DOI: 10.7860/JCDR/2017/21438.10282

Original Article

Obstetrics and Gynaecology Section

Effect of Transdermal Nitroglycerine on Doppler Velocity Waveforms of the Uterine, Umbilical and Fetal Middle Cerebral Arteries in Patients with Chronic Placental Insufficiency: A Prospective RCT

SURUCHI GUPTA[1], MEENAKSHI CHAUHAN[2], JYOTSNA SEN[3], SMITI NANDA[4]

ABSTRACT

Introduction: Increase in Nitric Oxide (NO) may be important in vascular adaptation needed to accommodate increased uteroplacental blood flow as pregnancy advances. Hence, in certain conditions like Pregnancy Induced Hypertension (PIH) and Fetal Growth Restriction (FGR), NO donors may play an effective role in increasing uteroplacental perfusion. Transdermal route appears to be a safe and effective route.

Aim: To evaluate the effect of nitroglycerine patch on Doppler velocity waveforms of the uterine, umbilical and fetal middle cerebral arteries in patients with chronic placental insufficiency.

Materials and Methods: A prospective randomized controlled clinical trial was conducted on eighty consecutive pregnant women with FGR with or without PIH and having evidence of altered waveform velocimetry in uterine, umbilical and fetal middle cerebral artery. They were divided into two groups- study and control group. Transdermal nitroglycerine patch (10 mg per 24 hours) was applied in study group for three consecutive days. Changes in various Doppler indices were noted after three days of patch application and compared between the two groups. Analysis was carried out using SPSS (Statistical Package for Social Studies) for Windows version 20.0 and online GraphPad software (Prism 5 for Windows) version 5.01.

Results: A significant fall in the systolic and diastolic ratio (S/D), Pulsatility Index (PI) and Resistivity Index (RI) of the uterine (3.07±0.52, 1.04±0.14 and 0.54±0.10 respectively, $p<0.001$) and umbilical artery (3.73±3.30, 1.18±0.21and 0.64±0.07 respectively, $p<0.001$) was noted after three days of patch application. No such significant change was observed in the middle cerebral artery indices.

Conclusion: The therapeutic approach of NO donor administration via transdermal route in pregnant patients with chronic placental insufficiency, apparently improved both maternal and fetoplacental haemodynamics, thus may help in improving perinatal outcome.

Keywords: Nitric oxide, Pregnancy, Pulsatility index, Resistivity index, S/D ratio

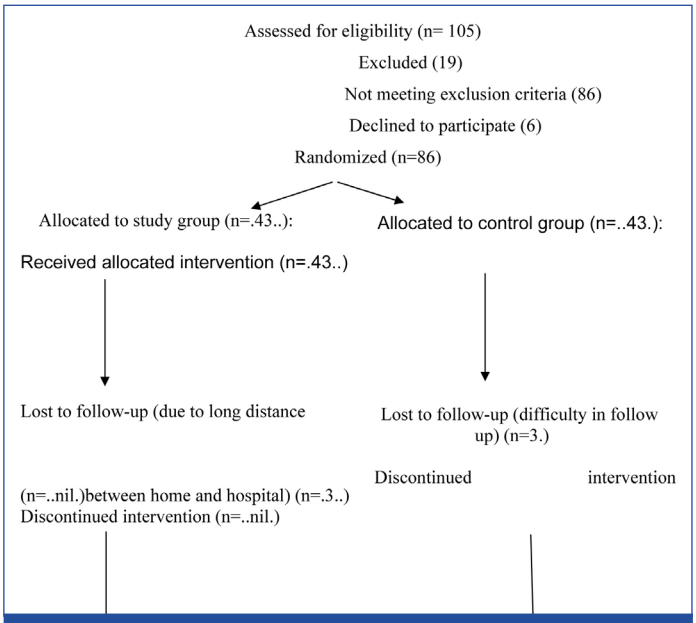
INTRODUCTION

Nitric Oxide (NO) has been reported to be an important bio-regulatory molecule in the regulation of vascular tone [1]. During pregnancy, there is an increase in the expression of nitric oxide synthase in various organs including the placenta with a consequent increase in the circulating levels of nitrite and nitrate, which are the stable oxidation products of nitric oxide. Because NO causes vasodilatation, relaxes smooth muscle and inhibits platelet aggregation and leucocyte adhesion, it may prevent maternal hypertension and maintain placental circulation during pregnancy. Increased NO synthase activity has been observed in villous trophoblast cells and increase in NO may be important in vascular adaptation needed to accommodate increased uteroplacental blood flow as pregnancy advances [2]. Hence, in certain conditions like PIH and fetal FGR, NO donors may play an effective role in increasing uteroplacental perfusion because of its rapid oxygenation, NO should be given continuously and for this purpose a patch releasing nitroglycerine steadily over 24 hours might be convenient, especially for pregnant women who seem to tolerate it without marked side effects.

