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Comparison of the Efficacy of vaginal Progesterone and Nifedipine in inhibiting Threatened preterm labour: A randomized controlled study

Obstetrics & Gynecology

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ABSTRACT

Background: Preterm labour (before 37 weeks of gestation) is a significant cause of mortality as well as a significant cause of death and long-term loss of human potential. To prevent premature delivery, both nifedipine and progesterone can be administered as tocolysis.

Aim of the work: To investigate the effectiveness and safety of nifedipine and progesterone in sustaining tocolysis during preterm labour arrest, as well as their perinatal consequences.

Patients and methods: Our study included 60 women with a history of preterm labour to compare the efficacy and safety of nifedipine and progesterone for tocolysis maintenance and preterm labour prevention.

Results: Showed that there are high statistically significant higher gestational age, less preterm birth, decrease NICU admission and duration, with less complications as hypotension, headache, and tachycardia with p-value <0.001, <0.001, 0.026, 0.008.

Conclusion: Progesterone exhibited a superior tocolytic effect than nifedipine for preventing premature labour, with more pregnancy duration and less NICU admission with shorter NICU stay, higher gestational age, and fewer adverse symptoms such as hypotension, headache, and tachycardia.

Keywords: Preterm birth; Tocolysis; Nifedipine; Progesterone.

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INTRODUCTION

Preterm birth (delivery before 37 weeks of gestation) is a "major cause of (postnatal) mortality" as well as a substantial source of long-term human potential loss.¹ When compared to full-term kids, preterm birth has a severe long-term health impact due to an increased risk of mortality as well as the development of a wide range of chronic physical and neurological abnormalities.²

Preterm birth is responsible for around 70% of neonatal deaths, 36% of infant deaths, and 25–50% of cases of long-term neurologic disability in children. Despite the fact that some extremely low-income and middle-income countries have estimated their preterm fatalities within a decade, fewer countries have made minor improvement, resulting in a huge survival disparity for preterm babies in different countries, with more neonatal deaths in African babies.³

The rate of under-5 deaths from preterm birth problems remains high in Egypt, and our country ranks 144th out of 162 countries in terms of prematurity-related deaths, accounting for 28.5 percent of all under-5 deaths in Egypt.⁴

Tocolysis is the pharmacological suppression of uterine contractions, and it is now the major preterm birth prevention strategy, and will remain so until the aetiology of early labour is well understood. Acute

tocolysis delays preterm labour by 48 hours, which is the critical period of prenatal steroid therapy for foetal lung development.⁵ Only successful maintenance tocolysis will have a major influence on neonatal death and morbidity.⁶

Maintenance tocolysis is the continuing of tocolysis after preterm labour has been terminated in order to prevent preterm labour pain from recurring. The oral route of treatment is less costly and has the potential to lower newborn morbidity, hence calcium channel blockers are preferred. Nifedipine has been demonstrated to be a safe and effective therapy for acute tocolysis, with little adverse effects. However, its use in maintenance tocolysis has had inconsistent results.⁷

Progesterone is an important hormone in uterine quiescence. It is increasingly being used in women at high risk of preterm labour, as well as for tocolysis maintenance.⁸ In an observational study conducted in 1980, nifedipine was discovered to be an effective tocolytic drug with low adverse effects.⁹

It is a safe and efficient tocolytic medicine with a simple oral delivery technique, few adverse effects, and a low risk of neonatal complications. It should, however, be used with caution in those who have damaged cardiovascular systems since they are at risk of pulmonary edoema and cardiac failure. The effectiveness of long-term tocolytic treatment after a

successful premature labour arrest is still being debated.¹⁰

The current study examined the effectiveness and safety of nifedipine and progesterone for sustaining tocolysis during preterm labour arrest, as well as their perinatal outcomes.

PATIENTS AND METHODS

This was a randomised controlled research on 60 women diagnosed with imminent preterm labour who were seen and followed up on at El Hussein University Hospital's outpatient clinic after providing written consent.

