ORIGINAL ARTICLE

# EFFECTIVENESS OF TRANSDERMAL NITROGLYCERINE COMPARED TO ORAL NIFEDIPINE IN PREVENTION OF PRETERM LABOUR

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**Background:** Preterm labour is a major complication of pregnancy associated with perinatal mortality and morbidity. Various drugs and strategies have been used for the treatment of preterm labour. The objective of this study was to compare the efficacy of transdermal nitroglycerine patch versus oral nifedipine in prevention of preterm labour. **Methods:** A randomized controlled trial was designed and conducted at the Department of Obstetrics/Gynaecology, Ayub Teaching Hospital, Abbottabad. The participants were randomly divided into 2 groups: the transdermal nitroglycerine group and oral nifedipine group with 63 participants in each group. Nitroglycerine transdermal patch of 5 mg was applied over the anterior abdominal wall in the first group and oral nifedipine was administered orally to second group. The efficacy in terms of delay in delivery by 48 hours was noted for each intervention and recorded in the proforma. Mean±SD were calculated for numerical variables. For the categorical variables, Chi-square ($\chi^2$) test was used, and $p \leq 0.05$ was considered as statistically significant. **Results:** Overall the given treatment was effective in 94 (75%) patients. In transdermal nitroglycerine group, the delay of delivery by 48 hours was found in 53 (85%) patients. In oral nifedipine group, delay of delivery by 48 hours was seen in 41 (65%) patients ($p<0.05$). **Conclusion:** Transdermal nitroglycerine patch is more effective to delay labour as compared to nifedipine. Therefore, it may be promisingly safe, effective, well-tolerated, cost-effective, and non-invasive method of tocolysis.

**Keywords:** Spontaneous preterm delivery, spontaneous preterm birth

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## INTRODUCTION

Pre term labour (PTL) is defined as the onset of labour after the age of viability (20–24 weeks) and before 37 completed weeks of pregnancy, and its incidence is 6–10% of all births in developed countrie.[1,2] It is determined by observable uterine contractions (at least once in 10 min), rupture of the membranes, and 2 Cm of cervical dilatation or the cervix length less than 1 Cm. It is the main confounding factor in neonatal mortality and its prevalence in developed countries is 5–10% in the past three decades.[2] Preterm birth occurs in up to 6–10% of all births and is associated with perinatal mortality and morbidity.[3] Preterm labour is the leading cause of long-term morbidity in babies including neurodevelopmental handicap, cerebral palsy, seizure disorders, blindness, deafness, and non-neurological disorders like bronchopulmonary dysplasia and retinopathy of prematurity.[4]

Treatment aim of pre-term delivery is to suppress the uterine contractions to delay preterm birth that allows administration of complete course of corticosteroids to reduce incidence of respiratory distress syndrome and subsequently transfer neonate to neonatal intensive care unit facility so as to reduce perinatal morbidity and mortality.[5] For this purpose, a wide variety of agents has been recommended and most of them require strict monitoring of both mother and foetus due to their adverse effects.[6,7] Nitroglycerine is a drug which is rapidly metabolized in the liver therefore transdermal use of nitroglycerin (25 mg) is beneficial. Nitroglycerin is a nitric oxide donor which activates Guanyl cyclase and enhances production of cyclic 3, 5 Guanosine monophosphate (cGMP) that leads to smooth muscles relaxation.[4] Release of intracellular calcium from sarcolemmal stores is inhibited and calcium efflux from the cell is increased. The decrease in intracellular free calcium results in calcium dependent MLCK (Myosin Light Chain Kinase) phosphorylation inhibition that leads to myometrial relaxation.[8]

Several studies[9,10] have been conducted to compare oral nifedipine, a calcium channel blocker, with nitroglycerine. Some studies favour the use of transdermal nitroglycerine patch due to its convenience of use and fewer adverse effects.[11] Preterm birth rate ranges from 5 to 7% of total live births in some developed countries and incidence is higher in the developing countries. Approximately 45–50% of preterm births are idiopathic, 30% are related to preterm rupture of membranes and another 15–20% is attributed to medically indicated or elective preterm deliveries.[3] Worldwide, preterm birth is the leading cause of child death.[11] The effects of preterm birth amongst some survivors, e.g., impaired neuro-developmental function, increased risk of cerebral palsy, learning impairment, visual disorders, long-term physical health issues, and higher risk of non-communicable disease may continue

throughout life.[11] These effects exert a heavy burden on families, society and the health system. Hence, preterm birth is one of the largest single conditions in the global burden of disease analysis with high mortality and considerable risk of lifelong impairment.[12] As there is hardly any local study comparing nitroglycerine transdermal patch with oral nifedipine, this study would guide us about better option amongst the two, and recommend a cost-effective therapeutic intervention for prevention of preterm labour.