Color Doppler is a non invasive modality for haemodynamic monitoring of patients with chronic placental insufficiency. Doppler velocimetry can guide us in the treatment of these pregnancies by identifying the fetuses at risk and can thus prevent perinatal morbidity and mortality. The uteroplacental vascular resistance, as assessed by the Doppler ultrasonographic method, is increased in pre-eclampsia but is unaffected by conventional antihypertensive treatment [3,4]. NO donors may play an effective role in decreasing this resistance. They have been used by various routes in the studies done in the past. Transdermal route appears to be a safe and effective mode but not enough studies have been done in the past using this mode. Hence, the present study was conducted to evaluate the effect of nitroglycerine patch on Doppler velocity waveforms of the uterine, umbilical and fetal middle cerebral arteries in patients with chronic placental insufficiency.

MATERIALS AND METHODS

A prospective randomized controlled clinical trial was conducted at our tertiary center between April 2012 to October 2013, using per-protocol type of analysis. An informed written consent was taken from all the patients. Ethical clearance and institutional review board clearance was taken for the study. Eighty consecutive pregnant women (power of the study 80%) with singleton live pregnancy and gestational age between 28-38 weeks admitted with FGR and/or PIH and having evidence of altered waveform velocimetry in uterine,



[Table/Fig-1]: Flow chart showing distribution of subjects.

umbilical and fetal middle cerebral artery. They were randomized through a computer generated table and divided into two groups [Table/Fig-1]:

A. **Study group:** Transdermal nitroglycerine patch (10 mg per 24 hours) was applied for three consecutive days along with anti-hypertensive treatment if required.

B. **Control group:** Nitroglycerine (NTG) patch was not applied but anti-hypertensive treatment if required was given.

Exclusion Criteria

Women with multiple pregnancies, any congenital fetal anomaly, gestational age <28 weeks, migraine, severe anaemia, raised intracranial tension and patients with other medical disorders.

Doppler ultrasound was used for the study of uterine artery, umbilical artery and fetal middle cerebral artery. Resistivity index, pulsatility index and systolic and diastolic ratio (S/D) of these three arteries were noted on the day of admission (Day 1). Patients showing alteration in the indices of any or all of these vessels were selected for the study. In study group, for three consecutive days, transdermal nitroglycerine patch was applied on the abdominal skin below the umbilicus, each for 16 hours a day. A patch free period of eight hours was provided each day to prevent tachyphylaxis. Premature interruption of therapy was planned to be done in cases of maternal undesirable side effects e.g., persistent headache, dizziness or if pregnancy had to be terminated on account of deteriorating fetal health parameters.

Color Doppler was repeated after three days of patch application (Day 3) and changes in various indices were noted. In all the patients, maternal and fetal monitoring was done. Blood pressure measurement was done twice a day in mild PIH and six hourly in severe PIH and change in it was also noted after the completion of patch therapy. Changes in the Doppler velocity waveforms were studied as the primary outcome. Secondary outcome included gestational age at delivery, mode of delivery, neonatal outcome and maternal effects if any. These outcomes were compared between the two groups.

STATISTICAL ANALYSIS

Analysis was carried out using SPSS (Statistical Package for Social Studies) for Windows version 20.0 and online GraphPad software (Prism 5 for Windows) version 5.01. Pearson's chi-square test was used to evaluate differences between groups for categorized variables. Normally distributed data were presented as means and standard deviation or 95% Confidence Intervals (CI). Student's t-test for independent samples was used for comparison between cases and controls. All tests were performed at a 5% level of significance, thus an association was significant if the p-value was less than 0.05.

RESULTS

[Table/Fig-2] demonstrates the base line characteristic of cases and controls. In our study, parity and gestational age at enrollment was comparable in both the groups.

