Preliminary Report

Safety and Efficacy of Oral Nifedipine versus Terbutaline Injection in Preterm Labor

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Objective: *To compare the safety and tocolytic efficacy of oral nifedipine with intravenous terbutaline for the management of threatened preterm labor.*
Material and Method: *Pregnant women between 24 and 36 completed weeks of single gestation with preterm labor were randomized to either oral nifedipine (n = 20) or intravenous terbutaline (n = 20) treatment. Nifedipine (immediate released capsule) 10 mg was crushed and swallowed, 10 mg every 20 minutes was allowed if necessary with a maximum 40 mg in the first hour. After that 20 mg nifedipine every 4 hours was given, up to 72 hours. Terbutaline was initially infused with the rate 10 µg/min with an increment 5 µg/min every 10 minutes if required, until 25 µg/min was reached. Once the contractions had stopped for 2-6 hours, the patients were switched to subcutaneous injection with 0.25 mg terbutaline every 4 hours for 24 hours. The main safety outcome was the changes in maternal diastolic blood pressure from baseline and 1 hour after starting the treatment (ΔDBP_{1hr}). Secondary outcomes were the efficacy to delay delivery $\geq$ 48 hours and 7 days, the adverse events and the birth outcomes.*
Results: *ΔDBP_{1hr} was greater in the terbutaline group than that in the nifedipine group with no statistically significant difference. Hypotension (defined as BP $\leq$ 90/60 mmHg) was found in one patient of the nifedipine group and two patients of the terbutaline group. Seventeen and 14 patients in the nifedipine group and 15 and 12 patients in the terbutaline group had delayed delivery $\geq$ 48 hours and 7 days, respectively. Mothers in the nifedipine group experienced fewer side effects than those in the terbutaline group. Maternal heart rate, at 1 hour after starting the treatment, increased significantly higher in the terbutaline group than in the nifedipine group. Birth outcomes were measured in all nifedipine group patients, but in only 16 of the terbutaline group patients. Six mothers in each group delivered after 37 weeks. Intraventricular hemorrhage (IVH) occurred in three babies (gestational aged 25, 29 and 37 weeks) born to mothers treated with terbutaline. In one baby, IVH related to trauma resulted from the delivery procedure.*
Conclusion: *The safety and efficacy of nifedipine compares with that of terbutaline for treatment of preterm labor.*

Keywords: *Nifedipine, Terbutaline, Preterm labor, Efficacy, Safety, Tocolysis*

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Preterm birth is the most important cause of neonatal morbidity and neurologic disability[1]. Tocolytics prolong pregnancies that allow corticosteroids to promote fetal pulmonary maturation and thus reduce negative consequences of preterm birth[2]. Several beta-adrenergic agonists (BAAs) have been used for tocolysis, but ritodrine is the only BBA approved by the US FDA[3], and thus most widely studied. Nifedipine, a calcium-channel blocker, has been used in preterm labor since 1986[4]. Nifedipine demonstrated similar efficacy with fewer maternal side effects and neonatal morbidity than ritodrine[5-10]. The study was a

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meta-analysis including 9 RCTs within 679 patients. It was a small trial of subcutaneous terbutaline in dosage of 0.25 mg/min and demonstrated that nifedipine was more effective than BBAs in delaying delivery at least 48 hours (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.03, 2.24) or over 34 weeks (OR 1.87, 95% CI 1.11, 3.15)[2]. Use of terbutaline in the management of preterm labor varied in dosage and routes of administration thus, might lead to differences in efficacy and side effects[11-16]. Intravenous infusion terbutaline is used as standard treatment for preterm labor in many hospitals in Thailand. However, the trials on intravenous regimens were very limited and varied in dose and duration[3,17,18]. Despite the promising safety of nifedipine, questions remained because these safety data were obtained from trials where terbutaline was given in a different manner to the presented dosing protocol. The authors, therefore, designed a study to evaluate whether the cardiovascular safety, especially the effect on blood pressure, of oral nifedipine is superior to the hospital standard dosing terbutaline intravenous infusion. Tocolytic efficacy outcomes including prolongation of delivery greater than 48 hours and 7 days were assessed.

