48-hours administration of nifedipine in spontaneous preterm labor – Doppler blood flow assessment of placental and fetal circulation

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Abstract

OBJECTIVES: The aims were to assess the placental and fetal circulation during nifedipine tocolysis within the first 48 hours of therapy.
METHODS: Placental and fetal circulation was assessed in Doppler ultrasound examination prior to nifedipine administration and then after 24 and 48 hours. Maternal heart rate and PI in uterine arteries were evaluated as well as FHR, RI and PI of UA and MCA. E/A-wave ratio for A-V valves, MPI and SF were calculated for both ventricles independently. To determine changes over time in all study variable analysis of variance (ANOVA) for repeated measurements followed by Tukey-Kramer's multiple comparison test was used. The effects of additional clinical covariates were checked.
RESULTS: Uterine and umbilical blood flow patterns were not altered significantly during administration of nifedypine tocolysis. While MCA Doppler indicies such as RI and PI were unchanged, the evaluation of MCA PSV revealed a transient significant decrease after 24 hours. A resolution of this distraction was observed within the following 24 hours. No significant changes were observed in direct fetal cardiac function parameters calculated separately for both ventricles.
CONCLUSIONS: The decrease of MCA PSV after 24 hours of treatment was isolated and transient hemodynamic distraction observed during treatment. Neither fetal cardiac parameters nor other Doppler indices were changed. Therefore oral administration of nifedipine seems not to alter uterine nor fetal arterial blood flow pattern seriously. As significant changes were observed by different authors, further studies should be performed to verify the optimal total dose of nifedipine and its influence on hemodynamic conditions.

ORIGINAL ARTICLE

Abbreviations:

A-V	- atrioventricular
E/A	- E- and A-wave ratio
CBC	- Calcium channel blocker
CPR	- cerebroplacental ratio
DV	- ductus venosus
FHR	- fetal heart rate
Hz	- Herz
MCA	- middle cerebral artery
MPI	- myocardial performance index
PI	- pulsatility index
PSV	- peak systolic velocity
RI	- resistance index
S/D	- systolic/diastolic index
SF	- shortening fraction
UA	- umbilical artery
UtA	- uterine artery

INTRODUCTION

The data about preterm birth is becoming increasingly worrisome. This complication is responsible for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities (Hack & Fanaroff 1999; Slattery & Morrison 2002). Apart from great progress in medical care, the rate of preterm labor seems to increase in most of Western countries (Hoyert *et al.* 2006; Langhoff-Roos *et al.* 2006). Present treatment policy in spontanous preterm labor is concentrated on postponing delivery for at least 48 hours. Benefits are associated with completing a course of steroids in order to induce fetal lung maturation and/or 'in utero' transfer to the referal centre.

Calcium channel blockers were primarily dedicated to treatment of coronary heart disease and hypertension. By binding L-type channels they block the flow of extracellular calcium into cardiac and smooth muscle cells. It results in relaxation of the muscles (Sorkin *et al.* 1985). Another important feature of CCBs is lack of tachyphylaxis or withdrawal symptoms (Childress & Katz 1994). Nifedipine is the most commonly used calcium channel blocker to delay preterm delivery with such indisputable advantages as oral administration and a low purchase cost. However, we should remember that this drug is not licensed specifically for tocolytic treatment (RCOG 2011). Hypotension, tachycardia, flushes, headache, increased liver enzymes, nausea and dizziness are well known maternal side effects of nifedipine administration (Cararach *et al.* 2006; Papatsonis *et al.* 2007). Potential side effects which are based on the cardiovascular mechanism of this potent drug may also affect the fetus. Nifedipine can easily cross the placenta with a high ratio of 0.93 between umbilical cord blood and maternal serum concentrations (Ferguson *et al.* 1990; Furuhashi *et al.* 1991; Manninen & Juhakoski 1991). The animal studies present data about impaired uterine blood flow, fetal hypoxia and acidemia after CCB's administration (Blea *et al.* 1997; Furuhashi *et al.* 1991; Harake *et al.* 1987; Holbrook *et al.* 1987). Although most studies in humans do not show serious alteration in uterine blood flow after nifedipine administration due to preterm labor symptoms, there are some controversial reports (Hanretty *et al.* 1989; Lindow *et al.* 1988; Moretti *et al.* 1990; Pirhonen *et al.* 1990).

