renal perfusion of the fetal kidneys. They have been linked to pulmonary hypoplasia, intrauterine growth restriction, renal dysgenesis, oligohydramnios due to fetal oliguria, and neonatal anuric renal insufficiency, which can result in the fetus's death [(20)].

CHOICE OF ANTIHYPERTENSIVE DRUGS

- **Mild PE**

First and second-line therapies should be distinguished from one another. It is generally agreed that the first-line therapy is the most effective way to treat the illness. Induction therapy, initial therapy, and primary therapy are other names for this therapy. When the first therapy is ineffective or ceases to be effective, the second-line therapy is used. One of the first-line therapy for this condition may be oral alpha-methyldopa 250 mg (2–3 tablets/day) or oral nifedipine 30–60 mg in slow-release formulations (once daily). The calcium channel antagonist nifedipine is characterized as a medication that is non-teratogenic, safe, and effective [(21)].

- **Severe PE**

The following describes the criteria used to diagnose severe PE: It is advised that the pregnant lady be admitted to the hospital right away and undergo ongoing monitoring due to the increased dangers that this version of the sickness entails. Clinicians should begin HTN medication as soon as possible and monitor for any indications of impending eclampsia. If necessary, they should also begin preventive anticonvulsive medication. All antihypertensive medications, though to varying degrees, pass the placenta, the majority fall under "Category C" [(21)].

IV labetalol is the first-line therapy that is advised by the various national and international recommendations that were examined. A 20 mg bolus should be given in 2 minutes to begin the infusion, and then dosages of 20–80 mg every 10 minutes (maximum cumulative dose: 300 mg) until the BP is less than 150/100 mmHg. 6–8 mL/h is the typical maintenance dosage. The goal is to keep the BP within the recommended range [(21)].

- **Eclampsia**

For eclampsia, anticonvulsive therapy is the most crucial therapy. Magnesium sulfate administered IV is the suggested medication. A maintenance dosage of 2-3 g (rate of 50-75mL/h of 50 mg/mL in a physiologic solution or glucose solution) should be administered after the first bolus of 4-6 g in 20 mins. The therapy needs to be continued for 24 hrs following the last convulsive episode, often known as postpartum [(4)].

Our study examined the effects of sublingual nifedipine, IV labetalol, and IV nitroglycerin on BP regulation in individuals with severe PE. In the event of an acute hypertensive crisis, an IV medication such as injectable labetalol is primarily utilized to quickly drop BP. However, the results may vary depending on the route of delivery [(22)].

LABETALOL

All four of the potential stereoisomers—(R, S)-labetalol, (S, R)-labetalol, (S, S)-labetalol, and (R, R)-labetalol—are present in about equal levels in labetalol, a diastereoisomeric combination. This adrenergic blocker is used to treat HTN. Alpha-adrenergic blockers, beta-adrenergic blockers, sympatholytics, and antihypertensive agents are some of its functions. (R, R)-labetalol, (S, S)-labetalol, (R, S)-labetalol, and (S, R)-labetalol are among its constituents [(23)].

Indications: The therapy of arterial HTN, encompassing both stable chronic HTN and acute hypertensive crises (emergency or urgent), is the FDA-approved indication for labetalol. Among the many prevalent off-label applications of labetalol in clinical practice are intracranial hemorrhage, particularly subarachnoid hemorrhage, acute HTN in pregnancy, and HTN linked to acute ischemic stroke. The immediate therapy of hypertensive crises is currently the typical use for labetalol [(24)]. Because it causes a dose-related drop in BP without reflex tachycardia and without causing a noticeable drop in heart rate, labetalol is frequently used by anesthesia doctors to treat acute HTN during surgery. It combines its alpha- and beta-blocking properties to create these effects. Labetalol's hemodynamic effects vary; some studies have reported slight, negligible reductions in total peripheral vascular resistance and slight inconsequential improvements in cardiac output. This hemodynamic profile is advantageous in the perioperative context when the anesthesiologist wants to quickly lower BP without causing reflex tachycardia, which might worsen individuals' hemodynamics while they are under general anesthesia. Similar to this, labetalol is frequently used as an antihypertensive in the post-anesthesia care unit because it conserves heart rate and improves BP management [(25)].

