



## Effectiveness of Nifedipine and Transdermal Nitroglycerin in Treatment of Preterm Labor

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### Authors' contributions

The work was carried out in collaboration among all authors. Authors FT and NG analyzed data and co-written the paper, author SH collected and analyzed data, author RSH designed the object and edited the article. Author FSH performed experiments and Data collection. All authors read and approved the final manuscript.

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### ABSTRACT

**Background:** Preterm labor (PTL) is one of the most serious complications of pregnancy and major cause of mortality in neonates. The present study aimed to compare the effectiveness of nifedipine and transdermal nitroglycerin in the treatment of PTL.

**Materials and Methods:** This randomized clinical trial was carried out on a total of women with PTL referring to Imam Reza Hospital of Mashhad University of Medical Sciences, Iran, during September 2016 to October 2017. The study participants were randomly divided into groups I and II with the administration of nifedipine and transdermal nitroglycerin. All the vital signs, fetal heart rates, contractions, dilation, and effacement, and Gestational Age (GA) at the time of delivery were

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monitored and evaluated in both groups. The main goal of this study was the postponement of delivery to secure the most beneficial effect of primary corticosteroid administration on the fetus.

**Results:** This study was conducted on a total of 112 women with a mean age of  $27.12 \pm 3.37$  years. There was a significant association between the average of GA in two groups ( $P=0.012$ ), indicating group I with lower mean GA than that reported for group II at delivery. The difference regarding the average of labor suppression was statistically significant between the two groups ( $P=0.002$ ). The obtained results of this study showed the neonates in the transdermal nitroglycerin group with higher Apgar scores of the first and fifth minutes than those in the nifedipine group. Moreover, the number of side effects of the transdermal nitroglycerin group (i.e., tachycardia and nausea) was higher than those reported for the nifedipine group ( $P=0.019$ ).

**Conclusion:** The obtained results of this study demonstrated that the administration of transdermal nitroglycerin was more effective than that of nifedipine to stop the uterine contractions and consequently could slow the progression of delivery more efficiently. Furthermore, both medications were reported with some side effects for mothers; however, the number of the side effects of nifedipine was lower than that reported for transdermal nitroglycerin.

*Keywords: Nifedipine; preterm labor; pregnancy; transdermal nitroglycerin.*

## 1. INTRODUCTION

Preterm labor (PTL) is considered the most common cause of neonatal mortality and morbidity worldwide [1]. The PTL is a clinical recognition determined by cervical change with regular uterine contractions occurring at the delivery time of a fetus before 36 weeks of gestation [2]. The prevalence of PTL is estimated at 10% of all births worldwide [3]. The major cause of perinatal mortality is prematurity caused by PTL in developed countries [4].

The preterm neonates are at increased threat of gastrointestinal and respiratory complications and long-term neuro-developmental disabilities [5]. The treatment of premature contractions of the uterus and delayed delivery are essential in order to give time to the administration of corticosteroids [6]. Therefore, it is necessary to choose the best drug for the treatment of PTL for the prevention of neonatal mortality and morbidity.

Nifedipine as a calcium channel blocker is a medication used for the management of PTL and could be used as a first-line tocolytic agent [7]. The administration of nifedipine leads to inhibiting the entry of calcium through the cell membrane channels and can decrease the threat of delivery within 7 days of the initiation of treatment and delivery before 34 weeks of gestation. In addition, it can result in the improvement of some clinically vital neonatal outcomes, such as intraventricular hemorrhage, necrotizing enterocolitis (NEC), and respiratory distress syndrome [8]. The administration of nifedipine is not associated with serious maternal

adverse drug reactions except for hypotension and tachycardia [9].

Transdermal nitroglycerin belongs to a class of drugs identified as nitrates that can lengthen pregnancy among women in PTL via a specific effect on uterine smooth muscle and reduce the risk of severe neonatal outcomes [10]. Transdermal nitroglycerin is quickly metabolized in the liver; therefore, its administration is considered beneficial [11]. Transdermal nitroglycerin may be an effective tocolytic with rare serious side effects for the mother and fetus [12].

