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MATERNO-FETAL MEDICINE

Hypotension in normotensive pregnant women treated with nifedipine as a tocolytic drug

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Abstract
Objective To determine hypotensive effect of nifedipine in the treatment of preterm labor.
Methods A descriptive analytic study was conducted on pregnant women treated with nifedipine as tocolytic drug for preterm labor. Maternal blood pressure before and at 15, 30, 45 and 60 min after administration of nifedipine was evaluated and analyzed. Hypotension was defined as a decrease in systolic or diastolic blood pressure of 15 mmHg or more.
Results A total of 157 pregnant women met the inclusion criteria. The mean systolic and diastolic blood pressure before treatment was 109.4 and 72.5 mmHg, respectively. The blood pressure following treatment with nifedipine was significantly decreased both systolic and diastolic blood pressure ($p < 0.05$) at 30, 45 and 60 min. Of 157 patients, 28 (17.8%) and 27 (17.2%) had systolic and diastolic hypotension, respectively. Of the patients with decreased blood pressure, the mean decrease of systolic and diastolic blood pressure was 16.3 and 14.5 mmHg, respectively.
Conclusion Nifedipine was associated with a minimal but significant decrease in blood pressure. 17% of cases have hypotension. However, hypotension secondary to nifedipine was not associated with significant clinical symptoms, suggesting that nifedipine is relatively safe in terms of hypotensive effect.

Keywords Maternal hypotension · Nifedipine · Preterm labor

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Introduction

Preterm labor, defined as labor occurring prior to 37 weeks of gestation which occurs in 6.8–11% of pregnancies worldwide [1–4]. Preterm birth has been a major cause of perinatal morbidity and mortality. In preterm labor, tocolysis has been commonly used to prolong pregnancies that allow corticosteroid administration to promote fetal pulmonary maturation and thus reduce negative consequences of preterm birth. Terbutaline (beta-adrenergic agonists) has been used as a tocolytic drug for a long time. Nevertheless, many serious side effects are associated with beta-adrenergic agonists, such as hypotension, tachycardia, headache, tremor, nausea, anxiety and disturbances in metabolism (elevated liver enzymes, hypokalemia, and hyperglycemia) and maternal pulmonary edema. The beta-adrenergic agonists cause an increase in fetal heart rate and neonatal hypoglycemia [5–7]. Currently, nifedipine (calcium channel blocker) has demonstrated similar or even more efficacy with fewer maternal side effects and neonatal morbidity than beta-adrenergic agonist (terbutaline) [8–12], resulting in increasing use and becoming more popular recently. Nifedipine acts to inhibit the entry of calcium through channels in the cell membrane. Several authors have found that nifedipine is safer and more effective tocolytic agent than beta-agonists [10, 13, 14]. However, though nifedipine is now widely accepted as tocolytic, it has been developed to treat hypertension and is not aimed for use in normotensive patients. Therefore, this drug may potentially be associated with severe hypotension when used as tocolytic in normal pregnant women. Though efficacy of nifedipine has been reported several times, hypotensive effect of nifedipine in normotensive pregnant women has never been thoroughly studied. The objectives of this study were to evaluate the hypotensive effects of

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nifedipine administered as a tocolytic agent to normotensive women with preterm labor.

Materials and methods

This prospective descriptive study was conducted at the Department of Obstetrics and Gynecology, Maharaj Nakorn Chiang Mai Hospital, Thailand, between 1 January 2004 and 31 December 2008. A total of 161 pregnant women were included in this study. The inclusion criteria consisted of normotensive pregnant women who received nifedipine for tocolytic therapy according to clinical practice guidelines of Maharaj Nakorn Chiang Mai Hospital and reached the maximum loading dose, 40 mg. The clinical practice guidelines for preterm labor at Maharaj Nakorn Chiang Mai Hospital is a nifedine as a tocolytic therapy with 10 mg orally for loading dose, up to 4 doses every 15 min then 4–6 h follow with maintenance dose of 60 mg (control release) orally for 48 h or not exceeding 7 days. The main outcome measured was maternal blood pressure after nifedipine administration. Maternal blood pressure was recorded before and at 15, 30, 45 and 60 min after first dose of nifedipine. Hypotension was defined as a decrease in systolic blood pressure (SBP) or diastolic blood pressure (DBP) of at least 15 mmHg from baseline blood pressure (before first dose of nifedipine administration). The exclusion criteria were inability to follow the practice guideline mentioned above such as receiving loading dose of nifedipine less than 40 mg, incomplete medical data, and receiving other medications which affects nifedipine action such as magnesium sulfate. Palpitation, headache and other side effects were also prospectively recorded. This study was conducted with approval of Research Ethics Committee 3, Faculty of medicine, Chiang Mai University, Chiang Mai, Thailand.