Mechanism of action: Because it combines non-selectively, competitive beta-adrenergic (B1 and B2) blocking action with selective, competitive alpha1-

adrenergic antagonism, labetalol is a valuable drug. According to laboratory analysis, the alpha to beta-blockade activity ratio after oral and IV therapy is around 1 to 3 and 1 to 7 respectively [26].

Administration: A 10- to 20-mg IV push is the recommended first dosage for acute HTN episodes (emergent/urgent). Repeat boluses are given every 10 minutes until the SBP falls within the target range or a maximum dose of 300 mg per 24-hour period is reached. For an 80-kg patient, a dosage of 20 mg corresponds to around 0.25 mg/kg. Another option is a continuous infusion, which might be titrated up to 10 mg per minute after starting at 0.5-2 mg per minute [27]. When labetalol is broken down by the liver, an inactive glucuronide conjugate is produced. It takes effect between two and five minutes, peaks between five and fifteen minutes later, has a half-life of 5.5 hours for elimination, and lasts for up to four hours [27].

Adverse effects: Labetalol is generally well tolerated. Most side effects are usually minor and temporary. Individuals may have symptomatic postural hypotension if they are tilted or permitted to transition from a sitting or supine position to a standing one too rapidly. When treating a hypertensive individual on labetalol who is otherwise ambulatory to the restroom, this is particularly crucial in the post-operative phase (PACU or the ward). Labetalol usage has been associated with increased flushing and sweating [25].

NITROGLYCERIN

Indications: The main purpose of nitroglycerin, a vasodilatory medication, is to relieve anginal chest discomfort. Since 2000, the FDA has authorized nitroglycerin, which was initially marketed under a brand name. For the immediate therapy of an attack or the acute prevention of angina pectoris brought on by coronary artery disease, the FDA has granted it approval. Off-label, non-FDA-approved applications include the management of chronic anal fissures, coronary artery spasm, cocaine-related angina, hypertensive urgency/emergency, and CHF [28].

Nitroglycerin has a vasodilatory impact on veins and arteries, although venodilation is the main mechanism responsible for the drug's profoundly desired effects. Venodilation results in blood pooling in the venous system, which lowers the heart's preload and, in turn, cardiac work, hence lowering demand ischemia-induced angina symptoms. The alleviation of anginal symptoms will still be aided by arterial vasodilation. Although coronary artery vasodilation will improve blood flow to the heart, hence boosting perfusion, the impact is still negligible in comparison with venodilation [29].

Mechanism of action: Nitroglycerin is converted by the body to NO, just as other nitrates used to treat anginal chest discomfort. In vascular smooth muscle and other tissues, NO subsequently triggers the guanylyl cyclase enzyme, which changes guanosine triphosphate (GTP) into guanosine 3',5'-monophosphate (cGMP).

The kinase-dependent phosphorylations of several proteins are subsequently triggered by cGMP, which improves calcium absorption into the sarcoplasmic reticulum, raises extracellular calcium, and opens the calcium-gated potassium channel. In the end, this causes the smooth muscle fibers' myosin light chains to become dephosphorylated. The intended vasodilatory effect is produced by this action, which relaxes the smooth muscle inside blood vessels [30].

Nitroglycerin is administered IV, most frequently in ICUs and emergency rooms. When sublingual nitroglycerin has not been able to relieve symptoms or if quick and sustained symptom relief is required, it is recommended to deliver a 5% dextrose infusion. The therapy of acute coronary syndromes, hypertensive emergencies, and acute CHF exacerbations often involves IV nitroglycerin [30].

Adverse effects: Nitroglycerin has a number of significant side effects, the most of which are caused by the medication's vasodilating properties. Symptoms include dizziness, weakness, palpitations, vertigo, migraines, nausea, vomiting, diaphoresis, and syncope [27].

NIFEDIPINE

One calcium channel antagonist that is a member of the dihydropyridine subclass is nifedipine. Its main medicinal uses are as an antihypertensive and antianginal drug [28].

Indications:

- Chronic stable angina: In the IMAGE study, nifedipine increased the mean amount of time spent exercising and decreased the frequency of angina. The inclusion of a beta-blocker can overcome the potential restriction of its efficacy caused by reflex tachycardia. An extended-release formulation with a lengthy half-life is ideal.
- Vasospastic angina: It can be applied as a follow-up therapy.
- HTN: It can be used alone or in conjunction with a number of other drugs, including thiazide diuretics, ACE inhibitors, and ARBs, to treat HTN [25].

