

Role of Nitroglycerin Transdermal Delivery System in the Management of Pre-Eclampsia

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ABSTRACT

Background: Hypertensive disorders complicating pregnancy along with hemorrhage and infections form a deadly triad contributing to maternal morbidity and mortality in the developing countries. Many causative theories have been proposed over the years. There is increasing evidence indicating endothelial dysfunction in the wide spectrum of clinical presentation of preeclampsia. The primary objective of the study was to assess the efficacy of Nitroglycerin patch in the management of pre-eclampsia in patients of presenting to the Obstetrics & Gynecology Department of a tertiary care teaching institution in northern India. Fetal outcomes and associated adverse events were also noted. **Methods:** A randomized clinical trial was conducted among 47 antenatal women admitted in the Department of Obstetrics and Gynecology, who were diagnosed with pre-eclampsia. After the detailed obstetrical history, examination and investigations, the Nitroglycerin patch was applied daily from 32 weeks onwards till the date of delivery. Their blood pressure, urinary proteins were measured and fetal outcome was noted. **Results:** The majority of patients were below 30 years of age. There were 16 (34%), 26 (55%), 3(6.38%), 2(4.26%) in the age group of 20-25, 26-30, 31-35 and 36-40 years respectively. 52% were nulliparous. On applying the Nitroglycerin patch, there was a 1.43% increase in pulse rate, which was not statistically significant. There was good control of systolic and diastolic blood pressure. Systolic blood pressure fell by -9.11 ± 5.74 (p-value 0.0001) and diastolic blood pressure dipped by -10.52 ± 5.93 (p-value- 0.0001) throughout the treatment period. There was a significant improvement in urinary protein status after treatment. Overall (68%) patients had undergone vaginal delivery as compared to 32 % Lower Segment Caesarean Section (LSCS). 48.94% of patients complained of headaches which got relieved after some time. **Conclusion:** The nitroglycerin patch is a very good alternative to the present anti-hypertensive agents. We need more studies to further explore its possible future use as a common antihypertensive medication in pregnancy.

Keywords: Pre-Eclampsia, Transdermal, Nitroglycerin.

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INTRODUCTION

Preeclampsia is defined by the working group of the National High Blood Pressure Education Program,^[1] as hypertension more than 140/90 mm Hg using Korotkoff's V sound for diastolic blood pressure associated with proteinuria (300 mg in 24 hours urine). In Preeclampsia, although proteinuria is an important diagnostic marker, multi-system involvement due to endothelial leakage is seen. The American College of Obstetrics and Gynecology (ACOG) Taskforce therefore included thrombocytopenia, renal dysfunction, hepatocellular necrosis, central nervous system perturbations, or pulmonary edema in diagnosis.^[2]

Some of the currently accepted hypothesis about the pathophysiology of pre-eclampsia include abnormal trophoblastic invasion of uterine vessels, increased vasopressor response and vasospasm, immunological intolerance to the fetus and genetic

abnormalities. There is increasing evidence that endothelial cell dysfunction is responsible for the most significant biochemical changes and spectrum of clinical presentations that characterize preeclampsia.^[3,4] It is due to an imbalance between the vasodilators and vasoconstrictors.^[4] Robert et al. proposed that a maternal endothelial dysfunction is a big event resulting in diverse clinical manifestations of preeclampsia.^[5] The increased vascular resistance has been attributed to decreased endothelial production as well as the resistance of vasculature to the normal vasodilatory effect of Nitrous Oxide (NO).

MATERIALS & METHODS

The present study was a prospective interventional study carried out in the Department of Obstetrics and Gynaecology, Chhatrapati Shahuji Maharaj University, from September 2007 to August 2008. The study was conducted on 47 pregnant women with a singleton pregnancy and diagnosed with preeclampsia.

Detailed obstetric and menstrual history was taken; antenatal records were scrutinized for correct gestational age. A previous history of preeclampsia was noted. Thorough physical examination of patients including pulse rate, blood pressure,

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temperature, weight and height was done. Routine antenatal investigations were done along with liver and kidney function tests and fundus examination.

