Original Article

Comparative study of transdermal nitro-glycerine versus oral nefidipine with respect to mean prolongation of pregnancy in preterm labour

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Abstract

Background: Preterm labour is defined as the onset of labour after the age of viability (20-24weeks) and before 37 completed weeks of pregnancy and its incidence is 6-10% of all births in developed countries. **Aims and Objectives:** To Comparetransdermal nitro-glycerine versus oral Nefidipine with respect to mean prolongation of pregnancy in patients with preterm labour. **Methodology: T**his randomized controlled study was conducted in the department of obstetrics and Gynaecology, SMGS Hospital, Jammu over period of one year. Fifty-seven patients presented with features of preterm labour during the said study period, but it was seen that out of these 57 patients, contractions subsided after 1 hours of bed rest and hydration in 4 patients, and 3 patients were lost to follow –up, hence were not the candidates for tocolytic therapy. Total of 50 patients were enrolled-25 were in transdermal nitroglycerine group (study group) and 25 in oral nifedipine group (control group)**.** Descriptive statistics, that is mean, standard deviation and frequency distribution were calculated for each and every variable, wherever applicable, to see significant difference between the groups according to the different categories. For the continuous variable, student 't'-test (unpaired) was applied and to see for the association among the variables, chi-square test was used. 'p'-value of <0.05 was considered as level of statistical significance. SPSS version 7.5 was used for statistical analysis. **Result:** The age of patients in the present study ranged from 20 to 32 years. The mean age of the study group was 25.28±3.16 years, and of the control group was 25.84 ± 4.27 and was not statistically significant. Parity: the mean parity of the study group was 1.04± 1.27 and of the control group 0.84±0.68. The difference between the two groups was not statistically significant. Fourteen (56%) women in the study group are multiparous as compared to 17 (68%) in the control group. Previous preterm delivery: two (8%) women in the study group had previous preterm birth as compared to 3(12%) women in the control group. Statistically, the difference was non-significant Pregnancy was prolonged by 28.56 ± 22.89 days in the study group and by 21.78±22.95 days in control group (p=0.311). Mean gestation at delivery in the study group was 35.58±2.59 weeks and in the nifedipine group 34.91±2.825 weeks. Seven women (28%) in the study group and 11 (44%) in the control group delivered within one week of the randomization (p=0.15). the number of women delivered by 34th week, between 34th and 37th week and after 37th week gestation were 10 (40%), 9 (36%) and 6 (24%) in the study group and 12 (52.17%), 5 (21.73%) and 6(26.08%) in the control group, respectively. The percentage prolongation of gestation in the study group was 89.86±57.98% as compared to 85.25±51.52% in the control group (p=0.77) which was not statistically significant. **Conclusion:** Pregnancy was prolonged by atleast 48 hours in 92% of women in nitroglycerine group and 86.9% of women in nifedipine group.

Key Words: Transdermal nitro-glycerine, Nefidipine, Mean prolongation of pregnancy.

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INTRODUCTION

Preterm labour is defined as the onset of labour after the age of viability (20-24weeks) and before 37 completed weeks of pregnancy and its incidence is 6-10% of all births in developed countries.[1] It is common in patients with low body weight, short stature, unsupported mothers, smokers and lower social classes.[2] Risk factors that have been linked to preterm delivery include cervical

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incompetence, haemorrhage like placental abruption, genital tract infection like bacterial vaginosis, hormonal changes due to maternal or foetal stress, multifetal pregnancy and previous history of preterm labour.[3] Incidence of preterm labour is 23.3% and of preterm delivery 10-69% in India.[4]The tocolysis used to prevent preterm labour basically aims prolonging the pregnancy at least for 48 - 72 hrs and so provides adequate time to administer [5] doses of corticosteroids which would help in preventing respiratory distress syndrome in newborn. If delivery occurs in 7 days it will also provide opportunity to transfer the women to a higher medical centre where adequate NICU facilities can be provided to the neonate as and when required. [5] Over the past few years variety of tocolytic drugs (Isoxsuprine, Ritodrine, Nifidepine)with different pharmacological action have been used to supresspretemlabour. The Ca2+ channel blockers have occupied the first Choice as tocolytic therapy in various world medical centres, Brazil. [6] Nitroglycerin is a drug with high first pass inactivation in liver by Glutathione dependent organic nitrate reductase. To avoid it transdermal use of drug is benificial[7]

