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Research

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Assessment of Maternal Nifedipine as a Tocolytic Agent on the Doppler Indices of Uterine and Fetal Umbilical and Middle Cerebral Arteries

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ABSTRACT

Objective: This study was designed to assess the effects of maternal nifedipine administration on blood flow resistance in uterine, umbilical and fetal middle cerebral arteries by evaluating resistance index (RI) and pulsatility index (PI).
Patients and Methods: This was a prospective, observational, analytic cohort study performed in 50 pregnant women undergoing nifedipine tocolysis, all women with a singleton pregnancy between 24 and 34 weeks of gestation, each subject acting as her own control. Doppler assessment of uterine, umbilical and fetal middle cerebral (MCA) arteries was performed before and 24 h and 72 h after an initial 20 mg oral dose, which was repeated at 20 min intervals if contractions failed to diminish up to a total maximum dose of 60 mg. The maintenance dose consisted of 20 mg orally every 6 h. We analyzed whether there was a time effect and compared values at the different time-points.
Results: The research showed that the UtA-RI has increased significantly after 24 h and after 72 h of nifedipine administration (0 h=0.53; 24 h=0.56; 72 h=0.55; p=0.002, p=0.015 respectively). The MCA-RI had decreased significantly after 24 h (p=0.003) of tocolysis returning to baseline after 72 h (0 h=0.75; 24 h=0.73; 72 h=0.74; p=0.150). The MCA-PI had decreased significantly after 24 h (P=0.024) of tocolysis returning to baseline between 24 h and 72 h (0 h=1.85; 24 h=1.75; 72 h=1.79; p=0.204), with no differences in UtA-PI or in the umbilical arteries Doppler (RI & PI) or in the MCA to umbilical artery ratio.
Conclusions: Nifedipine tocolysis is associated with a reduction in RI and PI in the MCA, and an increase in RI in uterine arteries after 24 h but returning to baseline within 72 h, with no long-term effect on fetomaternal circulation in pregnant women at risk of preterm delivery.

KEY WORDS: Preterm; Nifedipine; Doppler.

ABBREVIATIONS: MCA: Middle Cerebral Artery; PI: Pulsatility Index; RI: Resistance Index; UtA: Uterine Artery.

INTRODUCTION

Preterm labor is one of the biggest challenges for obstetricians and so are the preterm babies for the neonatologists. Preterm delivery is defined as labor beginning before completed 37 weeks of gestation. The incidence of preterm labor is reported by the WHO to be 5-11%.[1] Preterm delivery is an international health problem and is responsible for approximately two-thirds of early neonatal morbidity and mortality.[2,3]

Yet, current evidence shows that it is possible to reduce the complications caused by prematurity.[4,5] Consequently, 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 ben-

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eficial effect of steroids on fetal lung maturity; and prolonging pregnancy in an attempt to improve perinatal outcome.[6,7]

Many pharmacological agents that inhibit uterine contractions are used in clinical practice in an attempt to prevent preterm delivery such as β2 agonists, calcium channel blockers (as nifedipine), progesterone, magnesium sulfate, oxytocin antagonists and anti-prostaglandins (as indomethacin). The maternal and fetal side-effect profiles of tocolytic agents are important considerations in the choice of these agents. According to the most recent Cochrane database review, the use of calcium channel blockers over other tocolytic agents is likely to increase.[8,9]

Nifedipine, a dihydropyridine calcium channel blocker, has emerged as an effective alternative tocolytic agent for management of preterm labor. Although, nifedipine is an effective tocolytic agent with low toxicity and teratogenicity but it has cardiovascular side effects that may affect the mother as well as the fetus.[10,11]

Animal studies suggest that use of calcium channel blockers may result in impaired uterine blood flow, potentially resulting in fetal hypoxemia and academia.[12] This may result in differential changes in the placental and cerebral blood flow resistances which may affect the cerebroplacental Doppler ratio and the overall distribution of cardiac output. However, studies in human pregnancies did not confirm significant alterations in uterine blood flow.[13,14]

PATIENTS AND METHODS

This prospective, observational, analytic cohort study was conducted on 50 pregnant women presented with preterm labor admitted in Department of Obstetrics & Gynecology in University Hospitals of Tanta, Egypt between December 2015 to June 2016 after approval of the ethical committee.