Nitroglycerin patch (5-10mg/24hr) was applied to the abdominal wall and replaced 24 hours daily till delivery. During therapy, patients were strictly watched for any side effects. Blood pressure and proteinuria were measured daily and entered in the datasheet for comparisons.

Spontaneous vaginal delivery was recommended in all cases until there was a fetal or maternal indication of doing a caesarean section. Neonatal outcome was recorded in terms of mode of delivery, birth weight, neonatal complications and Apgar score. Data was entered in proforma tabulated and analyzed with appropriate statistical tests.

Inclusion criteria:

Antenatal women of 32 to 36 weeks gestation with preeclampsia, admitted to the hospital.

Exclusion criteria:

Pregnancy less than 32 weeks, pre-eclampsia with chronic hypertension, pre-eclampsia with intrauterine fetal death, pre-eclampsia with premature rupture of membrane, any major medical illness, or post-dated pregnancy.

Drug Delivery System- Transdermal Nitroglycerin Patch (Nitroderm TTS)

The transdermal therapeutic system, which was a breakthrough in drug delivery systems, was developed by CIBA GEIGY in collaboration with another firm, Alza. The transdermal therapeutic system can take Nitroglycerin, a drug with a short biological half-life (which normally requires frequent administration) through the skin to the bloodstream by way of controlled administration over 24 hours.

Drug transport through the skin occurs by passive diffusion in the following stages:

- Absorption into stratum corneum
- Diffusion through the skin layers
- Diffusion through the skin layers
- Absorption into micro-circulation

Therefore Nitroderm TTS is not just another topical preparation, but a drug delivery system, which

ensures continuous delivery of a drug into the micro-circulation without peaks and troughs. The following two systems are available:

	Nitroderm TT 5	Nitroderm 10
Rate of release of nitroglycerine	0.2 mg /hour	0.4 mg /hour
Content of nitroglycerine	25 mg.	50 mg
Contact surface	10cm ²	20 cm ²

The excess of Nitroglycerin in each of the two systems act as a drug reservoir and is not released during normal use. After 12 hours, for example, the system will have delivered 10% of its original content of NTG. Since Nitroglycerin is released from Nitroderm TTS at a constant rate per cm², the size of the dose administered depends solely on the size of the system's contact surface.

An appropriate ethics committee and patient consent were obtained.

RESULTS

Demographic Profile

The majority of patients were below 30 years of age. There were 16 (34.0 4%), 26 (55.32%), 3 (6.38%) and 2(4.26%) patients in age group 20-25 years, 26-30 years, 31- 35 years, 36-40 years, respectively. The majority of the patients, 51.06% were nulliparous. Gestational age ranged between 32-38 weeks. Out of 47 patients, 25 were in 32-34 weeks, 21 were in 35-37 weeks and 1 patient was above 37 weeks.

The pulse rate before therapy was 90.92± 4.82/min and after 2 weeks of intervention, it changed to 92.40 ± 6.11 (1.43% increase). Although there was slight tachycardia after starting patch therapy it was not statistically significant.

On comparing the change in blood pressure after therapy, it was found that there was a mean decrease of 9.11± 3.47 mm of Hg in systolic blood pressure and 10.5 2 ± 5.93 mm of Hg in diastolic blood pressure respectively. Mean pre-treatment SBP was 151.90±6.39 mm Hg and mean DBP was 93.32±5.09 mm Hg which decreased to 138.92±6.50 mm Hg and 82.41±5.82 mm Hg respectively after treatment.

