Effects of Nifedipine Therapy for Preterm Labor on Placental and Fetal Doppler Parameters in the First 24 Hours

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Abstract

Objective: To assess the effects of nifedipine administration for 24 hours on placental and fetal cerebral blood flow as well as on fetal cardiac function.

Subjects and Methods: This prospective observational study involved 30 pregnant women with a single fetus of 30-34 weeks’ gestation undergoing tocolysis with nifedipine. We assessed pulsatility index (PI) of the umbilical artery, middle cerebral arteries (MCA) and ductus venosus (DV) twice, immediately before initial nifedipine dose and after 24 hours of therapy.

Results: The mean age was 30.1 ± 4.6 years. The pretreatment gestational age was 32.6 ± 2.2 weeks. Hemodynamic studies proved non-significant change of maternal blood pressure and fetal heart rate and clinically insignificant drop of maternal heart rate. Treatment resulted in statistically non-significant change of PI of the umbilical artery and statistically significant decrease of PI of the MCA and ductus venosus. However, the decrease was within clinically acceptable levels.

Conclusion: Nifedipine tocolytic therapy is safe on maternal cardiovascular system and fetal circulatory status up to 24 hours after starting therapy.

Key Words: Nifedipine therapy – Preterm labor – Placental and fetal Doppler parameters.

Introduction

PRETERM birth is a significant cause of perinatal morbidity and mortality. The World Health Organization defines preterm birth as the delivery of an infant between 20 and 37 weeks’ gestation. The preterm birth rates have been reported as 11% in the United States, 5-7% in Europe and 8.2% in Saudi Arabia [1-3].

Management of preterm labor should be directed towards establishing the cause, ensuring delivery under optimal conditions, and consideration of delaying delivery to increase gestational age [4]. No progress in reduction of preterm births has been made. However, some benefits are gained through prolongation of pregnancy to enable corticosteroid administration to accelerate fetal lung maturation [5]. A variety of pharmacological agents have been used to stop preterm uterine contractions to delay delivery in cases of preterm labor.

Ritodrine, salbutamol and terbutaline were most widely tested tocolytic agents. These beta-mimetics were reported to be effective in delaying delivery by up to 7 days [6,7]. Calcium channel blockers (CCB) were preferred over other tocolytic agents according to Cochrane database review [8]. CCB are non-specific smooth muscle relaxants, used mainly for the treatment of hypertension. Their tocolytic effect is mediated by preventing the influx of extracellular calcium ions into the myometrial cells [9].

Nifedipine, a dihydropyridine is the most widely used and studied CCB. Nifedipine was first introduced in 1980 as an effective tocolytic with minimal side-effects [10]. CCBs such as nifedipine are considered the first line tocolytic agent, not only for the higher efficacy in comparison to beta-mimetics, but more importantly because use of betamimetics is known to be associated with many side effects. Papatsonis et al. [11] reported that, in addition to the well-known tachycardia, the use of ritodrine is associated with significantly lower diastolic blood pressures when compared with nifedipine.

However, clinicians are often concerned with the theoretical risk of hypotension with nifedipine. Animal studies suggest that administration of calcium channel blockers may cause impaired uterine blood flow that may lead to fetal hypoxemia.
Effects of Nifedipine Therapy for Preterm Labor on Doppler Parameters

and academia [12,13]. This was not confirmed in human pregnancies in some studies [14-17]. Guclu et al. [18] showed that nifedipine maintenance therapy was associated with a significant decline in uterine and middle cerebral artery Doppler indices after 24h.

The purpose of this study was to assess the effects of nifedipine administration for 24 hours on placental and fetal cerebral blood flow as well as on fetal cardiac function.

Subjects and Methods

This prospective observational study was carried out in Kasr El-Aini University Hospital between January 2010 and January 2011. We assessed Doppler velocimetry parameter; pulsatility index (PI) of the umbilical artery, middle cerebral arteries (MCA) and ductus venosus (DV) in 30 pregnant women undergoing tocolysis with nifedipine. All women were between 20 and 40 years old, with a single fetus of 30-34 weeks’ gestation and intact amniotic membranes.

Preterm labor was defined according to ACOG guidelines as painful uterine contractions with a frequency of 2/10min. or 4/1 hour, which result in at least 2cm cervical dilatation and 75% ripening of the cervix [19].

Exclusion criteria included medical complications of pregnancy as heart or disease, hypertension and diabetes, premature rupture of membranes, intrauterine growth restriction and fetal malformations.

Characteristics of the patients including age, gravidity, parity and gestational age were recorded. Afterwards, nifedipine was administered according to Guclu et al. [18] as an initial sublingual dose of 20mg repeated at every 20min. if contractions did not weaken to a maximum dose of 60mg. Then the maintenance dose was 20mg per os/6 hours for 24 hours.

