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Evaluation of Atosiban Therapy in the Management of Preterm Labour in Indian Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author BD was involved in conception and design of the study. Author BD reviewed and edited the manuscript. Author SN managed the literature searches and drafted the manuscript. Author SS performed the statistical analysis, reviewed the protocol. Additionally, all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To assess the efficacy and fetomaternal safety of atosiban among Indian pregnant women presenting with preterm labor.
Study Design: Prospective, open-label, multicentric, non-comparative, phase-IV clinical study.
Place and Duration of Study: Department of Obstetrics and Gynaecology at nine hospitals across India from October 2016 to December 2019.
Methodology: A total of 212 pregnant women admitted with preterm labour between 24 and 36 weeks of gestation were administered intravenous atosiban up to 48 hours. Efficacy was defined as the successful delay of delivery without the need of an additional or alternative tocolytic agent for 72 hours. Safety was evaluated by recording the occurrence of adverse events in the mother, fetus and neonate.
Results: Tocolytic efficacy of Atosiban was 84.88% at 48 hours and 74.15% at day 7 without additional tocolytic agent or retreatment after 48 hours. The mean number of days gained after the

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start of atosiban tocolysis were 29.15 ± 1.82 days with mean gestational age at delivery of 35.1 ± 3.33 weeks. Atosiban reduced the frequency of contractions from 4.3 ± 1.47 to 0.67 ± 1.13 contractions/30 min at 72 hours. The proportion of neonates with birth weights more than 2,500 gm was 41.67%. A total of 205 neonates out of 216 (94.95%) had APGAR score more than 7 after 5 minute. Atosiban successfully delayed the labour in 92.31% (n=13) of "Twin pregnancy" patients for 48 hours and beyond 7 days in 9 patients (69.2%). There were no serious adverse events reported.

Conclusions: In patients with threatened preterm birth, 48 hour tocolysis with atosiban was found to be safe and effective in preventing imminent preterm birth even when it was a twin pregnancy or associated with co-morbidities. Atosiban showed favorable side effects profile and improved the perinatal outcomes.

Clinical Trial Registry of India Number: CTRI/2017/03/008065;

Keywords: Preterm labour; effectiveness; atosiban; India; tocolytic.

1. INTRODUCTION

Preterm Birth (PTB), defined as birth before 37 weeks of gestation, is one of the major contributor to perinatal mortality and morbidity, mostly due to respiratory system immaturity, intracranial haemorrhage and infections. These conditions can have long-term neurodevelopmental sequelae such as cognitive impairment, cerebral palsy, visual and hearing deficiencies [1]. Preterm birth complications are the leading cause of death among children under 5 years of age [2]. Of the four million neonatal deaths that occur annually worldwide, it is estimated that 28% are due to PTB. [3] India records the highest number of preterm births worldwide, with more than 3.5 million preterm babies born every year and this number is rising [2].

The morbidity and mortality rates associated with PTB, are inversely related to the gestational age at birth [3]. Therefore, to improve the outcomes of premature neonates, the most common approach is to provide tocolytics to women as labor-inhibiting agents that postpone delivery by inducing uterine quiescence through myometrial relaxation. For each day prolongation, survival rate improves by 3% allowing the administration of alternative rescue treatments [4]. The main indications for the use of tocolytics are to delay delivery in the short term (48-hours) for gaining the time to administer a course of antepartum glucocorticoids and to arrange the transfer in utero to a centre with Neonatal Intensive Care Unit (NICU) facilities [3]. The tocolytic agents currently available for the treatment of Spontaneous Preterm Labour (SPTL) differ with respect to their mechanism of action, evidence based, safety, efficacy and whether or not they are licensed for use. β_2-agonists and vasopressin/oxytocin receptor antagonists (atosiban) are licensed for use but other tocolytics e.g. Calcium Channel Blockers (CCBs)Prostaglandin Synthetase Inhibitors (PGSIs), magnesium sulphate are not permitted because of their side effects. [3]

Only oxytocin/vasopressin receptor antagonists (atosiban) are utero-specific and were developed specifically to treat SPTL. The remaining tocolytics (PGSIs, CCBs, β2-agonists and magnesium sulfate) were developed and introduced for other medical indications, but co-incidentally were found to have tocolytic properties. Accordingly, these drugs have multi-organ neonatal and maternal adverse effects. [3,5]

Atosiban, a synthetic nonapeptide, and an analogue of Oxytocin (OT), is a uterine-specific, competitive inhibitor of the V_{1a} Arginine Vasopressin (AVP) and oxytocin receptors in the myometrial cell membrane. [3] Atosiban was found not only directly to halt contractions and decrease release PGF2α in human uterine smooth muscles but also preferentially to relax uterine arteries improving the uterine blood supply. [6,7]

The evidence to support the use of magnesium sulfate as a tocolytic is poor. Maternal safety concerns have reduced the use of β2-agonists worldwide and mainly used as second-line therapy. [3] Fetal safety and gestational age restrictions have largely condemned PG synthetase inhibitors to second-line therapy. First-line therapy in Europe and other parts of the world is limited to oxytocin receptor antagonists (atosiban) and CCBs (nifedipine). With respect to efficacy, the robustness of the evidence favours atosiban. With respect to safety, atosiban is

clearly the safest tocolytic available as there are fetomaternal concerns with nifedipine. [3,8]

Atosiban introduced not more than a few years back in India, offers a safe and effective treatment option for prevention of SPTL in Indian population. The current study was conducted with an aim to assess the atosiban efficacy in terms of prolongation of pregnancy and fetomaternal safety in Indian pregnant women presenting with Preterm Labour (PTL).

