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## Original Research Article

# Oral nifedipine versus nitroglycerine patch for tocolysis in preterm labour

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## ABSTRACT

**Background:** Preterm delivery is a major cause of neonatal mortality and morbidity. Various modalities have been used to prediction of patient at risk of preterm labor. But due to multi-factorial etiology these predictors are not always useful. Tocolysis has a major role in arresting preterm labor. The purpose of this study was to compare the safety and efficacy of oral nifedipine with transdermal nitroglycerine in the inhibition of preterm labour.

**Methods:** This single blinded randomized control trial was conducted in the labour room of department of Obstetrics and Gynecology from January 2011 to June 2012. One hundred women with singleton pregnancy between 28 weeks to 34 weeks preterm labour and no contraindication for tocolysis were enrolled in the study. After taking the informed consent subjects were randomized into two groups. Randomization was done by random number table. Fifty-one subjects in nifedipine group received oral nifedipine (Tab Depin 10mg). Forty-nine subjects receiving transdermal nitroglycerine patch (Nitroderm Patch 10) were included in NTG group. The variables analysed were delay in delivery for 48 hours, 7 days or more than 7 days, period of gestation at delivery and side effect profile of drugs.

**Results:** The percentage of women delivering after 48hours of administration of nifedipine group (52.9%) and nitroglycerine group (53.1%). Failure of tocolysis, defined as delivery within 48 hours, with nitroglycerine group (32.7 %) was comparable to nifedipine (33.3 %). Headache was significantly higher in nitroglycerine group as compared to nifedipine group ( $p \leq 0.001$ ). Maternal tachycardia was more common in nifedipine group compared to NTG group ( $p = 0.001$ ).

**Conclusions:** Oral nifedipine and transdermal nitroglycerine have similar efficacy as tocolytic agent in patients with preterm labour.

**Keywords:** Nifedipine, Nitroglycerine, Preterm labour, Tocolysis

## INTRODUCTION

Preterm birth remains one of the main causes of perinatal mortality and long-term morbidity. More than 70% of the total perinatal mortality can be attributed to preterm birth.<sup>1</sup> Preterm birth is also a major contributor to neonatal morbidities including weakening neurodevelopment capacities, learning impedance, visual disorders and secondary effects in long term health.<sup>2</sup>

Decreasing the preterm birth rate significantly below the current levels may be difficult to achieve because of the association of preterm labour with maternal medical and obstetrical complications and accompanying premature rupture of membranes.<sup>3</sup> However, Premature birth due to spontaneous preterm labour without any apparent medical or obstetric complications, may be amenable to treatment with tocolytics and may contribute to a significant decrease in the incidence of prematurity and neonatal

morbidity and mortality. Various methodologies had been used like screening for patients who are at risk of preterm birth, progesterone therapy, treatment of infections and tocolytic therapy.<sup>2,3</sup>

The goal of tocolytic therapy is to reduce neonatal morbidity and mortality by delaying birth, allowing for corticosteroid administration and maternal transfer to a tertiary care centre.<sup>4,5</sup> Hence, inhibition of preterm labour has assumed special importance in the practice of obstetrics and gynaecology. RCOG states that tocolysis should be considered if a delay of labour for a few days will allow completion of a course of corticosteroids or facilitate in utero transfer.<sup>6</sup>

Different tocolytic agents have been used to inhibit preterm uterine contractions to postpone delivery namely betamimetics, Magnesium sulphate (MgSO<sub>4</sub>), Prostaglandin synthetase inhibitors, Nitric oxide donors and Calcium channel blockers.

