The Effect of Isosorbide Dinitrate on Placental Blood Flow and Maternal Blood Pressure in Women With Pregnancy Induced Hypertension

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The effect of isosorbide dinitrate (ISDN) on maternal and fetal circulation was assessed in 23 women with pregnancy induced hypertension (PIH). A double-blind randomized design was employed. Each woman was given a sublingual tablet of ISDN (5 mg) or placebo. Maternal blood pressure (BP) and heart rate (HR) were measured before and every 2 min after the medication or placebo, for a total of 20 min. Flow velocity waveforms in the uterine and umbilical arteries were recorded at the same time periods, using pulsed Doppler ultrasound. The ratio of peak systolic to end-diastolic flow velocity (S/D) in those vessels was calculated. After ISDN mean maternal BP fell from 103 ± 6 to 90.5 ± 2.9 mm Hg at 14 min (P < .0001) and mean maternal HR increased from 97.3 ± 3.8 beats/min to 115.7 ± 3.5 beats/min at 12 min (P < .0001). The mean S/D in the umbilical artery fell from 3.07 ± 0.33 to 2.58 ± 0.23 at 8 min (P < .0007). The mean S/D in the uterine artery fell from 3.27 ± 0.6 to 2.38 ± 0.28 at 10 min (P < .0001). In seven of 12 women with an early diastolic notch in the uterine artery flow velocity waveform the notch diminished or disappeared within the first 6 min after the medication. No significant change in any of the measured parameters was observed in the placebo group. Our finding that ISDN altered maternal and fetal hemodynamics in PIH lends support to the further exploration of nitric oxide donors in the treatment and prevention of pregnancy induced hypertension. Am J Hypertens 1999;12:341–347 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Nitric oxide donors, flow velocity waveforms, uterine artery, umbilical artery, diastolic notch.

Normal pregnancy is characterized by vasodilatation of the maternal systemic circulation and decreased vascular reactivity to vasoconstrictors. These changes are regulated at least in part by endothelium-derived nitric oxide (NO). Preeclampsia, a major cause of maternal and perinatal morbidity, is characterized by increased pressor sensitivity and peripheral resistance, activation of the coagulation cascade, and hypoperfusion of many vascular beds. Many clinical and experimental studies imply that impaired endothelial cell function with reduced NO formation and
action may account for the hemodynamic alterations in pregnancy induced hypertension. Impairment of basal and stimulated NO activity was also demonstrated in the fetoplacental circulation during preeclampsia. In human pregnancies complicated by preeclampsia, a decrease in placental NO synthase (NOS) activity has been reported. Recently, a linkage between the endothelial NO synthase gene and familial pregnancy induced hypertension syndrome was demonstrated, which further emphasizes the association between NO and this disorder.

If endothelial cell dysfunction plays an important role in the pathogenesis of preeclampsia, leading to insufficient synthesis and release of NO from the perturbed vascular endothelium, as previously suggested, then NO deficiency, with an imbalance of vasodilating and vasoconstricting substances, might be corrected by administration of nitric oxide donors.

The aim of this study was to investigate the effect of isosorbide dinitrate (ISDN), a donor of nitric oxide, on flow velocity waveforms in the uterine and umbilical arteries and on maternal heart rate (HR) and blood pressure (BP), and to compare the use of this drug with placebo in women with pregnancy induced hypertension.

MATERIALS AND METHODS

A double-blind randomized placebo-controlled study of women with pregnancy induced hypertension was performed. Included in this study were 23 nonsmoking women with singleton pregnancies. All were admitted to the high-risk obstetrical unit at the Rambam Medical Center because of pregnancy induced hypertension. The latter was defined as two recordings of diastolic BP ≥ 90 mm Hg, 4 h apart, at any stage after 20 weeks’ gestation. Daily protein excretion did not exceed 300 mg in any patient.

All women had been normotensive and nonproteinuric before 24 weeks of gestation. None suffered from other medical problems. Each woman was given a sublingual tablet of 5 mg ISDN (Cordil, Dexxon, Haifa, Israel) or placebo, until completely dissolved. Twenty-three sealed envelopes were provided by the pharmaceutical company, each containing an identical tablet (medication or placebo). The women were randomized by selecting the next sealed numbered opaque envelope in sequence. Measurements of maternal BP, HR, and the ratio between peak systolic to end-diastolic flow velocity (S/D) in the uterine and umbilical arteries were obtained before and every 2 min after the administration of drug or placebo, for a total of 20 min. Time count commenced as soon as the tablet was placed sublingually.

