International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Dewan B et al. Int J Reprod Contracept Obstet Gynecol. 2023 Jun;12(6):1862-1865
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20231569

Original Research Article

Clinical safety and efficacy of atosiban brief duration 14-hour treatment regimen in delaying preterm labor

Bhupesh Dewan*, Siddheshwar Shinde

Medical Services, Zuventus Healthcare Limited, Mumbai, Maharashtra, India

Received: 24 April 2023
Accepted: 15 May 2023

***Correspondence:**
Dr. Bhupesh Dewan,
E-mail: bhupesh.dewan@zuventus.com

ABSTRACT

Background: For preventing preterm labor, the recommended duration of atosiban infusion is 48 hours and the patient has to be hospitalized during the course of treatment. The treatment consists of administering one vial of 0.9 ml as a bolus and then an infusion at a rate of 300 mcg/min for 3 hours followed by 100 mcg/min for the next 45 hours, utilizing nine vials of 5 ml. The objective of the study was to evaluate an alternative brief duration (14-hour) of atosiban treatment involving a bolus dose of 0.9 ml followed by an infusion of 300 mcg/min for 2 hours and 100 mcg/min for the next 12 hours utilizing 3 vials of 5 ml. The advantage being that the treatment could be completed in an outpatient setup and be convenient for the patient as well as for the healthcare staff. This would also reduce the overall cost of the treatment. This prospective single-center study was conducted to evaluate the efficacy and safety of an atosiban brief duration (14-hour) treatment regimen to prevent preterm labor.

Methods: A total of 50 patients with symptoms of preterm labor were enrolled in the study. The efficacy of tocolysis was determined by the percentage of patients who remained undelivered up to 48 hours after atosiban therapy initiation and the follow-up of the patients was done up to delivery. Safety was assessed in terms of the number of maternal and fetal adverse events reported.

Results: The mean gestational age at the enrolment was 32.1±2.6 weeks and the delivery were delayed by a mean of 18.13±17.97 days (range 1-62 days). Thirty-five (70%) patients remained undelivered at 48 hours and 29 (58%) at 7 days. No maternal or fetal adverse events were reported during the study.

Conclusions: A favourable safety and efficacy profile of a brief duration atosiban regimen was observed resulting in ease of administration and a shorter stay in the healthcare facility providing convenience to both patient and hospital staff. The overall cost of the therapy was also reduced. Further clinical trials with larger sample size are required to confirm the findings.

Keywords: Preterm labor, Brief duration regimen, Atosiban, Tocolysis, Efficacy, Patient convenience

INTRODUCTION

Preterm birth is the most common reason for antenatal hospitalization. About 25 million children are born every year in India and approximately 13.6% of all live births occur before term.[1,2] Babies born at earlier gestations have immediate and long-term neonatal complications. Preterm birth accounted for 15.6% of children aged less than 5 years' deaths in India.[3]

The prevention of preterm birth through tocolysis is an established clinical strategy that involves pharmacological inhibition of preterm uterine contractions. Atosiban is a competitive oxytocin receptor antagonist and is approved in the UK, European countries and India for clinical use in patients facing imminent preterm labor.[4,5] Many randomized clinical trials have confirmed the efficacy and safety of atosiban in delaying preterm labor.[6-9]

The use of brief duration treatment of atosiban can vary with the clinical situation and patient needs. The potential advantages of brief duration treatment of atosiban include: more flexibility in managing preterm labor. The treatment can be completed in the outpatient setup of the hospital. Moreover, the decision to continue or discontinue atosiban treatment can be made based on the patient's clinical response. Brief-duration treatment allows for earlier discharge from the hospital, reducing the risk of hospital-acquired infections and improving patient comfort. Brief duration (14-hour) atosiban regimen is less expensive than a long-duration (48-hour) treatment due to the lower cost of medication and shorter stay in the hospital and other tocolytic agents in the treatment of preterm labor.[10-13] Lesser exposure to atosiban results in reduced incidence of adverse events.

Considering the advantages of atosiban as a tocolytic agent using a brief duration regimen, we aimed to evaluate the safety and efficacy of a bolus followed by a 14-hour atosiban infusion in Indian patients to delay preterm labor.

