

ORIGINAL ARTICLE

Use of Nitroglycerine Patch in the Management of Preterm Labor

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ABSTRACT

Background: Preterm birth is the delivery of the baby before 37 completed weeks of pregnancy. The goal of tocolytic therapy is to reduce neonatal mortality and morbidity by delaying birth, allowing for corticosteroid administration and maternal transfer to the tertiary care center. This study was conducted to observe the tocolytic efficacy of GTN transdermal patches in preterm labor between 28 – 36 weeks of pregnancy.

Methods: This cross-sectional study was done in Obstetrics & Gynecology Department at Mufti Mehmood Memorial Hospital, Dera Ismail Khan, from July 2017 to December 2017. Non-probability consecutive samplings of 186 pregnant women with preterm labor were included in the study. Detailed history and examination, routine investigations and ultrasound were performed to confirm viability, gestational age and exclusion of multiple pregnancies, lethal fetal malformation and intrauterine death. Effectiveness of the GTN patch was considered successful if the cessation of uterine contraction occurred within 24 hours of the application of the GTN patch and persisted for 48 hours to achieve the effect of steroids.

Results: Tocolytic efficacy of GTN transdermal patch in preterm labor between 28 to 36 weeks of pregnancy was 88.71%. Regarding the parity of the women, 75.8% of women had multipara (parity 2 to 5) and 24.2% had primipara. The average gestational age was 33.15±2.28 weeks. Two to three uterine contractions per 10 minutes were observed in 75.8% of women while four uterine contractions per 10 minutes were observed in 24.19% of cases. 2cm cervical dilatation was observed in 82 women (44.09%) and 3cm was 75 women (40.32%).

Practical implication: The incidence of preterm delivery can be minimized using GTN patch to reduce the uterine contractions and increase the fetal viability inside the womb.

Conclusion: There is no better incubator than a mother's womb. The GTN patch appears to be a safe, non-invasive method of suppressing uterine contractions in pre-term labor and also a simple, quicker and cost-effective tocolytic agent.

Keywords: Pre-term labor; Tocolytic; Transdermal patch; Uterine contractions.

INTRODUCTION

Preterm birth is the delivery of the baby before 37 completed weeks of pregnancy. The incidence of preterm birth in the developed world is between 7 % and 12 %¹. Wide-scale National data is lacking in this respect to show the incidence in our country². The Preterm Birth, the leading cause of neonatal morbidity and mortality, is a major contributor to loss of life, long-term disability and health care costs. For children born before 37 weeks, 25% and 45% respectively; require special education³. According to the Pakistan Demographic and Health Survey (PDHS) 2006 – 2007 perinatal mortality rate is 159/1000 pregnancies & prematurity is a major contributor. One study in Civil Hospital Karachi found 77 % of perinatal deaths are in preterm and 23 % in term pregnancies⁴.

The goal of tocolytic therapy is to reduce neonatal mortality and morbidity by delaying birth, allowing for corticosteroid administration and maternal transfer to tertiary care center⁵. Available tocolytics like betamimetics, have proven efficacy, but they have potentially serious side effects like cardiac arrhythmia and hypokalemia in the mother & affect fetal heart rate, prostaglandin synthesis inhibitor (indomethacin) is also effective but with fetal side effects like premature closure of ductus arteriosus after 32 weeks, Ca Channel Blockers like nifedipine is safe and effective but dangerous in women with cardiovascular disease, magnesium sulfate is an ineffective tocolytic agent with adverse outcome, oxytocin receptor antagonist atosiban is effective but expensive, difficult to administer and not universally available. Glyceryl trinitrate (GTN) transdermal patches have the attraction of convenience, potential effectiveness, low cost and few side effects⁶. Several studies have reported varying degrees of success with this approach of tocolysis^{7,8}. The pharmacological active principle of Glyceryl trinitrate is nitrous oxide, which is an important mediator of relaxation of various smooth muscles including vascular, gastrointestinal and urogenital. Few studies were done in Pakistan which represent the patients of urban areas, One was in Karachi shows that around 46% of pregnant women at 28-34 weeks of gestation with preterm labor had complete cessation of

uterine contraction within 24 hours and 64% had successful tocolysis of 48 and more than 48 hours, while in Lahore, 14% of the pregnant women responded after application of single patch while 86% responded after second patch^{8,9}. Commonly used tocolytic agents, betamimetics and calcium channel blockers have proven efficacy but have potential side effects like cardiac arrhythmia, hypokalemia, and dizziness hypotension in mothers while the GTN patch is free of many side effects. GTN patch can also be used in patients when preterm labor is associated with diabetes, hypertension, pulmonary edema, or arrhythmia in the mother⁹. Despite this, the GTN patch is not being practiced all over Pakistan, although two studies have been conducted locally with inadequate sample sizes.

