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Original Research Article

Comparison of the effect of vaginal progesterone and oral nifedipine for maintenance tocolysis after arrested preterm labour, to prolong the pregnancy and the neonatal outcome

Mahendra Kumar Bairwa[1]*, Charu Taneja[2], Monica Sharma[1], Khushboo Yadav[1]

[1]ESIC Model Hospital and PGIMSR, Basaidarapur New Delhi, India
[2]ESIC Hospital and Medical College NIT-3, Faridabad, Haryana, India

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***Correspondence:**
Dr. Mahendra Kumar Bairwa,
E-mail: Kumarmahendra126@gmail.com

ABSTRACT

Background: Preterm birth is a major determinant of neonatal morbidity and mortality and has long term adverse consequences. It is defined as childbirth occurring at less than 37 weeks of gestation. Various drugs with different doses and routes have been used for maintenance tocolysis has been used. Aims and objectives were to compare the effect of vaginal progesterone and oral nifedipine for maintenance tocolysis after arrested preterm labour and their effect concerning the neonatal outcomes.
Methods: This study was conducted in the department of obstetrics and gynecology, Mata Chanan Devi hospital, New Delhi in collaboration with the department of pediatrics. The 90 pregnant women who fulfilled inclusion criteria were recruited and were randomized into 2 groups namely nifedipine and progesterone group.
Results: The mean gestational age at delivery in the nifedipine group was 35 weeks, while in the progesterone group it was 37 weeks, and it was a significant difference ($p=0.002$). There was a significant difference in the prolongation of pregnancy between both the groups ($p<0.001$). Mean prolongation of pregnancy in the nifedipine group was 18 days, and 38 days in the progesterone group which was significant ($p=0.000$). The mean APGAR score at five minutes was 7 for the nifedipine group and 8 for the progesterone group. The mean duration of the NICU stay was 5 days in the nifedipine group and 2 days in the progesterone group.
Conclusions: Progesterone was found to be a better drug for maintenance tocolysis compared to nifedipine. It is associated with better maternal and perinatal outcomes when used as a maintenance tocolytic as compared to nifedipine.

Keywords: Preterm premature rupture of membrane, Fetal growth restriction, Intrauterine death, Fetal fibronectin

INTRODUCTION

Preterm birth, defined as childbirth occurring at less than 37 completed weeks of gestation, is a major determinant of neonatal mortality and morbidity and has long-term adverse consequences, making it a leading cause of under 5 mortalities.[1,2] Every year 15 million babies are born preterm and this number is rising.

Preterm labor is defined as regular uterine contractions 4 times in 20 minutes or 8 times in 60 min with progressive cervical dilatation greater than 1 cm and effacement at least 80%.[3] Threatened preterm labour is defined as >4 contractions per hour without cervical changes.[4]

Current management of preterm labour includes 'acute tocolysis' for 48 hrs-providing time for corticosteroids administration for fetal lung maturation and maternal transport to a facility with a neonatal intensive care unit. For initial tocolysis, nifedipine is comparable with magnesium sulphate and superior to ritodrine and atosiban.[5-7]

Arrested preterm is defined as 12-hour contraction free interval after acute tocolysis has been discontinued. After preterm labor is arrested with acute tocolysis, continuing a tocolytic agent for some days more to reduce the risk of recurrent preterm labor is called 'maintenance tocolysis'. There are several reasons to consider maintenance tocolysis. First, perinatal morbidity and mortality are inversely related to gestational age therefore delaying delivery may improve perinatal outcome. Second, after an episode of preterm labor, the stimulus for preterm labor may remain and the patient remains at increased risk for preterm delivery.[8]

Various drugs with different doses and routes have been used for maintenance tocolysis (Ritodrine, terbutaline, indomethacin, nifedipine, and magnesium sulphate) but no significant prolongation of pregnancy or improved perinatal outcome has been noted.[9-11] Progesterone has also been used as maintenance therapy after the inhibition of preterm labour however number of trials comparing progesterone to placebo or other tocolytics is small.

