



Nitroglycerin versus labetalol to control the blood pressure in acute severe pre-eclampsia

Rania M Ali and Dina Salah

Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: Acute severe pre-eclampsia (PE) requires urgent antihypertensive therapy to reduce the incidence of adverse outcome. There is currently very limited evidence for the role of nitric oxide donors as antihypertensive therapy for acute severe PE. The aim of this study was to evaluate the efficiency and tolerability of nitroglycerin compared to labetalol in terms of acute control of blood pressure in severe PE.

Patients and methods: Two hundred patients with severe PE were admitted prepartum to the ICU to stabilize blood pressure. They were randomly assigned to one of two groups; Group N received nitroglycerin intravenous infusion (1 mg/ml) and Group L received labetalol intravenous infusion (10 mg/ml). The starting infusion rate was 5 ml/hr and was titrated to stabilize systolic blood pressure at 130–140 mmHg and diastolic blood pressure at 80–90 mmHg (study end point).

Results: Reduction of blood pressure at 90 minutes to the desired end point was achieved in 96% and 87% of the patients by nitroglycerin and labetalol infusion respectively. Nitroglycerin showed significantly faster control and lower incidence of persistent hypertension. The number of attacks of hypotension was comparable between both the groups. Headache, flushes, and tachycardia were significantly higher in N group compared to the L group, while bradycardia was significantly lower in the N group compared to the L group. Fetal side effects were comparable between the two groups.

Conclusion: Nitroglycerin can be considered an important alternative to labetalol for controlling the blood pressure in acute severe PE.

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1. Introduction

Pre-eclampsia (PE) is one of the most frequent pregnancy complications and is one of the main causes of maternal and fetal morbidity and mortality in its severe form [1]. Prompt control of blood pressure is of crucial importance to avert maternal and fetal complications. There is no consensus on the most appropriate acute antihypertensive therapy. The choice of agents primarily depends on availability of an agent and the experience of the provider [2].

The primary pathophysiology of pre-eclampsia is most likely inadequate placentation, leading to endothelial dysfunction and reduced nitric oxide bioavailability [3]. Therapeutic modalities that can target the underlying pathophysiological changes and reverse the endothelial dysfunction could potentially help to ameliorate the systemic manifestations in patients with severe PE. Nitroglycerin, as nitric oxide donor that targets the underlying molecular processes, represents a potential alternative to conventional acute antihypertensive therapy. Intravenous hydralazine and labetalol as well as oral nifedipine have been considered first line therapy for the management of acute severe hypertension in PE [4]. Previous studies demonstrated that nitroglycerin is an effective and

safe alternative therapy to sublingual nifedipine [5] and hydralazine [6] as antihypertensive therapy in the acute management of patients with severe PE. To our knowledge, this is the first randomized controlled trial comparing nitroglycerin and labetalol for acute control of blood pressure in severe PE. The aim of this study was to evaluate the efficiency of controlling blood pressure and tolerability of nitroglycerin compared to labetalol in terms of acute control of blood pressure in severe PE before delivery.

2. Patients and methods

The study was conducted in the intensive care unit (ICU) of the Obstetrics and Gynecology Hospital of Ain Shams University as a randomized, double-blind, and controlled study on patients diagnosed with severe PE from August 2019 to June 2022. The study was approved by Ethical Research Committee at Ain Shams University (ethical number FMASU R 47/2019), clinical trial number (NCT05310929) and all participants provided written informed consent.

Women eligible for this study were aged between 18–40 years old at greater than 34 weeks of gestation having severe PE. Its diagnosis is made in patients with

pre-eclampsia who have severe hypertension and/or significant end-organ dysfunction. Severe hypertension was diagnosed by Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg. Significant end-organ dysfunction was presented by the presence of one or more of the following after exclusion of alternative diagnoses: new-onset cerebral or visual disturbance, severe headache that persists and progresses despite analgesic therapy, serum transaminase concentration >2 times the upper limit of the normal range or severe persistent right upper quadrant or epigastric pain unresponsive to medication, thrombocytopenia $<100,000$ platelets/microL, serum creatinine >1.1 mg/dL or doubling of the serum creatinine concentration, or pulmonary edema [7]. Exclusion criteria were patients with chronic hypertension, active asthma, or congestive heart failure, or any known allergy to one of the study drugs or life-threatening fetal heartbeat changes.