## MATERIAL AND METHODS

A randomized controlled trial was designed and conducted at the Obstetrics/Gynaecology Unit of Ayub Teaching Hospital, Abbottabad after seeking formal approval from the Hospital Ethical Committee. The sample size of 126 was calculated by using World Health Organization (WHO) software sample size calculator (estimating a population proportion with a specified absolute precision), where confidence level (1-α)= 95%, and Power= 80%. Anticipated population proportion (P1)= 86.7% and anticipated population proportion (P2)= 68.3%.[13] Participants were randomly divided into 2 equal groups, the transdermal nitroglycerine group and oral nifedipine group. Written informed consent was taken. Consecutive (non-probability) sampling technique was used. The subjects with gestational age 28–34 weeks, maternal age 20–35 years, parity up to 4, and singleton pregnancy were included in this study. The subjects with the history of hypertensive disorders and major cardiac disease, diabetes mellitus, polyhydramnios, antepartum haemorrhage, foetal anomaly, foetal distress, intrauterine death, and uterine anomalies like bicornuate uterus or uterine fibroids were excluded from this study.

Nitroglycerine transdermal patch of 5 mg was applied over the anterior abdominal wall. Uterine contractions were recorded on the pre-designed proforma. The 2nd patch of same strength was applied after 12 hours. To avoid expected hypotensive effect of glyceral trinitrate patch, prophylactic infusion of 500 ml of normal saline was given to all participants of that group and blood pressure monitored every 30 minutes for 3 hours, and 6 hourly afterwards. Oral nifedipine was administered to all participants of second group as 20 mg stat and then 20 mg orally after 30 minutes if contractions persist, followed by 20 mg orally every 3–8 hours for 48–72 hours with a maximum dose of 160 mg. The efficacy in terms of delay in delivery by 48 hours was noted for each intervention and recorded in the proforma.

The data were analysed using SPSS-17. Mean±SD were calculated for numerical variables like maternal age and gestational age. For the categorical variables, Chi-square ($\chi^2$) test was used to compare the delay of delivery up to 48 hours in the two treatment groups, and $p \leq 0.05$ was considered statistically significant. The effect modifiers like maternal age, gestational age, and parity were controlled by the stratification method.

## RESULTS

A total of 126 patients participated in the study with mean age 24.45±4.38 years (range 20–35 years). Sixty-six (52.3%) patients had age 20–25 years, 49 (38.8%) had 26–30 years, and 11 (8.7%) of them had age 31–35 years. The mean gestational age was 30.21±1.49 weeks (range 28−34 weeks). Ninety-four (75%) patients had gestational age 28–31 weeks, and 32 (25%) had gestational age 32–34 weeks. (Table-1).

Transdermal nitroglycerine given to 63 patients was effective in 53 (85%) patients, while it was not effective in 10 (15%). Oral nifedipine given to 63 patients was effective in 41 (65%) patients, while it was not effective in 22 (35%) patients ($p$=0.04). (Table-2).

Out of 94 patients having gestational age 28–31 weeks, 40 were given transdermal nitroglycerine which was effective in 35 (88.5%) patients and had no effect in 5 (11.5%) patients. Oral nifedipine was effective in 35 (64.7%) out of 54 patients. It was not effective in 19 (35.3%) cases ($p$=0.03).

Thirty-two patients had gestational of 32–34 weeks. In this group, out of 22 patients, transdermal nitroglycerine showed effective results in 17 (78.6%) and no effects in 5 (21.4%) patients. Out of 10 patients, oral nifedipine showed significant results in 7 (66.7%) and no effects in 3 (33.3%) patients. The differences were not significant in group of 32–34 week gestational age ($p$=0.48).

Eighty-two (65%) patients had parity of 1−2 while 44 (35%) patients had parity of 3−4. In parity group of 1–2, transdermal nitroglycerine given to 41 patients, showed significant results in 33 (80.8%) patients and no effects in 8 (19.2%) patients. In the same parity group oral nifedipine was given to 41 patients, showing significant results in 27 (65.4%) and no effects in 14 (34.6%) patients ($p$=0.17). In parity group of 3–4, out of 22 patients, transdermal nitroglycerine was effective in 20 (92.9%) and ineffective in 2 (7.1%) patients. In the same parity group, out of 22 patients with oral nifedipine was effective in 14 (64.3%) and ineffective in 8 (35.7%) patients ($p$=0.08). (Table-3).

