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ATOSIBAN VS CONVENTIONAL TREATMENT FOR THREATENED PRETERM LABOUR

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ABSTRACT

Preterm birth, a birth that occurs before 37 weeks of gestation is the most importrant cause of neonatal mortality and morbidity worldwide. **Aim of the study:** To evaluate the efficacy of atosiban in cases of threatened preterm labour in different gestational age and compare it with the conventional treatment. **Material and methods:** The data of pregnant women with threatened preterm labor hospitalized in the department for peripartal intensive care were collected in a period of 2019- 2021. The study included an pregnant women between 18 and 45 years old in gestational age between 24 and 34+6 weeks that fulfilled the nececery criteria for threatened preterm contractions.Atosiban was compared to conventional treatment (indomethacin, magnesium sulphate and calcium channel blockers, alone or in combination). Data about the treatment, perinatal outcome and maternal safety information were all collected from medical record. **Results:** Significant difference was found in the atosiban group in means of prolongation of pregnancy compared to conventional treatment. There was significantly longer pregnancy length in atosiban treatment group compared to conventionaly treated when gestational week at admission was ≥ 28 + 0 days (p=0,034), no previous parity (p=0,013), and no history of previous preterm birth (p=0,016). In the atosiban group there was a significant moderate positive correlation between prolonged pregnancy in days and cervical length for r(40)=0,404; p=0,011. Therefore with increasement of cervical length there was a significant prolonged duration of pregnancy. **Conclusion:** We found that atosiban was more effective than conventional treatment in the gestational age >28 weeks.

KEYWORDS: atosiban, conventional treatment, preterm delivery.

INTRODUCTION

Preterm birth, a birth that occurs before 37 weeks of gestation is the most importrant cause of neonatal mortality and morbidity worldwide. It is also a majour cause of neonatal neural deficits, cerebral palsy,intellectual disabilities, vision and hearing impairment. About 15 million preterm neonates are born every year worldwide.[1]

Two-thirds of preterm births occur after the spontaneous onset of labor, whereas the remain are medically indicated because of maternal or fetal condition, such as preeclampsia, intrauterine growth restriction, diabetes, placenta praevia or placental abruption. Incidence is between 5 to 18% of pregnancies.[2]

Mechanisms of initiation of preterm contractions include: uterine overdistension, decline in progesterone action, infection, cervical factors, stress and decidual senescence.

Single course of corticosteroids and tocolytic treatment up to 48 hours is a standard clinical practice.Various types of tocolytics have been used during the past decades.

Atosiban, a selective oxytocin receptor antagonist is proposed as an effective tocolytic agent for women in preterm labour to prolong pregnancy.[4] Oxytocin stimulates contractions by inducing conversion of phosphatidylinositol to inositol triphosphate, which binds to a protein in the sarcoplasmic reticulum and causes release of calcium into the cytoplasm.

Tocolytic agents are various drugs (β-agonists, calcium channel blockers, magnesium sulphate and prostaglandin synthetase inhibitors) that can reduce preterm contractions. This may gain time to allow administration of antenatal corticosteroids for fetal lung maturation, and time for in utero transfer to a medical centre with neonatal intensive care unit.[5]

Atosiban is utero specific compared to other tocolytics. It is a powerfull addition to the other treatment options for preterm labor and should be used as a first-line therapy.[6,7]

Meta-analysis of nine RCTs determined that atosiban and betamimetics had similar efficacy in delaying preterm birth by at least 48 h but was associated with significantly fewer adverse events and is cost-saving versus other tocolytic drugs.[8]

There are data that indicate that Atosiban has an impact on the level of markers of oxidative stress, which is an important factor in the pathogenesis of preterm contractions.[9]

Recent studies suggest that connexin-43 (Cx43), an important contractile-associated protein, is dysregulated in spontaneous preterm labour myometrium. Pharmacologic inhibition of Cx43 may in future reduce contraction in human myometrial tissue and present a novel approach to tocolysis.[10]

Future studies of tocolytic agents and their combination should evaluate their effect and important short and long term perinatal outcome.