Before delivery, two hundred patients with severe PE were admitted prepartum to the ICU to stabilize blood pressure. Patients were allocated into two equal groups in a randomized manner using computer-generated number lists and the allocation was concealed by sealed envelope method. Group N received nitroglycerin intravenous infusion (Nitronal, Sunny) in a concentration of 1 mg/ml, thus 1 μ g/Kg/min equals to 4.8 ml/hr for an 80 Kg patient. Group L received labetalol intravenous infusion (Trandate, Gsk) in a concentration of 10 mg/ml, thus 50 mg/ml equals to 5 ml/hr. The starting infusion rate of the antihypertensive medication was 5 ml/hr. The infusion rate was titrated to stabilize systolic blood pressure (SBP) at 130–140 mmHg and diastolic blood pressure (DBP) at 80–90 mmHg (study end point) by adjusting the infusion rate as required either by maintaining the same infusion rate or by changing its infusion rate by 1 ml/hr up or down according to the clinical condition every 10 minutes. On any abrupt reduction in blood pressure below 120 mmHg for SBP or 80 mmHg for DBP, the infusion was immediately discontinued, and a bolus of 150 ml lactate ringer was given. All study drugs were prepared and administered by an independent investigator not involved in the observation.

Patients received full intensive care treatment for PE according to the standard protocol of the ICU of the Obstetrics and Gynecology Hospital of Ain-Shams University. Treatment for PE included infusion of lactated Ringer solution, at a starting rate of 80 ml/hr and then adjusted according to the fluid balance, magnesium sulphate, as seizure prophylaxis and its dose was adjusted according to renal function and its signs of toxicity in addition to antihypertensive medications according to the assigned group. The study solution was stopped if maternal pulse reached less than 60 bpm or raised more than 110 bpm.

Vital signs were monitored at admission and until patients were discharged from the ICU using ECG, pulse oximetry, continuous invasive arterial blood pressure monitoring, and urine output assessment. Fetal heart rate monitoring was done before starting of the study and continuously during the study time by cardiotocography (CTG).

Treatment failure was expressed by severe persistent hypertension. It was considered when SBP was greater than 160 mmHg or DBP was greater than 110 mmHg after the administration of maximum dose of allocated drug treatment: 20 ml/hr. Hence, hydralazine was added as a rescue drug after 2 hours of starting treatment with assigned drugs. After stabilization of the patient and once the target BP was achieved, delivery was conducted.

The following data were recorded and included demographic characteristics, the time taken to control blood pressure (time from starting infusion till reaching study end point), and number of attacks of hypotension (BP values below the study end point) and the incidence of severe persistent hypertension. In addition, side effects of drugs such as tachycardia (HR >100 bpm), bradycardia (HR <60 bpm) headache, nausea/vomiting, hypotension, flushing, dizziness were recorded. Fetal outcome as stillbirths and suspected fetal compromise by abnormal CTG were recorded. Fetal distress was manifested in the fetal heart rate tracing as decelerations, loss of beat-to-beat variability, and even bradycardia. 1 min Apgar score less than 7- and 5-minutes Apgar score less than 7 were also recorded.

2.1. Sample size determination

Sample size was calculated using PASS 11.0 sample size calculation program and according to a study carried out by Ali et al. [6], in 2015. 85 patients in each group achieve 80% power in detecting a 15% reduction in systolic blood pressure when the significance level is $\alpha = 0.05$ with two-sided testing showing normally distributed data and a standard deviation of 8 mmHg, so we included 100 patients in each group considering possible dropouts.

2.2. Statistical analysis

The statistical analysis was performed using a standard SPSS software package version 23 (Chicago, IL). Normally distributed numerical data are presented as mean \pm SD and differences between groups were compared using the independent Student's *t*-test, intragroup difference was compared using paired *t*-test and categorical variables were analyzed using the χ^2 test or Fisher's exact test and are presented as number. All P values are two-sided. $P < 0.05$ is considered statistically significant.

