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INITIAL EXPERIENCE WITH THE OXYTOCIN ANTAGONIST ATOSIBAN FOR PRETERM LABOR IN A TERTIARY CARE CENTRE: PROSPECTIVE OBSERVATIONAL COHORT STUDY

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ABSTRACT

Background: Preterm labor(PTL) leads to alarming situations and challenges for doctors and is a distressing condition for pregnant women and their families. Therapy with uterospecific tocolytic Atosiban is a common practice nowadays due its high efficacy and safety evidences in inhibiting the early uterine contractions thus delaying the delivery, permitting better fetal growth and reducing the newborn mortality and morbidity. **Aims:** To evaluate efficacy and safety of uterospecific tocolytic Atosiban in pregnant women with PTL. **Settings and Design:** Prospective observational cohort study was conducted in the Department of Obstetrics and Gynecology, Tertiary Care Hospital, North India. **Methods and Material:** 150 singleton/twin pregnant women were administered Atosiban intravenously for 48 hours. Efficacy was determined by the percentage of women who remained undelivered after therapy initiation up to 48 hours. Safety was assessed by the numbers of maternal, fetal or neonatal adverse events (AE) reported. **Statistical analysis used:** Intent-to-treat statistical analysis was used. Descriptive statistics were used to represent the data [expressed as Mean ± SD, N (%)]. **Results:** Atosiban successfully delayed the preterm deliveries by ≥ 48 hours in 146 (97.3 %) pregnant women, of which 140 pregnancies remained undelivered for >7 days and some of them even up to 5 weeks. No maternal and fetal AE were reported, 01 neonatal death occurred due to sepsis. **Conclusion:** Based on our initial clinical experience, we conclude that Atosiban is an effective and well tolerated drug in prolonging the duration of pregnancy in women with PTL.

KEYWORDS: Atosiban, Gestation, Labor, Oxytocin, Pregnant, Preterm, Prolongation, Tocolytic.

INTRODUCTION

Despite advances in obstetrics and perinatology, Preterm Labor (PTL) and preterm birth (PTB) are still the major contributors to death and lifelong disabilities amongst children under the age of five. More than a million infants, out of fifteen million born worldwide before the 37th week of gestation, die due to the complications related to PTB. India has been reported with the highest number of PTB.[1] Although the etiology of PTL is not clearly understood, it is defined as regular contractions of the uterus resulting in effacement and dilatation of cervix before attaining the fetal maturity.[2]

Tocolytics are currently among the top 10 recommendations given by World Health Organization for the improvement of PTB related outcomes.[3] The acute use of tocolytics is associated with prolongation of pregnancy by inhibiting preterm uterine contractions, thus facilitating the completion of a single course of antenatal corticosteroids given for overall fetal lung maturity and/or during in-utero fetal transfer in an appropriate neonatal healthcare setting.[4,5] Tocolytics are generally administered when a diagnosis of preterm labor is confirmed between $23^{0/7}$- and $33^{6/7}$-weeks of gestation.[6]

Treatments that have been tested for PTL include hydration, magnesium sulfate, antibiotic therapy, nitroglycerine, NSAIDs, calcium channel blockers, and betamimetics.[7] These were developed for other indications but were found to inhibit uterine contractions later on and thus were included under the tocolytics category. Due to lack of specificity, multiple organ side effects have been encountered with these agents along with higher incidence of maternal, fetal and neonatal adverse events.[8] Atosiban is the only tocolytic that has been developed specifically for the treatment of PTL and

is, therefore, the most uterospecific agent in this category.

Oxytocin and Vasopressin along with their receptors, located in the myometrium and the decidua have been implicated in the mechanism of human parturition.[9,10] Combined antagonism of Atosiban at oxytocin/vasopressin V1A receptors reduces uterine contractility with a corresponding reduction in intrauterine prostaglandin F2a production and improvement of uterine blood supply.[11]

Atosiban is recommended as the first line agent for the management of PTL in various countries.[12]

Keeping these facts in mind, the present study was conducted in a tertiary care hospital in India, with an aim to determine the effect of Atosiban in delaying parturition in women with established cases of PTL and to assess the validity of maternal, fetal and neonatal outcomes post treatment.

SUBJECTS AND METHODS

Trial design

This was a prospective observational cohort clinical study conducted at Department of Obstetrics and Gynecology of a Tertiary Care Hospital in India, over a period of 1 year from January 2019 to February 2020. The clinical trial protocol and other study related documents were approved by Hospital's Ethics Committee. This study was conducted in accordance with ICH Good Clinical Practice and Declaration of Helsinki.

