

A COMPARATIVE STUDY OF ORAL NIFEDIPINE AND TRANSDERMAL NITROGLYCERINE PATCH FOR TOCOLYSIS IN PRETERM LABOUR

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ABSTRACT

Background: Spontaneous preterm labour without any apparent medical or obstetric complications is one of the main reason for perinatal mortality. The present study was conducted to compare oral nifedipine and transdermal nitroglycerine patch for tocolysis in preterm labour to determine the decrease in neonatal and maternal comorbidities.

Materials and methods: 120 patients with preterm labour during 28 to 36 weeks gestational age were divided into two groups of 60 each. Patients in group I were given oral nifedipine and in group II transdermal nitroglycerine patch was applied.

Results: Comparison of maternal age in both the study groups. The distribution of maternal age is almost similar in both the groups. Comparison of mean prolongation duration according to gestational age in both the study groups indicate that overall duration of prolongation was better in oral nifedipine group compared to Nitroglycerine patch group. However, the differences were not statistically significant. Comparison of complications and their p values (<0.05) indicate that headache and hypotension was significantly higher in Nitroglycerine patch compared to oral nifedipine group. This also led to significantly higher discontinuation rate due to hypotension in Nitroglycerine patch group compared to oral nifedipine group. Tachycardia was significantly higher in oral nifedipine group compared to Nitroglycerine patch group with p value <0.01. Comparison of complications which lead to treatment discontinuation in both the study groups. In oral nifedipine group treatment was discontinued in one case due to severe headache, in four cases due to tachycardia, and in one case due to hypotension. In Nitroglycerine patch group treatment was discontinued in five cases due to severe headache, in two cases due to tachycardia, in five cases due to hypotension, and in one case due to palpitation. Out of 60 cases in oral nifedipine group in 6 cases treatment was discontinued while in Nitroglycerine patch group in 13 cases treatment was discontinued. This difference was statistically significant (p<0.05) indicating that treatment discontinuation was significantly higher in Nitroglycerine patch compared to oral Nifedipine.

Conclusion: Considering the availability and side effects we recommend to use oral nifedipine for tocolysis over Nitroglycerine patch.

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. 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. Decreasing the preterm birth rate significantly below the current levels may be difficult to achieve because of the association of preterm labor with maternal medical and obstetrical complications and accompanying premature rupture of membranes. However, Premature birth due to spontaneous preterm labor 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 mortality and morbidity. 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 center. RCOG

states that tocolysis should be considered if a delay of labor for a few days will allow completion of a course of corticosteroids or facilitate in utero transfer. Different tocolytic agents have been used to inhibit preterm uterine contractions to postpone delivery namely betamimetics, Magnesium sulphate (MgSO₄), Prostaglandin synthetase inhibitors, Nitric oxide donors and Calcium channel blockers.

MATERIALS AND METHODS:

- 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.
- After randomization, patients were divided in two groups : group A received Oral Nifedipine and group B received Transdermal Nitroglycerine Patch
- Blood pressure, pulse rate and uterine contractions were recorded hourly for the first 12 hours and then 4 hourly for next 60 hours in both the groups.
- Patients in both groups received **injection dexamethasone** for fetal lung maturity.

GROUP A : ORAL NIFEDIPINE

- Nifedipine group received oral nifedipine (Tab Depin 10mg). They were given tablet **nifedipine 30mg 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 72 hours**

GROUP B : TRANSDERMAL NITROGLYCERINE PATCH

- NTG group 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.
- At end of 24 hours, it was replaced by another patch for next 24hours.

OBSERVATIONS AND RESULTS:

Table 1: Comparison of maternal age in both the study groups

Maternal Age in years	Oral Nifedipine (n=60)		Nitroglycerine Patch (n=60)		P value*
	Cases	Percentage	Cases	Percentage	
18-20	7	11.67%	3	5.00%	0.167
21-25	26	43.33%	38	63.33%	
26-30	23	38.33%	18	30.00%	
30-34	3	5.00%	1	1.67%	
>=35	1	1.67%	0	0.00%	
Total	60	100.00%	60	100.00%	
Mean age in years	24.25±3.99		24.20±2.63		

*Chi square test applied for calculation of p value

Table 1 shows comparison of maternal age in both the study groups. The distribution of maternal age is almost similar in both the groups. The mean age in oral nifedipine group was 24.25 ± 3.99 years whereas in Nitroglycerine patch group 24.20 ± 2.63 years. P value is >0.05 indicating that there is no difference in age distribution of mothers in both the study groups. It means that age distribution of subjects was almost similar in both the groups.

