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Original Article

Obstetrics and Gynaecology Section

Comparison of Transdermal Nitroglycerine Patch and Oral Nifedipine for Tocolysis in Preterm Labour: A Prospective Interventional Study

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ABSTRACT

Introduction: Preterm labour and delivery have a major contribution to perinatal mortality and morbidity. Tocolytic therapy reduces neonatal mortality and morbidity by prolonging gestation, allowing for corticosteroid administration and in-utero transfer to a tertiary care centre. There is a need to find out better tocolytic agent that is most effective and with the least side-effects.

Aim: To compare oral Nifedipine and transdermal Nitroglycerine patch to achieve tocolysis in preterm labour.

Materials and Methods: A prospective interventional study was conducted in the Department of Obstetrics and Gynaecology at Uttar Pradesh University of Medical Sciences, Saifai, Etawah, from January 2020 to June 2021. A total of 100 women presenting with signs and symptoms of preterm labour with live singleton pregnancy and intact membranes were included. All the women were divided into Group-A (n=50) and Group-B (n=50). Group-A received oral Nifedipine 20 mg of oral initially and 10 mg Nifedipine repeated after 30 minutes if the contractions persisted. Oral Nifedipine 10 mg was repeated every six hours till contractions subsided, and a transdermal Nitroglycerin patch (25 mg) was directly applied to the skin of the abdomen in Group-B. Demographic profile, the number of patients in which tocolysis was successful, improvement in Bishop score, prolongation in gestational age, maternal side-effects, and foetal outcomes in the form of birth weight, APGAR score, and NICU admission were recorded in both the groups on Excel sheet. Chi-square test and t-test were used to test the significance of the difference between categorical and continuous variables respectively. A p-value less than 0.05 were taken as significant.

Results: In Group-A 94% (47 out of 50) achieved tocolysis while in Group-B 86% (43 out of 50) achieved tocolysis (p-value-0.182). The mean prolongation of pregnancy was 17.70±13.04 and 13.14±11.03 in Groups A and B, respectively. The maternal complication was significantly higher in Group-B as compared to Group-A (22% Vs 6%, p-value-0.0097). In Group-A mean birth weight was 2.422 kg±0.34 whereas in Group-B mean birth weight was 2.204±0.38 kg (p-value-0.0032).

Conclusion: Both drugs oral Nifedipine and transdermal Nitroglycerine were found to be effective in the treatment of preterm labour.

Keywords: Mortality, Pregnancy, Tocolysis

INTRODUCTION

Preterm labour and delivery have a major contribution to perinatal mortality and morbidity. More than 70% of the total perinatal mortality is caused due to preterm birth [1]. Of these around 40-50% of preterm births occur due to spontaneous onset of labour, and 30% occur in cases of preterm premature rupture of membranes, however, 30% are iatrogenic termination for maternal or foetal indications [2,3].

The aetiology remains obscure. Therefore, prevention is not very successful. However, to reduce perinatal morbidity and mortality, it is very essential to delay preterm labour [4]. The tocolytic therapy helps in reducing neonatal mortality and morbidity as it prolongs the gestation and also gives time to administer the corticosteroid and in-utero transfer to a center with good neonatal care [5,6]. Using tocolysis is the best approach to reduce morbidity and mortality that are associated with preterm birth as they cause partial uterine relaxation and hence helps in prolonging the pregnancy. Currently, the tocolytics which are being used are calcium channel blockers, progesterones, nitric oxide donors, oxytocin receptor antagonists, beta-adrenergic agonists, magnesium salts, and prostaglandin synthetase inhibitors. All these drugs act at the level of myocyte and stop uterine activity [7].