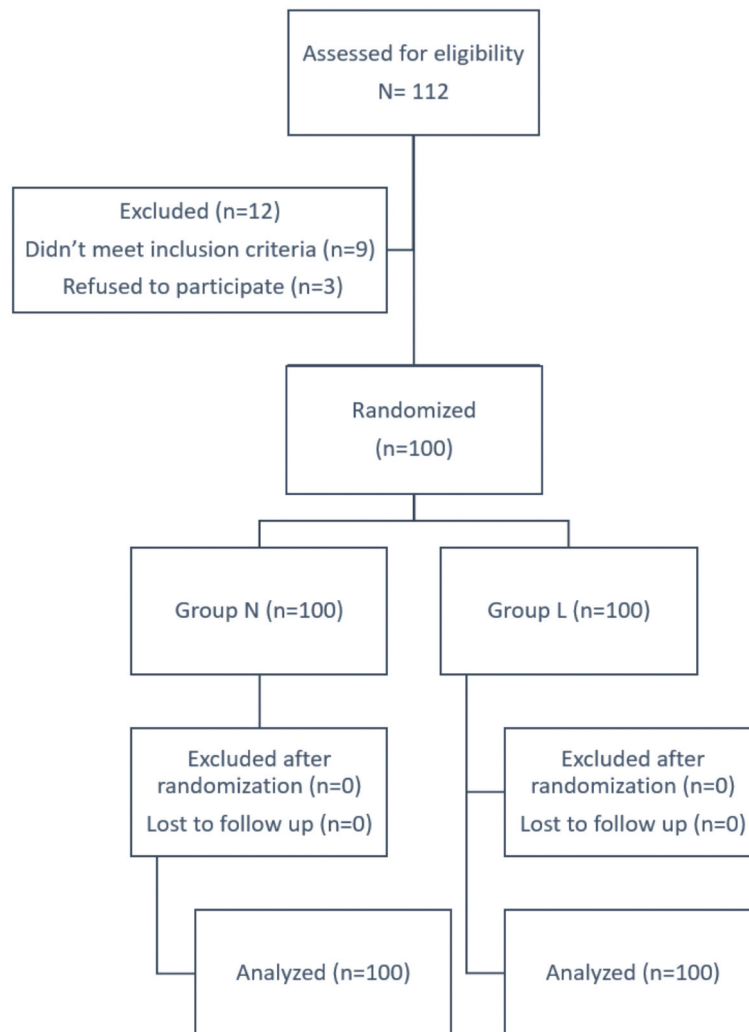


Figure 1. CONSORT flow diagram.

3. Results

Two hundred twelve patients with severe PE were admitted prepartum to the ICU to stabilize blood pressure (Figure 1). Two hundred patients were randomly assigned to one of two groups (100 in each group); Group N received nitroglycerin intravenous infusion and Group L received labetalol intravenous infusion.

Both groups were comparable regarding patients' characteristics (Table 1). As regards blood pressure parameters, baseline values (before start of study drug infusion, = 0 minutes) of SBP and DBP were

comparable in both groups. At 30 mins, 60 mins, 90 mins SBP and DBP were significantly lower when compared to baseline values in both groups and in the N group compared to the L group. The time to achieve blood pressure control was significantly shorter in the N group compared to the L group, though the number of attacks of hypotension was comparable between both groups. Severe persistent hypertension incidence was lower in N group compared to L group (Table 2). As regard maternal side effects, headache, flushes, and tachycardia were significantly higher in N group compared to the L group, while bradycardia was significantly lower in the N group compared to the L group (Table 3). Fetal side effects including fetal distress, Apgar scores and time to delivery were comparable between the two groups (Table 4).

Table 1. Patients' characteristics.

Variables	Group N (n = 100)	Group L (n = 100)	P-value
Age (years)	27.68 ± 2.84	28.26 ± 3.24	0.179
Parity (MP/PG)	66/34	74/26	0.28
BMI (Kg/m ²)	26.2 ± 2.2	26.52 ± 2.44	0.593
Gestational age (month)	38.1 ± 0.6	38.13 ± 0.72	0.289

Data are presented as mean ± SD, number of patients. P-value < 0.05 is considered statistically significant. MP: multipara, PG: primigravida

4. Discussion

In the current study, reduction of blood pressure at 90 minutes to the desired end point was achieved in 96% and 87% of the patients by nitroglycerin and

Table 2. Blood pressure parameters.