Material and Method

Design

The comparisons of safety and tocolytic efficacy of oral nifedipine with terbutaline intravenous infusion were conducted in a randomized controlled open trial. The blocks of size 4, 6, and 8 were used to randomize the patients in order to get the balance number of patients in both arms at any time of enrollment. The present study protocol was approved by the institutional review board. Written informed consent was obtained from all patients. A sample size of 40 (20 patients in each group) was selected. The assumption was made that the mean diastolic blood pressure (DBP) decreased from baseline, measured at 1 hour after initiation the treatment, was 10 mmHg lower in the terbutaline group. This sample size detected the effect difference with 90% power and significance of 0.05. Sample size calculation is described below.

$$n = (1+1/r)\,(\sigma/\Delta)^2\,(Z_{\alpha/2}+Z_{\beta})^2$$

Where; Δ = 10 mmHg difference in mean DBP between groups

σ = squared root pooled variance of DBP = 8.7 mmHg

r = ratio of the size of sample$_2$ to sample$_1$, in this case = 1

$Z_{\alpha/2} = 1.96$, $Z_{\beta} = 1.28$

$n_1 = n_2 = 15.9$

Study patients

The eligible population was the women diagnosed with preterm labor at 24-36 completed weeks of gestation, irrespective of the membranes status, who were admitted to the obstetric ward at a medical teaching hospital. The patients were selected into the study if they fulfilled the predefined criteria described below.

Inclusion criteria

Patients were eligible for inclusion if they had (1) $\geq$ 4 uterine contractions per 20 min, (2) cervical dilatation 1 to 4 cm, and/or (3) changing cervical effacement documented by the obstetricians[3,8].

Exclusion criteria

Patients were excluded from enrollment if they met any of the following criteria, heart diseases, renal diseases, hypertension, chorioamnionitis, placental abruption, placental previa, preeclampsia, multiple pregnancy, diabetes, and thyrotoxicosis.

Intervention

Each patient was treated according to the protocol, immediately after randomization. To enhance fetal lung maturation, patients with gestational age < 34 weeks were given 6 mg dexamethasone, intramuscularly, every 12 hours for 4 consecutive doses. The treatment protocol for each group was as follows.

Nifedipine group

The patient was given a 10 mg tablet of immediate-released nifedipine, crushed before swallowed. If uterine contraction continued, a crushed 10 mg tablet was given every 20 min with a maximum of 40 mg nifedipine within the first hour of treatment. After completing the first hour, 2 capsules of 10 mg nifedipine were given every 4 to 6 hours consecutively for 72 hours. Dosage schedule could be modified according to the patient's clinical symptoms and vital signs.

Terbutaline group

Initial infusion rate of terbutaline was 10 µg/min and increased by 5 µg/min every 10 minutes, until 25 µg/min was reached. The rates should be decreased if maternal heart rates > 130 beats/min (bpm) or hypotension developed. Once uterine contraction stopped, that labor-inhibiting infusion rate was maintained for

2-6 hours before switching to subcutaneous injections of terbutaline 0.25 mg every 4 hours for 24 hours. Terbutaline dose was then adjusted based on the patient's response until the uterine stopped contracting.

Alternative treatment protocol for tocolytic failure

The definitions of tocolytic failure were uterine contraction persisted when the maximum dose of the assigned tocolytic was reached, cervix dilated between 1 and 5 cm, or progressively changed of cervix. Patients failed to tocolysis were given the alternative treatment, indomethacin 25-50 mg every 6 hours, with a maximum daily dose 200 mg, for 48 hours. If spontaneous rupture of membranes occurred within 48 hours of treatment, delivery was considered.

Variables

Data were recorded by the obstetricians or nurses caring for the patients. All were trained about data collection before starting the study.