Statistical analysis

The data were analyzed using the statistical package for the social sciences (SPSS version 15.0). Descriptive data were presented as mean ± standard deviation, range and number. Differences in categorical and continuous data were assessed using the paired t test, respectively. A p value of 0.05 or lower was considered statistically significant.

Results

During the study period, a total of 161 pregnant women were diagnosed for preterm labor and received nifedipine for tocolytic therapy. Four of them were excluded due to inability to follow the practice guideline mentioned above. Finally, 157 cases were finally available for analysis. The mean maternal age was 28.2 years (range 14–45 years) and mean gestational age was 29.3 weeks. Eighty-two (52%) were nulliparous. One hundred and thirty-one (83%) women had a singleton pregnancy and 26 (17%) were twin pregnancies.

Before using nifedipine, the mean systolic and diastolic blood pressures were 109.4 ± 10.4 and 72.5 ± 7.9 mmHg, respectively. All cases had normal blood pressure and none of them had blood pressure less than 90/60 mmHg. In about one-third, blood pressure decreased after receiving nifedipine. After receiving nifedipine, blood pressure was decreased, or unchanged in most cases. Surprisingly, in some cases it was slightly increased. Overall, the systolic blood pressure was significantly decreased after using nifedipine at 30, 45 and 60 min ($p < 0.05$) and mean changes of blood pressure were 2.8, 3.3 and 4.5 mmHg, respectively. Likewise, diastolic blood pressure was significantly decreased after using nifedipine at 15, 30, 45 and 60 min ($p < 0.05$) and mean changes of diastolic blood pressure were 2.0, 3.1, 4.2 and 4.2 mmHg, respectively, as shown in Table 1. All cases received a maximum 40 mg of nifedipine in first hour.

Table 2 shows the rates of patients with hypotension defined as mentioned above at 15, 30, 45 and 60 min after nifedipine administration. Nevertheless, hypotension in most cases occurred in the same patients at various points of time. The overall rates of patients with systolic and diastolic hypotension (at least once at any time points) was

Table 1 Changes in blood pressure during the first hour of treatment

Time after treatment (min)	Systolic BP			Diastolic BP		
	Mean ± SD (mmHg)	BP changed from base line (mmHg) 95% CI	p value*	Mean ± SD (mmHg)	BP changed from base line (mmHg) 95% CI	p value*
Base line	109.4 ± 10.4	–	–	72.5 ± 7.9	–	–
15	107.9 ± 10.0	1.4, −0.1–3.1	0.079	70.4 ± 8.3	2.0, 0.6–3.4	0.003**
30	106.6 ± 10.0	2.8, 1.3–4.3	<0.001**	69.3 ± 9.3	3.1,1.5–4.7	<0.001**
45	106.1 ± 9.7	3.3, 1.9–4.8	<0.001**	68.2 ± 8.1	4.2, 2.8–5.7	<0.001**
60	104.9 ± 10.5	4.5, 2.7–6.2	<0.001**	68.3 ± 7.4	4.2, 2.8–5.5	<0.001**

* By the paired t test, ** p value < 0.05

Table 2 Incidence of hypotension (systolic and diastolic) within at various time points after first dose of nifedipine

Time points	Systolic hypotension		Diastolic hypotension	
	N out of 157	%	*N* out of 157	%
15 min	17	10.8	12	7.6
30 min	15	9.6	13	8.3
45 min	18	11.5	16	10.2
60 min	24	15.3	15	9.6
Total	28	17.8	27	17.2

Table 3 Incidence of hypotension (systolic < 90 mmHg or diastolic < 60 mmHg) of at least one time at various time points after first dose of nifedipine

Time points	Systolic hypotension		Diastolic hypotension	
	N out of 157	%	*N* out of 157	%
15 min	1	0.6	1	0.6
30 min	1	0.6	5	3.2
45 min	2	1.3	4	2.5
60 min	4	2.5	1	0.6
Total	5	3.2	6	3.8

Compared to the incidence before drug administration with McNamara Chi-square, $p > 0.05$ at 15, 30, 45 and 60 min)

28 (17.8%) and 27 (17.2%) out of 157, respectively. Of patients with decreased blood pressure, the mean decrease of systolic and diastolic blood pressure was 16.3 and 14.5 mmHg, respectively. However, none of them had blood pressure of lower than 80/40 mmHg. When using absolute definition of hypotension (one or more values of systolic or diastolic less than 90 or 60 mmHg, respectively, the incidence of hypotension at 15, 30, 45 and 60 min were between 0.6 and 3.8% as seen in Table 3 (McNamara Chi-square test $p > 0.05$ at all time points).

