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Dr. Pankaj Salvi
Associate Professor, Department of Obstetrics and Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, Pune, Maharashtra, India

Dr. Vidya Gaikwad
Professor and Head of Unit, Department of Obstetrics and Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, Pune, Maharashtra, India

Dr. Rashida Ali
Junior Resident, Department of Obstetrics and Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, Pune, Maharashtra, India

Dr. Aishwarya
Junior Resident, Department of Obstetrics and Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, Pune, Maharashtra, India

Dr. Hemant Deshpande
Professor, Head of Unit and Head of Department, Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, Pune, Maharashtra, India

Corresponding Author:
Dr. Rashida Ali
Junior Resident, Department of Obstetrics and Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, Pune, Maharashtra, India

Comparative study of oral Nifedipine tablet and transdermal Nitroglycerin patch in preterm labour

Dr. Pankaj Salvi, Dr. Vidya Gaikwad, Dr. Rashida Ali, Dr. Aishwarya and Dr. Hemant Deshpande

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Abstract
Preterm labour (PTL) is defined as the onset of labour in pregnancy from 28 weeks to 36weeks and 6 days. One of the most challenging problem of obstetrician in the era of modern obstetrics is the management of preterm labour and preterm births (PTB); Being the most common cause of perinatal morbidity and mortality PTB accounts for 70-80% of perinatal deaths. More than a million preterm infants die per year, worldwide.

Aim: To Compare the Tocolytic effect of Oral Nifedipine tablet and Transdermal Nitroglycerin (TDN) patch in preterm labour and its effect on maternal and fetal outcome.

Materials and Methods: It was a Double Blinded placebo controlled study conducted at Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, from November 2018 to April 2019. The study population comprised of patients who attended the casualty and outpatient department. Eighty-eight women with singleton pregnancy from 28weeks to 36weeks 6 days in preterm labour with intact membranes and cervical dilatation from 1 up to 3 cm; without contraindication for tocolysis were enrolled in the study. After taking the informed consent, subjects were randomised into two groups; 46 subjects in group A received oral Nifedipine tablet, out of which 4 left the study and 46 in group B received TDN patch. The variables analysed were, delay in delivery for 48 hours, 7 days or more than 7 days, period of gestation at delivery, effect on maternal and fetal outcome and side-effect profile of drugs.

Result: The percentage of women delivering after 48 hours of administration of oral Nifedipine were 66.67% and TDN patch were 76%. Failure of tocolysis, defined as delivery within 48 hours, was significantly more with Nifedipine group (8/42-19.05%) as compared to TDN patch group (3/46-6.5%). Headache was significantly higher in group B as compared to group A ($p< 0.001$). Maternal tachycardia was more common in group A compared to group B ($p< 0.001$).

Conclusion: Transdermal Nitroglycerin (TDN) patch is more effective than oral tablet Nifedipine in suppression of preterm labour and prolonging pregnancy. Although the rate of side effects were more with Nitroglycerin, most common was headache which can be controlled with analgesics. Cardiovascular side effect were nil compared with Nifedipine. Nitroglycerin is well tolerated and safe for the mother and fetus.

Keywords: Preterm labour (PTL), Tocolysis**,** Preterm births (PTB), Nifedipine, Nitroglycerin (NTG)

Introduction

Preterm labour (PTL) is defined as the onset of labour in pregnancy from 28 weeks to 36weeks and 6 days with intact membrane. One of the most challenging problem of obstetrician in the era of modern obstetrics is the management of preterm labour and preterm births (PTB). Being the most common cause of perinatal morbidity and mortality, PTB accounts for 70-80% of perinatal deaths. Perinatal mortality in preterm born infants is 5-7 times more than term born in India [1]. PTB is the leading cause of infant morbidity and mortality. More than a million preterm infants die per year worldwide. Real reduction of PTB will take place through an improved understanding of physiology of labour, identification of the patient in risk of preterm labour, prediction and prevention of its occurrence and early detection of its onset and effective tocolysis [2].

