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Multicentre, parallel group, randomised, single-blind study of the safety and efficacy of atosiban versus ritodrine in the treatment of acute preterm labour in Korean women

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Objective To compare the efficacy and safety of atosiban with those of ritodrine in preterm labour.

Design Multicentre, single-blind, randomised, controlled trial.

Setting Obstetric units in six referral centres in Korea.

Population Women with singleton pregnancies with preterm labour, between 24 and 33 + 6 weeks of gestation.

Methods One hundred and twenty-eight women were randomised to receive intravenous atosiban ($n = 63$) or ritodrine ($n = 65$) and were stratified by gestational age (<28 weeks and ≥28 weeks). Atosiban or ritodrine was administered for up to 48 hours. Progression of labour was assessed by the frequency of contractions and cervical dilatation and effacement. Alternative tocolysis could be given as rescue therapy.

Main outcome measure Efficacy was assessed as the proportion of women in each group who did not deliver and did not need alternative tocolytic therapy at 48 hours and 7 days after therapy initiation. Safety was assessed as the numbers of maternal adverse events and neonatal morbidity.

Results Tocolytic efficacy after 7 days was significantly better in the atosiban group than in the ritodrine group (60.3 versus 34.9%), but not at 48 hours (68.3 versus 58.7%). Maternal adverse events related to therapy were reported less frequently in the atosiban group (7.9 vs 70.8%; $P = 0.0001$), resulting in fewer early drug terminations due to adverse events (0 versus 20.0%; $P = 0.0001$). This, however, was not accompanied by a concurrent improvement in perinatal outcomes.

Conclusion The efficacy and safety of atosiban in the treatment of preterm labour were superior to those of ritodrine.

Keywords atosiban, preterm labour, ritodrine.

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Introduction

Perinatal morbidity and mortality related to spontaneous preterm labour and delivery are significant problems in obstetric practice. Spontaneous preterm labour with intact membranes is responsible for approximately 30–50% of preterm births, depending on the geographical and demographic features of the population.[1] In the United States, preterm births account for about two-thirds of all infant deaths, and nearly all preterm births are preceded by preterm labour, either alone or in combination with adverse fetal or maternal factors.[2]

The most common treatment used in the management of preterm labour involves pharmacological inhibition of preterm uterine contractions, usually with β-adrenergic agonists and magnesium sulphate. While β-agonists are effective in reducing delivery within 24 and 48 hours, such treatment does not appear to decrease the likelihood of preterm delivery

or reduce the risk of low-birthweight infants (<2.5 kg). In addition, the low uterospecificity of these tocolytic agents is associated with unwanted adverse effects, such as maternal tachycardia and palpitation, and fetal tachycardia, which may lead to discontinuation of the treatment.[3,4] Moreover, serious life-threatening adverse events have been reported, including myocardial ischaemia, pulmonary oedema and even maternal death.[5–7]

The oxytocin system, which acts via uterine oxytocin receptors, plays a central role in the mechanisms of human parturition.[8] Increased concentrations of oxytocin receptor also appear to be important in the onset of preterm labour.[9,10] Atosiban, an oxytocin derivative and competitive antagonist, has been used in the treatment of preterm labour. Atosiban has been shown to completely inhibit the uterotonic action of oxytocin in a competitive and dose-dependent manner,[11] as well as to downregulate oxytocin receptors.[12] In randomised controlled trials, atosiban has been shown to be as effective as β-adrenergic agonists in delaying the progress of continuing labour, while lacking significant cardiovascular, pulmonary, renal and central nervous system interactions.[13–15]

The objective of this trial was to compare the tocolytic efficacy and safety of atosiban and ritodrine in the treatment of preterm labour in Korean women. Ritodrine was chosen as the comparator because it is the most widely used β-adrenergic agonist in Korea.

Methods

This was a single-blind, parallel group, randomised, active controlled trial, carried out in the obstetric units of six Korean referral centres. The study protocols were approved by the institutional review boards of the participating centres and were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Each woman reviewed and voluntarily signed a written informed consent form prior to study entry.

