Original Article

Transdermal Nitro-Glycerine Versus Oral Nifedipine for Acute Tocolysis in Preterm Labour: A Randomised Controlled Trial

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Abstract

Objective: To compare the safety & efficacy of transdermal nitroglycerin with oral nifedipine in the inhibition of preterm labor.

Methodology: The study was conducted in the department of Obstetrics & Gynecology, Pakistan Ordinance Factories Hospital Wah from March 2017 to February 2018. This study included 100 women in preterm labor, randomly divided into two groups, 50 receiving oral nifedipine and 50, transdermal nitroglycerin (NTG). Patients in preterm labour with a single gestation, between the 28th and the 34th week and no contraindication for tocolysis were selected. Women with fetal malformation and medical or obstetric diseases were excluded. The variables analyzed were: delay in delivery for 48 hours, 7 days or more than 7 days, a period of gestation at delivery, side effect of drugs & neonatal outcomes.

Results: Mean prolongation of pregnancy with NTG (34.59 days) was similar to that of nifedipine (29.09 days). Nitroglycerine was significantly more successful in prolonging pregnancy beyond 48 hours. Failure of acute tocolysis, defined as delivery within 48 hours, was significantly more common with nifedipine (32%) as compared to transdermal nitroglycerin (12%). Headache was significantly higher in the nifedipine group (42%) compared to NGT group (4%). The neonatal outcomes in terms of the mean birth weight, the incidence of low birth weight and very low birth weight babies need and duration of neonatal intensive care was similar in both groups.

Conclusion: Transdermal nitroglycerine is a safe and effective tocolytic with a lower failure rate and better side effect profile as compared with oral nifedipine.

Keywords: Preterm labor, Nifedipine, Nitroglycerin, Tocolysis

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Introduction

World Health Organization (WHO) defined preterm labour as delivery of baby at a gestational age of <37 completed weeks from the first day of the last menstrual period.[1] The single largest cause of the perinatal morbidity and mortality in non-anomalous infants is preterm birth. About 70-80% of perinatal deaths occur in preterm infants.[2] Almost two third of deaths in preterm infants occurs in those born at less than 28 weeks of gestation.[2,3] The major neonatal morbidity includes respiratory distress syndrome, intraventricular haemorrhage, Patent ductus arteriosus, sepsis, necrotizing, enterocolitis, periventricular leukomalacia and retinopathy of prematurity.[4,5]

The non-neurologic long term sequelae can be chronic

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pulmonary disease or the compromise in the overall growth of the preterm baby.[6]

The basic aims of tocolysis is to prolong the pregnancy at least for 48-72 hours, to provide adequate time to administer two doses of corticosteroid to prevent respiratory distress syndrome in the newborn .[7] It also provides the opportunity to transfer the woman to a higher medical center where adequate NICU facilities can be provided.[8]

Over the few years, a variety of tocolytic drugs (Atosiban, Isoxsuprine, Ritodrine, and Nifedipine) are used to suppress preterm labor. Considerable maternal side effects (Like pulmonary oedema, arrhythmia, and myocardial ischemia) and fetal effects (like hyperglycemia, hypokalemia, neonatal hypoglycemia & paralytic ileus) are reported. [9, 10] Both nitroglycerin and nifedipine are effective in preterm labour.[11, 13]

In our study, we compared the safety and efficacy of oral nifedipine with transdermal nitroglycerin patches as tocolytic in the preterm. In transdermal drug administration, the drug is delivered at a constant and predictable rate so a smooth plasma concentration of the drug is reached without fluctuations.

Methodology

The study was conducted in the department of Obstetrics & Gynecology, Pakistan Ordinance Factories Hospital Wah from March 2017 to February 2018. Women presenting with preterm labor were admitted & those fulfilling the inclusion were randomized to tocolysis in one of the two groups- Group-I: Nitroglycerin (NTG) or Group-II: Nifedipine. The women were subjected to either treatment protocol after taking informed consent using convenient probability sampling. Preterm labor was defined as the presence of regular uterine contractions i.e. 4 in 20 min accompanied by any of the following cervical changes- Dilatation >2 cm or/& Effacement >70%. The exclusion criteria included any one of the following- hypotension (80 mm systolic/ <50 mm Hg diastolic), hypertensive disorders of pregnancy, antepartum hemorrhage, ruptured membranes or signs/symptoms of chorioamnionitis, cervical dilatation >4 cm, cardiac disease, known tocolytic exposure during current pregnancy, intrauterine fetal demise (IUFD), fetal malformation, severe intrauterine growth restriction (IUGR) & fetal distress.