However, in most of the presented publications the total dose of nifedipine was administered at least 100 mg daily. Therefore, it was our aim to evaluate maternal and fetal hemodynamic conditions using different nifedipine dosage protocols.

METHODS

The study was conducted in the Department of Feto-Maternal Medicine at the "Polish Mother" Memorial Research Institute, Medical University of Lodz, Poland. We established the following admission criteria: patients with singleton pregnancy, between 24–34 weeks' gestation with intact membranes and showing evidence of premature labor. This was diagnosed as painful and persistent contractions (at least four in an hour) associated with cervical changes and/or effacement (Hincz *et al.* 2002). Exclusion criteria included multiple pregnancy, chorioamnionitis, intrauterine growth restriction, fetal congenital malformations, vaginal bleeding and acute fetal distress. The patients with circulatory system diseases (e.g. heart defects, hypertension) as well as diabetes (both pre- and gestational), symptoms of infection or any other specific maternal contraindication for fenoterol treatment were excluded. The use of any tocolytic agents during pregnancy before admission to the hospital met also exclusion criteria. After precise patient evaluation, nifedipine medication was administered in accordance to the drug characteristic medical protocol and to our own clinical knowledge. The initial sublingual dose of 20 mg nifedipine (Cordafen 10 mg, Jelfa, Poland) was followed by 10 mg, administered every six hours. Such therapy was maintained during first 48 hours. Maternal steroid therapy was started right after admission to the hospital. Four intramuscular injections of 6 mg dexamethasone (Dexaven, Jelfa) were given 12 hours apart (NIH Consensus Development Panel 1995). Doppler examination was performed prior to nifedipine and corticosteroid administration and repeated after 24 and 48 hours of the therapy. The patient was lying in a left recumbent position to avoid orthostatic hypotension. A Voluson E8 ultrasound machine (GE, Medical Systems, Austria) with 3.5-MHz and 5-MHz convex probes was used. The same investigator (M.G.) performed all scans. The absence of uterine contractions, fetal body and breathing movements was a required condition to obtain precise evaluation. The high-pas filter was set at 100 Hz. Blood flow in DV was visualized using color Doppler and pulsatile Doppler. The sample volume size was adjusted due to the diameter of the vessel. The insonation angle was established as close to 0 degrees as possible and never

exceeded more than 30 degrees. Color flow imaging was used to visualize the flow through the main uterine artery medial to the external iliac artery. Furthermore the ascending branch was selected for PI calculation (Arduini *et al.* 1990). The waveforms were assessed for possible presence of notch and uterine artery score was calculated (Ghosh *et al.* 2006). This technique was the same for both sides. For umbilical artery Doppler sampling site was located at the half of the distance between fetal and placental end of the cord. The circle of Willis and the middle cerebral artery were identified when a transverse view of the fetal brain was obtained. The measurements were taken in the middle part of MCA. Peak systolic velocity, resistance (RI) and pulsatility (PI) index were calculated for both vessels. Finally the cerebroplacental ratio (CPR) based on MCA-PI/UA-PI formula was calculated (Baschat & Gembruch 2003).

Apical or basal approach was recommended to obtain the four chamber view of the fetal heart. Blood flow across atrioventricular valves was visualized in Color Doppler technique. The sample gate was placed distal to A-V valves at the brightest colors of the blood flow. Biphasic velocity waveforms were recorded with two diastolic peaks. The ratio between E- and A-waves were calculated. A-V valve insufficiency was recorded if present (Abuhamad & Chaoui 2010).

The myocardial performance index (MPI) for right and left ventricle was calculated *in two steps*; the first time period (isovolumetric (a)) was calculated between the end of the A-wave and the beginning of the next E-wave during the ventricular filling phase, and the second period (b), the ejection time, was recorded in the aortic or pulmonary outflow tracts. MPI value was calculated using formula (a–b)/b (Pellett *et al.* 2004; Tei *et al.* 1995).

The motion of ventricular walls and intraventricular septum were visualised in M-mode technique. Shortening fractions were calculated for both ventricles independently.

The results were analyzed according to well known statistical methods by using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc., Tulsa, USA). To compare changes in response to treatment analysis of variance (ANOVA) for repeated measuremenst with the Tukey-Kramer's post hoc test were used. The $p<0.05$ was used as a definition of statistical significance.

The project was approved by local Research Ethics Committee. All patients participating in the study gave their signed informed consent.