MATERIAL AND METHODS

This randomized study was conducted in the department of obstetrics and Gynaecology, SMGS Hospital, Jammu over the period of one year. Women with preterm labour between 26 weeks and 34 weeks gestation were studied. Preterm labour is defined as presence of regular and painful uterine contractions at the rate of 4 contractions in 20 minutes, with the evidence of cervical changes as effacement and/or dilatation. Women with singleton pregnancy, Gestational age between 26 weeks and 34 weeks, Presence of regular painful contraction occurring at the rate of 4 per 20 minutes, Cervical dilatation of greater than 1 cm and less than 4 cm, Cervical effacement 80% or more and Women with intact membranes were included into the study while the patients of Antepartum haemorrhage, Foetal anomalies incompatible with life, Intrauterine death of foetus, Pregnancy induced hypertension, Bronchial asthma, Imminent pre-eclampsia and eclampsia, Associated heart disease or renal disease. Multiple gestation, Cervical dilatation more than 4 cm, Sensitivity to nitroglycerine and Failure to give consent were excluded from the study. Fifty-seven patients presented with features of preterm labour during the said study period, but it was seen that out of these 57 patients, contractions subsided after 1 hours of bed rest and hydration in 4 patients, and 3 patients were lost to follow –up, hence were not the candidates for tocolytic therapy. Total of 50 patients were enrolled-25 were in transdermal nitroglycerine group (study group) and 25 in oral nifedipine group (control group). In the study group, tocolytic therapy consisted of application of two patches of transdermal nitroglycerine (25 mg each) which delivers 10 mg nitroglycerine per 24 hours on anterior abdominal wall. If the uterus was still actively contracting after 1 hours of application of patches (4 contractions in 20 minutes) or there was evidence of ongoing cervical changes, a second application of two patches (25 mg each) in addition to the first was applied. The same number of patches was replaced after 24 hours, the total duration of tocolysis being limited to 48 hours. In the control group, tocolytic therapy consisted of administration of oral nifedipine 30 mg stat followed by 10 mg 6 hourly for a duration of 48 hours. All women were examined at 30 minutes interval, to see for uterine contractions (frequency and strength). Patients with persistent uterine contractions but not further cervical changes were considered to have tocolytic failure if they did not achieve 12 hours of uterine quiescence. However, the therapy to which they were assigned was continued unless they had progressive cervical changes if the uterus was still actively contracting despite full doses of tocolytic therapy and, if there was evidence of progressive cervical changes, the tocolytic therapy was discontinued and labour allowed to progress. Tocolytic therapy was continued for 48 hours in both the groups following which the patients were kept on strict bed rest in the hospital the women in both the groups were followed till the time of delivery. In case a women presented again with preterm labour, she was offered a choice of tocolytic therapy and further course of pregnancy was noted. Descriptive statistics, that is mean, standard deviation and frequency distribution were calculated for each and every variable, wherever applicable, to see significant difference between the groups according to the different categories. For the continuous variable, student 't'-test (unpaired) was applied and to see for the association among the variables, chi-square test was used. 'p'-value of <0.05 was considered as level of statistical significance. SPSS version 7.5 was used for statistical analysis.