Parameters		Group 1 (n= 40)	Group 2 (n= 40)	p-value
*Age (yrs.)		25.98±4.74	26.48±4.95	0.646
*BMI (Kg/m^2)		26.52±5.04	26.44±5.22	0.949
**Residential status (%)	Rural	60	52.5	0.499
	Urban	40	47.5	
**BP on admission (%)	Normotensive	40	45	0.411
	Hypertensive	60	55	

[Table/Fig-2]: Demographic profile and baseline clinical characteristics among cases and controls at the time of inclusion in study.
*Mean±SD was used ** chi- square test was used

Uterine artery para-meters	Group 1 (n=40) mean±SD (95%CI)		p-value	Group 2 (n=40) mean±SD (95%CI)		p-value
	Day 1	Day 3		Day 1	Day 3	
S/D	3.35±0.16 (3.29-3.40)	3.07±0.52 (2.90-3.24)	0.001	3.33±0.16 (3.28-3.38)	3.34±0.16 (3.29-3.39)	0.242
PI	1.35±0.18 (1.25-1.39)	1.04±0.14 (1.11-1.25)	0.001	1.35±0.16 (1.23-1.37)	1.37±0.16 (1.25-1.39)	0.142
RI	0.68±0.05 (0.66-0.69)	0.54±0.10 (0.51-0.57)	0.001	0.69±0.06 (0.67-0.71)	0.70±0.06 (0.68-0.72)	0.065

[Table/Fig-3]: Effect of NTG on various uterine artery doppler parameters.
RI=Resistivity index, PI=pulsatility index and S/D= systolic and diastolic ratio paired student's t-test have been used.

[Table/Fig-3] shows significant decrease in Mean S/D ratio and PI, RI of the uterine artery in NTG patch therapy group during the study period.

Umbilical artery para-meters	Group 1 (n=40) (mean±SD) (95%CI)		p-value	Group 2 (n=40) (mean±SD) (95%CI)		p-value
	Day 1	Day 3		Day 1	Day 3	
S/D	3.92±3.26 (2.88 - 4.96)	3.73±3.30 (2.67 - 4.79)	0.001	3.90±3.27 (2.85 - 4.95)	3.91±3.26 (2.87 - 4.95)	0.795
PI	1.32±0.21 (1.25-1.39)	1.18±0.21 (1.11-1.25)	0.001	1.30±0.21 (1.23-1.37)	1.32±0.22 (1.25-1.39)	0.062
RI	0.73±0.06 (0.71-0.75)	0.64±0.07 (0.62-0.66)	0.001	0.73±0.06 (0.71-0.75)	0.72±0.06 (0.70-0.74)	0.134

[Table/Fig-4]: Effect of NTG on various umbilical artery doppler parameters.
RI=Resistivity index, PI=pulsatility index and S/D= systolic and diastolic ratio paired student's t-test have been used.

[Table/Fig-4] shows a significant decrease in mean S/D ratio, PI and RI of umbilical artery in NTG patch therapy group from Day 1 to Day 3.

No significant change was observed in mean fetal Middle Cerebral Artery (MCA) S/D ratio throughout the study period [Table/Fig-5] in both the groups.

The mean±SD ratio of the SBP of all the 40 women in the group 1 was 136.25±16.51 mmHg on Day 1 and 130.30±14.14 mmHg on Day 3. The difference was significant statistically (p<0.01). In contrast, there was a rise in mean systolic BP of women in group 2.

Middle cerebral artery parameters	Group 1 (n=40) (mean±SD) ((95%CI)		p-value	Group 2 (n=40) (mean±SD) ((95%CI)		p-value
	Day 1	Day 3		Day 1	Day 3	
S/D	3.87±0.53 (3.70-4.04)	3.86±0.54 (3.69-4.03)	0.071	3.84±0.47 (3.69-3.99)	3.83±0.47 (3.68-3.98)	0.081
PI	1.18±0.26 (1.09-1.26)	1.17±0.26 (1.09-1.25)	0.08	1.17±0.13 (1.13-1.21)	1.16±0.13 (1.11-1.20)	0.50
RI	0.62±0.11 (0.58-0.66)	0.61±0.11 (0.57-0.65)	0.08	0.60±0.10 (0.57-0.63)	0.60±0.11 (0.56-0.64)	0.299

[Table/Fig-5]: Effect of NTG on various middle cerebral artery doppler parameters. RI=Resistivity index, PI=pulsatility index and S/D= systolic and diastolic ratio paired student's t-test have been used.