All women with a singleton pregnancy between 24 and 34 weeks of gestation with intact amniotic membranes and showing evidence of premature labor. This was defined as painful and persistent uterine contractions (at least two contractions in 10 min or four in 1 h), resulting in changes in the cervix (at least 2 cm cervical dilatation and 80% ripening). All patients had accurate dating with a gestational age based on the last menstrual period that had been validated with a ultrasound (US) examination, during which crown-rimp length was measured between 11 and 14 weeks; if that wasn't possible, bi-parietal diameter measurement was used between 14 and 22 weeks.

Pregnant women with concomitant morbidities, such as heart or lung disease, high blood pressure, diabetes or infectious disease or an obstetric morbidity (e.g., pre-eclampsia, premature rupture of membranes, gestational diabetes, intrauterine growth restriction or acute fetal distress), were excluded from the study. Patients with maternal hypotension, amnionitis, fever of unknown origin, genital or fetal malformations or uterine fibroids, women already using another tocolytic agent and those in false premature labor were also excluded.

A written consent was taken from all studied women in this research. Full history was taken from all patients. General examination with special attention to blood pressure. For all patients, blood pressure was above 80/50 mmHg before the commencement of treatment.

Abdominal examination to measure the fundal level, palpate the uterine contractions and monitoring of the fetal heart rate. Pelvic examination: to assess the state of membranes and exclude their rupture, to exclude vaginal bleeding and assess the state of the cervix and measure the Bishop score. Sonographic assessment to estimate the gestational age, amount of liquor and to exclude placenta previa, placental abruption and major fetal congenital anomalies.

After Selection of the Cases

All patients received 12 mg intramuscular dexamethasone with another dose 12 hours later to promote fetal lung maturation. Administration of tocolytic agent in the form of oral nifedipine as an initial oral dose of 20 mg, repeated at 20 min intervals if contractions failed to diminish up to a total maximum dose of 60 mg. The maintenance regimen consisted of 20 mg taken orally every 6 h.

Doppler velocimetry on uterine, umbilical and fetal middle cerebral arteries were performed immediately prior to initial nifedipine administration, after 24 hours and 72 hours after therapy. Examinations were carried out with the patients in the semi-Fowler position to avoid orthostatic hypotension. Scans of the vessels were obtained during fetal inactivity, during periods of apnea and in the absence of uterine contractions. The examinations were performed by a specialist, using a Samsung ultrasound machine, model H60, USS- H60NF4K/WR (Samsung, Korea) with 3.5-MHz and 5-MHz convex probes were used. The high-pass filter was set at 100 Hz.

The sequence in which the vessels were examined were uterine arteries followed by the umbilical artery and then fetal MCA. Doppler flow velocimetry of the uterine arteries was performed according to the usual technique. After the ultrasound image of the intersection between the uterine artery and the iliac vessel was obtained, at the 'crossing' with the external iliac artery. The same technique was used for both left and right sides. For the umbilical artery, velocimetry was carried out at free-floating loop of the umbilical cord, and for the MCA it was performed in its peripheral portion. In addition, the cerebroplacental Doppler ratio was calculated.

Finally, all data were entered into and stored in a database. The sonographically measured Doppler indices obtained were correlated with each other and statistically analyzed.

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RESULTS

Maternal age ranged between 18-40 with the mean 25.70±4.94. Gravidity ranged between 1-5 with the mean 2.44±1.20. Parity ranged between 0-4 with the mean 1.33±1.15. Gestational age on admission ranged between 25-34 with the mean 30.33±2.54. Fetal weight ranged between 780-2432 with the mean 1611.56±459.73.

The results of the Doppler measurements are shown in Table 1 and Figures 1-4. Blood flow resistance in the placental circulation did not change in the maternal or fetal compartment.

We found that the UtA-RI has increased significantly after 24 h and 72 h of nifedipine administration. Also, the MCA-RI and PI had decreased significantly after 24 h of tocolysis returning to baseline after 72 h, with no differences in UtA-PI or in

Table 1: Doppler Indices before and after Nifedipine Tocolysis.