Participants

150 singleton or twin pregnant women aged ≥ 18-40 years having gestational age beyond 23 weeks + 6 days up to 33 weeks + 6 days, with regular uterine contractions (≥ 30 seconds in duration, at a rate of > 4 times in 30 mins), cervical dilatation of 0-3 cm, and cervical effacement of ≥ 50%, having intact amniotic membrane were included in this study. Pregnant women aged less than 18 years with gestational age less than 23 weeks + 6 days or > 34 weeks of gestation having multiple pregnancies (more than twins), non-reassuring fetal heart rate, chorioamnionitis, showing presence of ruptured membranes, suspected abruptio placenta, major vaginal bleeding (i.e. continuous fresh vaginal bleeding or volume > 100 ml), fever, tachycardia, severe hypertensive disorders / cardiovascular disease, elevated hepatic enzymes and positive C-Reactive Protein in blood on admission, patients with congenital/acquired uterine malformation or intrauterine growth restriction (< 5th percentile) and those requiring more than one tocolytic agent were excluded from this study.

Laboratory tests were carried out for all patients including a complete blood count, coagulation tests, renal and liver function tests and blood grouping. Cervical length of all cases was assessed by TVS, Fetal cardiac activity was regularly monitored in all cases and non-stress test was done for cases beyond 30 weeks gestational period. All eligible patients were admitted and the diagnosis of preterm labor was ascertained based on preliminary history and clinical examinations.

All the patients were enrolled in the study after obtaining written informed consent as per the study protocol.

Interventions

Atosiban acetate injection was given via intravenous route to eligible pregnant women for 48 hours in three consecutive stages; an initial bolus of 6.75 mg immediately followed by 300 g/min for 3 hours, followed by 100 g/min for up to 45 hours. Steroid inductions were given to all cases.

Outcomes

Primary efficacy outcome was defined as the percentage of women who remained undelivered till 48 hours owing to the completion of treatment phase and those who did not deliver for more than 7 days. Mean gestational period at birth, percentage of neonatal admission to intensive care unit (NICU), period of stay in NICU, percentage of neonatal respiratory distress or sepsis, neonatal requirement of ventilatory support or continuous airway pressure or surfactant, presence of necrotizing enterocolitis or hypoxic ischemic encephalopathy in the newborn, mode of deliveries were considered as a secondary outcome.

Safety endpoint was evaluated by recording the occurrence of maternal, fetal and neonatal adverse events.

Data analysis

A sample size (N) of the study was calculated using the formula: $N = (Z1 - \alpha/2)2*p*(1-p) / \delta 2$. The prevalence of target conditions (p) was considered as 0.8909 based on the published study.[13]

Other parameters were as follows: Precision (δ) = 0.05 (5%), Type I error (α) = 5%, $Z1 - \alpha/2 = 1.96$. Using the mentioned values, the required sample size for the study was found to be 150 pregnant women.

Analysis of the primary and secondary objectives was done through the descriptive statistics [expressed as Mean ± SD, N (%)]. Analyses were performed on an intention-to-treat basis.

RESULTS

A total of 150 PTL cases were studied. The baseline demographic profile and clinical characteristic of the patients are given in Table 1.

Table 1: Summary of baseline demographics and clinical characteristics (n=150).

Parameters	Mean ± SD / N (%)
Maternal Age (Years)	30.77 ± 4.12
POG at Presentation (Weeks)	29.04 ± 2.12
Gravidity	
Primigravida	87 (58.0%)
Multigravida	63 (42.0%)
Mode of Conception	
Spontaneous	38 (25.3%)
IVF	110 (73.3%)
Encerclage	
Performed	10 (6.7%)
Not Performed	140 (93.3%)
POG at Encerclage (Weeks)	16.59 ± 2.02
Number of Fetuses	
Singleton	78 (52.0%)
Twins	71 (47.3%)
Number of Contractions/30 Minutes	4.60 ± 0.77
Dilatation (cm)	1.87 ± 0.64
Effacement (%)	64.13 ± 6.15
Cervical Consistency	
Firm	1 (0.7%)
Soft	149 (99.3%)
Presence of Complications PTL	150 (100.0%)
Gestational Hypertension (HTN)	39 (26.0%)
Gestational Diabetes Mellitus (GDM)	50 (33.3%)
Intra hepatic Cholestasis (IHCP)	35 (23.3%)
Position of fetus	
Anterior	6 (4.0%)
Middle	39 (26.0%)
Posterior	105 (70.0%)
Station of Head	
1	1 (0.7%)
2	62 (41.3%)
3	87 (58.0%)