Individuals eligible for enrolment were women presenting with uterine contractions who fulfilled the following inclusion criteria: (1) regular uterine contractions (≥30 seconds in duration at a rate of ≥4/30 minutes, confirmed by at least 1 hour external tocography) with cervical dilatation of 0–3 cm and cervical effacement of ≥50%, (2) ≥18 years of age and (3) gestational age of 24–33 weeks 6 days (confirmed by ultrasound before 20 weeks and/or reliable menstrual dates). Exclusion criteria included multiple pregnancy, ruptured membranes, major vaginal bleeding, severe pre-eclampsia or hypertension, fever (body temperature >37.5°C), urinary tract infection, fetal/placental/amniotic fluid abnormalities (e.g. major fetal anomalies, chorioamnionitis, polyhydramnios, fetal growth restriction, placental previa), serious maternal disease (e.g. cardiovascular disease, hyperthyroidism, diabetes, pheochromocytoma, asthma), any contraindication to the use of β-agonists, alcohol or drug abuse, previous exposure to nonsteroidal anti-inflammatory drugs for tocolysis within 12 hours of study entry, history of hypersensitivity to any component of the study drugs and participation in a clinical trial within 1 month.

Two computer-generated randomisation lists were prepared and issued by CMIC Co., Tokyo, Japan. Women were stratified by gestational age <28 and ≥28 weeks at study entry to ensure that the two treatments were equally distributed between the gestational age subgroups. For each centre, atosiban and ritodrine were supplied in randomised boxes labelled with the centre code and case number. The investigational drug (Tractocile®) was supplied by Ferring AB (Limhamn, Sweden), and the reference drug was a preparation commercially available in Korea (Lavopa®; Choongwae Pharma Co., Seoul, Korea).

Women randomised to atosiban were given a single intravenous bolus dose (6.75 mg in 0.9 ml normal saline), followed by an intravenous infusion of 300 μg/minute atosiban in 5% dextrose for the first 3 hours and then 100 μg/minute atosiban in 5% dextrose for up to 48 hours. Separately but simultaneously, a placebo intravenous infusion of 5% dextrose was given, corresponding to ritodrine. Women randomised to ritodrine were given an intravenous infusion of ritodrine in 5% dextrose at a rate of 0.1–0.35 mg/minute for up to 48 hours, with 0.05 mg/minute increments every 10 minutes as required (0.35 mg/minute maximum), or until contractions ceased. After 12 hours of continuous infusion at the maximally effective dose or when contractions ceased, the dose was decreased every 30 minutes by 0.05-mg/minute steps. Separately but simultaneously, these women were given a single intravenous bolus injection of placebo (0.9 ml normal saline), followed by an intravenous infusion of 5% dextrose at a rate corresponding to the atosiban infusion. The dose regimen for atosiban was chosen according to the results of a previous phase III study[13] and the dose regimen for ritodrine was in accordance with the manufacturer's guidelines. All infusates were prepared by assigned nurses and administered by a piggy-back method to reduce any possible bias from investigators.

Primary end-points of interest were the efficacy and safety of atosiban versus those of ritodrine. Tocolytic efficacy endpoint was assessed as the proportion of women who were not delivered and did not need alternative tocolytic therapy after 48 hours and 7 days. Elapsed time (days) to delivery or therapeutic failure (progression of labour requiring alternative tocolytic therapy) was also assessed. As a safety endpoint, maternal adverse events and neonatal morbidity were assessed. Secondary end-points of interest were frequency of contractions with time, gestational age at birth, neonatal birthweight, duration of stay in the neonatal intensive care unit (NICU), duration of ventilatory care, concomitant diseases in neonates and neonatal death.

