

# The Effects of Glyceryl Trinitrate Patch on the Treatment of Preterm Labor: A Single-blind Randomized Clinical Trial

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## Abstract

**Background:** Preterm labor (PTL) is one of the main causes of neonatal mortality and morbidity. PTL leads to serious complications especially in the gestational age prior to 24-26 weeks. The aim of this study was to investigate the effect of glyceryl trinitrate (GTN) patch on the treatment and complications of PTL.

**Methods:** In this clinical trial, 84 singleton pregnant women with gestational age of 27-35 weeks were surveyed. PTL was clinically diagnosed and the patients were randomly divided into two groups who were treated with GTN or placebo for 48 hr. The consequences, complications and changes in some parameters in both groups were compared. Data were analyzed with chi square test, paired and unpaired t tests by SPSS software and  $p < 0.05$  was considered significant.

**Results:** No significant difference was observed between two groups in terms of successful tocolysis, receiving full dose of corticosteroids and the mean prolongation of the pregnancy. However, delivery times in patients who delivered during the hospitalization were  $31 \pm 4.4$  and  $18.3 \pm 2.2$  hr ( $p = 0.01$ ), respectively. Headache was more severe in control group ( $p = 0.007$ ). The systolic and mean arterial blood pressure decrease ( $p < 0.001$ ) and maternal heart rate increase ( $p = 0.01$ ) were significant in GTN group. The changes of vital signs were not significant in placebo group.

**Conclusion:** The effect of GTN in the treatment of PTL is similar to the placebo without any serious complication. However, GTN delays the delivery time in delivery during the primary hospitalization. Thus, further studies with larger sample size are needed to evaluate the exact effects of GTN on PTL.

**Keywords:** Glyceryl trinitrate patch, Obstetric labor, Premature, Tocolysis.

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## Introduction

Preterm labor (PTL) is referred to the occurrence or onset of delivery after the age of neonatal viability (20-28 weeks) and prior to 37 weeks or 259 days of pregnancy. The PTL is determined by observable uterine contractions (at least once in 10 min), rupture of the membranes, 2 cm cervical dilatation or the cervix length less than 1 cm. PTL is considered as the main confounding factor in the neonatal mortality (2). The prevalence of the preterm labor in developed

countries was 5-10% in the past three decades. In some areas, a slight increase has been seen in the last 5 years (1, 3). This is partly due to the very premature infants that had no viability previously (1) and preterm indicated labors (2). In the United States, about 11% of babies are born premature which causes respiratory problems, learning disabilities or even death (4). Preterm rupture of membranes and idiopathic preterm labor are the causes of 66% of preterm labors. Gestational hyperten-

sion and obstetric hemorrhage are other common causes that can lead to delivery or may be the reasons for indicated labor (1).

To reduce the complications and the costs associated with PTL, reducing the risk factors of preterm labor in the general population besides taking certain medications (tocolysis) for inhibiting initiated uterine contractions seem to be useful strategies. Previous studies have shown that prolonging pregnancy, not tocolysis, improves the neonatal outcomes. This interval may allow the patients to be transferred to a tertiary center and corticosteroid can be prescribed for them. The American College of Obstetrics and Gynecology (2003-2008b) concluded that despite a number of proposed treatment methods, the rate of preterm labor has not changed much over the past 40 years. The doubt on the best management of preterm labor continues up to now (2). Optimization of obstetric management besides tocolysis includes the stimulation of fetal lung maturation as a means of preventing respiratory distress syndrome in infant. Therefore, extending gestation for at least 48 *hr* is extremely important. Thus, delaying the delivery for at least 24-48 *hr* is the primary goal (5) because the corticosteroid therapy will be effective in the reduction of respiratory distress and neonatal mortality if the delivery is delayed for a minimum of 24 *hr* after administration of betamethasone.

Tocolysis being used currently does not lead to greater receipt of corticosteroids and improvement of neonatal outcomes (2). Furthermore, tocolysis treatment along with regimen that is currently used is considered to be a risk factor for pregnant women (1). Magnesium sulfate is the most commonly used injecting drug for tocolysis in North America. However, a recent systematic review on over 2,000 women in 23 studies showed no sufficient evidence to support the use of magnesium sulfate. Magnesium sulfate would not delay the delivery and does not prevent preterm labor (1, 2). The complications include vasodilatation, flushing, nausea, vomiting, heart palpitation and headache. The pulmonary edema is the most important complication. Careful monitoring is also required to avoid magnesium toxicity. Due to lack of efficacy and based on the aforementioned complications, it is difficult to justify the use of magnesium sulfate (1). The studies on calcium channel blocking agents revealed no beneficial or harmful effects in using them.  $\beta_2$  agonists especially ritodrine are used frequently. The previous studies

have shown that although it delayed the delivery for 24 *hr*, it did not have any other advantages (2).