All pregnant women were randomly allocated to one of two groups: Pregnant women in Group 1 took natural Progesterone 400mg per day vaginally as a tocolytic drug. Group 2: Pregnant females were given nifedipine 20mg orally every 30 minutes for three days, followed by maintenance with nifedipine SR 20mg every 12 hours.

Inclusion criteria include a singleton pregnancy with a cephalic presentation and a gestational age of 28-36 weeks. At least one uterine contraction every ten minutes. The test lasted no less than 30 minutes. Membranes that are still in tact. Cervical effacement of less than 20% and cervical dilatation of less than 2 cm. While the exclusion criteria were: serious maternal illness, cardiovascular diseases, diabetes mellitus, bronchial asthma, pregnancy induced hypertension, severe anemia, multiple pregnancy and polyhydromnios, and malpresentation,

The women will be subjected to the following:

Detailed history taking including: Maternal age, residence, parity, history of preterm labor, gestational age on admission, gestational age at delivery, duration of prolongation of pregnancy after used treatment, time of preterm labor (early, late, >37 weeks), mode of delivery, cervical dilatation, neonatal history of birth weight, morbidities related to prematurity, respiratory distress, NICU admission, and duration of NICU stay, side effects related to Nifedipine or progesterone as hypotension, headache, and tachycardia, and outcome related to neonatal

survive or death.

Clinical examination: (a) General examination: blood pressure, pulse, body weight, height, body mass index and temperature. (b) Abdominal examination: fundal level, fundal grip, umbilical grip, 1st pelvic grip, and fetal heart sound. (c) Local examination: cervical position, effacement, dilatation, and head station.

Ultrasonography is used to determine gestational age, fetal development, amniotic fluid, and to rule out any congenital malformations.

All routine investigations: C.B.C., Rh, blood grouping, blood sugar, kidney functions tests, liver enzymes.

Complete urine analysis, culture, and sensitivity tests.

Cusco examination under complete aseptic technique.

The key result was the prevention of threatened premature labour.

Treatment was continued to two weeks to inhibit contractions. The inhibition of labor had been prolonged until end of 37 weeks of gestation.

Statistical analysis:

SPSS program (Statistical Package for Social Science) version 24 and NCSS 12, LLC, USA was used to computerize and statistically analyze the collected data. The Shapiro Walk test was used to determine whether the data had a normal distribution. Frequencies and relative percentages were used to depict qualitative data. To calculate the difference between qualitative variables, the Chi square test (X²) and Fisher exact were used, as stated. The median and range were used to express quantitative data. For non-normally distributed variables, the Mann Whitney test was utilized to calculate the difference between quantitative variables in two groups. The Kaplan and Meier method was used to estimate time until term delivery, and the log rank test was performed to compare both arms. A P value of 0.05 was deemed significant.

RESULTS

There was no statistically significant difference between women who used nifedipine and those who used progesterone as regards clinicodemographic characters with p value > 0.05 (Table 1).

There was a highly statistically significant difference between the two groups in terms of gestational age on admission, with p value 0.001 being lower gestational age in the nifedipine group, and a highly statistically significant difference in terms of gestational age at delivery, with p value 0.001 being higher in the progesterone group. There is statistically significant difference as regards being late preterm labour with p value=0.01 being higher with nifedipine group, and being >37 w with p value< 0.001 being higher with progesterone group, and there is highly statistically significant difference between both groups as regards term delivery being more with progesterone group with p value < 0.001 (Table 2).

There was statistically significant increase of side effects including hypotension, headache and tachycardia in nifedipine group than progesterone group with p value= 0.002, 0.044, and 0.005 respectively (Table 3).

There was no statistically significant difference as regards survival outcome between progesterone and nifedipine group with p value>0.05 (Table 4).

There was higher gestational age in delivery was reached in progesterone group with statistically significant difference than nifedipine group with p value< 0.001 (Table 5).

More prolongation of pregnancy was achieved in progesterone group than nifedipine group with p value <0.001

(Table 6).

