Nifedipine versus Nifedipine and Progesterone Therapy in Acute Tocolysis in Preterm Labor and Their Effect on Maternal and Fetal blood flow

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ABSTRACT

Background: Preterm delivery is labor beginning before completing 37 weeks of gestation with progressive effacement and dilatation of the cervix in the presence of regular painful contractions. Preterm labor as one of the biggest challenges for obstetricians is a world health problem and is responsible for approximately two-thirds of early neonatal morbidity and mortality.

Objectives: To compare the effectiveness and safety of nifedipine therapy versus combined use of vaginal progesterone and nifedipine as acute tocolysis and their effect on maternal and fetal blood flow measured at 24 and 72 hours after their use. **Patients and Methods:** This prospective randomized observational comparative clinical study included 52 pregnant women with symptoms and signs of preterm labor that were randomly allocated into two groups each group consisted of 26 patients. This study was conducted in Obstetrics and Gynecology Department, Menoufia University Hospitals in the period between March 2019 and March 2020. Their gestational ages ranged from 28-34 completed weeks. **Result:** Time interval between last epilat capsules to tocolytic effect in minutes was significantly shorter in group B than in group A. There was no significant difference between the two groups in Doppler parameters with no long-term effect on fetomaternal circulation as tocolytics in acute preterm labor.

Conclusion: This study concluded that oral nifedipine plus vaginal progesterone is associated with more rapid response to tocolysis in threatened preterm labor compared to oral nifedipine alone with nearly the same effect on maternal and fetal blood flow.

Keywords: Preterm labor, Tocolytics, Nifedipine, Progesterone, Doppler.

INTRODUCTION

World Health Organization (WHO) defined preterm labor as the onset of labor after the age of viability and before completing 37 weeks of gestation. The conditions which determine the onset of labor include documented uterine contractions (at least 1 every 10 min), ruptured fetal membrane, documented cervical change with cervical length of about 1 cm or less and/or cervical dilation of more than 2 cm. Considering this, threatened preterm labor can be diagnosed when there are documented uterine contractions with no cervical changes [(1)].

Preterm birth is the leading cause of neonatal mortality and morbidity, as well as the most common reason for antenatal maternal hospitalization, which is associated with socio-economical burdens to the society [(2)]. In the world, about 15 million preterm infants are born every year [(3)].

Tocolytic therapy has a well-defined role in the management of preterm labor, accomplishing the following objectives: permitting transfer of the pregnant woman to a tertiary care center, prolonging pregnancy for at least 48 h to optimize the beneficial effect of steroids on fetal lung maturity and prolonging pregnancy in an attempt to improve perinatal outcome. Tocolysis is currently the principal preterm birth preventive measure and will remain so until the etiology of preterm labor is better-understood [(4)]. Many tocolytic agents are used in clinical practice in an attempt to prevent preterm delivery such as B2 agonists, calcium channel blockers (as nifedipine), progesterone, magnesium sulfate, oxytocin antagonists and anti-prostaglandins (as indomethacin) [(5)].

Nifedipine was first reported in 1980 in an observational study to be an effective tocolytic agent with minimal side effects [(6)]. It is an effective tocolytic agent, with an easy oral route of administration, few side effects and a low neonatal complications rate. However, it should be used with caution in patients with compromised cardiovascular condition as they may be at risk of pulmonary edema and cardiac failure [(7)].

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 [(8)]. Far too few studies have focused on the possible effects of progesterone on maternal or fetal circulation in late pregnancy, especially in high-risk women. Several mechanisms were described for the role of progesterone including anti-inflammatory effect, inhibition of gap-junction formation in the myometrium, and direct effect on the cervix [(9)].

The American College of obstetricians and Gynecologists (ACOG) gave this general recommendation for the use of tocolytic medication in the clinical management of preterm labor: "if tocolytic drugs are used, the choice of drug should be individualized and based on maternal condition, potential drug side effects, and gestational age" [(10)].

Aim of the work was to compare the effectiveness, the safety of nifedipine therapy versus combined use of

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vaginal progesterone and nifedipine in acute tocolysis in preterm labor and their effect on maternal and fetal blood flow 24 h and 72 h of their use.