POG: *Period of Gestation* ***SD:*** *Standard Deviation*

Primary Efficacy Outcomes

- **Efficacy analysis based on duration of pregnancy prolongation**

The primary aim of prolonging the pregnancy duration by ≥ 48 hours was achieved in 146 (97.3%) patients (Fig. 1), of which, 140 (93.33%) patients extended their delivery time by more than 7 days to up-to 5 weeks, 06 (4%) patients delivered between the duration ranged ≥ 48 hours to 7 days and 04 (2.67%) women delivered within 48 hours (Table 2). The mean time of gestational period prolongation was found to be 5 weeks.

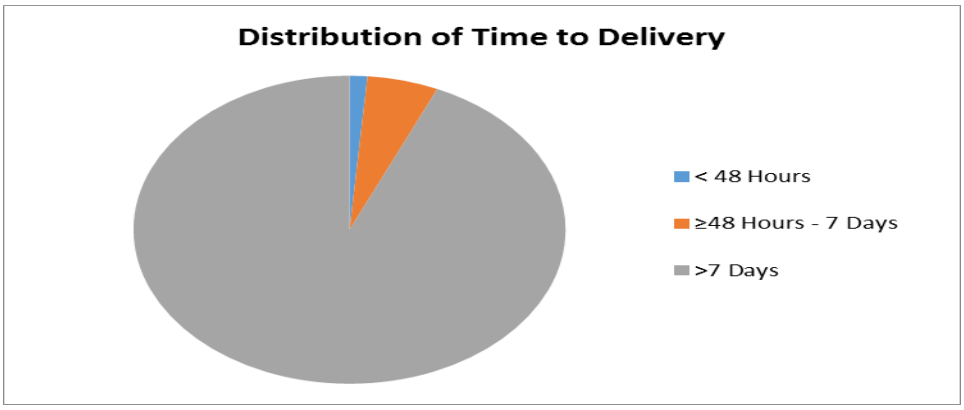

Fig. 1: Distribution of patients based on the delivery time.

Table 2: Distribution of the participants in terms of time to delivery (n = 150)

Sr. No	Time to Delivery	N	Percentage
1	**< 48 Hours**	3	2.67%
2	**≥48 Hours - 7 Days**	7	4%
3	**>7 Days - 5 weeks**	140	93.33%

❖ **Efficacy analysis based on time taken to stop preterm labor contractions**

The study drug Atosiban was found to be very effective in terminating the PTL contractions in 146 (97.33%) patients. Out of 146 pregnant women, 33 of them achieved uterine quiescence within 3 hours, 59 in 6 hours, 49 in the duration ranging from > 6 hours – 12 hours and 05 women between > 12 hours – 48 hours. Uterine contractions did not subside in 04 patients (Table 3). The mean time to stop the PTL contractions was observed as 7 hours after Atosiban administration.

Table 3: Summary of time taken to stop PTL contractions (n=150)

Sr. No.	Time to Stop PTL (Hours)	PTL Stopped- Yes N (%)	PTL Stopped- No N (%)	Total N (%)
1	**> 12 hrs – ≤ 48 hrs**	146 (97.33%)	04 (2.67%)	150 (100%)
2	**> 6 hrs – ≤ 12 hrs**	141 (94%)	09 (6%)	
3	**6 hrs**	92 (61.33%)	58 (38.67%)	
4	**3 hrs**	33 (22%)	117 (78%)	

PTL: *Preterm labour*

❖ **Efficacy analysis based on gestational weeks at the time of admission and delivery (N=150)**

The enrolled patients were categorized as per WHO preterm classification into three gestational age groups: [extremely preterm (< 28 weeks); very preterm (28 to < 32 weeks); moderate to late preterm (32 to < 37 weeks)].

Pre-Atosiban treatment, 47 (31.33%) patients were of 'extremely preterm category', 88 (58.67%) patients were of 'very preterm' patients. Mean gestational age at the time of admission was 29.04 ± 2.12 weeks. Pregnant women treated with Atosiban showed significant prolongation in their pregnancies. 20 (13.33%) patients delivered full-term babies (≥37 weeks) while 103 (68.67%) women delivered after attaining moderate/late preterm gestational age. Mean gestational age at the time of delivery was 34.43±2.69 weeks (Table 4).

Table 4: Summary of gestational period at time of admission and delivery.