		Arm				Total N=60		Test	P- value
		Nifedipine N=30		Progesterone N=30					
		N	%	N	%	N	%		
Maternal Age, years		30 (21-36)		30 (19-37)		30 (19-37)		-1.15	0.251
Residence	Rural	13	43.3%	8	26.7%	21	35.0%	1.83	0.176
	Urban	17	56.7%	22	73.3%	39	65.0%		
Parity	0	2	6.7%	2	6.7%	4	6.7%	5.13	0.4
	1	6	20.0%	4	13.3%	10	16.7%		
	2	14	46.7%	10	33.3%	24	40.0%		
	3	7	23.3%	8	26.7%	15	25.0%		
	4	1	3.3%	3	10.0%	4	6.7%		
	5	0	0.0%	3	10.0%	3	5.0%		
Previous Preterm Labor	0	16	53.3%	11	36.7%	27	45.0%	5.93	0.052
	1	14	46.7%	14	46.7%	28	46.7%		
	2	0	0.0%	5	16.7%	5	8.3%		

Table (1): Clinico-demographic data in both groups.

			Arm				Total N=60		Test	P-value
			Nifedipine N=30		Progesterone N=30					
			N	%	N	%	N	%		
Gestational age on admission			30 (28-33)		34 (29-35)		32 (28-35)		-5.41	<0.001
Gestational age at delivery			35 (31-38)		38 (33-39)		37 (31-39)		-4.72	<0.001
Prolongation of pregnancy/days			29 (12-42)		30 (18-50)		30 (12-50)		-1.01	0.313
Preterm labor	Early (24-34 w)	No	22	73.3%	27	90.0%	49	81.7%	2.78	0.095
		Yes	8	26.7%	3	10.0%	11	18.3%		
	Late (34-37 w)	No	10	33.3%	20	66.7%	30	50.0%	6.67	0.01
		Yes	20	66.7%	10	33.3%	30	50.0%		
	>37 w	No	28	93.3%	13	43.3%	41	68.3%	17.33	<0.001
		Yes	2	6.7%	17	56.7%	19	31.7%		
Term delivery		No	18	60.0%	3	10.0%	21	35.0%	16.48	<0.001
		Yes	12	40.0%	27	90.0%	39	65.0%		
Mode of delivery		CS	18	60.0%	19	63.3%	37	61.7%	0.07	0.791
		VD	12	40.0%	11	36.7%	23	38.3%		
Cervical dilatation	closed	No	14	46.7%	16	53.3%	30	50.0%	0.27	0.606
		Yes	16	53.3%	14	46.7%	30	50.0%		
	2cm	No	21	70.0%	19	63.3%	40	66.7%	0.30	0.584
		Yes	9	30.0%	11	36.7%	20	33.3%		
	3cm	No	25	83.3%	25	83.3%	50	83.3%	0.001	>0.999
		Yes	5	16.7%	5	16.7%	10	16.7%		

Table (2): Gestational age and labor data in both groups.

	Arm	Total	X ²	P-value
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		Nifedipine N=30		Progesterone N=30		N=60		Test	
		N	%	N	%	N	%		
Hypotension	No	18	60.0%	28	93.3%	46	76.7%	9.32	0.002
	Yes	12	40.0%	2	6.7%	14	23.3%		
Headache	No	24	80.0%	29	96.7%	53	88.3%	4.04	0.044
	Yes	6	20.0%	1	3.3%	7	11.7%		
Tachycardia	No	23	76.7%	30	100.0%	53	88.3%	7.92	0.005
	Yes	7	23.3%	0	0.0%	7	11.7%		

Table 3: Comparison of maternal side effects in both groups.

		Arm				Total N=60		X ² Test	P- value
		Nifedipine N=30		Progesterone N=30					
		N	%	N	%	N	%		
Survival	Died	5	16.7%	3	10.0%	8	13.3%	0.58	0.448
	Live	25	83.3%	27	90.0%	52	86.7%		
Cause	No	25	83.3%	27	90.0%	52	86.7%	0.58	0.448
	Prematurity	5	16.7%	3	10.0%	8	13.3%		

Table 4: Survival outcome in both groups.