Nifedipine is a pyridine derivative and the most common calcium channel blocker used for tocolysis. Nitroglycerine is a low molecular weight nitrate. Nitrates are rapidly denitrated in the smooth muscle cell to release nitric oxide. Nitric Oxide which is the active substance rapidly metabolises in the liver by a glutathione-dependent organic nitrate reductase. Transdermal use of the drug prevents its metabolism in the liver. This relaxes the smooth muscles of the uterus more effectively and improves blood flow to the uterus and placenta [8,9]. Therefore, the present study was conducted to compare oral Nifedipine and transdermal Nitroglycerine patch to achieve tocolysis in preterm labour.

MATERIALS AND METHODS

A prospective interventional study was conducted in the Department of Obstetrics and Gynaecology at Uttar Pradesh University of Medical Sciences, Saifai, Etawah from January 2020 to June 2021. Clearance was taken from the Institutional Ethical Committee (IEC) (ethical clearance number- 1701/UPUMS/dean(M)/ethical/2020-21). Written informed consent was taken from all eligible women who agreed to participate in the study.

A total of 100 women presented with signs and symptoms of preterm labour, (4 contractions in 20 minutes, each contraction lasting for 40 seconds, progressive cervical effacement up to 80%, and cervical dilatation less than 3 cm) were included.

Sample size: Based on the study conducted by Ghomian N et al., [10]. The minimum sample size for each group was 46. So 50 patients in each group i.e., a total of 100 patients were included in the present study.

Inclusion and Exclusion criteria: All the women in the age group of 18 years to 35 years, with live singleton pregnancies of less than 37 weeks gestation and intact membranes were included in the study. Women with the need for emergency management like foetal distress, antepartum haemorrhage, chorioamnionitis, etc., or premature rupture of membranes, major foetal congenital anomaly or Intra uterine foetal death or multiple pregnancies, other high- risk pregnancies, cervical dilatation of more than 3.0 cm and known hypersensitivity to Nifedipine or Nitroglycerine were excluded from the study.

A detailed history was obtained, general, systemic, per abdomen, and per speculum examination was done. Investigations like complete blood counts, urine routine and microscopy, and high vaginal swabs were sent. Four doses of dexamethasone (6 mg IM 12 hours apart) were administered to cases of gestational age less than 34 weeks.

All the included women were divided into two groups randomly by alternate method, Group-A and B. Group-A included 50 women who received 20 mg of oral Nifedipine initially and 10 mg of Nifedipine repeated after 30 minutes if the contractions persisted, maximum total dose of 60 mg. Oral Nifedipine 10 mg was repeated every six hours till contractions subsided. Group-B also included 50 women and Transdermal Nitroglycerin patch (25 mg) was directly applied to the skin of the abdomen. The assessment was done by a person other than the person who randomised the women into different groups.

Pulse, blood pressure, foetal heart rate, and uterine contractions were monitored every 15 minutes in the first two hours, then two hourly in the next six hours, and then six hourly for 48 hours in both groups. Side-effects like headache, dizziness, nausea, hypotension, and foetal and maternal tachycardia were noted. Treatment was considered successful if uterine contractions subsided and the uterus remained relaxed for more than 48 hours. In cases where tocolysis was effective, were followed weekly till 37 weeks of gestation or till delivery (if delivered before 37 weeks of gestation). Treatment was discontinued in both groups if headache, hypotension, premature rupture of membranes, persistent uterine contractions even after 48 hours, or foetal distress continued.

Outcomes studied: Data regarding the demographic profile, gestational age at onset of preterm labour, successful tocolysis, time taken to achieve tocolysis, Bishop score at onset of labour and improvement after tocolysis, maternal side-effects, and neonatal outcomes like birth weight, APGAR score, days of admission in NICU were studied.

STATISTICAL ANALYSIS

The data was recorded in an Excel sheet and analysis was done using the Epidemiological Information Package (EPI 2010). Chi-square test and t-test were used to test the significance of the difference between categorical and continuous variables respectively. A p-value less than 0.05 were taken as significant.

RESULTS

The maximum number of patients in both groups was in age groups 21-30 years (84% in Group-A and 82% in Group-B) [Table/Fig-1]. The mean age of women was 24.4±3.37 years in Group-A and was 24.48±3.36 years in Group-B. History of previous preterm labour was present in 20% of women belonging to Group-A and 12% of women of Group-B [Table/Fig-1] [11].