Recordings of fetal heart rate were obtained 20 min before the study began and throughout the study using the HP 50A (Hewlett Packard, Andover, MA) fetal heart rate recorder. Fetal heart rate data were sampled into a computer via a digital serial interface for subsequent analysis. Maternal BP and HR were recorded by an automatic blood pressure recorder (BP-1001S, Nippon Colin, Tokyo, Japan). Three premedication measurements were obtained and then averaged to represent the control value. Mean arterial pressure was calculated as diastolic BP + 1/3(systolic BP − diastolic BP). Blood flow velocity waveforms (FVW) were obtained from the ascending branch of the uterine artery at the nonplacental site at the level of the internal cervical os, as previously described. We employed a transvaginal image-directed pulsed Doppler ultrasound with a 6.5-MHz imaging transducer and a 5-MHz Doppler transducer (ESI 2000, Elscint Ltd., Haifa, Israel). Flow velocity waveforms from the uterine artery were continually recorded by one operator, taking care to place the sample volume in the same arterial segment. All waveforms were recorded on a video recorder with a built-in clock (National NV-180EN, Matsushita Electric Industrial Co. Ltd, Osaka, Japan). Measurements of S/D were obtained offline by subsequent replay of the video recorder. Each value obtained was calculated as the mean of three consecutive similar waveforms.

Flow velocity waveforms from the umbilical artery were obtained by another operator from a segment of the umbilical cord near the point of placental insertion. The equipment used was a 3.5-MHz duplex scanner (SSD-680, Aloka Co. Ltd., Tokyo, Japan). Measurements of S/D were performed online. Each value was calculated as the mean of three consecutive similar waveforms, displayed on the screen after frame freezing. A printout of the values obtained was produced during the time intervals between the sampling of Doppler flow waveforms, using a video printer (Sony UP-701, Sony Corporation, Tokyo, Japan). In both vessels, a high-pass filter (100 Hz) was used to eliminate low-frequency signals originating from vessel wall movements. Doppler flow velocity waveforms were obtained by the same operators in all women.

Statistical analyses were performed on a personal computer using the SAS statistical package (SAS Institute, Cary, NC). Data were analyzed for comparison between means with analysis of variance for repeated measures. Multiple comparisons to baseline were performed with the Dunnett test. Analysis of covariance was employed to compensate for the effect of heart rate on the resistance index in the uterine artery. A value of \( P < .05 \) was considered statistically significant. Results are expressed as the mean ± 1 standard error of the mean (SEM). The institutional review committee approved the study and patients gave their informed consent before the procedure.
TABLE 1. PATIENT CHARACTERISTICS, OUTCOME OF PREGNANCY, AND SERUM CREATININE, URIC ACID, AND ALBUMIN LEVELS IN THE TWO GROUPS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (Placebo) N = 11</th>
<th>Study Group (Isosorbide Dinitrate) N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>31.3 ± 7.3</td>
<td>30.9 ± 5.7</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Gestational age at study</td>
<td>36.3 ± 2.2</td>
<td>35.8 ± 2.3</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td>37.7 ± 2.1</td>
<td>38.0 ± 0.92</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2810 ± 687</td>
<td>2777 ± 664</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.86 ± 0.17</td>
<td>0.81 ± 0.12</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.94 ± 1.48</td>
<td>4.88 ± 1.18</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.49 ± 0.49</td>
<td>3.63 ± 0.29</td>
</tr>
</tbody>
</table>

RESULTS

Twelve women received ISDN and 11 women received placebo. The characteristics of the two groups are shown in Table 1. After sublingual ISDN, mean arterial blood pressure fell from a control value of 103.3 ± 1.8 mm Hg to a nadir of 90.5 ± 2.9 mm Hg at 14 min (a 12.4% change, \( P < .0001 \)). The lower part of Figure 1 shows the percent deviation from control value of mean maternal blood pressure after drug or placebo. The fall was already significant at 6 min, and continued so throughout the study. There were no significant changes in mean maternal blood pressure after placebo.

Mean maternal heart rate increased after the medication, from a control value of 97.3 ± 3.8 beats/min to 115.7 ± 3.5 beats/min at 12 min (a 19.8% change, \( P < .0001 \)). The lower part of Figure 1 shows the percent deviation from control value of mean maternal heart rate in women receiving drug or placebo. The increase in maternal heart rate was already significant at 4 min, and continued so throughout the study. There were no significant changes in mean maternal blood pressure after placebo.

DISCUSSION

Our data indicate that isosorbide dinitrate, a nitric oxide donor, may safely lower maternal blood pressure in patients with pregnancy induced hypertension, and decrease Doppler resistance indices in the uterine and umbilical arteries. The findings are consistent with an abnormal endothelial function in pregnancy induced hypertension leading to a reduced NO release, which might be correctable by NO donation by ISDN.

