International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2023; 7(3): 371-375
Received: 14-03-2023
Accepted: 15-04-2022

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Study to evaluate the efficacy and safety of Atosiban in preterm labour in North Indian population

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DOI: https://doi.org/10.33545/gynae.2023.v7.i3c.1336

Abstract
Background: Preterm birth occurs in 5-10% of all pregnancies, leading to an estimated 13 million preterm births worldwide. The goal of managing spontaneous preterm labour is to minimise perinatal morbidity and mortality while preserving maternal health. Improved outcomes are associated with administration of a full course of corticosteroids to aid fetal pulmonary maturation and timely in utero transfer to a specialist unit where the neonate can receive optimal care.
Methods: A prospective, open label, non-comparative study was conducted at Ganesh Shankar vidhyarthi memorial Medical College, Kanpur in the department of obstetrics and gynaecology over a period of one year. After informed consent and ethical clearance from institutional ethics committee, Kanpur, total 72 pregnant women were recruited for this study. Eligible patients received treatment with atosiban as intravenous (I.V.) infusion for 48 hrs in three successive stages. 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).
Results: Mean age of women was 24±3.6 years and gestational age was 32 ± 2.14 weeks. In this study atosiban was successful in delaying preterm labour for ≥ 48 hours in 23.50%, ≥ 72 hours in 70.50% while 5.80% women remained undelivered for ≥ 7 days who did not require an alternate tocolytic agent or retreatment which is similar to the study of Dewan *et al.* where for ≥ 48 hours in 84.88% while 74.15% for ≥ 7 days, the effect of atosiban treatment on fetal health was analysed in terms of APGAR score, in which out of total 72 preterm new borns, only 12 (16.66%) had APGAR score ≤ 7 while 60 (83.33%) had APGAR score of > 7.
Conclusion: The present study shows that atosiban is a safe and effective drug for the treatment of preterm labour. There were no serious maternal or fetal side effects.

Keywords: Atosiban, tocolytic, preterm, APGAR score, adverse effect

Introduction
Preterm birth occurs in 5-10% of all pregnancies, leading to an estimated 13 million preterm births worldwide [1, 2]. Preterm birth contributes significantly to perinatal death and neurodevelopmental defect, which can require lifelong care at considerable expense. Infants delivered preterm are susceptible to life threatening complications, such as respiratory distress syndrome, intracranial haemorrhage, necrotising enterocolitis, jaundice, hypothermia and hypoglycaemia [3].
The goal of managing spontaneous preterm labour is to minimise perinatal morbidity and mortality while preserving maternal health [4]. Improved outcomes are associated with administration of a full course of corticosteroids to aid fetal pulmonary maturation and timely in utero transfer to a higher center where the neonate can receive optimal care [5, 6]. The main aim of tocolysis is to delay delivery long enough to achieve this; the delay period generally is at least 48 hours [7]. Several drugs have been used to treat preterm labour, which includes β-agonists, COX inhibitors, Calcium channel blockers, Magnesium sulphate, and Nitric oxide donors [8]. These drugs can prolong pregnancy for up to 48 h but their non-specific mode of action results in an unfavorable systemic side-effects, particularly with respect to maternal cardiovascular events [9]. A recent guideline published by the Royal College of Obstetricians and Gynaecologists has stated that the most commonly used beta-agonist, ritodrine, no longer seems to be the best choice, and has suggested the oxytocin receptor antagonist atosiban as alternative, based on comparable efficacy and superior maternal and fetal adverse-event profiles [10].
Atosiban: an oxytocin antagonist, Atosiban acts as an oxytocin antagonist by competing with oxytocin for receptor sites in the uterus.

This results in a dose-dependent inhibition of uterine contractility. The specificity for oxytocin receptors in the uterus is the key to the clinical application of atosiban; since the major problem with all current tocolytic agents is their systemic activity, which causes potentially harmful multi-organ adverse events [11-13].