Variables	Group N (n = 100)	Group L (n = 100)	P- value
SBP (mmHg)			
At 0 minutes	169.3 ± 3.14	168.4 ± 2.75	0.057
At 30 minutes	152.6 ± 6.11	159.3 ± 3.4	<0.001*
	0.001†	<0.001†	
At 60 minutes	141.7 ± 7.8	144.8 ± 6.4	0.002*
	<0.001†	<0.001†	
At 90 minutes	135.2 ± 8.6	139.25 ± 6.9	<0.001*
	<0.001†	<0.001†	
DBP (mmHg)			
At 0 minutes	124.5 ± 4.23	123.7 ± 3.9	0.192
At 30 minutes	108.4 ± 6.3	113.7 ± 4.3	<0.001*
	<0.001†	<0.001†	
At 60 minutes	94.5 ± 9.4	98.62 ± 8	<0.001*
	<0.001†	<0.001†	
At 90 minutes	87.7 ± 9.5	90.64 ± 8.16	0.022*
	<0.001†	<0.001†	
Time to control BP (minutes)	60.5 ± 8.6	72.89 ± 10.8	<0.001*
Attacks of hypotension (n)	15	12	0.68
Severe persistent hypertension	4	13	0.04*

Data are presented as mean ± SD, number of patients. *p-value <0.05 is considered statistically significant between the 2 groups. †p-value <0.05 is considered statistically significant compared to the baseline values in same group.

Table 3. Maternal side effects.

Variables	Group N (n = 100)	Group L (n = 100)	P value
Tachycardia (n)	21	4	<0.001*
Bradycardia (n)	0	7	0.014*
Headache (n)	13	4	0.04*
N& V (n)	2	0	1
Flushes (n)	6	0	0.029*
Dizziness (n)	5	6	1

Values are expressed as number, *p < 0.05 is considered statistically significant.

Table 4. Fetal side effects.

Variables	Group N (n = 100)	Group L (n = 100)	P value
Time to delivery (hour)	6.34 ± 0.26	6.25 ± 0.26	0.057
Fetal distress (n)	4	3	0.621
Still births (n)	4	5	1
Apgar score 1 min (°7)	2	1	1
Apgar score 5 min (°7)	2	1	1
Birth weight (Kg)	2.76 ± 0.25	2.72 ± 0.2	0.185

Data are presented as mean ± SD, number of patients. *p < 0.05 is considered statistically significant.

labetalol infusion respectively. Nitroglycerin showed faster control and lower incidence of persistent hypertension. However, it caused more tachycardia, headache, and flushes than labetalol which caused more bradycardia. Both drugs showed comparable fetal tolerability.

Acute severe pre-eclampsia requires urgent antihypertensive therapy to reduce the incidence of adverse outcome [8]. Intravenous hydralazine and labetalol as well as oral nifedipine have been considered first line therapy for the management of acute severe hypertension in PE [4]. Cochrane database review reported lack of evidence regarding choice of antihypertensive [9]. Later systematic

review has declared all three drugs equally effective in controlling blood pressure in hypertensive emergencies in pregnant women [2].

Although antihypertensive therapy may diminish the maternal complications, it may also impair utero placental circulation. As rapid or excessive falls in maternal blood pressure may decrease placental perfusion and lead to placental abruption, CS, and low Apgar scores [10]. Consequently, identifying optimal antihypertensive therapy is warranted to ameliorate these risks.

Labetalol is a non-selective beta blocker and post synaptic alpha-1 blocking agent. The hypotensive effect of labetalol begins within 2–5 min after its intravenous administration, reaching a peak at 5–15 min after administration and lasting for about 2–4 hours [11]. Intravenous labetalol may be considered as first line drug treatment in severe PE. Labetalol preserves uteroplacental flow unchanged. Parental labetalol may cause neonatal bradycardia even though little placental transfer occurs that is mainly attributable to its negligible lipid solubility [12]. Labetalol should be avoided in women with asthma, heart disease or congestive heart failure [13]. Thus, labetalol would not be suitable as an antihypertensive in considerable part of the population. In this study, a slower rate of control of blood pressure was achieved by labetalol than that with nitroglycerin. This is consistent with several studies in which labetalol has slower achievement of goal BP with more use of rescue antihypertensive agents [14,15].