According to World Health Organization (WHO), preterm is defined as a gestational age of <37 completed weeks (259 days) from the first day of the last menstrual period. PTL is defined by WHO as the onset of labour in a pregnancy before the completion of 37 weeks of gestation and after 20 weeks of gestation [3]. As per American College of Obstetricians and Gynecologist (ACOG) criteria (1997), PTL is defined as the onset of labour in a pregnancy before the

completion of 37 weeks of gestation with the occurrence of regular uterine contractions of 4 in 20 mins or 8 in 1 hour plus progressive change in the cervix, cervical dilatation >1 cm, cervical effacement 80% or greater [4, 5].

Threatened Preterm (TPL) has been defined as the presence of at least 3 regular and painful uterine contractions within a 30-minute period[6], or the presence of at least two uterine contractions every 10 min for 60 minutes, in combination with cervical changes ascertained on digital examination, and/or cervical length <30 mm measured by transvaginal ultrasonography. Others have defined TPL as the occurrence of persistent premature uterine contractions between 20 and 37 weeks of gestation accompanied by other symptoms such as pelvic pressure, backache, increased vaginal discharge, menstrual-like cramps, bleeding/show and shortened cervix[7].

The tocolysis used to prevent PTL basically aims at prolonging the pregnancy for at least 48 -72 hrs, so as to provide adequate time to administer parenteral corticosteroid, in-utero transfer to higher medical center with adequate NICU facilities [8].

Compared to Beta 2 sympathomimetics (beta 2 agonist/stimulants), Oral tablet Nifedipine is associated with improvement in neonatal outcome. Nifedipine is significantly more successful in prolonging pregnancy beyond 48 hers and effective in delaying birth for up to 7 days. The use of calcium channel blockers rather than other tocolytic drug was associated with a reduction in the number of women giving birth within 7 days of giving treatments and before 34 weeks of gestation [9].

Nitroglycerin (NTG) is the drug with a high first pass metabolism in liver, active substance is rapidly metabolized in the liver by a glutathione dependent organic nitrate reductase. Adverse effects are headache. Transdermal Nitroglycerin (TDN) patch is safe and has rapid onset of action, bio-availability of 70-80%, steady delivery for 24 hours, low risk of side effects, well tolerated, cost effective, non-invasive method of tocolysis and minimum monitoring required [10].

Both NTG and Nifedipine have been shown to be effective in PTL. In this study, we compare the safety and efficacy of TDN with oral tablet Nifedipine as a tocolytic in preventing PTL.

Aim and Objectives

AIM: To study the effect of Transdermal Nitroglycerin (TDN) patch versus Oral Nifedipine tablet in Pretem labour (PTL).

Objectives

1. Acute tocolytic effect
2. Duration of prolongation of pregnancy
3. To compare the side-effects of both the drugs
4. To evaluate feto-maternal outcome.

Materials and Methods

It was a Double Blinded placebo controlled study conducted at Dr. D. Y. Patil Medical College, Hospital & Research Center, Pimpri, from November 2018 to April 2019. The study population comprised of patients who attended the casualty or outpatient department. Eighty-eight women with singleton pregnancy from 28 weeks to 36weeks 6 days in preterm labour with intact membranes with cervical dilatation from 1 up to 3 cm and no contraindication for tocolysis were enrolled in the study.

Inclusion criteria

- Singleton pregnancy with gestation age from 28 weeks to 36 weeks and 6 days.
- Regular painful uterine contractions minimum of two, every ten minutes and for more than 1 hour
- With intact membranes
- Cervical dilatation from 1 up to 3 cm.
- No medical condition obviating medical therapy
- No previous administration of tocolytics

Exclusion criteria

- Premature rupture of membranes
- Fetal distress
- Chorioamnionitis
- Antepartum hemorrhage
- Sensitivity or contraindication to Nifedipine / nitrates
- Systemic diseases like diabetes mellitus, cardiac diseases, liver or renal diseases, hypotension
- Obstetric complications like Hypertensive disorders of pregnancy, antepartum hemorrhage, ruptured membranes, dilatation of >3cm
- Fetal complications like chorioamnionitis, IUGR, congenital anomaly, fetal distress wherever early delivery is needed.
- Known Hypersensitivity to Nifedipine or NTG