RESULTS

Twenty-seven pregnant women met the inclusion criteria and joined the study. The mean maternal and gestational age was 29.4±4.4 years and 29.2±3.1weeks, respectively. The median gravidity was 1 with a quartile range of 1–2 and the median parity was 1 with a quartile range of 1–2. None of the patients delivered within 72 hours. We noticed that there were no significant changes in maternal heart rate when comparing pretreatment values (90.4±9.9 bpm) and those after 24 (90.5±13.6 bpm) and 48 hours of nifedipine administration (88.7±10.5 bpm). The Doppler examination of blood flow in uterine arteries revealed no changes during nifedipine tocolysis (Table 1). The measurements of RI, PI and PSV in umbilical arteries did not result in significant alterations (Table 2). The CPR calculations did not reveal significant changes after 24 and 48 hours of nifedipine administration (Figure 2). MCA PSV demonstrated decrease after 24 hours of nifedip-

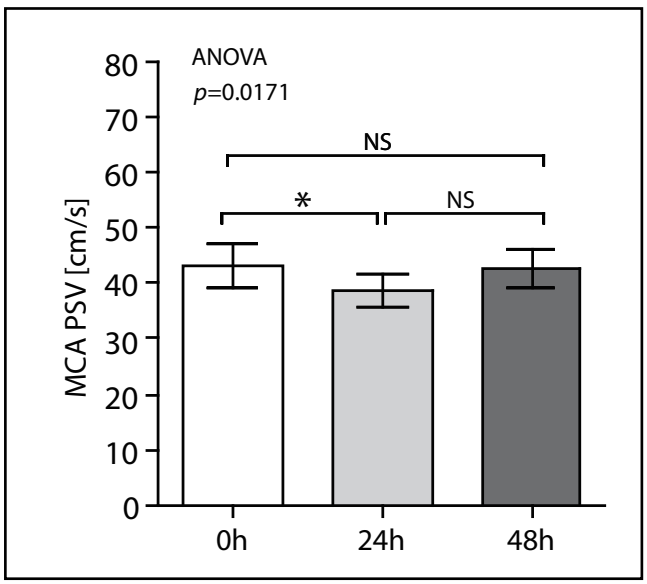

Fig. 1. Peak Systolic Velocity in middle cerebral artery (MCA) before and after (24/48 hours) nifedipine treatment.

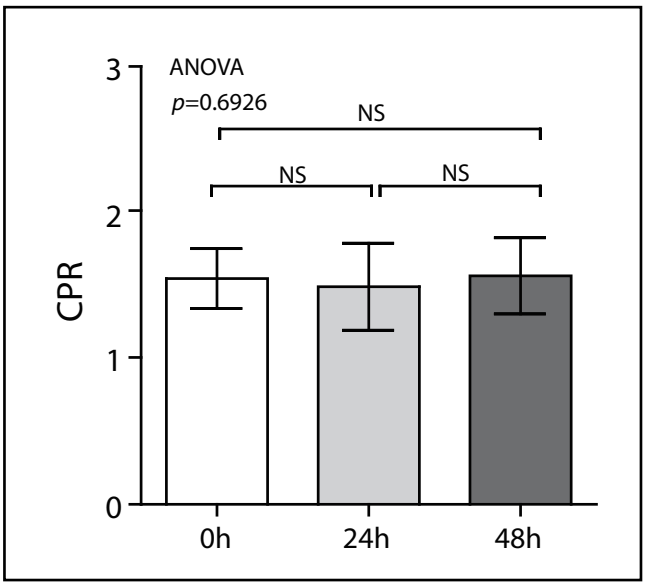

Fig. 2. Cerebroplacental ratio (CPR) before and after (24/48 hours) nifedipine treatment.

ine administration however, this change was transient (Figure 1). We noticed that there were no significant changes in maternal heart rate before nifedipine and when comparing 24 and 48 hours results. FHR as well as E/A ratio, SF, MPI values, calculated separately for each ventricle, revealed no changes in fetal cardiac function during treatment (Table 3). These observations were consistent with ANOVA post-hoc analysis. We did not observe the effect of gestational age and parity on the above results.

Tab. 1. Doppler indices in uterine arteries (UtA) before and after (24/48 hours) nifedipine treatment.

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
Right uterine artery	0.77±0.27	0.76±0.29	0.73±0.18	0.5911
Left uterine artery	0.80±0.21	0.80±0.25	0.85±0.30	0.3666

Tab. 2. Doppler indices in umbilical (UA) and middle cerebral arteries (MCA) before and after (24/48 hours) nifedipine treatment.