Baseline variables

The authors collected important baseline variables to measure the comparability at baseline. These included maternal age, gestational age at entry, history of preterm birth, number of parity, serum potassium, degree of cervical dilatation, and modification of the cervix.

Independent variables

The independent variables were the study groups, i.e., the nifedipine and the terbutaline groups.

Outcome variables

Primary outcome: The DBP changed from baseline, measured at 1 hour of treatment (DBP_{1hr}) was the primary outcome. BP measurements were taken every 15 minutes of the first hour of treatment, then every 60 minutes up to 6 hours, and before the next nifedipine dosing.

Secondary outcomes: Secondary outcomes were the efficacy, adverse events, birth outcomes, and economic outcomes.

Efficacy outcomes: Prolongation of pregnancy 48 hours and 7 days were determined.

Adverse events: In mothers, other adverse events were the changes from baseline of systolic blood pressure (SBP), heart rates, pulmonary edema, tachycardia, and chest pain, etc. Maternal serum potassium levels were measured at 24, and 48 hour of treatment. Fetal heart rates were recorded every 6 hours.

Birth outcomes: Birth outcomes were neonatal death rates, transfer to neonatal intensive care unit (NICU), gestational age at birth, birthweight, apgar scores at 1 and 5 minutes, intraventricular hemorrhage (IVH), and respiratory distress syndrome (RDS). All outcomes were determined by the responsible obstetricians.

Economic outcome: Direct medical costs including the total costs of the medicine and non-medical products required for drug administration were measured.

Statistical analysis

Descriptive statistics (mean $\pm$ SD) was used for summarizing the baseline variables. Between groups, comparisons were based on intention-to-treat analyses. Unpaired t-test was used to compare mean between two groups and Chi-square test or Fisher's exact test to compare between categorical data. Statistical analyses were performed using Stata/SE 8.0 software. A p-value of less than 0.05 was considered significant.

Results

Forty patients were randomized, 20 into each group. All patients completed the first hour of treatment protocol, after which 11 patients in the nifedipine group stopped nifedipine after the maximum 40 mg dose. Among these 11 patients, 3 were intolerable to side effects (1 patient had nausea, vomiting and dizziness, 1 had chest pain, and 1 developed hypotension), and 8 continued uterine contraction (progressive cervical change confirmed in 3 patients, no cervical change confirmed in 2 patients, and no cervical exam performed in the remainder). One patient delivered 2 hours later, and 10 were changing to terbutaline intravenous infusion.

Table 1 shows characteristics of the patients. The two groups were similar with respect to maternal age, gestational age, parity, history of preterm labor, and state of membranes and cervix. Table 2 summarizes the doses and duration of treatment. Among the patients in the nifedipine group, the results of those who completed the treatment protocol and those who did not were presented separately. Co-medications, morphine (10 mg intramuscularly) and diazepam (10 mg orally), aimed to treat false preterm labor were given to three of terbutaline-treated patients, but none of the nifedipine-treated ones. All patients who completed the nifedipine protocol received the same dose and

Table 1. Characteristics of the patients

Variable	Nifedipine (n = 20)	Terbutaline (n = 20)
Maternal age (years), mean ± SD	24.6 ± 6.9	23.9 ± 6.4
Gestational age at enrollment (weeks), mean ± SD	31.8 ± 2.0	31.3 ± 2.8
Effacement (%), mean ± SD	59.0 ± 16.8	63.5 ± 13.5
Cervical dilatation (cm), mean ± SD	1.4 ± 0.7	1.4 ± 0.6
Membranes status, n (%)		
Intact membranes	18 (90.0)	19 (95.0)
Ruptured membranes	2 (10.0)	1 (5.0)
History of preterm labor, n (%)	1 (5.0)	2 (10.0)
Number of parity, n (%)		
0	11 (55.0)	12 (60.0)
≥ 1	9 (45.0)	8 (40.0)