Complications that have been confirmed in controlled studies include heart palpitation, tremors, chest pain, hyperglycaemia, hypocalcaemia and rarely but serious pulmonary edema. However,  $\beta_2$  agonists constitute the original treatment regimen although the use of other regimes is increasing due to the same effect and less complications (1).

Nonsteroidal anti-inflammatory drugs (NSAIDs): Indomethacin is the most common drug in this group which acts through cyclooxygenase inhibition. The influence of indomethacin impact is being investigated. The effect of indomethacin was compared with rithoderine and magnesium sulfate. There was no difference in the efficacy of these drugs (2). Its complications include peptic ulcer, gastrointestinal bleeding, and thrombocytopenia, allergic reaction to the medication and less common complications such as the risk of postpartum hemorrhage, kidney disorders and hypertension (1).

**Oxytocin receptor antagonists:** Although the Food and Drug Administration (FDA) of America retracted its approval on its application, it is widely used in Europe (2). Atosiban has lower maternal complications and a higher price as compared to  $\beta_2$  agonists.

The results of several clinical trials have shown that the use of glyceryl trinitrate (GTN) patch is effective for inhibition of uterine contractions (5), pregnancy prolongation, improvement of neonatal outcome and increasing the corticosteroid intake (3, 6, 7) without any significant complications (5, 7, 8). However, in some studies, the effect of GTN on the delay of delivery and improvement of neonatal outcomes did not differ from placebo (1, 2, 6, 9, 10).

NO is a very reactive signaling molecule which is produced by many cells endogenously (11). NO lowers intracellular ionized calcium and causes relaxation of the smooth muscle by increasing GMP. NO is a very unstable molecule that is inactivated by superoxide free radicals (11). Thus, NO releasing agents are compounds with short-term effect that their metabolism is often performed in the vascular wall and red blood cells (12). The objective of the present study was to investigate the effect of GTN patch on delaying the delivery for 24 and 48 *hr* and its complication was compared to placebo.

## Methods

This was a single blind randomized controlled clinical trial conducted in the maternity unit of Imam Reza hospital (Kermanshah, Iran) during October 2011 to August 2012. The study was registered in the Iranian Registry of Clinical Trials (IRCT) with registration identification of 201108054025n3. All processes were approved in the Ethics Committee of Kermanshah University of Medical Sciences.

This study was carried out on 84 women with singleton pregnancy aged 15-35 years who had symptoms of preterm labor between 27-35 weeks of gestation. The gestational age was calculated based on LMP (first day of the last menstrual period) or early pregnancy ultrasound findings. Sample size was calculated according to the results of the previous studies with a confidence of 95% and a power of 80% (3, 6, 9).

Inclusion criteria included regular uterine contractions equal or more than four contractions within 20 *min* or Bishop score more than or equal to 3. Bishop score is an index in determining cervical ripening for delivery which is defined based on dilation, effacement, consistency, position and station of the cervix.

Exclusion criteria included any fetal or maternal indications for necessary termination of pregnancy, multiple pregnancy, preterm rupture of membranes (PROM), fetal anomalies, cervical dilatation equal or greater than 5 *cm*, treatment with other tocolytic agents 24 *hr* before delivery, previous cesarean delivery, susceptibility to nitroglycerin compounds or any contraindication of Nitro compounds and evidence of chorioamnionitis (maternal fever, leukocytosis, fetal tachycardia), maternal heart disease, placenta previa or vasa previa, vaginal bleeding except the minor bleeding caused by initial dilatation of the cervix (bloody show).

After hospitalization, the patients were divided into GTN patch or placebo groups according to the table of random numbers. At the start of the study, a fetal cardiograph was recorded using the electronic device for monitoring fetal heart rate for 20 *min* in both groups. Blood pressure (BP) and maternal heart rate (MHR) were measured as well. The fetal heart rate (FHR) was calculated based on the baseline in the primary fetal cardiograph.

