Comparison of the efficacy and adverse effects of nifedipine and indomethacin for the treatment of preterm labor

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ABSTRACT

Objective: To compare the effectiveness and adverse effects of nifedipine versus indomethacin in the treatment of preterm labor. Methods: In a randomized clinical trial, 79 women with labor pain at 26–33 weeks of gestation were treated with either oral nifedipine (n = 40) or rectal indomethacin (n = 39). Results: Twenty-five (50%) women in the indomethacin group, and 10 (25%) in the nifedipine group did not respond to treatment (P = 0.002). None of the 16 and 30 women remaining in the indomethacin and nifedipine groups, respectively, delivered during the subsequent 48 hours. Of these remaining women, 1 (6.25%) in the indomethacin group and 4 (13.3%) in the nifedipine group delivered between 48 hours and 7 days (P = 0.162). For the women who responded to treatment, the mean gestational age at time of delivery was 238.5 ± 19.4 days and 246.4 ± 15.4 days in the nifedipine and indomethacin groups, respectively (P = 0.184). Conclusion: Indomethacin was less effective than nifedipine for the fast treatment of preterm labor. For women who responded to treatment within 2 hours, however, the delaying of delivery by indomethacin was similar to that by nifedipine.

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1. Introduction

Preterm labor is an important obstetric problem and is the main cause of neonatal mortality and morbidity, even in developed countries [1,2]. Spontaneous preterm labor is the cause of about a third of preterm births [3] and is defined as the onset of labor pain before the completion of 37 weeks of pregnancy. This constitutes approximately 30%–45% of preterm births [4] in different populations, and is the cause of approximately two-thirds of mortalities in the first year of life [4,5]. The incidence of neonatal morbidity, whose main cause is prematurity of different organs, increases in infants born before 37 completed weeks of pregnancy as compared with term infants [6].

With respect to these problems, the management of spontaneous preterm labor has special importance, and many studies have been carried out using different methods of treatment based on various suggested etiologies [7]. So far, no tocolytic drug provides perfect and complete efficacy with no complications; in addition, tocolysis differ in their specific effect on the uterus, adverse effects and efficacy [8].

Nifedipine and indomethacin are among the best treatment options for spontaneous preterm labor. Nifedipine, which is a calcium channel blocking agent [49], has been suggested for inhibition of labor since the late 1970s, and has been reported as an effective treatment for preterm labor in different studies [8,10,11].

Prostaglandin inhibitors such as indomethacin have also been considered as a treatment for preterm labor. Zuckerman et al. [12] used indomethacin as a tocolytic for the first time in 1974. Indomethacin may induce its effect by inhibiting the prostaglandin synthesis [13]. Although indomethacin has been evaluated as a tocolytic more than any other anti-prostaglandins, it seems that—because of its neonatal adverse effects after prolonged use—it has a limited success rate [13]. With better recognition of the safety limitations, however, there has been a renewed interest in using indomethacin for acute tocolysis [14].

Indomethacin is administered by an oral or rectal route. A dose of 50–100 mg is given at 8-hour intervals, not exceeding a total dose of 200 mg in 24 hours [4]. Serum concentration usually reaches a peak 1–3 hours after oral administration, whereas levels after rectal use peak slightly sooner. In 1 study, short-term indomethacin therapy did not show any significant effect on amniotic fluid volume [15]. A meta-analysis that evaluated the safety of indomethacin for neonates reported no increased risk for neonatal complications [16], and its prolonged use has been reported to be associated rarely with ductus arteriosus constriction and oligohydramnios [17].

It has been estimated that about 73 000 women in the United States received tocolytics during 2006 [4]. Considering this number, the safety aspect, and the expense (all of which are important), nifedipine and indomethacin have both been suggested as a drug of choice for preterm labor on the basis of a cost-decision analysis [18].

To our knowledge, there are no published studies of a comparison between indomethacin and nifedipine in terms of effectiveness and complications. The aim of the present study was, therefore, to compare...
directly the efficacy and safety of indomethacin and nifedipine for the treatment of preterm labor.