The most commonly studied tocolytic agent is nifedipine, which is calcium channel blocker. It can be administered either orally or sublingually. Nifedipine appears to be a more effective tocolytic agent than  $\beta_2$ -adrenergic-receptor agonists resulting in an improvement in neonatal outcome and is better tolerated than  $\beta_2$ -adrenergic-receptor agonists and magnesium sulfate.<sup>7</sup>

Nitroglycerine (NTG) is a nitric oxide donor, which in turn is a potent endogenous smooth muscle relaxant. Smith et al conducted a randomized, double blind placebo-controlled study with an aim to assess the efficacy of NTG as a tocolytic agent as compared to a placebo.<sup>8</sup> They found that transdermal nitroglycerine may reduce neonatal morbidity and mortality by decreasing the rate of preterm delivery before 28 weeks, from 20.3 to 10.8%. Amorim et al found similar effectiveness of nitroglycerine and nifedipine in inhibiting preterm labor, with tocolysis achieved within 12 hours among 85% of women who received nitroglycerine and 87.5% of those receiving nifedipine.<sup>9</sup> There are very few studies directly comparing the efficacy and safety of nifedipine and nitroglycerine as a tocolytic agent.<sup>9-11</sup> Thus, the present study was planned to compare nitroglycerine with nifedipine as tocolytics for preterm labour.

## METHODS

This single blinded randomized control trial was conducted in labour room in department of Obstetrics and Gynaecology from January 2011 to June 2012.

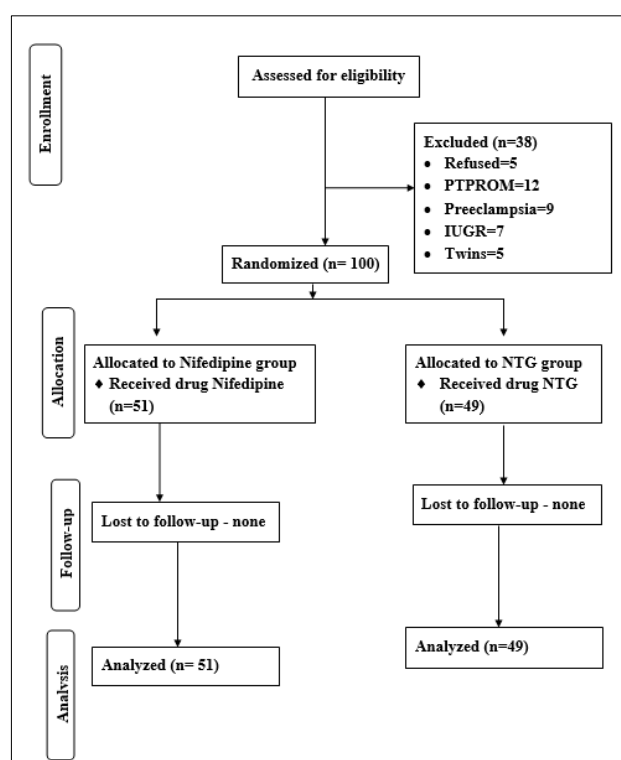
### Inclusion criteria

- One hundred women with singleton pregnancy between 28 weeks to 34 weeks preterm labour without contraindication for tocolysis were enrolled in the study as subjects.<sup>3</sup>

### Exclusion criteria

- Women with hypertensive disorder of pregnancy, antepartum haemorrhage, ruptured membranes or signs/symptoms of chorioamnionitis, cardiac disease, cervical dilatation more than 4cm, known tocolytic exposure during current pregnancy, intra uterine fetal demise, fetal malformation, severe intra uterine growth restriction and hypotension (BP less than 90mm systolic/less than 60mm diastolic) were excluded.

Flow diagram 1 shows the process of enrolment of subjects in the study. Informed consent was taken from all enrolled subjects. Randomization was done by random numbers using computer generated random number table.



**Figure 1: Flow diagram of the progress through the phases of the randomized trial comparing the two drugs.**

Nifedipine group had 51 subjects who received oral nifedipine (Tab Depin 10mg). They were given tablet nifedipine 20mg oral as loading dose. If contractions persisted after sixty minutes, additional oral dose of 10mg was given. If labour was suppressed after first/second dose, a maintenance dose of 10 mg orally every 6 hours was given starting 6 hours following the loading dose and continued until 48 hours.

NTG group had 49 subjects who received transdermal nitroglycerine patch (Nitroderm 10) which was applied on the abdomen. If contractions persisted at end of 1 hour, an additional patch was applied. Not more than 2

patches were applied simultaneously (20 mg). At end of 24 hours, it was replaced by another patch for next 24 hours. Blood pressure, pulse rate and uterine contractions were recorded hourly for the first 12 hours and then 4 hourly for next 36 hours in both the groups. Both drugs were to be bought by the subjects. Due to the nature of drugs and route of administration only statistician was blinded to the study.