Mechanism of action: Calcium ions enter smooth muscle cells through voltage-gated channels when they are depolarizing. By obstructing these voltage-dependent L-type calcium channels in cardiac and vascular smooth muscle cells, nifedipine prevents calcium ions from entering. Lower intracellular calcium lowers coronary artery dilatation and peripheral arterial vascular resistance, which lowers systemic BP and improves myocardial oxygen supply. Therefore, nifedipine has antianginal and hypotensive effects [31].

Administration: Both immediate-release and extended-release forms of nifedipine are accessible. It was first sold as a short-acting immediate-release version that needed to be taken many times a day. These preparations produced flushes, palpitations, and headaches as a result of their quick vasodilation and reflex sympathetic activation. Because of these adverse effects, extended-release formulations were introduced. They have been demonstrated to have less side effects and a sustained 24-hour anti-hypertensive action [(32)].

Adverse effects: Of individuals taking nifedipine, 20-30% have adverse effects. The main cause of them is nifedipine's vasodilatory effects. Headache, dizziness, flushing, and peripheral edema are the most frequent side effects. The extended-release forms of nifedipine have greater tolerance than the immediate-release forms. Pruritus, urticaria, and bronchospasms are examples of hypersensitivity responses that are very uncommon. Rebound HTN or angina might occur if the medication is abruptly stopped after extended usage [(31)].

A number of studies examined two antihypertensive medications in individuals with severe PE. At Sayed Galal Hospital in Egypt. **Abd El-Hamid *et al.*** [(32)] studied 100 women with severe PE in order to compare the effects of sublingual nifedipine and continuous IV nitroglycerine administration on the therapy of women with severe PE receiving controlled plasma volume expansion and $MgSO_4$ loading and maintenance doses. The study concluded that IV nitroglycerine infusion was a safe, effective, and alternative therapy for severe PE. Also, they demonstrated that the nitroglycerine group's SBP and DBP measurements were significantly lower than those of the nifedipine group, and that the feto-maternal safety margin was comparable between the two study groups.

Also, a study of 200 individuals with severe PE at Ain Shams University was carried out by **Ali and Salah** [(33)]. One of two groups was randomly allocated to them. Group L got an IV infusion of labetalol, whereas group N received an IV infusion of nitroglycerin. According to the study, infusions of nitroglycerin and labetalol reduced BP in 96% and 87% of individuals respectively to the intended end point at 90 minutes. The incidence of chronic HTN was reduced and management was considerably quicker with nitroglycerin. The N group experienced considerably more headaches, flushes, and tachycardia than the L group, whereas the N group experienced significantly less bradycardia than the L group.

Additionally, a study by **Wasim *et al.*** [(34)] in Pakistan compared the speed at which oral nifedipine and IV labetalol controlled BP in patients with severe PE. The patients were randomly assigned to receive either nifedipine or labetalol, and the results indicated that both medications were equally effective at controlling BP in patients with severe PE without causing any notable adverse effects.

In addition, a research by **Sathya Lakshmi and Dasari** [(35)] randomly assigned 100 women with hypertensive crises to either IV labetalol or oral nifedipine. Both the nifedipine and labetalol groups had lower SBP, DBP, and MAP than baseline at all follow-up time periods, according to the research. However, the labetalol group's decline in SBP, DBP, and MAP was more pronounced than the nifedipine group. 90% of the nifedipine group and 92% of the labetalol group were able to reach their target BP. Adverse effects on both the mother and the fetus were rare.

In another Indian study, **Kaur *et al.*** [(20)] randomly assigned 120 pregnant women with BP of ≥ 160/110mmHg. They found that IV labetalol restores BP more quickly than oral nifedipine in pregnant women with PE and could be used as a first-line medication for acute BP control in a pregnancy hypertensive emergency.

CONCLUSION

The following treatments were administered to women with severe PE: IV nitroglycerine, sublingual nifedipine, and a continuous infusion of labetalol. These treatments significantly decreased BP after administration compared to baseline, with the labetalol group experiencing a much greater reduction in mean arterial BP. The labetalol group achieved the desired BP considerably more quickly than the nitroglycerin and nifedipine groups, respectively.

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