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The Clinical Experience of Atosiban in Preterm Labour

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the efficacy, safety and tolerability of atosiban in delaying preterm labour.
Study Design: A prospective, open label, non comparative study.
Place of Study: Lokmanya Tilak Municipal Medical College Mumbai, India.
Methodology: Pregnant women (N=110) between the gestational age of 24 to 34 weeks, presenting with signs of preterm labour were enrolled in the study. Efficacy, safety and tolerability of Atosiban were assessed for a period of 72 hrs.
Results: Ninety Eight patients (89.09%) remained undelivered up to 72 hrs after completion of treatment phase and ninety seven patients (88.18%) till the end of their hospital stay (upto 7 days). There were six patients with twin and one with quadruplet pregnancy; atosiban therapy was successful in delaying labour upto discharge from hospital in all the seven patients. The study medication was well tolerated as no adverse events were observed throughout the study duration.
Conclusion: Atosiban, an oxytocin receptor antagonist, has proven to be an effective and well tolerated tocolytic drug and because of its favourable safety profile, it may be the best choice as a tocolytic therapy to delay the preterm labour.

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1. INTRODUCTION

Preterm birth is one of the major causes of perinatal morbidity and mortality. India has the highest number (3.5 million per year) of preterm births in the world [1,2]. Prompt recognition of preterm labour and an approach to mitigate it reduces the probability of preterm birth. Management of preterm labour through tocolysis is an established clinical strategy [3]. Tocolysis delays delivery sufficiently, allowing the administration of a complete course of antepartum glucocorticosteroids to the mother in order to reduce the severity of idiopathic respiratory distress syndrome in neonates and to make arrangements for *in utero* transfer to centers with neonatal intensive care facilities [4].

Currently used tocolytic agents include Calcium-Channel Blocker (CCB) like nifedipine and β-adrenergic agents such as fenoterol, ritodrine, isoxsuprine, salbutamol and terbutaline. Other agents being used off label are magnesium sulfate, cyclooxygenase inhibitors like indomethacin etc. These drugs have not been proven to be very effective as they are not utero-specific; therefore, multi-organ fetomaternal side effects are expected and observed [3]. Nifedipine usage as a tocolytic is commonly associated with side effects like tachycardia, palpitations, flushing, headaches, dizziness, and nausea. However, its main side effect is hypotension, which may cause a decrease in uteroplacental perfusion. Continuous monitoring of the patient's blood pressure and fetal heart rate is recommended as long as the patient has contractions. Use of β-adrenergic agonists is hampered by treatment limiting adverse reactions, including maternal cardiac arrhythmias, vasodilatation resulting in systolic hypotension, stimulation of the central nervous system, and altered thyroid function [5,6]. The efficacy of Magnesium sulfate is uncertain [7] though recent committee opinion of the American College of Obstetrician and gynecologists, continues to support its short term (usually less than 48 hour) use in Obstetric care, despite its change in Pregnancy category from A to D by USFDA [8]. Concerns regarding adverse fetal effects of cyclooxygenase inhibitors limit their use particularly at a gestational age above 30–32 weeks [9].

Atosiban, an oxytocin receptor antagonist, is a uterine specific tocolytic with more favourable safety profile. Oxytocin causes uterine contractions through a direct effect on membrane bound receptors in the uterus (myometrium). Atosiban is a synthesized cyclic nonapeptide that behaves as a competitive antagonist for oxytocin receptors in a dose-dependent manner thus leading to the inhibition of uterine contraction. It has been reported that there is a predisposition of increase in density of oxytocin and vasopressin V_{1a} receptors at the onset of preterm labour [10]. In addition to being an oxytocin receptor antagonist, atosiban is also an antagonist of vasopressin receptor [11]. During preterm labour, oxytocin assists in release of inositol 1, 4, 5 triphosphate (IP_3) from the myometrial cell membrane. Atosiban inhibits this release and thus reduces the subsequent release of calcium from their sarcoplasmic reticulum. Ultimately the influx of Ca^{2+} through the voltage gated ion channels is inhibited. Additionally, atosiban can also inhibit the oxytocin mediated release of prostaglandins (PGE and PGF) from deciduas. PGE and PGF series are mediators of uterine contractions, atosiban induced decrease in production results in decreased contractile activity [12]. A guideline published by the Royal College of Obstetricians and Gynaecologists (RCOG) has recommended atosiban as a first line agent, based on comparable efficacy and a superior fetomaternal side effects profile [13].