Atosiban demonstrated a similar efficacy but significantly fewer side effects as compared to commonly used nifedipine. Most of the adverse events associated with nifedipine were cardiovascular (hypotension, palpitations or tachycardia), while in case of atosiban group there were no adverse effects [14].

Materials and Methods

Setting

A prospective, open label, non-comparative study was conducted at Ganesh Shankar vidhyarthi memorial Medical College, Kanpur in the department of obstetrics and gynecology. The study was initially sponsored by Zuventus Healthcare Ltd and was later continued in department by itself 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).

Total 72 patients were enrolled in the study after insuring all the eligibility criteria. All the patients underwent a complete physical examination. 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. Other tocolytic agents were not permitted concomitantly with the study drug. Antibiotics and corticosteroid therapy was allowed when needed.

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 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), Chisquare test and through paired student t test.

Results

The demographic profile and baseline clinical characteristic of the patients is given in (Table 1).

Table 1: Baseline demographics of the patient

Parameters	Mean ± SD
Age (years)	24 ± 3.6
GA (weeks)	32 ± 2.14
Primipara	32
Multipara	40
Height (cm)	150 ± 3.35
Weight (kgs)	50.6 ± 4.93
Cervical dilatation (cm)	2.30 ± 0.42
Uterine contraction frequency (In 30mins)	0.83 ± 1.91

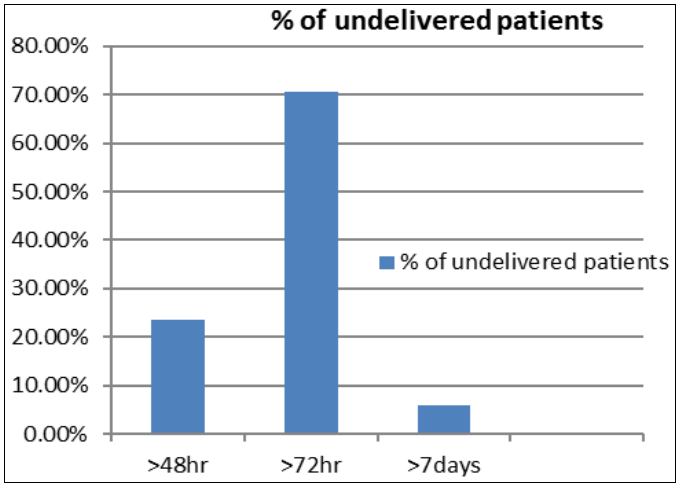


Fig 1: Percentage of patients remaining undelivered at > 48 hours, > 72 hours and > 7 days after administration of tocolytic

In this study patients were categorized into three gestational age groups as per World Health Organization (WHO) preterm classification [extremely preterm (<28 weeks); very preterm (28 to <32 weeks) moderate to late preterm (32 to <37 weeks)]; but no such patient were there in extremely preterm group. Figure-2 represents the status of delivery after receiving treatment with atosiban