METHODS

The study was conducted at the labor ward of Lokmanya Tilak Municipal General Hospital and Lokmanya Tilak Municipal Medical College, Mumbai, India and a total of 50 patients were enrolled between September 2018 and September 2022. All patients were above 24 weeks of gestation, presenting with preterm labor having uterine contractions with or without cervical changes. Patients with chorioamnionitis, ruptured membranes, vaginal bleeding, preeclampsia, intrauterine growth restriction, intrauterine fetal death, congenital or acquired uterine malformation, severe placental insufficiency, placenta previa, abruptio placentae, fetal distress or patients who were otherwise judged inappropriate for inclusion in the study by the investigator were excluded from the study. Written informed consent was obtained. Approval for the study was granted by the Institutional Ethics Committee of the hospital and is available at www.ctri.nic.in (CTRI/2017/03/008099). The study was performed in accordance with International Council for Harmonization for Good Clinical Practice, Declaration of Helsinki and New Drugs and Clinical Trials, Rules, 2019.

Brief duration regimen of atosiban (TosibanTM, Zuventus Healthcare Limited, India) consisted of administering a single intravenous bolus dose of 6.75 mg over 1 minute followed by an intravenous infusion at a speed of 300 mcg/min for 2 hours and 100 mcg/min for a period of next 12 hours thus a total duration of 14 hours. A provision of rescue medicine for patients with recurring symptoms of preterm labor was considered in the form of either repeated atosiban infusion or any other tocolytic agent at the investigator's discretion. All the enrolled patients were given a course of corticosteroid therapy at the start of the tocolytic treatment. The enrolled patients were observed for 7 days and were followed up till delivery.

The primary outcome of the study was the percentage of patients who remained undelivered at 48 hours after commencing the tocolytic therapy. The number of days gained *in utero* was observed and recorded. Safety was assessed as the incidence of maternal and fetal adverse events. Descriptive statistics were used to describe the baseline characteristics and represented as mean±standard deviation, median, and range. Categorical variables were presented as percentages and frequencies.

RESULTS

A total of 50 patients received a brief duration atosiban treatment for preterm labor. The median maternal age was 25 years (range: 18-39 years) and median gravidity and parity were 2 (range: 1-4), and 1 (range: 0-2) respectively. The demographic features are described in Table 1.

Table 1: General information about the brief duration treatment group.

Characteristics	Atosiban (n=50)
	N (%)
Maternal age (years)	25.74±5.17
Body mass index (kg/m^2)	24.36±3.70
Average gestational age at admission (week)	32.1±2.6
Type of gestation	
Nulliparous	20 (40)
Primiparous	20 (40)
Multiparous	10 (20)
Type of pregnancy	
Singleton	48 (96)
Twin	2 (4)
Gestational age groups (weeks)	
<28	2 (4)
≥28 to <32	11 (22)
≥32 to <37	37 (74)
Cervical dilatation (cm)	
<2 cm	26 (52)
≥2 cm	24 (48)
History of preterm delivery	22 (44)

Values are given as n (%), mean±SD.

Atosiban was successful in delaying delivery by ≥48 hours in 70% of the enrolled patients. The mean number of days gained after the start of atosiban was 18.13±17.97 days (median 14.46 days, range 1-62 days). Efficacy in terms of the type of gestation and pregnancy, cervical length, and gestation age are presented in Table 2. A total of 9 (18%) patients received re-treatment with atosiban immediately after a brief duration of atosiban therapy. Rescue therapy with an alternative tocolytic drug was not required. A significantly higher tocolytic success rate was observed in the group with cervical dilatation of <2 cm as compared to those with ≥2 cm at 48 hours (p=0.003, Pearson Chi^2 test) and 7 days (p=0.005 Pearson Chi^2 test).

Table 2: Tocolytic efficacy of atosiban brief duration.