Table 2. Summary of the dose and duration of tocolytic treatment

Variable[a]	Nifedipine (n = 19)[b]		Terbutaline (n = 20)
	Patients completed 72-hour treatment protocol (n = 9)	Patients received terbutaline after completing the first hour of treatment (n = 10)	
First hour dose	40±0 mg nifedipine	40±0 mg nifedipine[c]	600±0 µg/hr
Maintenance dose	20 mg nifedipine every 6 hrs, up to 72 hrs	364±185 (73-683) □g/hr, iv.[d] 2.0±3.3 (0-8) sc.[e]	522±198 (50-952) µg/hr[d] 4.8±3.0 (0-11) sc.[e]
Duration (hours)	72±0	35.1±40.4 (1.7-109), iv. 8.0±13.1 (0-32), sc.	32.1±17.4 (7.5-68.5), iv. 19.0±12.1 (0.0-44.0),sc.
Mothers received comedication, n (%)	0 (0)	0 (0)	3 (15.0)

[a] Values are expressed as mean ± SD (range)
[b] 1 patient in the nifedipine group stopped the treatment after completed the first hour of treatment and delivered 2 hours later. She received only 40 mg of nifedipine, excluded this patient from the analysis, the results are shown in Table 2
[c] All patients received 600 µg terbutaline, with infusion rate 10 µg/min, after switching.
[d] iv. maintenance infusion rate
[e] The mean number of doses, 0.25 mg subcutaneous maintenance therapy

duration of drug treatment, i.e., 40 mg in the first hour, followed by 20 mg every 4 hours up to 72 hours of treatment. Patients in the terbutaline group were initially infused with the rate 10 µg/min in the first hour of treatment, and then tailored according to the patients' tolerability. Mean infusion rate during maintenance therapy was lower than that of the initial therapy, and even lower among those initially treated with oral nifedipine. The amount of subcutaneous terbutaline (0.25 mg dose every 4 hours) used in the maintenance therapy was higher in the terbutaline group compared with those switched from nifedipine treatment (number of doses, mean ± SD 2.0 ± 3.3 versus 4.8 ± 3.0). The total duration of tocolytic treatment varied substantially among patients, with the mean ± SD [range] 35.1 ± 40.4 [1.7, 109] hours in the nifedipine group and 32.1 ± 17.4 [7.5, 68.5] hours in the terbutaline group.

Table 3 presents the changes in maternal blood pressure and statistic test results. DBP, the primary safety outcome, decreased slightly greater and

faster in the terbutaline group, with peak difference occurred within 30 and 60 minutes after treatment initiation. Differences in DBP were, however, not clinically significant. In the nifedipine group, DBP returned to normal slightly faster (12 hours after treatment initiation) than the other group. While the magnitude of DBP changes was slightly different in the two groups, this was not observed on the SBP. SBP were slightly less affected by tocolytics than DBP, with the peak mean SBP changed approximately 5 mmHg, which occurred within the first hour of treatment. Hypotension developed in one of the patient of the nifedipine group at 1 hour of treatment, and two patients of the terbutaline group (1 at 15 min, and the other at 30 min after treatment initiation). No hypotension was found thereafter (data not shown).

Maternal heart rates elevated much greater in the terbutaline group than the other, with peak increased heart rate (mean ± SD) of 29.6 ± 14.8 beats/min (bpm) at 30 minute, compared with 18.5 ± 13.8 bpm at 60 minutes in the nifedipine group (data not shown). No patient in the nifedipine group had heart rates > 130 bpm, while two patients (10.0%) in the terbutaline group did. Changes in fetal heart rates were not different between groups, and not clinically significant. Fetal heart rates > 160 bpm, however, were more common in the terbutaline group.