After taking the written and informed consent subject were randomised into two group, group A comprised of 46 subjects & received oral tablet Nifedipine 20 mg every 12 hourly, out of which 4 left the study. Group B comprised of 46 subjects & received transdermal Nitroglycerin (TDN) patch 10 mg every 24 hours (0.4mg per hour). Time needed for tocolysis, prolongation of pregnancy and the neonatal outcomes were observed. Results were meticulously analysed. All the patients received prophylactic parenteral antibiotics, Ceftriaxone 1gm injection (Ceftriaxone sodium I.P.), Injection Vitamin K 10mg IM (Menadione Sodium Bisulphite I.P.), 24mg intramuscular glucocorticoid injection as 4 doses in 48 hours in the form of injection Dexamethasone Sodium Phosphate I.P. 6mg IM given 12 hours apart.

Oral Nifedipine tablet (Group A)

Tablet Nifedipine 20mg oral loading dose was given, if contractions persist or increases at the end of 1 hour additional 10 mg Nifedipine tablet was given. If labour was not suppressed after 1 hour of second dose of 10mg, it was considered as a treatment failure and then third line of treatment was continued as per senior consultant advice. If contractions subsided at the end of 1 hour after initial dose of 20mg (or after further 60 minutes after 2nd dose of 10mg) then, a maintenance dose of oral Tablet Nifedipine retard 20mg as a sustained release preparation was given every 12 hourly orally for a total 48 hours. Monitoring was done as mentioned in chart M.

A placebo in the form of TDN patch had been applied by a ward nurse on the patient abdomen without removing the back (therapeutic) barrier film covering on the adhesive side of the patch (no release of NTG). The patch was held in place by an additional leucoplast on it and replaced by similar fresh placebo patch after 24 hours till further 24 hours (total 48 hour) (adhered) on the abdomen of patient as placebo with an opaque dermapore or leuco-adhesive superimposed on non-therapeutic patch and did not release any NTG.

In cases where additional dose of Nifedipine was given it was accompanied by 1 more placebo patch.

Transdermal Nitroglycerin patch (TDN) (Group B)

Patch delivering 10mg Nitroglycerin (NTG) over 24 hours (0.4mg per hour) was applied on patients abdomen as initial

treatment, via the adhesive side, by removing the therapeutic barrier film & was held further by an additional leucoplast on it covering it completely(to make it look alike the placebo patch as mentioned above). If contractions persisted or increase at the end of one hour, an additional therapeutic patch of 10mg NTG was also applied on the other side of abdomen and covered with leucoplast or opaque dermapore. No more than 2 therapeutic patches of 10mg each, were applied simultaneously, initially (total 20 mg). If tocolytic effect was seen at the end of 1 hour of initial patch (or 60 minutes after second TDN patch), then maintenance TDN patch was applied after 24 hours (10mg TDN for a period of further 24 hours as therapy). Previous one (or two) patch were removed when applied with this second day patch. Mild headaches were treated with tablet paracetamol 500 mg single dose. Thus, therapeutic patches remained on abdomen for 48hours after the initial contraction has ceased. All patches were covered by superimposed opaque transpore or leuco-adhesive barrier like in group A.

Patient also received placebo tablet of calcium 500mg (similar looking to Tablet Nifedipine) as in group A, 12 hourly for a total of 48 hours only, matching the dosing schedule as in group A.

Monitoring (Chart M)

Patients were monitored from the time of admission to the time of discharge. Maternal pulse rate, blood pressure, fetal heart rate and uterine contractions were monitored initially every 15 mins for first 2 hours. Then every 2 hours for 8 hours and every 8 hours for 48 hours.

Patients were not allowed to consume tea, coffee or grapes.