AIM OF THE STUDY

This study was designed to evaluate the efficacy of atosiban in cases of threatened preterm labour in different gestational ages and compare it with the conventional treatment.

MATERIAL AND METHODS

Longitudinal clinical study was performed at the University gynecology and obstetric clinic in Skopje, N. Macedonia in a period of 2019- 2021.All the data of pregnant women with threatened preterm labor hospitalized in the department for peripartal intensive carewere collected.

The study included pregnant women between 18 and 45 years old in gestational age between 24 and 34+6 weeks with live fetus, intact membranes, cervical dilatation of ≤4 cm and signed informed consent for tocolytic therapy. Cases of eclampsia, severe pre-eclampsia, fetal or placental abnormalities, suspected chorioamnionitis and premature rupture of the membranes were excluded.

Each patient fulfilled the nececery criteria for threatened preterm labour: presence of more than 4 uterine contractions within 30 min, lasting at least 40 s for each contraction, the dilatation of the cervix was 1–4 cm with effacement of more than 50%.

Atosiban was the first choice drug if it was available. The standard protocol for atosiban administration was: an initial bolus of 6.75 mg, followed by 300 mg/min for 3 h, then 100 mg/min for up to 45 h. The full treatment lasted 48 h with a total dose of atosiban of 330 mg.

Pregnant women with conventional treatment were used as control. Conventional treatment included treatment with indomethacin, magnesium sulphate and calcium channel blockers, alone or in combination, according to the current guidelines on the use of tocolytics.[11]

Data about the treatment, perinatal outcome, maternal safety information were all collected form medical record.

Statistics

The data were processed in SPSS software package, version 22.0 for Windows. The qualitative series were processed by determining the coefficient of relations, proportions, and rates. Quantitative series were analyzed with measures of central tendency (mean, median, minimum values, maximum values, interactive ranks), as well as by dispersion measures (standard deviation). The Shapiro-Wilk W test was used to determine the normality of frequency distribution of investigated variables. Pearson Chi square test, Fisher exact test and Fisher Feeman Halton test were used for determining assosiation between certain attributive variables. Pearson Correlation was used as a measure of the strength and direction of association that exists between two numerical variables. Mann Whitney U test was used for testing difference between two numeric parametars with non normal distribution. The Difference test was used to compare the proportions. A two-sided analysis with a significance level of $p< 0,05$ was used to determine the statistical significance.

RESULTS

Study included a group of 70 women which fulfilled the established inclusion and exclusion criteria. Atosiban therapy was given to 40 (57,14%), while conventional treatment was given to 30 (42,86%) women, without significant difference in percentage of both groups - Difference 14,28% [(-2,22 – 29,73) 95% CI]; p=0,0923).

Women in conventional group were borderly significantly older (p=0,044) compared to atosiban group 25,97±6,41 vs. 29,47±6,79 and 50% younger than 24 or 30 years (Table 1).

Significat association was not confirmed between the groups according to: nationality (p=0,6701); parity (p=0,4004); previous preterm birth (p=0,8496); positive history of spontaneous abortions in previous pregnancies (p=0,0927); in vitro pregnancies (p=0,2177) and cervical conisation p=0,3943.

According to gestational age at admission (p=0,0902) and gestational age at admission less than 27 weeks + 6 days vs. ≥ 28 weeks + 0 days, there was no significant difference between atosiban and conventional treatment group (p=0,2122).

Between both groups there was no significant difference according to cervical lenght mm (p=0,1039), and number

of contractions in 10 minute non stress test at admission (p=0,1784), table 1.

Significant difference in length of hospital treatment was not found between the pregnant women from both groups (p=0,6521). Caesarean section delivery was more often then vaginal delivery in both groups with no significancant association with the type of treatment women received. (p=0,4495) (Table 2).