According to the Cochrane database, it was demonstrated that the best-documented treatment for PTL is the administration of B-mimetics and oxytocin antagonists [13]. However, some studies suggested the use of transdermal nitroglycerine due to the convenient use and fewer side effects [14,15]. With this background in mind, due to the different effects of the two drugs, namely nifedipine and transdermal nitroglycerin, on the treatment of PTL, the present study aimed to compare the effectiveness of nifedipine and transdermal nitroglycerin in the treatment of PTL.

## 2. MATERIALS AND METHODS

### 2.1 Study Population

This clinical trial was carried out on a total of 112 women above 18 years of age with gestational age (GA) of 24-34 weeks with PTL at Imam Reza Hospital of Mashhad University of Medical Sciences, Iran, during September 2016 to October 2017. The inclusion criteria were a GA

of 26-34 weeks and symptoms of PTL, including more than four uterine contractions in 20 min.

The exclusion criteria were maternal and fetal indications for the termination of pregnancy, multiple pregnancy, prelabor rupture of membranes, intrauterine fetal demise, cervical dilatation of > 4 cm, administration of other tocolytic drugs during previous 24 h, allergy to nitroglycerin, and identification of the side effects, such as headache, tachycardia, nausea, vomiting, and hypotension. The CONSORT flowchart is shown in Fig. 1.

## 2.2 Study Protocol

Threatened PTL was identified as a condition in which pregnancy occurred within 26-34 weeks of

gestation with painful and regular uterine contractions at least once in every 10 min persisting for more than 30 min without the dilatation of the cervix. The uterine contractions were noted by the external electronic fetal heart rate monitoring for 30 min. The GA was measured since the last menstrual bleeding in all cases, and the results were confirmed by ultrasound in the first half of the pregnancy.

All the patients received 500 ml of normal saline for the prevention of hypotension after hospitalization. The two groups received intramuscular betamethasone every 24 h up to two doses. The patients were randomly assigned to two groups with blocks of two and four using the randomization method. A noninvolved researcher determined the random assignment