Sr. No.	Gestational Weeks	At admission N (%)	At delivery N (%)
1	**<28 weeks**	47 (31.33%)	03 (2%)
2	**28 to <32 weeks**	88 (58.67%)	24 (16%)
3	**32 to <37 weeks**	15 (10%)	103 (68.67%)
4	**≥37 weeks**	NA	20 (13.33%)
5	**Total**	150 (100%)	150 (100%)

❖ **Efficacy analysis based on association between PTL stopped and Number of fetuses/ Encerclage performed / Mode of Conception**

75 (51.7%) participants whose PTL stopped had singleton pregnancies whereas 70 (48.3%) having twin pregnancies showed PTL terminations. PTL did not stop in 3 (75%) singleton pregnancies and 01 (25.0%) twin pregnancy (Table 5). There was no significant difference between the two groups in terms of distribution of patients who did not show PTL termination (X^2 = 0.845, P = 0.622).

Table 5: Association between PTL stopped and number of fetuses.

Sr. No.	Number of Fetuses	PTL Stopped			Fisher's Exact Test	
		Yes	No	Total	X^2	P Value
1	**Singleton**	75 (51.7%)	3 (75.0%)	78 (52.3%)	0.845	0.622
2	**Twins**	70 (48.3%)	1 (25.0%)	71 (47.7%)		
3	**Total**	145 (100.0%)	4 (100.0%)	149 (100.0%)		

The mean time to stop PTL in the participant with cervical encerclage was found to be 7.62±2.72 hours, while in participant without encerclage was 7.27±5.7 hours. There was no significant difference between the two groups and the time to stop PTL (p < 0.230). Atosiban was found equally effective in both the groups irrespective of encerclage procedures performed or not. (Table 6)

Table 6: Association between PTL stopped and Number of Encerclage performed.

Encerclage	Preterm Labour Stopped			Fisher's Exact Test	
	Yes	No	Total	X^2	P Value
Done	9 (6.2%)	1 (25.0%)	10 (6.7%)	2.220	0.243
Not Done	137 (93.8%)	3 (75.0%)	140 (93.3%)		
Total	146 (100.0%)	4 (100.0%)	150 (100.0%)		

Among the two different subgroups of conception, 36 / 38 participants who conceived spontaneously showed PTL stoppage, whereas in the IVF conception subgroup, 108 / 110 participants showed termination of PTL ccontractions upon Atosiban administration. (Table 7) There was no significant difference between the subgroups of conception and PTL termination (X^2 = 1.275, P = 0.272). Atosiban was effective in terminating the preterm uterine contractions in patients who conceived spontaneously or via IVF mode.

Table 7: Association between PTL stopped and Mode of Conception.

Conception	Preterm Labour Stopped			Fisher's Exact Test	
	Yes	No	Total	X^2	P Value
Spontaneous	36 (25.0%)	2 (50.0%)	38 (25.7%)	1.275	0.272
IVF	108 (75.0%)	2 (50.0%)	110 (74.3%)		
Total	144 (100.0%)	4 (100.0%)	148 (100.0%)		

IVF: *In vitro fertilisation*

Secondary Efficacy Outcomes (Table 8)

The mean gestational age at the time of delivery was found to be 34.43 ± 2.69 weeks. 66 (44.0%) women delivered via vaginal route while 84 (56.0%) patients underwent caesarean deliveries. Total 96 (64%) neonates (43 of 78 singletons, 53 of 71 twins) were admitted to intensive care units. 01 singleton death was reported due to neonatal sepsis.

Table 8: Summary of delivery characteristics and neonatal outcomes.

Parameters	Mean ± SD / N (%)
Gestational age at delivery (Weeks)	34.43 ± 2.69
Mode of delivery	
Vaginal	66 (44.0 %)
LSCS	84 (56.0 %)
Admission to NICU	96 (64 %)
Duration of stay in NICU (Weeks)	3.60 ± 2.47
Neonatal respiratory sepsis	01 (0.67 %)
Neonatal necrotizing enterocolitis/ hypoxic ischemic encephalopathy	Nil

LSCS: lower (uterine) segment Caesarean section ***SD:****Standard deviation*

Safety Assessments

No maternal or fetal treatment emergent adverse events were reported. One neonatal (singleton) death occurred in this study due to sepsis.