For all cases, a therapeutic fluid containing 1 *L* of crystalloid (normal saline) was infused as a conservative treatment for preterm labor. Two

grams of intravenous ampicillin was administrated each 6 to 48 *hr*. Furthermore, 12 *mg/IM* of betamethasone was administered twice with an interval of 24 *hr*.

After randomization, informed consent was taken from the study group and then the drug (10 *mg* GTN patch, Schering Plough Company) or placebo (Sarang Shahr Art Group Company) was applied on top of the navel without informing the patient.

The blood pressure was measured every 15 *min* to an hour and then every 4 *hr*. One hour after treatment, the fetal cardiograph was recorded again (for 20 *min*). MHR and BP were measured. The vaginal examination was done. In case where no complication was observed, another patch was also added. After 24 *hr*, the patches were removed. Women were examined in terms of redness and irritation of the patch location and 12 *mg* of betamethasone was administered. Then two new patches were replaced. After 48 *hr*, GTN patches were removed as well. Finally, the required variables such as the number of non-delivery cases within the first 24 and 48 *hr* of randomization, successful tocolysis (non-delivery in the first 48 *hr*), the number of received corticosteroids doses, drug complications, the changes in maternal heart rate and blood pressure and the changes in the baseline of the fetal heart rate (FHR) prior and one hour after the application of GTN patch were studied. The data related to each patient were recorded on data collection forms. In the case of non-delivery, the treatment continued under the supervision of the relevant physician. In cases of patients discharge before delivery, the patients' delivery time was followed by calling them.

The collected data were analyzed by SPSS 16 after coding using descriptive statistics (mean, standard deviation and confidence interval) and the chi square test and Fisher's exact test to examine the complications and the effects of other qualitative variables. Moreover, independent t test was administered for quantitative variables. The p-value less than 0.05 was considered significant. Data were shown as Mean±SD unless otherwise stated.

## Results

From 84 subjects who entered the study, 4 patients were excluded due to an emergency cesarean delivery (2 patients in the intervention group due to preeclampsia and fetal distress and 2 pa-

tients in the control group due to meconium passage and fetal distress). The final analysis was performed on 80 patients. The comparison of demographic variables and the maternal and fetal vital signs in both study and control groups showed that despite minor differences, randomization process was successfully done and there was no significant difference between any of the variables in both groups (Tables 1 and 2).

The comparison of full-dose corticosteroid intake and non-delivery within the first 24 and 48 hr and successful tocolysis in both groups showed no significant difference of the outcomes in the two groups. In the case of 31 people who delivered during the primary hospitalization, the delivery interval from the time of admission was in the range of 7-72 hr. The mean values in the intervention and control groups were  $31 \pm 4.4$  and  $18.3 \pm 2.2$  hr, respectively ( $p=0.01$ ).

From the 49 patients discharged from hospital (27 patients in the GTN group and 22 patients in placebo group), 31 patients were followed (18 patients in the intervention group and 13 patients in the control group) and they delivered 5-80 days after discharge. In the case of 62 patients who delivered at the time of final study (within the primary hospitalization or after that), the average delivery times in the intervention and control groups were  $20.6 \pm 4.2$  and  $16.3 \pm 3.9$  days, respectively and the difference was not significant (Table 1).

Regarding incidence of complications, despite minor differences in the drug and placebo groups (Table 2), only headache had a statistically significant difference ( $p=0.007$ ).

In the GTN group, systolic blood pressure (SBP) and mean arterial blood pressure (MAP) showed a significant drop after the use of medication ( $p < 0.001$ ). Moreover, the maternal heart rate (MHR) indicated a significant increase ( $p=0.01$ ) (Table 1).

Moreover, the differences were compared between the mean values measured before and after use of patch in the drug and placebo groups (Table 3). There was a significant difference between the mean systolic blood pressure ( $p < 0.001$ ), mean arterial blood pressure ( $p=0.001$ ) and maternal heart rate ( $p=0.007$ ) in the drug and placebo groups.

### Discussion

The aim of using tocolytic agents in preterm labor is to delay the delivery at least 48 hr, given the proven effectiveness of corticosteroids for im-

proving neonatal outcomes. In addition to effectiveness, the evaluation of treatment includes complications, safety and risks that threaten the mother and the fetus as well. The results of most studies show that the treatment of acute tocolysis does not prevent preterm labor or does not reduce age-related neonatal complications (13).