Gestational age was determined by the date of last menstrual period (LMP) with a reliable menstrual history, an early urine pregnancy test and/or an ultrasound prior to 20 weeks of gestation. Demographic profile, detailed history with complete general physical examination including per abdominal examination and sterile per speculum examination to assess cervical dilatation and to exclude any rupture of membranes was done. Subjects were monitored for maternal and fetal wellbeing during the admission. Patients in both groups received injection betamethasone (Betnesol) 12mg intramuscular 2 dosage 24 hrs apart for fetal lung maturity.

If despite adequate therapy of 48 hours, labour progressed or if pulse rate was  $\geq 120$  beats/min or blood pressure was  $\leq 80/50$  mm of Hg, drug was discontinued. Inability of the drug to prolong gestation for a minimum period of 48 hours or persistence of uterine contractions even after 20mg of NTG or 30mg of nifedipine was considered to be treatment failure. Maternal outcome was measured in terms of duration of prolongation of pregnancy, gestational age at delivery and adverse drug reactions.

### Statistical analysis

Sample size of fifty patients in each group was calculated on the basis of  $\alpha$  error of 0.05 and power of 0.80. Data was entered in MS excel. SPSS-10 was used for statistical analysis. Student's t test and Chi square test were used for the comparison of drugs efficacy for successful tocolysis.

## RESULTS

Authors are reporting a single blinded randomized controlled trial comparing oral nifedipine and transdermal nitroglycerine for tocolysis in preterm labour. The baseline characteristic of subjects in both groups is shown in Table 1. No significant difference with respect to age, period of gestation or previous preterm birth was there between the two groups.

Table 2 shows the comparison of nifedipine and NTG as a tocolytic in preterm labour. Both drugs had equal effect on prolongation of pregnancy by more than 48hrs (52.9% in Nifedipine group, 53.1% in NTG group, p value=0.99) and till 7 days (13.7% in Nifedipine group, 14.3% in NTG group, p value=0.94). Comparable treatment failure had been found in both the groups (16/51 in Nifedipine group, 17/49 in NTG group, p value=0.94).

**Table 1: Baseline characteristics of both groups.**

Variables	Nifedipine group (n=51)	NTG group (n=49)	P-value
Age (years) <sup>a</sup>	24.4 $\pm$ 3.8	24.1 $\pm$ 2.8	0.66
Period of gestation on admission (weeks) <sup>a</sup>	32.8 $\pm$ 1.5	33 $\pm$ 1.1	0.39
Previous preterm delivery <sup>b</sup>	5 (18.5%)	7 (14.2%)	0.28
<b>On admission</b>			
Pulse rate (beats per min) <sup>a</sup>	84.6 $\pm$ 5.2	86.2 $\pm$ 6.8	0.12
Systolic blood pressure (mm of Hg) <sup>a</sup>	114.9 $\pm$ 9.5	111.6 $\pm$ 8.5	0.07
Diastolic blood pressure (mm of Hg) <sup>a</sup>	72.6 $\pm$ 9.1	69.3 $\pm$ 8.6	0.06
Bishop score <sup>c</sup>	5 (4-6)	5 (4-5)	0.98

<sup>a</sup> represents the values in mean $\pm$ SD, <sup>b</sup> represents the value in number (%), <sup>c</sup> is median (IQR)

The most common side effect in NTG group was headache (21/49) which was significantly more than in Nifedipine group (6/51) (p value <.001). These mild headaches were treated with paracetamol. Tachycardia was the most common side effect in Nifedipine group (23/51) and was significantly more than NTG group (p value 0.001). Six subjects in NTG group and 4 subjects in Nifedipine group had discontinuation of tocolysis due to side effect.