PATIENTS AND METHODS

A prospective randomized observational comparative clinical study was conducted on 52 women admitted to the Obstetrics and Gynecology Department of Menoufia University Hospitals with symptoms and signs of preterm labor. Their gestational ages ranged from 28-34 completed weeks. The study was conducted from March 2019 till March 2020. The patients were classified into 2 groups each group consisted of 26 patients.

Group A: Received calcium channel blocker in the form of nifedipine oral capsules (five epilat 10 mg capsules **(EIPICO)** with interval 20 minutes between one another).

Group B: Received the same as group A plus 400 mg of micronized progesterone vaginally at once with the first epilat capsule **(Prontogest R, MARCYL).**

We gave patients 1000 cc of isotonic saline to safeguard against hypotension.

Inclusion Criteria: Singleton pregnancy between 28 and 34 weeks of gestation with intact fetal membrane, having normal fetal heart rate, regular uterine contractions of at least 30 seconds duration at a rate of three or more contractions per 10 minutes by cardiotocography. Furthermore, cervical dilatation of 1-3 cm (0-3 for nulliparous) and effacement 50% or more and with absence of maternal or fetal indication requiring immediate intervention.

Exclusion criteria: Women with multiple pregnancies, cervical dilatation of 4 cm or more, clinical diagnosis of chorioamnionitis (Maternal fever, tachycardia, abdominal tenderness, vaginal discharge and fetal tachycardia) and women with gestational age below 28 or over 34 weeks. In addition, presence of fetal anomalies, intrauterine growth restriction, abnormal fetal heart rate, intrauterine fetal death, fetal distress requiring delivery, premature rupture of membrane and oligohydramnios or polyhydramnios. Besides, abruptio placentae, presence of maternal medical complications such as preeclampsia and eclampsia cardiac diseases, congenital heart disease and acquired heart disease as cardiac arrhythmia.

All patients are subjected to the following: Personal history with emphasis on; age, residence, occupation, parity and socio economic level**.** Past history and obstetric history with emphasis on previous laparotomy, previous C.S, past history of abortion and past history of preterm labor. Maternal medical conditions (e.g. hypertension, preeclampsia, diabetes, or thyroid or adrenal diseases), contraindications for progesterone and women who had received other tocolytic drugs such as MgSO4, non-steroidal anti-inflammatory drugs, and calcium channel blockers**.** Sexual history as recent intercourse within 48 h, menstrual history and last menstrual period date.

General examination was done to detect:

- Head and neck examination for pallor, jaundice, thyroid and lymph node enlargement.
- Vital signs include arterial blood pressure, Pulse, respiratory rate and Temperature.
- Examination of lower limb for edema and varicose vein.
- Chest and heart examination.

Abdominal examination was done to detect fundal level, fundal grip, pelvic grip, umbilical grip, fetal heart rate, fetal movement, fetal lie, fetal presentation, scar, uterine contractions, ensure singleton fetus, estimated fetal size and amniotic fluid volume.

Vaginal examination was done to detect cervical dilatation, effacement and state of fetal membranes, fetal presentation, fetal position and vaginal infection.

Abdominal ultrasound examination was done for every patient to exclude multifetal pregnancy and to ensure presentation, position, placental site, maturity grade, fetal viability, biometry for estimation of gestational age, fetal weight, amniotic fluid volume and gross fetal anomalies. Besides, color Doppler study was performed.

Prophylactic corticosteroid therapy to all patients to induce fetal lung maturity using a single course of dexamethasone (4 doses of 6 mg IM, 12 h apart).

Laboratory investigations: Blood group and Rh typing, complete blood picture including total and differential leucocyte count, ESR, CRP, complete urine analysis, serum glucose and creatinine.

Short-term tocolysis using single agent versus double agents according to the previously suggested protocol. The choice of drug or drugs for each patient to be randomly pre-selected by computer.

