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A prospective randomised trial of atosiban *versus* hexoprenaline for acute tocolysis and intrauterine resuscitation

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Objective The aim of this study was to compare the efficacy and side effect profile of atosiban with hexoprenaline when used for intrauterine resuscitation of intrapartum fetal distress.

Study design Women in labour with acute intrapartum fetal distress detected by cardiotocography were randomly assigned to receive intravenous atosiban or hexoprenaline.

Setting Department of Obstetrics and Gynecology, Karl Franzens University of Graz and General Hospital Graz, Austria.

Population or sample One thousand four hundred and thirty-one women with singleton pregnancy at term and cephalic presentation were enrolled in the study during October 2000 and May 2001.

Methods A prospective, randomised, pilot study with no *a priori* sample size calculation.

Main outcome measure Efficacy of treatment for stopping uterine contractions and the resumption of contractions determined by fetal heart rate monitoring.

Results Tocolysis was achieved in 92% (12/13) of the women receiving atosiban and 100% (13/13) of those receiving hexoprenaline. Maternal tachycardia developed in 1/13 women, receiving atosiban and 10/13 women hexoprenaline. Hypertension occurred in 1/13 on atosiban and 3/13 women on hexoprenaline. Palpitations were only reported by 10/13 women receiving hexoprenaline. Uterine contractions resumed after 8 minutes (±3) in the atosiban group and 14 minutes (±4) in the hexoprenaline group ($P < 0.001$).

Conclusion Atosiban and hexoprenaline were similarly effective for stopping uterine contractions. Women receiving atosiban had significantly fewer adverse events than those receiving hexoprenaline. Uterine contractions resumed more promptly in the atosiban group. Considering the low incidence of mild maternal adverse events, atosiban may be an option for acute intrapartum tocolysis for fetal distress.

INTRODUCTION

Fetal distress during labour is usually due to cord complications or abnormal contractions (increased frequency, intensity, duration or baseline tonus). Uterine contractions in these conditions interfere with the blood flow to the fetus, thus causing fetal distress.[1] To avoid an acidotic and depressed newborn infant, either emergency delivery or acute tocolysis is essential.[2] Beta-mimetic agents, such as hexoprenaline, can arrest uterine contractions in fetuses with fetal heart rate abnormalities during delivery.[3] However, the risks of tocolysis with beta-mimetics include side effects, such as tachycardia, palpitations and hypertension.

The favourable effect of tocolysis is attributed to the suppression of the ischaemic effect of contractions on the placental circulation.[3] Atosiban, an oxytocin receptor antagonist, has a high specificity for the uterus, with limited or no systemic effects. It mimics the normal physiological processes by competing with oxytocin for receptor sites in the myometrium. This results in a dose-dependent inhibition of uterine contractibility.

Atosiban has been used successfully in women with preterm labour.[4] It has also been proven to be as effective as beta-mimetics for treating preterm labour, but with fewer maternal side effects.[5] To date, there are no published reports of atosiban used for acute tocolysis and intrauterine resuscitation, and the agent has not been approved for this indication. The relative high doses of beta-mimetic agents used for intrauterine resuscitation, and the associated maternal side effects, led to the proposal of using atosiban for intrauterine resuscitation. Hexoprenaline is the standard medication for acute tocolysis at the Department of Obstetrics and Gynecology of the University of Graz.

METHODS

This was a prospective, randomised, pilot study with no *a priori* sample size calculation. There was no power calculation performed. In total, 1431 women with singleton pregnancy at term and cephalic presentation were enrolled

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Table 1. Demographic characteristics.

	Atosiban	Hexoprenaline
Age of mother (years)	28.4	27.5
Gestational age (weeks)	40.6	41.1
Spontaneous onset (minutes)	11	13
Induction with oxytocin	3	3
Induction with prostaglandins	1	1
Epidural	0	1
Birthweight (g)	3322	3465

into the study at the Department of Obstetrics and Gynecology, Graz, Austria during October 2000 until May 2001. All women in labour were consented to participate but only women with fetal bradycardia were randomised. Women were eligible if they were $\geq$38 weeks of gestation presenting with a diagnosis of intrapartum fetal distress (severe fetal bradycardia) requiring intrauterine resuscitation. Women with gestational ages <38 weeks were not randomised. Women were excluded if they had serious maternal diseases (pre-eclampsia, maternal hypertension, HELLP syndrome, metabolic diseases), or fetal or placental abnormalities (intrauterine growth retardation, fetal malformation). The study was approved by the Ethics Committee of the University of Graz, Austria, and all women gave their informed written consent.