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
Umbilical artery				
RI	0.63±0.06	0.60±0.07	0.62±0.07	0.1198
PI	0.98±0.14	0.90±0.19	0.95±0.17	0.1494
PSV (cm/s)	45.4±10.5	43.5±8.5	46.9±9.4	0.2849
Middle cerebral artery				
RI	0.79±0.06	0.77±0.05	0.79±0.05	0.3271
PI	1.75±0.33	1.71±0.30	1.81±0.31	0.5141
PSV (cm/s)	43.2±10.6	38.4±7.7	42.6±8.3	**0.0171**
CPR	1.82±0.36	1.87±0.63	1.95±0.41	0.6926

Tab. 3. Fetal cardiac function parameters before and after (24/48 hours) nifedipine treatment.

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
FHR (bpm)	145.5±7.9	142.1±7.4	141.6±8.2	0.5542
TV E/A	0.61±0.07	0.63±0.09	0.64±0.08	0.2602
MV E/A	0.63±0.07	0.62±0.09	0.61±0.09	0.5588
RV SF (%)	35.7±4.8	35.8±3.4	34.9±4.1	0.6974
LV SF (%)	36.7±4.7	37.9±3.5	36.8±4.3	0.5308
RV MPI	0.47±0.16	0.45±0.09	0.47±0.14	0.8866
LV MPI	0.48±0.12	0.46±0.10	0.46±0.11	0.7565

DISCUSSION

Hemodynamic conditions are particulary different during pregnancy. Animal studies presented conflicting data about changes in the circulatory system after nifedipine. Harake *et al.* (1987) detected reduction of uterine blood flow and oxygen content in fetal blood in instrumented pregnant sheep with nifedipine intravenous administration. Blea *et al.* (1997) used nifedipine doses corresponding with those in humans. They found the evidence of hypoxia and acidosis in the sheep fetus. No changes in maternal and placental compartments were detected. In Holbrook's *et al.* research (1989), a single bolus of another calcium channel blocker, nicardipine, was administered to instrumented sheep and no alteration in uterine and fetal arterial blood flow were observed.

In our study, analysis of blood flow dynamics revealed no changes in uterine artery PI as well as in the presence/absence of notch. The measurements of RI and PI as well as PSV in umbilical artery did not result in significant changes. Our results suggested that uteroplacental circulation remained unaffected during nifedipine treatment; however our examinations were performed at intervals of 24 and 48 hours from the administration of nifedipine.

Studies on the same subjects presented different observations. Guclu *et al.* (2004) examined the group of 21 pregnant women and fetuses prior to and after 3 hours of nifedipine loading. In such short term observation no changes in maternal and fetal compartment were observed. S/D and RI ratios were unchanged in both uterine and umbilical artery. These authors continued their research on the same problem, but Doppler examination was performed prior to and after 12, 24 and 48 hours of treatment. A significant fall in uterine artery pulsatility index were observed at 24 and 48 hours while no changes in the blood flow in umbilical artery were detected at the same point of time (Guclu *et al.* 2006). Pirhonen *et al.* (1990) reported significant decrease of uterine artery S/D ratio due to 20 mg oral nifedipine. Different observations concerning umbilical artery blood flow assessment were presented by several authors. Moretti *et al.* (1990) and Hanretty *et al.* (1989) found no hemodynamic changes after nifedipine treatment in uteroplacental circulation however they focused on pregnant women with preeclampsia. Transient significant reduction of umbilical artery PI was reported by Rizzo *et al.* (1987) but that change was withdrawn after 90 minutes. Lima *et al.* (2009) presented data about increase of mean peak systolic velocity in right uterine artery and umbilical arteries within 5 and 24 hours of tocolysis. The one-side change in uterine artery blood flow was probably due to placental location. The changes in UA PSV could be influenced by insonation angle and should have been further investigated according to authors' suggestions. In other studies no significant changes were detected if measure-

ments were performed at the interval of 2.5–5 hours since nifedipine application (García-Velasco *et al.* 1998; Mari *et al.* 1989; Meyer *et al.* 1990).