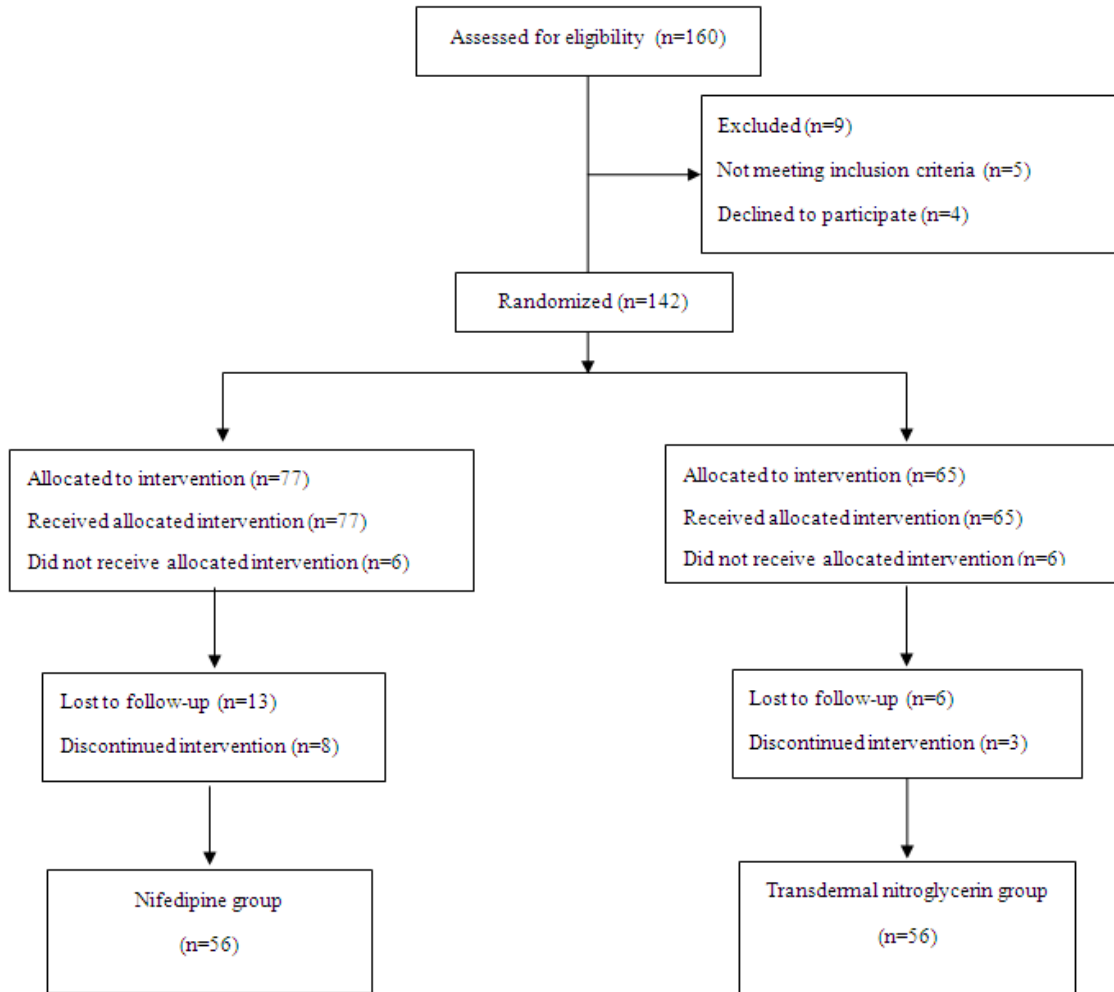


Fig. 1. Flowchart diagram of selection process of patients

sequencing in sampling using a statistical analysis system (i.e., computer software). Accordingly, the participants were given codes and assigned to the two groups of nifedipine (group I) and transdermal nitroglycerin (group II). Group I received 5-mg nifedipine capsule (one capsule every 20 min until 4 h, two capsules every 6 h until 24 h, one capsule every 6 h until 24 h, and one capsule every 8 h until 24 h).

Group II received nitroglycerin transdermal patch (including 37.4 mg of glyceryl trinitrate with a release rate of 10 mg/h). The patch was placed on the arm of the patient, and the contractions were controlled after 1 h. In addition, the second patch was used with a change in dilatation and effacement, and the contractions were re-controlled following 1 h.

The fetal heart rate was continuously monitored at the first 4 h and then alternately. The uterine contractions, dilatation, and effacement were checked every hour after the contractions were suppressed, and no change or intervention was performed regarding dilatation and effacement in both groups. The patients' conditions were controlled up to the end of pregnancy.

### 2.3 Statistical Analysis

The descriptive data were summarized as mean, standard deviation, and/or percentage. The normality of the data was checked prior to data analysis using the One-Sample Kolmogorov-Smirnov test. The descriptive statistics, such as frequency and relative frequency, student's t-test, and Chi-square test were used to analyze the data. All the analyses were performed using SPSS software (version 18). A p-value of less than 0.05 was considered statistically significant.

### 3. RESULTS

A total of 112 (56 patients in each group) women participated in the study, with a mean age of  $27.12 \pm 3.37$  years (Max: 35, Min: 21). The mean values of age in groups I and II were  $26.77 \pm 3.46$  and  $27.46 \pm 3.23$  years, respectively. The mean values of age were compared using a student's t-test indicating no significant difference between the two groups ( $P=0.274$ ). The obtained results showed that the mean of pregnancies was  $1.77 \pm 0.88$  (Min: 1, Max: 4) in all the patients. The mean numbers of pregnancies were compared

using a student's t-test revealing no significant differences between the two groups ( $P=0.517$ ).