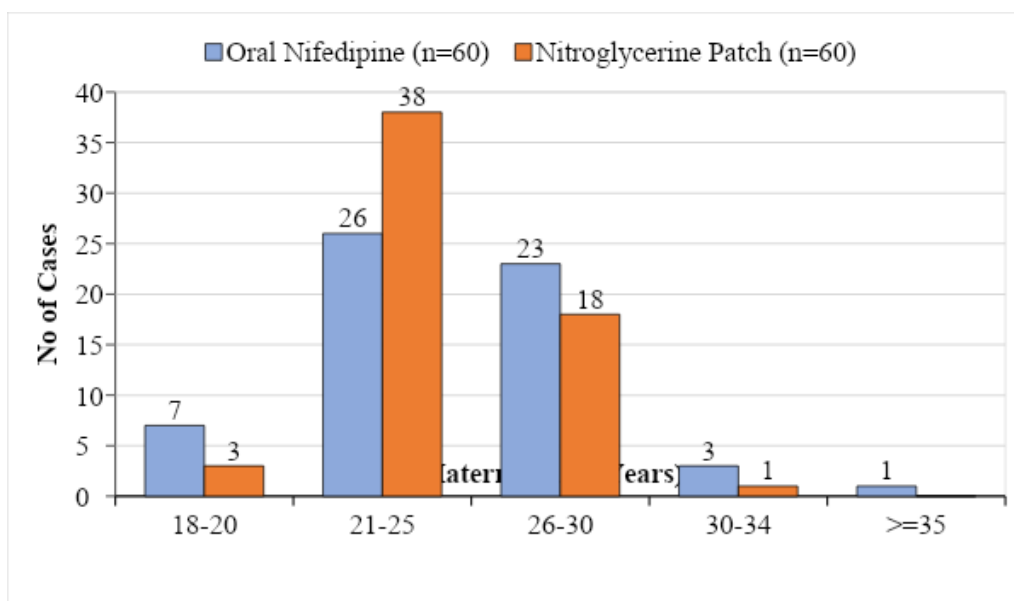


Figure 1: Comparison of maternal age in both the study groups

Table 2: Comparison of Gestational age at the time of reporting in both the study groups

GA at the time of Reporting	Mean Prolongation in days (up to 7 day f/up)		P value*
	Oral Nifedipine (n=60)	Nitroglycerine Patch (n=60)	
28-30 weeks	3.01 ± 2.06	2.76 ± 1.24	0.422
30-32 weeks	3.49 ± 2.22	2.67 ± 2.76	0.075
32-34 weeks	3.71 ± 1.65	2.93 ± 2.73	0.060
35-36 weeks	3.53 ± 2.26	3.06 ± 1.69	0.209

*Unpaired t test applied for calculation of p value

Table 2 shows comparison of Gestational age at the time of reporting in both the study groups. The mean prolongation days at 28-30 weeks of GA was 3.01 ± 2.06 in oral nifedipine group whereas in nitroglycerine patch group it was 2.76 ± 1.24 . The mean prolongation days at 35-36 weeks of GA was 3.53 ± 2.26 in oral nifedipine group whereas in nitroglycerine patch group it was 3.06 ± 1.69 . Comparison of mean prolongation duration according to gestational age in both the study groups indicate that overall duration of prolongation was better in oral nifedipine group compared to Nitroglycerine patch group. However, the differences were not statistically significant.