Therapy with the study drug could be discontinued under the following circumstances: (1) the occurrence of serious adverse events, (2) therapeutic failure, (3) membrane rupture, (4) a significant protocol violation, (5) patient's request and (6) the development of an intercurrent illness that could have put the woman at increased risk or invalidated the study results. Alternative tocolysis could be given as rescue therapy if therapy with the study drug failed, due to either progression of labour or intolerable adverse events as judged by the investigator. Alternative tocolysis with ritodrine or magnesium sulphate was decided by the investigator. Combinations of alternative drugs could be given, but atosiban was not used as rescue therapy for women in the ritodrine group.

Progression of labour, defined as initial therapy failure, was assumed when any two of the following three criteria occurred: (1) frequency of contractions ≥4/hour, (2) ≥1 cm increase in cervical dilatation from the first examination and (3) ≥25% increase in cervical effacement from the first examination. Efficacy assessment could be performed at 6 or 12 hours if the investigator was concerned that labour was progressing despite study drug administration. Women who had a recurrence of preterm labour at any time after the cessation of study drug could be re-treated with the same intravenous drug, provided that the previous treatment was successful and no alternative tocolytic therapy was given, gestational age was <34 weeks and all other inclusion criteria were still fulfilled.

The frequency of uterine contractions was monitored continuously for the first 2 hours after therapy initiation using external tocography, and then for 60 minutes at 6, 12, 24 and 48 hours after therapy initiation or until four contractions were detected. Maternal and fetal heart rates and maternal blood pressure were recorded prior to study drug administration, every 10 minutes for the first hour, every 2 hours for 24 hours and every 4 hours thereafter. Maternal and fetal tachycardia were defined as heart rates of >120 and >170 beats/minute, respectively. Routine laboratory parameters were recorded for all treated women at baseline and after completion or termination of study drug.

All statistical analyses were performed using SAS software, version 8.1. Assuming that the tocolytic efficacy at 7 days would be 64% in the atosiban group and 52% in the ritodrine group[13] and that the difference in response between the treatments would remain within a lower bound of 10% or less to establish noninferiority between the treatments, approximately 63 women were required in each group. This sample size provides at least 80% power and a type I error (α) of 0.05. All efficacy analyses were conducted according to the intention-to-treat (ITT) principle that all randomised women who received any study drug and who had at least one follow-up assessment, whether prematurely withdrawn from the trial or not, were included in the analysis. The comparability of the study groups at baseline was analysed using chi-square test, Fisher's exact test and two-way analysis of variants (ANOVA). For evaluation of the primary end-point, tocolytic efficacy was analysed using the Cochran–Mantel–Haenszel test, a stratified test controlling for the centre effect, and Kaplan–Meier survival analysis. The frequency of contractions with time was analysed using repeated measures ANOVA. Other secondary end-points were analysed using odds ratio with 95% confidence intervals (99% confidence intervals in subgroup analysis), chi-square test and Fisher's exact test depending on whether the data were categorical or continuous. Safety analyses were performed on all women receiving at least one dose of study drug.

Results

A total of 128 women were randomised to treatment with atosiban (n = 63) or ritodrine (n = 65) at six study centres in Korea from August 2002 to August 2004. A trial flowchart is shown in Figure 1. Since two women, both in the ritodrine group, did not fulfil the inclusion/exclusion criteria, a total of 126 women were included in the ITT analysis and 128 in the safety analysis. In the ITT population, 93 women (46 in the atosiban group and 47 in the ritodrine group) completed treatment, defined as preventing/delaying labour, whereas 33 women (17 and 16, respectively) discontinued treatment. Baseline demographics (Table 1) were well matched between the two treatment groups, with the exception that a greater number of women who had received previous tocolytic therapy were allocated to the atosiban group (P = 0.03).

