

Efficacy of Glyceryl Trinitrate Transdermal Patch in The Management of Preterm Labour

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Abstract

Objective: To observe the tocolytic efficacy of *Glyceryl trinitrate* transdermal patches in preterm labour between 28 – 36 weeks of pregnancy.

Study duration: Study duration was 6 months January 2014 to June 2014.

Methodology: This descriptive cases series study was conducted at the obstetrics & Gynaecology Department at Peoples Medical University of Medical and Health Sciences for women Nawabshah. A 10 mg of transdermal GTN patch was applied on the anterior abdominal wall and replaced by the second patch of the same dose after 24 hours (if contraction does not cease the second patch can be repeated after 12 hours if required). The effectiveness of GTN patch was considered successful if the cessation of uterine contraction occurred within 24 hours of the application of GTN patch & persisted for 48 hrs to achieve the effect of steroids. All the data was entered in the proforma.

Results: Total 186 pregnant women with preterm labour were selected. The average age of the women was 30.46 ± 5.24 years. According to the parity of the women, 75.8% women were multipara. Average gestational age was 33.15 ± 2.28 weeks. Tocolytic efficacy of Glyceryl trinitrate transdermal patch in preterm labour was 88.71%. No significant difference was observed in the efficacy of Glyceryl trinitrate according to age groups, parity, gestational age, number of uterine contraction and cervical dilatation.

Conclusion: There is no better incubator than a mother's womb. The Glyceryl trinitrate patch appears to be a safe, non-invasive method of suppressing uterine contractions in pre-term labour.

Key Words: Tocolytic, pre-term labour, GTN transdermal patch.

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Introduction

Preterm birth is a delivery of the baby before 37 completed weeks of pregnancy. The incidence of the 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 country.² 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 cost. For children born before 37 weeks, 25% and 45% respectively; requiring the special education.³ According to the Pakistan Demographic and Health Survey (PDHS) 2006 – 2007 perinatal mortality rate is 159/1000 pregnancies &

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prematurity is a major contributor. One study in Civil Hospital Karachi found 77% perinatal deaths are in preterm and 23% in term pregnancies.⁴

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 centre.⁵ Available tocolytics like betamimetics, have proven efficacy, but they have potential serious side effects like cardiac arrhythmia and hypokalemia in mother & effect on 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 sulphate is ineffective tocolytic agent with adverse outcome, oxytocin receptor antagonist atosiban is effective but expensive, difficult to administration and not universally available. Glyceryl trinitrate (GTN) transdermal patch have the attraction of convenience, potential effectiveness, low cost and few side effects.⁶ Several studies have reported varying degree of success with this approach of tocolysis.^{7,8} The pharmacological active principle of Glyceryltrinitrate is nitrous oxide, which is 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, in one of them around 46% of pregnant women at 28-34 weeks of gestation with preterm labour had complete cessation of uterine contraction within 24 hours and 64% had successful tocolysis of 48 and more than 48 hours, while in another study 14% of the pregnant women responded after application of single patch while 86% responded after second patch.^{8,9} Commonly used tocolytic agents, are betamimetics and calcium channel blockers have proven efficacy but having potential side effects like cardiac arrhythmia, hypokalemia, dizziness hypotension on mother while GTN patch is free of many side effects. GTN patch can also be used in patients when preterm labour is associated with diabetes, hypertension, pulmonary oedema or arrhythmia in mother.⁹ In spite of this, GTN patch is not being practised in all over Pakistan, although two studies have been conducted locally but with inadequate sample size. In our catchment area mostly, the patients received from rural side which are anaemic (Hb<7g/dl) and they are not screened for cardiovascular diseases (arrhythmia, hypertension) and diabetes. The present study is first ever study with

adequate sample size which will help is to check GTN patch as valuable, cost effective & alternative in such type of patients of rural areas.

Methodology

This descriptive cases series study was conducted at the obstetrics & Gynaecology Department at Peoples Medical University of Medical and Health Sciences for women Nawabshah. All pregnant women with preterm labour of age (20–40) and 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 the Obstetrics & Gynaecology Department at PUMHSW Nawabshah were included in the study. All the women with multiple gestations, ruptured membrane, intrauterine fetal demise, suspected lethal fetal anomalies, known sensitivity to GTN, failure to consent, cervical dilatation > 4cm, maternal or fetal condition necessitating delivery (severe pre-eclampsia, eclampsia, fetal distress) were excluded. Detailed history and examination was taken by the researcher herself and patient was selected in 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 were received 500 ml normal saline infusion over 30 minutes as a prophylaxis against potential GTN induced hypotension and Betamethasone (12 mg intramuscular 24 hours x 2) were administered to all patients who had not received corticosteroid. A 10mg of transdermal GTN patch was applied on the anterior abdominal wall and replaced by the second patch of the same dose after 24 hours (if contraction does 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 on predesigned Proforma. The effectiveness of GTN patch was considered successful if the cessation of uterine contraction occurred within 24 hours of the application of GTN patch & persisted for 48 hrs to achieve the effect of steroids. The variables in our study were age, parity, gestational age, number of uterine contractions (assessed on clinical basis), cervical dilatation, and number of patches, duration of tocolysis (hrs) and efficacy.