Table 4 shows other adverse effects found in mothers during the first 24 hours of treatment. Fifteen (75%) patients in the nifedipine group and all (100%) in the terbutaline group experienced at least one adverse effect. Unfortunately, these data after the first hour of treatment were underreported among patients in the nifedipine group who changed to receive terbutaline, as their data were no longer recorded. These adverse effects, such as tachycardia, nausea, lightheadedness, were more common in the terbutaline group. Most adverse effects disappeared after 1 hour in nifedipine-treated patients, while they persisted throughout the first 24 hours of observation in terbutaline-treated patients, with some additional cases. These side effects required dose reduction from 10 µg/min to 5-7.5 µg/min in 19 patients treated with terbutaline. Four patients in the terbutaline group developed hypokalemia, but no pulmonary edema was found.

Tocolytic efficacy and birth outcomes are presented in Table 5. These outcomes were determined in all of the patients in the nifedipine group, and 16 in the terbutaline group (4 were lost to follow-up). No difference in tocolytic efficacy (prolongation of pregnancy ≥ 48 hours and 7 days) and birth outcomes between the two groups were found. Less than half of the patients in each group gave births after 37 weeks' gestation or birth weight > 2500 g. Neonatal

Table 3. Changes in blood pressure during the first hour of treatment

Variable	BP (mmHg), mean ± SD		BP (mmHg) changed from baseline, Mean ± SD		Between group difference in BP changed from baseline, mean ± SE [95% CI]	p-value[a]
	Nifedipine (n = 20)	Terbutaline (n = 20)	Nifedipine (n = 20)	Terbutaline (n = 20)		
Diastolic BP						
Baseline	70.2 ± 5.5	73.6 ± 5.9	-	-	-	-
15 min	68.6 ± 6.2	67.4± 7.4	-1.6 ± 7.8	-6.2 ± 7.6	4.6 ± 2.5 [-0.4, 9.6]	0.0682
30 min	65.2 ± 7.4	62.8 ± 6.8	-4.9 ± 8.3	-10.8 ± 7.8	5.8 ± 2.6 [0.6, 10.9]	0.0288
45 min	66.3 ± 9.1	63.6 ± 10.8	-3.9 ± 10.6	-10.0 ± 12.7	6.1 ± 3.7 [-1.4, 13.6]	0.1075
60 min	66.0 ± 9.2	63.4 ± 8.2	-4.2 ± 10.3	-10.2 ± 9.9	5.9 ± 3.2 [-0.5, 12.4]	0.0706
6 hr	67.9 ± 6.9	68.0 ± 9.0	-4.8 ± 2.7	-5.5 ± 2.4	0.7 ± 4.0 [-7.5, 8.9]	0.8584
12 hr	70.2 ± 6.2	68.5 ± 5.9	-0.4 ± 2.1	-5.0 ± 1.8	2.6 ± 3.0 [-3.6, 8.8]	0.3987
Systolic BP						
Baseline	111.1 ± 6.5	113.9 ± 5.8	-	-	-	-
15 min	110.6 ± 6.0	112.0 ± 9.9	-0.6 ± 6.8	-2.0 ± 10.1	1.4 ± 2.7 [-4.1, 6.9]	0.6108
30 min	107.2 ± 7.3	108.5 ± 10.2	-4.0 ± 7.6	-5.4 ± 10.6	1.4 ± 2.9 [-4.4, 7.4]	0.6220
45 min	108.6 ± 8.9	110.1 ± 9.6	-2.6 ± 9.2	-3.8 ± 11.3	1.2 ± 3.3 [-5.4, 7.9]	0.7044
60 min	106.1 ± 8.9	112.2 ± 8.7	-5.0 ± 9.9	-1.7 ± 9.8	-3.3 ± 3.1 [-9.6, 3.0]	0.2989