The choice of tocolytic agent depends mainly on the drug efficacy, the fetal and maternal safety profiles and the availability following regulatory approval in the country. Atosiban was approved and registered in the European Union in April 2000 as a tocolytic agent and it has been approved in 68 countries across the globe, as of now [14,15]. The current study was conducted with an aim to establish the efficacy and safety of atosiban (7.5 mg/ml) in Indian patients presenting with preterm labour.

2. MATERIALS AND METHODS

A prospective, open label, non comparative study was conducted at Lokmanaya Tilak Municipal Medical College, Mumbai. The study was sponsored by Zuventus Healthcare Ltd in accordance with the Declaration of Helsinki, International Conference of Harmonization- Good Clinical Practice (ICH-GCP) and Indian regulatory guidelines for conducting clinical trials (Schedule-Y). The protocol was approved by the

Institutional Ethics Committee (IEC) of the hospital. Written informed consent was obtained from all patients before participation in the study. The trial has been registered with the Clinical Trial Registry of India (Reg. No: CTRI/2013/11/004166).

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 was 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 (primiparous 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); 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 (< 5th 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 women who were otherwise judged inappropriate for inclusion in the study by the investigator.

Patients were screened prior to enrollment and eligibility was assessed according to the specified inclusion and exclusion criteria. All the patients underwent a complete physical examination and their relevant demographic details were noted. Laboratory investigations, including complete blood count, hemoglobin, hepatic and renal function tests, were carried out in all the patients. Eligible patients received treatment with atosiban as intravenous (i.v.) infusion for 48 hrs 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 100 µg/min up to 48 hrs. As per protocol, intravenous treatment was to be discontinued if there was progression of labour or rupture of membranes occurred. The exact dose of the investigational drug administered to the patient and the need and frequency of re-treatment were assessed. The patients could receive either re-treatment with atosiban or an alternative tocolytic agent post initial treatment at investigator's discretion if deemed necessary. Other tocolytic agents were not permitted concomitantly with the study drug. Antibiotics and corticosteroid therapy was allowed when needed. Any concomitant treatment given was recorded in the Case Report Form (CRF).

The primary objective of the study was to evaluate the efficacy of atosiban in delaying preterm labour. Secondary objective was to evaluate the safety and tolerability of the investigational product. Patients were assessed at 24 hrs, 48 hrs and 72 hrs after treatment, followed by an end of study assessment at discharge (or on the 7th day, whichever was earlier). Efficacy was assessed by the proportion of women remaining undelivered at 72 hrs and not requiring any alternative tocolytic within 48 hrs post administration of study medication. Maternal parameters like uterine contraction frequency, cervical dilation and cervical effacement were also analyzed to assess the efficacy of atosiban. Cardiotocography was performed to monitor the changes in fetal heart rate and uterine contraction frequency. Safety outcomes were assessed in terms of maternal and fetal adverse events reported during the entire study duration.

Statistical analysis of the primary and secondary objectives was done through the descriptive analysis (expressed as Mean ± SD) and frequency distribution table which included all patients who received at least the initial bolus dose of the study drug. Categorical measurements were compared using the Chi-square test. The effect of tocolytic treatment on uterine activity was analyzed through paired student t test. Differences were considered significant if P <.05

3. RESULTS

A total of 110 patients meeting the eligibility criteria were enrolled in the study to receive treatment with atosiban. The demographic profile and baseline clinical characteristic of the patients is given in Table 1.

