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Study on Safety and Efficacy of Atosiban and Nifedipine in the Management of Threatened Preterm Labour

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ABSTRACT

Background: Preterm birth is the primary cause of newborn mortality and morbidity globally. The ideal drug of choice should have favourable safety profile for both the mother and foetus. It should also reduce neonatal morbidity and mortality at a reasonable cost. In the recent past Nifedipine was the drug of choice as a tocolytic drug. But now Atosiban is the new drug which seems to have a lot of advantages over Nifedipine.

Methods: The present study was undertaken on 150 women admitted to labour room attending the Antenatal OPD in the Department of Obstetrics and Gynaecology S.N. Medical College and Hospital, Agra, India between September 2017 to August 2019. These women were randomly divided into two groups-Atosiban groups and Nifedipine group.

Results: Women with Bishop score >7 needed more than 132.75 mg of total Atosiban drug in 6.67% of cases (n=60). About 28% of women among the total participants felt adverse effects. None of the women needed early drug termination due to adverse effects in the Atosiban group; the most common side effect was mild gastrointestinal upset (28%, n=60). About 54% of women needed early drug termination in the Nifedipine group (n=70); the most common adverse effect was hypotension (21.42%, n=70). Atosiban infusion has overall 95% (n=60) undelivered women at the end of 48 hours, 96.49% remain free from contraction for the first 24 hours.

Conclusion: Atosiban is better tolerated by women as compared to Nifedipine. Atosiban showed the best safety and maternal profile. It is important to compare oxytocin antagonists and calcium channel blockers directly for tocolytic efficacy and effects on neonatal outcomes.

Key-words: Atosiban, Bishop score, Contraction, Nifedipine, Oxytocin antagonists, Preterm labour

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INTRODUCTION

Threatened preterm labour (TPTL) is referred to as documented uterine contractions with no signs of cervical irregularity. Preterm birth is a significant public health issue in terms of life loss, long-term disability, and medical expenses. It is the primary cause of infant morbidity and mortality globally. The gestational age at birth has an immediate impact on the prognosis of preterm babies. Any birth that occurs between the age

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of viability and 37 full weeks of gestation is considered preterm [1]. In most of the developed and developing countries, the incidence of preterm birth ranges from 10%–15%. However, it is still increasing worldwide attributed to better dating scans, a rise in multiple gestations through assisted reproductive techniques, and iatrogenic deliveries [2].

The chance of survival increases by 3% for every day that a baby is delivered between 22 and 28 weeks of gestation. Numerous studies have demonstrated that tocolysis postpones delivery long enough to allow for the administration of an entire course of antepartum glucocorticoids and to make the transition from the uterus to a tertiary care unit where newborn care will be optimum. These are associated with improved maternal and foetal outcomes. Prenatal glucocorticoids lower the risk of respiratory distress syndrome, periventricular leucomalacia, intraventricular haemorrhage, and necrotizing enterocolitis. When compared to postnatal transportation, in-utero transfer is linked to lower rates of morbidity and mortality as well as less hospital-based intervention.

Tocolysis (a term proposed by Mosler and Schwalm in Germany) refers to the pharmacological suppression of preterm labour (PTL). Various tocolytic agents have been tested in the past. Though their use in recent times is controversial, they should still be considered at least to keep patients undelivered for the short time necessary for glucocorticoid treatment.

Many different substances have been recommended to suppress uterine contractions. Currently, nitric oxide donors, prostaglandin synthetase inhibitors, beta-agonists, calcium channel blockers, and oxytocin receptor antagonists are in use. A new drug in the spectrum of tocolytics is Atosiban, which is an oxytocin receptor antagonist. It has recently become available in India. The optimal medication should be safe for both the mother and the foetus and should lower the risk of newborn morbidity and death at a reasonable cost.

In the recent past, Nifedipine was the drug of choice as a tocolytic. But now Atosiban is the new drug with lots of advantages over Nifedipine. While Nifedipine may result in fatal death and severe hypotension, Atosiban is regarded to be fully safe for mothers. As compared to all the tocolytics, nifedipine significantly reduced delivery within 7 days of starting medication. It also reduces the frequency of neonatal respiratory distress syndrome, neonatal jaundice, necrotizing enterocolitis, and intraventricular haemorrhage. However additional side effects associated with the use of Nifedipine include hypotension, tachycardia, headache, and vertigo.

In the clinical context, TPTL is frequently used to describe uterine contractions that have been observed but do not result in cervical change. However, if suspicion of progression to true PTL is high it is reasonable to offer hospital admission and consideration of corticosteroid and tocolytic therapy. Keeping in view all of the evidence this study has been planned to study the efficacy and safety profile of Atosiban and Nifedipine in TPTL management.

