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The short-term effect of nifedipine tocolysis on placental, fetal cerebral and atrioventricular Doppler waveforms

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KEYWORDS: atrioventricular valves; Doppler; middle cerebral artery; nifedipine; tocolysis; umbilical artery; uterine artery

ABSTRACT

Objective *To evaluate the effect of nifedipine on placental and fetal middle cerebral and atrioventricular Doppler waveforms.*

Methods *Doppler waveforms of uterine (UtA), umbilical (UA) and middle cerebral (MCA) arteries and both atrioventricular valves were measured from 21 pregnant women/fetuses prior to and during nifedipine therapy for preterm labor. Maternal and fetal heart rates (FHR), maternal systolic and diastolic blood pressure, the Doppler pulsatility index and systolic/diastolic ratio of the UtA, UA and MCA were measured. The total time velocity integrals (TVI) of tricuspid and mitral valves and their E-wave/A-wave (E/A) TVI ratios were measured. Wilcoxon signed pairs test was used to compare the differences in Doppler parameters before and at 3 h after nifedipine loading up to a maximum dose of 40 mg.*

Results *Fetal arterial and UtA Doppler parameters were not different before and after nifedipine therapy. Blood flow across the atrioventricular valves and the TVI were equally unaffected by nifedipine. The TVI × FHR product was also unchanged following nifedipine therapy.*

Conclusions *In women with otherwise uncomplicated pregnancies, nifedipine loading and tocolysis are generally well tolerated by the mother. Placental and fetal cerebral arterial blood flow, fetal systolic and diastolic cardiac function and downstream distribution of fetal cardiac output are unaffected by nifedipine loading. These results apply to women with unchanged vital parameters. Further studies are necessary to show long-term effects of nifedipine therapy and may help to refine choice of tocolytic agents. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Preterm delivery remains one of the top three causes of perinatal morbidity worldwide. Various pharmacological agents have been used to stop preterm uterine contractions in an attempt to prevent preterm delivery. When using tocolytic agents the maternal and fetal side-effect profiles are important considerations. Following the most recent Cochrane database review the preferential use of calcium channel blockers over other tocolytic agents is likely to increase[1]. Nifedipine, a dihydropyridine calcium entry blocker, is an effective tocolytic agent with low toxicity and teratogenicity but has potential cardiovascular side effects that may affect the mother as well as the fetus[2,3]. Animal studies suggest that administration of calcium channel blockers may result in impaired uterine blood flow, potentially resulting in fetal hypoxemia and acidemia[4,5]. However, studies in human pregnancies did not confirm significant alterations in uterine blood flow[6–8]. Fetal cardiovascular responses to nifedipine (other than those observed in the placental circulation) have not been reported in detail. The cerebral circulation in the human fetus is capable of active autoregulation and a decrease in blood flow resistance with perceived hypoxemia ('brain sparing')[9]. In addition, differential changes in the placental and cerebral blood flow resistances may affect the cerebroplacental Doppler ratio and the overall distribution of cardiac output[10]. In addition, cardiac effects of nifedipine may affect the contractility and diastolic cardiac function.

The aim of this study was to assess the acute effects of maternal nifedipine administration on placental and fetal cerebral blood flow resistance as well as on diastolic fetal cardiac function.

METHODS

The study was conducted between February 1st 2002 and February 1st 2003 at the Dokuz Eylül University

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Hospital, Izmir. Patients were considered eligible for the study if they were admitted to the labor ward with the diagnosis of preterm labor between the gestational ages of 24–34 weeks. Exclusion criteria included multiple pregnancy, chorioamnionitis, congenital anomalies of the fetus, a clinical diagnosis of partial placental abruption, severe fetal growth restriction, and any maternal contraindication for the use of nifedipine. Twenty-one healthy pregnant women with singleton fetuses gave informed written consent to participate in the study. A priori sample size calculation was accomplished with an α of 0.05, a β of 0.20 and an estimated incidence of cerebroplacental ratio of 2.10 ± 0.5 between 27 and 33 gestational weeks. A total sample size of 17 pregnant women was estimated to set a difference of 0.5 in cerebroplacental ratio before and after the treatment. All patients had accurate dating with a gestational age based on the last menstrual period that corresponded to a second examination performed before 20 weeks' gestation.