Doppler velocimetry was performed twice, immediately before initial nifedipine dose and after 24 hours of therapy. Examinations were done with the patients in the semi-sitting position, with scanning during fetal quiescence in the absence of uterine contractions. Scans were performed using a Voluson E6 (GE). Measurements were done twice for each vessel, and then the mean value was recorded.

Blood flow was obtained using a triplex system (two-dimensional image, color Doppler and pulsatile Doppler) with color mapping, equipped with a 3.75-MHz convex transducer. Low-frequency (100Hz) filters were used to minimize the possibility of error due to movement of the vascular walls. Scans with a minimum of six uniform waves were analyzed. The sample volume size was adjusted according to the diameter of the vessel to be studied and the angle of insonation was kept as close to 0° as possible. When a good signal was obtained, the image was frozen and the Doppler flow velocimetry parameters were automatically provided by the equipment’s software.

The umbilical artery was examined first followed by MCA and ductus venosus. For the umbilical artery, velocimetry was carried out at the midpoint between the placental and abdominal insertions of the vessel. For studies of the MCA, the circle of Willis was localized with color Doppler according to the method described by Arbeille et al. [20] and the Doppler gate placed on the MCA close to its origin from the internal carotid artery. The insonation angle was always kept as close to zero as possible, typically within +15°. Ductus venosus Doppler waveforms was obtained from a transverse view of the fetal abdomen at the same anatomic plane of the abdominal circumference. By superimposing color flow Doppler to the grayscale image, the ductus venosus can identified as it branches from the umbilical vein. Turbulence is commonly seen within the ductus venosus given its narrow lumen. The presence of turbulence on color flow Doppler helps in identifying the ductus venosus. Ductus venosus Doppler waveforms are biphasic in shape, with the first phase corresponding to ventricular systole, the second phase to early diastole, and the nadir of the second phase to late diastole or the atrial kick.

Statistical analysis:

Assuming a mean change in the middle cerebral artery of 0.04 with a SD of 0.05, a sample size of 23 subjects was required for a pair sample test with an alpha error of 0.05 and a power of the study of 90%. We anticipated failure of study procedure of 20%; hence we included 30 participants to share in this study. Data was analyzed using SPSSwin statistical package version 15 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher’s exact test) was used to examine the relation between qualitative variables. Comparison of repeated measures was done using paired t-test. A p-value <0.05 was considered significant.
Results

The study included 30 pregnant women under nifedipine tocolytic therapy with a mean age of 30.1±4.6 years. The pretreatment gestational age was 32.6±2.2 weeks.

Hemodynamic studies proved non-significant change of maternal blood pressure and fetal heart rate. There was statistically significant drop of maternal heart rate ($p=0.027$), however, this change was clinically insignificant (Table 1).

Table (2) shows that treatment resulted in non-significant change of PI of the umbilical artery and statistically significant decrease of PI of the MCA and ductus venosus. However, the decrease was within clinically acceptable levels.

### Table (1): Maternal and fetal hemodynamic variables of the studied group before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before ttt</th>
<th>After ttt</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal heart rate (bpm)</td>
<td>79.77±2.75</td>
<td>78.20±2.23</td>
<td>0.027</td>
</tr>
<tr>
<td>Fetal heart rate (bpm)</td>
<td>141.13±4.13</td>
<td>143.37±4.80</td>
<td>0.075</td>
</tr>
<tr>
<td>Maternal systolic blood pressure (mm Hg)</td>
<td>118.57±4.45</td>
<td>116.67±5.66</td>
<td>0.157</td>
</tr>
<tr>
<td>Maternal diastolic blood pressure (mm Hg)</td>
<td>71.73±2.29</td>
<td>70.60±3.02</td>
<td>0.189</td>
</tr>
</tbody>
</table>

### Table (2): Pulsatility indices (PI) of the umbilical artery, middle cerebral artery (MCA) and ductus venosus of the studied group before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before ttt</th>
<th>After ttt</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical Artery PI</td>
<td>0.98±0.05</td>
<td>0.97±0.01</td>
<td>0.399</td>
</tr>
<tr>
<td>Middle Cerebral Artery PI</td>
<td>1.99±0.17</td>
<td>1.86±0.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Ductus venosus PI</td>
<td>0.84±0.07</td>
<td>0.82±0.07</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Fig. (1): Picture showing typical wave of umbilical artery showing no change after nifedipine administration.

Fig. (2): A patient with Doppler waveform from the MCA before nifedipine administration with the angle of insonation less than 15° showing a PI=1.82.

Fig. (3): Ductus venous typical waveform with its biphasic pattern, following nifedipine administration a lower PI was noted with no clinical significance.