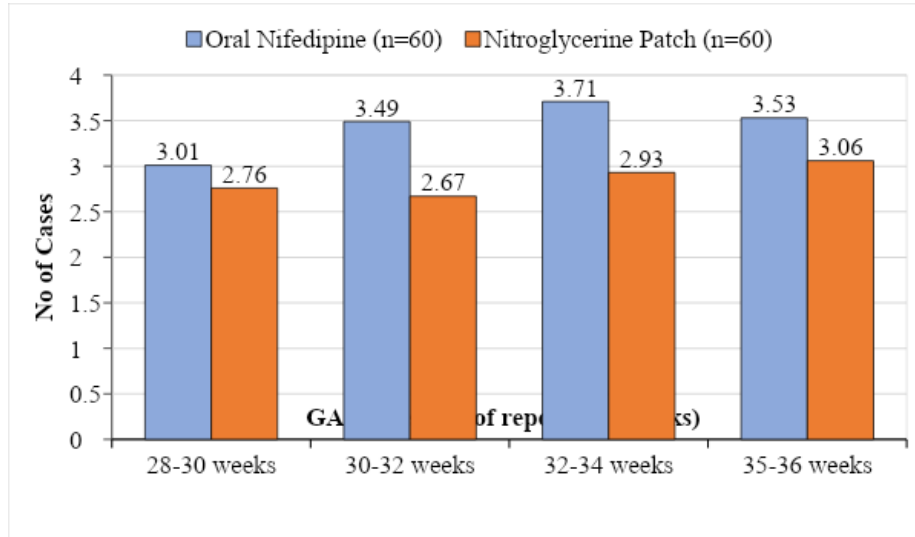


Figure 2: Comparison of Gestational age at the time of reporting in both the study groups

Table 3: Comparison of complications in both the study groups

Complications	Oral Nifedipine (n=60)		Nitroglycerine Patch (n=60)		P value*
	Cases	%	Cases	%	
Severe Headache	4	6.67%	15	25.00%	0.005
Tachycardia	16	26.67%	5	8.33%	0.001
Hypotension	2	3.33%	8	13.33%	0.047
Palpitation	4	6.67%	2	3.33%	0.402

*Chi square test applied for calculation of p value

Table 3 shows comparison of complications in both the study groups. Out of 60 cases in oral nifedipine group common complications were 16 (26.67%) tachycardia, 4 (6.67%) headache and 4 (6.67%) palpitation. Out of 60 cases in nitroglycerine patch group common complications were 15 (25%) headache, 8 (13.33%) hypotension, 6 (10%) cases were discontinued the treatment due to hypotension and 5 (8.33%) were found tachycardia. Comparison of complications and their p values (<0.05) indicate that headache and hypotension was significantly higher in Nitroglycerine patch compared to oral nifedipine group. This also led to significantly higher discontinuation rate due to hypotension in Nitroglycerine patch group compared to oral nifedipine group. Tachycardia was significantly higher in oral nifedipine group compared to Nitroglycerine patch group with p value <0.01.

