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ORIGINAL ARTICLE

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Tocolysis with atosiban: experience in the management of premature labor before 24 weeks of pregnancy

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Abstract *Objective*: Atosiban has been shown to be an effective tocolytic agent with a low rate of side effects during 24 to 33 weeks of gestation. Atosiban acts through selective, competitive inhibition of both oxytocin and vasopressin, so that there are reasons to assume that a tocolytic effect can also be achieved earlier in the pregnancy. *Study design*: In this prospective, randomized pilot study, 20 women in the 18th through 24th week of gestation who presented at our hospital with preterm labor were treated with atosiban. In the control group 20 women received saline infusions. All patients received antibiotic therapy. A cervical cerclage was performed when indicated as was correction of the vaginal pH. *Results*: The tocolytic effect began after 3–10 min (median: 6.5 min). Treatment time until the complete absence of contractions was 3–12 h (median: 7.5 h). Pregnancies were prolonged between 11.1 and 21.7 weeks (median: 15.6 weeks) in the atosiban group vs. 10.5–19.1 weeks in the control group. If well tolerated, atosiban was continued. There were no significant alterations in the routine laboratory parameters, circulation parameters, and fluid balance. *Conclusion*: In summary, atosiban showed itself to be effective for tocolytic treatment for premature labor, even during 18 and 24 weeks of pregnancy, while exhibiting its known, favorable profile of side effects.

Keywords Tocolytics · Atosiban · Pregnancy · Oxytocin receptor · Preterm labor

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Introduction

With regard to tocolytic effectiveness, atosiban (Tractocile, Ferring Arzneimittel GmbH, Kiel, Germany) has been shown to be equivalent to beta-mimetics in all previous comparative studies, while having a significantly more favorable side effect profile [22, 31, 38, 40]. As there is a chemical homology between oxytocin and atosiban, the mechanism of action can be explained by competitive inhibition of oxytocin at its receptor level [2, 5, 15]. Based on recent results, significantly more oxytocin receptors than previously assumed are expressed in the nonpregnant uterus as well as during early gestation [11, 12, 25, 27–29, 33]. The extent to which atosiban binds to the vasopressin V_{1A} receptor currently remains controversial [1, 3, 6, 7, 35, 37].

The gestational-related indication spectrum for tocolytic treatment with atosiban is oriented firstly, by previous findings in regard to the myometrial oxytocin receptor density in the pregnant uterus [9–11, 19, 20, 26] and, second, by recent advances in neonatal intensive care that allow the survival of neonates as early as 24 weeks of gestation [13, 16].

The scientific literature has taken little notice of tocolytic treatment for premature labor before 24 weeks of pregnancy. Cerclage and the total occlusion of the external os of the cervical canal have been primary therapeutic principles—often with disappointing results [24]. In addition, current antibiotic treatment has made significant contributions to the treatment of ascending infections which are frequently associated with preterm labor [18, 21, 34, 36, 39].

In the Western world where an increasing number of women are over 35 years of age for their first pregnancy—often achieved through assisted reproductive technology—we will increasingly be faced with obstetric borderline cases, i.e., premature births at the very limit. This scenario is also likely to be associated with increasing social pressure.

The present investigation was designed to assess the effectiveness and safety of atosiban in cases of impending pregnancy loss in the 18th through 24th week of gestation.

Materials and methods

A prospective randomized design was chosen. Twenty patients (31–42 years; median: 37 years) between 18 and 24 weeks of preganancy (range 17.3–23.4 weeks; median 20.8 weeks) were treated with atosiban, 20 patients who received saline solution served as controls (31–41 years; median: 36 years; gestational age: 16.8–23.2 weeks; median 20.8 weeks). Both groups are characterized in Tables 1 and 2. Measures upon admittance were as follows:

- Complete gynecological/obstetrical history
- Obstetric findings, microbiological smear
- Examination for amniotic fluid loss (Amnicheck, MAST Diagnostica, Reinfeld, Germany)
- Transabdominal sonographic evaluation of the fetal biophysical profile
- Transvaginal sonographic measurement of cervix length
- Tocometry
- Routine lab tests (blood count, C-reactive protein, electrolytes, gamma glutamyl transpeptidase (gamma gT), glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lactate dehydrogenase (LDH), creatinine, uric acid, Quick test, partial thromboplastine time, blood sugar)
- Urine status
- Maternal vital parameters (blood pressure, heart rate, temperature); maternal ECG; maternal fluid balance

