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COMPARISON OF NIFEDIPINE AND PROGESTERONE FOR MAINTENANCE TOCOLYSIS AFTER ARRESTED PRETERM LABOUR

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ABSTRACT

Objective: The aim was to compare the efficacy and safety of nifedipine and progesterone for maintenance tocolysis after arrested preterm labor and their perinatal outcomes. **Background** Preterm birth (before 37 completed weeks of gestation) is a 'major cause of death' and a significant cause of long-term loss of human potential. Maintenance tocolysis is continued tocolysis after arrested preterm labor to prevent the recurrence of preterm labor pains. **Patients and methods** A prospective randomized comparative clinical study was carried out on 78 pregnant women who had preterm labor (7 cases lost to follow-up) and attended the Obstetrics and Gynecology *TISHREEN UNIVERSTY* Hospital during the period March 2021 and February 2022. Detailed history, laboratory investigations, obstetric, and ultrasound follow-up study were performed. **Results** There was no significant difference ($P > 0.5$) between nifedipine and progesterone groups regarding maternal age and gestational age on admission (weeks), mode of delivery. However, there was a statistically significant difference ($P \leq 0.05$) regarding mean blood pressure before and after treatment in nifedipine group, and neonatal birth weight between nifedipine and progesterone groups. There was a significant difference in the gestational age at delivery between the two groups. **Conclusion:** We found a superiority of progesterone over nifedipine for maintenance tocolysis. We would only comment that progesterone looks like a promising drug in this regard, and further large studies are required to establish this fact.

KEYWORDS: maintenance tocolysis, nifedipine, perinatal outcome, preterm, progesterone.

INTRODUCTION

Preterm birth (before 37 completed weeks of gestation) is a 'major cause of (postnatal) death' and a significant cause of long-term loss of human potential.[1] Preterm labour is a leading cause of neonatal mortality and morbidity with long-term neuro developmental sequelae (Morrison 1998). Preterm birth aff ects 12% of all births. In the last decade, preterm birth has increased by 27% and accounts for 85% of all perinatal morbidity and mortality (ACOG 2005). There is a substantial long‐term health effect from preterm birth owing to increased risk of both death and developing a wide range of chronic physical and neurological disabilities compared with full-term births.[2] Treating preterm labour is a major obstetric challenge. Acute tocolysis delays preterm birth by 48 h, the critical period of antenatal steroid administration for fetal lung maturity. A major effect on the associated neonatal mortality and morbidity will be achieved only with effective maintenance tocolysis to prolong pregnancy to term (Morrison 1998). After arrested preterm labor with acute tocolysis, maintenance tocolysis should be continued with the goals of prolonging gestation and improving neonatal outcome. There are several reasons to consider maintenance tocolysis. First, perinatal morbidity and mortality are inversely related to gestational age[3] 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. The oral route of administration has low cost and a possible efficacy in reducing neonatal morbidity favoring the use of calcium channel blockers. Nifedipine is found to be a safe and effective drug for acute tocolysis, with minimal adverse effects. However, its use for maintenance tocolysis has yielded conflicting results.[5] Progesterone is an important agent for maintaining uterine quiescence. It is increasingly used in women at high risk for preterm

labor and for maintenance tocolysis.[2]

However, the effectiveness of mainteance tocolysis is unclear. Our present study aimed to evaluate the effect of progesterone and nifedipine as the maintenance tocolysis therapy after arrested preterm birth.

MATERIALS AND METHODS

This study was a randomized control clinical trial carried out in the department of Obstetrics and Gynaecology, Tishreen University in latakia ,between March 2021 and February 2022. Institute review board approval and institute ethical committee approval was obtained. Pregnant women who were fulfi-lling the inclusion criteria with preterm labour or threatened preterm labour were included in the study after an informed written consent. Preterm labour was defined as occurrence of regular uterine contractions (≥ 4 in 20 min) and cervical changes (effacement ≥ 80% and cervical dilatation ≥ 1 cm) in women with intact membranes and gestational age of < 37 weeks.