Data Analysis Procedure: Data was analyzed by spss Version 16. Frequency and percentage were calculated for qualitative variables like a number of age groups, 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 were computed for age and gestational age. Stratification was done with respect to maternal age, parity, gestational age, cervical dilatation and no of patches, chi-square test was applied and P-value <0.05 was taken as significant.

Results

There were 186 pregnant women with preterm labour according to inclusion criteria were selected in this study. The average age of the women was 30.46 ± 5.24 years. According to the parity of the women, 75.8% women were multipara and 24.2% were primipara. Average gestational age was 33.15 ± 2.28 weeks. Two to three uterine contractions per 10 minutes were observed in 75.8% women while four uterine contractions per 10 minutes were observed in 24.19% cases. 2cm cervical dilatation was observed in 82 women (44.09%) and 3cm was 75 women (40.32%). Table I

Table I: Patients distribution according to demographic characteristics (n=186)

Demographic characteristics	Frequency	Percentage
Age groups	90	21.1%
<30 years	245	57.5%
>30 years	91	21.4%
Total	186	100.0%
Gestational age		
29-32 weeks	74	39.78%
33-36 weeks	112	60.22%
Total	186	100.0%
Parity		
Primipara	45	24.2%
Multipara	141	75.8%
Total	186	100.0%
Cervical dilatation		
1.5cm	29	15.59%
02cm	82	44.09%
03cm	75	40.32%
Total	186	100.0%
Age and gestational age	Mean$\pm$SD	
Patients age	30.46 ± 5.24 years	
Gestational age	33.15 ± 2.28 weeks	

A number of patches required for arresting preterm labour and in 11.8% pregnant women only single patch of 10 mg was used but the majority of the women 88.2% responded after the application of 2nd patch.

Figure 1

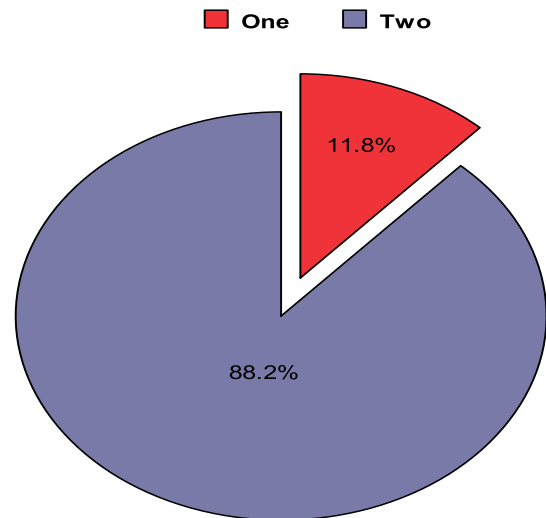


Figure 1. Number of Patch (n=186)

63.44% of pregnant women with 28-34 weeks of gestation with preterm labour 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. **Figure 2**

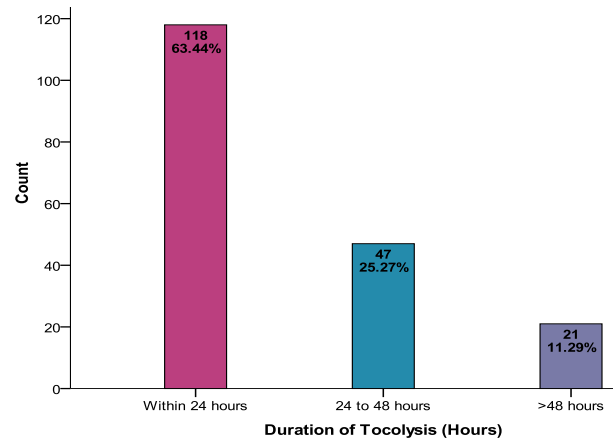


Figure 2. Complete cessation of uterine contraction of preterm labour with respect to time (n=186)

According to operational definition, the tocolytic efficacy of GTN transdermal patch in preterm labour between 28 to 36 weeks of pregnancy was 88.71%. **Figure 3**