Treatment was discontinued, if there were any one or more side effects like;

- Fall of BP less than 90/60 mmHg or
- If the pulse rate was more than 140/ mins or
- If the patient had premature rupture of membrane or
- Signs of fetal distress
- Any Serious systemic side effects

Treatment Failure: Persistence of uterine contractions at the end of one hour, even after total 20mg of TDN or 30mg of oral Tab Nifedipine after initiating the therapy OR

Inability of the drug to prolong gestation for a minimum of 48 hours from the start of the therapy.

The study outcomes were recorded in terms of Delay in delivery for 48 hours, 7 days and more than 7 days, period of gestation at delivery, onset of subsequent labour -spontaneous or induced, any side effect of each drug and the neonatal outcomes, recorded as birth weight, Apgar score, respiratory distress, need and duration of NICU care, neonatal complications and any perinatal mortality

Random selection and allocation of Groups details were known only to 3rd party staff nurse and the non-studying faculty (Consultants). Therapy was kept blinded to participating patient and investigating PG student doctor (outcome assessor), although not to nurses (Group selector-allocator and drug dispenser).

Risk of bias

- Randomisation (selection bias): Low risk; (randomization by nurse using chit randomization number).
- Allocation concealment (selection bias): Low risk.
- Blinding of participants and personnel (performance bias): Low risk; (participants and doctors blinded, not nurses who applied the patch and who gave the tablets).
- Blinding of outcome assessment (detection bias): Low risk; (outcome assessors, investigating doctor blinded).
- Incomplete outcome data (attrition bias): Low to moderate risk; [92 women were randomized but 88 women were accounted for the analysis as 4 women in group A left the study in middle, group A comprised of 46 -(minus) 4 = 42(n) and group B comprised of 46(n)].
- Other bias: Low risk; (baseline characteristics of groups appeared similar).

Statistical analysis done by

Appropriate statistical methods and tests were applied.

The collected data was analyzed by using statistical tools (SPSS version 16) using descriptive statistics (mean, standard deviation and confidence interval) and the chi square test to compare the efficacy and adverse maternal and fetal outcomes. The p value less than 0.05 was taken to denote significant relationship.

Results and Discussion

Table 1: Comparison of Mean age

Group	Mean ± S.D	P Value
GROUP A (n =46-4=42)	25.8 ± 2.60	0.07 (NS)
GROUP B (n=46)	27.0 ± 3.06	

Baseline characteristics of two groups were comparable. [NS=not significant]

Study included eighty eight women with preterm labour, randomized to Group A Nifedipine (n=46-4=42) and Group B NTG (N=46), the mean age of women in the two groups were comparable (25.8-\+2.60) Years +SD in group A versus (27.0+/-3.06) Years +SD in group B.

Table 2: Comparison based on parity.

Parity	Group A (n=46-4=42)	Group B (n=46)	P Value
PRIMI	18(42.8%)	22 (47.82%)	0.51 (NS)
PARA 1	16(38.16%)	20(43.47%)	
PARA 2	8(19.04%)	4(8.71%)	
TOTAL	42(100%)	46(100%)	

There was no significant difference in parity between the two groups, with primigravida women predominating in both groups 18 (42.8%) women in group A and 22(47.82%) in group B were primigravida.

Table 3: Comparison based on mean gestational age in weeks at the onset of preterm labour.

Group	Mean ± S.D	P Value
GROUP A (n=46-4=42)	34.71 ± 1.25	0.06 (NS)
GROUP B (n=46)	35.43 ± 1.63	

The mean gestational age of the onset of preterm labour in the two groups (34.71 weeks +/-1.25 SD) and 35.43 weeks +/-1.6 SD) in group A and B respectively.

P value is not significant.

Table 4: Distribution of cases based on H/O of preterm.

H/o of preterm	GROUP A	GROUP B	P VALUE
Positive	8 (19.05%)	10(21.74%)	0.1(NS)
Negative	34 (80.95%)	36 (78.26%)	
Total	42 (100%)	46 (100%)	

History of previous preterm delivery (PTD) was present in only 18 of the 88 women (20.45%).
8 women (19.05%) in group A has previous preterm delivery versus 10 (21.74%) in group B, which was comparable.