2. MATERIALS AND METHODS

2.1 Design and Setting

An open-label, multicentric, prospective, non-comparative, phase IV clinical trial in Indian pregnant women with PTL was conducted in the Department of Obstetrics and Gynaecology at nine hospitals across India over a period of 3 years from October 2016 to December 2019. This study was conducted in accordance with the International Council for Harmonization for Good Clinical Practice and Declaration of Helsinki. The study was registered at the Clinical Trial Registry of India. (CTRI/2017/03/008065).

2.2 Participants

Two hundred and twelve pregnant women who fulfilled study eligibility criteria were assigned to the treatment with atosiban. Both women with a singleton and a multiple pregnancy were included. Pregnant women aged ≥ 18 years with gestational age from 24 until 36 completed weeks presented with Preterm labor, defined as regular uterine contractions of 4 contractions of 30 seconds' duration during 30 minutes (confirmed by cardiotocography) and were documented. Criteria for cervical changes were a) Nulliparous women: a single cervical examination demonstrating dilatation of 0 cm to 3 cm and effacement of at least 50% and b) Multiparous women: a single cervical examination demonstrating dilatation of 1 cm to 3 cm and effacement of at least 50%.

Exclusion criteria were a contraindication for tocolysis e.g. vaginal bleeding, placenta previa, abruption placentae, eclampsia and severe pre-eclampsia, severe placental insufficiency, chorioamnionitis, preterm rupture of membranes. Women with a fetus showing signs of fetal distress, intrauterine growth restriction, intrauterine fetal death or a fetus suspected of chromosomal or structural anomalies. The details of the disposition of the subjects are given in Fig. 1.

2.3 Interventions

The treatment protocol for atosiban was as follows: Atosiban is administered intravenously in 3 successive stages: an initial bolus dose of 6.75 mg (0.9 ml) over 1 minute, immediately followed by a continuous high dose loading infusion with 300µg/min of atosiban (using 37.5 mg/5 ml vials in 0.9% Normal Saline) for 3 hours, followed by a lower dose atosiban infusion with 100 µg/min (using 37.5 mg/5 ml vials) for up to 45 hours. The total duration of the treatment is 48 hours. The total dose given during a full course of atosiban therapy should preferably not exceed 330.75 mg of atosiban.

Patients could be re-treated with the study drug if there is a recurrence of preterm labor and if the eligibility criteria are still fulfilled. Investigator could give re-treatment or rescue tocolysis with an alternate tocolytic agent as per his/her discretion.

2.4 Outcome Measures

The primary outcomes were to determine the tocolytic efficacy, defined as the proportion of women remaining undelivered and who did not require an additional or alternative tocolytic or retreatment at 72 h from the start of atosiban treatment. In addition, tocolytic efficacy was assessed in terms of the total number of women who had not delivered at 48 hours and at 7 days after starting the treatment, time gained in utero, gestational age at delivery, percentage reduction in uterine contractions, proportion of women re-treated with atosiban and proportion of women who required an additional or alternative tocolytic agent.

Secondary outcomes included the proportion of maternal and fetal, neonatal adverse events reported during the study period. Other secondary outcomes were neonatal morbidity and mortality related to prematurity that were assessed until either discharge from the hospital or neonatal death.

2.5 Data Analysis

All the participants who received atosiban therapy were considered for efficacy and safety outcomes analysis. Descriptive statistics were used for the presentation of primary and