Comparrison of 1st, 5th minute Apgar score, neonatal birth and weight didn't show significance with type of tocolitic treatment.

Significant difference in the prolongation of pregnancy was found in favor of the atosiban group compared to conventional treatment for 24,72±19,69 and in 50% with prolongation <24 days vs. 14,37±14,42 and in 50% with prolongation <8 days respectively (Table 3 and Graph 1).

Pregnancy length was significantly longer in atosiban compared to conventionaly treated group related to gestational week at admission ≥ 28 + 0 days (p=0,034), no previous parity (p=0,013), and no history of previous preterm birth (p=0,016) (Table 4). Significant difference in pregnancy length was not found related to of history of previous spontaneous abortions (Table 4).

In the atosiban group there was a significant moderate positive correlation between prolonged pregnancy in days and cervical length (mm) for r(40)=0,404; p=0,011. This correlation in conventional group was insignificant. In both groups there was insignificant linear correlation between prolonged pregnancy in days and non stress test- contractions in 10 minute period (Table 5 and Graph 2).

Side effects were not significantly associated with the treatment, and were present in 2 (5%) women treated with atosiban and in 5 (16,67%) treated conventionaly.

Anex 1/ Tables and Graphs

Table 1: Demographic, anamnestic and clinical characteristics according to groups.

Parametars	Groups		p
	Atosiban	Conventional treatment	
Number			
N (%)	40 (57,14%)	30 (42,86%)	p=0,0923
Maternal age (years)			
Mean ±SD	25,97±6,41	29,47±6,79	Z=2,118; p=0,044*
Min/ Max (Range)	17/42	20/44	
Median (IQR)	24 (21-31,5)	30 (24-34)	
Nationality			
Macedonian	12 (30%)	11 (36,67%)	[1]p=0,6701
Albanian	20 (50%)	14 (46,67%)	
Gypsie	7 (17,5%)	3 (10%)	
Turkish	1 (2,5%)	2 (6,67%)	
Gestational age at admission			
Mean ±SD	31,39±2,06	33,58±12,99	Z=0,122; p=0,0902
Min/ Max (Range)	27/34	25,2/101	
Median (IQR)	31,9 (30 – 33,1)	31,8 (30,2 – 33,4)	
Gestational age at admission			
≤ 27 weeks + 6 days	37 (92,50%)	24 (82,76%)	[2]p=0,2122
≥ 28 weeks + 0 days	3 (7,50%)	5 (17,24%)	
Parity			
None	22 (55%)	20 (66,67%)	[1]p=0,3806
One	14 (35%)	6 (20%)	
More	4 (10%)	4 (13,33%)	
Previous preterm birth			
No	34 (85%)	25 (83,33%)	X^2=0,036; df=2; p=0,8496
Yes	6 (15%)	5 (16,67%)	
Spontaneous abortion history			
None	31 (77,5%)	19 (63,33%)	[1]p=0,0927
One	4 (10%)	9 (30%)	

More	5 (12,5%)	2 (6,67%)	
In vitro pregnancy			
No	38 (95%)	26 (86,67%)	^{2}p=0,2177
Yess	2 (5%)	4 (13,33%)	
Cervical conisation			
No	39 (97,5%)	28 (93,33%)	^{2}p=0,3943
Yess	1 (2,5%)	2 (6,67%)	
Cervical lenght (mm)			
Mean ±SD	21,80±7,89	18,53±7,50	Z=1,626; p=0,1039
Min/ Max (Range)	5/37	2/34	
Median (IQR)	20 (16 – 28,5)	19 (15 – 25)	
NST –contractions in 10 minutes at admisiion			
Mean ±SD	3,67±0,85	3,37±1,00	Z=1,346; p=0,1784
Min/ Max (Range)	2/5	2/5	
Median (IQR)	4 (3 – 4)	3 (3 – 4)	
Z=Mann-Whitney U Test ^{1}Fisher Freeman Halton test ^{2}Fisher exact test X^2=Pearson Chi-square test Significant for p<0,05			

Table 2: Characteristics of delivery and neonatal outcome according to treatment.