The mean number of deliveries was  $0.52 \pm 0.73$  (Min: 0, Max: 4) in all the women. The means of the number of deliveries were compared using a student's t-test showing no significant differences between the two groups ( $P=0.123$ ). The average of miscarriages was  $0.24 \pm 0.49$  (Min: 0, Max: 2) in all the subjects. The averages of miscarriages in the two groups were compared using a student's t-test indicating no significant difference between the two groups ( $P=0.177$ ). The evaluation of the history of stillbirth in the studied groups demonstrated that the mean of stillbirths was  $0.05 \pm 0.29$  (Min: 0, Max: 2) in all the women. The numbers of stillbirths were compared using a student's t-test indicating no significant difference between the two groups ( $P=0.202$ ).

The assessment of the vital signs of patients on admission by a student's t-test showed that the average body temperature ( $P=0.922$ ) and diastolic ( $P=0.112$ ) and systolic ( $P=0.661$ ) blood pressure revealed no significant differences between the two groups (Table 2). The mean values of GA and fundal height were  $220.03 \pm 14.64$  days and  $31.03 \pm 1.57$  cm on admission based on ultrasound, respectively. The averages of GA ( $P=0.408$ ) and fundal height ( $P=0.952$ ) were compared using a student's t-test showing no significant differences between the two groups.

The mean of GA was reported as  $240.43 \pm 17.48$  days (Min: 182 days, Max: 266 days) at delivery. In addition, the mean values of GA were  $236.30 \pm 20.08$  and  $244.55 \pm 13.36$  days in groups I and II, respectively. The averages of GA in the two groups were compared using a student's t-test indicating a significant association between GA and administered medication ( $P=0.012$ ). In this regard, group I had a lower mean value of GA than that reported for group II at delivery.

The rates of labor suppression were reported as 17.86% and 44.64% 48 h after the intervention based on the Chi-square test in groups I and II, respectively. The difference between the two groups was statistically significant in this regard ( $P=0.002$ ). Table 3 tabulates the results of neonatal conditions after birth. The means of Apgar scores at the first ( $P=0.000$ ) and fifth ( $P=0.004$ ) minutes after birth were compared using a student's t-test reflecting a significant

association between the Apgar score and administered medication.

The average of neonatal weight at birth ( $P=0.396$ ) and duration of hospitalization ( $P=0.520$ ) were compared using a student's t-test showing no significant association between the neonatal weight and administered drug. Furthermore, respiratory distress syndrome, patent ductus arteriosus, and NEC were reported in 41.96%, 0.83%, and 1.78% of the neonates, respectively.

The obtained results of the current study indicated the side effects of the drugs, including headache in 16 cases (28.57%) in both groups, tachycardia and nausea in 5 cases (8.92%) in group II, and hypotension in 16 cases (28.57%) in group I and 14 cases (25%) in group II. However, no local reaction to drugs was observed in both groups (Table 4). There were no significant differences regarding the side effects of the medications between the two groups using the Chi-square test ( $P=0.019$ ).

**Table 1. Characteristic of two groups**

Variable	Group		Total (n=112)	P-value
	Nifedipine (n=56)	Transdermal nitroglycerin (n=56)		
Age (year)	26.77±3.46	27.46±3.23	27.12±3.37	0.274
Gravidity	1.71±0.93	1.82±0.81	1.77±0.88	0.517
Number of deliveries	0.41±0.68	0.62±0.78	0.52±0.73	0.123
Number of miscarriages	0.30±0.57	0.18±0.39	0.24±0.49	0.177
Number of stillbirths	0.09±0.39	0.02±0.13	0.05±0.29	0.202

