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Atosiban– Its Impact on Uterine Activity in Preterm Labour

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Authors' contributions

This work was carried out in collaboration between all authors. Author BD designed the study and wrote the protocol. Author SS wrote the first draft of the manuscript and performed the statistical analysis. Authors RM and YN managed the analyses of the study. Author AB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To study the effect of Atosiban on Uterine activity using tocodynamometer and to evaluate the extent to which the delivery was delayed with the administration of oxytocin receptor antagonist.
Study Design: Open label, prospective, non-comparative study.
Place and Duration of Study: The study was conducted at a tertiary care centre, Lokmanya Tilak Municipal Medical College and Hospital, Sion, Mumbai, India over a period of 1 year.
Methodology: A total of 60 women with established preterm labour were enrolled in the clinical study. The enrolled patients were administered Atosiban - an oxytocin receptor antagonist, as a 48 hours infusion with concomitant administration of corticosteroids. The frequency, amplitude and duration of uterine activity were recorded on admission, at 24 hours and after completion of the treatment. The efficacy of Atosiban along with maternal and fetal safety was evaluated.

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Results: Atosiban administration successfully delayed the preterm labour by 48 hours and beyond in 86.7% of the patients. The frequency, amplitude, duration and mean uterine activity reduced significantly ($p<0.05$) at the end of 48 hours.
Conclusion: It can be concluded that Atosiban is an efficacious tocolytic agent with minimal to no adverse effects hence it is recommended as the drug of choice for preterm labour in delaying imminent preterm birth.

Keywords: Atosiban; oxytocin receptor antagonist; preterm labour; tocolysis; uterine activity.

1. INTRODUCTION

Preterm birth remains one of the major causes of death in newborns and is associated with an increased risk of neonatal complications and long-term morbidity [1]. India incurs the highest burden of preterm labour worldwide. According to WHO, in 2010 an estimated 14.9 million babies (11.1% of all live births) were born preterm globally, of which around 3.1 million lives were lost annually in the neonatal period itself due to complications from preterm birth [2]. Apart from being the direct leading cause of mortality in neonates, it is the second leading cause of death in children under 5 years of age. Preterm infants succumb to respiratory distress syndrome due to hyaline membrane disease and intraventricular hemorrhage. The ones who survive, struggle with lifelong disabilities such as chronic lung disease and impaired neurologic functions. Since the pathophysiology of preterm labour is multifactorial, the aim for management of preterm labour is to arrest uterine activity. Hence it becomes imperative to effectively delay preterm birth by administration of tocolytics.

Tocolytics are an imperative part of the management of preterm labour. According to NICE guidelines (November 2015), treatment with tocolytics should be promoted in cases of established preterm labour with no underlying clinical condition contraindicating their use. The gestational age of the patient also plays an important part for maximizing the benefit of tocolysis. The aim of tocolytic pharmacotherapy is to reduce uterine activity to achieve the resultant delay of imminent preterm birth and prolongation of gestational age. The rationale for tocolysis is to facilitate ante-natal corticosteroid administration and *in utero* transfer to a tertiary care facility where neonatal care will be optimal [3]. Both these measures have been associated with improved prognosis as corticosteroids administration decreases the incidence of respiratory distress syndrome, intraventricular hemorrhage, periventricular leucomalacia and necrotizing enterocolitis. In utero transfer results in improved neonatal outcome [3-5]. Since steroid administration over 48 hours has effectively proven to tide over above mentioned crisis, an efficacious tocolytic agent that delays labour by 48 hours with least side effects is the need of the hour.

The conventional tocolytics: Magnesium sulphate, calcium channel blockers, prostaglandin synthase inhibitors, nitric oxide donors, and β – sympathomimetics (β agonists) have been proven to be effective in achieving the aim of tocolysis [6]. Each tocolytic has its advocates but given the problems of systemic adverse effects with them, it is not surprising that gamut of new drugs have been developed and tested in clinical trials. A recent guideline published by the Royal College of Obstetricians and Gynecologists (RCOG) has suggested the oxytocin receptor antagonist - Atosiban as the tocolytic of choice, based on comparable efficacy and superior maternal and fetal safety profile [7-9].