Table 2 shows the proportion of women who were not delivered regardless of alternative tocolytic therapy and the tocolytic efficacy. At the 7-day end-point, tocolytic efficacy was significantly better in the atosiban group than in the ritodrine group (60.3 versus 34.9%; P = 0.005). When women were stratified by gestational age <28 and ≥28 weeks at randomisation, there were higher proportions of women in both gestational age groups randomised to atosiban who were not delivered and who did not need alternative tocolytic therapy. Women in the ritodrine group received alternative tocolytic therapy more frequently at the 7-day end-point, and the difference was statistically significant (34.9 versus 55.6%). The time to delivery or therapeutic failure was significantly longer in the atosiban group (median, 20 days; range, 0–107 days) than in the ritodrine group (median, 4 days; range, 0–83 days, P = 0.0094). Similar findings were observed in the subgroup of gestational age <28 weeks (median, 19 days; range, 0–107 days, versus median, 4 days; range, 0–83 days; P = 0.0082). In the subgroup of gestational age ≥28 weeks, however, this difference was not statistically significant. This is reflected in the survival curves for the time to delivery or therapeutic failure (Figure 2).

The two treatment groups were comparable in terms of mean initial contraction frequency (7.7 versus 8.0 contractions/30 minutes). Six hours later, a noticeable decrease

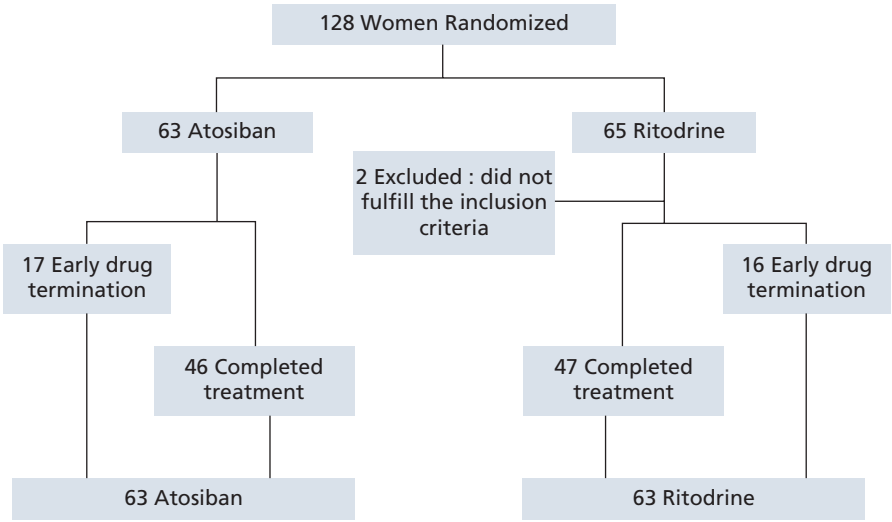

Figure 1. Study profile.

in mean values was observed in both treatment groups (2.0 versus 0.5 contractions/30 minutes). Thereafter, negligible changes in mean contraction frequency were observed until at 24 hours in both groups (0.9 versus 0.9 contractions/30 minutes). The two treatment groups were comparable in their overall decrease in contraction frequency over time ($P = 0.22$).

Table 3 demonstrates the perinatal outcomes. There were no fetal deaths, but three neonatal deaths were reported during the study period (one in the atosiban group and two in the ritodrine group). The gestational age at delivery, infant birthweight and infant Apgar scores did not differ significantly between the two treatment groups. There are increases in the number of neonates and duration (>7 days) of NICU admission and ventilation therapy in the atosiban group; they were not significantly different between the two treatment groups. There were 55 neonatal morbidities, 29 in the atosiban group and 26 in the ritodrine group, in 40 neonates, 19 (30.1%) in the atosiban group and 21 (33.3%) in the ritodrine group ($P = 0.70$). The treatment groups did not differ significantly with respect to neonatal morbidities, although infection, intraventricular haemorrhage, respiratory distress syndrome and patent ductus arteriosus were more frequently reported in the atosiban group.