Mean baseline maternal heart rate was 89.6 ± 14.8 bpm and changed significantly after 45 and 60 min of nifedipine administration, as presented in Table 4. The maximum level of heart rate was 93.4 ± 12.8 bpm at 45 min after nifedipine administration. Additionally, none of them had maternal heart rates more than 120 bpm. Seven of 157 women had minor side effects after treatment including palpitation in six women (3.82%) and mild headache in one patient. None of them was intolerant to the side effects.

Table 4 Changes in heart rate during the first hour of treatment

Time after treatment (min)	Heart rate		
	Mean ± SD (bpm)	Increased from base line (bpm)	*p* value*
Base line	89.6 ± 14.8	–	–
15	89.9 ± 12.8	0.3	0.703
30	91.9 ± 12.2	2.3	0.016**
45	93.4 ± 12.8	3.7	<0.001**
60	93.2 ± 13.2	3.6	<0.001**

* By the paired *t* test, ** *p* value < 0.05

Discussion

The use of nifedipine has become commonplace in management of preterm labor. Several relatively small randomized trials have compared calcium channel blockers (nifedipine) with beta-agonists and the meta-analyses of these studies have demonstrated superior or comparable efficacy of nifedipine and a fewer adverse effects. However, the safety of calcium channel blockers in pregnancy has not been rigorously evaluated [15, 16].

Although nifedipine has hypotensive effect for treatment of hypertension, several studies have demonstrated that hypotension secondary to nifedipine in normotensive women treated for preterm labor is minimal and not clinically significant [8, 10, 17]. In some reports, however, this hypotensive effect can be severe enough to cause fetal death [18]. To date the safety of nifedipine in the term of hypotension is yet a subject to be elucidated. Unlike several studies in which no details of systolic and diastolic blood pressure were given at different time periods after drug administration, this study focused on blood pressure at various time points after receiving nifedipine. As expected, nevertheless, our results showed that blood pressure was slightly decreased after nifedipine administration but not clinically significant in terms of fetal well-being and maternal symptoms. Only 17% of case had hypotension within 60 min after receiving nifedipine but no severe hypotension or fetal death was observed in 157 women. Notably, most women (more than 80%) had no hypotension at any recorded time point within 60 min of treatment. In other words, blood pressure in normotensive women treated with nifedipine as a tocolytic was unchanged in most cases. Surprisingly, despite a significant decrease in both diastolic and systolic blood pressure, no other adverse effects such as headache, dizziness, nausea or clinical symptoms of hypotension were observed in most of them. Although an increase in maternal heart rate also was commonly found, tachycardia or arrhythmia was not seen as reported in other previous reports [17, 19]. Only 7 out of 157 had minor adverse effects (palpitation and headache) and all of them could tolerate such effects. Nevertheless, the advantage of the study is that it is the largest study focusing on hypotensive effect. The results of this study supports that nifedipine can be safely used in preterm birth without profound hypotension though close monitoring of vital signs is warranted.

The weakness of this study is that the regimen used in this study was a low-dose one; therefore, the result of hypotensive effect may not represent the other higher dose regimens of nifedipine. Additionally, the main outcomes included only blood pressure measured within 60 min, not included thereafter or during the maintenance doses since the dosage after initial phase was usually varied depending on patients' response. Therefore, our results can represent the hypotensive effects of nifedipine only during initial phase of treatment. Finally, variation of blood pressure changes may be influenced by other confounding factors which might have not been perfectly controlled, such as techniques or position in the measurement.

In conclusion, nifedipine for treatment of preterm labor in normotensive women was associated with a minimal but significant decrease in blood pressure with 17% rate of hypotension. However, hypotension secondary to nifedipine was not associated with significant clinical symptoms. The present study suggests that nifedipine is relatively safe in term of hypotensive effect when used as an alternative tocolytic agent.

Conflict of interest None.

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