Group I Nitroglycerin group: Women were given a transdermal nitroglycerin patch, Nitroderm, which delivers 5 mg NTG over twelve hours and it was applied to the woman's abdomen. If contractions persisted at the end of one hour an additional patch was applied. No more than 2 patches were worn simultaneously (10 mg). At the end of 12 hours these were replaced by a fresh patch. Mild headaches were treated with paracetamol. Patches remained in place for 12 hours after the contractions had ceased.

Group II Nifedipine group: Tocolysis was initiated with an oral loading dose of nifedipine 10 mg. If contractions persisted after 60 minutes, a similar dose was repeated. If labor was suppressed after the first or second dose, a maintenance dose of 10 mg orally every 8 hours was given starting 8hours following the last dose and continued until 48 hours.

All women were screened for urinary tract infections (UTI)/bacterial vaginosis with a mid-stream clean catch sample & a high vaginal swab respectively and antibiotics are given if indicated. All patients received two doses of 12 mg betamethasone intramuscularly, first at admission and a second dose twelve hours later, to accelerate the fetal lung maturity.

Treatment failure: The inability of the drug to prolong gestation for a minimum period of 48 hours or persistence of uterine contractions even after 10 mg of NTG or 20 mg of Nifedipine was considered to be a treatment failure. Under such circumstances, the therapy was discontinued and subsequent management was left to the labor ward team.

The study outcomes were recorded in terms of delay in delivery for 2 days and more than 7 days period of gestation at delivery, any side effects of each drug & the neonatal outcomes, recorded as- birth weight, Apgar score, respiratory distress, need, and duration of NICU care, neonatal complications and any perinatal mortality. The statistical analysis was performed using the statistical package-SPSS-20. The two groups were analyzed using the Chi-square test and the Student’s t-test, as required.

Results

The study included a hundred women with preterm labor. The mean age of women was 30.43±5.76 in Group I and 26.07±4.39 years in Group II. There was no significant difference in parity between the two groups, with primigravida women predominating in both groups. 28(56.1%) women in Group I were primigravidas and 26 (52 %) in Group II. The mean gestational age at the onset of preterm labor was

similar in both groups (31.43 weeks and 31.23 weeks in groups I and II respectively. The mean prolongation of pregnancy was 14.98±2.01 days in Group I versus 17.09 ± 2.61 days in Group II (Table II), which was not statistically significant. However, failure of acute tocolysis, defined as delivery within 48 hours, was significantly more with nifedipine (16/50 women-32%) as compared to NTG (6/50 women-12 %) table II. In the NTG group, 33 women (66 %) delivered after 34 weeks of gestation and 11 (22.0%) after 37 weeks as compared to 26 (52%) after 34 weeks and 8 (16%) after 37 weeks of gestation in nifedipine group. This however did not reach statistically significant proportions. Also, the mean gestational age at delivery was similar in both groups- 35.59 ± 2.84 weeks in NTG group as against 34.59 ± 2.79 weeks in the nifedipine group.

There was no significant difference in the neonatal outcomes and complications like respiratory distress syndrome (RDS), birth asphyxia, hypoglycemia, sepsis, need for neonatal intensive care unit (NICU) admission and mean duration of stay. Neonatal Jaundice was the commonest complication 48/100 women (48%) followed by RDS 12/100 (12%).

Among maternal side-effects (Table IV), headache was significantly higher in the nifedipine group compared to nitroglycerine group (24/50, 42 % versus 2/50, 4%, p value 0.001). Hypotension was exclusively seen with nifedipine (2 women- 4.7%). However, the incidence of other maternal complications was not significantly different in the two groups. More number of women required discontinuation of treatment with nifedipine (4/50, 8%) compared to nitroglycerin (1/50, 2%). However statistical difference could not be established.

Table I: **Comparability of Group I and II with respect to baseline variables amongst the patients**.

Variables	Nitrogycirine group I(n=50)	Nifedipine Group II (n=50)	P value
Mean Age (years)	30.43±5.76	26.07±4.39	.002
Primigravida	28 (56%)	26 (52%)	
Para 1	13 (31.7%)	17 (39.5%)	
Para 2 or >	5 (12.2%)	4 (9.3 %)	
Mean gestational age at presentation weeks± SD	31.43±1.41	31.23±0.43	0.46
Mean gestational age at delivery weeks ± SD	35.59±2.84	34.59±2.79	0.72

Table II: **Comparison of prolongation of pregnancy between the two groups**

Prolongation of pregnancy	Nitroglycerine Group I (n=50)	Nifedipine Group II (n=50)	P value
>2 days	22(44%)	9(18%)	0.002
>7 days	7(14.6 %)	10 (20 %)	0.625
Mean (days±SD)	14.98±2.01	17±1.06	0.625

Table III: Neonatal outcomes in the two groups.