Table 1. Baseline demographics of the study population

Characteristics	Atosiban ($n = 63$)	Ritodrine ($n = 63$)
Maternal age (years)	29.1 ± 3.5	30.5 ± 3.7
Gestational age (weeks)	30.8 ± 2.7	31.1 ± 2.6
Gestational age groups		
<28 weeks	10 (15.9%)	9 (14.3%)
≥28 weeks	53 (84.1%)	54 (85.7%)
Primigravida	27 (42.9%)	25 (39.7%)
Previous preterm delivery (<37 weeks)		
0	61 (96.8%)	56 (88.9%)
1	2 (3.2%)	7 (11.1%)
Contraction frequency (per 30 minute)	7 (4–20)	8 (4–15)
Cervical dilatation (cm)	1.0 (0.5–3.0)	1.0 (0.5–2.0)
Use of corticosteroid	33 (52.4%)	36 (57.1%)
Previous tocolytic therapy	8 (12.7%)	1 (1.6%)

Values are given as *n* (%), mean ± SD or median (range).

A total of 152 maternal adverse events, 13 in the atosiban group and 139 in the ritodrine group, were reported in 51 women, 5 (7.9%) in the atosiban group and 46 (70.8%) in the ritodrine group ($P < 0.0001$, Table 4). The proportion of women who discontinued treatment prematurely as a result of an adverse event only was 0% in the atosiban group and 20.0% in the ritodrine group ($P = 0.0001$). The most frequently reported adverse events in the ritodrine group were cardiovascular, including palpitation, chest tightness, dyspnoea and tachycardia. Notably, the incidence of at least one maternal cardiovascular adverse event was lower in the atosiban group than in the ritodrine group (7.9 versus 72.3%; $P < 0.0001$). No serious incidents of maternal morbidity, such as pulmonary oedema or myocardial infarction, were observed in either group. In the atosiban group, mean maternal and fetal heart rate changed only slightly during treatment (maternal: 81.1 versus 82.3; fetal: 146.1 versus 145.0). However, clinically relevant increases in mean maternal and fetal heart rate were observed in the ritodrine group (maternal: 83.4 versus 108.6; fetal: 147.3 versus 153.2).

Table 2. Tocolytic efficacy at 24 hours, 48 hours and 7 days by gestational age

	Atosiban (n = 63)	Ritodrine (n = 63)	OR	95% or 99% CI*
Women undelivered				
At 24 hours	59 (93.7%)	60 (95.2%)	0.74	0.16–3.44
48 hours	58 (92.1%)	59 (93.7%)	0.79	0.20–3.08
7 days	57 (90.5%)	56 (88.9%)	1.19	0.38–3.75
Tocolytic efficacy				
At 24 hours	45 (71.4%)	47 (74.6%)	0.85	0.39–1.87
<28 weeks	7/10 (70.0%)	5/9 (55.6%)	1.87	0.16–22.27
≥28 weeks	38/53 (71.7%)	42/54 (77.8%)	0.72	0.23–2.29
At 48 hours	43 (68.3%)	37 (58.7%)	1.51	0.73–3.14
<28 weeks	7/10 (70.0%)	2/9 (22.2%)	8.17	0.54–124.57
≥28 weeks	36/53 (67.9%)	35/54 (64.8%)	1.15	0.40–3.30
At 7 days	38 (60.3%)	22 (34.9%)	2.83	1.37–5.84
<28 weeks	6/10 (60.0%)	0/9 (0.0%)	—	—
≥28 weeks	32/53 (60.4%)	22/54 (40.7%)	2.22	0.80–6.12
Use of alternative tocolytic therapy				
At 24 hours	16/63 (25.4%)	13/63 (20.6%)	0.76	0.33–1.76
48 hours	18/63 (28.6%)	22/63 (34.9%)	1.34	0.63–2.85
7 days	22/63 (34.9%)	35/63 (55.6%)	2.33	1.14–4.78

Values are given as n (%).
*For subgroup analysis, 99% confidence intervals were presented.