Threatened preterm labour was defined as contractions as defined above, without any appreciable cervical changes. Exclusion criteria were antepartum haemorrhage, lethal fetal anomaly, IUGR, chorioamnionitis, cerclage, maternal medical complications contraindicating tocolysis, multiple pregnancy, cervical dilatation>4 cm and ruptured membranes. Threatened preterm or preterm labour was arrested with acute tocolysis using tab nifedipine 30 mg stat followed by 20 mg Q 8-hourly. Injection dexamethasone 6 mg intramuscular was given 12-hourly for 4 doses, to effect fetal lung maturity. Patients with a singleton live pregnancy with arrested preterm labour were included in the study. Arrested preterm labour is defined by a 12-hour contraction free interval aft er the last dose of nifed ip ine. The women were randomised into two groups: nifedipine and progesterone groups, using a computer generated random number table. A total of 78 eligible women were recruited, out of which four women were lost to follow-up in the nifedipine group and three in the progesterone group. The sample size was 36 women in the nifedipine group and 35 women in progesterone group; a total sample size of 71 women. Women in the nifedipine group received 20 mg of nifedipine Q 12-hourly. Women in the progesterone group received 400 mg of micronised progesterone vaginally at bed time. If the women were stable and undelivered after 48 h of maintenance tocolysis, they were discharged and followed-up in the antenatal clinic. At every visit, fetal growth was assessed clinically and patients were evaluated for side-effects. Maintenance tocolysis was given until 37 weeks or until the onset of spontaneous labour, whichever was earlier. The parameters studied were age, gravidity, parity, history of abortions (1st and 2nd trimester), gestational age at admission, cervical dilatation, The outcome measures studied were mean prolongation of pregnancy and neonatal outcome like birth weight, gestational age. Side-eff ects of either drug assessed were headache, hypotension, tachycardia, sleeplessness and shortness of breath.

Statistical analysis was done using the χ 2 -square or Fisher 's exact test for categorical variables and Student ' s *t* -test for continuous variables. A *p* value of _ 0.05 was considered significant.

RESULTS

Out of the 78 women recruited, four patients were lost to follow-up in nifedipine group and three patients were lost to follow-up in the progesterone group. The final sample size was 36 women in the nifedipine group and 35 women in the progesterone group. There was no significant difference in the mean age or parity of patients between the two groups. The previous abortion rate was 22.22% in the nifedipine group and 22.86 % in the progesterone group; this was not statistically significant (*p* _ 0.9). There was no significant difference in the number of previous preterm deliveries between the two groups (*p* _ 0.5). In total, 22.22 %of women in the nifedipine group and 40 % of women in the progesterone group delivered at > 37 weeks. There was a significant difference in the gestational age at delivery between the two groups, the *p* value being (0.001) (Table 1).

Table 1: Gestational age at delivery.

Gestational age at delivery (weeks)	Progesterone n (%)	Nifedipine n (%)	p value
< 37 Weeks	21(60%)	28(77.78%)	0.005
>37 Weeks	14(40%)	8(22.22%)	
Mean ± SD	35.55 ±2.11	34.12±2.43	0.001

Th e mean prolongation of pregnancy in the nifedipine group 23.27 days, and 36.92 days in the progesterone group, which was significan (*p* _ 0.001) (Table 2).

Table 2: Prolongation of pregnancy.

Prolongation of pregnancy (days)	Progesterone n (%)	Nifedipine n (%)	p value
<7 days	4 (11.43%)	7(9.44%)	0.046
8 – 21	3 (8.57%)	13(36.11%)	0.001
22 - 35	8(22.86%)	7(9.44%)	0.5
36 - 49	13(37.14%)	5(13.9%)	0.001
>49 day	7 (20%)	4(11.11%)	0.025
Mean ± SD	36.92 ± 10.04	23.27±9.13	0.001

Some 90.74% of women in the nifedipine group and 87.74% of women in the progesterone group were delivered by spontaneous vaginal delivery. There was nosignificant difference in the mode of delivery between the two groups. Regarding neonatal outcome, there was a significant difference in the birth weights between the two groups (p _ 0.001). The mean birth weight in the nifedipine group was 2138g and 2850g in progesterone groups (table 3).