Mean diastolic BP in group 1 was 89.55±12.29 mmHg on Day 1 and 87.93±11.59 mmHg on Day 3. This fall in DBP was significant statistically (p<0.01). However, there was no significant difference in DBP in control group.

Out of 40, 25 women (62.5%) in case group delivered normally, 15 women (37.5%) delivered by caesarean section. Of these, one woman (3.33%) whose color Doppler showed absent diastolic flow in umbilical artery already had severe IUGR with severe oligohydramnios had intrauterine death which was then delivered vaginally. All other infants born had uneventful perinatal outcome. In group 2 patients, only 11 (27.5%) patients delivered vaginally, while remaining 29 (72.5%) patients required caesarean section, fetal distress being the indication in majority of cases. Of these, 1 woman (3.33%) had intrauterine death, while neonates of two other women had resuscitation failure.

In case group, 14 (35%) patients delivered at <37 weeks and rest 26 (65%) delivered after 37 weeks gestation i.e., at term. But in controls, 23 (57.5%) women had preterm delivery and 17 (42.5%) delivered at term. This reduction in rate of preterm deliveries in NTG patch group is significant (p=0.044). No significant difference was seen in the mean birth weight and Apgar score at 1 minute and 5 minute between both the groups. In group 2, total of 33 (82.5%) neonates got admitted in NICU after delivery whereas only 26 (65%) neonates of patients in group 1 were transferred to NICU. This decrease in the rate of NICU admission is statistically significant (p= 0.045). On the similar pattern, duration of nursery stay was also significantly less in neonates of group 1 women. Mean duration of nursery stay in group 1 was 5.55±6.33 days while in group 2, it was 8.60±7.792 days. This difference is significant statistically (p=0.05).

Out of total 40 women in group 1 on whom NTG patch was applied, 22 (55%) experienced the various side effects of the NTG patch. Out of these, 16 (40%) had headache which started 5-7 hours after application. One woman (2.5%) out of them also experienced nausea and vomiting. Two women had only vomiting. Two (5%) women had mild itching after patch application.

DISCUSSION

Conditions with chronic placental insufficiency like PIH and FGR are common causes of increased risk to both mother and fetus. Very high antenatal blood pressure, visual disturbance, seizures, growth retardation, prematurity, scanty liquor amnii, accidental haemorrhage and traumatic delivery, all contribute to dismal perinatal and maternal morbidity and mortality.

Recognition of serious perinatal risks has led to clinician's intense interest in ultrasonographic diagnostic modalities, biochemical evaluation and clinical management protocols. Accurate diagnosis, proper and timely management can result in significant reduction in both perinatal morbidity and mortality. Several regimens were tried in attempt to arrest the progression of disease, allow pregnancy to continue safely, keep the fetal well being and modify the perinatal outcome in pregnancies complicated by various types and severities of preeclampsia and FGR. One of these regimens was the use of antihypertensive agents e.g., methyldopa and beta blockers. However, inspite of the reduction of the maternal blood pressure either they have no beneficial effect on fetal growth or have adverse effect on it. Recently, nitric oxide pathway represents a new approach to the physiology of pregnancy and to the pathophysiology of placental insufficiency. Moreover, many authors consider nitric oxide donors as new promising therapeutic agents in preeclampsia and FGR. NO is potent vasodilator and inhibitor of platelet aggregation [5].

Clinical significance of FGR due to its high incidence and associated adverse obstetric outcome in our country encouraged us to carry out this study.

Uterine Artery

A significant decrease was observed in the mean S/D ratio and PI. PI of the uterine artery in NTG patch therapy group during the study period [Table/Fig-3] pointing out that the blood flow in the uterine artery is highly increased after NTG patch treatment which can be beneficial in high risk women significant decrease in the mean RI of uterine artery in case group suggest increased uteroplacental circulation. In control group however, no significant change was observed in the mean PI and RI throughout the study period.