Obstetric ultrasound with Doppler flow assessment

Study of placental and fetal cerebral blood flow was done through color Doppler of uterine, umbilical and fetal middle cerebral artery (MCA) waveforms. The pulsatility index (PI) and resistance index (RI) of the uterine, umbilical artery and fetal MCA were measured prior, 24 and 72 hours after the administration of the tocolytic therapy. The cerebroplacental ratio (MCA-PI/ umbilical artery PI) was calculated.

Ethical and patients' approval: The study was approved from the Ethics Committee for Human Research of the Faculty of Medicine of Menoufia

University. Written informed consents data were expressed as number (No), percentage (%) mean ($\bar{x}$) and standard deviation (SD). Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Chi-square test (χ^2) was used to study association between qualitative variables. Whenever any of the expected cells were less than five, Fischer's Exact test was used. ANOVA (with or without Bonferoni correction) with Mauchly test for sphereicty test were used for comparison among three or more consecutive measures in the same group of quantitative variables. Assumed spherecity was used for normally distributed data while Greenhouse-Geisser was used for not normally distributed data. Two-sided P- value of $\leq$ 0.05 was considered statistically significant.

RESULTS

Table (1): Basic obstetric data to all patients

Variables	Group A (n=26) Mean ± SD	Group B (n=26) Mean ± SD	Test of significance	P value
Age (y)	25.80 ± 5.82	24.03 ± 4.08	t=1.26	0.211
Maternal BMI	24.88 ± 2.91	24.49 ± 2.04	t=0.561	0.577
Residence **Rural** **Urban**	 11 (42.3) 15 (57.7)	 15 (57.7) 11 (42.3)	χ^2=1.23	0.406
Occupation **Housewife** **Working**	 17 (65.4) 9 (34.6)	 19 (73.1) 7 (26.9)	χ^2=0.361	0.764
Parity **Primipara** **Multipara**	 4 (15.4) 22 (84.6)	 10 (38.5) 16 (61.5)	χ^2=3.52	0.060
Gestational age (in weeks)	31.11 ± 1.88	30.84 ± 2.07	t=0.490	00.626
Uterine Contractions before tocolysis in 10 min	3.00 ± 0.00	3.00 ± 0.00	----	----
Cervical dilatation before tocolysis in cm	1.53 ± 0.64	1.38 ± 0.57	U= 0.889	0.374
Cervical effacement before tocolysis in %	51.15 ± 3.25	53.07 ± 4.70	χ^2=1.173	0.094

t= students t test, χ^2 =chi square

There was no significant difference between the two groups regarding basic obstetric data (Table 1).

Table (2): Response to tocolytics among the studied groups

Character	Group A (n=26) No. (%)	Group B (n=26) No. (%)	U	P value
Response time in minutes	138.46 ± 17.93	112.50 ± 8.39	5.41	<0.001
Effacement after treatment	58.46 ± 9.24	63.46 ± 10.93	1.79	0.072
Dilatation after treatment	2.30 ±0.54	2.15 ± 0.46	1.13	0.256
Time interval between last epilat capsule to tocolytic effect in minutes	58.07 ± 18.22	32.50 ± 8.39	5.31	<0.001
Recurrence **Absent** **Present**	 24 (92.3) 2 (7.7)	 26 (100.0) 0 (0.0)	FE=0.149	0.490

t= students t test, U= Mann Whitney test, χ^2 =chi square

The response time and time interval between last epilat capsules to tocolytic effect in minutes were significantly shorter in group B than in group A. there was no significant difference regarding the cervical effacement or dilatation after treatment. The recurrence was not significantly different between the two groups either (Table 2).

Table (3): Umbilical artery Doppler [resistance index (RI), pulsatility index (PI)] different time measures among the studied groups

Groups	Umbilical a RI			F test	P value	
	Baseline Mean ± SD	24 h Mean ± SD	72 h Mean ± SD			
Group A	0.58 ± 0.05	0.55 ± 0.05	0.58 ± 0.05	2.55	0.100	
Group B	0.60 ± 0.05	0.57 ± 0.07	0.57 ± 0.05	1.87	0.163	
Test of significance	t=1.62	U=0.83	U=0.71			
P value	0.110	0.402	0.474			
Groups	**Umbilical a PI**			**F test**	**P value**	**Paired testing**
	Baseline Mean ± SD	24 h Mean ± SD	72 h Mean ± SD			
Group A	0.79 ± 0.08	0.71 ± 0.12	1.02 ± 0.06	87.28	<0.001	P1 0.029, P2 <0.001, P3 <0.001
Group B	0.83 ± 0.07	0.73 ± 0.12	1.04 ± 0.08	83.67	<0.001	P4 0.002, P5 <0.001, P6 <0.001
Test of significance	t=1.56	U=0.74	U=0.98			
P value	0.124	0.457	0.326			