**Table 2. Vital signs of patients on admission**

Variable	Group		Total (n=112)	P-value
	Nifedipine (n=56)	Transdermal nitroglycerin (n=56)		
Suppression of contractions after 48 h n (%)	10 (17.86)	25 (44.64)	35 (31.25)	0.002
Body temperature (°C)	36.97±0.03	36.99±0.13	36.99±0.10	0.922
Diastolic blood pressure (mmHg)	70.73±2.60	69.38±5.79	70.05±4.52	0.112
Systolic blood pressure (mmHg)	108.75±5.50	108.30±5.25	108.53±5.35	0.661
Gestational age (day)	218.88±9.26	221.18±18.55	220.03±14.64	0.408
Fundal height (cm)	31.04±1.56	31.02±1.60	31.03±1.57	0.952

**Table 3. Results of neonatal condition after birth**

Variable	Group		Total (n=112)	P-value
	Nifedipine (n=56)	Transdermal nitroglycerin (n=56)		
Apgar score at first minute	7.07±0.71	7.64±0.88	7.36±0.85	0.000
Apgar score at fifth minute	7.64±1.12	8.27±1.05	7.96±1.17	0.004
Baby weight (g)	2226.573±50	2139.29±511.10	2183.04±542.53	0.396
Duration of hospitalization (day)	2.86±4.38	3.41±4.69	3.13±4.53	0.520
Respiratory distress syndrome (%)	41.07	42.86	41.96	0.848
Patent ductus arteriosus (%)	0.83	0	0.83	0.408
Necrotizing enterocolitis (%)	1.78	0	1.78	0.952

**Table 4. Distribution of drug side effects**

Group	Headache n (%)	Tachycardia n (%)	Nausea n (%)	Hypotension n (%)	Local reaction n (%)
Nifedipine	16 (28.57)	0 (0.0)	0 (0.0)	16 (14.28)	0 (0.0)
Transdermal nitroglycerin	16 (28.57)	5 (8.92)	5 (8.92)	14 (12.50)	0 (0.0)
Total	32 (28.57)	5 (8.92)	5 (8.92)	30 (26.78)	0 (0.0)

#### 4. DISCUSSION

Controlling the PTL has been always a challenge to obstetricians; on the other hand, in patients with PTL, the choice of appropriate treatment is of particular importance due to the shorter duration of treatment. The current study investigated the effectiveness of nifedipine and transdermal nitroglycerin administration in 112 women with PTL. The difference regarding GA was significant between the two groups. In this regard, group I had a lower mean of GA than that reported for group II at delivery.

The obtained results of the present study demonstrated that the administration of transdermal nitroglycerin was more effective than that of nifedipine to stop the uterine contractions and consequently could slow the progression of delivery more efficiently. There was a statistically significant difference between the two groups regarding the average of labor suppression. The obtained results of this study showed that the transdermal nitroglycerin group was reported with higher Apgar scores of the first and five minutes than those of the nifedipine group. Moreover, the side effects of the transdermal nitroglycerin group (i.e., tachycardia and nausea) were more than those reported for the nifedipine group.

The PTL remains an unsolved problem in obstetrics and neonatology the treatment of which is still difficult in clinical practice [16]. The PTL can be treated with the administration of drugs that can effectively prolong pregnancy. However, efforts are made to choose well-tolerated, efficacious, and safer medications, with fewer side effects.

Still, there has been disagreement about the treatment of PTL. In fact,  $\beta$ -mimetics are likely to be excluded and replaced with nifedipine with fewer side effects, which is preferred in terms of its effectiveness [17]. In addition, the evidence on the effectiveness of magnesium sulfate as a tocolytic is under question in this regard [18]. Atosiban, as an oxytocin antagonist, is also a good treatment, with few side effects; nevertheless, it is expensive and does not have the approval of FAD (Food and Drug Administration). Moreover, it is not available in all countries, including Iran. However, there has not been much information about the effect of atosiban on neonates and mortality and morbidity of newborns [19,20].

Multiple studies reported that tocolytics are the best options for the inhibition of preterm contractions [21]. Tocolytics include calcium channel blocker agents, prostaglandin inhibitors, beta-adrenergic receptor agonists, oxytocin antagonists, nitric oxide, and calcium magnesium sulfate; however, these drugs have been reported with several side effects [22].