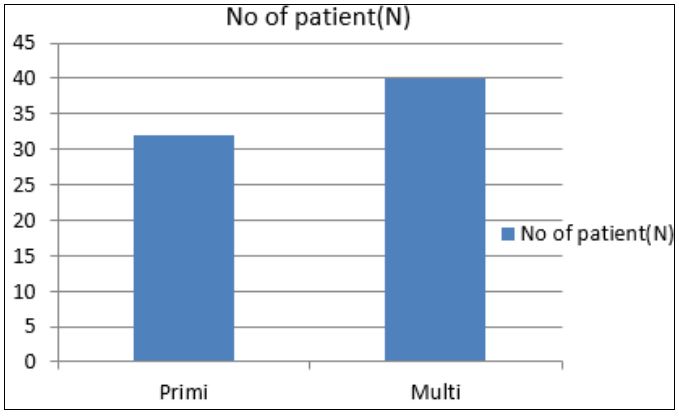
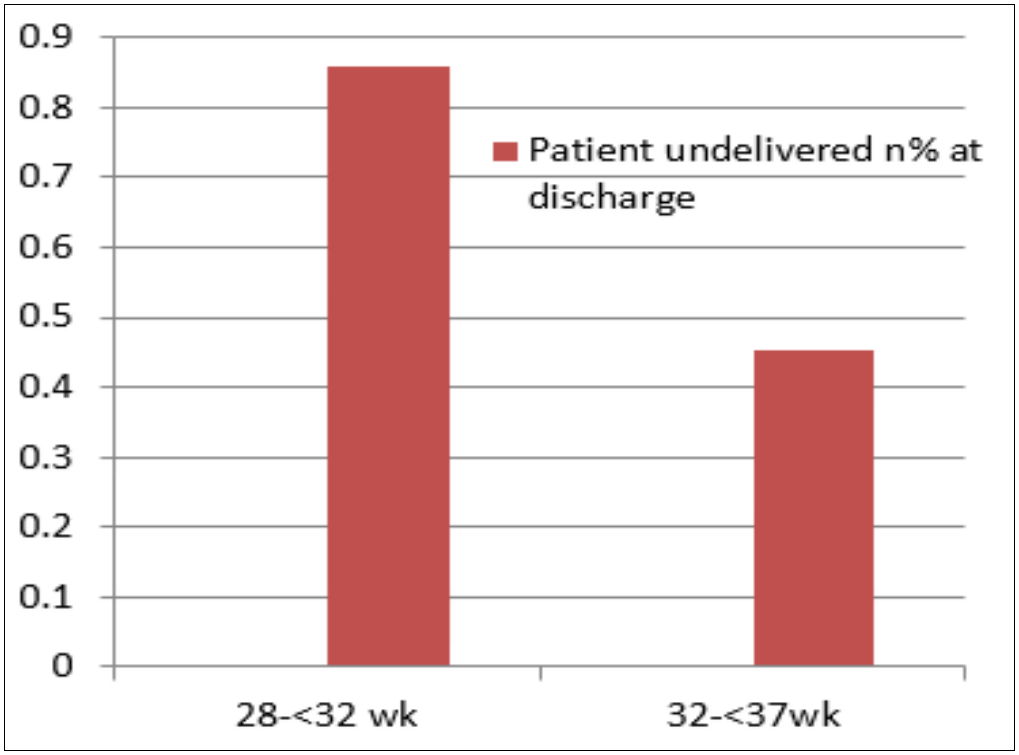


Fig 2: Delivery status based on gestational age (N=72)

Tocolytic efficacy of atosiban was analyzed on the basis of parity. Atosiban was slightly more effective in multiparous but was not significant. This might be because of more compliance in multiparous towards treatment protocol (Figure 3).



*Where n=28 for < 32 weeks and N=44 for < 37 weeks

Fig 3: Efficacy of atosiban in prime & multiparous patient (N=72)

Efficacy was analyzed based on the changes observed in cervical dilation, cervical effacement and uterine contraction frequency after treatment with the study medication, described in table (2) none of the parameters were significant might be because of small sample size.

Table 2: Changes of maternal characteristics after treatment with atosiban (N=72)

Time Point	Cervical Dilatation (cm)	Cervical Effacement	Uterine contraction (in 30min)
0hrs	2.30±0.42	51.10±4.71	0.83±1.91
48hrs	2.31±0.68	47.2±11.79	0.20±0.94
72hrs	2.69±1.94	50±17.15	0.3±1.41
Discharge	2.69±1.94	50±17.15	
Mean Difference (0-48hrs)	0±0.54	3.89±16.5	0.60±1.46
Mean Difference (0-72hrs)	0.39±1.73	1.11±20.83	0.50±1.42
Mean Difference (0hr -till discharge)	0	1.11±20.83	0

All the patients except 1, 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 except 2 patients who had fetal distress which was relieved after discontinuation of treatment. So, the study medication was well tolerated as no major maternal or fetal adverse events were observed. Table (3)

Table 3: Analysis of side effects after t/t with atosiban

Side effects after drug intake	No. of Patients	Type of S/E
3hrs	2	Foetal Distress
24hrs	0	-
48hrs	1	Severe Gastritis

Out of total 72 preterm new borns only 12 (16.66%) had APGAR score ≤ 7 while 60 (83.33%) had APGAR score of > 7. Table (4).