Few controlled studies have been conducted to investigate the effect of GTN. A few studies have compared the effect of GTN with betamimetics or examined its effect descriptively. In these studies, the successful tocolysis ranges from 63% to 85% (3, 7, 9, 14). Although these results are significant in descriptive studies (7, 9) there was no significant difference between GTN and placebo or betamimetics in controlled trials (3, 14).

In the present study, the proportions of non-delivery cases within the first 24 and 48 hr in the drug and placebo groups were 72.5% and 62.5%, respectively. But the difference was not significant. In the case of full-dose corticosteroids intake, no significant difference was observed as well ( $p=0.36$ ).

In the case of all the people who were followed during the study, the average delivery times in the drug and placebo groups were  $20.6 \pm 4.2$  and  $16.3 \pm 3.9$  days, respectively ( $p=0.45$ ). The difference was not significant. The average delivery times in patients who delivered during the hospitalization were  $31 \pm 4.4$  and  $18.3 \pm 2.2$  hr in the drug and placebo groups, respectively ( $p=0.01$ ). This delayed time was significant as compared to placebo and it seems that tocolysis is efficient. However, its effectiveness is not long lasting.

Because it is in the appropriate range of time, it results in the effectiveness of corticosteroid. This may improve neonatal outcomes, particularly in the case of very premature neonates. Smith's trial also shows that GTN can reduce neonatal morbidity and mortality as a result of decreasing the risk of birth before 28 weeks (3, 6).

The average prolongation of the pregnancy in the GTN group ranged from 9.5 days in the study conducted by Bisits on PROM and fibronectin-positive women (1) to 20.9 days (3), 34 days (10) and 42 days (15) in studies where their inclusion criterion was uterine contractions. The observed difference is partly due to methodological differences and the inclusion criteria of patients in these studies. In a study by Smith which was a fully controlled trial with the same methodology as the present study, despite the same pregnancy duration in the drug group (20.9), the observed differ-

**Table 1.** Comparison of demographic characteristics on admission and time of delivery in GTN and control groups (Mean±SD)

Variables	GTN	Placebo	p-value
Age (year)	24.9±0.84	26.3±0.77	0.23
Gestational age on admission (months)	31.5±0.4	31.3±0.4	0.66
Gravid women	1.7±0.13	2±0.2	0.19
Cervical dilatation on admission (cm)	1.8±0.14	1.7±0.13	0.52
Systolic blood pressure (mmHg)	113.0±15	110.5±17	0.74
Diastolic blood pressure (mmHg)	70.1±1.02	72.3±1.06	0.14
Mean arterial pressure (mmHg)	97.6±1.3	97.8±1.4	0.9
Maternal heart rate	88.6±1.3	90.1±1.5	0.44
Fetal heart rate	145±0.8	142±0.97	0.05
Delivery time after admission (day)	20.6±4.2	16.3±3.9	0.45
Delivery time after admission in case of delivery within the first 3 days (hr)	31±4.4	18.3±2.2	0.01

**Table 2.** Comparison of received corticosteroids dose number and complications in two groups

Variables No (%)	GTN	Placebo	p-value
Full-dose corticosteroids intake	35 (87.5%)	32 (80%)	0.36
Delivery within the first 24 hr	5 (12.5%)	8 (20%)	0.58
Delivery within 24-48 hr	6 (15%)	7 (17.5%)	0.58
Delivery after 48 hr	29(72.5%)	25 (62.5%)	0.58
Delivery during hospitalization	13 (32.5%)	18 (45%)	0.25
Palpitations	6(15%)	4(10%)	0.49
Headache	14(35%)	4(10%)	0.007
Nausea	3(7.5%)	1(2.5%)	0.3
Skin redness	3(7.5%)	1(2.5%)	0.3

ence in the control group was statistically significant. This significant difference was due to shorter interval of the admission to delivery in the placebo group (3).

In other controlled studies, no significant difference was observed in the prolongation of pregnancy between the GTN and placebo or betamimetics groups (10, 12, 15).

Following a review of 5 clinical studies involving 466 women, the Cochrane Database concluded that the nitric oxide donors do not cause delayed delivery compared with placebo and other tocolysis. There is not enough evidence to show that whether nitric oxide can reduce preterm labor or not (16, 17).

Despite the benefits to the fetus, the use of any tocolytic agents is associated with risks for the mother and fetus. The complications are completely known in the case of magnesium sulfate,

indomethacin, calcium channel blocking agents (1, 2) and betamimetics (1, 2, 9, 14). However in most studies, these drugs did not improve the neonatal outcomes (2).