Our present study aims to evaluate effect of progesterone and nifedipine as the maintenance tocolysis therapy after preterm labour has been arrested with acute tocolysis.

Aims and objectives

Aim and objectives were to compare the effect of vaginal progesterone and oral nifedipine for maintenance tocolysis after arrested preterm labour, to prolong the pregnancy and the neonatal outcome.

METHODS

This study was conducted in the department of obstetrics and gynecology, Mata Chanan Devi hospital, New Delhi in collaboration with the department of pediatrics. This study was carried out between January 2019 to January 2020. It was a randomised comparative clinical study.

The ninety pregnant women who fulfilled inclusion criteria were recruited for the study and were randomized into two groups namely nifedipine as well as the progesterone group using the computer-generated random number table.

Study algorithm

As per inclusion and exclusion criteria. Written informed consent taken.

Table 1: Tocolytics for preterm labour.[12]

Type of agent	Dose	Mechanism of action	Side effects (maternal)	Side effects (fetal)	Contraindication
Beta 2 agonist (terbutaline)	0.25 mg SC	Decrease myometrial contractions	Tachycardia, hypotension, pulmonary edema, nausea	Hypoglycaemia, intra-vascular hemorrhage	Uncontrolled diabetes
Ccb (nifedipine)	20-30 mg PO	Decrease myometrial contractions	Hypotension, headache, flushing	Non reassuring fetal status due to maternal, hypotension	Cardiac disease, renal disease, hepatic disease
Cycloxigenase inhibitor (indomethacin)	50-100 mg PO	Inhibiting prostaglandin production	Nausea, heartburn	Closure of ductus arteriosus oligohydramnios	Thrombocytopenia, coagulation, disorders
Magnesium sulphate	4-6 gm IV loading ten 1-2 gm/hr	Decrease calcium uptake into myometrium	Muscle weakness, lethargy, cardiac arrest	Hypotonia respiratory depression	Maternal neuromuscular disorders

Inclusion criteria

Singleton pregnancies with gestational age between 28 to 36 completed weeks who were cases of preterm labour who have been successfully arrested with acute tocolysis were included.

Exclusion criteria

Patients who were cases of antepartum hemorrhage, lethal fetal anomaly, intrauterine growth restriction, chorioamnionitis, circlage. any maternal medical complications contraindicating tocolysis, multiple pregnancies and ruptured membranes were excluded.

Statistical analysis done by using SPSS software.

RESULTS

This was a study comparing oral nifedipine and vaginal progesterone for maintenance tocolysis after arrested preterm labour. Pregnant women with preterm or threatened preterm labour who were fulfilling the inclusion criteria were selected and received acute tocolysis with nifedipine. The patients with successfully arrested preterm labour were randomized into 2 groups nifedipine group and progesterone group for maintenance tocolysis. The 90 eligible women were recruited, out of

which 45 women were in the nifedipine group and 45 in the progesterone group for maintenance tocolysis.

Table 2: Gestational age at delivery.

Gestational age at delivery (weeks)	Drug				P value
	Group N		Group Pr		
	N	%	N	%	
28-30+6	2	4.4	2	4.4	0.002
31-32+6	5	11.1	0	0.0	
33-34+6	15	33.3	7	15.6	
35-37+6	19	42.2	18	40.0	
38-40+6	4	8.9	18	40.0	
Total	45	100	45	100	
Mean±SD	34.76±2.17		36.84±2.33		<0.001

The 40% of patients in the progesterone group and only 9% of patients in the nifedipine group delivered >37+6 weeks.

One patient in each group who delivered before 30 weeks gestation received magnesium sulfate for neuroprotection after discontinuing tocolysis.

The mean gestational age at delivery in the nifedipine group was 35 weeks, while in the progesterone group it was 37 weeks, and it was a significant difference (p=0.002).

Table 3: Prolongation of pregnancy.