**Table 2: Comparison of nifedipine and NTG between the two groups.**

Variable	Nifedipine group (n=51)	NTG Group (n=49)	P value
<b>Prolongation of pregnancy (days)<sup>a</sup></b>			
<2	17 (33.3%)	16 (32.7%)	0.95
2-7	27 (52.9%)	26 (53.1%)	0.99
>7	7 (13.7%)	7 (14.3%)	0.94
<b>Completion of antenatal steroid cover<sup>a</sup></b>			
Yes	40 (78.4%)	38 (77.6%)	0.91
No	11 (21.6%)	11 (22.4%)	
Treatment failure <sup>a</sup>	17 (33.3%)	16 (32.7%)	0.95
<b>Side effects<sup>a</sup></b>			
Headache	6 (11.8%)	21 (42.9%)	<0.001**
Hypotension	1 (2%)	7 (14.3%)	0.03*
Tachycardia	23 (45.1%)	7 (14.3%)	0.001**
Treatment discontinuation	4 (7.8%)	6 (12.2%)	0.52

<sup>a</sup> represent the data in number of patients (%)

Table 3 compares the fetal outcome in both groups. No statistically significant difference was found in the gestational age at the time of delivery (p value 0.42) and birth weight (p value 0.10) between the two groups. Birth asphyxia was comparable in two groups (p=0.36). One

neonatal death occurred in nifedipine group and there was none in NTG group.

**Table 3: Comparison of fetal outcome in both groups.**

Variable	Nifedipine group (n=51)	NTG group (n=49)	P-value
Gestational age at delivery (weeks) <sup>a</sup>	33.1±1.5	33.1±1.1	0.42
Birth weight (kg) <sup>a</sup>	1.79±0.35	1.81±0.27	0.10
Apgar score <sup>b</sup>	9 (9-9)	9 (9-9)	0.50
<b>Neonatal complications<sup>c</sup></b>			
Birth asphyxia	4 (7.8%)	1 (2%)	0.36
Death	2 (3.9%)	0 (0%)	0.49

<sup>a</sup> represents the values in mean±SD, <sup>b</sup> is median (IQR), <sup>c</sup> represents the number of patients (%)

## DISCUSSION

Primary goal of tocolysis is to have some time to administer antenatal corticosteroid which leads to reduce neonatal morbidity and mortality. In present study, authors found that the prolongation of pregnancy >2 days could be achieved in 34/51 and 33/49 in Nifedipine group and NTG group, respectively. Also, the effect of nitroglycerine was non-inferior to nifedipine. Amorim et al enrolled 50 patients and compared the effect of oral nifedipine and NTG as a tocolytic agent. They found the rate of preterm delivery in the first 48 hours was 15.4% and 12.5% respectively in nitroglycerin and nifedipine groups. Both drugs were found to be almost equally efficacious. Headache was significantly more in NTG group than nifedipine (30.8% versus 8.3%,  $p=0.04$ ). Similar results are found in present study (42.9% versus 11.8%,  $p=0.001$ ).<sup>9</sup> Dhawle A et al compared the tocolytic effect of nifedipine and NTG in 43 and 41 patients in each group, respectively. They found that delivery within 48 hours, was significantly more with NTG as compared to Nifedipine ( $p=0.02$ ). The neonatal outcomes in terms of the mean birth weight, need and duration of neonatal intensive care was similar in both groups as observed in present study too.<sup>10</sup> Kashanian et al, did a randomised clinical trial comparing NTG and nifedipine as a tocolytic agent. They found that more number of women in NTG group delivered after 48 hours (52 women (86.7%) vs 41(68.3%),  $P=0.016$ ) and after 7 days (47 (78.3%) vs 37 (61.7%),  $P=0.046$ ), than women in the nifedipine group. Fetal outcomes like Apgar score, neonatal weight were better in NTG group. Also, the neonatal intensive care unit (NICU) admission and duration of NICU stay were less in the NTG group. Adverse effects were similar and minimal in both groups.<sup>11</sup>

The American College of Obstetricians and Gynaecologists supports the use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids. However, tocolytic

therapy has no direct favourable effect on neonatal outcomes.<sup>12</sup> As it is a randomized control trial, so this is the strength of present study. However, authors have not compared the cost effectiveness of both drugs is the weakness.

## CONCLUSION

To conclude present study showed transdermal nitroglycerine to be noninferior to oral nifedipine for tocolysis in preterm labor.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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