[a] Statistic test of results obtained from intention-to-treat analyses

Table 4. Adverse events in mothers treated with tocolytic agents

Symptom[a]	1-hour treatment, n (%)			Post 1-hour to 24-hour treatment, n (%)		
	Nifedipine (n = 20)	Terbutaline (n = 20)	p-value[b]	Nifedipine (n = 9)	Terbutaline (n = 20)	p-value[b]
Flushing	1 (5.0)	6 (30.0)	0.0460	0 (0.0)	2 (10.0)	0.2440
Nausea	3 (15.0)	6 (30.0)	0.2250	0 (0.0)	9 (45.0)	0.0010
Vomiting	3 (15.0)	3 (15.0)	0.6690	0 (0.0)	3 (15.0)	0.1150
Chest pain	0 (0.0)	3 (15.0)	0.1150	0 (0.0)	4 (20.0)	0.0005
Tachycardia	5 (25.0)	11 (55.0)	0.0530	0 (0.0)	14 (70.0)	0.0005
Dizzy	3 (15.0)	5 (25.0)	0.3470	0 (0.0)	2 (10.0)	0.2440
Headache	3 (15.0)	4 (20.0)	0.6770	1 (11.1)	6 (30.0)	0.0460
Lightheadedness	5 (25.0)	8 (40.0)	0.3110	0 (0.0)	4 (20.0)	0.0530
Tremor	0 (0.0)	8 (40.0)	0.0020	0 (0.0)	10 (50.0)	0.0005

[a] Numbers (%) of patients experienced at least 1 adverse effect were 15 (75%) in the nifedipine group and 20 (100%) in the terbutaline group

[b] p-value was obtained from 1-sided Fisher's exact test

Table 5. Tocolytic efficacy and birth outcomes

Variable	Nifedipine (n = 20)	Terbutaline (n = 16)	p-value[b]
Prolongation of pregnancy			
≥ 48 hours, n (%)	17 (85.0%)	15 (75.0)[a]	0.2395
> 7 days, n (%)	14 (70.0)	12 (75.0)[a]	0.8495
Gestational age (GA) at birth (week), mean ± SD	34.5±2.9	34.6±3.6	0.8719
GA > 37 weeks, n (%)	6 (30.0)	6 (37.5)	0.4510
Birthweight (g), mean ± SD	2,330±732	2,368±731	0.8785
Birthweight > 2,500 g, n (%)	8 (40.0)	6 (37.5)	0.577
Apgar scores, 1 min < 7, n (%)	2 (22.2)	2 (12.5)	-[c]
Apgar scores, 5 min < 7, n (%)	1 (11.1)	0 (0.0)	-[c]
IVH, n (%)	0 (0.0)	3 (18.7)	-[c]
RDS, n (%)	2 (22.2)	2 (12.5)	-[c]
Transfer to NICU, n (%)	1 (11.1)	2 (12.5)	-[c]
Neonatal death, n (%)	0 (0.0)	1 (6.2)	-[c]

[a] n = 20 where specified, otherwise n = 16

[b] Statistic test of results obtained from intention-to-treat analyses

[c] Statistic test was not performed

complications were similar between groups, but 3 babies (born at 25, 29, and 37 weeks of gestation) in the terbutaline group developed IVH. In one baby, IVH was caused by the trauma resulted from delivery procedure. The costs of treatment (mean ± SD) were 80 ± 0 Baht for the nifedipine group, and 570 ± 300 Baht for the terbutaline group, which were quite different.

Discussion

Nifedipine seems to provide comparable safety and efficacy to terbutaline. Very few patients, in both groups, developed hypotension. In the terbutaline group, however, maternal and fetal heart rates greater elevated and adverse effects were more common. Efficacy in prolongation of delivery 48 hours and 7 days were similar between groups. Although birth outcomes were comparable, the serious adverse birth outcomes, IVH and hypokalemia, were found in the terbutaline group only. The direct medical cost was lower in the nifedipine group.

