Atosiban and nifedipin for the treatment of preterm labor

M. Kashanian a,*, A.R. Akbarian b, M. Soltanzadeh a

a Iran University of Medical Sciences and Health Services, Department of Obstetrics and Gynecology, Akbar Abadi Teaching Hospital, Tehran, Iran
b Iran University of Medical Sciences and Health Services, Department of Obstetrics and Gynecology, Hazrat Rasool Hospital, Tehran, Iran

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Abstract

Objective: To perform a comparison between atosiban (oxytocin antagonist) and nifedipin (calcium channel blocker) for acute treatment of preterm labor and their maternal safety. Methods: A randomized controlled trial study was performed on 80 pregnant women with preterm labor, between 26 and 34 weeks of pregnancy, in Akbar Abadi Teaching Hospital in Tehran, Iran. 40 women (the atosiban group) were compared with another 40 women (the nifedipin group) for the drugs’ efficacy in delaying delivery for more than 48 h in order to undergo steroid therapy, and for more than 7 days or more, and also to assess their maternal safety. The duration between the drugs’ administration and delivery were compared. The statistical analysis was performed using the Statistical Package for Social Science (SPSS). Results: There was no statistically significant difference between the two groups in the treatment of preterm labor. Atosiban was effective in 82.5% of cases, and nifedipin in 75% of the cases ($p=1.000$), for delaying delivery for more than 48 h. Atosiban was effective in 75% of the cases, and nifedipin in 65% of the cases, for delaying delivery for more than 7 days. The maternal side effects in the atosiban group were 17.5%, and in the nifedipin group they were 40%, which had a statistically significant difference ($p=0.027$). The duration between treatment and delivery was 29.03 $\pm$ 16.12 days in the atosiban group and 22.85 $\pm$ 13.9 days in the nifedipin group with no statistically significant difference ($p=0.79$). Conclusion: Atosiban is an effective and safe...
1. Introduction

Preterm labor is one of the complications of pregnancy, and finding a safe and also effective method for its treatment has been continually under investigation [1].

Atosiban, which is an oxytocin–vasopressin competitive antagonist, was recently used for the treatment of preterm labor [2,3] and was able to inhibit the uterine contractions. In the studies performed, it was observed that atosiban has the same efficacy as other tocolytics, but had lower side effects [4–7].

The plasma concentration of atosiban reaches a steady state 1 h after the beginning of its infusion. Its half-life is about 18 ± 3 min; therefore, after finishing the infusion, its plasma concentration decreases rapidly [8]. During the first 3 h of treatment, the number of contractions decreases by about 75%. The predicted side effects include; nausea, vomiting, headaches and chest pains [8].

Another good and safe method of treatment for preterm labor is nifedipin [9,10], which is a calcium channel blocking agent [11,12] and inhibits the contractions by decreasing the calcium concentration. Its main side effect is hypotension, which may cause a decrease in utero-placental perfusion [11]. After oral administration, 90 percent is absorbed rapidly through the gastrointestinal tract, and maximum serum concentration is obtained within 30–120 min. After sublingual administration, a lowering effect on the blood pressure is reached after 5 min. The main side effects include; headaches, syncope, weakness, dizziness, hypotension and palpitations [11].

The objective of this study is to compare between atosiban and nifedipin in the acute treatment of preterm labor and their maternal complications.

2. Materials and method

This study has been performed as a randomized controlled trial in Akbar Abadi Teaching Hospital in Tehran, Iran, between March 2002 and February 2003.