In a study done by Cacciatore B et al., with NO donor patch therapy on the uterine blood flow velocity waveform of pre-eclamptic women at mid-gestation, RI was significantly reduced. The uterine PI decreased significantly. The bilateral notch present at baseline levelled out during NTG in 60% women. In addition, PI and RI returned to pre-treatment values within 12 hours after removal of the last patch suggesting the specificity of the nitroglycerine effect [6]. Similar results were observed in a study conducted by Nakatsuka M et al., where a diastolic notch in the uterine artery flow velocity waveform, diminished or became smaller during administration of Isosorbide Dinitrate (ISDN). The PI was significantly reduced by treatment [7]. As shown by a study performed by Dawoud MF et al., there was significant decrease in S/D ratio (p<0.05) and RI (p<0.05) of uterine artery in preeclamptic subgroup treated with NTG patches compared to preeclamptic subgroup undergone expectant treatment [8]. Thaler I et al., conducted a study in which a decrease in the mean S/D in the uterine artery was observed and in seven of 12 women with an early diastolic notch in the uterine artery flow velocity waveform the notch diminished or disappeared. No significant changes were observed in the placebo group [9]. Hence, our study showed the comparable effect of nitroglycerine on uterine artery waveforms, S/D, PI and RI with these studies.

Umbilical Artery

In the present study, a significant decrease was observed in mean S/D ratio, PI and RI of umbilical artery in NTG patch therapy group from Day 1 to Day 3 [Table/Fig-4] indicating improvement in uterine blood flow leading to decrease in distress level to the fetus.

Similarly, mean SD ratio, PI and RI in the umbilical artery was comparable in both Groups 1 and 2 at the start of the study. Significant difference occurred in RI after three days of study (p= 0.001). But no significant difference was found in SD ratio and PI between Group 1 and 2.

In another study done on five pregnant women using glyceryl trinitrate, umbilical artery S/D ratio decreased from baseline by 17% at 10 minutes; after 20 minutes, the mean reduction was 21% (p<0.006), with return to baseline after 30 minutes of removal of glyceral trinitrate [10].

ISDN patch therapy significantly reduced the increased RI values of the umbilical artery in preeclamptic women without any change in systemic blood pressures, but the RI values of the uterine artery were not significantly attenuated. This change in RI values might be due to the improvement of end-diastolic flow velocity [11].

In an another study done by Nakatsuka M et al., it is stated that the normal umbilical artery third trimester S/D ratio is 2.5±0.4 with

cut off value of 3 and PI is 0.89±0.12 with cut off value of 1.1. The utilization of nitroderm patches significantly reduced the umbilical artery S/D ratio and PI [12].

In a study done by Grunewald C et al., on 12 women with singleton pregnancies with PIH with or without IUGR using nitroglycerine infusion, the umbilical artery PI decreased significantly (p<0.01), with more pronounced decrease in women with high basal value [13]. As shown by a study conducted by Nakatsuka M et al., the PI in the umbilical artery was significantly reduced by treatment with NO donors with p-value <0.004 [7]. Similar results were observed in studies done on preeclamptic women by Dawoud MF et al. and Thaler I et al. [8,9].

In our study also, there was reduction in S/D ratio, PI and RI of umbilical artery and this was comparable to previous studies. Reduction of the uterine or umbilical artery indices suggests that nitroglycerine improves fetoplacental circulation. We speculate that at least three beneficial biological effects of NO were involved in the improvement of fetoplacental circulation that we observed. The first was vascular relaxation, as noted in the uterine artery, UA and the placental vasculature [14-18]. Because endothelial cells, which are major sources of NO, are known to be injured in preeclamptic women, NO donors may assume the role of the impaired NO synthesis in the vascular vessels of these patients. The second effect was relaxation of the smooth muscle of the uterus [19,20]. Mild uterine contraction is often complicated by preeclampsia. Uterine contraction causes direct compression of the umbilical cord and chronic disturbance of fetoplacental circulation. The third effect was prevention of microthrombosis in fetoplacental circulation. It is known that platelet activation occurs in healthy pregnancy and is more pronounced in preeclampsia [21]. Nitric oxide is known to inhibit activation of platelets and adhesion of leukocytes to the endothelial surface and it may prevent thrombosis in a preeclamptic mother and in the fetus despite high viscosity and a high haematocrit level [22,23].

Middle Cerebral Artery (MCA)

No significant change was observed in mean fetal MCA S/D ratio throughout the study period [Table/Fig-5] in both the groups implicating that transdermal administration of nitroglycerine caused no change in the impedance to flow in the fetal middle cerebral artery, which is most sensitive to hypoxemia. The mean PI and RI showed a statistically insignificant decrease in both the groups after NTG patch application.