	Before Mean±SD	24 h Mean±SD	72 h Mean±SD	*p* value Before & 24 h	*p* value Before & 72 h	*p* value 24 h & 72 h
RI Uterine	0.53±0.05	0.56±0.05	0.55±0.05	0.002*	0.015*	0.462
PI Uterine	0.73±0.095	0.77±0.092	0.75±0.087	0.068	0.335	0.385
RI Umbilical	0.57±0.05	0.56±0.04	0.57±0.05	0.422	0.965	0.397
PI Umbilical	1.0±0.21	1.05±0.19	1.02±0.16	0.579	0.211	0.473
RI MCA	0.75±0.03	0.73±0.03	0.74±0.04	0.003*	0.150	0.118
PI MCA	1.85±0.19	1.75±0.21	1.79±0.18	0.024*	0.204	0.313
RI Umbilical/ MCA ratio	0.76± 0.05	0.78±0.05	0.78±0.04	0.268	0.339	0.879

MCA: Middle Cerebral Artery; PI: Pulsatility Index; RI: Resistance Index.

Figure 1: (a) Comparison between Resistive Index of Uterine Artery. (b)Comparison between Pulstility Index of Uterine Artery.

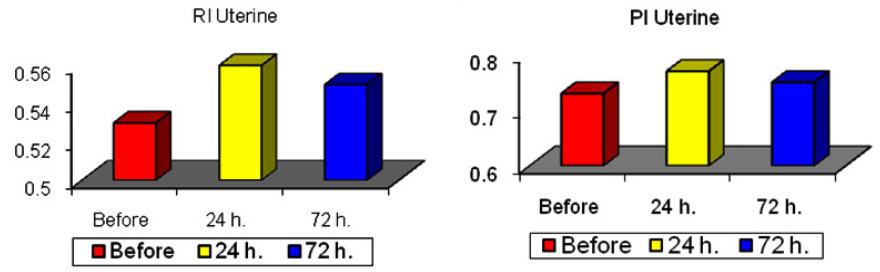


Figure 2: (a) Comparison between Resistive Index of Umbilical Artery. (b) Comparison between Pulsatility Index of Umbilical Artery.

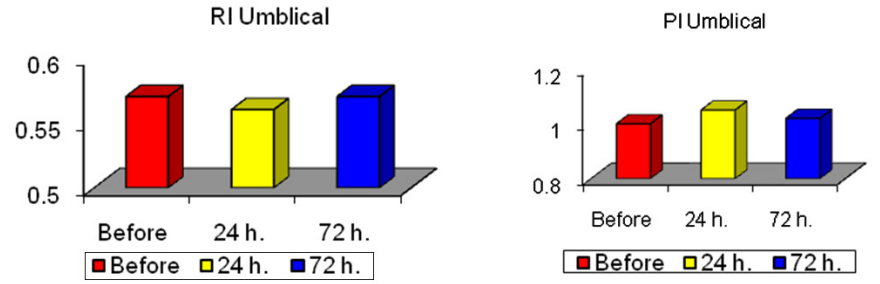
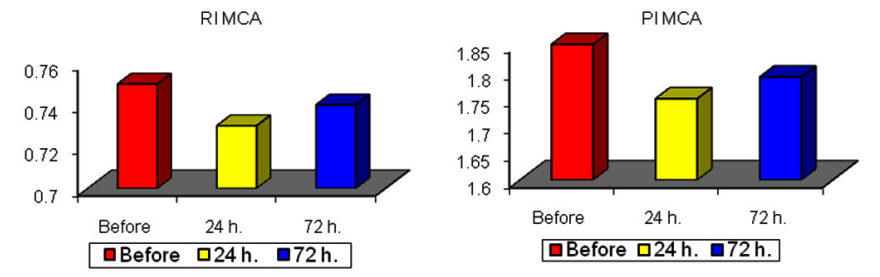


Figure 3: (a) Comparison between Resistive Index of MCA Artery. (b) Comparison between Pulstility Index of MCA Artery.



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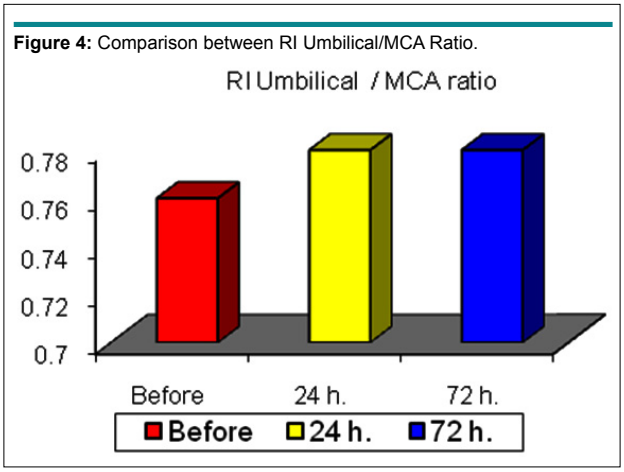

Figure 4: Comparison between RI Umbilical/MCA Ratio.

the umbilical arteries Doppler (RI and PI). The cerebroplacental ratio was equally unaffected.

