Atosiban Versus Nifedipin for the Management of Preterm Labor: A Prospective Study

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Abstract

Objective: This study to compare the effectiveness and the safety of atosiban (oxytocin antagonist) and nifedipin (calcium channel blocker) as a tocolytic agent in preterm labor.

Patients and Methods: This prospective randomized controlled study was performed in the Department of Obstetrics and Gynecology, Sharurah Armed forces Hospital (SAFH), Saudi Arabia. It involved one hundred and twenty pregnant women diagnosed with preterm labor at 24-34 gestational weeks from March 2012 to August 2013. They were randomized to receive Atosiban intravenously (n=60) or Nifedipin orally (n=60) as a tocolytic. The two groups compared for effectiveness in delaying delivery for more than 48h in order to undergo steroid therapy, and also to assess their maternal safety.

Results: There was no statistically significant difference between the two groups in the effectiveness in treatment of preterm labor. Atosiban was effective in 81.7% of cases, and nifedipin in 75.0% of the cases (p-value=1.000), for delaying delivery for 48h. 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 18.3%, and in the nifedipin group they were 40%, which had a statistically significant difference (p<0.001). The duration between treatment and delivery was 31.06±16.12 days in the atosiban group and 24.61±14.6 days in the nifedipin group with no statistically significant difference (p=0.79).

Conclusion: Both Atosiban and Nifedipin are effective in treatment ofpreterm labour with a comparable effectiveness, but atosiban with less side effects and can be used in patients with heart diseases, and patients with multifetal pregnancy with minimal adverse effects.

Key Words: Atosiban — Nifedipin — Preterm labor.

Introduction

PRETERM delivery is defined by a birth occurring before 37 weeks of gestation or before 259 days from the last menstrual period. Prematurity is multifactorial and its incidence has increased during the last decade in most occidental countries, probably due to increased risk factors responsible for elective prematurity [1-3].

The mechanisms for preterm labour are still unclear. It could be associated either with a premature activation of the physiological contracting process or with a pathological factor responsible for uterine contractions, leading to preterm delivery [1-3].

Premature birth is responsible for between 75 and 90% of neonatal mortalities, not due to congenital anomalies, and is also responsible for up to 50% of cases of neurodevelopment disability [4]. The majority of cases of adverse outcome occur in those cases under 34 weeks' gestation. There is now growing evidence that the moderately preterm group (delivered between 32 and 37 weeks) are also at increased risk of infant death [5,6].

Finding a safe and also effective method for the treatment of preterm labour has been continually under investigation [7]. Atosiban, which is an oxytocin-vasopressin competitive antagonist, was recently used for the management of preterm labor [8,9] and was able to inhibit the uterine contractions. In the new studies performed, it was noticed that atosiban has the same efficacy as other tocolytics, but had lower side effects [10-13]. The plasma concentration of atosiban reaches a steady state 1 h after the beginning of its infusion. Its half-life is about 18±3min; therefore, after finishing the infusion, its plasma concentration decreases rapidly [14]. During the first 3h of treatment, the number of contractions decreases by about 75%. The predicted side effects include; nausea, vomiting, headaches and chest pains [14].
Atosiban is widely used in clinical practice because of its low side effects profile [15,16]. A German meta-analysis based on 6 randomized trials, among them 3 double blind studies, confirmed a similar tocolytic action for atosiban and β3 adrenergic receptor agonists. A significantly low incidence of adverse effects is reported. Moreover, a lower cost saving in terms of hospital length and extra tests for excluding morbidity causes is found for the atosiban treated patients when compared to continuous fenoterol administration controls [17].

Another good and safe method of treatment of preterm labor is nifedipin [18,19], which is a calcium channel blocker [20,21] and inhibits the uterine contractions by inhibiting the sliding of actin over myosin in the myometrial cell membrane. Its main side effect is hypotension, which may lead to decrease in uteroplacental perfusion [20]. After oral administration, 90 percent is absorbed rapidly through the gastrointestinal tract, and maximum serum concentration is observed within 30-120min. The main side effects of nifedipin include; headaches, syncope, weakness, dizziness, hypotension and palpitations [20].