Endothelial dysfunction and disruption of nitric oxide bioavailability are major contributors to the manifestations of PE [3]. Therapeutic options that focus on reversing the underlying endothelial dysfunction would potentially be translated into new treatment modalities for this condition. There is currently very limited evidence for the role of nitric oxide donors as antihypertensive therapy for acute severe PE. The most established nitric oxide donors that have been studied in the context of pre-eclampsia is organic nitrates in particular nitroglycerin [5,6,16–18].

Nitroglycerin is a nitric oxide donor that produces a marked vasodilator effect on veins and a modest vasodilator effect on arteries [19]. It has the advantage of targeting the underlying pathophysiological changes of PE and reverse the endothelial dysfunction. The use of the intravenous nitroglycerin results in an immediate peak effect, a duration of 3–5 minutes, with a half-life of 1–4 minutes. Owing to its rapid onset and brief half-life, nitroglycerin antihypertensive effect is predictable and can be titrated easily by adjusting the dose according to the patient response to avoid excessive reduction in blood pressure [5]. Uncontrolled reduction of maternal blood pressure can cause reduction in utero placental circulation and fetal distress.

Nitroglycerin has been previously studied in several obstetric complications, including premature labor [20–22], prevention of pre-eclampsia [23], intrauterine growth restriction [24].

The development of tolerance with nitroglycerin can be a restriction against its use for long-term control of blood pressure in women with pre-eclampsia. However, in the case of acute severe elevation of the blood pressure before delivery transient administration for a limited time would allow its use without tolerance [25].

In one study, intravenous nitroglycerin infusion was effective in lowering maternal blood pressure and in blunting the hemodynamic responses to endotracheal intubation in women with severe PE [26].

In one more study, continuous infusion of intravenous nitroglycerine reduced blood pressure faster, to a greater extent, and more precisely with less variability than sublingual nifedipine administered to women with severe pre-eclampsia. Heart rate also increased in the nifedipine-treated group; it was almost two-fold that in the nitroglycerin-treated group even though both are vasodilatory therapy. There were no significant changes in fetal heart rate in response to vasodilator therapy. The frequency of perinatal fetal-maternal adverse effects was similar in both groups [5]. These findings are consistent with the present study.

In another study, although both hydralazine and nitroglycerin infusions were effective in acute control of hypertension in patients with severe PE before delivery, the therapeutic goal was reached faster with nitroglycerin and with greater safety profile than with hydralazine [6].

The European society of cardiology recommended the use of nitroglycerin infusion in patients with PE complicated with pulmonary edema [27].

As women with pre-eclampsia are usually intravascularly volume depleted, theoretically it may be prudent to choose an antihypertensive that is a rapid acting venodilator like nitroglycerin [28]. However, hypotensive attacks were comparable between the nitroglycerin group and the labetalol group in the current study. Likewise, in a previous study both nitroglycerin and hydralazine groups were comparable regarding the incidence of hypotension throughout the acute controlling of hypertension in patients with severe PE before delivery [6].

Maternal headache, flushes, and tachycardia were more frequent in nitroglycerin group which were attributed to its potent vasodilator effect and its unique mechanism of action which was consistent with other studies [17,18], while maternal bradycardia was more frequent in labetalol group due to its alpha and beta blocking effect which was reported by other researchers [29]. Fetal side effects including fetal distress, Apgar scores and time to delivery were

comparable between the two groups. These results are consistent with other study [6]. Future research should further explore the effect of nitroglycerine on fetal liver and methemoglobinemia.

In conclusion, labetalol is an effective and safe anti-hypertensive drug in severe pre-eclampsia with minimal side effects. However, nitroglycerin showed faster control, limited adverse effects, and lower incidence of failure presented by persistent hypertension. Therefore, it can be considered an important alternative to labetalol in acute severe pre-eclampsia.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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