Discussion

The results of this multicentre, randomised, single-blind study demonstrate that the tocolytic efficacy of atosiban, as defined in this study, is superior, and for selected measures comparable, to that of ritodrine. In a previously reported head-to-head study of atosiban and various β-adrenergic agonists in the treatment of preterm labour, atosiban was shown to be superior with respect to safety and was as effective as β-adrenergic agonists.[16]

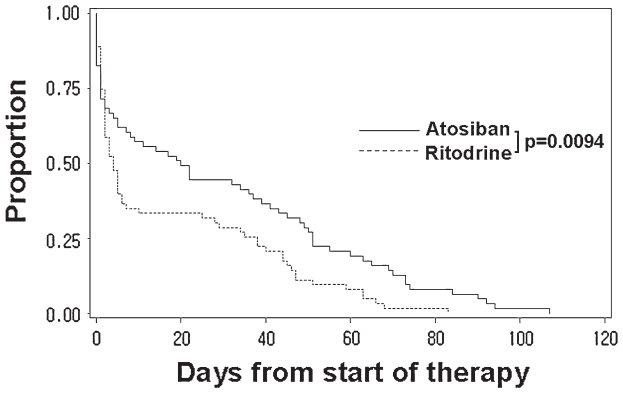

Figure 2. Kaplan–Meier curves for the relationship between delivery rate and time to delivery interval or therapeutic failure for atosiban and ritodrine.

Because most previous studies were performed in Europe and North America, in women of various ethnic origins, we performed this study in the Korean population, which has a relatively homogenous ethnic origin. To our knowledge, no randomised trial has specifically examined the safety and efficacy of atosiban in the primary treatment of preterm labour in an Asian population.

We measured tocolytic efficacy as the proportion of women who were not delivered and who did not need alternative tocolytic therapy. This end-point is a composite outcome of the delay of preterm delivery and drug tolerability. Atosiban treatment resulted in significantly higher efficacy after 7 days, a finding similar to that of an active controlled trial with atosiban.[13]

Though the numbers of women in the subgroup analysis were too small to give a meaningful answer with adequate statistical power, in women of gestational age <28 weeks at randomisation, atosiban showed better outcome after 48 hours and 7 days of initiation of therapy than women of gestational age ≥28 weeks. Similar results were observed in the difference in time to delivery or therapeutic failure between atosiban and ritodrine. These findings imply that atosiban, like ritodrine, may be more effective in women of gestational age <28 weeks than in those closer to term. Indeed, earlier results suggested that ritodrine might not be recommended in women of gestational age >28 weeks.[4]

Our study confirmed that atosiban has a good safety profile, and the use of atosiban at the proposed dosage was shown

Table 3. Perinatal outcomes according to the therapy

	Atosiban (n = 63)	Ritodrine (n = 63)
Gestational age at delivery (weeks)	37.3 ± 3.5	37.3 ± 3.1
Birthweight (g)	2906 ± 763	3017 ± 631
1-minute Apgar <7*	7/53 (13.2%)	5/48 (10.4%)
5-minute Apgar <7*	1/53 (1.9%)	1/48 (2.1%)
NICU admission	14 (22.2%)	10 (15.9%)
>7 days	11 (17.5%)	8 (12.7%)
Ventilator use	6 (9.5%)	2 (3.2%)
>7 days	4 (6.3%)	1 (1.6%)
Neonatal death	1 (1.6%)	2 (3.2%)
Neonatal morbidity		
Infection	4 (6.3%)	2 (3.2%)
Intraventricular haemorrhage	3 (4.8%)	1 (1.6%)
Respiratory distress syndrome	3 (4.8%)	0
Patent ductus arteriosus	2 (3.2%)	0
Seizure	0	0
Hypoglycaemia	0	2 (3.2%)
Hypotension	0	0

Values are given as n (%) and mean ± SD.
*Data were not available for 10 infants in the atosiban group and 15 in the ritodrine group.

to be practically devoid of any effects on the cardiovascular system. In contrast, clinical signs of cardiovascular distress are relatively common in women treated with ritodrine. In our women treated with atosiban, cardiovascular effects were infrequent, transient and mild to moderate in severity, and the mean maternal heart rate remained unchanged during treatment. All women who discontinued ritodrine treatment prematurely for adverse events had at least one cardiovascular adverse event. In accordance with previous reports, these observations suggest that the high uterus selectivity of this oxytocin antagonist led to an improvement in safety profiles.