-P1: baseline Vs 24-hour, P2: baseline Vs 72-hour, P3: 24-hour Vs 72-hour in Group A
-P4: baseline Vs 24-hour, P5: baseline Vs 72-hour, P6: 24-hour Vs 72-hour in Group B
F test: repeated measures ANOVA, t= students t test, U= Mann Whitney test

There was no significant difference between the two groups regarding umbilical artery RI at the baseline, 24-hours or 27-hours. There was no significant difference among the three measures of umbilical artery RI inside each group. There was no significant difference between the two groups regarding umbilical artery PI at the baseline, 24-hours or 27-hours. However, inside each group, umbilical artery PI decreased significantly at 24-hours than the baseline then increased again at 72-hours (Table 3).

Table (4): Uterine artery Doppler [resistance index (RI), pulsatility index (PI)] different time measures among the studied groups

Groups	Uterine a RI			F test	P value	Paired testing
	Baseline Mean ± SD	24h Mean ± SD	72h Mean ± SD			
Group A	0.47 ± 0.07	0.39 ± 0.06	0.58 ± 0.06	49.05	<0.001	P1 <0.001, P2 <0.001, P3 <0.001
Group B	0.47 ± 0.11	0.38 ± 0.06	0.58 ± 0.07	34.92	<0.001	P4 0.002, P5 <0.001, P6 <0.001
Test of significance	t=0.00	U=0.59	U=0.33			
P value	1.00	0.551	0.740			
Groups	**Uterine a PI**			**Test of significance**	**P value**	**Paired testing**
	Baseline Mean ± SD	24h Mean ± SD	72h Mean ± SD			
Group A	0.86 ±0.10	0.63 ±0.19	1.02 ±0.19	48.63	<0.001	P1 <0.001, P2 0.001, P3 <0.001
Group B	0.83 ± 0.15	0.65 ± 0.14	1.06 ± 0.14	62.19	<0.001	P4 <0.001, P5 <0.001, P6 <0.001
Test of significance	U=0.16	t= 0.34	U=0.458			
P value	0.869	0.730	0.647			

-P1: baseline Vs 24-hour, P2: baseline Vs 72-hour, P3: 24-hour Vs 72-hour in Group A
-P4: baseline Vs 24-hour, P5: baseline Vs 72-hour, P6: 24-hour Vs 72-hour in Group B
F test: repeated measures ANOVA, t= students t test, U= Mann Whitney test.

There was no significant difference between the two groups regarding uterine artery RI at the baseline, 24-hours or 27-hours. However, inside each group, uterine artery RI decreased significantly at 24-hours than the baseline then increased again at 72-hours. There was no significant difference between the two groups regarding uterine artery PI at the baseline, 24-hours or 27-hours. However, inside each group, uterine artery PI decreased significantly at 24-hours than in the baseline then increased again at 72-hours (Table 4).

Table (5): Middle cerebral artery Doppler [resistance index (RI), pulsatility index (PI)] different time measures among the studied groups

Groups	MCA RI			Test of significance	P value	Paired testing
	Baseline Mean± SD	24h Mean± SD	72h Mean± SD			
Group A	0.78 ± 0.10	0.67 ± 0.09	0.80 ± 0.10	26.32	<0.001	P1 <0.001, P2 1.00, P3 <0.001
Group B	0.80 ± 0.10	0.69 ± 0.10	0.81 ± 0.10	12.28	<0.001	P4 0.004, P5 1.00, P6 <0.001
Test of significance	t= 0.64	t=0.77	U=0.60			
P value	0.523	0.445	0.545			
Groups	**MCA PI**			**Test of significance**	**P value**	**Paired testing**
	Baseline Mean± SD	24h Mean± SD	72h Mean± SD			
Group A	1.34 ± 0.21	1.26 ± 0.19	1.70 ± 0.36	25.56	<0.001	P1 <0.001, P2 <0.001, P3 <0.001
Group B	1.44 ± 0.20	1.33 ± 0.17	1.66 ± 0.17	77.70	<0.001	P4 <0.001, P5 <0.001, P6 <0.001
Test of significance	U=1.71	U=1.41	U=0.60			
P value	0.087	0.158	0.545			