Few other studies also observed the similar results for MCA Doppler velocimetry as in our study [6,12]. Nakatsuka M et al., conducted a study in which it was found that no significant changes occored in the PI in the MCA but the ratio of the PI of the umbilical artery over the PI of the MCA, which also indicates fetal hypoxia, was significantly reduced by treatment with transdermal ISDN (p<0.003) [7].

So, there has been consistent opinion regarding no effect on fetal MCA S/D, PI and RI after NTG therapy. This might be explained by the fact that the disappearance of brain sparing effect precedes the fetal death and is very critical to the fetus. At the start of our study, majority of patients had no significant alteration in fetal MCA indices on color Doppler. Also, on the basis of uterine and umbilical artery Doppler, obstetrical intervention is usually carried out much before this effect could have occurred. [Table/Fig-6] showing various studies on effect of NTG on Doppler parameters.

Systolic Blood Pressure (SBP)

In our study, mean±SD ratio of the SBP of all 40 women in Group 1 was 136.25±16.51 mmHg on Day 1 and 130.30±14.14 mmHg on Day 3. This fall in SBP is highly significant statistically. In contrast, there was a rise in the mean SBP of women in group 2. Cacciatore B et al., did a study in which the SBP fell from 150±12 mmHg to 143±8 mmHg with p-value <0.01 after 12 hours of treatment with NTG patch. The SBP remained at this level until last patch was removed [6]. In studies done by Nakatsuka M et al., and Grunewald C et al., the SBP of women was significantly suppressed during treatment [7,13]. Hartung J et al., did a study constituting severe preeclampsia group using glyceryl trinitrate in which it observed significant reduction in SBP (p<0.05) [4]. The decrease in SBP with nitroglycerine in our study is comparable to all the above quoted studies.

Diastolic Blood Pressure (DBP)

In the present study, mean diastolic BP in NTG patch therapy group was 89.55±12.29 mmHg on Day 1 and 87.93±11.59 mmHg on Day 3. This fall in DBP is highly significant statistically (p-value<0.001). At the same time, there was no significant difference in DBP in control group. The results of our study was comparable with a few other studies which also observed significant reduction in DBP after transdermal NTG administration [7,9,24]. However, in a study by Cacciatore B et al., no significant decrease was observed in mean diastolic BP after NTG patch on patients [6]. But since this is in contradiction to almost all other studies, we can attribute it to the small sample size. In agreement with our results, a study stated that nitric oxide donors reduce the mean maternal blood pressure by affecting both SBP and DBPs; platelet activation and improved haematology, liver biochemistry and liver functions with significant improvement in the uteroplacental and fetoplacental blood flow [12]. Thus nitric oxide donors may be beneficial in the management of preeclampsia as they have a relatively greater vascular than anti-platelet action and reduces blood pressure without affecting uterine artery perfusion.

Perinatal Outcome

Relative reduction was observed in the rate of caesarean section in Group 1 i.e., after NTG patch application as compared with controls. Similar observations were made in some other studies also [6,7]. This was presumably because uncontrollable maternal hypertension and fetal distress were prevented. But, in another study by Dawoud MF et al., there was no statistically significant difference between the gestational age at the time of onset of labour, mode of delivery or neonatal weight after birth in both the groups (preeclamptic women on nitroderm and preeclamptic women on expectant treatment) [8].

In the present study, significant reduction in rate of preterm deliveries in NTG patch group is observed. No significant difference was seen in the mean birth weight and Apgar score at delivery between both the groups. But nursery admissions as well as nursery stay were reduced significantly in neonates of NTG group which may be attributable to the decreased rate of preterm deliveries in NTG therapy group.

Thus, the perinatal outcome in the present study corroborated with similar studies done in the past [6,7]. Although, immediate perinatal outcome (mean birth weight and apgar score) were similar in both the groups, the beneficial effect of NTG on uteroplacental flow and improved fetal growth may be evident in the neurological and behavioural outcome on long term clinical follow up of these children. The clinical efficacy of transdermal NO donor could not be determined, as a larger scale controlled study will be required to evaluate the effect on clinical outcome properly.