Parameters	48 hr	72 hr	Day 7
	N (%)	N (%)	N (%)
Tocolytic efficacy (n=50)	35 (70)	34 (68)	29 (58)
Type of gestation			
Nulliparous (n=20, 40%)	12 (60)	12 (60)	10 (50)
Primiparous (n=20, 40%)	16 (80)	15 (75)	14 (70)
Multiparous (n=10, 20%)	7 (70)	7 (70)	5 (50)
Type of pregnancy			
Singleton (n=48, 96%)	35 (72.92)	34 (70.83)	29 (60.42)
Twins (n=2, 4%)	0	0	0
Cervical dilatation at the start of treatment			
<2 cm (n=26, 52%)	23 (88.46)	23 (88.46)	20 (76.92)
≥2 cm (n=24, 48%)	12 (50.0)	11 (45.83)	9 (37.5)
Gestational age at PTL			
24 to <28 weeks (n=2, 4%)	0	0	0
≥28 to <32 weeks (n=11, 22%)	7 (63.64)	7 (63.64)	7 (63.64)
≥32 to <37 weeks (n=37, 74%)	28 (75.68)	27 (72.97)	22 (59.46)

The atosiban treatment was well tolerated by the patients. No maternal-fetal adverse effects were reported during the study and all the neonates survived at delivery which confirmed the safety of the atosiban brief duration regimen.

DISCUSSION

Uterine contractions are influenced by oxytocin and vasopressin by directly affecting the membrane-bound receptors. Atosiban is an oxytocin and vasopressin antagonist that competitively antagonizes the oxytocin-vasopressin receptor and inhibits oxytocin-induced uterine contractions.[14] The atosiban tocolysis suggests that the bolus dose achieves immediate uterine quiescence, followed by a maintenance dose at a steady state concentration during the infusion period ensuring optimal drug exposure to the uterus. In a pharmacokinetic study, the plasma concentration of atosiban achieved a steady state level in 1 hour at a 300 mcg/min infusion rate for 6 hours and the 75% uterine contractions decreased in the first 3 hours of infusion.[15]

In the current trial, a brief duration (14-hour) regimen of atosiban was found to be safe and effective in delaying preterm labor and allowing sufficient time for the corticosteroids to be given. The pregnancy was prolonged for 48 hours in 70% of the patients, and out of those patients, approximately 83% continued their pregnancy for at least 7 days. Similar findings were reported for atosiban in earlier published brief-duration studies. Goodwin et al reported that a 12-hour duration of atosiban resulted in successful tocolysis in 71% of patients.[16] In another study by Goodwin et al in a dose-ranging study, a 12-hour atosiban regimen delayed pregnancy in 67% of patients.[17] In a comparative trial, 18-hour atosiban treatment was as effective as ritodrine in prolonging pregnancy by 48 hours in 71.4% of patients in the atosiban group (vs. 66.9% in the ritodrine group) and better tolerated than the ritodrine.[18] Another comparative trial reported the tocolytic efficacy of 18-hour atosiban treatment in 82% of patients.[19] Clinical experience has provided evidence that the efficacy of 18-hour atosiban treatment in preterm labor cases involving twin pregnancies, resulting in a 48 hours prolongation of pregnancy in 73% of patients. Notably, no maternal or fetal complications were observed.[20] This evidence suggested that brief-duration atosiban treatment may be a viable option for patients at risk of preterm labor.

Opting for a short-duration regimen in preterm labor had the dual advantage of prolonging delivery in a short hospital stay, and limiting the potential side effects that can arise from longer hospital stays. This regimen allowed sufficient time for the administration of antenatal corticosteroids, required for favourable fetal outcomes. It was important to note that the optimal duration of atosiban treatment depended on several factors, including the individual patient's clinical status, the severity of preterm labor, the gestational age of the fetus, and the overall health of the mother and baby. The decision to use brief-duration or long-duration atosiban should be based on careful consideration of these factors and in consultation with a healthcare provider.

Brief-duration atosiban regimen for delaying preterm labor offers comparable safety and efficacy with the added benefits of managing preterm labor economically and conveniently. The sample size of this study was small, and a control group was not set up. We recommend further larger randomized controlled trials be performed to validate the findings obtained in the current study.