In our study area, most of the patients belonged to rural areas. They were mostly anemic (Hb<7g/dl) and they were not screened for cardiovascular diseases (arrhythmia, hypertension) and diabetes. The present study is the first-ever study with an adequate sample size (186) that will help to determine the tocolytic capability and efficacy of GTN transdermal patches in preterm labor between 28 – 36 weeks of pregnancy.

MATERIAL AND METHODS

Study Location and Time Period: This cross-sectional study was conducted in Obstetrics and Gynecology unit in Mufti Mehmood Memorial Hospital, Dera Ismail Khan, from July 2017 to December 2017. A non-probability consecutive sampling of 186 pregnant women with preterm labor was included in the study.

Inclusion and Exclusion Criteria: All pregnant women with preterm labor of age(20 – 40) & parity (primi and multigravida) between 28 – 36 weeks of gestation (based on 1st-trimester ultrasound) with 2 – 4 uterine contractions / 10 minutes and cervical dilation < 4 cm presenting to Obstetrics & Gynecology unit in MMM Hospital were included in the study. Females with multiple gestations, ruptured membrane, intrauterine fetal demise, suspected lethal fetal anomalies, known sensitivity to GTN, Cervical dilatation > 4cm, and maternal or fetal condition

necessitating delivery (severe pre-eclampsia, eclampsia, fetal distress) were excluded.

Study Design: All the patients with preterm labor were admitted to Obstetrics & Gynecology Department at MMM Hospital. Detailed history and examination were taken by the researcher herself and the patient was selected for the study. Written informed consent was obtained from the patients. All the routine investigations were sent, ultrasound was performed to confirm viability, gestational age and exclusion of multiple pregnancies, lethal fetal malformation and intrauterine death. Cervical dilatation was assessed by digital vaginal examination.

Selected subjects received 500 ml normal saline infusion over 30 minutes as prophylaxis against potential GTN-induced hypotension and Betamethasone (12 mg intramuscular 24 hours x 2) was administered to all patients who had not received corticosteroid. A 10 mg of transdermal GTN patch was applied on the anterior abdominal wall and replaced by a second patch of the same dose after 24 hours (if contraction did not cease the second patch can be repeated after 12 hours if required). Maternal blood pressure was monitored every 15 minutes for 1 hour & every 4 hours thereafter. Fetal heart rate & contraction of the uterus was monitored and data was obtained through the attached Performa. The effectiveness of GTN patch was considered successful if the cessation of uterine contraction occurred within 24 hours of the application of the GTN patch & persisted for 48 hrs to achieve the effect of steroids. The variables in my study were age, parity, gestational age, number of uterine contractions (assessed on clinical basis), cervical dilatation, and number of patches, duration of tocolysis (hours) and efficacy.

Statistical Analysis: After the collection of data, the analysis was conducted by using Statistical Package for Social Science (SPSS) software, Version 16. Frequency and percentage were calculated for qualitative variables like several uterine contractions, cervical dilatation, no of patches, duration of tocolysis and efficacy of the drug to stop the uterine contractions for > 48 hrs. Mean and standard deviation was computed for age, gestational age and parity. Stratification was done concerning maternal age, parity, gestational age, and cervical dilatation and no patches were done to see the effect of these outcome variables and a post-stratification chi-square test was applied to see a significant difference. P-value < 0.05 was taken as significant.