Side Effects

Out of total 40 women in group 1 on whom NTG patch was applied, 22 (55%) experienced the various side effects of the NTG patch. Out of these, 16 had headache which started five to seven hours after application. Of these seven required oral analgesics in the form of paracetamol for first day but the headache decreased in intensity on second and third day and did not necessitate analgesics further. One woman experienced severe headache for three days and higher analgesics like oral tramadol was needed to relieve her symptoms. She (2.5%) also experienced nausea and vomiting

Authors	No. of patient	Duration and Route	Patient Profile	Uterine Artery	Umbilical Artery	MCA Artery
Cacciatore B et al., [6]	17	• 3 days • transdermal	Preeclampsia and IUGR	S/D(not observed) PI ↓ RI ↓	No change	No change
Nakatsuka M et al., [12]	4	• 4-16 days • transdermal	Preeclampsia with/ witout IUGR/ oligohydramn-ios	S/D(-) PI ↓ RI↓	S/D(-) PI ↓ RI↓	No change
Current study	40	• 3 days • transdermal	IUGR with/ without PIH	S/D↓ PI ↓ RI↓	S/D↓ PI ↓ RI↓	No change

[Table/Fig-6]: Effect of nitroglycerine on Doppler parameters in various studies.

which necessitated antiemetic for one day. Two women had only vomiting. Two women had mild itching after patch application. But in all the 22 women, all the side effects were tolerable and controlled with medication. This did not necessitate the discontinuation of the patch therapy. Similar side effects were observed in a study performed by Cacciatore B et al., also [6]. In another study by Nakatsuka M et al., except mild temporary headache in four of the 12 women no other side effects were observed when treated with ISDN [7]. So, unlike other antihypertensive agents, continuously released low doses of NO from NTG patch may limit acute side effects such as hypotension, which causes insufficient blood flow to the uterus leading to fetal distress. However, it is still possible that NO donors may cause bleeding tendency and may cause placental injury due to the formation of peroxynitrite, a potent antioxidant formed by reaction of NO and a superoxide anion [8]. They may also cause inadequate uterine contraction during delivery and in the puerperium. Although we did not observe any of these side effects, women must be closely monitored for them.

LIMITATION

The clinical efficacy of transdermal NO donor could not be determined, as a larger scale controlled study will be required to evaluate the effect on clinical outcome properly.

CONCLUSION

Transdermal nitroglycerine caused a significant reduction in the impedance to flow in the uterine artery and umbilical artery. It also caused significant fall in both mean systolic and diastolic BP. The therapeutic approach of NO donor administration via transdermal route in pregnant patients with chronic placental insufficiency, apparently improved both maternal and fetoplacental haemodynamics, thus may help in improving perinatal outcome. This promising therapeutic protocol may be validated by larger series with randomised controlled trials to offer any recommendation for the use of the nitroglycerine patch in routine clinical practice.

REFERENCES

[1] Sladek SM, Magness RR, Conrad KP. Nitric oxide and pregnancy. Am J Phsyiol. 1997;272:441-63.

[2] Ramsay B, Sooranna SR, Johnson MR. Nitric oxide synthase activities in human myometrium and villous trophoblast throughout pregnancy. Am J Obstet Gynecol. 1996;87:249-53.

[3] Bhatt CJ, Arora J, Shah MS. Role of color doppler in pregnancy induced hypertension (a study of 100 cases). Indian J Radiol Imaging. 2003;13:417-20.

[4] Hartung J, Kalache KD, Heyna KS, Kuhling M, Wauer R, Bollmann R, et al. Outcome of 60 neonates who had ARED flow prenatally compared with a matched control group of appropriate-for-gestational age preterm neonates. Ultrasound Obstet Gynecol. 2005;25:566-72.

[5] Jouppila P, Rasanen J, Alahuhta S, Jouppila R. Vasoactive drugs in obstetrics: a review of data obtained by Doppler and color Doppler methods. Hypertens Pregnancy. 1995;14:261-75.

[6] Cacciatore B, Halmesmaki E, Kaaja R, Teramo K, Ylikorkala O. Effects of transdermal nitroglycerin on impedance to flow in uterine, umbilical, and fetal middle cerebral arteries in pregnancies complicated by preeclampsia and intrauterine growth retardation. Am J Obstet Gynecol. 1998;179:140-45.

[7] Nakatsuka M, Takata M, Tada K, Asagiri K, Habara T, Noguchi S, et al. A long term trandermal nitric oxide donor improves uteroplacental circulation in women with preeclampsia: Am J ultrasound Med. 2002;21:831-36.

[8] Dawoud MF, Salim H, Saied AF. Maternal and fetal evaluation in patients with preeclampsia managed by transdermal nitroglycerine patch. Tanta Medical Sciences Journal. 2007;2:240-53.