3.1 Efficacy Analysis Based on Duration of Tocolysis

After completion of 48 hrs of infusion, 89.09% (98/110) patients remained undelivered at 72 hrs. Successful tocolysis was noted in 88.18% (97/110) patients at the time of their discharge from hospital (Fig. 1).

Table 1. Demographics of enrolled patents at baseline (N=110)

Parameters	Mean ± SD
Age (years)	23±4.01
Gestational Age (weeks)	30.6±2.49
Type of Gestation (No.)	
Primiparous	42
Multiparous	68
Height (cm)	152.38±4.25
Weight (kg)	49.93±5.39
Cervical Dilation (cm)	2.56±0.84
Uterine contraction frequency (in 30 mins)	4.81±1.48

Average stay of patients in the hospital was 4 days but there were 11 patients who stayed in the hospital for more than 7 days. Out of them only one patient delivered and remaining ten patients continued with their pregnancy till the time of discharge. The description of these patients is given in the Table 2.

3.2 Efficacy Analysis Based on Demographics

Subgroups analysis was conducted for gestational age, parity of pregnancy and multifetal gestation. The results of subgroup analysis are as follows:

3.2.1 Gestational age wise subgroup analysis

The data obtained from the enrolled patients during analysis was categorized into three gestational age groups as per World Health Organization (WHO) preterm classification updated in November 2015 [extremely preterm (<28 weeks); very preterm (28 to <32 weeks); moderate to late preterm (32 to <37 weeks)]. Table 3 represents the status of delivery after receiving treatment with atosiban.

3.2.2 Tocolytic effect based on Parity of pregnancy

Tocolytic efficacy of atosiban was analyzed on the basis of parity. Atosiban was equally effective (*P* =.98) in both the groups (Table 4).

3.2.3 Multifetal gestation

There were seven patients having multifetal gestation with 'imminent risk' of preterm delivery, all of them remained undelivered after the treatment with atosiban till the observation period of one week.

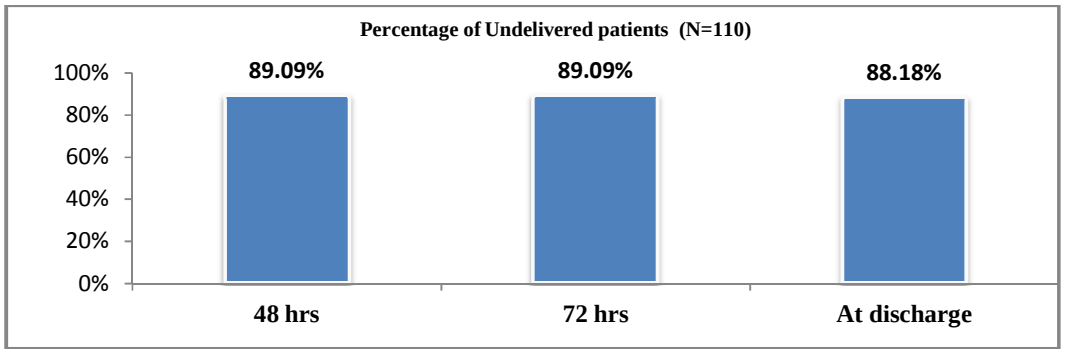

Fig. 1. Percentage of patients remaining undelivered at 48 hrs, 72 hrs and at discharge (≤7 day)

Table 2. Description of patients (n=11) with more than seven days of hospital stay

S. no.	Age (years)	Gestational age at discharge (weeks)	Duration of hospital stay (days)	Delivery status
1.	23	35	8	Undelivered
2.	21	32	8	Undelivered
3.	32	27	8	Undelivered
4.	26	35	8	Delivered
5.	25	25	8	Undelivered
6.	26	30	9	Undelivered
7.	21	31	9	Undelivered
8.	20	34	11	Undelivered
9.	22	35	11	Undelivered
10.	26	33	16	Undelivered
11.	20	37	19	Undelivered