The present study was conducted with the aim to determine the efficacy and safety of Atosiban on uterine activity and the proportion of patients in whom the delivery was delayed by 48 hours.

2. MATERIALS AND METHODS

The study was conducted at a tertiary care centre, Lokmanya Tilak Municipal Medical College and Hospital, Sion, Mumbai in India over a period of 1 year after obtaining Institutional ethics committee approval (IEC//DISS/ 62/ 12). It was an open label, prospective, non-comparative study involving 60 patients with preterm labour.

The eligibility criteria for the patient to be enrolled in the study included the following: Women >18 years of age; Gestational age between 24 to 34 weeks which has been documented by a definite last menstrual period (LMP); the presence of 4 or more uterine contractions over 30 minutes, each lasting at least 30 seconds, and documented cervical changes (nulliparous women: a single

cervical examination demonstrating dilatation of 0 cm to 4 cm, multiparous women: a single cervical examination demonstrating dilatation of 1 cm to 4 cm); and effacement of at least 50%.

Women with any of the following criteria were not enrolled in the study: chorioamnionitis; preterm rupture of membranes; vaginal bleeding; severe hypertensive disorders; intrauterine growth restriction (<10th percentile), non-reassuring fetal heart rate; maternal contraindications including chronic hypertension; systolic blood pressure < 90 mm Hg; cardiovascular disease; elevated hepatic enzymes; congenital or acquired uterine malformation or any condition where continuation of pregnancy was deemed to put the mother at risk. Patients of >34 weeks of gestation were not included in the study as Respiratory Distress Syndrome due to immature lung system is less likely and of lesser severity after 34 completed weeks. Hence, there is less likelihood of perinatal morbidity and mortality from it [10].

Medical history of the enrolled patients pertaining to obstetric factors such as gravida status, parity, present gestational age, number of pregnancies, prior history of preterm labour or spontaneous abortions and their outcomes were recorded. Laboratory parameters like Complete Blood Count (CBC), liver function tests, renal function tests and blood sugar (fasting and post prandial) were checked at the time of admission and after completion of treatment. Additional lab tests including routine urine microscopy and culture sensitivity, high vaginal swab to rule out any urogenital infections were done. Ultrasound Sonography (USG) was performed in order to detect any feto-maternal abnormalities. The various hemodynamic parameters like pulse, blood pressure, respiratory rate and fetal well being by means of fetal heart rate were monitored at the time of admission, at 24 hour and 48 hours. APGAR score was determined for neonates delivered within 48 hours of starting Atosiban therapy.

All patients were administered Atosiban as a continuous I.V. infusion over 48 hours in three successive stages. The treatment was initiated by an initial bolus dose (6.75 mg) administered over 1 minute, then continuous high dose infusion (300 µg/min) for a period of 3 hours followed by a low dose infusion of 100µg/min up to 48 hrs. The primary outcome of the study was to access the following parameters: 1) Proportion of patients in whom delivery was delayed by 48 hrs 2) Reduction in the uterine activity. The secondary outcome of the study was to access the proportion of adverse events reported during the study.

During the hospital stay, patients were evaluated for their uterine activity at 24 hours and at 48 hours after treatment with Atosiban. Evaluation of patients was done on the basis of Consolidated Uterine Activity Score which was calculated by summing up scores assigned to the following individual parameters: 1) Frequency of contractions 2) Duration of contractions 3) Amplitude of contractions; as measured on external tocodynamometer. This score was specifically developed for this study to quantify the uterine activity.

The scores were assigned to each parameter as follows:

Mean frequency of contractions

Score	Contractions (per 10 minutes)
0	0 (Braxton Hicks contractions)
1	3 contractions
2	4 contractions
3	5 or more contractions

Mean Amplitude of contractions:

Score	Mean amplitude of contractions
0	0 - 20
1	20 - 30
2	30 - 50
3	50 - 60

Mean Duration of contractions:

Score	Mean duration of contraction (time in seconds)
0	< 20 s
1	20 - 30 s
2	30 - 40 s
3	40 - 50 s

The Consolidated Uterine Activity Score was considered as follows:

Score	Uterine activity
0-2	Baseline uterine activity
3-4	Minimal uterine activity
5-7	Moderate uterine activity
8-9	Advanced uterine activity

Uterine activity, cervical dilatation and cervical effacement were assessed at the time of admission, after 24 hours, 48 hours and at the

time of discharge. Accordingly, the progress or arrest of labour was monitored. The change in mean frequency, duration, amplitude and consolidated uterine activity were evaluated using Paired t test.