At the Dokuz Eylül University Hospital, preterm labor was diagnosed when regular uterine contractions were associated with cervical change. Our management protocol under ongoing surveillance of maternal vital signs in such instances is as follows: nifedipine therapy is initiated with a 10-mg capsule sublingually when contractions persisted following hydration. If uterine contractions persisted after 15 min, a second dose of 10 mg was given. This was repeated two more times if necessary up to a maximum dose of 40 mg nifedipine in the first hour. Depending on the therapeutic dose required during the first hour of loading therapy a maintenance dose between 60–160 mg of slow-release nifedipine daily was selected. Depending on the clinical condition, nifedipine was decreased progressively after 3 days.

To study the acute effects of nifedipine administration, paired Doppler examinations were performed prior to nifedipine administration and 3 h after the first dose. This time frame was chosen since the onset of action following an oral nifedipine dose is less than 20 min and peak plasma concentrations are reached in 1 h, with a half-life of 3 h[11]. A Sonoline Elegra ultrasound machine (Siemens, Erlangen, Germany) with 3.5-MHz and 5-MHz convex probes was used. The high-pass filter was set at 100 Hz. The same investigator (S.G.) performed all measurements during periods without uterine contractions with the mother lying in a left recumbent position. Doppler measurements were obtained from the uterine artery (UtA) at the 'crossing' with the external iliac artery and of the umbilical artery (UA) at the midsection of the umbilical cord. The distal middle cerebral artery (MCA) was insonated through the temporal or occipital bone windows after its origin from the circle of Willis was identified on an axial section of the fetal brain. Color Doppler imaging was used to optimize placement of the pulsed wave Doppler gate by adjusting the velocity scale to identify area and direction of maximum blood flow. The insonation angle was kept as close to 0° as possible and the sample volume adjusted to cover the entire vessel. The pulsatility index (PI) and systolic-diastolic (S/D) ratio were calculated as the mean value from five consecutive Doppler waveforms of the UA, MCA, and UtA obtained in the absence of fetal breathing and movement. The S/D ratio and PI were selected because they have different variance and measurement distributions and may therefore be affected differently by changes in the input pressure waveform[12]. The resistance index was not used in the analysis because it only has a small measurement range (0–1) and may not show significant differences in Doppler measured blood flow resistance. In addition, the cerebroplacental Doppler ratio (MCA-PI/UA-PI) was calculated.

The atrioventricular valves were examined from an apical, or basal four-chamber view of the heart. After placement of the sampling gate just distal to the mitral (MV) and tricuspid (TV) valves the time velocity integrals (TVI) for the respective valves were measured. The fetal heart rate (FHR) was measured and multiplied with the TVI to provide an index of cardiac output[13]. The flow velocity waveforms at the level of the MV and TV are characterized by two diastolic peaks, corresponding to early ventricular filling (E-wave) and to active ventricular filling during atrial contraction (A-wave). E and A peak velocities were measured and the E/A ratio calculated.

The Wilcoxon signed pairs tests were used to compare differences in the measurements before and after nifedipine therapy according to their distribution. $P < 0.05$ was considered as significant.

RESULTS

The median maternal age was 29 (range, 24–36) years and gestational age at enrollment was 30 (range, 27–33) weeks. The median gravidity was 2 with a range of 1–5. The maternal heart rate systolic and diastolic pressures

Table 1 Maternal vital signs before and after nifedipine tocolysis

	Before nifedipine tocolysis (mean ± SD)	*After nifedipine tocolysis (mean ± SD)*	P
Maternal heart rate (bpm)	75.05 ± 4.00	75.71 ± 3.59	NS
Fetal heart rate (bpm)	143.05 ± 9.52	141.61 ± 6.94	NS
Maternal systolic blood pressure (mm Hg)	110.0 ± 9.35	110.5 ± 7.95	NS
Maternal diastolic blood pressure (mm Hg)	66.66 ± 6.39	66.19 ± 4.44	NS

NS, not significant. All tests Wilcoxon signed pairs test.