Prolongation (weeks)	Drug				P value
	Group N		Group Pr		
	N	%	N	%	
≤1	11	24.4	2	4.4	<0.001
>1-3	21	46.7	4	8.9	
>3-5	5	11.1	12	26.7	
>5-7	8	17.8	16	35.6	
>7	0	0.0	11	24.4	
Total	45	100	45	100	

The 25% of women in the progesterone group had a prolongation of pregnancy of >7 weeks, whereas no women in the nifedipine group had a prolongation >7 weeks.

Table 4: Mean prolongation of pregnancy.

Drug				P value
Group N		Group Pr		
Mean±SD	Median	Mean±SD	Median	
18.11± 14.12	12.00	37.49± 15.07	42.00	0.000

As depicted in the table, mean prolongation of pregnancy in the nifedipine group was 18 days, and 38 days in the progesterone group which was significant (p=0.000).

Table 5: Mode of delivery.

Mode of delivery	Drug				P value
	Group N		Group Pr		
	N	%	N	%	
LSCS	8	17.8	16	35.6	0.160
NVD	36	80.0	28	62.2	
Forceps	1	2.2	1	2.2	
Total	45	100	45	100	

LSCS=lower segment cesarean section; NVD=normal vaginal delivery.

The 80% of women in the nifedipine group and 62.2% of women in the progesterone group delivered by spontaneous vaginal delivery.

There was no significant difference in the mode of delivery between the two group

Table 6: Mean birth weight.

Group N	Group Pr	P value
Mean±SD	Mean±SD	
1916.44±586.10	2454.44±611.20	<0.001

The mean birth weight in the nifedipine group was 1916 grams and 2454 gm in the progesterone group.

There was a significant difference in the birth weights between the two groups (p<0.001). This was mainly due to longer prolongation of pregnancy in progesterone group.

Table 7: Neonatal mortality.

Mortality	Drug				P value
	Group N		Group Pr		
	N	%	N	%	
Yes	3	6.7	1	2.2	0.616
Nil	42	93.3	44	97.8	
Total	45	100	45	100	

The 3 out of 45 babies in the nifedipine group expired and one out of 45 babies in progesterone group expired.

There was no significant difference in neonatal mortality between the two groups (p=0.616).

Table 8: APGAR score.

Variables	Group N	Group Pr	P value
	Mean±SD	Mean±SD	
Apgar score 1 (out of 10)	6.04±1.55	7.09±1.28	0.001
Apgar score 5 (out of 10)	7.20±1.41	8.18±1.09	<0.001

Statistically, there was a significant difference in the APGAR scores at one minute and five minutes between the two groups (p=0.001 and <0.001).

Mean APGAR score at one minute was 6 for the nifedipine group whereas it was 7 for progesterone group. Also, the mean APGAR score at five minutes was 7 for the nifedipine group and 8 for the progesterone group. This difference was statistically significant.

Table 9: Mean duration of NICU stays.

Drug				P value
Group N		Group Pr		
Mean±SD	Median	Mean±SD	Median	
4.76±7.46	0.00	1.53±3.31	0.00	0.037

The mean duration of the NICU stay was 5 days in the nifedipine group and 2 days in the progesterone group.

This difference was statistically significant (p=0.037).

DISCUSSION

Preterm birth is the leading cause of neonatal mortality and morbidity with long term neurological handicaps. Prevention of preterm birth is a public health priority and is a major challenge for the obstetrician. Primary prevention is desirable but not always possible as the pathophysiology is multifactorial and poorly understood.

Pharmacological therapy with a variety of drugs of differential categories has been the primary method of treating acute preterm labour. Patients with arrested preterm labour are at increased risk for the recurrence of preterm labour and here comes the role of maintenance tocolysis.

In this prospective randomized study undertaken, we compared the efficacy of nifedipine and progesterone for maintenance tocolysis after arrested preterm labour.

The 90 eligible women with gestational age between 28 to 36 completed weeks were included in the study. All of them received acute tocolysis with nifedipine. After successfully arrested preterm labour, 45 women received nifedipine for maintenance tocolysis, and 45 received progesterone.

In the present study, the mean gestational age at entry was 32.2 weeks in the nifedipine group and 31.5 weeks in the progesterone group.