Table 1: Comparison of hemodynamic parameters before & after the intervention

Parameter	Group I (n = 47) Mean ± SD	t-value	p-value
Pulse rate (before therapy)	90.92 ± 4.82	1.30	0.196(NS)
Pulse rate (after therapy)	92.40 ± 6.11		
% change in pulse rate	1.43 ± 5.74		

Table 2: Comparison of changes in blood pressure before and after an intervention

Parameter	Patient on therapy (n = 47) Mean ± SD	t-value	p-value
Systolic Blood Pressure (before therapy)	151.90 ± 6.39	12.21	0.0001(HS)
Systolic Blood Pressure (after therapy)	138.92 ± 6.50		
change in systolic pressure	-9.11 ± 5.74		
Diastolic Blood Pressure (before therapy)	93.52 ± 5.09	9.67	0.0001(HS)
Diastolic Blood Pressure (after therapy)	82.41 ± 5.82		
change in diastolic pressure	-10.52 ± 5.93		

Table 3: Urinary protein status of patients before intervention

Urinary Protein Status	Group I (n = 47)	Percentage
1+	36	76.6
2+	9	19.15
3+	2	4.26

$\chi^2 = 35.93$ (df = 2); p-value = 0.0001

Table 4: Urinary protein status of patients after the intervention

Urinary Protein Status	Group I (n = 47)	Percentage
1+	36	76.6
2+	9	19.15
Traces	2	4.26

$\chi^2 = 40.963$ (df = 2); p-value = 0.0001

Table 5: Mode of delivery at a various gestational age

POG at termination (in weeks)	No. of cases	Indication of LSCS					Vaginal
		Fetal distress	Failure of induction	Non-progress of labor	Failure of control of BP	Others	
32-34		-	-	-	-	-	-
34-36	10	4	0		-	-	6
≤37	37	6	1	2	1	1	26
Total	47	10 (21.27%)	1 (2.13%)	2 (4.26%)	1 (2.13%)	1 (2.13%)	32(68.08%)

There was a significant improvement in proteinuria status. The basic mechanism of action of Nitroglycerin in lowering the blood pressure in a preeclamptic patient by reversing the endothelial dysfunction is manifested by its ability to reduce proteinuria [Table 4].

The above table shows the outcome of cases according to the mode of delivery, the incidence of cesarean Section was 32% and the indication in most of the cases was fetal distress. The majority of them had a vaginal delivery (68%) as compared to LSCS (32%).

At one minute only, 34.0 4% neonates had Apgar score less than 7 and 65.9 6% neonates had more than 7. At 5 minutes, 6.38 percent neonates had Apgar score less than 7 whereas 91.07% neonates had Apgar score more than 7. There were 47 live births and no IUD among them, 87.2 3% neonates had birth weight between 2.6-3kg and mean birth weight was 2.72 ± 0.16 kg. The mean increase in fetal weight which was observed after two weeks of therapy was 0.477 ± 0.032 .

The major side effect was headache which was present in 48.9 4% of patients and it got relieved by symptomatic treatment.

Table 6: Distribution of side effects of Nitroglycerin

Side effect	No. of cases (n= 47)	Percentage
Systemic		
Headache	23	48.94
Nausea / Vomiting	10	21.28
Hypotension	-	-
Tachycardia	-	-
Local		
Allergic reactions like itching/rashes	3	6.38

DISCUSSION

Seven to 10% of all pregnancies are complicated by some form of hypertensive diseases, in developing

countries. Vascular tone is an essential target of the paracrine and endocrine regulations during pregnancy. Nitric Oxide (NO) synthesized in the placental vasculature may be crucial in maintaining a low fetoplacental perfusion pressure. It is synthesized from the physiologic precursor L-arginine by the stereospecific enzyme, NO synthase via the L-arginine/ NO pathway. Many drugs for the treatment of preeclampsia are available, yet no one has been proved to be beneficial in targeting this crucial pathway.

The role of endogenous Nitric oxide in pathophysiology and its usage as a therapeutic target in the management of pre-eclampsia has a long history. Fickling et al. noted a significant increase in the concentration of endogenous nitric oxide inhibitor in patients of preeclampsia as compared to normotensive pregnancy.^[6] If the hypothesised endothelial dysfunction in preeclampsia and disturbed nitric oxide formation is the underlying pathophysiological process responsible for preeclampsia, treatment with nitric oxide donor would be an effective therapeutic alternative.