MATERIALS AND METHODS

Research Design- It was a randomized control study conducted on women admitted in the labour room and attending antenatal OPD in the Department of Obstetrics and Gynaecology, S.N. Medical College and Hospital, Agra, India during the study period from November 2017 to July 2019. A total of 1000 women attending the antenatal clinic and labour room were screened for PTL based on inclusion and exclusion criteria. Patients were randomly placed into two groups after taking detailed history and examinations. After careful selection women were randomized to receive Atosiban or Nifedipine.

Group I-Atosiban group (Oxytocin receptor antagonist)- This group consisted of 60 women (patients receiving intravenous Atosiban). Women received an initial bolus dose i.v (6.75 mg/0.9 ml) for injection immediately followed by continuous high dose infusion of Atosiban with an infusion rate of 30 drops/minute (300 µg/min) for infusion in 5% dextrose for 3 hours followed by a lower dose of Atosiban 100 µg/min in 5% dextrose at the rate of 10 drops per minute for infusion up to maximum 45 hours.

Group 2- Nifedipine group (Calcium channel blocker)- This group consisted of 70 women (patients receiving oral Nifedipine). Patients received immediate-release tablets or capsules of Nifedipine 20 mg up to a maximum dose of 40 mg during the first hour. The maximum dose used in this study was 100-120 mg.

Inclusion criteria

- Women who gave consent to participate in the study.

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- Women who were at threatened risk of preterm birth.
- Women aged >18 years, with TPTL and gestational age between 25-34 weeks.
- Women with cervical dilatation >1 cm and <3 cm and intact membranes.
- Women with painful uterine contractions of 4 in 20 min or 8 in 60 min.
- Women with cervical effacement of >80%.

Exclusion criteria

- Patients with eclampsia, severe preeclampsia, and antepartum haemorrhage.
- Patients with heart disease causing moderate-to-severe functional impairment, and severe anaemia.
- Cases of foetal demise, foetal congenital malformations, cervical dilatation >3 cm, documented ruptured membranes, and chorioamnionitis.
- Contraindication or sensitivity to Atosiban.

Statistical Analysis- The collected data were analyzed using SPSS version 23. Descriptive statistics was undertaken, and a chi-square test was applied to establish a significant relationship between both the groups (p-value<0.05).

Ethical Consideration- The ethical clearance was obtained from the Institutional Ethical & Review Committee of S.N. Medical College and Hospital, Agra, India. This study was conducted according to the guidelines of the World Medical Association (WMA) Declaration of Helsinki.

RESULTS

Table 1 shows that 1% of women needed 132.75 mg of the drug, the average dose needed was 43 g. About 41.7 cases needed an average of 7.5 hours of Atosiban infusion to completely stop the contraction. It was found in this study that more than 50% of the contractions were stopped by 20 mg oral Nifedipine followed by 20 mg Nifedipine given at an interval of 6-8 hours.

Table 1: Distribution of cases according to dose of Atosiban to stop contractions and duration of treatment to completely stop contractions.

No cases with Atosiban infusion (100 µg/min) after giving bolus +3 h (%) maintenance therapy (N=60)	Total dose required (in mg) (bolus+3 h infusion therapy+100 µg/min)	Total duration of treatment in hours with Atosiban to completely stop contraction (h)
13 (21.7)	102.75	10
10 (16.7)	96.75	9
12 (20)	108.75	11
7 (11.7)	84.75	7
4 (6.67)	90.75	8
5 (8.33)	78.75	6
2 (3.33)	126.75	14
2 (3.33)	66.75	4
1 (1.67)	132.75	15
1 (1.67)	120.75	13
1 (1.67)	72.75	5
2 (3.33)	114.75	12

Table 2 shows that maternal side effects were more common in the Nifedipine group i.e. 54% as compared to the Atosiban group which was 28%. Tachycardia and gastrointestinal upset were the most common side effects observed in Atosiban group, whereas hypotension, tachycardia and headache were the most common maternal side effects with Nifedipine. Early drug termination due to adverse effects was not seen in the Atosiban group.

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Table 2: Distribution of women according to maternal side effects.

Maternal side effects	Group-1 Atosiban group (%) (N=60)	Group-2 Nifedipine group (N=70) (%)
Total number of women with adverse events	19 (28)	38 (54)
Early drug termination due to adverse	0 (0)	5 (7.14)
Tachycardia	6 (10)	12 (17.12)
Hypotension	4 (6.67)	15 (21.42)
Headache	3 (5)	8 (11.42)
Gastrointestinal tract upset	5 (8.33)	3 (4.29)
Chest pain	0 (0)	3 (4.29)

Table 3 depicts that 40% of patients had a foetal heart rate in the range of 140-160 per min in both groups. Not much difference was observed in both the groups as validated by the statistical test.

Table 3: Distribution of cases according to association of foetal heart rate before during and after therapy.