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Table 2 Doppler indices before and after nifedipine tocolysis

	Before nifedipine tocolysis (mean ± SD)	*After nifedipine tocolysis (mean ± SD)*	*95% CI*	P
RUtA				NS
PI	0.67 ± 0.09	0.66 ± 0.08	−0.0115 to 0.0239	
S/D ratio	1.82 ± 0.14	1.80 ± 0.12	−0.0030 to 0.0439	
LUtA				NS
PI	0.68 ± 0.06	0.67 ± 0.05	−0.0112 to 0.0131	
S/D ratio	1.91 ± 0.11	1.89 ± 0.13	−0.0071 to 0.0424	
UA				NS
PI	0.96 ± 0.18	0.95 ± 0.18	−0.0246 to 0.0417	
S/D ratio	1.89 ± 0.3	1.87 ± 0.29	−0.0142 to 0.0618	
MCA				NS
PI	1.96 ± 0.22	1.94 ± 0.20	−0.0223 to 0.0423	
S/D ratio	3.59 ± 0.36	3.58 ± 0.34	−0.0194 to 0.0499	
Cerebroplacental ratio	2.13 ± 0.57	2.14 ± 0.56	−0.094 to 0.083	NS
MV TVI (cm)	0.10 ± 0.01	0.10 ± 0.02	−0.0137 to 0.022	NS
MV TVI × FHR	15.07 ± 1.90	15.37 ± 2.083	−1.8107 to 0.6526	NS
TV TVI (cm)	0.10 ± 0.02	0.10 ± 0.01	−0.0097 to 0.0069	NS
TV TVI × FHR	15.10 ± 2.53	15.29 ± 2.68	−1.1609 to 1.0980	NS
E/A TVI of TV	0.58 ± 0.05	0.57 ± 0.08	−0.0140 to 0.0092	NS
E/A TVI of MV	0.63 ± 0.04	0.64 ± 0.03	−0.0097 to 0.0125	NS

E/A, E/A waves; FHR, fetal heart rate; LUtA, left uterine artery; MCA, middle cerebral artery; MV, mitral valve; NS, not significant; PI, pulsatility index; RUtA, right uterine artery; S/D, systolic/diastolic; TV, tricuspid valve; TVI, time velocity integral; UA, umbilical artery. All tests Wilcoxon signed pairs tests.

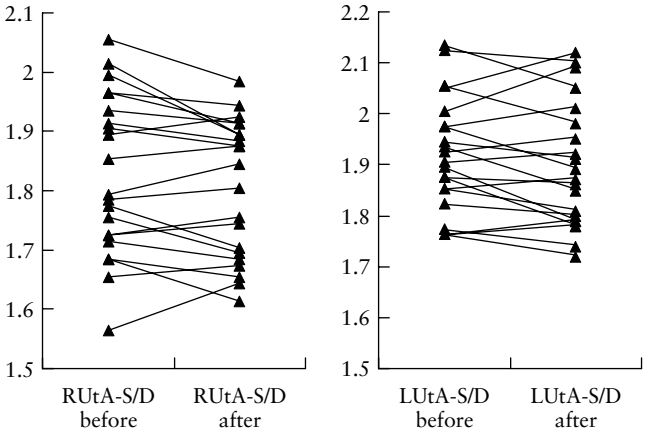

Figure 1 Systolic/diastolic (S/D) Doppler ratio indices of right and left uterine artery before and 3 h after therapy with nifedipine. The ratios were not altered. Results from individual patients are connected with solid lines. LUtA, left uterine artery; RUtA, right uterine artery.

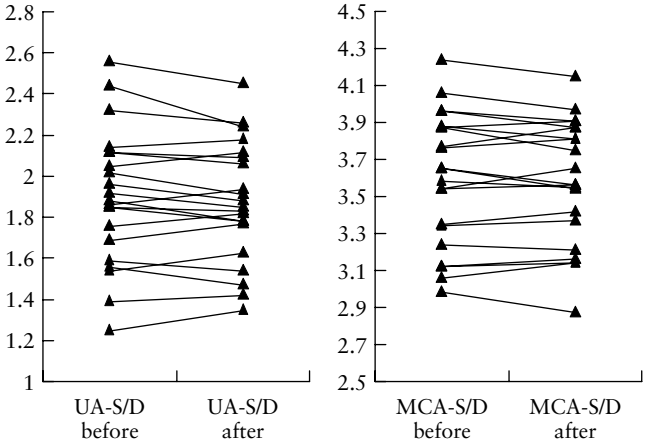

Figure 2 Systolic/diastolic (S/D) Doppler ratio indices of umbilical and middle cerebral artery before and 3 h after therapy with nifedipine. The ratios were not altered. Results from individual patients are connected with solid lines. MCA, middle cerebral artery; UA, umbilical artery.

were not significantly altered by nifedipine therapy. The fetal heart rate was similarly unaffected (Table 1).