Arm	Total N	N of Preterm	Censored N (%)	Gestational age at delivery, wks				Term delivery rate %	P-value
				Mean ±SE	95% CI for mean	Median ±SE	95% CI for median		
Nifedipine	30	18	12 (40%)	35.3±0.4	34.5-36.2	35.0±0.4	34.1-35.9	40.0%	<0.001
Progesterone	30	3	27 (90%)	38.4±0.3	37.8-39.0	NR	NR	90.0%	

SE: standard error; 95%CI: 95% confidence interval, P< 0.001 is highly significant compared by log rank test.

Table 5: Kaplan– Meier curves analysis for the differences in gestational age at delivery in both arms.

Arm	Total N	N of Preterm	Censored N (%)	Prolongation of pregnancy/days				Term delivery rate%	P-value
				Mean ±SE	95% CI for mean	Median ±SE	95% CI for median		
Nifedipine	30	18	12 (40%)	30.4±2.0	26.6-34.3	30.0±3.3	23.4-36.6	34.8%	<0.001
Progesterone	30	3	27 (90%)	47.0±1.6	43.8-50.2	NR	NR	87.3%	

SE: standard error; 95%CI: 95% confidence interval, P< 0.001 is highly significant compared by log rank test.

Table 6: Kaplan– Meier curves analysis for the differences in the prolongation of pregnancy/days in both arms.

DISCUSSION

With a p-value of 0.251, our study found no statistically significant difference in age between the groups of women who used progesterone and those who used nifedipine. This is consistent with the findings of Rabei and colleagues, who conducted a research on women with preterm labour to assess the efficacy of both nifedipine and progesterone and discovered no statistically significant difference between the two groups in terms of maternal age.¹¹ Similarly, Kamat et al.¹² discovered no significant difference in maternal age between women who used progesterone and women who used nifedipine.

In terms of past preterm labour experience, the current study demonstrated no statistically significant difference between the nifedipine and progesterone groups (p-value =0.052). This is similar with the findings of the Rabei et al. research, which found no

statistically significant difference in preterm delivery history between the nifedipine and progesterone groups. In contrast to Eldesouky et al.⁴, who showed a statistically significant difference in preterm labour history between the nifedipine and progesterone groups, the progesterone group was more likely.

The current study discovered a statistically significant increase in gestational age in the progesterone group compared to the nifedipine group, with a p-value of 0.001. In contrast to Abdelgaied et al.¹⁰, who reported no statistically significant change in gestational age on admission between the nifedipine and progesterone groups with a p-value of 0.92.

With a p-value of 0.313, the present study found no statistically significant difference between the nifedipine and progesterone groups in terms of pregnancy extension duration. In contrast to Kamat et

al.¹², who discovered a statistically significant lengthening of pregnancy duration in the progesterone group (40.14 days) compared to the nifedipine group (16.63 days) with p-value =0.000.

The current work discovered a statistically significant difference in preterm labour (late preterm) and 37th weeks of GA being late preterm less in the progesterone group than the nifedipine group with p-value =0.01 and more after 37th weeks GA in the progesterone group than the nifedipine group with p-value =0.01. This was verified by Ding's study, which found that progesterone was more effective than nifedipine in maintaining tocolysis following an arrested preterm birth.¹³

Likewise, Abdelgaied et al.¹⁰ discovered a highly significant difference between the nifedipine and progesterone groups in terms of preterm labour after 32-34 weeks and preterm labour after 37th week GA, as preterm labour after 32-34 weeks was significantly less frequent in the progesterone group than the nifedipine group, and preterm labour after 37th week was significantly more frequent in the progesterone group than the nifedipine

With a p-value of 0.791, the current study demonstrated no statistically significant difference in method of delivery between the progesterone and nifedipine groups. According to the Rabei et al research, the difference in mode of birth between the nifedipine and progesterone groups was statistically insignificant, with vaginal delivery happening in 70.7 percent of the nifedipine group and 80 percent of the progesterone group.¹¹

The present study demonstrated no statistically significant difference in cervical dilatation between the nifedipine and progesterone groups with p-values greater than 0.05. Kamat et al.¹² found no statistically significant difference in cervical dilatation and effacement at admission between the progesterone and nifedipine groups. In contrast to Fonseca et al.¹⁴, who discovered that short cervix progesterone therapy decreased the risk of spontaneous early preterm birth when compared to placebo.