A sample size of 40 in each group \( \alpha = 0.05, \beta = 0.20, \) P1 (atosiban) = 0.8, P2 (nifedipin) = 0.5 [13] was randomly selected (4-part, ABCD, block-random allocation was used), the main outcome being to delay delivery for more than 48 h in order to undergo steroid therapy. In one group (40 women) nifedipin (NIFEDIPIN; Zahravi, Tabriz, Iran) and in the other (40 women) atosiban (TRACTOCILE; Ferring, pharmaceuticals, A/S, Copenhagen, Denmark) was administered. Because the two drugs are completely different in shape and form a blind study was not an option. The inclusion criteria for research were:

1. Gestational age between 26 and 34 weeks of pregnancy, which had been documented by a definite LMP and sonography in the first trimester.
2. Contractions occurring at a frequency of four in 20 min or eight in 60 minutes, and a cervical dilatation of 1 cm or greater and cervical effacement of 50% or more [11]. Patients with PROM, vaginal bleeding, fetal death or fetal distress, IUGR, a history of trauma, a cervical dilatation greater than 3 cm, systemic disorders of the mother, a known uterine anomaly (by history or sonography), and a blood pressure of less than 90/50 mmHg were excluded.

All vaginal examinations and drug administration were performed by the same investigator, and written informed consent was obtained from all participants.

At first in the atosiban group, a urine analysis was done in order to measure the specific gravity because of the possible anti-diuretic effect of atosiban, and then atosiban was administered at a rate of 300 \( \mu \)g/min [4] by venous infusion via microset, 48 drops [14]. Atosiban was continued for a maximum of 12 h, or 6 h after the patient’s contractions ceased. Maintenance tocolytics were not employed in either group. If contractions continued without any changes and the dilatation of cervix improved, the drug was discontinued and it was noted as a failure of the treatment. During this period the urine output was measured, and also the fluid intake recorded. In addition, after finishing the protocol another urine analysis for specific gravity was performed.
In the nifedipin group the initial dose was 10 mg (one capsule) sublingually every 20 min for four doses. If the contractions were inhibited, nifedipin was continued orally (20 mg) every 6 h for the first 24 h, and then every 8 h for the following 24 h, and finally 10 mg every 8 h for the last 24 h. If the contractions continued and the dilatation of the cervix progressed, or the blood pressure decreased below 90/50 mmHg, the use of nifedipin was discontinued [9,10].

During this period, patients were monitored for uterine contractions and also for any possible side effects. Corticosteroids in the form of dexamethasone was administered intramuscularly, 5 mg every 12 h for 48 h in both groups, and then all patients were monitored for the evaluation of the tocolytic’s effects.

If the presence of any severe side effects were observed, the drug’s administration was discontinued. Although the main outcome was to delay delivery for more than 48 h, all patients were checked until the delivery, and interval between the treatment and delivery, was also recorded. Because some of patients did not give birth in this hospital, and the date of delivery were checked by telephone, it was not possible to evaluate the neonates precisely. Therefore, the neonatal safety was not considered in the present study. The statistical analysis was performed using the Statistical Package for Social Science (SPSS Chicago, IL).

The $\chi^2$ test was used to compare the categorical variable where appropriate. Unpaired Student’s $T$ tests were used to compare the continuous variables with normal distribution.

3. Results

There were no statistically significant differences between the maternal age, parity, twin pregnancy or not, gestational age, history of preterm delivery, cervical dilatation and cervical effacement at the beginning of the treatment, the duration of uterine contractions, and the number of contractions in the two groups.

In 33 cases (82.5%) of the atosiban group and 30 cases (75%) of the nifedipin group, delivery was delayed for 48 h; there was no statistically significant difference between them. In 3 cases (7.5%) of the atosiban group and 4 cases (10%) of the nifedipin group, delivery occurred between 48 h and 7 days after treatment, which did not have a significant difference. In 7 cases (17.5%) in the atosiban group and 10 cases (25%) in the nifedipin group, they did not respond to treatment, and delivery occurred in less than 48 h; again there was no significant difference between them (the mean interval between the beginning of treatment and delivery was $12.25 \pm 8.09$ h in the atosiban group and $8.78 \pm 3.67$ h in the nifedipin group). In patients with response to treatment, the mean interval between the beginning of treatment and delivery in the atosiban and nifedipin group was $29.03 \pm 16.12$ and $22.85 \pm 13.9$ days, respectively, with no significant difference (Table 1). There were side effects in 7 cases (17.5%) in the atosiban group and in 16 cases (40%) in the nifedipin group, with a statistically significant difference ($p = 0.027$, Table 2).