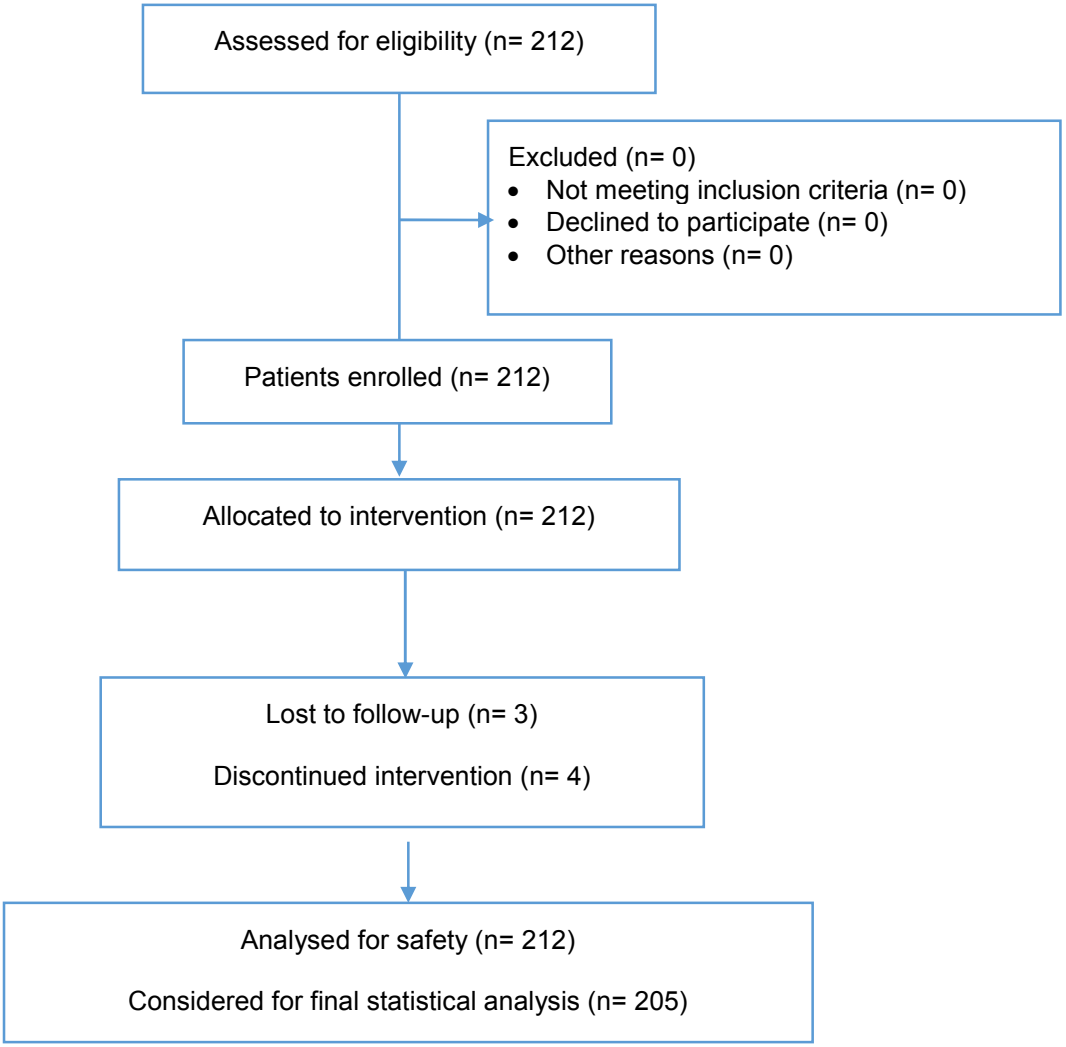

Fig. 1. Disposition of subjects enrolled in trial

secondary outcomes, expressed as Mean ± SD, N (%).The changes in maternal characteristics after treatment with atosiban were analyzed using nonparametric tests (Friedman test followed post-hoc analysis by Bonferroni-Dunn test). Differences were considered significant if P <.05.

3. RESULTS AND DISCUSSION

A total of 212 women presented with preterm labor were assessed for eligibility. Four women discontinued the treatment while three women lost to follow-up. Patient disposition is given in Fig. 1. Two hundred and twelve women were considered for safety analysis and 205 women were available for the efficacy evaluation. There were 192 women with a singleton pregnancy and 13 with a twin pregnancy. The baseline demographics and clinical characteristics of patients are given in Table 1.

3.1 Efficacy Assessments

3.1.1 Tocolytic efficacy of atosiban at 48, 72 hours, 7 days and after 7 days

The success rate of tocolysis (efficacy) was assessed in terms of the total number of women undelivered after 72 h of starting treatment. The tocolytic efficacy of atosiban assessed as the proportions of women who remained undelivered at 48 hr, 72 hr, 7 days and >7 days was 85.37% (175/205), 77.56% (159/205), 74.63% (153/205) and 67.80% (139/205).The tocolytic efficacy of atosiban at 48hr, 72hr, 7 days and after 7 days are presented in Table 2.

Efficacy analysis based on proportion of women, who remained undelivered and who did not receive re-treatment or an alternative tocolytic agent are given in Fig. 2. Out of 205 women treated with atosiban, 3 patients (1.46%)

Table 1. Maternal/fetal baseline demographics and clinical characteristics

Populations	Subjects (N=205)
Age (Years), Mean ± SD	25.05 ± 4.69
Weight (Kg), Mean ± SD	56.02 ± 10.67
Height (cm), Mean ± SD	155.01 ± 7.03
BMI (Kg/m^2), Mean ± SD	23.19 ± 3.32
Type of Gestation	
Nulliparous N (%)	97 (47.32)
Primiparous N (%)	68 (33.17)
Multiparous N (%)	40 (19.51)
Type of pregnancy	
Singleton, N (%)	192 (93.66)
Twin, N (%)	13 (6.34)
Average Gestational age (Week), Mean ± SD	30.9 ± 2.35
Gestational age at enrollment, N (%)	
≤28 weeks	32 (15.61)
>28 to ≤32 weeks	102 (49.76)
>32 to ≤37 weeks	71 (34.63)
Cervical dilatation (cm)*	2 (0-3)
Contraction frequency/30 min (N)*	4 (2-16)
Cervical effacement (%)*	50 (10-80)
Previous preterm delivery, N (%)	13 (6.34%)
Previous spontaneous abortion, N (%)	1 (0.49%)
Previous LSCS, N (%)	4 (1.95)
Maternal comorbidities N (%)	
Anemia	98 (47.80)
Gestational diabetes	5 (2.44)
Gestational hypertension	1 (0.49)
Intrahepatic cholestasis of pregnancy	3 (1.46)
Hypothyroidism	2 (0.98)
Epilepsy	1 (0.49)
Chronic kidney disease	1 (0.49)
Urinary tract infection	1 (0.49)
Fundal fibroid	1 (0.49)

