

Acute Tocolysis Using a Single Bolus Dose of Atosiban for Preterm Labor Management: A Prospective Study

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Abstract: *Background:* Preterm labor poses a significant challenge within obstetrics, carrying the potential for diverse complications for both maternal and neonatal well-being. Extensive clinical data indicates that atosiban stands as a secure and well-tolerated therapeutic alternative, exhibiting fewer adverse effects on both the mother and fetus compared to other tocolytic treatments. The investigation aimed to assess the feasibility of achieving optimal medical care by employing a solitary atosiban bolus dose. This approach holds the promise of mitigating the necessity for hospitalization, potentially enabling outpatient management of the condition. *Aim:* The purpose of the study was to assess the efficacy and safety of using a single bolus dose of atosiban to delay premature delivery. *Material and Methods:* The study included 75 patients experiencing symptoms of preterm labor. These patients were administered a single bolus dose of atosiban (6.5 mg/0.9mL). The study was conducted between August 2019 and July 2023. *Results:* The study successfully used a single bolus dose of atosiban to delay delivery by up to 48 hours, enabling corticosteroid prophylaxis. The participants' average gestational age was 32.1 weeks. Atosiban effectively delayed delivery in 68% of patients for an average of 13.3 days, with a range of 0-62 days. No adverse effects were reported by either mothers or fetuses during the study period. *Conclusion:* The study findings suggest that a single bolus dose of atosiban is an effective and safe treatment option for delaying preterm labor. The treatment provides short-term relief for an average of 13 days, with potential benefits over other tocolytics like isoxsuprine, ritodrine, and nifedipine due to fewer side effects. The intravenous bolus dose of atosiban has a quick onset and long-lasting effects, making it convenient for both patients and physicians. The approach is cost-effective and could be repeated after a few days if necessary. Overall, the study demonstrates the potential of using a single bolus dose of atosiban as an outpatient treatment to manage preterm labor effectively, offering benefits in terms of safety, convenience, and cost.

Keywords: Preterm Labor, Atosiban, Tocolytic Treatment, Bolus Dose, Delivery Postponement, Tocolytic Alternatives

1. Introduction

The underlying causes of preterm labor remain elusive, yet the ramifications of premature birth are well-documented. [1] Gestational age at birth emerges as a pivotal determinant influencing the peril of neonatal morbidity and mortality. As gestational age increases, the risk of both morbidity and mortality significantly decreases. [2] Employing tocolytic agents to extend pregnancy during instances of preterm labor is contingent upon patient-specific conditions and healthcare institution protocols. [3] The overarching objective frequently centers on stalling labor, thereby facilitating the

administration of corticosteroids or facilitating maternal transfer to specialized facilities.

The contemporary landscape witnesses an extension of tocolytic use beyond its intended scope in the realm of preterm labor. This broadened utilization can be attributed to their ability to selectively target uterine smooth muscle, which has led to their adoption for off-label applications. It is evident from clinical observations that complications arising from tocolysis are largely specific to the medication employed. Flushing, typically linked to tocolytics, exhibits mild characteristics primarily tied to peripheral vasodilation. [4] On the contrary, cardiac ramifications (including cardiac arrhythmias, hypotension, fetal tachycardia), pulmonary

edema, and respiratory arrest align with beta-mimetics (ritodrine, terbutaline, isoxsuprine) [5], nifedipine [6], and magnesium sulfate [7]. In contrast, the oxytocin receptor antagonist, atosiban, displays a uterine-specific effect and boasts commendable tolerability, showcasing minimal maternal side effects. [8] Furthermore, its administration remains unhampered by contraindications such as cardiac ailments, diabetes mellitus, thyroid disorders, or renal and hepatic impairments. [9]

Numerous randomized clinical trials have substantiated atosiban's efficacy as a tocolytic agent. [10-12] However, while the recommended dosage regimen of atosiban holds efficacy, its extended duration of administration contributes to prolonged hospital stays and augmented medication costs. [13] Notably success rate in prolonging pregnancy has been observed with a concise regimen lasting merely 14 hours. [14] Both the extended and abbreviated regimens share a commonality in initiating treatment with a solitary bolus dose (6.75mg/0.9mL) of atosiban. The pertinent query regarding the feasibility of managing acute preterm labor effectively and economically through the administration of a single atosiban bolus injection.