A significant difference was not observed in the efficacy of GTN between age groups ($p=0.24$). Similarly, the efficacy of GTN transdermal patch in preterm labour was also not observed significant for parity, gestational

age, number of uterine contraction, cervical dilatation. GTN transdermal patch in preterm labour was 13.3% of the pregnant women responded after application of single patch while 86.7% responded after the second patch ($p=0.018$). Table II

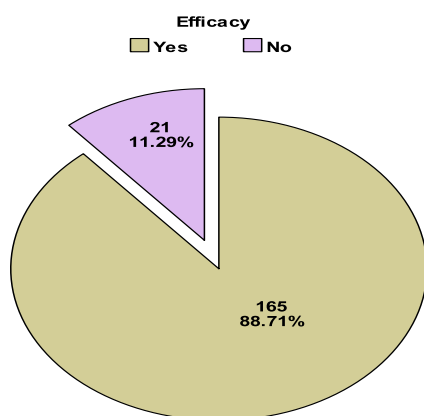


Figure 3. Tocolytic efficacy of GTN transdermal patch in preterm labour between 28 to 36 weeks of pregnancy (n=186)

Table II: Tocolytic efficacy according to age, gestational age, parity and cervical dilatation (n=186)

Demographic characteristics	Tocolytic efficacy		
	Yes (n=165)	No (n=21)	P-value
Age groups			
<30 years	72(43.6%)	12(57.1%)	0.24
>30 years	93(56.4%)	09(42.9%)	
Gestational age			
29-32 weeks	62(37.6%)	12(57.1%)	0.08
33-36 weeks	103(62.4%)	09(42.9%)	
Parity			
Primipara	37(22.4%)	08(38.1%)	0.11
Multipara	128(77.6%)	13(61.9%)	
Cervical dilatation			
1.5cm	26(15.8%)	03(14.3%)	0.08
02cm	77(46.7%)	06(23.8%)	
03cm	62(37.6%)	13(61.9%)	
Number of patch			
01	22(13.3%)	0(0%)	0.01
02	143(86.7%)	21(100%)	

Discussion

Delaying the delivery has two-fold benefits: one is to get enough time to complete the course of antepartum glucocorticosteroids in order 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 perinatal mortality and morbidity associated with severe prematurity. The main aim of tocolytic therapy is to improve perinatal outcome by suppressing preterm labour.¹⁰⁻¹² Tocolytic drugs have been tried for 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 Journal.¹³ 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 the varying degree of success with this approach of tocolysis.^{14,15} It is a vasodilator that is essential for 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 on myometrium in vitro, inhibition of spontaneous and oxytocin-induced activity was found when amplitude or force of contraction was measured.¹⁶ Pregnancy is prolonged by its direct effect on the uterine blood flow.¹⁷

In this study 186 pregnant women at 28-36 weeks of gestation were recruited after they met the selection criteria with average age 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 the second patch of the same dose after 24 hours 86.7% responded after the second patch. This is similar to a study by Affifa Waheed et al,⁹ conducted at Ghurki Trust Teaching Hospital, Lahore where 54% of pregnant women were between G2 - G4. The majority (48%) of the women presented between 31 - 34 weeks of gestation. Majority (86%) responded after application of second patch (10 mg glyceryl trinitrate patch).⁹

Anne D. Walling¹⁸ also used a 10 mg patch and like our study used the 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 al¹⁹ who did a prospective study on 100 patients of preterm labour 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 al²⁰ 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 reaching 37 weeks and when cervical dilatation was 3cm, 37% of cases had succeeded to reach 37 weeks.

In a study at Pune India, by Dr. Sachin Dagade, sixty women admitted with preterm labour were included over 18 months. 60% cases had succeeded to reaching 37 weeks when cervical dilatation was of 1cm, 50% cases succeeded when was 2cm but at 3 cm. no case had succeeded.²¹ This correlates with the findings of a study by Ajay Dhawle et al, where at a cervical dilatation of >3 cm, the mean pregnancy prolongation was only 0.56 days with NTG.²²

Our study found 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 the delivery.^{16,23-25} Valuable and desirable results achieved with the GTN, its straightforward administration and safety suggest there shall be multicenter comparative trials of GTN with established therapy or placebo involving larger number of recruited populations. Its secure use on record shall make it an alternative to other tocolytic agents, like salbutamol, ritodrine or calcium channel blockers for pre-term labour and could make a major involvement in the management of pre-term labour. The preventive strategy is important, especially when causes of pre-term labour are not known.

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 labour and also simple, quicker and cost-effective tocolytic agent. Current trials with nitric oxide donors may lead to a major breakthrough in the treatment of pre-term labour to decrease perinatal mortality.

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