The 69% of patients in the nifedipine group and 53% of patients in the progesterone group were admitted between 31 to 34 weeks. There was no significant difference in the gestational age at admission between the 2 groups.

In the present study, the mean gestational age at delivery in the nifedipine group was 34 weeks, which was comparable to the study by Aggarwal et al.[13,16] In the progesterone group, the mean gestational age at delivery was 37 weeks which was comparable to other studies.[14,16] In the present study, 40% of patients in the progesterone group, and only 9% of patients in the nifedipine group delivered >37+6 weeks. The mean gestational age at delivery in the nifedipine group was 35 weeks, while in the progesterone group it was 37 weeks, and it was a significant difference.

In the present study, the mean prolongation of pregnancy in the nifedipine group was 18 days, and 38 days in the progesterone group which was highly significant.

There was no significant difference in the mode of delivery between the two groups. 80% of women in the nifedipine group and 62.2% of women in the progesterone group delivered by spontaneous normal vaginal delivery. The rate of LSCS was 36% in the progesterone group and 18% in the nifedipine group (not significant).

The mean birth weight of neonates in the nifedipine group was 1900 gm, while in the other studies it was approximately 2500±200 gm.[13,14,16] The mean birth weight in the progesterone group was 2400 gm which is comparable to other studies.[3,14] In the present study, there was a significant difference in the birth weight between the two groups. This was a direct consequence of a longer duration of pregnancy with progesterone.

Mean APGAR score at one minute was 6 and 7 for nifedipine and progesterone group respectively. Also, the mean APGAR score at five minutes was 7 for the nifedipine group and 8 for the progesterone group. This difference was statistically significant.

The mean duration of NICU stay in the nifedipine group was 5 days in the present study which was comparable to the study by Aggarwal et al.[13] In the study by Parry et al it was 27 days.[14] The mean duration of NICU stay in the progesterone group was 2 days which was comparable to other studies.[14,16]

Thus, in this study, it was observed that progesterone significantly prolongs pregnancy when compared to nifedipine. Though there was no significant difference in neonatal mortality, there was a significant reduction in neonatal morbidity and improvement in birth weight and APGAR score in the progesterone group.

The mean duration of NICU stay in the nifedipine group was 5 days in the present study which was comparable to the study by Aggarwal et al.[13] In the study by Parry et al it was 27 days.[14]

The mean duration of NICU stay in the progesterone group was 2 days which was comparable to other studies.[15,16]

The mean duration of NICU stay was more in the nifedipine group as compared to the progesterone group and this difference is statistically significant. There was no significant difference in the mortality between the two groups.

Table 10: Comparison between nifedipine and progesterone for maintenance tocolysis in present study.

Characteristics	Nifedipine	Progesterone
Age (in years)	27.04±5.13	26.40±5.07
Primipara (%)	82.2%	80.0%
Multipara (%)	17.8%	20.0%
Prior preterm delivery	8.9	13.3
Mean gestational age at admission (weeks)	32.2	31.5
Mean gestational age at delivery (weeks)	34.76±2.17	36.84±2.33
Mean cervical dilatation	1.36±0.93	1.22±0.90
Mean cervical effacement	22.78±16.47	24.78±19.36
Mean prolongation (days)	18.11±14.12	37.49±15.07
Mean birth weight (gm)	1916.44±586.10	2454.44±611.20
Composite morbidity	44.4%	20%
Days in NICU	4.76±7.46	1.53±3.31

Limitations

The sample size was relatively small (90). Thus, this analysis may have limited power in assessing the differences between the two groups. Only singleton pregnancies were selected. Thus, the findings of this study can only be interpreted in women's low risk for preterm labour. Further multicentric trials or analyses of similar studies may be useful in assessing the effectiveness of nifedipine and progesterone for maintenance tocolysis.

CONCLUSION

Thus, in this study, it was observed that progesterone significantly prolongs pregnancy when compared to nifedipine. Though there was no significant difference in neonatal mortality, there was a significant reduction in neonatal morbidity and improvement in birth weight and APGAR score in the progesterone group.

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