Patients were kept under observation till the uterine quiescence was attained and contractions had ceased. The status of the women at discharge (undelivered or delivered) was noted. In case of delivery, the various delivery characteristics like time of delivery after initiating treatment, mode of delivery and perinatal outcomes for the fetus were also noted.

The statistical analysis plan of the study was devised to derive the efficacy and safety of Atosiban in Indian patients. Descriptive statistics was used to represent the data (expressed as Mean ± SD). The effect of tocolytic treatment on uterine activity (reduction in the frequency, amplitude and duration of uterine contractility) was analyzed through paired student t test. Significance level was set at $p<.05$. To evaluate the success rate of tocolysis in the population, percentage of women remaining undelivered at 48 hrs were calculated. The proportion of adverse events reported during the study was also analyzed in order to determine the safety after treatment with Atosiban.

3. RESULTS AND DISCUSSION

3.1 Results

All the enrolled 60 patients belonged to the age group of 18 - 32 years. The mean age of the enrolled women was 23 (± 3.65) years and mean gestational age was 30.5 (± 2.35) weeks.

Among these 60 patients, 22 (36.6%) patients were primigravida, 16 (26.6%) were second gravid whereas 22 (36.6%) were multigravidas. Labour pain was experienced by 07 (11.6%) patients at less than 28 weeks, 26 patients (43.3%) experienced them at 28–32 weeks and 27 patients (45%) between 32-34 weeks. Out of all 60 patients, 54 (90%) had singleton pregnancy whereas 5 (8%) patients had twins and one patient had quadruplet pregnancy conceived after infertility treatment with Assisted Reproductive Technology (ART) procedures and had refused selective embryo reduction.

Overall 13 (34.66%) patients had a history of preterm delivery in their previous pregnancies; 2 of these patients also had had a spontaneous miscarriage. The remaining patients had no apparent risk factors for preterm birth.

The primary aim of prolonging pregnancy and administration of a complete course of ante partum corticosteroids to the mother in order to attain fetal lung maturity was achieved in 52 (86.7%) patients owing to 48 hours of tocolytic therapy. The remaining 8 (13.3%) patients delivered within 48 hours. The patient with quadruplet pregnancy delivered after 72 hours on day 4.

Table 1. Effect of Atosiban on patients

Time interval	No. of cases undelivered	No. of cases delivered
Patients enrolled at 0 hours	60	0
< 24 hours	52 (86.7%)	08 (13.3%)
24 - 48 hours	52 (86.7%)	Nil

Table 2. Effect of gestational age on outcome of treatment (48 hours)

Gestational age (weeks)	Outcome	
	No. of cases undelivered	No. of cases delivered
24 - <28	07 (100%)	NIL
28 - <32	22 (84.6%)	04 (15.4%)
32 - 34	23 (85.18%)	04 (14.8%)

In the present study, the mean cervical dilatation was 3 ± 0.73 cm on admission; with gradual reduction to 2.87 ± 0.81 cm and 2.5 ± 0.66 cm at 24 hours and 48 hours respectively. These changes though statistically significant (paired t test, $P < 0.01$) were not clinically significant.

The mean frequency of uterine contractions per 10 minutes showed a gradual fall from 4.22 ± 1.044 to 1.94 ± 0.98 from the time of admission to completion of treatment. Similarly the mean duration of contractions gradually reduced from 33 ± 2.25 seconds to 28.63 ± 0.94 seconds at the end of 48 hours. The mean amplitude of contractions as measured on external tocodynamometer reduced from 39.66 ± 3.3 to 18.9 ± 3.4 after the completion of treatment with Atosiban. All these parameters showed a significant change (paired t test, $P < 0.01$) from baseline thus establishing Atosiban as a potent tocolytic drug.