Nakatsuka et al (1999) studied treatment with long-term transdermal ISDN in preeclampsia to reduce maternal hypertension, intrauterine growth retardation and fetal distress.^[7] In 2002, his group performed a similar study to estimate the effects of long term transdermal administration isosorbide dinitrate (ISDN), a nitric oxide donor, (range, 4-30 days mean \pm SD; 11.1 ± 7 days) in preeclamptic women.^[8] It significantly lowered the blood pressure of patients along with reductions in the pulsatility index (PI) in the umbilical artery with a demonstrated increase in the size of the amniotic fluid pocket. Transdermal administration of ISDN on a long term basis improved the fetoplacental circulation and was proved as an effective therapy for avoiding maternal hypertension.

Further support for the usage of NO donor therapy came from Skarsgard et al. in 1999, who found that Nitroglycerin infusion, reduces the maternal mean arterial pressure at a dosage of 10 micro/Kg/minute with no change in blood gas value, no effect on fetal carotid blood flow, flow variability or cerebral substrate metabolism.^[9] In the year 2007, Smith and Walker conducted a randomised trial of transdermal nitroglycerin for preterm labor.^[10] They found that infants born to mothers on transdermal Nitroglycerin had reduced composite outcome due to reduced morbidity and mortality in neonates.

Women at either end of reproductive age are considered to be more susceptible to nationwide in India. In our study, the majority of patients were below 30 years of age. The mean age of the patients was 26.86 ± 4.26 years. Comparing the decrease in blood pressure after the intervention, there was a significant decrease in both systolic and diastolic blood pressure which was significant. There was a fall of 9.11 ± 3.47 mm Hg in the patch group in systolic blood pressure. The mean fall in Diastolic blood pressure was 10.52 ± 5.93 mm in the patch group. This shows that the Nitroderm patch is effective in controlling blood pressure.

In the study by Cacciatore et al, the use of transdermal Nitroglycerin led to a decrease in mean arterial pressure from 122 ± 8 mm Hg to 177 ± 7 mm Hg ($p < 0.05$).^[11] It was more reflected in systolic blood pressure than the diastolic blood pressure. However, in our study, it was observed that the Nitroderm patch was efficacious in reducing both systolic and diastolic blood pressure and thus means arterial pressure.

Buhmisch et al. also corroborated the role of nitric oxide in the maintenance of blood pressure in an animal model by using chronic nitric oxide synthase inhibitors in unrestrained rats. This result was consistent with the result we got from our study group after the use of the Nitroglycerin patch.^[12] Tripani et al. prospective study on 30 singleton pregnancies of gestational age range 24-31 weeks with severe pre-eclampsia and abnormal uterine and umbilical artery.^[13] Doppler waveforms also proved Nitroglycerin is helpful in improving the abnormal Doppler indices in uterine and umbilical arteries apart from being an excellent antihypertensive. They noted a significant decrease in pulsatility (PI) and resistance indices of uterine, umbilical arteries respectively, as compared to the first day without medication, though no change was observed in the pulsatility and resistance index of the middle cerebral artery.

El-Sayed S El-Ebshehy et al. conducted a prospective clinical trial in women with severe preeclampsia at Tanta University with 50-mg transdermal NTG.^[14] It leads to a significant decline in PI of uteroplacental and fetoplacental blood flow and maternal blood pressure.

CONCLUSION

The study shows that the Nitroglycerin patch in preeclampsia lowers blood pressure effectively; as a result, the fetal growth is better. Hence, the Nitroderm patch proved to be a good alternative therapy in preeclamptic patients. The small number of patients in this study is the major limitation. However, the results of the study are promising and a larger study would help us gain more confidence in using Nitroglycerin as a preferred antihypertensive in cases of preeclampsia.

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