2. Materials and methods

The present randomized clinical trial was performed at Akbarabadi Teaching Hospital, Tehran, Iran, between May 21, 2008, and March 29, 2009. Women who presented at the hospital with preterm labor were considered for the study. The inclusion criteria were nulliparity, gestational age between 26 and 33 weeks (according to reliable last menstrual period and ultrasound confirmation of first trimester), uterine contractions with a frequency of 4 per 20 minutes or 8 per 60 minutes, cervical dilatation of 1 cm or more, and cervical effacement of 50% or more.

The exclusion criteria were multi-fetal pregnancy, rupture of membranes, vaginal bleeding, fetal death, fetal distress and intra-uterine growth retardation, trauma, cervical dilatation of 4 cm or more, systemic disorders and preeclampsia, known uterine anomalies (according to history and ultrasound), smoking, history of any drug use except ordinary supplements, polyhydramnios and oligohydramnios, fetal anomalies, any suspicious intrauterine infection according to vital signs and maternal condition or fetal tachycardia, previous use of tocolytic during the present pregnancy, blood pressure less than 90/50 mm Hg, and women whose continuation of pregnancy would be dangerous for them.

Written consent was obtained from all participants, who were fully informed about the study. Approval from the Institutional Review Board and Institutional Ethics Committee was given for the study, which was also registered with the Iran Registry of Clinical Trials (IRCT).

Eligible participants were randomly assigned to 1 of 2 groups to receive either nifedipine or indomethacin treatment by a 4-part, block random approach using sealed, sequentially distributed envelopes to which the letters A, B, C, and D had been allocated. Letters A and C corresponded to the nifedipine group, and letters B and D corresponded to the indomethacin group. Each patient chose an envelope, which was opened by the investigator, and treatment was given accordingly.

One investigator performed all examinations and drug administration. Because the shape and route of administration of the 2 drugs were different (nifedipine orally and indomethacin rectally), the study could not be performed blind, but the investigators assessing the outcome were blind to group assignment.

In the nifedipine group (n=42), 10 mg (1 capsule) of nifedipine (Zahravi, Tabriz, Iran) was prescribed every 20 minutes up to a maximum of 4 doses. In women whose contractions had subsided, 20 mg (2 capsules) was prescribed every 6 hours for the first 24 hours; 20 mg every 8 hours for the second 24 hours; and lastly, 10 mg every 8 hours for the next 24 hours (total duration of treatment, 3 days). For women with continued contractions or blood pressure less than 90/50 mm Hg, administration of nifedipine was discontinued [9].

In the indomethacin group (n=40), 100 mg (1 suppository) of indomethacin (Abureihan, Tehran, Iran) was administered rectally; if contractions continued, a repeat dose of 100 mg was prescribed 1 hour later. The maximum dose was 200 mg daily (total duration of treatment, 2 hours) [4].

In both groups, 12 mg of betamethasone every 24 hours was prescribed up to 48 hours to accelerate fetal lung maturity [4]. Blood pressure was monitored before nifedipine administration, every 15 minutes after prescription for up to 2 hours, and then every 4–6 hours. Uterine contractions were monitored every 15 minutes in the first 2 hours, and then every 4–6 hours. Efficacy was defined as cessation of contractions for the first 2 hours.

The delaying of delivery for up to 48 hours or up to 7 days was also recorded. If patients had contractions after 2 hours of the initiation of tocolytic treatment, the drug was considered to have failed and another tocolytic treatment was started. Adverse effects of the drugs (including hypotension, tachycardia, skin rash, intestinal symptoms, headache, dizziness, and dyspnea) were also recorded. All women were followed up until delivery.

A sample size of 25 women in each group was considered sufficient for the study (α=0.05, 1–β=80%). Data were analyzed using SPSS version 13 (SPSS, Chicago, IL, USA). The t test, χ² test, and Mann–Whitney U test were used for analysis. P<0.05 was considered to be statistically significant.