The most common complication was headache in 14 patients (35%) ( $p=0.007$ ). Other complications including heart palpitation, nausea and skin irritation did not differ from placebo. Vomiting, dizziness or the need for treatment termination were not observed. In the Smith's study, the most common complication was headache in 42 patients in the drug group ( $p=0.001$ ). In the case of local irritation, a significant difference was observed ( $p=0.04$ ) (3). In the study conducted by Leszczynska, a transient headache was observed in 36.67% of cases and there were no other complications (like this study) (5). In Bisits's study, women who received GTN suffered from headache to a higher extent ( $p<0.001$ ) (14). In the study conducted by Perveen, the most common complication was the maternal headache (40%). Other complications included local irritation (24%), hypotension (8%) and flushing (4%), respectively. Fetal complications were not observed (7).

In the study conducted by Rai, it was shown that the most common complication was headache (18%) and other complications were tachycardia (13.7%), nausea (0.05), hypotension (0.03%) and local irritation (0.017%), respectively (9). In a descriptive study conducted by Lees, the headache occurred in 1/3 of patients (10). In Cochrane Database, in a review on 5 clinical studies, the most common complication was headache (16, 17).

**Table 3.** Comparison of the vital signs and fetal heart rate and the mean difference of the index before and one hour after using patch in GTN and placebo groups

Vital Signs	Groups	Before	After	p-value	Mean difference	p-value
<b>SBP (mmHg)</b>						
	GTN	111.3±15.0	102.9±16.0	<0.001	-8.42	<0.001
	Placebo	110.5±1.7	109.2±1.37	0.22	-1.37	
<b>DBP (mmHg)</b>						
	GTN	70.1±1.02	69.1±0.96	0.15	-1.02	0.86
	Placebo	72.3±1.06	71.5±1.08	0.25	-0.85	
<b>MAP (mmHg)</b>						
	GTN	97.6±1.3	91.6±1.3	<0.001	-5.95	0.01
	Placebo	97.8±1.4	96.6±1.1	0.15	-1.2	
<b>MHR (Beat/min)</b>						
	GTN	88.6±1.3	91.1±1.5	0.019	2/52	0.007
	Placebo	90.1±1.5	89.1±1.3	0.18	-1/05	
<b>FHR (Beat/min)</b>						
	GTN	145±0.8	144.5±0.85	0.44	-0.52	0.73
	Placebo	141.5±0.97	142±0.97	0.2	-0.85	
<b>Vaginal exam (cm)</b>						
	GTN	1.8±0.14	2.3±0.16	<0.001	0.52	0.11
	Placebo	1.6±0.13	2.02±0.18	<0.001	0.32	

The reduction of systolic blood pressure and mean arterial blood pressure and the increase of maternal heart rate have been observed previously and their differences were significant before using the GTN. However, hypotension and problematic tachycardia were not observed in the present study. In the similar studies consistent with the present study, although the reduction of systolic blood pressure and mean arterial blood pressure was observed, it was rarely in the range for an intervention. This is probably due to the dose, method of administration and fluid therapy that have been done before treatment (3, 5, 6, 8, 15).

Fetal complications associated with GTN have not been reported. Human Doppler studies have shown that GTN has no effect on placental uterine blood flow (5, 8). In the present study, no changes in the fetal cardiograph and FHR were observed during GTN administration.

The results of the present study showed that there was no significant difference between GTN and placebo groups in terms of non-delivery within the first 48 hr of admission and full dose corticosteroid intake. But the average delivery time after admission in the GTN group was longer than placebo group. This difference was statistically significant (p=0.01). This time interval is worthwhile regarding the injection and effectiveness of corticosteroids. In this study, the most common

complication was headache and other serious complications were not observed. Application of GTN patch is easy, low cost and without serious complications. Therefore, conducting further controlled studies for covering the possible neonatal outcomes are recommended. This can be effective in the improvement of neonatal outcomes, especially in the case of very premature infants that their outcome depends on the effectiveness of corticosteroid intake.

**Conclusion**

The effect of glyceryl trinitrate in the treatment of preterm labor is similar to the placebo without any serious complication. However, in delivery during the primary hospitalization, glyceryl trinitrate delays the delivery time. Thus, further studies with larger sample size are needed to evaluate the exact effects of glyceryl trinitrate on preterm labor.

**Conflict of Interest**

This work was performed in partial fulfillment of the requirements for Ph.D., of Parnian Kord Jamshidi.

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