The mean time observed in Group-A was 4.38 hours and in Group-B was 4.6 hours [Table/Fig-2]. In Group-A, 94% of women achieved tocolysis while in Group-B, 86% achieved tocolysis [Table/Fig-2].

Demographic variables		Group-A (n=50)	Group-B (n=50)	p-value
Age group (years)	<20 years	5 (10%)	5 (10%)	0.925
	21-30 years	42 (84%)	41 (82%)	
	>30 years	3 (6%)	4 (8%)	
Socio-economic status [11]	Lower middle	21 (42%)	11 (22%)	0.093
	Upper lower	15 (30%)	22 (44%)	
	Upper middle	14 (28%)	17 (34%)	
Booking status	Booked	18 (36%)	23 (46%)	0.309
	Unbooked	32 (64%)	27 (54%)	
History of preterm labour	Present	10 (20%)	6 (12%)	0.275
	Absent	40 (80%)	44 (88%)	
Gestational age (weeks)	28-30	6 (12%)	5 (10%)	0.483
	31-33	20 (40%)	26 (52%)	
	34-36	24 (48%)	19 (38%)	

[Table/Fig-1]: Demographic profile of patients.
Chi-square test was used

Time needed for tocolysis	Range	Mean±SD	p-value
Group-A (n=50)	1-12 h	4.38±2.85	0.704#
Group-B (n=50)	1-12 h	4.6±2.93	
Tocolysis achieved	Yes	No	0.182*
Group-A (n=50)	47 (94%)	3 (6%)	
Group-B (n=50)	43 (86%)	7 (14%)	

[Table/Fig-2]: Tocolysis success and time needed for tocolysis.
(*Chi-square test was used to compare the variables). #t-test was used

The mean gestation prolongation was 12.8 days and 22.92 days in Group-A and B respectively in the women who had gestational age of 31 to 33 weeks on admission and this difference was statistically significant [Table/Fig-3]. Of the total 50 women in Group-A, 2 (4%) of women delivered within 24 hours despite starting the tocolysis; whereas 6 (12%) of women in Group-B delivered within 24 hours of starting the tocolysis.

Gestational age (weeks)	Number of cases		Prolongation of days of pregnancy (Mean±SD)		p-value
	Group-A	Group-B	Group-A	Group-B	
28-30	6 (12%)	5 (10%)	21.17±17.57	7.20±7.66	0.1352
31-33	20 (40%)	26 (52%)	12.80±11.39	22.92±14.00	0.0117
34-36	24 (48%)	19 (38%)	14.84±11.20	15.80±10.95	0.779

[Table/Fig-3]: Gestational age on admission and mean prolongation of pregnancy based on gestational age.
t-test was used

In women, where the bishop score on admission was above 4, mean prolongation in gestational age was 17.4 days and 8.19 days in Group-A and B, respectively and this difference was statistically significant (p=0.0014) [Table/Fig-4].

Bishop's score	Number of cases		Prolongation of days of pregnancy (Mean±SD)		p-value
	Group-A (n=50)	Group-B (n=50)	Group-A (n=50)	Group-B (n=50)	
Upto 4	13 (26%)	23 (46%)	18.54±13.49	18.96±9.72	0.915
Above 4	37 (74%)	27 (54%)	17.41±13.06	8.19±6.69	0.0014

[Table/Fig-4]: Bishop score on admission and prolongation of pregnancy on basis of Bishop score.
t-test was used

The maternal complication was significantly higher in Group-B as compared to Group-A (22% Vs 6%, p-value-0.0097) [Table/Fig-5].

There was statistically significant difference (p-value-0.0032) observed in the birth weight of the babies in both groups. There was a statistically significant difference (p-value-0.032) in neonatal

ICU admissions between both groups (14% neonates in Group-A Vs 32% neonates in Group-B) [Table/Fig-6].