Fig. (4): A case after administration of nifedipine with the FHR=134b/m with no significant change noted.
Discussion

Nifedipine has the potential for cardiovascular side effects. In this study, we are concerned with the side effects of nifedipine on maternal and fetal circulation. We evaluated the impact of maternal tocolysis on fetal cardiovascular state (umbilical arteries, MCA and ductus venosus). Nifedipine easily crosses the placenta with a fetal versus maternal ratio of 0.93 between umbilical cord blood and maternal serum concentrations [21,22].

In our study, nifedipine therapy was not associated with a significant change in maternal systolic and diastolic blood pressure after 24h, with minor insignificant effect on maternal heart rate. Fetal heart rate was not affected after therapy. Fetal Doppler study found no clinically significant effect on the pulsatility index (PI) of umbilical and middle cerebral artery and ductus venosus. These findings ensure safety of the drug on the maternal and fetal aspects.

Previous studies have evaluated the effect of nifedipine loading on maternal and fetal circulation. Similar to our results, Guclu et al. [17] found no significant alterations maternal vital signs and Doppler waveform indices. MCA blood flow dynamics and distribution of cardiac output were unaltered. There was also no measurable change in atrioventricular blood flow, FHR and cardiac output. This data emphasizes that nifedipine tocolysis is well tolerated by the mother and that placental and fetal cerebral arterial blood flow are unaffected by nifedipine therapy.

In fact, the safety of calcium channel blockers in pregnancy was not thoroughly evaluated. A recent prospective cohort study [23] was done in 28 hospital including 1920 consecutive women treated with tocolytics for threatened preterm labor. They reported an incidence of serious adverse drug reactions of 0.9% for nifedipine in comparison to 1.7% for β mimetic agents. Nifedipine-related were mainly on blood pressure, hypotension developed usually within two to four hours after the start of tocolysis. There was no fetal compromise in the 542 women treated with nifedipine. The treatment regimen was usually 10mg sublingual nifedipine, 2-4 doses every 15 minutes, then 20mg slow release nifedipine every 4 hours. Such a regimen produces a peak plasma level to within 60-80 minutes with associated with a fall in blood pressure [24].

Since calcium channel blockers are not licensed in USA as tocolytic agents, as a result, adverse events may be underreported. In the 1980s, the drug was described as being ‘almost devoid of side effects’ [25]. Use of CCBs is based on apparently superior efficacy and significantly improved safety compared with β-agonists [26]. Iatrogenic fetal distress was the main concern of using antihypertensive drugs in pregnancy [27].

Cases of severe hypotension and fetal distress following a relatively low dose of sublingual nifedipine (10mg) administered to control pregnancy-induced severe hypertension have been reported [28]. Serious cardiac and pulmonary adverse events that have been associated with the administration of nifedipine include dyspnoea, myocardial infarction, severe hypotension, hypoxia and elevated liver enzymes [29-36].

Some animal studies report changes in uterine blood flow and fetal acidosis after CCB administration [12,37,38]. Holbrook et al. [37] suggested that fetal acidosis after CCB infusion is primarily due to a decrease in uterine blood flow rather than a direct fetal effect of the drug. Blea et al. [38] found hypoxia and acidosis in the sheep fetus without persistent decreases in uteroplacental or fetoplacental blood flows or blood pressures.

On the otherhand, most human studies show no decrease in uterine blood flow after nifedipine administration to pregnant women [15,39-42]. Also, no changes in uterine and fetal Doppler flow velocity waveforms after oral nifedipine therapy in hypertensive pregnant women in two studies [40,42]. Other studies included normotensive women [15,17,42,43], one study found a transient short term decrease in umbilical artery pulsatility index (PI) 15 after 10mg sublingual nifedipine [43]. However, other studies found no changes in the fetal or uteroplacental circulation [15,42]. Cararach et al. [44] found no effect of nifedipine on fetal biophysical profile. Oei et al. [45] found no negative effects on psychosocial and motor functioning of 48 children exposed in utero to nifedipine at 9 to 12 years of age.

A systematic review of 12 randomized controlled trials with a total of 1029 participating women was performed. In this review, calcium channel blockers were shown to be a more effective tocolytic agent than betamimetics with improvement in some clinically important neonatal outcomes (less RDS, intraventricular haemorrhage, necrotising enterocolitis, jaundice and admissions to NICU) and a marked reduction in adverse maternal side-effects [8].

In conclusion, this study proves safety of nifedipine tocolytic therapy on maternal cardiovascular system and fetal circulatory status up to 24 hours.
after starting therapy. However, an apparent limitation of this study is the relatively small size. Further studies are necessary to confirm intermediate and long-term effects of nifedipine therapy that may help adjust dosing of this commonly used tocolytic agent.

References