DISCUSSION

Several classes of tocolytic agents are used 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. 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 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.

Our data showed that nifedipine tocolysis is associated with an increase in the UtA-RI after 24 h of nifedipine administration, with a reduction in RI and PI in the MCA, returning to baseline after 72 h, with no differences in UtA-PI or in the umbilical arteries Doppler (RI and PI) or in the MCA to umbilical artery ratio. Thus, MCA blood flow dynamics and distribution of cardiac output was unaltered. These data suggest that sequential nifedipine is not associated with any maternal and fetal side effects. 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.

Grzesiak showed that uterine blood flow patterns were not altered significantly during administration of nifedipine tocolysis.[15]

Studies on similar subjects presented different observations. In contrast to our findings, Guclu et al detected significant fall in uterine artery pulsatility index at 24 and 48 h of tocolysis.[16] Similar to our findings they showed no changes in the blood flow in umbilical artery (RI and PI) at the same point of time.

The present study showed no significant difference in the mean UtA-RI measured after 72 h of using oral nifedipine compared with measurements at 24 h (p=0.462). This is consistent with the study done by Baykal and Avcıoğlu where they did not find any significant difference in Doppler ultrasonography measurements of UtA or between Doppler indices for MCA at 2 h (early phase) and 48 h (late phase) after nifedipine treatment (p>0.05).[17]

Our data showed that nifedipine tocolysis produced no differences in the umbilical arteries Doppler (RI and PI) or in the MCA to umbilical artery ratio, similar to the findings of Karahanoglu et al who found that RI, the PI and the S/D ratio of UA did not change after treatment with nifedipine.[18] Also, de Heus et al showed that over the 5-day study period. The use of tocolytics did not significantly alter the time courses of PI-values for UA (p=0.37).[19]

Whereas, Ulubaşoğlu et al found in cohort study of 65 pregnant women undergoing nifedipine tocolysis, that there was a decrease in the 24 h values of the UA pulsatility index with nifedipine therapy in comparison with the values recorded prior to nifedipine therapy. However, these differences were not statistically significant. There were no statistically significant differences between the data recorded prior to nifedipine administration and those obtained at 48 h and 1 week after treatment.[20]

When comparing the MCA Doppler, it was found that After 24 h of tocolysis with oral nifedipine compared with prior to administration of the drug, there was a significant decrease in the mean RI of the MCA artery (p=0.003). However, there was no significant difference in the mean RI measured after 72 h of using oral nifedipine compared with measurements at 24 (p=0.118). These results agreed with a study done by Lima et al to evaluate Doppler velocimetry who showed 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

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MCA.[21] The significant decrease in MCA PI after 24 hours of tocolysis in our study was previously reported by Guclu et al. In such short-term observation no changes in maternal and fetal compartment was observed. We found no statistically significant differences in the MCA to umbilical artery RI ratio (p=0.485), similar to that reported by Guclu et al.[22]

On the other side, While MCA Doppler indices (RI and PI) were unchanged in the study of Grzesiak et al. The evaluation of MCA PSV revealed a transient significant decrease after 24 h. A resolution of this distraction was observed within the following 24 h.[15]

Another study performed by Cornette et al in which 15 healthy normotensive pregnant women with an uncomplicated singleton pregnancy between 35 and 37 weeks was studied. Then, one 10 mg capsule of nifedipine was administered twice with a 20 min interval to assess maternal and fetal hemodynamic effects of nifedipine in normotensive pregnant women. They found that nifedipine had no influence on the uteroplacental and fetal circulations.[23]

Thus oral nifedipine is a safe tocolytic agent with no long-term effect on fetomaternal circulation in pregnant women at risk of preterm delivery as fetal and maternal blood flow dynamics and distribution of cardiac output were unaltered.

CONCLUSION

Nifedipine tocolysis is associated with a reduction in RI and PI in the MCA, and an increase in RI in uterine arteries after 24 h but returning to baseline within 72 h, with no differences in UA-PI or in the umbilical arteries Doppler (RI and PI) or in the MCA to umbilical artery ratio.

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CONFLICTS OF INTEREST

No conflicts of interest exists in relation to this manuscript.

DISCLOSURE

All authors were contributed significantly and are responsible for the content of this manuscript.

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