The doses of nifedipine and terbutaline used in the present study were relatively high compared with other studies[2,3,6,17-20]. In most trials, nifedipine was given with 10 mg dose every 15-20 minutes, with a maximum 40 mg dose in the first hour of treatment, followed by maintenance therapy with the doses ranged from 30 to 160 mg/day up to 3 days. Longer treatment duration was done by Papatsonis et al where nifedipine was given until 34 weeks among women with gestational age 20-33.5 weeks at enrollment[8]. The proportion of women giving birth after 37 weeks was, however, not significantly higher (29/68, 43.4%) compared with the present study (6/20, 30.0%) and that conducted by Weerakul, et al (29/68, 43.4%)[17]. This might imply that longer treatment might be necessary if the women have preterm labor very early in their pregnancies. Studies on terbutaline are very limited. It was first studied with a low dose regimen, i.e., started at 2.5 μg/min with an increments of 2.5 μg/min every 20 minutes until labor stopped, then reduced to the lowest rate[3]. Giving terbutaline in this fashion provide 300 μg in the first hour with very slow increased rates. This low dose provided relatively low efficacy, i.e., postponement of delivery ≥ 7 days 8/27 (29.6%). Studies conducted thereafter used the higher doses, and better efficacy were reported, e.g., postponement of delivery ≥ 7 days 87/129 (67.4%) when terbutaline was infused with the rates 5-20 μg/min for 13-18 hours[18] as well as that found in the present study (12/16, 75%). Other tocolytic efficacy outcomes, e.g., gestational age at birth, and birthweight, etc, were also related to the dose[3,17]. Patients' tolerability (% interruption of treatment due to side effects) were similar either at the low dose (3/27, 11.0%)[3] or at the high dose (6/44, 13.6%)[17]. The authors, therefore, suggest that the starting dose of 5 μg/min terbutaline, with an increment of 5 μg/min every 15-20 minutes until labor stopped, and followed by 5-10 μg/min during the maintenance therapy is appropriate for tocolytic therapy in the study population.

The present study primarily concerned on safety of the two tocolytic agents. The results demonstrated that nifedipine seemed to have a better safety profile than terbutaline. Changes in maternal and fetal vital signs were similar to that previously reported[3,6,17]. In the study conducted by Weerakul, et al. using dosage regimens very similar to that used in the present study, 93.2% of patients in the terbutaline group and 4.4% in the nifedipine group experienced side effects. Although the percentage of women having side effects in the terbutaline groups was very close to that found in the present study, that figure in the nifedipine was much lower than that presented in the present study (75%). However, another study using similar dosing protocol of immediate released nifedipine reported only 13.2% of women experienced side effects[6]. The difference might be resulted from the way the data were collected. The present study suggests that nifedipine is an alternative tocolytic agent that possesses good safety profile.

The present study had some limitations. Difference in dosage form, sterile injection versus oral capsule, resulted in clinician preference of terbutaline injection, as it was easier for dosage adjustment than the other. Some obstetricians were not familiar with treating preterm labor with nifedipine, and thus, not too aware on its safety. The safety profile of nifedipine at least seems to be comparable to that of terbutaline even if it was potentially over-reported.

The safety of nifedipine was comparable with that of terbutaline as tocolytic agents, while the efficacy should be studied in more pregnancies.

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ความปลอดภัยและประสิทธิภาพของยารับประทาน nifedipine กับยาฉีด terbutaline สำหรับรักษาภาวะเจ็บครรภ์คลอดก่อนกำหนด

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วัตถุประสงค์: เปรียบเทียบความปลอดภัยและประสิทธิภาพของยารับประทาน nifedipine กับยาฉีด terbutaline ในการรักษาภาวะเจ็บครรภ์คลอดก่อนกำหนด