DISCUSSION

Tocolytics have an important role in the management of PTL by prolonging the gestation time and preventing PTB. Unfortunately, clinically used tocolytics are frequently inefficient and cross the placenta causing fetal side effects.[14,15] An absence of dangerous systemic effects on the mother and the fetus and a minimal fetal transfer distinguishes Atosiban from other tocolytic drugs and suggests its use as a first-line drug.[15,16]

The current study was conducted with the aim to assess the efficacy and safety of Atosiban in 150 Indian patients presenting with PTL at a tertiary care center. Atosiban was found to be very effective in delaying preterm labor ≥ 48 hours in 146 (97.3%) patients, of which 140 patients remained undelivered for more than 7 days. The delay in labor observed in our study was similar to that observed in already published articles.[13,17] Interestingly, the time of delivery with Atosiban treatment extended for the maximum period of 5 weeks with the mean POG at delivery of 34.43 weeks. A remarkable finding of Atosiban is its high efficacy in extending the time of delivery compared to other tocolytic agents, like Nifedipine –and calcium channel blocker, which could extend the time of delivery up to 7 days (range 2-7 days)[18], while β-agonists could extend the same up to 24 to 48 hrs.[19]

By the end of the treatment phase, preterm uterine contractions stopped in 146/150 (97.33%) women treated with Atosiban. Atosiban was successful in delaying PTL in all the gestational age groups (24 to 34 weeks). Moreover, it also reduced the PTB risk in the patients without encerclage procedure.

The evidence for the use of tocolytics in twins is limited. The preterm birth prevention strategies applied to singleton pregnancies have not been found to be effective in twin pregnancies.[20] However, in present study, Atosiban was found to be effective in suppressing oxytocin-induced contractions in 75/78 singletons as well as 70/71 twins.

The live birth rates have been found declining with IVF conceptions worldwide despite increasing concepyion rates.[21] Our present study confirms the beneficial effects of Atosiban in improvement of pregnancy outcomes with IVF. Of the 110 conceived women via IVF, 109 (99.09%) patients successfully delivered live babies. Newborns exposed to Atosiban for several hours before delivery experienced no deleterious effects. 65% of the neonates that were admitted to NICU were discharged within 2 weeks. Only 01 infant expired due to sepsis which had no causal relationship with Atosiban administration. Mean birth weight of infants was found to be 2.27 ± 0.71 kg.

The current study is in line with the latest 2019 official guideline of the German Society for Gynecology and Obstetrics (DGGG), the Austrian Society for Gynecology and Obstetrics (ÖGGG) and the Swiss Society for Gynecology and Obstetrics (SGGG) which say that, Atosiban can delay the birth by 48 h in 75–93% of cases and by 7 days in 62–78% of cases in PTL with cervical dilation.[22] A number of post marketing studies of Atosiban are available worldwide. In a Efficacy Assessment Survey conducted in 91 centers across six European countries, significantly fewer maternal ($p < 0.01$) and fetal ($p < 0.03$) side effects were reported with Atosiban when compared with alternative care modalities (β-agonists, calcium channel blockers and bed rest).[23] The success rate with Atosiban was found to be 79.4% (in extreme preterm) and 76.8% (in moderate preterm) in a multicentric study conducted in Europe involving 585 patients.[24] In another clinical trial conducted in USA, 100% success rate was found in extreme preterm and 68.8% in moderate preterm cases.[25] Atosiban was also found effective in delaying PTL in 78.4% of women as compared to 66.7% of women exposed to β-agonists group (Fenoterol) at the end of 7 days in a study conducted in Germany.[26] While no significant differences were observed between Atosiban and β-agonists in delaying delivery for 48 hours (88.1% vs 88.9%; P=0.99) or 7 days (79.7% vs 77.6%; p=0.28) in studies conducted across Australia, Canada, Czech Republic, Denmark, France, Israel, Sweden and UK, maternal side effects were reported more frequently in β-agonists group (8.3% vs 81.2%, P<0.001) compared to Atosiban.[25]

The present study has its limitations as it restricts the ability to establish the superiority of the Atosiban over other treatment options because of lack of comparator group(s). The scope of the present study was limited to observe its effect on immediate neonatal outcome. Further observational study is needed to evaluate the relative effect of Atosiban on long term morbidities of babies.

CONCLUSION

The findings from this clinical study, supports the use of Atosiban for delaying PTB. Atosiban therapy resulted in more women remaining undelivered for maximum of 5 weeks with better maternal, multifetal and neonatal outcomes. This study re-confirms the results of the already published Atosiban efficacy and safety studies. Healthcare professionals, other stakeholders and the healthcare institutions need to ignite their efforts to prevent PTL using effective tocolytic drug Atosiban.

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