Table3: Neonatal birth weight.

Neonatal birth weight(g	Progesterone	Nifedipine	p value
Mean	2850	2138	0.001
S.D	688	521	

DISCUSSION

The current study showed that there was no statisticallysignificant difference between the nifedipine and progesterone groups regarding maternal age (years). The same finding was supported by Rabei *et al.*[6] who compared nifedipine and progesterone in inhibiting threatened preterm labor and found that there was no statistically significant difference between nifedipine and progesterone groups regarding the maternal age. In addition, Kamat *et al.*[7] compared the efficacy and safety of nifedipine and progesterone for maintenance tocolysis after arrested preterm labor, and they found that there was no significant difference in maternal age between the two groups.

The current study showed that there was no statistically significant difference between the nifedipine and progesterone groups regarding parity. The same finding was supported by Kamat *et al.*[7], as they found that there was no significant difference between the nifedipine and progesterone regarding parity.

Our results agree with Rabei *et al.*[6] and Chawanpaiboon *et al.*[8] as they found that there was no statistically significant difference between nifedipine and progesterone groups regarding parity.

The current study showed that there was no statistically significant difference between the nifedipine and progesterone groups regarding previous preterm labor.This result is in disagree with Eldesouky *et al.*[4] who found a significant difference between placebo and progesterone groups with respect to history of preterm delivery. Our results agreement with Kamat *et al.*[7] who found that there was no significant difference in the previous preterm deliveries between the nifedipine and progesterone groups. Moreover, Rabei *et al.*[6] showed no statistically significant difference between the progesterone and nifedipine groups regarding the previous preterm.

The current study showed that there was a statistical significant difference between the nifedipine and progesterone groups regarding GA on admission (weeks). The same results were supported by Kamat *et al.*[6] who found that there was a statistically significant difference between nifedipine and progesterone groups regarding GA.

the current study showed that vaginal delivery occur in 90.74% and 87.74% in nifedipine and progesterone, respectively, whereas cesarean birth occurred in 9.26 %and 12.26 % in nifedipine and progesterone, respectively, which was no statistically significant in both studied groups. These results matched with a study of Kamat *et al.*[7]

Additionally, the current study indicated that neonatal birth weight was higher in progesterone group (2850 g) than nifedipine group (2138 g) that there was a statistical significant difference between the nifedipine and progesterone groups.These results agreed with the results of Kamat *et al.*[6] who found that the mean fetal birth weight in nifedipine group was1806 g, and whereas in the progesterone group was 2506 g, and the difference was a statistically significant.

Regarding maternal heart rate before and after treatment, it was statistically significant in nifedipine group versus in progesterone group, which was not statistically significant. This is similar to the result of the study conducted by Ahtisham *et al.*[9] who found increase in maternal heart rate following each dose of nifedipine .The current study revealed that there were statistically significant differences between studied groupsregarding

maternal mean blood pressure (mmHg) before and after treatment. Maternal mean blood pressure decreased significantly after treatment as compared before treatment. This agreed with Ahtisham *et al.*[9] Moreover, Haas *et al.*[11] studied tocolytic therapy for preterm delivery. They found that prostagl and in inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternaloutcomes. In contrast to our study, Abdel Hak and Gafaar.[10]

Nifedipine was more commonly associated with side-eff ects compared with progesterone in our study. However, no women in our study discontinued medication due to adverse eff ects ormedication intolerance. A total of 25 % of women in the nifedipine group had tachycardia, as against 2.86 %women in the progesterone group, which was significant. Of women in the nifedipine group, 8.3 had hypotension, as agains 0% women in the progesterone group which was significant. of women in the nifedipine group 19.44 % had headache,. as agains 2.86 % women in the progesterone group , which was significant. These results matched with a study of Kamat *et al.*[7] (table 4)

Table 4: Side-eff ects.

Side-eff ects	Progesterone n (%)	Nifedipine n (%)	p value
Hypotension	0	3(8.33%)	0.002
Headache	1(2.86%)	7(19.44%)	0.0004
Tachycardia	1(2.86%)	9(25%)	0.0001

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