** Median (Range)*

Table 2. Tocolytic efficacy* of atosiban at 48 hr, at 72 hr, at 7 Days and after 7 days

Parameters	48 hr, %(n)	72 hr, %(n)	7 days, %(n)	After 7 days, %(n)
Tocolytic efficacy % (n=205)	85.37 (175)	77.56 (159)	74.63 (153)	67.80 (139)
Type of gestation				
Singletons (n=192)	84.90 (163)	77.08 (148)	74.48 (143)	67.71 (130)
Twin (n=13)	92.31 (12)	84.62 (11)	76.92 (10)	69.23 (9)
Type of pregnancy				
Nulliparous (n=97,47.32%)	81.44 (79)	71.13 (69)	69.07 (67)	62.89 (61)
Primiparous (n=68, 33.17%)	89.71 (59)	79.41 (54)	75 (51)	66.18 (45)
Multiparous (n=40, 19.51%)	92.50 (37)	90 (36)	87.50 (35)	82.50 (33)
Cervical dilation at the start of treatment				
< 2 cm (N=92)	85.87 (79)	80.43 (74)	78.26 (72)	78.26 (72
≥2 cm (N=113)	84.96 (96)	75.22 (85)	71.68 (81)	59.29 (67)
Gestational age at PTL				
≤ 28 weeks(n=32)	90.62 (29)	87.50 (28)	84.37 (27)	81.25 (26)
>28 to ≤ 32 weeks (n=102)	85.29 (87)	78.43 (80)	76.47 (78)	72.54 (74)
>32 to ≤37 weeks(n=71)	83.09 (59)	71.83 (51)	67.60 (48)	54.92 (39)

**Proportion of women remained undelivered including with alternative tocolytic agent or re-treatment*

received retreatments with atosiban and 3 (1.46%) women were offered nifedipine as a second-line rescue tocolytics.

Efficacy based on Type of gestation (Singletons or twins) and parity is also assessed and presented in provided in Table 2. Higher number of multiparous women remained undelivered at 7 days. Impact of initial cervical dilatation on the success of atosiban in terms of prolongation of pregnancy is also assessed and given. Our results demonstrate atosiban has similar success rate based on cervical dilatation (<2 cm or ≥ 2 cm) at 72 hours, however more number of women remained undelivered after 7 days in women with < 2cm cervical dilatation provided as presented in Table 2.

3.1.2 Efficacy analysis based on gestational weeks at the time of admission and at delivery

As per World Health Organization, PTL cases are categorized into three groups based on gestational age: [extremely preterm (< 28 weeks); very preterm (28 to < 32 weeks); moderate to late preterm (32 to < 37 weeks)]. Mean gestational age at the time of admission was 30.9 ± 2.36 w and at the time of delivery was found to be 35.1 ± 3.33 w. The gestational age details of pregnant women at admission and at time of delivery is given in Table 2.

3.1.3 Efficacy analysis based on changes in uterine characteristics from baseline

Gestational age, uterine activity and cervical dilatation were assessed at the time of admission, at 48 h and 72 h, the comparative details are presented in Tables 3a, b, c.

The mean cervical dilatation was 1.69 ± 0.75 cm on admission; with a gradual reduction to 1.23 ± 0.92 cm and 0.96 ± 0.85 cm at 48 hours and 72 hours respectively. The mean frequency of uterine contractions per 30 min showed a gradual fall from 4.33 ± 1.47 to 1.07 ± 1.26 from the time of admission to completion of treatment (i.e. 48 h) and 0.67 ± 1.13 at 72 h. Similarly, the mean duration of contractions cervical effacement (%) gradually reduced from 46.98 ± 14.62 to 30.39 ± 18.72 and 23.11 ± 20.57 at the 48 hours and 72 hours respectively. All these parameters showed a significant change (Friedman's test, P < 0.001) from baseline and presented in Table 4.