RESULTS

There were 186 pregnant women with preterm labor according to including criteria selected in this study. The average age of the women was 30.46±5.24 years. The average gestational age was 33.15±2.28 weeks and the distribution of gestational age is shown (Figure 1; Table 1). Regarding the parity of the women (p< 0.05), 75.80% of women had multipara (parity 2 to 5) and 24.19% had primipara (Figure 2), (Table 2). Two to three uterine contractions per 10 minutes were observed in 59.67% of women while four uterine contractions per 10 minutes were observed in 40.32% of cases. 2cm cervical dilatation was observed in 81 women (43.54%) and 3cm was 105 women (56.45%) (Table 3). In 11.82% of pregnant women only a single patch of 10 mg was used but the majority of the women 88.18% responded after the application of 2nd patch (Figure 3). 43.44% of pregnant women at 28-34 weeks of gestation with preterm labor had complete cessation of uterine contraction within 24 hours and 25.27% had successful tocolysis of 24 to 48 hours and 11.29% had more than 48 hours (Table 4). According to the operational definition, the tocolytic efficacy of GTN transdermal patch in preterm labor between 28 to 36 weeks of pregnancy was 88.71%.

Stratification analysis was also performed; the efficacy of GTN transdermal patch in preterm labor was 43.6% in ≤ 30 years of age and 56.4% above 30 years of age (p< 0.05). A significant difference was not observed in the efficacy of GTN between age groups (p=0.24). GTN transdermal patch in preterm labor was 13.3% of the pregnant women responded after the application of a

single patch while 86.7% responded after the second patch (p=0.018).

Table 1: Age-wise description of the participating women

S. No	Variable	Range	Mean+SD
1	Age (Years)	27-45	30.46+5.24
2	Gestational Age (Weeks)	29-39	33.15+2.28

Table 2: Parity-wise description of the women

S. No	Parity	Number of cases (n)	Frequency (%)	p-value
1	Primipara	45	24.19	0.00001* (Significant)
2	Multipara	141	75.80	

Table 3: Uterine contractions and cervical dilations in the patients

S. No	Study Parameters	Number of subjects (n) Range	Frequency (%)	p-value
1	Uterine contractions 2-3 contractions/ 10 mins	111	59.67	0.00001* (Significant)
		75	40.32	
2	Cervical dilation < 2 cm	81	43.54	0.1775 (Non-significant)
		105	56.45	

Table 4: Application of GTN patches for ceasing uterine contractions

S. No	GTN Patch	Ceased uterine contractions	Patients (n)	Frequency (%)
1	1 st patch	24-48 hours	22	11.82
2	2 nd patch	24-48 hours	164	88.18