3. Results

For 2 women, nifedipine was discontinued because of hypotension; as a result, 40 women in the nifedipine group and 39 women in the indomethacin group completed the study. Among the 2 groups, there were no significant differences in age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), gestational age at the time of enrollment, initial cervical dilatation, or cervical effacement or consistency (Table 1).

After 2 hours, 23 women (59%) in the indomethacin group and 10 women (25%) in the nifedipine group had not responded to treatment, and their uterine contractions continued (P=0.002). None of the 16 women remaining in the indomethacin group or the 30 remaining in the nifedipine group delivered for up to 48 hours. Therefore, in patients in whom indomethacin stopped contractions for the first 2 hours, the effect of the drug was sustained for the next 48 hours and was not significantly different from the effect of nifedipine (Table 2).

Of the 16 and 30 remaining women, respectively, 1 (6.3%) in the indomethacin group and 4 (13.3%) in the nifedipine group delivered between 48 hours and 7 days (P=0.162) (Table 2). The mean gestational age at the time of delivery (for women who responded to treatment during the first 2 hours) was 238.5±19.4 days and 246.4±15.4 days in the nifedipine and indomethacin groups, respectively (P=0.182) (Table 2).

Overall, 17 women (42.5%) in the nifedipine group and 11 women (28.2%) in the indomethacin group showed adverse effects (P=0.184) (Table 3). In the nifedipine group, 2 women (5%) had intolerance (blood pressure was monitored before nifedipine administration, every 15 minutes after prescription for up to 2 hours, and then every 4–6 hours. Uterine contractions were monitored every 15 minutes in the first 2 hours, and then every 4–6 hours. Efficacy was defined as cessation of contractions for the first 2 hours.

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Overall, 17 women (42.5%) in the nifedipine group and 11 women (28.2%) in the indomethacin group showed adverse effects (P=0.184) (Table 3). In the nifedipine group, 2 women (5%) had intolerance (blood
pressure <90/50 mm Hg, causing serious patient discomfort) to treatment as compared with none in the indomethacin group. In the nifedipine group, 2 women (5.1%) had rectorrhagia (which recovered spontaneously without any treatment). There were 2 (5.1%) neonatal deaths (owing to prematurity and respiratory distress syndrome) in the indomethacin group, but none in the nifedipine group (P = 0.4).

When the 2 groups were subdivided according to whether the participants responded to treatment, there were no significant differences in age, gestational age, BMI, or cervical dilatation (Table 4).

### 4. Discussion

In the present study, nifedipine was found to be superior to indomethacin for arresting uterine contractions during the first 2 hours; for those patients who responded to indomethacin in the first 2 hours, however, there was no significant difference between indomethacin and nifedipine in delaying delivery for up to 48 hours or up to 7 days. In addition, there was no significant difference in the mean gestational age at time of delivery among patients who responded to treatment during the first 2 hours.

It seems that if indomethacin can stop uterine contractions, its effect can be continued. Therefore, the present study may suggest the following treatment protocol: indomethacin could be administered initially as an indomethacin challenge test (owing to its shorter duration of treatment and fewer adverse effects) for all patients with preterm labor in order to differentiate between those patients who are refractory to indomethacin and need nifedipine, and those who respond to indomethacin. For the former group of patients, nifedipine treatment should then be started. Such a protocol takes into consideration the fact that the total duration of nifedipine administration is longer and that nifedipine has more adverse effects than indomethacin. In fact, indomethacin could be used to identify those women who require nifedipine; however, further studies are necessary to verify this idea.

At present, controversies remain on the options for treating preterm labor [19]. It seems that β-mimetic agents are being phased out gradually and that nifedipine, which is more effective and has fewer adverse effects, is being used instead [2,19]. Documents showing the effectiveness of magnesium sulfate as a tocolytic agent are questionable [2,19,20]. Another tocolytic, atosiban, which is an oxytocin antagonist and effective drug with few adverse effects [2,10], is expensive, does not have Food and Drug Administration (FDA) approval, and is not accessible in all countries of world (e.g. Iran) [18,19]; there is also insufficient information about its effects on neonatal mortality and morbidity. Prostaglandin inhibitors are among other agents suggested for the treatment of preterm labor. Although indomethacin has been shown to be effective [4,20], it should be used only for short durations owing to fetal safety.