The mean urine specific gravity before and after the treatment of the atosiban group was $1016.17 \pm 5.32$ and $1020.06 \pm 5.83$, respectively, with a statistically significant difference ($p = 0.05$), which means that the S.G. before treatment was less than that after treatment, but these changes of S.G. were in the normal range [15]. The mean urine output in patients in the atosiban group was $46.6 \text{ cm}^3/\text{h}$.

4. Discussion

In this study atosiban has been compared with nifedipin for the treatment of preterm labor. To the
best of our knowledge, this is the first direct comparison between atosiban and nifedipin.

According to the results of this study the efficacy of both medications was the same, but the adverse effects of nifedipin were significantly more than atosiban.

Coomarasamy et al. [16] compared atosiban with nifedipin for the treatment of preterm labor. In this meta-analysis nine randomized controlled trial studies on the comparison between nifedipin versus beta antagonists and four randomized clinical trial studies on the comparison between atosiban and beta agonists were evaluated. However, there was no study that directly compared atosiban with nifedipin, therefore previous studies are indirect.

This study showed that two drugs had good efficacy, but nifedipin tocolysis was associated with a significant reduction in respiratory distress syndrome, compared with atosiban, and increased the number of women whose delivery was delayed by 48 h, although the result was not statistically significant. They concluded that when indirectly compared with atosiban, nifedipin is more effective. It would point to the fact that direct studies comparing the two drugs should be performed.

In an RCT study which was performed by Moutquin et al. [5], atosiban was compared with ritodrin for the treatment of preterm labor. In this study, in agreement with the present study, the success rate (delaying delivery for 48 h) was 84.9% for atosiban and 86.8% for ritodrin, without a significant difference, but the side effects of atosiban were significantly lower than ritodrin. Also in another study by Goodwin et al. [4], delaying delivery for 48 h using atosiban was 70.5% effective and the side effects, including, nausea, vomiting, headaches, and chest pain, were mild and tolerable.

In one study [7], atosiban has been used as a maintenance treatment for reducing the preterm labor attacks (after one course of treatment with atosiban for inhibiting the acute attack of preterm labor) and has been compared with a placebo. The mean interval between the drug’s administration until the first recurrence of preterm labor in the atosiban group was significantly higher than the placebo, and the side effects were similar. In the present study, atosiban has not been used as a maintenance treatment, and it is suggested that it be used in this way in a further study.

In one study [17] in which atosiban was compared with terbutaline, both drugs had the same efficacy, but the side effects of terbutaline were more than those of atosiban. The comparison between atosiban and salbutamol [18] showed that their efficacy was similar, but the neonatal and maternal side effects of atosiban were less than salbutamol.

Richter et al. [19], used atosiban for the treatment of preterm labor before 24 weeks of gestation, and compared it with a placebo (between 18 and 24 weeks).

In this study atosiban was more effective than the placebo, and also the side effects were mild and tolerable. They concluded that this drug is effective and safe even used on a lower gestational age.

Atosiban also has been used for the treatment of uterine hyperactivity in the active phase of labor [20], and was effective and well tolerated by the patients, and also the abnormal pattern of FHR recovered after its administration. Another study has been performed by Afshar et al. [21] comparing between atosiban and hexoprenaline for the treatment of fetal distress during labor in order to perform intrauterine resuscitation. Both drugs inhibited contractions well and the fetal distress was recovered, but the side effects of atosiban were less than hexoprenaline. Moreover, as soon as the drug was discontinued, contractions returned faster than with hexoprenaline, suggesting that atosiban is a suitable option for tocolysis during labor in order to relieve fetal distress.

Regarding atosiban’s lower side effects in comparison with other tocolytics, Tsatsaris et al. [3] concluded that atosiban is a drug of choice for the treatment of preterm labor, especially in patients who are at risk from the cardiovascular effects of these drugs, such as multifetal pregnancies and cardiac disease during pregnancy.

Based on the findings of the present and previous studies, it is recommended to carry out more trials with a sample size large enough to find out the ideal method for the treatment of preterm labor, which would be more conclusive.

References