Table 5: Distribution of cases based on H/O of recurrent pregnancy loss.

H/o of recurrent pregnancy loss	Group A	Group B	P Value
Positive	4(9.52%)	3 (6.52%)	0.06(NS)
Negative	38(90.48%)	43(93.48%)	
Total	42 (100%)	46 (100%)	

History of recurrent pregnancy loss was present in only 7 of the 88 women (7.95%).
4 women (9.52%) in group A has history of recurrent pregnancy loss versus 3 (6.52%) in group B, which was comparable.

Table 6: Distribution of cases based on urine culture and sensitivity.

Urine cs	Group A	Group B	P Value
Positive	9(21.43%)	7(15.22%)	0.1 (NS)
Negative	33 (78.57%)	39 (84.78%)	
Total	42 (100%)	46 (100%)	

Table 7: Distribution of cases based on Steroid administration.

Steroid administration	Group A	Group B	P Value
Positive	32(76%)	40(86.7%)	0.10 (NS)
Negative	10 (24%)	6 (13.3%)	
Total	42 (100%)	46 (100%)	

In group A 76% of women of gestational age <34 weeks with preterm labour pain completed the course of steroid (4 doses of injection dexamethasone 6mg IM given 12hours apart) while in group B 86.7% of women were able to complete the course of steroid. However, the difference between two groups were not statistically significant (p=0.10).

Table 8: Comparison based on mean duration of prolongation of pregnancy in days.

Group	Mean ± S.D	P value
GROUP A (n=46-4=42)	7.46 ± 6.86	0.89 (NS)
GROUP B (n=46)	7.70± 6.39	

Table 9: Comparison of duration of prolongation of pregnancy.

Duration of prolongation of pregnancy	Group A	Group B	P Value
24 Hours	8(19.05%)	3(6.52%)	0.04(S)
48 hours	6(14.28%)	8 (17.39%)	0.91
72 hours	4 (9.52%)	4(8.69%)	0.95
7 days	12(28.57%)	12(26.08%)	0.93
>7 days	12(28.57%)	19(41.30%)	0.81
Total	42 (100%)	46 (100%)	

In present study, we compared the duration of prolongation of pregnancy in both the groups. The mean prolongation of pregnancy was 7.46+/-6.86 days in group A versus 7.70 +/- 6.39 days in group B, was not stastically significant. However, failure of acute tocolysis defined as delivery within 48 hours was significantly more with Nifedipine (8/42—19.05%) as compared to NTG (3/46—6.5%).
The duration of prolongation of pregnancy exceeded more than 7 days in 12 (28.57%) women in group A as compared to 19 (41.30%) in group B, although the difference was not statistically significant, because of small sample size (P =0.81).

Table 10: Comparison of prolongation of pregnancy with cervical dilatation <3 cm.

Duration of prolongation of pregnancy	Group A	Group B	P value
21 days	12	19	0.40 (NS)
Total	42	46	

Cervical dilatation at the start of tocolysis is the most important factor influencing prolongation of pregnancy.
In Nifedipine group 12 out of 42 (28.57%) women presenting with a dilatation of <3 cm had a pregnancy prolongation beyond 3 weeks,
In NTG group 19 of the 46 women (41.30%) presenting with dilatation of <3 cm had a pregnancy prolongation of at least 21 days.
Comparing two groups with respect to both cervical dilatation at the onset of tocolysis and mean prolongation of pregnancy when the cervical dilatation was <3cm, there was no significant difference between the two groups (P value is 0.40).

Table 11: Distribution of cases based on mode of delivery

Mode of delivery	Group A Nifedipine	Group B transdermal Nitroglycerin	P Value
Vaginal	35 (83.3%)	40 (86.7%)	0.061
LSCS	7 (16.7%)	6 (13.3%)	
Total	42 (100%)	46 (100%)	

The comparison of mode of delivery (vaginal/cesarean) between the two groups was not statistically significant (p=0.061). In group A 83.3% women delivered vaginaly compared to group B 86.7% women delivered vaginaly.