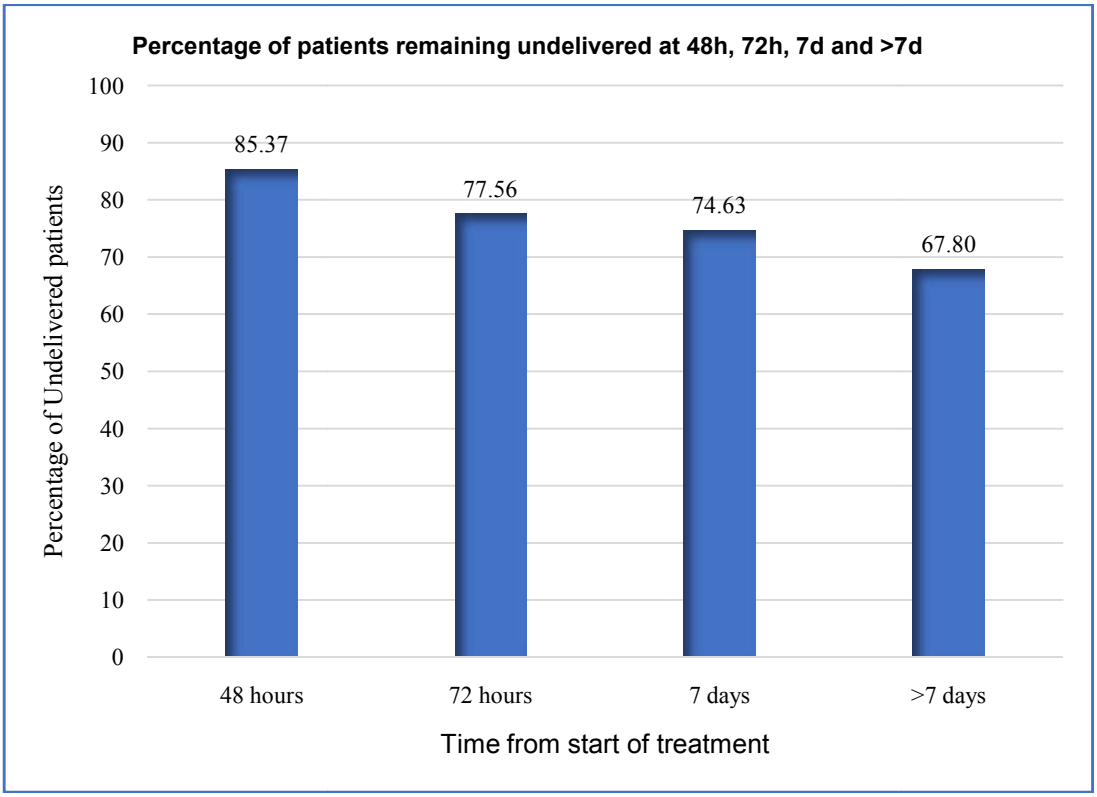

Fig. 2. Percentage of patients remaining undelivered at 48h, 72h, 7d and >7d

Table 3a. Perinatal outcomes of pregnancies

Gestational age at delivery (Weeks)		**Mean ± SD**
Gestational age at delivery (n=205)		35.1 ± 3.33
Cervical dilatation < 2 cm (n=92)		35.86 ± 3.41
Cervical dilatation ≥ 2 cm (n=113)		34.42 ± 3.10
Time gained in utero (in days)		**Mean ± SEM**
Time gained in utero (n=205)		29.15 ± 1.82
Gestational age at admission ≤28 w (n=32)		52.16 ± 5.54
Gestational age at admission ≤32 w (n=102)		30.66 ± 2.38
Gestational age at admission ≤37 w (N=71)		16.59 ± 1.97
Days Gained according to Type of Gestation		**Mean ± SD**
Singleton Pregnancy (n=192) Mean ± SD		30.05 ± 26.45
Twin Pregnancy (n=13) Mean ± SD		15.77 ± 11.59
Gestational Age	**At admission in study, n (%)**	**At birth, n (%)**
≤28 weeks	32 (15.61)	6 (2.93)
>28 to ≤34 weeks	160 (78.05)	79 (38.54)
>34 to ≤37 weeks	13 (6.34)	63 (30.73)
>37 weeks	0 (0.00)	57 (27.80)

Table 3b. Neonatal birth record

Birth Weight (gm)	**Mean ± SD**
Birth weight (n=216)	2249.73 ± 593.3
Singleton (gm) Mean ± SD	2282.22 ± 579.24
Twins (gm) Mean ± SD	1761.46 ± 536.97
Neonates with birth weights more than 2,500 gm, % (n)	41.67% (90)
APGAR score characteristics	
APGAR score 1 minute after birth, Mean ± SD	7.80 ± 1.50
APGAR score 5 minute after birth,Mean ± SD	8.75 ± 1.27
APGAR score more than 7 after 1 minute, % (n)	84.72% (183)
APGAR score more than 7 after 5 minute, % (n)	94.95% (205)
NICU admission, % (n)	22.02% (48)
Neonatal mortality, % (n)	3.67% (8)

3.1.4 Time gained in utero after initiation of treatment and gestational age at the time of delivery

Representation of the time gained in utero from start of atosiban treatment till the time of delivery and gestational age at the time of delivery is given in Table 3aand Figure 5.

3.2 Safety Assessments

Safety analysis was performed in 212 women who had received atosiban treatment and for whom the presence or confirmed absence of adverse events were available for statistical analysis.