The current study found no statistically significant difference in baby respiratory distress between the nifedipine and progesterone groups, with a p-value of 0.08. In terms of newborn respiratory distress, there was no statistically significant difference between the nifedipine and progesterone groups, as in the Ding et al.¹³ study. In contrast to Carolien et al.¹⁵, who observed that surfactant-treated newborn respiratory distress syndrome happened in 12 (6%) more cases in the progesterone group than in the nifedipine group (6.8 percent).

With a p-value of 0.08, the current study found no statistically significant difference in the need for NICU hospitalisation between the nifedipine and progesterone groups. Similarly to the Ding et al.¹³ study, there was no statistically significant difference in the need for NICU hospitalisation between the nifedipine and progesterone groups. In contrast to Papatsonis et al.¹⁶, who observed that progesterone reduced infant ICU hospitalisation compared to

nifedipine, as well as a lower significant risk for RDS with a p-value of 0.05.

The current study revealed that the nifedipine group had a statistically significant longer NICU stay than the progesterone group, with a p-value of 0.026. Similarly, Harrison et al.¹⁷ discovered that, while there was no significant difference in the need for NICU hospitalisation between the nifedipine and progesterone groups, the nifedipine group was more protracted than the progesterone group (p-value=0.02).

The present study found that the progesterone group had a statistically significant greater birth weight than the nifedipine group, with a p-value of 0.008. This is consistent with the findings of Eldesouky et al.'s research, which discovered a statistically significant increase in birth weight in the progesterone group (3.0260.570kg) over the placebo group (2,7880.749 kg). In contrast to Chawanpaiboon et al.¹⁸, who discovered that the mean foetal birth weight in the nifedipine group was 2.856.351kg and 2.685.456kg in the progesterone group, no significant difference was seen. The discrepancies across studies may be related to variances in the time of when progesterone is administered, whether during the threatening stage of preterm labour or after tocolysis in established preterm labour, as well as disparities in sample size.¹⁰

With p-values =0.002, 0.044, and 0.005, the current study revealed a statistically significant rise in issues such as hypotension, headache, and tachycardia in the nifedipine group over the progesterone group. Similarly, Kamat et al.¹² found statistically significant increased complications in the nifedipine group compared to the progesterone group with p-values of 0.03, 0.03, and 0.01 in hypotension, headache, and tachycardia, respectively, in a study of 110 pregnant women divided into two groups (nifedipine and progesterone groups).

With p-values larger than 0.05, the current study found no statistically significant difference in outcome (died or survived) between the nifedipine and progesterone groups. This is congruent with the findings of the Ding et al.¹³ study, which comprised nine trials to explore the influence of nifedipine and progesterone in tocolysis and found no statistically significant difference in infant mortality with p-values better than 0.05 between the two groups.

With a p-value of 0.001, 95 percent CI, Roc curve analysis revealed that progesterone increased gestational age and pregnancy duration. Similarly, Kamat et al.¹² presented a ROC analysis for the efficacy of nifedipine and progesterone in terms of pregnancy prolongation, and progesterone considerably outperformed nifedipine in terms of pregnancy prolonging and gestational age, with p-value=0.0001 and CI95 percent. This is consistent with the findings of Ding et al.¹³, who found that progesterone significantly prolonged pregnancy and increased gestational age, with 95 percent CI and p-values of 0.00001 and 0.001, respectively.

CONCLUSION

Progesterone exhibited a superior tocolytic effect than nifedipine for preventing premature labour, with more pregnancy length and less NICU admission with shorter NICU stay, higher gestational age, and less adverse symptoms such as hypotension, headache, and tachycardia.

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