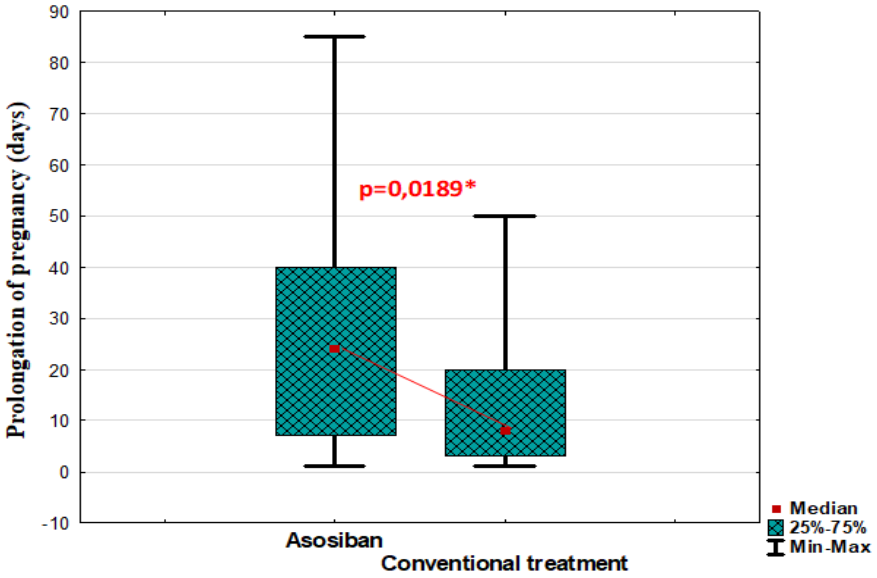
Parametars	Groups		p
	Asosiban	Conventional treatment	
Hospitalisation(days)			
Mean ±SD	**6,20±6,67**	**7,80±11,74**	**Z=0,4509; p=0,6521**
Min/ Max (Range)	**1/40**	**1/60**	
Median (IQR)	**5 (3 – 6)**	**4 (2 – 7)**	
Way of delivery			
Spontaneous	**19 (48,72%)**	**11 (36,67%)**	**X^2=1,002; df=1; p=0,4495**
Cesarean section	**20 (51,28%)**	**19 (63,33%)**	
AS 1st minute			
Mean ±SD	**7,08±1,40**	**7,05±1,48**	**Z=-0,071; p=0,9431**
Min/ Max (Range)	**3/10**	**2/9**	
Median (IQR)	**7 (6 – 8)**	**7,5 (6 – 8)**	
AS 5th minute			
Mean ±SD	**7,95±1,23**	**7,96±1,26**	**Z=0,000; p=1,0000**
Min/ Max (Range)	**4/10**	**5/10**	
Median (IQR)	**8 (7-9)**	**8 (7 – 9)**	
Weight (g)			
Mean ±SD	**2442±660,82**	**2405±1015**	**Z=0,472; p=0,6365**
Min/ Max (Range)	**1290/4050**	**1080/5000**	
Median (IQR)	**2510 (1980-2700)**	**2200 (1620-2920)**	
Length (cm)			
Mean ±SD	**46,37±3,17**	**44,74±5,35**	**Z=552; p=0,5806**
Min/ Max (Range)	**40/52**	**33/51**	
Median (IQR)	**46 (45 – 48)**	**47 (41 – 49)**	
Z=Mann-Whitney U Test X^2=Pearson Chi-square test Significant for p<0,05			

Table 3: Comparrison of length of prolonged pregnancy according to treatment.

Parametars	Groups		p
	Asosiban	Conventional treatment	
Length of prolongred pregnancy (days)			
Mean ±SD	**24,72±19,69**	**14,37±14,42**	**Z=2,348; p=0,0189***
Min/ Max (Range)	**1/85**	**1/50**	
Median (IQR)	**24 (7 – 50)**	**8 (3 – 20)**	
Z=Mann-Whitney U Test		**Significant if p<0,05**	

Table 4: Prolongation of pregnancy (days) according to selected parametars in both groups.