วัสดุและวิธีการ: ทำการศึกษาในหญิงตั้งครรภ์เดี่ยวอายุครรภ์ 24-36 สัปดาห์ (กลุ่มละ 20 คน) ได้รับยาโดยวิธีสุ่ม กลุ่ม nifedipine รับประทานยาครั้งแรก 10 มก. กัดเม็ดยาแตกก่อนกลืน สามารถรับประทานเพิ่มครั้งละ 10 มก. ทุก 20 นาที ขนาดสูงสุด 40 มก. ใน 1 ชั่วโมงแรก ตามด้วย 20 มก. ทุก 4 ชั่วโมง จนครบ 72 ชั่วโมง ส่วนกลุ่ม terbutaline ได้รับยาโดยหยดเข้าเส้นเลือดดำด้วยอัตรา 10 μg/min ปรับเพิ่มครั้งละ10 μg/min ทุก 10 นาที จนครบ 1 ชั่วโมง ได้อัตราสูงสุด 25 μg/min เมื่อมดลูกหยุดหดรัดตัว 2-6 ชั่วโมง เปลี่ยนเป็นฉีดเข้าใต้ผิวหนัง ครั้งละ 0.25 mg ทุก 4 ชั่วโมง จนครบ 24 ชั่วโมง ผลลัพธ์หลักด้านความปลอดภัย คือ ค่าความดันโลหิต diastolic ที่เปลี่ยนแปลงจากค่าเริ่มต้นวัดที่ 1 ชั่วโมงหลังการให้ยา (ΔDBP_{1hr}) เปรียบเทียบความแตกต่างระหว่างกลุ่มที่ระดับนัยสำคัญ 0.05 ผลลัพธ์รองได้แก่ ผลลัพธ์ด้านประสิทธิภาพคือเลื่อนการคลอดออกไปมากกว่า 48 ชั่วโมง และ 7 วัน ผลไม่พึงประสงค์อื่น ๆ และผลลัพธ์การคลอด

ผลการศึกษา: พบมารดากลุ่ม nifedipine 11 ราย (55%) ที่พิจารณาว่าล้มเหลวในการรักษาเมื่อสิ้นสุด 1 ชั่วโมงแรก เปลี่ยนไปใช้ยาฉีด terbutaline เนื่องจากทนอาการข้างเคียงไม่ได้ 3 ราย มดลูกยังมีการหดรัดตัว 8 ราย ΔDBP_{1hr} (mean $\pm$ SD) ในกลุ่ม terbutaline ลดลงมากกว่ากลุ่ม nifedipine มารดาที่เกิดภาวะความดันโลหิตต่ำ มีค่าความดันโลหิต $\leq$ 90/60 mmHg ในกลุ่ม nifedipine พบ 1 ราย กลุ่ม terbutaline พบ 2 ราย พบการคลอดเลื่อนไปมากกว่า 48 ชั่วโมง และ 7 วัน ตามลำดับ ดังนี้ กลุ่ม nifedipine 17 ราย และ 14 ราย และกลุ่ม terbutaline 15 ราย และ 12 ราย ซึ่งไม่แตกต่างกันทางสถิติ พบมารดามีอาการไม่พึงประสงค์อย่างน้อย 1 อย่าง ในกลุ่ม nifedipine 15 ราย กลุ่ม terbutaline 20 ราย มารดาในกลุ่ม terbutaline มีอัตราการเต้นหัวใจที่ 1 ชั่วโมงหลังเริ่มให้ยาเพิ่มขึ้นมากกว่ากลุ่ม nifedipine ติดตามผลลัพธ์การคลอดได้ครบในกลุ่ม nifedipine แต่กลุ่ม terbutaline ติดตามได้ 16 ราย พบการคลอดที่อายุครรภ์ > 37 สัปดาห์ กลุ่มละ 6 ราย กลุ่มได้รับ terbutaline ทารกมีเลือดออกในโพรงสมอง 3 ราย อายุครรภ์ที่คลอดคือ 25, 29 และ 37 สัปดาห์ 1 ใน 3 มีสาเหตุเกี่ยวข้องกับการ บาดเจ็บจากวิธีการคลอด

สรุป: ยารับประทาน nifedipine มีความปลอดภัยและประสิทธิภาพพอ ๆ กับยาฉีด terbutaline ในการรักษาภาวะเจ็บครรภ์คลอดก่อนกำหนด