In our exhaustive review of existing literature, a conspicuous absence of focused clinical investigations evaluating the impact of an atosiban bolus dose in acute preterm labor was observed. The preliminary exploratory study has demonstrated the efficacy of a 5 mg atosiban dosage in inhibiting uterine contractions. [15] Moreover, two pilot studies have exhibited the capacity of a 6.75 mg intravenous atosiban bolus dose to effectively mitigate uterine hyperactivity during active labor. [16, 17] It is crucial to underline the paucity of comprehensive literature in this specific domain, warranting further research to ascertain the optimal atosiban dosage and its potential merits as a bolus treatment for managing acute preterm labor. Given the pivotal role of clinical evidence in guiding healthcare decisions, the study was undertaken to meticulously evaluate the efficacy and safety profile of a single atosiban bolus dose in the context of preterm labor, and its place of therapy in an outpatient care setting.

2. Materials and Methods

This prospective study was conducted at the Obstetric Unit of Lokmanya Tilak Municipal General Hospital and Lokmanya Tilak Municipal Medical College (LTMGH-LTMMC), located in Mumbai, India. The study

spanned a comprehensive duration of four years, ranging from August 2019 to July 2023. Ethical clearance for the study was granted by the institutional ethics committee of LTMGH-LTMMC, adhering diligently to the principles of good clinical practice and the Declaration of Helsinki. Before enrolment, written informed consent was obtained from each participating patient.

A total of 75 patients, with a gestational age exceeding 24 weeks and presenting with preterm labor, were enrolled in the study. The selection process involved excluding women with instances of lethal fetal abnormalities, chorioamnionitis, ruptured membranes, vaginal bleeding, and preeclampsia. An intravenous single bolus dose (6.75mg/0.9mL) of Atosiban (Tosiban™, Zuventus Healthcare Limited, India) was administered over a span of one minute. Following drug administration, vigilant monitoring was maintained to promptly detect any potential adverse events. Over a span of 48 hours, labor progression was carefully observed, and comprehensive delivery information was obtained from the patients, enabling the evaluation of in-utero time gained. This metric was quantified as the additional number of days beyond the initiation of preterm labor subsequent to the introduction of tocolysis.

3. Results

The average age of the participating patients was 26.51 ± 5.11 years, with a range from 18 to 46 years. The mean gestational age stood at 32.1 ± 2.8 weeks, encompassing a range from 24 to 36 weeks. Approximately half of the patients (48%) were experiencing their first pregnancy, while multigravida patients (60%) were more prevalent in the study.

Among the participants, 68% of patients experienced a prolongation of pregnancy exceeding 48 hours (Table 1). On average, patients demonstrated an increase in gestation age of $13.3 (\pm 15.58)$ days, with the range spanning from 0 to 62 days. The collective rate of deliveries that occurred after the 34-week in 58.66% of patients. Notably, among these instances, full-term deliveries were recorded for 16 patients, accounting for 21.33% of the cases. The mean gestational age at the time of delivery was 34.17 ± 3.21 weeks. In terms of tocolytic success rates at the 48-hour juncture, comparable outcomes were noted among patients stratified based on cervical dilation at enrollment, 76.19% (32 out of 42) success rate in patients with <2 cm dilation, while the ≥ 2 cm dilation group displayed a success rate of 57.58% (19 out of 33) ($p=0.086$, Pearson chi-square test).

Table 1. Tocolytic efficacy of a single bolus dose of atosiban.