Table 3. Delivery status at discharge based on gestational age (N=110)

Gestation weeks	No. of patients	Patients undelivered n (%)
24 weeks- <28 weeks (extremely preterm)	14	14 (100%)
28 weeks- <32 weeks (very preterm)	58	46 (79.31%)
32 weeks- <37 weeks (moderate preterm)	38	37 (97. 37%)

Table 4. Efficacy of atosiban in primiparous and multiparous patients (N=110)

Type of pregnancy	Number of patient	Patients undelivered till discharge n(%)
Primiparous	42	37 (88%)
Multiparous	68	60 (88.23%)

P value = .98 *by Chi square test*

Table 5. Efficacy of atosiban in patients having multifetal gestation

No. of fetus	Number of patients	Patients undelivered till discharge n (%)
Twins	6	6 (100%)
Quadruplet	1	1 (100%)

3.3 Efficacy Analysis Based on Changes in Maternal Characteristics

Efficacy was analyzed based on the changes observed in cervical dilation, cervical effacement and uterine contraction frequency after treatment with the study medication. There was a significant difference from the baseline in all the three parameters demonstrating the efficacy of atosiban in delaying labour.

3.4 Need for Rescue Medication

None of the patients (n=110) required any alternative tocolytic agent or retreatment with atosiban throughout the study period. The total dose given during a full course of atosiban therapy did not exceed 330 mg of the active substance.

3.5 Safety and Tolerability

All the patients who completed the treatment regimen as per the protocol rated the treatment as pleasant and showed no signs of discomfort throughout the treatment and follow-up phase. Cardiotocography was performed to analyze the effect of the tocolysis on fetal heart rate (FHR). There were no major alternations in the FHR after administration of atosiban. The study medication was well tolerated as no maternal or fetal adverse events were observed.

4. DISCUSSION

Tocolytic drugs play a very important role in managing preterm labour and extend the length of pregnancy thus preventing both maternal and neonatal risks. The potential advantages of prolonging pregnancy should be balanced against medication related potential adverse outcomes. The intervention used to delay preterm labour should not only increase the survival rate of the fetus but also should avoid any severe disability of the survivors [3,4]. The use of β-agonists like ritodrine, isoxsuprine, fenoterol, salbutamol, and terbutaline for preventing preterm birth are associated with a high incidence of serious adverse drug reactions including tachycardia, hypotension, palpitations, shortness of breath, chest pain, pulmonary edema, etc. [16]. Although adverse events occur less frequently with usage of nifedipine

Table 6. Changes in the maternal characteristics after treatment with atosiban (N=110)

Time points	Cervical dilation (cm)	Cervical effacement (%)	Uterine contraction frequency
0 hrs	2.56±0.84	49±7.1	4.71±1.4
48 hrs	1.18±1.03	23.7±16.1	1.53±1.27
72 hrs	0.52±0.81	9.7±13.8	0.27±0.65
Discharge	0.28±0.53	3.9±6.0	0.03±0.17
Mean Difference (0-48 hrs)	-1.38 * (-1.53 to -1.22)	-25.3 * (-28.5 to -22.0)	-3.18 * (-3.58 to -2.79)
Mean Difference (0-72 hrs)	-2.04 * (-2.21 to -1.87)	-39.3 * (-42.3 to -36.3)	-4.44 * (-4.78 to -4.11)
Mean Difference (0 hr-till discharge)	-2.29 * (-2.45 to -2.13)	-45.1 * (-46.9 to -43.3)	-4.65 * (-4.93 to 4.36)

* ***P <.001*** *vs baseline (paired student t test)*

as compared to β-agonists [17], maternal adverse events like hypotension and flushing have been reported and can be troublesome in patients at risk of cardiovascular complications [18-21]. Atosiban demonstrated comparable efficacy to the other tocolytics without any major side effects reported with other classes of such drugs [22]. Literature reports of mild adverse effects associated with atosiban include nausea and the major cause for stopping the treatment was 'injection site reaction' [23-25], though in our study no side effects were observed in any of the patients on atosiban treatment.