[9] Thaler I, Amit A, Kamil D, Itskovitz-Eldor J. The effect of isosorbide dinitrate on placental blood flow and maternal blood pressure in women with pregnancy induced hypertension. Am J Hypertens. 1999;12:341–47.

[10] Giles W, O'Callaghan S, Boura A, Walters W. Reduction in human fetal umbilical-placental vascular resistance by glyceryl trinitrate. Lancet. 1992;340:856.

[11] Makino Y, Izumi H, Makino I, Shirakawa K. The effect of nitric oxide on uterine and umbilical artery flow velocity waveform in pre-eclampsia. 1997;73:139-43.

[12] Nakatsuka M, Tada K, Kimura Y, Asagiri K, Kamada Y, Takata M, et al. Clinical experience of long term transdermal treatment with nitric oxide donor for women with preeclampsia. Gynecol Obstet Invest. 1999;47:3-19.

[13] Grunewald C, Kublickas M, Carlstrom K, Lunell NO, Nisell H. Effects of nitroglycerine on the uterine and umbilical circulation in severe preeclampsia. Am J Obstet Gynecol. 1995;86:600-04.

[14] Wheeler AS, James FM III, Meis PJ, Rose JC, Fishburne JI, Dewan DM, et al. Effects of nitroglycerin and nitroprusside on the uterine vasculature of gravid ewes. Anesthesiology. 1980;52:390–94.

[15] Pinto A, Sorrentino R, Sorrentino P, Guerritore T, Miranda L, Biondi A, et al. Endothelial-derived relaxing factor released by endothelial cells of human umbilical vessels and its impairment in pregnancy-induced hypertension. Am J Obstet Gynecol. 1991;164:507–13.

[16] Izumi H, Garfield RE, Makino Y, Shirakawa K, Itoh T. Gestational changes in endothelium-dependent vasorelaxation in human umbilical artery. Am J Obstet Gynecol. 1994;170:236–45

[17] Myatt L, Brewer A, Brockman DE. The action of nitric oxide in the perfused human fetal-placental circulation. Am J Obstet Gynecol. 1991;164:687–92.

[18] Yallampalli C, Garfield RE, Byam-Smith M. Nitric oxide inhibits contractility during pregnancy but not during delivery. Endocrinology. 1993;133:1899-902.

[19] Lees C, Campbell S, Jauniaux E, Brown R, Ramsay B, Gibb D, et al. Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. Lancet. 1994;343:1325–26.

[20] Leszczynska-Gorzelak B, Laskowska M, Marciniak B, Oleszczuk J. Nitric oxide for treatment of threatened preterm labor. Int J Obstet Gynaecol. 2001;73:201-06.

[21] Hardy E, Rubin PC, Horn EH. Effects of nitric oxide donors in vitro on the arachidonic acid-induced platelet release reaction and platelet cyclic GMP concentration in pre-eclampsia. Clin Sci (Lond). 1994;86:195–202.

[22] Nakatsuka M, Osawa Y. Selective inhibition of the 12-lipoxygenase pathway of arachidonic acid metabolism by L-arginine or sodium nitroprusside in intact human platelets. Biochem Biophys Res Commun. 1994;200:1630–34.

[23] Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogeneous modulator of leukocyte adhesion. Proc Natl Acad Sci USA. 1991;88:4651–56.

[24] Cetin A, Yurtcu N, Guvenal T, Imir AG, Duran B, Cetin M. The effect of glyceryl trinitrate on hypertension in women with severe preeclampsia, HELLP syndrome and eclampsia. Hypertens Pregnancy. 2004;23:37-46.

PARTICULARS OF CONTRIBUTORS:

1. Medical Officer, Department of Obstetrics and Gynaecology, Safdurjung Hospital, Delhi, India.
2. Professor, Department of Obstetrics and Gynaecology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India.
3. Professor, Department of Radiodiagnosis, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India.
4. Professor and Head of Department, Department of Obstetrics and Gynaecology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Suruchi Gupta,
Medical Officer, Department of Obstetrics and Gynaecology, Safdurjung Hospital, Delhi-110029, India.
E-mail: drsuruchi87@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **May 15, 2016**
Date of Peer Review: **Jul 06, 2016**
Date of Acceptance: **Nov 14, 2016**
Date of Publishing: **Jul 01, 2017**