3.2.1 APGAR tests of new-born

APGAR score is a quick test to assess the health of new born children. APGAR score is determined by evaluating the new born on five categories (Appearance, Pulse, Grimace, Activity and Respiration). APGAR score ranges from 0 to 10 where a score of ≥7 is considered normal. APGAR test was performed at 1 min and 5 min after birth. The mean of APGAR scores at 1 min was 7.80 ± 1.50 and at 5 min of birth was 8.75 ± 1.27. Out of 216 neonates, 205 (94.95%) had APGAR score more than 7 after 5 minute. The details of neonatal birth are given in Table 3b.

3.2.2 Neonatal birth weight

The average neonatal (n=216) birth weight was 2249.73 ± 593.3 gm. Higher neonatal birth weight was reported in singleton pregnancy (2282.22 ± 579.24 gm) as compared to twin pregnancy (1761.46 ± 536.97). A total of 90 (41.67%) babies were born weighing more than 2,500 gm. Data presented in Table 3b.

3.2.3 Safety analysis based on maternal, fetal and neonatal Adverse Events (AE)

The treatment with atosiban injection was well tolerated by the patients. Total 10 Adverse Events (AE) were reported during study treatment. Pregnant mothers experienced 5 AE of which 2 were severe (gastritis, breast engorgement) and other 3 were of mild to moderate severity (headache, itching, fever). No maternal deaths were reported. Three fetal AE (bradycardia, non-reassuring heart sound) reported. No Intrauterine deaths reported. All AE were resolved without any sequelae at the end of the study. Eight neonatal deaths occurred in this study. Six neonates were admitted to neonatal intensive care unit, but died a few days later. None of the deaths was considered by the investigators to be related to the study medication, atosiban and common reasons were low gestational ages (prematurity), Low birth weight, neonatal severe respiratory distress at birth, the details are given in Table 3c.

Table 3c. Neonatal mortality characteristics (n=8)

SR	Gestational age at birth (weeks)	Birth weight (g)	Neonatal Status at birth	APGAR score after 5 min	Causes of death
1	35.7	1710	Normal but weak	9	Low birth weight
2	27.7	1080	Very weak, needed medical attention	3	Low birth weight
3	31.9	1200	Very weak, needed medical attention	8	Prematurity, Low birth weight
4	26.1	700	Very weak, needed medical attention	3	Neonatal respiratory distress syndrome, Low birth weight
5	31.8	800	Did not survive	3	Neonatal respiratory distress syndrome, Low birth weight
6	29.7	1640	Normal but weak	8	Prematurity with Transient tachypnea of the new-born (TTN)
7	32.1	1300	Very weak, needed medical attention	6	Low APGAR score, Low birth weight
8	38.4	2600	Did not survive	8	Neonatal respiratory distress syndrome

Table 4. Changes in the maternal characteristics after treatment with atosiban

Time points	Cervical dilatation(cm)	Cervical effacement (%)	Uterine contractions/30min
0 h (N=205) [#]	2 (1, 2)	50 (40, 50)	4 (4, 5)
48 h (N=175) [#]	1 (0.5, 2)	30 (20, 50)	1 (0, 2)
72 h (N=161) [#]	1 (0, 1.5)	20 (0, 50)	0 (0, 1)
0-48 h			
Mean Difference	0.553	17.20	3.21
95% CI	4.42 to 6.64	14.56 to 19.84	2.95 to 3.47
P value	< 0.001*	< 0.001*	< 0.001*
0-72 h			
Mean Difference	0.689	21.93	3.52
95% CI	5.78 to 8.00	19.29 to 24.57	3.26 to 3.78
P value	< 0.001*	< 0.001*	< 0.001*

[#]*Data represented as Median (Interquartile range).* Friedman test followed post-hoc analysis by Bonferroni-Dunn test*