Parameters	6 hr, n (%)	12 hr, n (%)	24 hr, n (%)	48 hr, n (%)	Day 7, n (%) ^a
24 to <28 weeks	8/8 (100)	8/8 (100)	8/8 (100)	6/8 (75)	5/8 (62.5)
28 to 32 weeks	19/21 (90.48)	18/21 (85.71)	13/21 (61.90)	8/21 (38.10)	7/21 (33.33)
≥ 32 to 37 weeks	44/46 (95.65)	44/46 (95.65)	43/46 (93.48)	37/46 (80.43)	21/46 (45.65)
Overall	71/75 (94.67)	70/75 (93.33)	64/75 (85.33)	51/75 (68)	33/75 (44)

^a Based on patient-reported data

Patients exhibited favorable tolerance toward the atosiban injection. Throughout the observation period, 4% (3 out of 75)

of patients required a repeated bolus dose, whereas 28% (21 out of 75) received a short-acting beta-agonist, Isoxsuprine. Post the study period, data on the use of rescue medications wasn't collected. Significantly, no maternal adverse effects were reported during the observational span. Patient feedback indicated that all newborns survived, underscoring the safety of atosiban usage.

4. Discussion

In the present study, our focus centered on assessing the efficacy and safety of a single bolus dose of atosiban in preventing preterm labor. This particular approach holds the potential to shed light on the benefits of atosiban usage in cases of acute preterm labor where comprehensive medical resources might not be readily accessible.

The study's findings revealed that following atosiban bolus administration, more than 90% of patients sustained their pregnancies for the initial 12 hours post-tocolysis. Intriguingly, insights gleaned from the Effective Perinatal Intensive Care in Europe (EPICE) study have highlighted an association between corticosteroid administration and mortality risk. According to the study, administering corticosteroids between 6 to 12 hours prior to delivery correlates with a remarkable 51% reduction in mortality risk. [18] This underscores the significance of delaying delivery through prompt initial treatment within primary care settings, allowing crucial time for interventions aimed at enhancing fetal development.

The recorded 58.66% delivery rate beyond the 34-week mark

indicates a notable delay in delivery for a substantial portion of patients, thus surpassing the critical preterm threshold. Remarkably, among those who didn't require alternative tocolysis, a commendable 63% managed to effectively postpone their pregnancies for a span of up to 48 hours. When contemplating tocolysis as a whole, including alternative tocolytic strategies, the study demonstrates that 68% of patients succeeded in prolonging their pregnancies by at least 48 hours, exemplifying favorable outcomes in the context of acute tocolysis. The retrospective analysis highlighted that a single bolus dose of atosiban extended pregnancies in 65% of patients. [19] Notably, within the most susceptible group (gestational age <28 weeks), the atosiban bolus dose exhibited promising outcomes with a 100% successful tocolysis for 24 hours and one-third of these cases extending to 48 hours.

In terms of prolonging pregnancy, atosiban exhibits comparable efficacy to other tocolytics (Table 2). However, the distinct advantage lies in its ability to achieve suppression of preterm labor pain through a single bolus injection. This is a contrast to alternative tocolytic agents that typically necessitate 12 to 24 hours of initial treatment to achieve similar suppression. During acute tocolysis, facilitated by a single intravenous dose, atosiban yields rapid and profound impacts on uterine contractions, maintaining minimal influence on maternal and fetal heart rates. [20] The current study firmly establishes that the atosiban administration does not impose adverse effects on either the mother or the fetus, aligning consistently with previously documented studies. [21] This solidifies the safety profile of atosiban as a reliable tocolytic agent.

Table 2. Efficacy and safety of various tocolytics used in acute preterm labor.