Table 4. Maternal adverse events relative to primary treatment drug

	Atosiban (n = 63) No. (%)	Ritodrine (n = 65) No. (%)
Total No. of women with adverse events	5 (7.9)	46 (70.8)
Early drug termination due to adverse events	0	13 (20.0)
Adverse event		
Palpitation	2 (3.2)	31 (47.7)
Tachycardia	1 (1.6)	13 (20.0)
Chest tightness	3 (4.8)	17 (26.2)
Dyspnoea	2 (3.2)	17 (26.2)
Hypotension	0	1 (1.5)
Nausea	0	0
Vomiting	0	3 (4.6)
Headache	1 (1.6)	5 (7.7)
Tremor	0	4 (6.2)
Nervousness	0	4 (6.2)
Hot flush	0	2 (3.1)
Hyperglycaemia	10 (15.9)	12 (18.5)
Hypokalaemia	0	7 (10.8)

Values are given as n (%).

We found that the incidence of hyperglycaemia was comparable in both the atosiban and ritodrine groups, but that hypokalaemia was notably higher in women receiving ritodrine. Ritodrine-induced hypokalaemia may be due to its direct stimulation of cellular potassium uptake. Moreover, the increases in plasma glucose and insulin levels during ritodrine treatment may contribute to hypokalaemia.[17]

The incidence of neonatal morbidity in this study was less common than in previous studies because multiple pregnancies were not included. Only 12% of atosiban has been found to cross the placenta to the fetal circulation.[18] We found that all neonatal deaths occurred in those delivered at a gestational age <27 weeks. None of these deaths was considered related to study treatment; rather, they were probably related to the extreme prematurity.

The overall goal of tocolytic therapy is to improve perinatal outcome by transferring a woman to a tertiary care centre and by prolonging pregnancy in order to administer antenatal corticosteroids. Despite our finding that atosiban significantly reduced the likelihood of delivery within 7 days, we found that atosiban did not improve perinatal outcome. Serious neonatal morbidities such as infection and intraventricular haemorrhage occurred more frequently rather in the atosiban group than in the ritodrine group. The number of women enrolled in the study, however, was not high enough to detect significant drug-related differences in perinatal outcome. A larger trial, in which the primary end-points are perinatal outcomes, may be required.[19]

Some study limitations have to be taken in account in evaluating the results of the present study. First, it was not a double-blind trial. We did not use a double-blind, double-dummy design because the sizes and shapes of the study drugs were different. It was therefore impossible to get placebo ampoules of ritodrine without the cooperation of the manufacturer of the control drug. To minimise any possible investigator bias, however, infusates were administered using a piggy-back method and we maintained the investigator-blinded methods in assessing outcomes. It was difficult, however, to maintain the double-blind method because the adverse effect profile of ritodrine may have compromised the actual double-blind design during treatment.[14] A second limitation of our study was that nine women, eight (12.7%) in the atosiban group and one (1.6%) in the ritodrine group, received tocolytic treatment (ritodrine) before randomisation (P = 0.03). However, women who received previous tocolytic

treatment had a 6-hour wash-out period between dosing,[13] a period thought to be sufficient to minimise the effects of previously administered ritodrine.

In conclusion, we have shown here that atosiban is an effective tocolytic agent with highly uterospecific properties. Its clinical benefits (efficacy and adverse events) were superior to those of ritodrine. Our results indicate that atosiban may be recommended as a first-line treatment option for the management of women with preterm labour.

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