Nifedipin is the most commonly used drug for preterm labor inhibition at a daily dose of 30-60mg daily [22]. A Cochrane Database review met analysis published in 2003, reported a decreased number of deliveries within 7 days following treatment and also, a reduced incidence of neonatal respiratory distress syndrome [23]. These data confirm that nifedipin is an efficient tocolytic agent, with an easy oral route of administration, few side effects, and a low neonatal complications rate. However, it should be used with caution in patients with compromised cardiovascular condition as they may be at risk of pulmonary edema and cardiac failure [15].

The objective of this study is to compare the effectiveness and the safety of atosiban (oxytocin antagonist) and nifedipin (calcium channel blocker) as a tocolytic agent in preterm labor.

**Patients and Methods**

This prospective randomized controlled study was performed in the Department of Obstetrics and Gynecology; Sharurah Armed forces Hospital (SAFH), Saudi Arabia. It involved one hundred and twenty pregnant women diagnosed with preterm labor at 24-34 gestational weeks from March 2012 to August 2013. They were randomized to receive Atosiban intravenously (n=60) or Nifedipin orally (n=60) as a tocolytic. The two groups compared for effectiveness in delaying delivery for more than 48h in order to undergo steroid therapy, and also to assess their maternal safety.

**The inclusion criteria for this study were:**
1- Contractions occurring at a frequency of four or more in 20 minutes.
2- Cervical dilatation of 0-3cm (in nulliparae) or 1-3cm (in multiparae) and cervical effacement of 50% or more.
3- Gestational age between 24 and 34 weeks of pregnancy, which had been confirmed by a reliable menstrual date and sonography in the first trimester [20].

**The exclusion criteria for this study were:**

- High order multiple pregnancy greater than twins, ruptured membranes, vaginal bleeding, severe pre-eclampsia or hypertension, fever (body temperature >37.5°C), fetal/placental abnormalities, serious maternal disease, any contraindication or hypersensitivity to any component of the study drugs, fetal death or fetal distress, IUGR, a history of trauma, a known uterine anomaly, and a blood pressure of less than 90/50mmHg.

All vaginal examinations and drug administration were done by the same investigator, and written informed consent was obtained from all patients. Atosiban was administered at a rate of 300μg/min by venous infusion via micro set, 48 drops [10]. Atosiban was continued for a maximum of 12h, or 6h after the patient's contractions stopped. If the contractions continued and the dilatation of the cervix increased, or the blood pressure decreased below 90/50mmHg, the use of nifedipin was discontinued [18,19].

In the nifedipin group the initial dose was 10mg (one capsule) sublingually every 20min for four doses. If the contractions were ceased, nifedipin was continued orally (20mg) every 6h for the first 24h, and then every 8h for the following 24h, and finally 10mg every 8h for the last 24h. If the contractions continued and the dilatation of the cervix increased, or the blood pressure decreased below 90/50mmHg, the use of nifedipin was discontinued [18,19].

During this period, patients were observed for uterine contractions and also for any possible side effects. Corticosteroids in the form of dexamethasone were given intramuscularly, 6mg every 12h for 48h in both groups, and then all patients were observed for the evaluation of the tocolytic's effects. If severe side effects were observed, the drug's administration was discontinued. Although the
main outcome was to delay delivery for more than 48h, all patients were followed 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 verified by telephone, it was not possible to evaluate the neonates precisely. Therefore, the neonatal safety was not considered in the present study.

The \( x^2 \) 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.

**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 49 cases (81.7%) of the atosiban group and 45 cases (75%) of the nifedipin group, delivery was delayed for 48h; there was no statistically significant difference between them. In 4 cases (6.6%) of the atosiban group and 6 cases (10%) of the nifedipin group, delivery occurred between 48 h and 7 days after treatment, which did not have a significant difference.

In 11 cases (18.3%) in the atosiban group and 15 cases (25%) in the nifedipin group, they did not respond to treatment, and delivery occurred in less than 48h; again there was no significant difference between them (the mean interval between the beginning of treatment and delivery was 12.25±8.09h in the atosiban group and 8.78±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 31.06±17.11 and 24.61±14.6 days, respectively, with no significant difference (Table 1).