In the treatment group atosiban was administered as follows in accordance with the standard protocol: initial intravenous bolus injection (approximately 1 min, 6.75 mg of atosiban in 0.9 ml of sodium chloride), followed immediately by high-dosage saturation infusion with atosiban in 0.9% sodium chloride for 3 h (300 μg/min) followed by a low-dosage continuous infusion with atosiban in 0.9% sodium chloride for up to 45 h (100 μg/min). In the control group saline solution was continuously given via intravenous infusion. For both groups conventional treatment for premature labor was also applied (antibiotics, bedrest, correction of the vaginal pH, cervical cerclage). A detailed description of the inclusion and exclusion criteria is given in Table 3.

Patients were closely monitored. After receiving comprehensive information concerning their situation as well as an explanation of alternative therapeutic options, all patients gave their written consent for the investigation. Approval from the local ethical committee was obtained prior to the study.

The effectiveness of the tocolytic treatment was assessed by:

1. Measuring the time to the onset of the tocolytic effect
2. The interval until uterine contractions completely ceased
3. The duration of complete absence of uterine contractions
4. The average prolongation of pregnancy

Table 1 Categories of patients by anamnestic means

	Treatment group number of patients	Control group number of patients
Age: 30–35/36–40/ > 40	7/11/2	9/9/2
First pregnancy	12	11
Significant history including one or more miscarriages or premature births	14	12
Assisted reproduction	8	6

Table 2 Conservative management for both groups and the associated patient numbers

	Treatment group	Control group
Cervical cerclage	2	5
Antibiotics	14	15
Correction of vaginal pH	12	15
Bed rest	20	20

Analogous to previous studies concerning the tocolytic effectiveness and therapeutic safety of atosiban [22, 31, 38], observation periods of 48 h and 7 days after the beginning of treatment were chosen for our investigation.

Initially, tocometry was performed for 2 h or until complete absence of uterine contractions was reached. Further monitoring was performed every 6 h up to 24 h after the beginning of treatment (lasting for 30 min) followed by monitoring intervals of 12 h for the next 48 h. After 6, 12, 24, and 48 h, or in the case of persistent contractions, a vaginal examination plus trans-vaginal ultrasonographic examination was performed in addition to the regular tocometry. Additional tocometry was performed depending on the clinical situation.

The atosiban treatment was discontinued when complete uterine quiescence was achieved, if preterm labor persisted, if chorioamnionitis developed, or if severe side effects occurred. In cases of successful inhibition of uterine contractions but with persisting cervical dilatation the patient was informed about the option of a cerclage and/or total occlusion of the cervix. In cases of recurrent contractions (after having been initially inhibited with atosiban), repeat treatment cycles under certain conditions were given (Table 3), taking the maximum cumulative dosage for atosiban into account (330 mg, according to the official recommendation by Ferring, Kiel, Germany). The fetal biophysical profile was determined by sonography. No prophylaxis for respiratory distress syndrome was performed. If a vaginal infection was evident antibiotic treatment with cephazoline and metronidazole was administered. Antibiotics were switched, if required, according to the antibiogram.

In order to evaluate the therapeutical safety, all patients were hospitalized during the entire observational period. Attention was paid to maternal side effects in regard to cardiovascular or cardiopulmonary problems (e.g., tachycardia, hypertension, pulmonary edema, difficulty breathing etc.) and vegetative symptoms (such as nausea, vomiting, headaches, and tremors).

Data are presented as median (minimum–maximum). As the sample size was too small to reach sufficient statistical power comparative testing for significant differences between groups was not performed. For calculations, the Stat View 5.0 statistical software (SAS Institute Inc., Cary, NC, USA) was used.

Results

Forty patients completed the study. At the time of admission, the median number of uterine contractions was 8 in 30 min in the treatment group (range: 6–15) and seven contractions in the control group (range: 5–14), the median dilatation of the cervix was one 1 cm (range: 0–3 cm) in both groups. Initial transvaginal sonography of cervix length showed values between 18 and 32 mm (median: 25 mm) in the treatment group and 20–35 mm (median: 28 mm) in the control group.