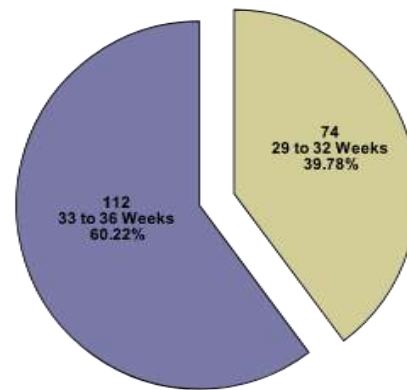


Figure 1: Gestational age of the women

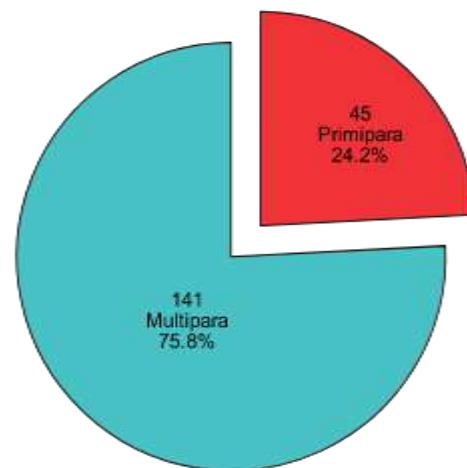


Figure 2: Parity distribution of the women

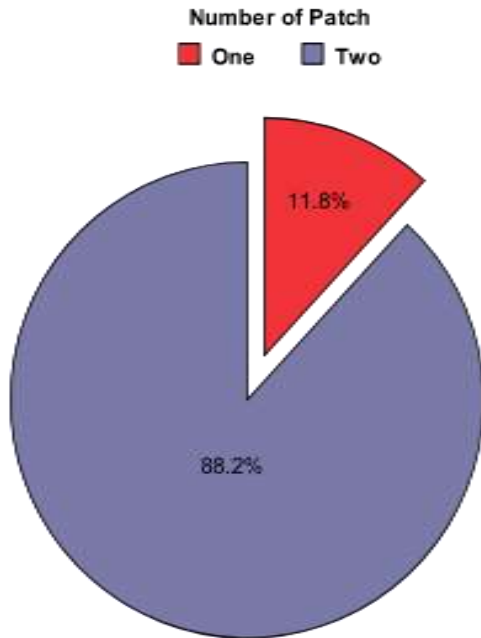


Figure 3: Number of patches applied to the women to cease uterine contractions

DISCUSSION

Delaying the delivery has two-fold benefits: one is to get enough time to complete the course of antepartum glucocorticosteroids to reduce the incidence and severity of respiratory distress syndrome while arranging for in-utero transfer to a center with services for dealing with even extreme prematurity, and the second benefit is to reduce the prenatal mortality and morbidity associated with severe prematurity. The main aim of tocolytic therapy is to improve prenatal outcomes by suppressing preterm labour¹⁰⁻¹². Tocolytic drugs have been tried for a long and even glyceryl trinitrate (GTN) is not a new drug as more than 100 years ago nitric oxide donor was used in pregnancy and was first reported in the British Medical Journal¹³. Glyceryl trinitrate is convenient in its application and cost-effective also. GTN skin patches have the attraction of convenience, potential effectiveness, low cost & few side effects. Several studies have reported varying degrees of success with this approach of tocolysis¹⁴⁻¹⁵. It is a vasodilator that is essential for the maintenance of normal smooth muscle tone of the uterus. There is now considerable evidence that nitric oxide is involved in the regulation of myometrial contractility during pregnancy, where nitric oxide donors have been applied to myometrium in vitro, and inhibition of spontaneous and oxytocin-induced activity was found when amplitude or force of contraction was measured¹⁶. Pregnancy is prolonged by its direct effect on the uterine blood flow¹⁷.

Our findings in 186 pregnant women at 28-36 weeks of gestation were recruited after as per selection criteria with an average age of 30.5 years and median parity of 2. A 10 mg of transdermal GTN patch was applied on the anterior abdominal wall and replaced by a second patch of the same dose after 24 hours 86.7% responded after the second patch. Our findings were correlated with the study by Affifa Waheed et al, conducted at Ghurki Trust Teaching Hospital, Lahore from (February 10, 2006 - February 10, 2007) where 54% of pregnant women were between G2 - G4. The majority (48%) of the women presented between 31 - 34 weeks of gestation. The majority (86%) responded after the application of the second patch (10 mg glyceryl trinitrate patch).¹⁸

Krishna et al¹⁹ also used a 10mg patch as in my study and Walling²⁰ also used a 10 mg patch and used a second patch after

one hour if there was no reduction in contraction. Most of the pregnant women in this study delivered after 48 hours of tocolysis which was statistically significant and was also supported by Aruna Kumar et al.²¹ who did a prospective study on 100 patients of preterm labor to assess the efficacy of glyceryl trinitrate as tocolytic and concluded delay of delivery for 48 hours was observed in 95% patients. Similar results were also noted in a study conducted by Parveen S et al²² who concluded that 64% had successful tocolysis of 48 and more than 48 hours.

In our study 2cm cervical dilatation was observed in 44.09% and 3cm was 40.32% when cervical dilatation was 2cm, 46.7% of cases had succeeded in reaching 37 weeks and when cervical dilatation was 3cm, 37% of cases had succeeded to reach 37 weeks. Our findings were corroborated with the study conducted in Pune India, in which sixty women admitted with preterm labor were included over 18 months. 60% of cases had succeeded in reaching 37 weeks when cervical dilatation was 1cm, 50% of cases succeeded when was 2cm but at 3 cm, no case had succeeded²³. Similar results were correlated with the findings of Ajay Dhawle et al, where at a cervical dilatation of >3 cm, the mean pregnancy prolongation was only 0.56 days with NTG²⁴

Our study revealed that the maximum prolongation of pregnancy was 35 days, which is comparable with other national and international trials that also supported GTN as effective in delaying delivery²⁵⁻²⁷. Similar results were achieved with GTN, its administration and safety suggested there shall be multicenter comparative trials of GTN with established therapy or placebo involving a larger number of recruited populations.

CONCLUSION

There is no better incubator than a mother's womb. The GTN patch appears to be a safe, non-invasive method of suppressing uterine contractions in pre-term labor and also a simple, quicker and cost-effective tocolytic agent. Current trials with nitric oxide donors may lead to a breakthrough in the treatment of pre-term labor to decrease perinatal mortality.

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