Tocolytic Agent	Study	Acute Tocolysis Dosage	Tocolytic Efficacy	Adverse Events (Incidences in %)
Atosiban	The present study	Single IV injection 6.75 mg/0.9 mL	85.33% in 24 h 68% in 48 h	None
	Khoiwal S et al. [22]	10 mg IM injection every 6 h for 48 h	84.37 in 48 h	Hypotension (15.62%), Tachycardia (9.37%)
Isoxsuprine	Mahajan A, et al. [23]	40 mg IV infusion then 10 mg IM injection every 6 h for 24 h	66% in 48 h	Hypotension (18%), Tachycardia (14%), Nausea (8%)
	Jain P, et al.[24]	40 mg IV infusion then oral 10 mg every 8 h for 7 days	76% in 48 h	Tachycardia (50%), Hot flushes (39%), Hypotension (36%), Nausea/Vomiting (34%)
	Jaju P, et al. [25]	100 mg infusion for 24 h	68.3% in 48 h	Palpitation (41.6%), Breathlessness (5%), Pulmonary edema (4%)
Ritodrine	The Canadian Preterm Labor Investigators Group Study [26]	Infusion for at least 6 h then 10 mg x 12 tablets daily for 5 days	78.6 % in 48 h	Palpitation (53.4%), Tremor (39.2%)
	Kim et al. [27]	6.4 mg/h with increments of 3.2 mg/h infusion every 15 minutes until the cessation of uterine contractions	79.6% in 48 h	Hypokalemia (39.2%) Dyspnea (15.1%) Pulmonary edema (0.3%) Palpitation (81.7%), Tremor (57.9%), Tachycardia (47%), Tachypnea (20.7%)
	Khooshideh M, et al. [28]	10-20 mg oral every 6 h for 48 h	70% in 24 h 14.5% in 48 h	Pulmonary edema (3%) Hypotension (6.4%) Postpartum hemorrhage (0.9%)
Nifedipine				Flushing (50%), Headache (46.9%), Hypotension (43.8%), Palpitation (40.6%)
	Al-Omari et al. [29]	10-40 mg oral every 4-6 h for 48 h	65.6 % in 48 h	

Tocolytic Agent	Study	Acute Tocolysis Dosage	Tocolytic Efficacy	Adverse Events (Incidences in %)
	Dhawle et. al. [30]	20 mg oral every 6 h for 48 h	88.4% in 48 h	Tachycardia (25.6%), Palpitations (9.3%), Hypotension (4.7%)

The findings of the study pave the way for a promising trajectory in the management of acute preterm labor. The introduction of atosiban via an intravenous bolus presents a critical time window for medical interventions, optimizing fetal development to ensure secure delivery. Furthermore, insights from a cost-effectiveness analysis suggest that adopting a tocolytic regimen incorporating short-duration atosiban treatment ensures safety and efficacy and results in substantial cost savings as compared to alternative tocolytics. [13] The convenience associated with administering a solitary intravenous injection augments its attractiveness, facilitating early initiation within outpatient contexts and potentially curtailing hospital stays and associated side effects. It's important to acknowledge that these findings are derived from a limited sample size and the absence of a control group. Consequently, we recommend further randomized trials encompassing larger cohorts to fortify the robustness of these findings.

5. Conclusion

The study culminates in offering invaluable insights into the efficacy and safety of employing a single bolus dose of atosiban. The therapeutic approach proffers a succinct yet meaningful respite spanning up to 62 days (with an average duration of 13 days). Noteworthy is the regimen's manifestly reduced incidence of side effects in comparison to isoxsuprine, ritodrine, and nifedipine, positioning it as a notably favorable treatment modality for preterm labor. The prompt onset and sustained impact achievable through an intravenous bolus dose of atosiban, administered within a brief 1-minute interval, serve to distinguish it from the daily doses of alternative tocolytics. Moreover, the added advantage of avoiding hospitalization further amplifies its appeal, contributing to the convenience of administration for both medical practitioners and patients alike. The cost-effectiveness of a short regimen, coupled with its ease of administration, presents a win-win situation for both healthcare providers and patients, even if repeat dosing may be required after a few days.

In summation, the study underscores the potential of a single bolus dose of atosiban as a paramount strategy in the management of preterm labor. Its distinct advantages in terms of efficacy, safety, rapid action, and convenience make it a cornerstone in the armamentarium against preterm labor. However, it is essential to acknowledge that while the study's outcomes are promising, the limitation of a modest sample size and the absence of a control group necessitates further exploration through extensive randomized trials. This endeavor would robustly validate the pivotal role that the atosiban bolus regimen can play in transforming the landscape of preterm labor management.

Conflict of Interest

The authors declare no conflict of interest.

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