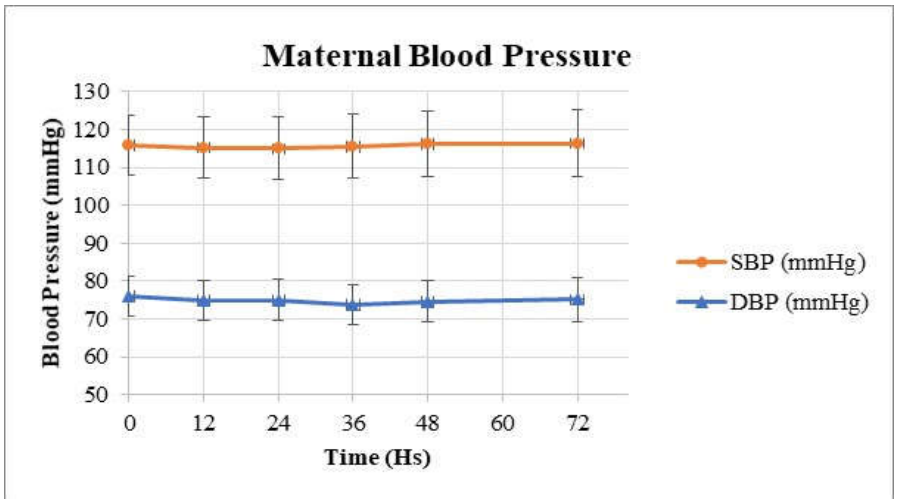

Fig. 3. Maternal blood pressure

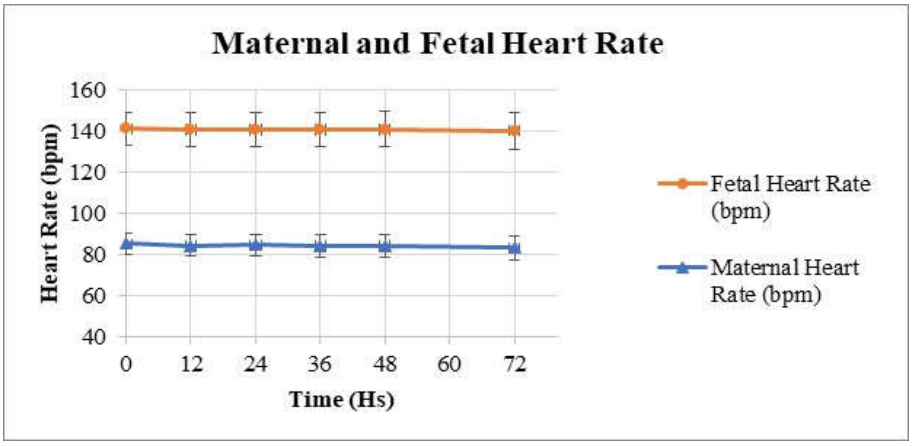

Fig. 4. Maternal and fetal heart rate

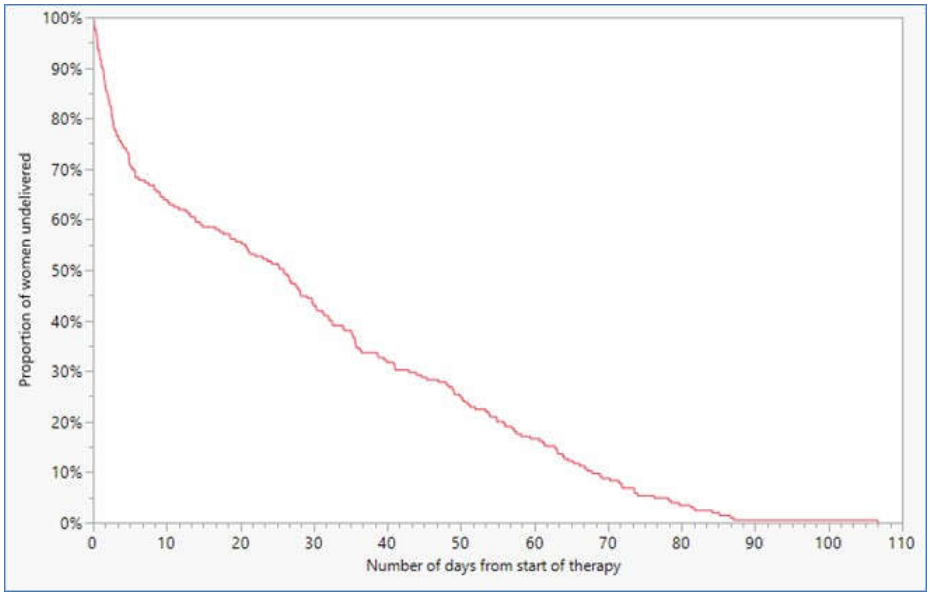

Fig. 5. Kaplan-Meier estimates for time to delivery from start of atosiban therapy

3.2.4 Safety analysis based on clinical laboratory tests, vital sign examination and fetal heart rate

After completion of treatment, no clinically significant changes were noted in laboratory data of the patients compared to baseline. Vital signs examination during the study showed no clinically significant changes when compared to baseline data. Along with maternal hemodynamic parameters fetal well-being by means of fetal heart rate were monitored using cardiotocography at the time of admission, and after every 12 hours till 72 hours, the details are presented in Figs. 3 and 4.

3.3 Discussion

It is important to note that each extra day in uterus before term will results in a significant reduction in morbidity, mortality and cost, both in the NICU and in the long term, [9] thus improving neonatal outcome is the ultimate goal of tocolysis [10]. The perfect tocolytic does not exist, however atosiban is the most effective uterospecific tocolytic with placebo level fetomaternal and neonatal side effects. Other two tocolytics used in India are β2-agonists and nifedipine, since these drugs are not uterospecific, they have multi-organ side effects. [3]The current study was undertaken to assess the tocolytic efficacy and safety of atosiban in a ‘‘real-life’’ clinical setting among Indian pregnant women presenting with preterm labor. Atosiban was successful in delaying preterm labour for ≥ 48 hours in 84.88% while 74.15% women remained undelivered for ≥ 7 days who did not require an alternate tocolytic agent or retreatment. Atosiban success rate is consistent with the previously published Indian and international randomized controlled trials. [11,12,13] The latest 2019 official guideline of the German Society for Gynecology and Obstetrics (DGGG), Austrian Society for Gynecology and Obstetrics (ÖGGG) and Swiss Society for Gynecology and Obstetrics (SGGG) mention that, Atosiban can delay the preterm birth by 48 hours in 75–93% of cases and by 7 days and beyond in 62–78% of cases in PTL with cervical dilation. [14]

Mean gestational age at delivery for all participants in our study was 35.1 ± 3.33 weeks. Overall mean number of days gained in utero after the start of atosiban tocolysis were 29.15 ± 1.82 days, whereas in the subgroup analyses of women showed a greater prolongation of pregnancy (52.16 ± 5.5 days) in women enrolled at a gestational age ≤28 weeks. Similar results were reported by previous studies with overall mean number of days gained in utero with atosiban ranged from 31 to 35 days. [15,16,17] Interestingly the number of patients reaching a gestation age > 37 weeks were 57 (27.80%), which shows a very promising activity of the drug for the preservation of maternal and fetal wellbeing.