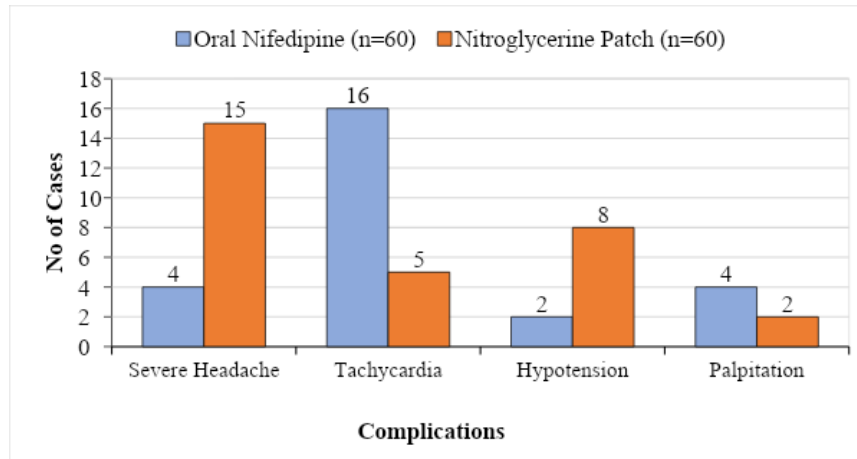


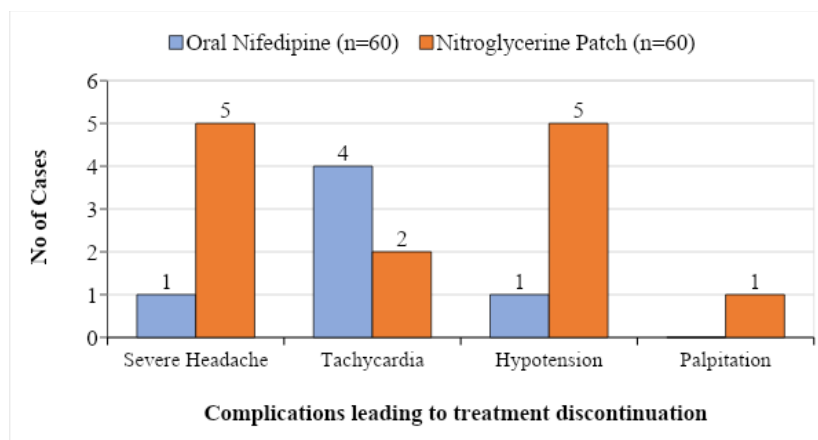
Figure 3: Comparison of complications in both the study groups

Table 4: Comparison of treatment discontinuation in both the study groups

Complications leading to treatment discontinuation	Oral Nifedipine (n=60)		Nitroglycerine Patch (n=60)		P value*
	Cases	%	Cases	%	
Severe Headache	1	1.67%	5	8.33%	
Tachycardia	4	6.67%	2	3.33%	
Hypotension	1	1.67%	5	8.33%	
Palpitation	0	0.00%	1	1.67%	
Total	6	10.00%	13	21.67%	0.04

*Chi square test applied for calculation of p value

Table 4 shows comparison of complications which lead to treatment discontinuation in both the study groups. In oral nifedipine group treatment was discontinued in one case due to severe headache, in four cases due to tachycardia, and in one case due to hypotension. In Nitroglycerine patch group treatment was discontinued in five cases due to severe headache, in two cases due to tachycardia, in five cases due to hypotension, and in one case due to palpitation. Out of 60 cases in oral nifedipine group in 6 cases treatment was discontinued while in Nitroglycerine patch group in 13 cases treatment was discontinued. This difference was statistically significant ($p < 0.05$) indicating that treatment discontinuation was significantly higher in Nitroglycerine patch compared to oral Nifedipine.



DISCUSSION:

The present study was conducted among 120 pregnant mother to compare the tocolytic effect of Oral Nifedipine Tablet and Transdermal Nitroglycerine Patch in preterm labor. In present study, the distribution of maternal age is almost similar in both the groups. The mean age in oral nifedipine group was 24.25 ± 3.99 years whereas in Nitroglycerine patch group 24.20 ± 2.63 years. P value is >0.05 indicating that there is no difference in age distribution of mothers in both the study groups. It means that age distribution of subjects was almost similar in both the groups. Similar results observed in the study by Sharma N et al (2019), Kaur P et al (2021), In the study by Sharma N et al (2019), the mean age in nifedipine group was 24.4 ± 3.8 years whereas in NTG group it was 24.1 ± 2.8 years. P value was 0.66. There is no significance difference found in both the groups. This result is comparable with our study. In study by Kaur P et al (2021), in the NTG Group, the majority of patients (52% of the total) are between the ages of 20 and 24, whereas in Group B, the majority of patients (52%) are between the ages of 25 and 29. In Group A, the mean age was 24.52 years, but in the nifedipine group, it was 24.26 years.

Amorim et al (2009) engaged 50 patients to test the effects of NTG as a therapeutic drug vs oral nifedipine. They discovered that the rates of preterm birth in the first 48 hours were 15.4% in the nitroglycerin group and 12.5% in the nifedipine group. The tocolytic effects of nifedipine and NTG were compared in 43 and 41 patients in each group, respectively, by Dhawle A et al (2013). When compared to Nifedipine, they discovered that delivery within 48 hours was considerably higher with NTG ($p=0.02$). NTG and nifedipine were compared in a randomised clinical trial by Kashanian et al (2014). as a tocolytic agent. In comparison to the nifedipine group, more women in the NTG group delivered after 48 hours (52 women, or 86.7% vs. 41 women, or 68.3%, $P=0.016$), and after 7 days (47 women, or 78.3% vs. 37 women, or $P=0.046$). Neonatal weight and foetal outcomes like Apgar score were improved in the NTG group.