Table 12: Distribution of study participants based on neonatal outcome

Neonatal outcome	Group A	Group B	P Value
BW <2.5KG	12(28.57%)	10(21.74%)	0.48
BW <2.5KG+ NJ	7 (16.66%)	6 (13.04%)	0.41
Hypoglycemia	4 (9.52%)	6 (13.04%)	0.46
Neonatal Jaundice	12 (28.57%)	16 (34.78%)	0.43
RDS BW<2.5KG	6 (14.28%)	6 (13.04%)	0.44
SEPSIS	1 (2.4%)	2 (4.36%)	0.47
TOTAL	42 (100%)	46 (100%)	

The two groups performed similarly with respect to the mean birth weight, incidence of low birth weight (LBW) and very low birth weight (VLBW) babies and mode of delivery. Similarly, there was no significant difference in the neonatal outcome complication like respiratory distress syndrome (RDS), birth asphyxia, hypoglycemia and sepsis, need for neonatal intensive care unit (NICU) admission and mean duration of stay. Neonatal jaundice was the commonest complication 28 out of 88 (31.81%) followed by RDS 12 out of 88 (13.63%).

Table 13: Distribution of study participants based of maternal side effect

Maternal side effect	Group A	Group B	P Value
Headache	2(4.76%)	28(60.86%)	0.04(S)
Flushing	4(9.52%)	3(6.52%)	0.48
Nausea	0	0	
Hypotension	0	2(4.34%)	0.46
Palpitation	19(38%)	2 (4.34%)	0.046(S)
Headache + nausea	3 (7.14%)	3(6.52%)	0.47
Headache+ hypotension	0	0	
Headache +palpitation	3 (7.14%)	2 (4.34%)	0.42
Headache +tachycardia	12(26.11%)	6 (13.04%)	0.48
Hypotension +tachycardia	0	0	
Total	42(100%)	46 (100%)	

We also assessed the clinical side effect of Nifedipine and Transdermal Nitroglycerin patch (TDN). In present study, headache occurred in 60.86% of women in group B while 4.76% of women in group A, the difference was statistically significant (P=0.04). On visual analogue scale the severity of pain in group B was found to be mild in 70% of women and moderate in 30% of women, however none of the women suffered from severe headache. Palpitation and tachycardia were observed in 64.11% of women in group A and while 17.38% in group B, the difference was significant, P value was significant (P=0.046)

In our study, preterm labour was common in Primigravida in age group of 20-30 years accounting for 45.45%.

The percentage of women delivering after 48 hours of administration of oral Nifedipine was 66.67% and transdermal Nitroglycerin patch (TDN) was 76%. Failure of tocolysis, defined as delivery within 48 hours was significantly more with Nifedipine Group A (8/42 – 19.05%) as compared to transdermal Nitroglycerin patch (TDN) Group B (3/46 – 6.5%). Headache was significantly higher in group B as compared to group A ($p< 0.05$). Maternal palpitation was more common in group A compared to group B ($p< 0.05$).

Conclusion

To conclude, double blind placebo study showed Transdermal Nitroglycerin (TDN) patch to be more effective than Nifedipine in suppression of preterm labour and prolonging pregnancy. In developing countries neonatal intensive care are usually found in tertiary referral hospitals but not all such units have the required treatment capabilities. There is statistically significant benefits of TDN over Nifedipine in suppressing the uterine contractions for in utero transfer and in reducing neonatal respiratory distress syndrome. Side-effects were more with TDN, most common being headache, which can be controlled with analgesics. In addition TDN has an option of stopping, halting and modifying the NTG drug delivery. Cardiovascular side-effects were nil compared to Nifedipine. Nitroglycerin is well tolerated and safe for the mother and fetus and its low cost can make TDN amongst the first line tocolytic agents.

Ethical approval: The study was approved by the institutional ethical committee.

Conflict of interest: None declared.

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