The above reports suggest that there is no obvious first-line tocolytic. On the basis of cost, both nifedipine and indomethacin should be the first choice [18]. In addition, a meta-analysis of 19 clinical trials [18] found that the incidence of adverse effects was 57.9% for terbutaline, 22% for magnesium sulfate, 27.2% for nifedipine, and 11.4% for indomethacin. Therefore, it seems that the last 2 agents have the fewest adverse effects, a finding that is compatible with the present study.

Studies have shown the efficacy of indomethacin for delaying delivery for up to 48 hours; however, its safety has been questioned. One study in 1993 concluded that indomethacin as a treatment for preterm labor was related to serious adverse effects in neonates who were born before 30 weeks of pregnancy [21]. Another study reported that in preterm neonates with patent ductus arteriosus, and whose mothers had received indomethacin for tocolysis, there was an increased need for surgical ligation of patent ductus arteriosus [22]. By contrast, other studies have concluded that prolonged use of indomethacin is associated rarely with oligohydramnios and ductus arteriosus constriction [15,17].

A meta-analysis of 46 studies on the adverse effects of indomethacin reported that, overall, there was no significant risk of indomethacin in terms of adverse effects; however, more randomized trial studies with better statistical power should be performed to reach a final conclusion [16]. In the present study, the adverse effects of indomethacin were not serious. Indomethacin was not found to be effective for preventing preterm birth in women with cervical dilatation in the second trimester [23]; in addition, its administration in women who had an indication for cerclage on the basis of ultrasound examination did not reduce the incidence of spontaneous preterm birth [24].

By contrast, an analysis that assessed 10 studies on the efficacy of indomethacin for treating preterm labor concluded that cyclooxygenase inhibitors such as indomethacin could reduce preterm births before 37 weeks of gestation, increase in gestational age at time of delivery, and birth weight [25]. In addition, the incidence of a maternal drug reaction requiring cessation of treatment was low. However, better-designed clinical studies are needed to confirm these results.

In conclusion, the results of the present study indicate that indomethacin might be considered an effective, low-cost, and safe treatment for preterm labor, but further comparative studies should be carried out regarding the use of nifedipine and indomethacin.

### Acknowledgments

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### Conflict of interest

The authors have no conflicts of interest.

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**Table 3**

Adverse effects among the participants.

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Nifedipine group (n = 40)</th>
<th>Indomethacin group (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3 (7.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9 (22.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>3 (7.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>0 (0.0)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Rectal irritation</td>
<td>0 (0.0)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Rectorrhagia</td>
<td>0 (0.0)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Intolerance</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>17 (42.5)</td>
<td>11 (28.2)</td>
</tr>
</tbody>
</table>

*Values are given as number (percentage).*

---

**Table 4**

Characteristics of women according to response to treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Response</th>
<th>Nifedipine group (n = 40)</th>
<th>Indomethacin group (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Yes</td>
<td>24.5 ± 4.9</td>
<td>24.5 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>25.6 ± 6.2</td>
<td>24.2 ± 5.6</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>Yes</td>
<td>30.8 ± 2.3</td>
<td>30.8 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>31.0 ± 3.2</td>
<td>30.7 ± 1.7</td>
</tr>
<tr>
<td>BMI</td>
<td>Yes</td>
<td>27.5 ± 2.5</td>
<td>27.9 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27.1 ± 1.5</td>
<td>26.2 ± 5.9</td>
</tr>
<tr>
<td>Cervical dilatation, cm</td>
<td>Yes</td>
<td>1.7 ± 0.7</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2.0 ± 0.7</td>
<td>2.0 ± 0.6</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

*Values are given as mean ± SD unless otherwise indicated.*
References