CONCLUSION

A favorable safety and efficacy profile of a brief duration atosiban regimen was observed resulting in ease of administration and a shorter stay in the healthcare facility providing convenience to both patient and hospital staff. Larger multicentric clinical trials are recommended to be conducted to confirm the findings.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Rahul Mayekar (Lokmanya Tilak Municipal General Hospital and General Hospital, Mumbai, Maharashtra, India) for conducting the clinical trial.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. UNICEF. Fact sheet: Key data. Available at: https://www.unicef.org/india/key-data. Accessed on 5 April 2023.
2. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: A systematic review and modelling analysis. Lancet Glob Health. 2019;7(1):37-46.
3. Dandona R, Kumar GA, Henry NJ, Joshua V, Ramji S, Gupta SS, et al. Subnational mapping of under-5 and neonatal mortality trends in India: The Global Burden of Disease Study 2000-17. Lancet. 2020;395(10237):1640-58.
4. Lamont CD, Jørgensen JS, Lamont RF. The safety of tocolytics used for the inhibition of preterm labour. Expert Opin Drug Saf. 2016;15(9):1163-73.
5. Central Drugs Standard Control Organization Atosiban. New Drugs Approved by Central Drugs Standard Control Organization, India. Available at: https://cdscoonline.gov.in/CDSCO/Drugs. Assessed on 5 April 2023.
6. Yu Y, Yang Z, Wu L, Zhu Y, Guo F. Effectiveness and safety of atosiban versus conventional treatment in the management of preterm labor. Taiwan J Obstet Gynecol. 2020;59(5):682-5.
7. Saleh SS, Al-Ramahi MQ, Al Kazaleh FA. Atosiban and nifedipine in the suppression of pre-term labour: a comparative study. J Obstet Gynaecol. 2013;33(1):43-5.
8. Dewan B, Shah D. The clinical experience of atosiban in preterm labour. J Adv Med Med Res. 2016;13(7):1-9.
9. Baev OR, Vasilchenko ON, Karapetyan AO, Tetruashvili NK, Khodzhaeva ZS. A comparison of tocolysis with nifedipine or atosiban in preterm labor. Obstetr Gynecol. 2018;5:50-6.
10. Wex J, Abou-Setta AM, Clerici G, Di Renzo GC. Atosiban versus betamimetics in the treatment of preterm labour in Italy: clinical and economic importance of side-effects. Eur J Obstet Gynecol Reprod Biol. 2011;157(2):128-35.
11. Wex J, Connolly M, Rath W. Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation. BMC Pregn Childbirth. 2009;9:23.
12. Sebastian E, Bykersma C, Eggleston A, Eddy KE, Chim ST, Zahroh RI, et al. Cost-effectiveness of antenatal corticosteroids and tocolytic agents in the management of preterm birth: a systematic review. E Clinic Med. 2022;49:101496.
13. Hrubý K. Comparison of the cost of treatment of premature labor with atosiban or beta-sympathomimetics from the perspective of the health care payer--a pharmacoeconomic model. Ceska Gynekol. 2004;69(2):96-105.
14. Fullerton GM, Black M, Shetty A, Bhattacharya S. Atosiban in the management of preterm labour. Clinical Medicine Insights: Women Health. 2011;4:9-16.
15. Goodwin TM, Millar L, North L, Abrams LS, Weglein RC, Holland ML. The pharmacokinetics of the oxytocin antagonist atosiban in pregnant women with preterm uterine contractions. Am J Obstet Gynecol. 1995;173:913-7.
16. Goodwin TM, Valenzuela G, Silver H, Hayashi R, Creasy GW, Lane R. Treatment of preterm labor with the oxytocin antagonist atosiban. Am J Perinatol. 1996;13(3):143-6.
17. Goodwin TM, Valenzuela GJ, Silver H, Creasy G. Dose ranging study of the oxytocin antagonist atosiban in the treatment of preterm labor. Atosiban Study Group. Obstet Gynecol. 1996;88(3):331-6.
18. Moutquin JM, Sherman D, Cohen H, Mohide PT, Hochner-Celnikier D, Fejgin M, et al. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. Am J Obstet Gynecol. 2000;182(5):1191-9.
19. Lin CH, Lin SY, Shyu MK, Chen SU, Lee CN. Randomized trial of oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of spontaneous preterm labor in Taiwanese women. J Formos Med Assoc. 2009;108(6):493-501.
20. Ya-Juan X, Li-Min R, Xiao-Hua L, Shan-Shan Z, Zhong-Yuan Z, Ying-Ying Z, et al. Clinical efficacy of atosiban treatment in late abortion and preterm labour of twin pregnancy. Int J Clin Exp Med. 2016;9(2):3946-52.

Cite this article as: Dewan B, Shinde S. Clinical safety and efficacy of atosiban brief duration 14-hour treatment regimen in delaying preterm labor. Int J Reprod Contracept Obstet Gynecol 2023;12:1862-5.