Table 3 Eligibility criteria

Inclusion criteria	Exclusion criteria
Regular uterine contractions: duration > 30 s, rate ≥4/30 min	Serious maternal disease
Cervical effacement: > 50%	Temperatures > 37.5°C
Cervical dilatation:	Preterm rupture of the membranes (PROM) with anhydramnia
Nulliparous women: 0–3 cm	Major vaginal bleeding
Primiparous and multiparous women: 1–3 cm	Fetal abnormalities (major congenital syndrome, growth restriction)
	Chorioamnionitis
	Polyhydramnia
	Intrauterine fetal death
	Multiple pregnancy (≥triplets)
	Alcohol abuse and drug abuse
	Hypersensitivity to atosiban and its components
	Previous study participation within the last 6 months

In the treatment group, a rapid tocolytic effect occurred immediately after the initial bolus within 3–10 min (median: 6.6 min). The number of contractions was reduced to 4–9/30 min (median: 5) during the first 2 h. Uterine contractions ceased after 3–12 h at a mean treatment time of 7.5 h. Forty-eight hours after beginning the treatment 19 patients, and 7 days thereafter 18 patients were still pregnant. The remaining two patients underwent termination of pregnancy (i.e., abortion) because of preterm rupture of the membranes (PROM) and impending chorioamnionitis. All other patients in the treatment group showed no significant change in the median cervix length nor dilatation during the observation period.

After 48 h in the control group 3 patients, and after 7 days another 2 patients suffered a miscarriage because of continuing or recurrent labor followed by PROM, chorioamnionitis and progressive cervical dilatation.

A vaginal flora imbalance occurred in 16 patients in the treatment group and 17 patients in the control group presenting with Gardnarella infection, Candida colpitis or nonspecific colpitis. In addition, β-hemolytic streptococci, *Escherichia coli*, *Enterobacter* species, as well as *Chlamydia trachomatis* were identified in some patients. Thus, most of these patients underwent antibiotic treatment, tailored to the specific antibiogram (Table 2).

In the treatment group three patients required repeat tocolytic treatment and two patients required one atosiban cycle 3–5 days after a McDonald's cerclage within the first 48 h. However, in the control group the saline infusion was continued throughout the entire observational period and cervical cerclage was performed in five cases (Table 2).

Maternal vital parameters (heart rate, blood pressure) remained in normal range in both groups and exhibited no significant findings during the entire examination period (data not shown).

With the exception of the patients who exhibited PROM, all the above-examined laboratory findings including the infection parameters, the urine findings, and the body temperature remained in the normal range in both groups throughout the entire examination period. The fluid balance of all patients always remained in balance without additional supportive treatment.

With regard to maternal side effects, the following observations were made: palpitations (2 patients), tachycardia (1), hypertension (2), hypotension (1), pulmonary edema (0), chest pains (1), difficulty breathing (1), nausea (4), vomiting (2), headaches (2), tremors (1).

In all patients of the treatment group the side effects occurred during the bolus injection and disappeared completely with no need for additional therapeutic measures, allowing all patients to continue the tocolytic treatment.

Overall, a median prolongation of pregnancy of 17.1 weeks (range: 11.1–21.7 weeks) in the treatment group and 15.6 weeks (range: 10.5–19.1) in the control group was achieved. Patients gave birth between 31 and 42 weeks in the treatment group (median: 38.7 weeks) and 30–40 weeks in the control group (median 37.2 weeks).

Discussion

This paper was designed to present our experience with the tocolytic treatment with the specific oxytocin receptor antagonist atosiban in the management of extreme preterm labor in the 18th through 24th week of gestation. Treatment of preterm labor with atosiban was previously successfully performed in the late 1980s with small numbers of subjects treated [2, 5]. Further studies involving larger numbers of patients ($n = 501$) have shown that atosiban provides a significantly better tocolytic effect at or beyond 28 weeks of pregnancy when compared to placebo [31].

In addition, the successful, intravenous emergency treatment with atosiban followed by a maintenance treatment with subcutaneous administration of atosiban via an infusion pump resulted in significant prolongation of pregnancy when compared to placebo [38]. When compared to the β-sympathomimetic drug ritodrine, atosiban exhibited an equivalent level of effectiveness with a significantly better profile of side effects [22].