The treatment-related side-effects of transdermal nitroglycerine and oral nifedipine are described in Table-4.

**Table-1: Mean age and mean gestational age of treatment groups**

| Study groups | Transdermal nitroglycerine | Oral nifedipine |
|---|---|---|
| **N** | 63 | 63 |
| **Mean age (Years)** | 21.50±1.48 | 29.40±2.15 |
| **Gestational age (Weeks)** | 30.60±1.58 | 29.82±1.31 |

**Table-2: Efficacy of treatment in treatment groups**

| Efficacy of treatment | Transdermal Nitroglycerine | Oral Nifedipine | Total |
|---|---|---|---|
| Yes | 53 (85%) | 41 (65%) | 94 (75%) |
| No | 10 (15%) | 22 (35%) | 32 (25%) |
| Total | 63 (100%) | 63 (100%) | 126 (100%) |

**Table-3: Comparison of efficacy of treatment in study groups with respect to gestational age and parity [n (%)]**

| Efficacy of treatment | | Study Groups: Transdermal Nitroglycerine | Study Groups: Oral Nifedipine | Total | *p* |
|---|---|---|---|---|---|
| **Gestational period** | | | | | |
| 28–31 weeks | Yes | 35 (88.5) | 35 (64.7) | 70 (75) | 0.03 |
| | No | 5 (11.5) | 19 (35.3) | 24 (25) | |
| Total | | 40 (100) | 54 (100) | 94 (100) | |
| 32–34 weeks | Yes | 17 (78.60) | 7 (66.70) | 24 (75) | 0.48 |
| | No | 5 (21.4) | 3 (33.3) | 8 (25) | |
| Total | | 22 (100) | 10 (100) | 32 (100) | |
| **Parity** | | | | | |
| Parity 1–2 | Yes | 33 (80.8) | 27 (65.4) | 60 (73.1) | 0.17 |
| | No | 8 (19.2) | 14 (34.6) | 22 (26.9) | |
| Total | | 41 (100) | 41 (100) | 82 (100) | |
| Parity 3–4 | Yes | 20 (92.9) | 14 (64.3) | 34 (78.6) | 0.08 |
| | No | 2 (7.1) | 8 (35.7) | 10 (21.40) | |
| Total | | 22 (100) | 22 (100) | 44 (100) | |

**Table-4: Treatment-related side-effects of transdermal nitroglycerine and oral nifedipine (%)**

| Transdermal Nitroglycerine | | Oral Nifedipine | |
|---|---|---|---|
| Hypotension | 5 | Hypotension | 8 |
| Headache | 2 | Headache | 1 |
| Dizziness | 2 | Dizziness | 4 |
| Flushing | 3 | Dyspnoea | 6 |
| Foetal bradycardia | 0 | Foetal bradycardia | 1 |
| Local irritation | 1 | | |

## DISCUSSION

The available treatments of preterm labour can prolong pregnancy sufficiently but still efforts are being directed to find alternatives that are safer, better tolerated, and efficacious in prolonging pregnancy.[14] Since discovery of first β-sympathomimetic drug (isoxsuprine) in 1961 to inhibit preterm labour, the researchers are still in search of a safer and an effective agent. Recently various studies has been conducted worldwide on glyceral trinitrate (GTN) suggesting that these are equally or more efficacious in comparison to betamimetics with fewer side-effects.[15] The findings of our study are in accordance with the findings of Ghomian *et al*[16] who compared transdermal nitroglycerine with oral nifedipine for suppression of preterm labour. The suppression of uterine contractions after 48 hours of medication was significantly more common in the GTN group than in the nifedipine group. Another study reported that in females treated with nitroglycerine (NG), delivery was postponed for 2 hours, moreover, after 48 hours, the deliveries remained postponed in nitroglycerine (NG) group compared to nifedipine group, favouring our results.[13]

Dhawle *et al*[14] reported that prolongation of pregnancy for 48 hours was higher in nifedipine group (88.4%) compared to nitroglycerine group (68.3%) but mean prolongation of pregnancy was same in both groups. Another study documented that both nitroglycerin dermal patch and nifedipine postponed deliveries for 48 hours. However, nifedipine was found to be superior to nitroglycerin dermal patch in prolongation of gestational age at the time of delivery, perinatal outcome, and maternal acceptance.[17] Sharma *et al*[18] also observed effects of these drugs on delivery after 48 hours. According to them, the deliveries after 48 hours in nifedipine group were almost equal to the nitroglycerine group. Similarly, failure of tocolysis (delivery occurring within 48 hours) in nitroglycerine group (32.7%) was almost close to nifedipine group (33.3%) demonstrating similar effectiveness of both drugs as tocolytic agents.[18] Our study reports that transdermal nitroglycerine patch is more effective in delaying delivery compared to nifedipine due to its supply at constant and predictable rate without fluctuation of plasma concentration.