Additionally, the NTG group had fewer admissions to the newborn intensive care unit (NICU) and shorter stays there. Both groups' negative impacts were comparable and barely noticeable. Kaur P et al (2021) discovered a difference in the mean length of pregnancy between the two study groups that was statistically significant. In present study, the mean prolongation days at 28-30 weeks of GA was 3.01 ± 2.06 in oral nifedipine group whereas in nitroglycerine patch group it was 2.76 ± 1.24 . The mean prolongation days at 35-36 weeks of GA was 3.53 ± 2.26 in oral nifedipine group whereas in nitroglycerine patch group it was 3.06 ± 1.69 . Comparison of mean prolongation duration according to gestational age in both the study groups indicate that overall duration of prolongation was better in oral nifedipine group compared to Nitroglycerine patch group. However, the differences were not statistically significant.

In study by Kaur P et al (2021), both in NTG Group and nifedipine Group, the mean length of the pregnancy varied significantly with gestational age upon admission. The mean prolongation in NTG Group was 2.79 ± 1.41 days and in nifedipine Group it was 3.70 ± 1.77 days when the gestational age was between 32.1 and 34.0 weeks. There was a statistically significant difference between them. In present study, out of 60 cases in oral nifedipine group common complications were 16 (26.67%) tachycardia, 4 (6.67%) headache and 4 (6.67%) palpitation. Out of 60 cases in nitroglycerine patch group common complications were 15 (25%) headache, 8 (13.33%) hypotension, 6 (10%) cases were discontinued the treatment due to hypotension and 5 (8.33%) were found tachycardia. Comparison of complications and their p values (<0.05) indicate that headache and hypotension was significantly higher in Nitroglycerine patch compared to oral nifedipine group.

This also led to significantly higher discontinuation rate due to hypotension in Nitroglycerine patch group compared to oral nifedipine group. Tachycardia was significantly higher in oral nifedipine

group compared to Nitroglycerine patch group with p value <0.01. In the study by Kaur P et al (2021), out of 50 cases in NTG group common complications were headache 21 (42%), Tachycardia 10 (20%), Hypotension 1 (2%) and Palpitation 3 (6%). Out of 50 cases in nifedipine group common complications were headache 3 (6%), Tachycardia 14 (28%), Hypotension 2 (4%) and Palpitation 5 (10%). The NTG group (42%) experienced headaches more frequently than the nifedipine group (6%). 20% of the women in Group A and 28%, 4%, and 10% of the women in Group B, respectively, had tachycardia, hypotension, and palpitations. Similar to our study, Dhawle et al found that the overall incidence of adverse events was 48.7% with NTG against 34.88% with nifedipine.

With NTG, headache rates were substantially higher (41.5% vs. 4.7%). Between the two groups, there was no difference in the frequency of tachycardia or palpitations. The most frequent side effects of nifedipine, in contrast to these trials, were headache (32%), followed by palpitations (8%) and hypertension (8%), according to Yasmin et al. With 48% of patients reporting no side effects, the NTG patch had a better adverse effect profile. However, headache (32%) was the most common complaint with it. The American College of Obstetricians and Gynaecologists endorses the short-term (up to 48 hours) prolonging of pregnancy with beta-adrenergic agonist therapy, calcium channel blockers, or NSAIDs in order to facilitate the delivery of prenatal steroids. Tocolytic treatment does not, however, directly improve new-born outcomes. Additionally, it should be remembered that tocolysis is utilised for preterm infants who are already likely to be brought to the NICU for prematurity and disorders associated to prematurity, yielding higher likelihood of nursery admission than term infants.

An economic analysis of the trial was conducted as a secondary analysis. Oral nifedipine is less expensive than the more expensive transdermal nitroglycerine.

CONCLUSION:

- Duration of Prolongation of pregnancy was better in oral nifedipine group compared to nitroglycerine patch; however the difference was statistically non-significant. (p value >0.05). Significantly higher discontinuation rate due to hypotension was reported in Nitroglycerine patch group compared to oral nifedipine group which is statistically significant (p value <0.05). So, finally we can conclude that tocolytic effect of both, oral nifedipine and Nitroglycerine patch was statistically almost similar. However, considering the availability and side effects we recommend to use oral nifedipine for tocolysis over Nitroglycerine patch.

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