There were side effects in 11 cases (18.3%) in the atosiban group and in 24 cases (40%) in the nifedipin group, with a statistically significant difference (\( p<0.0001 \), Table 2).

In some patients, there were 2 or 3 side effects (Tachycardia, Hypotension, Palpitation) simultaneously, so total number of patients with side effects is 11 patients in Atosiban group and 24 patients in Nifedipin group.

<table>
<thead>
<tr>
<th>Response to treatment</th>
<th>Atosiban Group</th>
<th>Nifedipin Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Delivery in less than 2 days (48h)</td>
<td>11 (18.3)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Delivery from 2-7 days</td>
<td>4 (6.6)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Delivery after 7 days</td>
<td>45 (75)</td>
<td>39 (65)</td>
</tr>
</tbody>
</table>

Table (2): Maternal side effects after use of atosiban or nifedipin as a tocolytic agent.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Atosiban Group</th>
<th>Nifedipin Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0 (0)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0 (0)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.6)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Flank pain</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.6)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Tremors</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (1.6)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

**Discussion**

Medical treatment of preterm labor is of great importance regarding to the amount of neonatal death due to prematurity [24]. Nifedipin has a proven therapeutic effect as a tocolytic agent. However, due to lack of uterine specificity, nifedipin is associated with significant maternal side effects. A new therapeutic approach is the use of uterine specific Oxytocin receptor antagonists (Atosiban) [25].

In the previous studies the success rate of the pharmacologic substance, either Atosiban or nifedipin was not related to gestational age at treatment. To our opinion it could be of great importance in the choice of drug agent. Myometrial sensitivity to oxytocin increases with gestational age due to an upregulation of the oxytocin receptor, which has been demonstrated towards the end of pregnancy. This relative lack of oxytocin receptors earlier in pregnancy might contribute to a possibly reduced efficacy of Atosiban [26].

There are many possible interventions aiming to treat this multifactorial syndrome called preterm delivery. As described here, only some drugs have been proved to be effective on the contraction process, but there is no clear evidence of associated
improved neonatal outcome. Some drugs are used as first-line single therapy such as β3 adrenergic receptor agonists and atosiban in Europe [17].

In our study atosiban has been compared with nifedipin for the treatment of preterm labor. According to the results of this study the efficacy of both medications was similar, but the adverse effects of nifedipin were significantly more than atosiban.

Coomarasamy et al., [27] compared atosiban with nifedipin for the treatment of preterm labor. 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 48h, although the result was not statistically significant. They concluded that when indirectly compared with atosiban, nifedipin is more effective.

In a study performed by Moutquin et al., IIII, 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 48h) 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., [10], delaying delivery for 48h using atosiban was 70.5% effective and the side effects, including, nausea, vomiting, headaches, and chest pain, were mild and tolerable.

Valenzuela et al., [13] have been used atosiban 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 have been compared with a placebo. The mean interval between the drug’s administrations until the first recurrence of preterm labor in the atosiban group was significantly higher than the placebo. 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 a study done by European Atosiban Study Group [28] in which atosiban was compared with terbutalin, both drugs had the same efficacy, but the side effects of terbutalin were more than those of atosiban. The comparison between atosiban and salbutamol [29] showed that their efficacy was similar, but the neonatal and maternal side effects of atosiban were less than salbutamol.

Atosiban also has been used for the treatment of uterine hyperactivity in the active phase of labor [30], 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., [31] comparing between atosiban and hexoprenaline for the treatment of fetal distress during labor. Both drugs inhibited contractions well and the fetal distress was recovered, but the side effects of atosiban were less than hexoperenalin. Moreover, as soon as the drug was discontinued, contractions returned faster than with hexoperenalin, 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., [9] 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 during using these drugs, such as cardiac disease during pregnancy and multifetal pregnancies.

**Conclusion:**

Both Atosiban and Nifedipin are effective in treatment of preterm labour with a comparable effectiveness, but atosiban with less side effects and can be used in patients with heart diseases, and patient with multifetal pregnancy with minimal adverse effects.

**References**