Tocolytic efficacy of atosiban was also demonstrated through significant reduction in the uterine contraction frequency, cervical dilation and effacement from the baseline (P< 0.001). Atosiban decreased the frequency of contractions from 4.3 ±1.47 contractions /30 min before treatment to less than zero (0.67 ±1.13 contractions/30 min) at 72 hours after the start of treatment (P<0.001). The mean cervical dilatation was also reduced from1.69 ± 0.75 cm on admission; with gradual reduction to 0.96 ± 0.85 cm at 72 hours. (P<0.001). Initial cervical dilatation has a significant impact on the success of tocolysis and the prolongation of pregnancy. [18] Present study demonstrate that Atosiban is equally effective in both groups (cervical dilatation <2 and ≥2cm) in delaying delivery for 48 hours (85.85% vs 84.96%), however those women with cervical dilatation of < 2 cm were more likely to remain undelivered after 7 days (78.26% vs. 60.20%).

The average birth weight was 2249.73 ± 593.3 gm. The proportion of neonates with birth weights more than 2,500 gm was 41.67%, leading to better survival. Out of 216 neonates, 205 (94.95%) had APGAR score more than 7 after 5 minute, thus avoiding the need of hospitalisation. Only 5% neonates had APGAR score less than 7 after 5-minutes of birth which speaks volumes for the better overall adaptability to new environment and lung maturity after birth. It is already proven that multiple pregnancies are at higher risk of preterm birth with worse neonatal morbidity. [19]In present study, out of 13 twin pregnancies, 92.31% had not been delivered after 48 hours and 69.23% were still pregnant after 7 days and beyond. [20] Our findings are in agreement with previous study of atosiban in preterm labour of twin pregnancy that reported 96.7% efficacy at 48 hours and 80% at day 7. Even repeated cycles of atosiban are safe and have shown effectiveness in delaying delivery in twin pregnancies [21].

In present study, no fetal side effects were observed and maternal side effects are very mild

in nature e.g. headache, nausea, vomiting and no serious side effects were reported. These findings are in line with previous studies where incidence of adverse effects was less than 1%.[22] In an Efficacy Assessment Survey conducted in 91 centres across six European countries (Austria, France, Germany, Italy, Spain and UK), significantly fewer maternal and fetal side effects were reported with Atosiban when compared with 'usual care' [23]. We did not find any significant changes in mean maternal Heart Rate (HR), BP and Fetal Heart Rate (FHR) during the study period of 72 hours. Published Studies have shown a minimal placental transfer of atosiban even at high doses and exposure for several hours before delivery did not show any deleterious effect on new-born or did not increase maternal blood loss at delivery.[24] The overall tolerability of atosiban is in agreement with previous randomised controlled trials and did not show significant changes in maternal HR, FHR.[25,26] Our study did not show any atosiban related adverse event in participant with comorbidities like anemia, gestational diabetes and hypertension etc. These findings are in line with previous research supporting atosiban as first-choice tocolytic in patients at risk of cardiovascular complications, gestational diabetes, multi-fetal pregnancies (twins), anemia, where β-agonists and nifedipine are contraindicated.[21,27,28,29] Analysis of currently available tocolytics demonstrate that atosiban has more robust evidence base than any other tocolytic and without doubt, atosiban has the best all round feto-maternal safety profile of all tocolytics.[8]

This study is associated with some limitations in term of absence of control groups, thus restricting the ability to establish the comparative superiority of the treatment. Present study did not evaluate long-term outcomes in atosiban-exposed children, though the literature shows good safety after several years of follow-up.

4. CONCLUSION

Our study findings showed that 48 hours tocolysis with atosiban resulted in majority of women in preterm labour remaining undelivered whether singleton or multiple pregnancy, even when associated with co-morbidities and did not require an additional or alternative tocolytic agent or retreatment after 48 hours. Atosiban presents no safety concerns for either mother or fetus regardless of the gestational age it is administered. Favourable safety profile, allows prolonged atosiban administration, which results in a successful outcome for both mother and baby, demonstrated via maternal tolerance and high Apgar score thus avoiding the need of hospitalisation. The study findings strongly favours the use of atosiban as a first-line tocolytic drug to delay imminent pre-term birth in pregnant women.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Patients were included in the study after obtaining informed consent, medical history and demographic details.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Study protocol and related documents were approved by the Institutional Ethics Committee (IEC) at each hospital study centre.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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