Table 3. Effect of Atosiban on mean frequency, amplitude and duration of uterine contractility

Time interval	Mean frequency (per 10 mins)	Mean amplitude	Mean duration (secs)
On admission	4.22 ± 1.044	39.66 ± 2.25	33 ± 2.25
24 hours	3.74 ± 0.84	21.92 ± 3.5	30 ± 0.85
	(*P* < .001)	(*P* < .001)	(*P* < .001)
48 hours	1.94 ± 0.98	18.9 ± 3.4	28.6 ± 0.94
	(*P* < .001)	(*P* < .001)	(*P* < .001)

Consolidated Uterine Activity Score, obtained by summing up score assigned to the amplitude, frequency and duration of uterine contractions of each patient showed a significant fall from 7.9 ± 0.43 to 4.8 ± 1.88 (paired t test, *P* < .001) with continuous I.V. infusion of Atosiban. The Consolidated Uterine activity score indicates that lower the consolidated score, lesser the cumulative uterine activity with the maximum score being 9 and the least being 3.

Table 4. Consolidated uterine activity score

Time interval	Mean uterine activity score	P value
On admission	7.9 ± 0.43	----
24 hours	6.25 ± 0.62	*P* < .001
48 hours	4.88 ± 1.88	*P* < .001

At the time of admission, 54 (90%) patients had consolidated uterine activity scores in the range of 8-9, denoting higher score range thus signifying a clinically high uterine activity, whereas only 6 (10%) patients had intermediate scores and none were in the lower ranges. After the completion of treatment with Atosiban, none of the patients had higher range score, 40 (76.93%) had intermediate score whereas 12 (23.07%) had lower range score. Before the completion of the complete course of treatment, 8 patients had delivered.

Table 5. Consolidated uterine activity score: Patient distribution

Score	On admission	At 24 hours	At 48 hours
8 – 9	54	2	0
5 – 7	6	50	40
3 - 4	0	0	12
Total	60	52	52

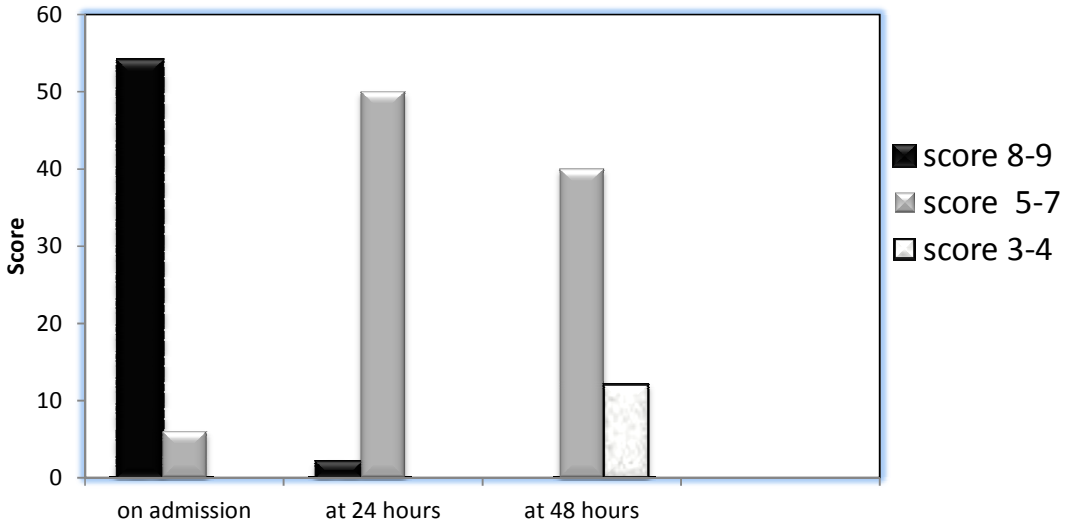

Fig. 1. Consolidated uterine activity score

The treatment was reported as pleasant and showed no signs of discomfort as per the patients' perspective. The study medication was well tolerated and no serious maternal or fetal adverse events were observed during the entire course of treatment and follow-up. The adverse events reported during the study were of mild severity and are represented in the following table (Table 6).