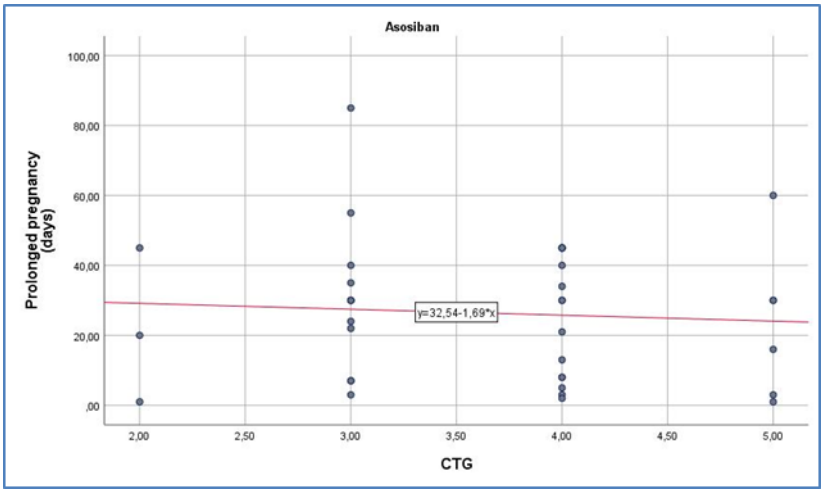
Prolongation of pregnancy (days)	Groups		p
	Asosiban	Conventional treatment	
Gestational age at admission - ≤ 27 weeks + 6 days			
N	3	5	Z=-1,350; p=0,250
Mean ±SD	25±4,58	13,8±20,28	
Min/ Max (Range)	21/30	3/50	
Gestational age at admission - ≥ 28 weeks+ 0 days			
N	36	24	Z=-2,120; p=0,034*
Mean ±SD	24,69±20,48	14,25±13,75	
Min/ Max (Range)	1/85	1/40	
Parity– No			
N	21	20	Z=-2,472; p=0,013*
Mean ±SD	29,42±20,09	14,3±15,29	
Min/ Max (Range)	1/85	1/50	
Parity–Yess			
N	18	10	Z=-0,722; p=0,494
Mean ±SD	19,22±18,23	14,50±13,26	
Min/ Max (Range)	1/60	1/40	
History of preterm delivery – no			
N	33	25	Z=-2,417; p=0,016*
Mean ±SD	26,67±19,75	14,56±14,99	
Min/ Max (Range)	1/85	1/50	
History of preterm delivery – yess			
N	6	5	Z=-0,185; p=0,931
Mean ±SD	14,01±16,95	13,40±12,54	
Min/ Max (Range)	1/45	1/30	
Spontaneous abortions history- no			
N	30	19	Z=-1,769; p=0,077
Mean ±SD	28,80±19,89	18,10±15,32	
Min/ Max (Range)	2/85	1/50	
Spontaneous abortions history - yess			
N	9	11	Z=-1,102; p=0,295
Mean ±SD	11,11±11,61	7,91±10,39	
Min/ Max (Range)	1/30	1/30	
Z=Mann-Whitney U Test, significant - p<0,05			