-P1: baseline Vs 24-hour, P2: baseline Vs 72-hour, P3: 24-hour Vs 72-hour in Group A
-P4: baseline Vs 24-hour, P5: baseline Vs 72-hour, P6: 24-hour Vs 72-hour in Group B
F test: repeated measures ANOVA, t= students t test, U= Mann Whitney test.

There was no significant difference between the two groups regarding MCA RI at the baseline, 24-hours or 27-hours. However, inside each group, MCA RI decreased significantly at 24-hours than in the baseline then increased again at 72-hours. There was no significant difference between the two groups regarding MCA PI at the baseline, 24-hours or 27-hours. However, inside each group, MCA PI decreased significantly at 24-hours than in the baseline then increased again at 72-hours (Table 5).

DISCUSSION

The current study showed that there was non-statistically significant difference between group A and B regarding maternal age (year), maternal BMI, residence, occupation or parity. This is supported by **Ashraf** [(11)] who compared efficacy and safety of oral nifedipine with or without vaginal progesterone in management of threatened preterm labor and found that there was no statistically significant difference between the two groups regarding the maternal age, maternal BMI, residence, occupation or parity.

There was no significant difference between two groups regarding clinical characteristics; gestational age, frequency of uterine contractions, cervical dilatation or effacement. The gestational age at presentation varied from 28 to 34 weeks with a mean of 31.11 ± 1.88 in group A, while it was 30.84 ± 2.07 in group B. This is in agreement with **Kamat *et al.*** [(12)] who compared the efficacy and safety of nifedipine with or without vaginal progesterone for acute tocolysis in preterm labor; they found that there was no significant difference in sociodemographic characters or clinical characters between the two groups.

Several classes of tocolytic agents are used in the management of threatened preterm delivery. Calcium channel blockers are among the most widely used and studied. In the choice of the appropriate agent, the side effect profile is an important consideration. We performed this study to concurrently evaluate safety, effectiveness and the effects of oral nifedipine loading for tocolysis with or without vaginal progesterone on the fetoplacental circulation. Potential effects on placental blood flow dynamics were evaluated by examination of the maternal (UtA) and fetal (UA) compartments. Effects on cerebral blood flow and downstream distribution of cardiac output were evaluated by measurement of the MCA and the cerebroplacental ratio.

The importance of progesterone in maintaining pregnancy has long been recognized. Progesterone is a multifaceted hormone that has several crucial functions during pregnancy. For instance, it supports uterine quiescence, suppresses contractile genes and prevents the rejection of the fetus by the mother through suppressing the cellular component of the immune system. Despite the apparent benefits of progesterone in high-risk populations, progesterone has largely been studied only as a prophylactic method in asymptomatic women, not as a tocolytic agent in women with symptoms of threatened PTL [(11)]. One study showed that the use of additional vaginal progesterone with nifedipine tocolysis resulted

in significant prolongation of pregnancy. It also resulted in reducing neonatal ICU admissions as well as the rate of low birth weight among the neonates [11].

In our study, the use of additional vaginal progesterone with nifedipine resulted in significant shortening of the response time to tocolysis making achievement of tocolysis more rapid than nifedipine alone. The current study is consistent with the study done by **Nisa *et al.*** [13], which showed that oral nifedipine plus progesterone is associated with higher efficacy for tocolysis of threatened preterm labor as compared to oral nifedipine alone. Tocolysis was achieved when uterine activity declined to less than four contractions per hour with the absence of any further cervical changes. Tocolytic failure could be defined as delivery within less than 48 hours after initiation of studied agent.