There is good evidence that NO synthesis is significantly increased in the uterine artery during normal gestation and that endothelial vasodilator influences are augmented during pregnancy in uterine arteries by enhanced release of nitric oxide. These changes may mediate the increased blood flow to the uterus that is characteristic of pregnancy. In preeclampsia, the flow-mediated vasodilation, considered to be a physiologic response to nitric oxide release, is impaired, thus contributing to the elevation of blood pressure and to the increase in peripheral vascular resistance. A significant loss of endothelium-dependent relaxation in myometrial resistance arteries, which may contribute to the altered vasoreactivity seen in this condition, and particularly to the increased resistance and the decreased flow through the
uterine vascular bed, has been demonstrated in pre-eclampsia. Abnormal Doppler flow velocity waveforms in the uterine artery were described in pregnancies complicated by hypertension. In particular, the presence of an early diastolic notch was reported to be a good predictor of poor perinatal outcome. Endothelium-derived nitric oxide has also been implicated in the maintenance of low placental blood-flow resistance. It was suggested that basal and stimulated NO activity is impaired in the fetoplacental circulation during preeclampsia. A reduction of placental NO synthase (NOS) activity, which may have an adverse effect on placental hemodynamic function, as reflected by the development of the high-impedance fetoplacental circulation, was demonstrated in preeclampsia. Placental NOS activity was significantly lower in women with abnormal umbilical artery flow velocity waveforms compared with women with normal flow patterns. Increased Doppler resistance indices in the umbilical artery in hypertensive pregnancies are associated with adverse perinatal outcome. Improvement of abnormal or absent end-diastolic umbilical artery velocimetry is related to improved perinatal outcome.

We observed a significant fall in S/D in the umbilical artery after ISDN. As a functioning baroreceptor mechanism has been demonstrated in the fetus, the lack of significant change in fetal HR implies that there were no significant changes in fetal arterial pressure. Thus, the fall in S/D in the umbilical artery may well

FIGURE 1. Changes in mean arterial pressure (upper trace) and heart rate (lower trace) after 5 mg ISDN (solid line) or placebo (broken line). The changes are expressed as percent deviation from control value.
reflect a reduced resistance in the fetal placental circu-
lion. This was also demonstrated in another study per-
formed in women with severe preeclampsia. \(^2^8\) Af-
ter intravenous infusion of nitroglycerine the pulsatility index in the umbilical artery decreased by 12% but there were no significant changes in fetal heart rate. In another study, sublingual glycerol trinitrate was given to women with pregnancy induced hypertension or impaired fetal growth at 34 to 38 weeks' gestation. \(^2^9\) Umbilical artery S/D at 10 min was 17% less than baseline, similar to our observation.

We have also observed a significant fall in S/D in the uterine artery after ISDN. When an early diastolic notch was present, it either diminished or disappeared. A significant fall in uterine artery resistance was also reported after intravenous infusion of S-nitrosoglutathione, a nitric oxide donor, to women with severe preeclampsia. \(^3^0\) This was also accompanied by a significant fall in mean arterial pressure and an increase in maternal heart rate. The Doppler resistance index in the umbilical artery did not change significantly. The mean gestational age was 29 weeks and most women in the study were already taking oral antihypertensives. Eight of 10 fetuses were growth restricted.

In a different study, an intravenous infusion of ni-

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**FIGURE 2.** Changes in S/D in the umbilical artery after 5 mg ISDN (solid line) or placebo (broken line). The changes are expressed as percent deviation from control value. S/D, peak systolic to end-diastolic flow velocity ratio.

**FIGURE 3.** Changes in S/D in the uterine artery after 5 mg ISDN (solid line) or placebo (broken line). The changes are expressed as percent deviation from control value. S/D, peak systolic to end-diastolic flow velocity ratio.
Triglycerine caused a significant decrease in umbilical but not uterine artery resistance in severely pre-eclamptic women, despite similar changes in maternal blood pressure and heart rate. The mean gestational age at examination was higher than in the former study (33 weeks) and only 17% of the fetuses were growth restricted. The different results obtained regarding Doppler resistance indices in the uterine and umbilical arteries in those studies could be accounted for by the differences in the study populations, but may also be due to the different drugs used. In addition, if morphologic changes in placental vessels are extensive (as may well be the case in the presence of early fetal growth restriction associated with markedly elevated resistance indices in the umbilical artery), exogenous nitric oxide may not exert a measurable vasodilator effect.

We have recently observed a significant reduction in the Doppler resistance indices in the umbilical artery in preeclamptic patients treated by dermal patches of ISDN (unpublished data). In this study we only investigated the short-term effects of a single administration of a NO donor. Our results, if supported by other studies using long-acting NO donors, imply the need for an appropriate clinical trial of NO donor therapy for improved fetal and maternal outcomes in pregnancy induced hypertension.

REFERENCES