Continuous fetal heart rate monitoring was mandatory during the active phase of labour for all women. Fetal heart rate was monitored for at least 30 minutes using Hewlett-Packard monitors. The diagnosis of severe fetal bradycardia was established by the presence of a fetal heart rate of less than 80 beats per minute for more than 3 minutes.[6]

Women were randomly allocated to receive treatment intravenously with either atosiban (6.75 mg diluted in 4.9 mL of physiological saline) administered over a 1-minute period or hexoprenaline (5 μg diluted in 10 mL physiological saline) administered over a 5-minute period. Atosiban was administered by intravenous bolus dose over a 1-minute period compared with 5 minutes for hexopenaline. Randomisation was performed by treatment boxes at the Department of Obstetrics and Gynecology, University of Graz.

The primary end points of the study were the efficacy of treatment for stopping uterine contractions and the resumption of contractions determined by fetal heart rate monitoring. The primary fetal outcomes were the Apgar scores at 1, 5 and 10 minutes, umbilical artery pH values and admission to the NICU. Secondary end points of the study included maternal side effects, such as tachycardia, hypotension and palpitation. Maternal blood pressure and heart rate were measured 10 minutes after the administration of the drug.

Numeric data were normally distributed and compared with Student's *t* test, categorical data were compared with Fisher's exact test using Statistical Package for Social Sciences software. Six patients were given oxytocin in the first stage of labour, 2.8 minutes mean time after discontinuing the infusion. Two patients were given prostaglandin before the first stage of labour. The prostaglandin was removed in the first stage of labour. One patient delivered by caesarean section and one by forceps delivery.

RESULTS

In total, 13 women were randomised to receive atosiban and 13 women received hexoprenaline. The women's demographics and characteristics are shown in Table 1 and maternal clinical outcomes are presented in Table 2.

There were no perinatal deaths. One infant in the atosiban group had Apgar scores at 1 minute less than 7 compared with two infants in the hexoprenaline group (Table 2). All of

Table 2. Maternal and fetal outcomes in women receiving atosiban or hexoprenaline for intrauterine resuscitation. Standard deviation (SD) values are in parentheses.

Parameter	Atosiban (n = 13)	Hexoprenaline (n = 13)	P
Maternal outcome			
Tocolysis	12	13	
Restart of contractions (minutes)	8 (3)	14 (4)	
Palpitations	0	10	
Tachycardia	1	10	
Maternal pulse	84 (11)	111 (19)	0.384
Mean arterial maternal blood pressure (mm Hg)	94 (13)	97 (10)	0.426
Fetal outcome			
Apgar scores <7			
1 minute	8	8	
5 minutes	9	9	
10 minutes	9	9	
Umbilical artery pH values	7.2 (0.08)	7.2 (0.06)	0.176
Recovery to normal fetal heart rate	12	13	
Minutes	2	3	0.0267
Duration of fetal bradycardia (minutes)	5.6 (2.1)	6.5 (1.7)	0.072

the infants had scores of 7 or more at 5 minutes. None of these infants were transferred to the NICU. Twenty-four neonates were delivered vaginally. One infant was delivered by caesarean section. One infant in the hexoprenaline group was taken to the NICU for observation, following a forceps delivery. This infant was discharged in good condition five days after delivery.

CONCLUSIONS

The results of this pilot study found that the administration of an intravenous bolus of hexoprenaline or atosiban resulted in a rapid improvement of the fetal heart rate in nearly all the women. In most cases, the cause of the fetal bradycardia was dystocia. Only one woman in the atosiban group showed no reaction to the drug and labour continued and the baby was delivered vaginally. This lack of the drug effect could be due to the fact that the drug was given during the second stage of labour. In all the other women, the drugs were administered during the first stage of labour. The use of atosiban for fetal distress may also allow extra time for preparing for caesarean section or operative delivery, setting up regional analgesia, transferring a women from home to hospital or transferring the women from a unit without the necessary neonatal and surgical facilities to a more appropriate unit/hospital (*in utero* transfer). Atosiban was also more convenient to administer because the intravenous bolus dose could be given over a 1-minute period compared with 5 minutes for hexoprenaline, which is highly beneficial during delivery (because intrauterine resuscitation is an emergency situation and a short term onset of effect is highly beneficial).

Another important rationale for investigating atosiban as a treatment for intrauterine resuscitation is the fact that it has been shown to have significantly less maternal adverse effects than other tocolytics. This was confirmed in this study, where there were significantly fewer maternal side effects in the atosiban group, as already shown in several studies in cases of preterm labour.[7]

According to the results of our pilot study, atosiban may be an attractive alternative for the treatment of intrauterine resuscitation. A clinical trial with a larger number of women is warranted and will be a further challenge.

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Conflict of interest statement

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