However, no study was able to show an improvement in the neonatal outcome. In this regard, the management of preterm labor continues to be one of the most difficult and complex problems in obstetrics.

Among the causes cited for the ''premature labor syndrome'' are preterm uterine contractions, decidual activation, as well as cervical incompetence [30]. Based on current knowledge, these processes are receptor-mediated, with a central role being ascribed to the activation of the oxytocin/oxytocin receptor system, particularly in regard to uterine contractions as well as decidual activation.

Compared to the nonpregnant uterus, studies concerning the myometrial oxytocin receptor density during the course of pregnancy have shown an approximately sixfold increase between 13 and 17 weeks of pregnancy, increasing to nearly 80-fold by term, with an additional increase during parturition [8, 9]. More recent findings from research of both the non-pregnant uterus as well as the uterus during the early stages of pregnancy have shown that significantly more oxytocin receptors are expressed than previously assumed [11, 12, 25, 27–29, 33].

The aim of the present study was to examine the therapeutical concept of supplementing the current antibiotic and/or cerclage treatment—which is the most common but also the least successful measure in these desolate obstetric situations—with a tocolytic treatment which is known to have a low rate of side effects. It should be noted that the study was designed as a pilot project preceding a larger randomized trial, and that the results must certainly be interpreted critically—the more so as the number of patients involved is small.

Initially, the results in regard to the effectiveness of atosiban in the early weeks of pregnancy were surprising. In contrast to what was expected (based on the data for oxytocin receptor density) atosiban performed quite well if the time interval until the onset of the tocolytic effect, the time until cessation of uterine contractions, the contraction-free interval, and the prolongation of pregnancy are looked at. The results in regard to the myometrial oxytocin receptor density as well as the oxytocin plasma levels during the early stages of pregnancy allow the assumption that the uterine hemostatic imbalance is the result of an increased affinity of oxytocin to its receptor, which could also explain the effectiveness of atosiban.

Recent studies have shown that preterm uterine contractions—particularly before the 30th week of gestation—are frequently the result of a bacterial infection [14]. In this context, the effectiveness of tocolytics also depend on the antibiotic treatment—although data from recent meta-analyses are conflicting [21, 36]. Based on our experience and in contrast to earlier studies [39], the combination of tocolytics and antibiogram-adapted antibiotic treatment has proven to be effective (unpublished data).

As in other studies, typical side effects such as nausea, vomiting, and headaches primarily occurred in association with the initial bolus injection. Side effects regressed spontaneously without additional supportive treatment, and in no case did the treatment have to be discontinued.

Aside from preterm uterine contractions, another problem in the therapy of extreme premature labor lies in the treatment of the cervical dilatation which in most cases arises concurrently. The frequently performed emergency cerclage procedure often results in a termination of the pregnancy due to infection. When a vaginal infection is already present, a cerclage must be viewed as being contraindicated [17, 23]. This is in accordance with our observations (data not shown). It may be speculated, whether less cervical cerclages in the treatment group are a result of performed tocolysis with atosiban. Larger numbers of patients are required in order to reach sufficient statistical power to address that important clinical question. Recent randomized studies comparing emergency cerclage with expectant management have shown controversial results [4, 32].

Regarding costs in comparison to other tocolytic drugs—in particular β-sympathomimetics or magnesium, but also prostaglandin inhibitors and calcium channel inhibitors or NO-donators—the tocolytic therapy with atosiban currently is the most expensive treatment. But within this context the current societal demands on child-bearing desires and increasing costs for assisted reproduction as well as the available comparative data for effectiveness and safety of tocolytics have to be considered. Thus, as maximum therapeutical effectiveness and safety for the mother and the unborn child have to be achieved, therapy costs for atosiban seem to be warranted, in particular in the presented clinical condition.

In summary, due to the rate of side effects of the tocolytic agents employed to date—particularly the β-sympathomimetics—their use as a tocolytic treatment for extreme premature labor may not be justified due to the lack of neonatological consequences while putting the mother at risk. Therefore, further randomized controlled trials are needed to answer the question as to whether or not atosiban will be a valid alternative —in addition to the current therapeutical concepts—in the management of extreme preterm labor.

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