RESULT

Table 1: Population characteristics

Characteristics	Nitroglycerine(study group) (n=25)	Nifedipine (control group) (n=25)	P=value
Maternal age	25.28±3.16	25.84±4.27	0.60
Parity	1.04±1.27	0.84±0.68	0.493
Multi parity	14(56%)	17(68%)	0.175
Previous preterm	2(8%)	3(12%)	0.63
Multiple pregnancy	1(4%)	1(4%)	NS
Gestational age at admission	31.24±2.49	31.52±2.01	0.66
No. of contractions per 20 minutes	3.96±0.35	4±0.40	0.711

Maternal age: The age of patients in the present study ranged from 20 to 32 years. The mean age of the study group was 25.28±3.16 years, and of the control group 25.84 ± 4.27 was not statistically significant.

Parity: The mean parity of the study group was 1.04± 1.27 and of the control group 0.84±0.68. the difference between the two groups was not statistically significant. Fourteen (56%) women in the study group are multiparous as compared to 17 (68%) in the control group.

Previous preterm delivery: Two (8%) women in the study group had previous preterm birth as compared to 3(12%) women in the control group. Statistically, the difference was non-significant.

Multiple Pregnancies: One patient in each study and control group have multiple pregnancy.

Gestational age at admission: 31.24± 2.49 weeks in study group and 31.52 ± 2.01 weeks in controlled group.

No. of contractions: 3.96± 0.35 were in study group and 4± 0.40 in control group.

Table 2: Prolongation of pregnancy

Prolongation	Nitroglycerine(study group) (n=25)	Nifedipine(control group) (n=25)	p-value
≤48 hours	2	3	0.31
≥ 48 hours	23	22	1

Two patients in nitroglycerine group and 3 patients in nifedipine group delivered before the completion of tocolytic therapy and were recorded as treatment failure. Pregnancy was prolonged by at least 48 hours in 23 women in nitroglycerine group and 22 women in the nifedipine. The difference in two groups was not significant (p=0.311).

Table 3: Mean prolongation of pregnancy

Mean prologation of pregnancy	Nitroglycerine (studygroup) (n=25)	Nifedipine (control group) (n=23)	P-value
Mean absolute prolongation of gestation (days)	28.56±22.89	21.78±22.95	0.311
Mean gestation at delivery (weeks)	35.58±2.59	34.91±2.82	0.397
No.(%age) delivered by 1 week	7(28%)	11(47.8%)	0.15
No.(%age) delivered by 34th week	10(40%)	12(52.17%)	0.39
No.(%) delivered between 34th and 37th week	9(36%)	5(21.73%)	0.25
No.(%) delivered after 37th week	6(24%)	6(26.08%)	0.86
Mean %age prolongation of pregnancy	89.86±57.98	85.25±51.52%	0.77

The effect of the two tocolytic agents, in the present study, in prolonging pregnancy was compared as mean prolongation (in days) from the time of presenting with preterm labour and mean gestation (in weeks) at delivery. Further, percentage of patients who delivered within one week of randomization, by 34th week, between 34th and 37th week and after 37th week gestation was calculated. Pregnancy was prolonged by 28.56 ± 22.89 days in the study group and by 21.78±22.95 days in control group (p=0.311). mean gestation at delivery in the study group was 35.58±2.59 weeks and in the nifedipine group 34.91±2.825 weeks. 7 women (28%) in the study group and 11 (47.8%) in the control group delivered within one week of the randomization (p=0.15). the number of women delivered by 34th week, between 34th and 37th week and after 37th week gestation were 10 (40%), 9 (36%) and 6 (24%) in the study group and 12 (52.17%), 5 (21.73%) and 6(26.08%) in the control group, respectively. The effect of the two tocolytic agents compared on prolongation of pregnancy, as judged by the above parameters, was not statistically different *i.e.* both tocolytics were equally effective and caused slightly better prolongation in the study group as compared to control group following use in treatment of preterm labour. The effect on prolonging the pregnancy was also compared as mean percentage prologation, which was defined as time from randomization to delivery, censored at 37th week gestation and expressed as a percentage of time from randomization to 37th week. This measure focused on the effects of the two tocolytic agents on preterm delivery and was approximately independent of gestational age at randomization. The percentage prolongation of gestation in the study group was 89.86±57.98% as compared to 85.25±51.52% in the control group (p=0.77) which was not statistically significant.