Transdermal nitroglycerin causes a significant reduction in the contractility of human myometrium in pregnant and non-pregnant women *in vitro* [23]. Leszczynska-Gorzela et al. demonstrated that transdermal nitroglycerin can reduce the uterine contractions in pregnant women of 27-34 weeks without any side effects on fetal cardiotocography and heart rate [24]. Shaikh et al. showed that transdermal nitroglycerin was an effective and safe tocolytic medication capable of prolonging pregnancy; therefore, transdermal nitroglycerin could decrease neonatal intensive care unit costs, significantly recover neonatal outcomes, and reduce neonatal morbidity and mortality [25].

On the other hand, nifedipine as a tocolytic agent gained popularity due to the oral route of administration, accessibility of immediate- and slow-release arrangement, and adequate effects on PTL treatment. However, there has been increasing concern regarding the overall neonatal outcomes and possible harmful maternal and fetal events [26].

In studies carried out by Ghomian et al., [27], Kashanian et al., [28], and Bashir et al., the effectiveness of transdermal nitroglycerin and nifedipine was compared regarding labor suppression [12]. According to the results, it was shown that the suppression of uterine contractions 2 to 48 h following the administration of the medication was significantly more common in the transdermal nitroglycerin group than those reported for the nifedipine group. The aforementioned findings are similar to the results of the present study. Accordingly, transdermal nitroglycerin was a more effective drug than nifedipine in terms of labor suppression.

However, both transdermal nitroglycerin and nifedipine may have some maternal adverse effects, including hypotension, tachycardia, headache, asthenia, syncope, diarrhea, muscle cramps, and heartburn [12]. The results of the current study indicated that transdermal nitroglycerin had more side effects (i.e.,

tachycardia and nausea) than nifedipine. Nevertheless, Flenady et al. demonstrated that nifedipine as a calcium channel blocker was beneficial for the prolongation of pregnancy; however, this drug has serious side effects, such as neonatal morbidity and maternal adverse effects [22].

Smith et al. showed that transdermal nitroglycerin caused significant side effects, especially headaches in mothers. Transdermal nitroglycerin may reduce neonatal morbidity and mortality as a result of decreased risk of birth before 28 weeks of gestation; however, it can be associated with several side effects for the mother [29]. Therefore, both nifedipine and transdermal nitroglycerin are associated with some side effects in mothers. It is required to carry out further studies regarding the selection of the best drug for the treatment of PTL.

Based on the results of the present study, the administration of transdermal nitroglycerin was more effective than that of nifedipine to stop the uterine contractions; however, the side effects of nifedipine were fewer than those reported for transdermal nitroglycerin. In addition, it has been recently suggested to use the combination therapy for the inhibition of PTL. In this regard, Kashanian et al. reported that combination therapy with nifedipine and indomethacin was more effective than monotherapy with either of these two medications in the prolongation of pregnancy [8]. However, it is required to carry out further studies regarding the advantages and disadvantages of this therapy. The main limitations of the current study were the small sample size of the study and no placebo-controlled design; therefore, it is suggested to perform more randomized clinical trials with a larger sample size and placebo-controlled design.

## 5. CONCLUSION

The obtained results of this study revealed that both drugs have some side effects for mothers; however, the side effects of nifedipine are fewer than those reported for transdermal nitroglycerin. The obtained results of the current study demonstrated that the administration of transdermal nitroglycerin was more effective than that of nifedipine to stop uterine contractions and consequently could slow the progression of delivery more efficiently. On the other hand, the potential efficiency, economic features, side effects, and simplicity of administration of

transdermal nitroglycerin lead obstetricians to use this drug. Therefore, it is highly recommended to carry out further randomized placebo-controlled clinical trials and combination therapy to survey the possible neonatal outcomes.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

The study protocol was reviewed and approved by the Ethics Committees of Mashhad University of Medical Sciences (no.: T-2655). The current study was successfully registered with the clinical trial services of the United States National Institutes of Health (ClinicalTrials.gov Identifier: NCT02583633).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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