## CONCLUSION

Transdermal nitroglycerine patch was more effective to delay labour and prolong pregnancy as compared to nifedipine. Transdermal nitroglycerine may be promising safe, effective, well-tolerated, cost-effective, and non-invasive method of tocolysis.

## RECOMMENDATION

This study was performed in pregnant women of different age, gestational age and parity. The results cannot be applied on all age groups as well as gestational age groups. Further studies are recommended for comparison among other age groups. Further studies can be conducted to compare the side effects of these drugs in mother and new born.

## REFERENCES


1. Nankali A, Jamshidi PK, Rezaei M. The effects of glyceryl trinitrate patch on the treatment of preterm labor: a single-blind randomized clinical trial. J Reprod Infertil 2014;15(2):71–7.
2. Shaikh S, Shaikh AH, Akhter S, Isran B. Efficacy of transdermal nitroglycerine in idiopathic pre-term labour. J Pak Med Assoc 2012;62(1):47–50.
3. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. Semin Perinatol 2017;41(7):387–91.
4. Bivi S, Ramesh G. Role of transdermal nitroglycerine patch as tocolytic in preterm labour. Int J Contemp Surg 2016;4:58–62.
5. Bouchet N, Gayet-Ageron A, Lumbreras Areta M, Pfister RE, Martinez de Tejada B. Avoiding late preterm deliveries to reduce neonatal complications: an 11-year cohort study. BMC Pregnancy Childbirth 2018;18(1):17.
6. Haram K, Mortensen JH, Morrison JC. Tocolysis for acute preterm labor: does anything work. J Matern-Fetal Neonat Med 2015;28(4):371–8.
7. Soliman EA, Emara MA, Hamza HA, Al-Sabaawy AH. Prophylactic oral nifedipine to reduce preterm delivery: A

randomized controlled trial in women at high risk. Egypt J Hospital Med 2018;71(4):2907–12.
8. Kaur M, Goel B, Singh J. Comparative study of nitroglycerin dermal patch versus nifedipine in the management of preterm labour. Int J Reprod Contracept Obstet Gynecol 7(10):4244–8.
9. Haas DM, Benjamin T, Sawyer R, Quinney SK. Short-term tocolytics for preterm delivery —current perspectives. Int J Womens Health 2014;6:343–9.
10. Ishaq N, Ishaq Z, Mushtaq A, Ishaque I, Ishaq A. Comparative study of tocolytic efficacy of nifedipine and nitroglycerine. J Soc Obstet Gynaecol Pak 2017;7(2):96–100.
11. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, *et al*. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. The Lancet 2015;385(9966):430–40.
12. Ashraf B. Efficacy and safety of oral nifedipine with or without vaginal progesterone in the management of threatened preterm labor. Int J Reprod Biomed (Yazd) 2019;17(9):629–36.
13. Kashanian M, Zamen Z, Sheikhansari N. Comparison between nitroglycerin dermal patch and nifedipine for treatment of preterm labor: a randomized clinical trial. J Perinatol 2014;34(9):683–7.
14. Dhawle A, Kalra J, Bagga R, Aggarwal N. Nifedipine versus nitroglycerin for acute tocolysis in preterm labour: a randomised controlled trial. Int J Reprod Contracept Obstet Gynecol 2013;2(1):61–6.
15. Rekha S, Pooja G, Patel M, Shipra C, Reshu A. Clinical evaluation of transdermal nitroglycerine in preterm labor in tertiary care teaching hospital in North India. Int J Sci Res Pub 2012;2(3):1–7.
16. Ghomian N, Vahedalain SH, Tavassoli F, Pourhoseini SA, Heydari ST. Transdermal nitroglycerin versus oral nifedipine for suppression of preterm labor. Shiraz E-Med J 2015;16(11−12):e59923. doi: 10.17795/semj31018.
17. Hawkins JS, Wells CE, Casey BM, McIntire DD, Leveno KJ. A randomized double-blinded placebo-controlled trial of nifedipine for acute tocolysis of preterm labor. Am J Obstet Gynecol 2019;220(1 Suppl):S59.
18. Sharma N, Rani S, Huria A, Chawla D, Oral nifedipine versus nitroglycerine patch for tocolysis in preterm labour. Int J Reprod Contracept Obstet Gyenecol 2019;8(1):174–8.

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