Neonatal outcomes	Group I Nitroglycerin (*n*=50)	Group II Nifedipine (*n*=50)	*p* value
Birth weight <2.5 kg	33 (66%)	30 (60 %)	0.684
Birth asphyxia	3 (7.3%)	2 (4.7 %)	0.602
Neonatal jaundice	21 (42%)	20 (40%)	0.896
RDS	8 (16%)	5 (10 %)	0.291
Hypoglycemia	0 (0)	2 (4 %)	0.154
NICU care	5 (10 %)	6 (12 %)	0.782
Mean duration	13 ± 6.377	14.2 ± 10.964	0.853

Table IV: Comparison of side-effect profile between the two groups.

Side Effects	Group I Nitroglycerin (*n*=50)	Group II Nifedipine (*n*=50)	*p* value
Palpitations	3 (6 %)	4 (8 %)	0.742
Headache	2(4%)	20 (42 %)	0.001
Tachycardia	10 (20 %)	13 (26 %)	0.506
Hypotension	2(4.7 %)	0(0%)	0.999
Treatment discontinuation	1 (2 %)	5 (10 %)	0.386

Discussion

Prolongation of pregnancy beyond 48 hours allows the beneficial effect of corticosteroids on fetal lung maturity to come into play. Two of the studies found that nitroglycerine prolonged gestation beyond 2 days in 84 % & 91% patients when compared with compared ritrodine (88%) respectively.[11] A direct comparison of Nitroglycerine with nifedipine by showed that the rate of preterm delivery within 48 hours after the start of tocolysis was 15.4% with Nitroglycerine and 12.5% in the nifedipine group.[12] In our study, NGT was also significantly better in pregnancy prolongation for 2 days (44% women in NGT group versus 18% in the Nifedipine group). The difference is due to the high dose in our study.

Nitroglycerine delay delivery beyond 7 days and 14 days in 87 % & 85 % of patients respectively compared to 73% & 69% in ritodrine group[13]. In the trial by Papatsonis et al,[4] nifedipine was found to delay childbirth beyond 7 & 14 days in 72.1% and 64.7%

patients respectively, compared to 50% and 40.7% prolongation in the ritodrine group. In the present study, Nitroglycerine delayed delivery beyond 7 days in 14.6% which was not significantly different to that seen with nifedipine (20%). The mean pregnancy prolongation in the present study was 34 days in the NTG group against 33 days in the nifedipine group, which was similar to the results in other studies.[14, 15]

Several studies[4,13,15] have quoted that nifedipine decreases the incidence of RDS, similarly, one study[16] reported that fewer neonates in the Nitroglycerine group suffered RDS compared to placebo, although no conclusion could be drawn because of the small sample size. In the present study, the birth weights of less than 2kg in the two groups were 66% (NTG) and 60% (nifedipine) respectively. The incidence of RDS was 08 in NTG group and 10% in the nifedipine group and the difference was statistically not significant. Neonatal jaundice was the most common complication in the present study, (40-42% of neonates from either group), which is comparable to other studies.[13,14] This was because majorities of the babies in this study were born preterm at less than 37 weeks of gestation.[16]

The studies[12,13] compared the side effects of Nitroglycerine and nifedipine and found that the only side effect with NTG was headache, which was more common when two patches were worn simultaneously. Our study also found similar results. Papatsonis et al[4] found the incidence of side effects with nifedipine to be significantly less when compared to ritodrine (18.9% versus 36%). They also found the incidence of hypotension with nifedipine to be 27.7%.[3] In the present study, the headache was significantly more associated with nifedipine (42% versus 4%). 4 women (8%) in the nifedipine group required treatment discontinuation compared to a two woman (4%) in the NTG group, which, however, was not statistically significant.

Conclusion

Transdermal NGT is more effective than oral nifedipine in prolonging pregnancy beyond 48 hours. The neonatal outcomes and other side effects were comparable between the two groups. However further studies with greater number of subjects and ones where either cervical length measurement using transvaginal sonography or fetal fibronectin are incorporated into the definition of preterm labour need to be done to arrive at a final conclusion.

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