There was no significant difference between the two groups regarding, hypotension, tachycardia, headache, palpitation, flushing, dyspnea, nausea & vomiting or chest tightness. Flushing was the most common maternal side effect in both groups. Some patients showed more than one side effect. The current study is consistent with the study done by **Guclu *et al.*** [14] where flushing was the most common complication to nifedipine tocolysis.

Our data showed that there was no significant difference between the 2 groups regarding Umbilical artery PI at the baseline, 24-hours or 27-hours. However, inside each group, umbilical artery PI decreased significantly at 24-hours than in the baseline then increased again at 72-hours. This is in accordance with the study of **Asem *et al.*** [15] who found a significant reduction of umbilical artery PI and MCA PI values at 24-hours after oral nifedipine therapy in their comparative study between nifedipine, ritodrine and magnesium sulfate as tocolytics in cases of preterm labor and their effect on utero-placental perfusion.

There was no significant difference between the 2 groups regarding uterine artery RI at the baseline, 24-hours or 72-hours. However, inside each group, uterine artery RI decreased significantly at 24-hours than in the baseline then increased again at 72-hours.

There was no significant difference between the 2 groups regarding uterine artery PI at the baseline, 24-hours or 72-hour. However, inside each group, uterine artery PI decreased significantly at 24-hours than in the baseline then increased again at 72-hours. This is in accordance with the study of **Guclu *et al.*** [14] who found significant fall in uterine artery and fetal MCA PI and RI at 24 h of tocolysis with nifedipine in their study on the short-term effect of nifedipine tocolysis on placental, fetal cerebral and atrioventricular Doppler parameters in the first 48 hours. Furthermore, the study of **Namazov *et al.*** [16] is in agreement with our study. They found a significant reduction of fetal middle cerebral artery and maternal uterine artery PI and RI values at 24-hours after oral nifedipine therapy on fetoplacental blood flow. The study of Ugwumadu ***et al.*** [17] found a significant reduction of maternal uterine artery and umbilical artery PI and RI values 24-hours after oral nifedipine therapy in comparison with values recorded prior to nifedipine therapy. Also **Lima *et al.*** [18] found a significant reduction of fetal MCA, maternal uterine artery and umbilical artery PI and RI values 24-hour after oral nifedipine therapy in comparison with values recorded prior to nifedipine therapy on Doppler velocimetry of the uterine, umbilical and fetal middle cerebral arteries in pregnant women undergoing tocolysis with oral nifedipine.

There was no significant difference between the 2 groups regarding MCA RI at the baseline, 24-hours or 72-hours. However, inside each group, MCA RI decreased significantly at 24-hour than in the baseline then increased again at 72-hours.

There was no significant difference between the 2 groups regarding MCA PI at the baseline, 24-hours or 72-hours. However, inside each group, MCA PI decreased significantly at 24-hours than in the baseline then increased again at 72-hours.

There was no significant difference between the 2 groups regarding CRP at the baseline, 24-hours or 72-hours. Inside group A, there was no significant change of CRP at any time measure from the baseline. However, inside group B, CRP decreased significantly at 72-hours than in both the baseline and 24-hours. In partial contrast to our study **Abdellateef *et al.*** [19] showed that nifedipine tocolysis is associated with an increase in the UtA-RI after 24-hours of nifedipine administration with no differences in UtA-PI or in the umbilical arteries Doppler (RI and PI). The same study showed a reduction in RI and PI in the MCA after 24 hr, returning to baseline after 72-hours and no difference in the cerebrplacental ratio after nifedipine tocolysis, which are similar to our study. The same study showed a reduction in RI and PI in the MCA after 24-hours, increase again after 72-hours and no difference in the cerebrplacental ratio after nifedipine tocolysis, which is similar to our study.

CONCLUSION

(1) Oral nifedipine plus vaginal progesterone is associated with more rapid tocolysis in threatened preterm labor compared to oral nifedipine alone with nearly the same effect on maternal and fetal blood flow. (
(2) The superiority of adding vaginal progesterone to oral nifedipine over oral nifedipine alone for acute tocolysis looks a promising drug, and further large studies are required to establish this fact.

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