Table 6. Adverse events reported during the study (N=60)

Event	No. of events n (%)
Nausea	6 (10%)
Headache	1 (1.6%)
Hyperglycaemia	4 (6.66%)

3.2 Discussion

The present study was conducted to evaluate the efficacy of Atosiban- an oxytocin receptor antagonist as a tocolytic, and its impact on uterine activity in Indian patients. It was carried out with the intention to treat 60 women presenting with preterm labour. A concomitant administration of Corticosteroids was administered to ensure fetal lung maturity to prevent the crisis of respiratory distress.

The main finding of this study is that Atosiban was effective in delaying preterm labour by 48 hours in 52 (86.7%) patients. The delay in labour observed in our study was very similar to that observed by Moutquin et al. [11], Romero et al. [12], and The Tractocile efficacy survey in Europe [13].

The mean uterine activity adjudged on the basis of means of frequency, amplitude and duration of contractions showed significant reduction from the start of treatment with Atosiban. "Calcium sensitization" induced by oxytocin or PGF2a is an important physiological phenomenon which happens after the stimulation of uterine muscles with an agonist such as oxytocin or PGF2a, a given rise in [Ca+2]i results in a *stronger than expected force of contraction*. This physiological phenomenon is known as "Calcium sensitization". With the onset of Atosiban induced uterine quiescence, as more and more receptors get occupied by the oxytocin antagonist, the calcium sensitization is hindered resulting in reduced uterine activity [14].

As explained by Nagarajan et al. [15] the formation of electrical synapses and gap junctions that mediate intracellular communications between myometrium, and coupling between cells which is dependent on oxytocin, decreases gradually with progressive action of Atosiban. The resultant effect is a fall in the number and amplitude of action potentials leading to decrease in frequency and intensity of contractions. The results of electromyographic investigations on uterine contractions of the present study are similar to those by Berkman et al. [16] and Hadar et al. [17].

Several studies have compared the efficacy and safety of Atosiban with the conventionally available tocolytics. High frequency of unpleasant and sometimes severe and potentially life threatening adverse effects have been reported following beta-agonist use. Reported adverse effects for nifedipine, the most widely used calcium antagonist, include flushing, palpitations, nausea, vomiting and hypotension. Nifedipine is contraindicated if the woman has cardiac disease and should be used with caution if she has diabetes or multiple pregnancy, owing to the risk of pulmonary oedema [8]. Published literatures have proven that Atosiban had similar efficacy but was associated with fewer side effects and presented no safety concerns for either the mother or the fetus [18]. It was also found to be safe for the treatment of preterm labour in patients with diabetes, cardiac disease and multifetal pregnancies [19]. In the present study, safety of Atosiban was evaluated by recording adverse events in patients during treatment and assessing the final outcome of pregnancy. Consistent with previous studies, no serious adverse event occurred in patients during the study period [20,21].

One of the disadvantages of the current study was that high risks patients were not included due to the associated medical conditions. Lack of control group can also be considered as a limitation of the present study as it restricts the ability to establish the superiority of the treatment. Further studies on a larger population pool are required to ascertain efficacy and superior safety profile of Atosiban as compared to the other tocolytics. Atosiban being an oxytocin receptor antagonist significantly reduced the frequency, duration and amplitude of uterine contractions. The consolidated uterine activity score also showed a significant reduction, implying Atosiban as an effective tocolytic agent. Atosiban was effective in significantly delaying delivery by 48 hours, in 52 (86.7%) patients including one quadruplet pregnancy. Hence

Atosiban should be considered as the treatment of choice in preterm labour.

4. CONCLUSION

It can be concluded that Atosiban is an efficacious tocolytic agent with minimal to no adverse effects hence it is recommended as the drug of choice for preterm labour in delaying imminent preterm birth.

CONSENT

All authors declare that written informed consent was obtained from all the enrolled patients prior to the administration of tocolytic treatment. A record of the same is maintained with the Institutional Ethics Committee (IEC).

ETHICAL APPROVAL

All authors hereby declare that all the studies performed have been examined and approved by the Institutional Ethics Committee (IEC Registration: ECR/266/Inst/MH/2013; IEC Approval: IEC//DISS/ 62/ 12) and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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