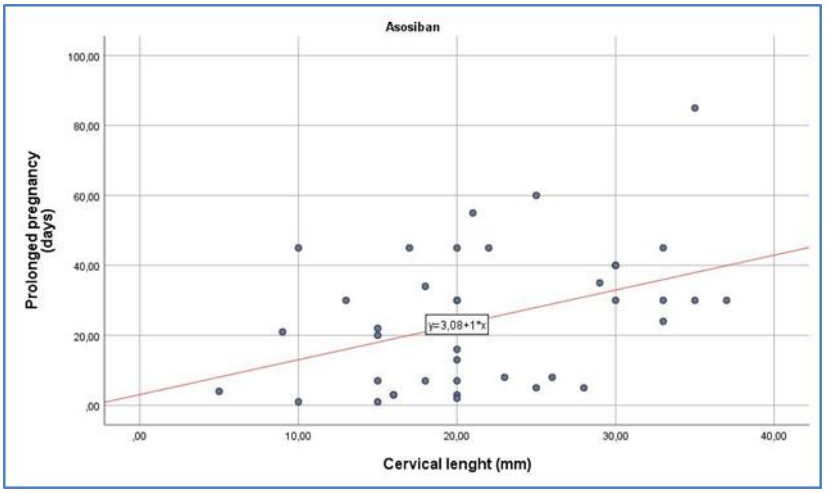


Graph 1. Comparrison of prolongation of pregnancy in days between the 2 groups.

Table 5. Correlation of prolonged pregnancy in days according to certain parameters in both groups

Prolonged pregnancy (days)	Asosiban	Conventional treatment
Cervical lenght (mm)	$r_{(40)}$=0,404; p=0,011*	$r_{(30)}$=0,162; p=0,391
NST – contractions in 10 minute period at admission	$r_{(37)}$=-0,074; p=0,667	$r_{(27)}$=0,012; p=0,954
Significant for p<0,05		





Graph 2. Correlation of prolonged pregnancy with selected parameters according to groups.

DISCUSSION

Atosiban acts as a competitive oxytocin antagonist at human uterine oxytocin receptors.[3] In our study, we compared the efficacy of atosiban with conventional treatment.

There was no significat difference between the groups in means of socio demographic characteristics, parity, obstetric history (previous preterm birth, spontaneous abortions, in vitro pregnancies and cervical conisation).

According to gestational age at admission there was no significant difference between atosiban and conventional treatment group (p=0,2122), no difference in cervical length in mm (p=0,1039) and number of contractions in 10 minute non stress test at admission (p=0,1784). Significant difference in length of hospital treatment was not found between the pregnant women from both groups (p=0,6521). Most women were delivered by caesarean section but with no significance in mean of delivery and type of treatment. (p=0,4495).

Neonatal outcome (1st, 5th minute Apgar score, neonatal lenght and weight) didn't show significance with type of tocolitic treatment.Our data was similar to most studies that show no statistically significant difference in perinatal outcome between Atosiban and other tocolytic drugs.[4,7] These data indicate that atosiban is comparable to usual tocolytic therapy in delaying preterm delivery but is probably better tolerated by the women.

The efficacy of Atosiban was compared between different gestational ages. In our results prolongation of pregnancy was significantly longer in atosiban group compared to conventionaly treated when gestational week at admission was ≥ 28 + 0 days (p=0,034), no previous parity (p=0,013), and no history of previous preterm birth (p=0,016).

Probably atosiban is more effective at later gestational age due to upregulation of oxytocin receptors and increased myometrial sensitivity to oxytocin.[3]

In the atosiban group there was a significant moderate positive correlation between prolonged pregnancy in days and cervical length (mm) for r(40)=0,404; p=0,011 or with increasment of cervical length there was a significant prolonged duration of pregnancy.

In relation to side effects there was no significant difference between the groups. Side effects (tachycardia, discomfort, headache, redness) were present in 2 cases of Atosiban group vs 5 cases of the conventionaly treated women, with no significant difference between them. Atosiban is reffered as a drug with good maternal and fetal safety.

Moreover, the therapy efficacy between different gestational ages and fetal safety need to be further investigated.

CONCLUSION

We found that the clinical effectiveness of atosiban was comparable to the conventional treatment in the early gestational age, but atosiban was more effective than conventional treatment in the gestational age >28 weeks. Therefore we conclude that Atosiban would appear to be advance over current tocolytic therapy especially for the high gestational age. Future studies of tocolytic agents and their combination should evaluate their effect and important short and long term perinatal outcome.

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