DISCUSSION

PTL and delivery could have devastating impacts on both the mother and the infant. Yet, management of this problem has always been a challenge for obstetricians. In this study, we compared the effectiveness of transdermal GTN and oral nifedipine for controlling PTL, and we discovered that transdermal GTN is better able to cease the uterine contractions and can thus slow the progress of delivery more efficiently. GTN, a nitric oxide donor, has been shown to produce a significant decrease in the contractility of human myometrium in pregnant and non-pregnant women in vitro[14,15,16]. In 1994, Lees *et al.*[8] reported that transdermal nitroglycerin patches suppressed uterine contractions in all 20 episodes of preterm labor that occurred in 13 consecutive women enrolled in a pilot study, and they hence suggested that

this nitric oxide donor could be an effective and safe tocolytic agent. The actual introduction of transdermal nitroglycerin for controlling preterm labor dates back to 1996, when it was beneficial in ten women[15]. In 1999, Lees *et al*.[16] compared the efficacy of ritodrine and GTN, and they found that there was no significant difference in acute tocolysis between these two medications; however, the overall preterm delivery rate was less in GTN patients. Also, glyceryltrinitrate had less adverse side effects. Black *et al*. [8] evaluated the maternal and fetal cardiovascular effects of transdermal GTN compared with ritodrine for acute tocolysis in a multicenter clinical trial involving 60 women. They reported that transdermal GTN had only trivial effects on maternal pulse rate, blood pressure, and FHR, and, therefore, it had significantly fewer adverse cardiovascular effects than intravenous ritodrine. As a consequence, transdermal GTN could be a safer and more convenient treatment option for women suffering from PTL. In 2001, a study of 30 pregnant women of 27 to 34 weeks of GA who were diagnosed with PTL reported a decrease in uterine contractions in all women without any side effects on fetal cardiotocography and heart rate [9]. In 2010, Smith *et al*. [10] indicated that a reduction in overall neonatal outcome with transdermal GTN compared with a placebo was mainly due to a 23-day prolongation of pregnancy and a trend toward ending a course of corticosteroids in the subgroup randomized prior to 28 weeks' gestation. The present comparative study of transdermal nitroglycerine and oral nifedipine in treatment of preterm labour was done over a period of 1 year. Total of 50 women were enrolled presenting with preterm labour between 26 weeks and 34 weeks of gestation in the department of Obstetrics and Gynecology Govt. Medical college, Jammu.

Table 4: Mean prolongation of pregnancy

Trial	Mean prolongation of pregnancy (days)
Nitroglycerine	
Lees *et al*. (1999)	36.9
Smith *et al*. (1999)	22
Smith *et al*. (2007)	20.9
Present study (2009) NTG	28.56
Present Study (2009) Nifedipine	21.78

The mean prolongation of gestation in present study was 28.56 days in the nitroglycerine group and 21.78 days in the nifedipine group (p>0.005). The mean prolongation of gestation was 36.9 days in the study by lees *et al*. (1999), 22 days in the study by smith *et al*, (1999), and 20.9 days in study by smith *et al*. (2007) in the nitroglycerine group. The mean prolongation of pregnancy was 43.71 days in study by Garcia-velasco and Gonzalez-Gonzalez (1998) in the nifedipine group which was higher than the present study (21.78 days).

CONCLUSION

Both transdermal NTG and Oral Nefidipine were found to be equally effective in the treatment of preterm labour. Pregnancy was prolonged by 48 hrs in 89.86 % of women in nitroglecerine group and 85.25 % of women in Nefedipine group. However, trandermal Nitroglycerene due to its safety, easier application and effective means of Tocolysis can be used as an alternative drug in the treatment of preterm labour. However, before its widespread use large multicentric trials are needed to prove its efficacy for use as a tocolytic agent.

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