Table 4: Relation of neonatal outcome with gestational age after treatment with atosiban

Gestational age (weeks)	APGAR at 5min (N=72)			
	≤ 7	>7	Total	N%
28- < 32	N = 4	N = 22	26	38.88
32- < 37	N = 8	N = 38	46	61.11
	12(16.66%)	60(83.3%)	72	

Discussion

Atosiban is a synthetic peptide which acts as a competitive oxytocin antagonist at human uterine oxytocin receptors [15]. Oxytocin can not only cause uterine contractions, but also lead to cervical ripening by stimulating the release of prostaglandins in the decidual and fetal membranes [16].

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 [17], thus improving neonatal outcome is the ultimate goal of tocolysis [18].

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 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. [19]. Although adverse events occur less frequently with usage of nifedipine as compared to β-agonists [20], maternal adverse events like hypotension and flushing have been reported and can be troublesome in patients at risk of cardiovascular complications [14, 21-23]. Atosiban demonstrated comparable efficacy to the other tocolytics without any major side effects reported with other classes of such drugs [24]. Though in our study no major side effects were observed except severe gastritis in one and fetal distress in 2 patients.

Mean age of women was 24 ± 3.6 years and gestational age was 32 ± 2.14 weeks. In this study atosiban was successful in delaying preterm labour for ≥ 48 hours in 23.50%, ≥ 72 hours in 70.50% while 5.80% women remained undelivered for ≥ 7 days who did not require an alternate tocolytic agent or retreatment which is similar to the study of Dewan *et al.* where for ≥ 48 hours in 84.88% while 74.15% for ≥ 7 days [25].

Journal of Advances in Medicine and Medical Research
32(24): 76-88, 2020; Article no.JAMMR.63972
ISSN: 2456-8899

Journal of Advances in Medicine and Medical Research
32(24): 76-88, 2020; Article no.JAMMR.63972
ISSN: 2456-8899

Atosiban was successful in delaying labour in all the gestational age groups (28 to 37 weeks). Successful tocolysis was noted in very preterm (85.71%, N=6/7) but not very satisfactory in moderate or late preterm (45.45%, N=5/11). 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 [26]. 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) [27].

Atosiban was slightly more effective in multiparous (55.55%) but was not significant. This might be because of more compliance in multiparous towards treatment protocol.

Tocolytic efficacy of atosiban was demonstrated through reduction in the uterine contraction frequency, cervical dilation and cervical effacement from the baseline after treatment with atosiban but none of the value was statistically significant, might be because of small sample size.

In this study, the effect of atosiban treatment on fetal health was analysed in terms of APGAR score, in which out of total 72 preterm new borns, only 12 (16.66%) had APGAR score ≤7 while 60 (83.33%) had APGAR score of >7. Similar finding was also found in the study Dewan *et al.* where 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 [25].

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 in this study similar to Dewan *et al.* [28]. 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 [27, 29-32,]. 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 recommendation for atosiban in treatment guidelines.

Conclusion

The present study shows that atosiban is a safe and effective drug for the treatment of preterm labour. There were no serious maternal or fetal side effects. 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.

Acknowledgment

This study was conducted at Ganesh Shankar vidhyarthi memorial Medical College, Kanpur in the department of obstetrics and gynecology. And was initially sponsored by Zuventus Healthcare Ltd and was later continued in department by itself 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. The trial has been registered with the Clinical Trial Registry of India (Reg. No: CTRI/2013/11/004166). There is no conflict of interest**.**

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Gupta N, Jahan U, Shukla S, Usmani F. Study to evaluate the efficacy and safety of Atosiban in preterm labour in North Indian population. International Journal of Clinical Obstetrics and Gynaecology. 2023;7(3):371-375.