The fetal Doppler examination performed by Lima *et al.* (2009) showed the alteration of MCA blood flow between 5 and 24 hours from the time of administered medication. Authors suggested that decreased resistance ratio could be related to decrease peak systolic velocity in MCA. The significant decrease in MCA PI after 24 hours of tocolysis was reported by Guclu *et al.* (2004). Furthermore, a significant drop was observed after 48 hours of treatment. In our study Doppler velocimetry evaluation revealed a significant decrease of MCA peak systolic velocity after 24 hours of treatment. After next 24 hours the PSV values returned to the initial, basal line. We quoted Limas' *et al.* research (2009) discussing the similar change in MCA PSV. However, opposite to Lima *et al.* we have not observed any changes in resistance index. We cannot agree with these authors' citation that MCA resistance index was evaluated by Guclu *et al.* (2006) thus they had reported only a measurement of PI in their publication. Therefore we are of the opinion that further studies to evaluate additional parameter such as S/D ratio, are essential to explain MCA blood flow changes in our material.

As in our results umbilical artery and MCA pulsatility index ratio were not altered, cerebroplacental Doppler ratio didn't change significantly during tocolysis treatment. It may suggest that short term changes observed in MCA PSV did not have an influence on fetal well-being. As we are searching for an explanation of differences existing in reviewed publications and our results we paid close attention to dose regimens for nifedipine. Guclu *et al.* (2006) administered a maximum loading dose of 40 mg nifedipine in the first hour. The required maintenance dose was depended on the loading dose and did not exceed the level of 120 mg daily. Lima *et al.* (2009) presented similar medication protocol. They started with a maximum first hour dose of 60 mg nifedipine. The total daily dose was 100 mg (apart of 2 patients with 120 mg). In our study initial oral dose of 20 mg was followed by 10 mg four times daily with total nifedipine dose of 60 mg per day. As there is no clear nifedipine medication protocol in tocolytic treatment, maximum daily dose of 100 mg is recommended (RCOG 2011). However, there is evidence that total dose above 60 mg is probably responsible for three- to four-fold increase in adverse events such as hypotension (Khan *et al.* 2010). This finding may directly influence the circulatory system and result in blood flow changes in different compartments. As potential impact of nifedipine on cardiac function was an important issue, we evaluated several hemodynamic parameters like E/A ratio, MPI and SF. Early/Atrial ratio is well known as a marker of ventricular diastolic function while shortening fraction is a parameter representing cardiac contractility (Godfrey *et al.* 2012). MPI a precise tool to assess global cardiac function which is not dependent of fetal heart rate and ventricular structure (Pellett *et al.* 2004; Tei *et al.* 1995). The advantage of all these parameters is that both sides of fetal heart can be assessed independently. Guclu *et al.* (2004; 2006) assessed cardiac function by examination of E/A ratio and an index of cardiac output. Although we used mostly different cardiac parameters the conclusions were similar. We did not find any alterations of cardiac function, therefore a direct impact of nifedipine on fetal heart was not observed. In our study maternal corticosteroids administration was a part of general tocolytic strategy. Therefore, an important question arose, if steroids may interfere with hemodynamic changes. Literature review brought conflicting data reporting different observations. Fetal heart rate was mildly modified while short and long term variations were decreased (Lunshof *et al.* 2005). Urban *et al.* (2005) presented data suggesting significant decrease in MCA PI and CPR index after dexamethasone. Chitrit *et al.* (2000) reported a significant decrease in fetal MCA impedance after maternal steroid therapy. Senat and Ville (2000) assessed blood flow in uterine arteries, umbilical arteries, descending aorta and middle cerebral arteries in the group of growth restricted fetuses after maternal management of bethamethasone or dexamethasone. No significant changes were found in Doppler measurements. The important issue is that most of the alterations in fetal arterial hemodynamics were observed after 72 hours from the administration of the first dose. Our research was focused on the period of first 48 hours of tocolytic treatment. We cannot conclude definitely that there are absolutely no changes in the hemodynamic condition due to corticosteroids. On the basis of our results we may only assume that steroid administration did not interfere with placental and fetal circulation.

In summary, of our study, hemodynamic cardiac activity in fetuses was unaffected during treatment. Although transient MCA PSV decrease was recorded after 24 hours of treatment a resolution of this distraction was observed within next 24 hours. Therefore oral administration of nifedipine seems not to alter uterine nor fetal arterial blood flow pattern seriously. As significant changes were observed by different authors further studies should be performed to verify the optimal total dose of nifedipine and its influence on hemodynamic conditions.

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