Complication	Group-A (n=50)	Group-B (n=50)	p-value
No	47 (94%)	39 (78%)	0.0097
Dizziness	1 (2%)	5 (10%)	
Nausea	2 (4%)	0	
Headache	0	6 (12%)	

[Table/Fig-5]: Maternal complications.
(*Chi-square test was used to compare the variables)

Neonatal outcome		Group-A (n=50)	Group-B (n=50)	p-value
Birth weight (kg)	Mean±SD	2.422±0.34	2.204±0.38	0.0032#
APGAR at 1 minute	Less than 7	6 (12%)	19 (38%)	0.0026*
	More than 7	44 (88%)	31 (62%)	
APGAR at 5 minute	Less than 7	5 (10%)	16 (32%)	0.006*
	More than 7	45 (90%)	34 (68%)	
Neonatal morbidity (NICU admission)	No	43 (86%)	34 (68%)	0.032*
	Yes	7 (14%)	16 (32%)	

[Table/Fig-6]: Neonatal outcome.
(*Chi-square test was used to compare the variables). #t-test was used

DISCUSSION

The mean age of women in the study was 24.4 years in both groups. On comparing the data with other studies, baseline features were similar to other studies. In a study by Rita D et al., mean age of females included in the study was 26±3.62 years and also in Kaur P et al., study mean age of females was 24.4±3.8 [12,13]. In Sharma N et al., mean age of females included is 24.4 years [14].

In the present study, In Group-A maximum patients belonged to 34 to 36 weeks (48%) gestational age while in Group-B maximum patients were in 31 to 33 weeks (52%) gestational age group on admission. Rita D et al., study included 28 to 36 weeks gestation age patients. In Kaur P et al., study they included women of 28-34 weeks of gestation, in a study by Sharma N et al., they also included women of 28 to 34 weeks gestation [12-14].

The present study revealed a history of previous preterm labour in 12.0% of patients. Alijahan R et al., in their study observed that out of all women who had preterm birth, 7.2% of women had history of preterm labour in previous pregnancy, whereas among women who delivered at term, only 1.2% of women had history of preterm labour in previous pregnancy (the odds ratio of 2.7 at 95% CI). This difference was statistically significant (p-value 0.000) [15].

In the present study, oral Nifedipine was effective in achieving tocolysis in 94% women and Nitroglycerin in 86% of cases. Whereas in the study conducted by Wilson A et al., the effective tocolysis was 87.5% with Nifedipine and 84.6% with the nitroglycerin [16].

The average time needed for tocolysis in our study was 4.38 hours in Group-A and 4.6 hours in Group-B, whereas in the study by Wilson A et al., the average time needed to achieve tocolysis was 5.8 hours with oral Nifedipine and 6.6 hours with Nitroglycerine patch which was more than observed in this study [16].

In this study, there was a statistically significant difference observed between both the groups in APGAR score at one minutes and five minutes. In concordance with this study, Apgar score of minute 5, (P=0.03) was significant and observed in nitroglycerine group in study conducted by Kashanin M [17].

Similarly, the study conducted by Jamil M et al., reported that headache as a side-effect was more in Nifedipine group (14%) as compared to Nitroglycerin group (4%) [18], whereas in a study conducted by Wilson A et al., observed headache as a side-effect in 30% women of nitroglycerin group and 8.3% of women in the Nifedipine group. Because of minimal side-effects, Nifedipine is considered safer than Nitroglycerin [16].

Limitation(s)

The present study is a single-centre study with less number of subjects which is a limitation of this study. More randomised and larger multicentric trials are needed to compare these drugs for better results.

CONCLUSION(S)

Both drugs oral Nifedipine and transdermal Nitroglycerine were found to be effective in the treatment of preterm labour. Oral Nifedipine is better in terms of neonatal outcome with lesser maternal side-effects therefore it can be considered the drug of choice.

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