Foetal heart rate	Atosiban group (%) (N=60)	Nifedipine group (%) (N=70)	Chi-square value	p-value
Before therapy (>160)	35 (58.33)	39 (55.71)	0.759	0.684
During therapy (140-160)	24 (40)	28 (40)		
After therapy (140-160)	1 (1.6)	4 (6.67)		

Table 4 shows that Atosiban infusion had 95% success rate for tocolysis as compared to the Nifedipine group with 80% success rate. A statistically significant difference was observed using the chi-square test, showing a higher success rate in the Atosiban group.

Table 4: Distribution of cases according to success/failure rate for Atosiban and Nifedipine group

Success/Failure rate	Atosiban group (N=60)	Nifedipine group (N=70)	Chi-square test value	p-value
Success	57 (95%)	56 (80%)	6.4	0.011*
Failure	3 (5%)	14 (20%)		

**Statistically Significant*

DISCUSSION

In the present study, the success rate with Atosiban was 95% in patients treated for PTL. The success rate was between 91-97% for Atosiban-treated patients for tocolysis. Of these, 96.49% of women remained free from contraction.

Moutquin *et al.* [6] performed a study to compare Atosiban with Ritodrine for the treatment of PTL. Comparable results were reported with a success rate (delaying delivery for 48 h) of 84.9% for Atosiban and 86.8% for Ritodrine, without a significant difference. However, fewer adverse effects of Atosiban were noticed as compared to Ritodrine. [6,7] The study involved one round of treatment with Atosiban for inhibiting the acute PTL attack, followed by its use as a maintenance treatment to reduce PTL attacks. The obtained results were also compared with a placebo. It was observed that the Atosiban group had a substantially higher mean delay between drug administrations until the first

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recurrence of PTL when compared to the placebo group. Atosiban is used as a maintenance treatment, and a study of its application is recommended for better understanding.

European Atosiban Study Group [8] conducted a study in which Atosiban was compared with Terbutaline. Both the drugs showed the same efficacy, but the side effects of Terbutaline were more as compared to those of Atosiban. Similar findings were reported by Santos *et al.* [9] showing more acidosis and higher levels of lactate in patients who received Terbutaline in comparison to patients receiving Atosiban. A meta-analysis by Ma *et al.* [10] indicated the association of Salbutamol with side effects such as palpitation and tachycardia. The French/Australian Atosiban Investigators Group compared the efficacy of Atosiban and Salbutamol in PTL and concluded that their efficacy was similar, but the associated maternal and neonatal side effects of Atosiban were less as compared to Salbutamol [11].

Moreover, Atosiban infusion showed 95% success rate for tocolysis in the present study. These findings agreed with a study by Lurie *et al*. [12] utilizing Atosiban to treat uterine hyperactivity during the labour's active phase. Following treatment, the patients responded favourably and also the abnormal pattern of foetal heart rate was recovered. However, contradictory results were reported in another study showing no modulation in heart rate [13]. Studies favouring Nifedipine as the first-line tocolytic drug are also reported in the case of PTL management [14,15]. Another study was performed by Afshar *et al.* [16] comparing Hexoprenaline and Atosiban for the treatment of foetal distress during labour. Both the drugs were found to inhibit contractions fairly and the foetal distress was recovered. The side effects of Atosiban were less in comparison to Hexoprenaline. Moreover, contractions returned faster as soon as the drug was discontinued, suggesting that Atosiban is the drug of choice for tocolysis during labour to relieve foetal distress.

Atosiban showed lower side effects as compared to Nifedipine in the present study. Similar studies comparing Atosiban with other tocolytics are available. Tsatsaris *et al*. [17] opined Atosiban is the drug of choice for treating PTL, especially in high-risk patients of cardiac disease during pregnancy and cases of multifoetal pregnancies. Wang *et al.* [18] supported this finding and concluded that Atosiban enhances pregnancy outcomes in women undergoing IVF or those with repeated embryo implantation failure.

Few studies investigated the efficacy of combination therapy of Atosiban combined with Ritodrine for treating TPTL and found favorable results. One such study by Li *et al*. [19] found improvement in the condition of TPTL patients and a reduction in adverse pregnancy events. This combination therapy has also shown improvement in the levels of platelet-activating factor and foetal fibronectin levels [20]. The present study did not consider combination therapy as an alternative, however owing to positive results this prospect could be explored in future studies.

CONCLUSIONS

Atosiban is better tolerated by women as compared to Nifedipine with the best maternal and safety profile. It is imperative to directly compare oxytocin antagonists and calcium channel blockers in terms of effects on neonatal outcome and tocolytic efficacy. Additionally, studies with large sample sizes and different nifedipine dose regimens are required to compare the efficacy and maternal side effects of this drug.

Moreover, research on combination therapy could be explored for prospects of drug regimens in TPTL. Furthermore, to compare efficacy and adverse effects on mothers, larger research utilizing various nifedipine dosing regimens is required.

CONTRIBUTION OF AUTHORS

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