Published literature references serve to be the evidence base for atosiban as a safe and efficacious tocolytic. Atosiban has shown a consistent efficacy and promising safety in various ethnic groups. In a study conducted in Germany, atosiban was effective in delaying preterm labour in 78.4% women as compared to 66.7% in the β-agonists group (fenoterol) at the end of 7 days [26]. In another study conducted in Israel, comparing atosiban with nifedipine it was found that 78.6% women remained undelivered at 7 days from enrollment [27]. In the current study, successful tocolysis was observed in 88.18% patients at 7th day of enrollment. Though the current study was a non-comparative study, but it points towards a similar success rate of tocolysis in Indian patients depicting no major ethnic variation in the response rate worldwide.

Atosiban was successful in delaying labour in all the gestational age groups (24 to 34 weeks). Successful tocolysis was noted in 100% and 97.37% patients of extreme preterm and moderate preterm labour group respectively. Tocolytic efficacy of atosiban was demonstrated through significant reduction in the uterine contraction frequency, cervical dilation and cervical effacement from the baseline after treatment with the study medication ($P < .001$). These results are similar to that observed in a clinical trial conducted in USA where the success rate was found to be 100% in extreme preterm and 68.8% in moderate preterm [28]. Similarly in a multicentric study conducted in Europe involving 585 patients in 6 countries, the success rate was 79.4% (in extreme preterm) and 76.8% (in moderate preterm) [29]. The efficacy of atosiban in achieving retardation in uterine activity for prolongation of pregnancy can be attributed to its affinity to antagonize the oxytocin and vasopressin V_{1a} receptors [10,30].

In multifetal gestation, there is no clear guidance on the use of tocolytic agents to inhibit preterm labour and they have not been proven to reduce the risk of preterm birth or improve neonatal outcomes [31-33]. Conventional tocolytic agents like beta agonists and calcium channel blockers, are associated with increased number of adverse events like dyspnoea, hypotension, hypoxia, tachycardia and lung edema [34]. A series of case reports have suggested an association between nifedipine's use in multifetal gestation and pulmonary oedema [35]. In the present study, 7 patients having multiple fetuses were treated with atosiban and preterm labour was delayed without developing any adverse events This observation in a small subset of patients justifies the need for further study on larger number of patients to support the recommendation of atosiban therapy in multiple pregnancy. Similar findings were observed by Tsatsaris et al. [19] who concluded that atosiban is a drug of choice for the treatment of preterm labour in patients having multifetal gestation, [36].

The current study was conducted with the aim to establish the efficacy and safety of atosiban in Indian patients presenting with preterm labour. The overall usage of atosiban was found to be effective and well tolerated. There is a wide experience for the usage of Atosiban in Europe and all the published literature hints towards the best safety profile of Atosiban amongst all the tocolytics [23,29,34,36,37]. Probably this was the reason for the recommendation by the Royal college of Obstetrics and gynaecology to recommend it as the First line drug for the management of preterm labour. Further comparative studies should be conducted in larger population in reputed institutions in India, so as to develop a local recommendations for atosiban in treatment guidelines.

5. CONCLUSION

The results of the present study show that atosiban is a safe and effective drug for the treatment of preterm labour. There were no serious maternal or fetal side effects and none of the patients were withdrawn due to drug intolerance. Further comparative studies in larger population should be conducted to establish the recommendation for usage of atosiban as the first choice of tocolytic therapy in the management of preterm labour.

ETHICAL APPROVAL

All authors hereby declare that the trial has been examined and approved by the institutional

ethics committee of Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai and have therefore 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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