Maternal side effects related to nifedipine therapy were as follows: flushing in 16 patients (76.2%), headache in six patients (28.5%) and nausea in three patients (14.2%). None of the patients had tachycardia or hypotension; additionally they did not have elevation of the liver enzymes. The mean number of days gained *in utero* was 31.2 ± 13 for all patients included in this study. There was only one patient who delivered within the 48 h. The mean birth weight and the mean gestational age at birth were 2602 ± 466 g and 34.6 ± 2.1 weeks, respectively.

The results of the Doppler measurements are shown in Table 2 and in Figures 1 to 4. Blood flow resistance in the placental circulation did not change in the maternal or fetal compartment as both the PI and S/D ratios in the UtA and UA remained unaffected by nifedipine therapy. The same was observed for the PI and S/D ratios in the MCA. The cerebroplacental ratio was equally unaffected.

Diastolic filling of the heart also appeared unaltered by nifedipine therapy. Neither the E/A ratios, nor the TVI for either atrioventricular valve nor the product of TVI × FHR were different between the study points.

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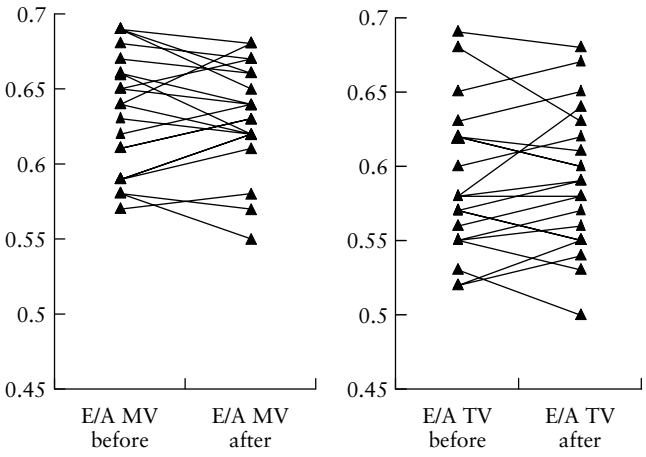

Figure 3 E-wave/A-wave (E/A) ratios of mitral and tricuspid valves before and after therapy with nifedipine. The ratios were not altered and were unaffected by nifedipine loading. Results from individual patients are connected with solid lines. MV, mitral valve; TV, tricuspid valve.

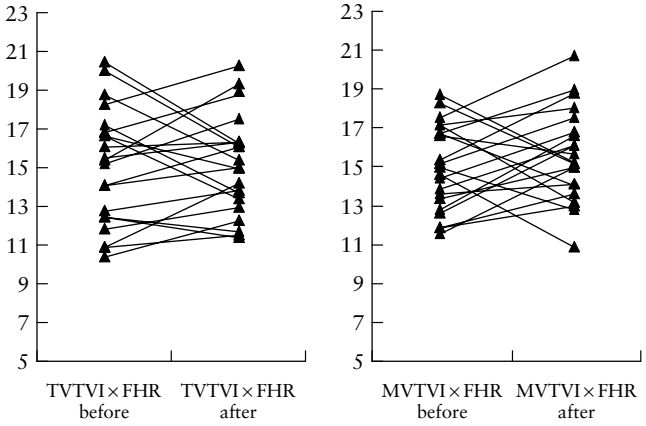

Figure 4 Time velocity integral (TVI) × fetal heart rate (FHR) values for the tricuspid and mitral valves, which were unaffected by nifedipine loading. Results from individual patients are connected with solid lines. MV, mitral valve; TV, tricuspid valve.

DISCUSSION

Several classes of tocolytic agents are employed in the management of threatened preterm delivery. Of these, sympathomimetics and agents such as magnesium and calcium channel blockers are among the most widely studied. In the choice of the appropriate agent, the side effect profile is an important consideration. Maternal side effects can be readily assessed by clinical examination. Fetal side effects are less apparent since they require the use of additional diagnostic modalities. Nifedipine, as one of the major classes of tocolytic agents by virtue of its effects on calcium channels, has the potential for cardiovascular side effects. We performed this study to concurrently evaluate the effects of oral nifedipine loading for tocolysis on several aspects of 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. Possible impacts on cardiac function were assessed by examination of the E/A ratio and an index of cardiac output (the product of the atrioventricular TVI and FHR). The latter has been found to be a reliable marker of absolute cardiac output[13]. The E/A ratio is a widely accepted index of ventricular diastolic function as it relates to cardiac compliance and the preload conditions[14].

Our data show that none of the mothers had significant alterations in their vital signs with the described nifedipine administration protocol. There was no measurable difference in UtA and UA Doppler waveform by either Doppler index. 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. These data suggest that sequential nifedipine loading at a maximum dose of 40 mg in the first hour is not associated with any maternal and fetal side effects. These results also emphasize that there are no 'hidden' fetal effects if the maternal vital signs are unchanged during nifedipine loading.

Although more clinicians are currently considering the use of nifedipine as the first line tocolytic agent, they are often concerned over the theoretical risk of maternal hypotension and placental hypoperfusion. Our data show that the use of nifedipine is not associated with a significant decrease in blood pressure. Other investigations that have focused on the maternal and fetal safety of nifedipine tocolysis have yielded conflicting results. The potential detrimental effect on uterine perfusion and fetal oxygenation suggested by clinicians[15] has been confirmed in some animal experiments[4,5] while others could not find any change[16,17]. The effect of nifedipine therapy on various placental and fetal Doppler waveforms has been previously analyzed. Pirhonen *et al.* found that 20 mg of oral nifedipine significantly decreased UtA S/D ratio without any significant changes in arcuate artery waveforms[18]. The UA was examined by several investigators. Rizzo *et al.* found a transient significant decline in the UA-PI after 15 min with return to baseline levels at 90 min[19]. Other studies that performed Doppler investigation at a later point (2.5–5 h after nifedipine) failed to show any significant change in the UA Doppler waveform[20–22]. Mari *et al.* also evaluated the cerebral, renal and central arterial circulations (ductus arteriosus, ascending aorta and pulmonary artery). Again, nifedipine administration did not have a measurable effect on Doppler waveforms[20]. In all of these investigations FHR appeared unaffected and only Rizzo *et al.* reported a transient increase in maternal heart rate (normalized by 45 min)[18–22].

Comparative Doppler studies of patients receiving nifedipine and sympathomimetics indicate that fetal cardiovascular changes are more apparent in the latter. Garcia-Velasco *et al.* found no differences in UA waveforms between patients receiving ritodrine and

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nifedipine[22]. However, other investigators have recently shown that ritodrine augments fetal aortic blood flow and left-sided cardiac output[2]. Increase in blood pressure, associated redistribution and augmentation of cerebral blood flow have been put forward as possible explanations for the higher rate of intracranial hemorrhage observed in preterm neonates receiving ritodrine[2].

The combination of these studies and our own data illustrate several important points. In women with otherwise uncomplicated pregnancies, nifedipine loading and tocolysis are generally well tolerated by the mother. While there may be transitory short-term effects in the umbilical circulation these resolve quickly. There appear to be no changes in arterial blood flow in the majority of fetal vascular beds. Distribution of fetal cardiac output and fetal cardiac function, both systolic and diastolic, is equally unaffected. These findings can only be generalized for patients that show no changes in vital signs. The effects of maternal cardiovascular changes on placental blood flow and fetal cardiovascular status requires further scrutiny. Doppler examination of fetal cardiovascular responses to various tocolytic agents is of importance. Perhaps the choice of agent should no longer be determined by clinical efficacy alone, but rather account for the fetal side effect profile. Further studies need to clarify confounding effects of antenatal steroid administration, long-term tocolysis and effects on neonatal outcomes.

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