Ritodrine in Oral Maintenance of Tocolysis after Active Preterm Labor: Randomized Controlled Trial

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Aim To assess the efficacy of oral ritodrine in the form of sustained-release capsules for maintenance of uterine quiescence after successful treatment of threatened preterm labor.

Methods We randomized 120 women with singleton pregnancy who were successfully treated for threatened preterm labor before 34 completed weeks to receive either maintenance tocolysis with two 40 mg ritodrine sustained release capsules three times a day (study group, n = 62) or no treatment (control group, n = 58) for three days. The primary outcome measure was the recurrent episode of threatened preterm labor within 72 hours, which was defined as regular palpable uterine contractions and change in cervical effacement or cervical dilatation on clinical examination. Secondary outcome measures included the incidence of preterm birth, neonatal adverse outcomes, and maternal side effects.

Results There was no difference in the frequency of recurrent episodes of threatened preterm labor requiring another course of intravenous treatment between the study (8/62) and control (6/58) group of women (P = 0.879). No differences were found between the study and control groups in any of the predefined secondary outcome measures, ie, delivery before 37 weeks (13/62 vs 7/58, respectively; P = 0.288), delivery before 34 weeks (3/62 vs 1/58, respectively; P = 0.682) and birth weight (3037 ± 573 g vs 3223 ± 423 g, respectively, P = 0.862). There were more reported maternal side effects in the study group than in control group (47/62 vs 23/58, respectively; P<0.001).

Conclusions Additional maintenance ritodrine therapy was unnecessary in women with singleton pregnancy who had an episode of threatened preterm labor successfully treated with intravenous tocolytic therapy.

Clinical Trial Registration ClinicalTrials.gov Identifier: NCT00290173

A substantial proportion of women experiencing an episode of threatened preterm labor do not progress to delivery if actively treated with intravenous (IV) tocolytic therapy (1). After cessation of IV therapy, many of them continue taking oral tocolytic drugs. However, despite a relatively common use of oral maintenance therapy, there is weak evidence from controlled studies about its effectiveness in these women irrespective of the sort of medication used (1-3). Evidence supporting such approach mostly shows lower incidence of relapses and longer relapse intervals, but no reduction in the frequency of preterm delivery or significant improvement in perinatal mortality and morbidity (1,4-6). Ritodrine is still one of the commonly used drugs in tocolytic therapy (1,5-8). As the bioavailability of ritodrine and its short half life were blamed for its relative inefficacy, the attempt was made to improve them by use of sustained-release preparations (9,10). Except fewer metabolic and cardiovascular side effects, no other important benefits were found. However, ritodrine may have side effects that can be serious not only for the mother, but also for the fetus because it crosses the placenta (5,7,11-13).

We performed a prospective randomized controlled trial to determine the effect of oral ritodrine in the form of sustained-release preparation for maintaining uterine quiescence after successful treatment of active preterm labor with ritodrine IV preparations.

Patients and methods

Patients

Eligible participants were women with symptoms of preterm labor admitted to the Department of Obstetrics and Gynecology at the Holy Ghost Hospital, tertiary referral center, between January 2003 and June 2005. The preterm labor was diagnosed if the following criteria were met: gestational age between completed 24 and 34 weeks of gestation, more than 5 contractions per hour for 2 hours, 1-3-cm cervical dilatation on a single examination, and effacement of at least 75% or dilatation of 4 cm with effacement of at least 50%, ie, modified Bishop score ≥3 (*http://www.mother-care.ca/bishop.htm*). All women received corticosteroids for promotion of fetal lung maturation and IV ritodrine treatment for reduction of uterine contractions, according to the defined protocol. Women with recurrent episodes of preterm labor before completed 34 weeks of pregnancy were treated by IV ritodrine according to the hospital protocol, but were not offered to participate in the trial. The decision for repeated IV treatment was made by the senior consultant on call, and none of the investigators was involved in this process.

In total, 199 pregnant women admitted to the Department with the symptoms and signs of preterm labor were eligible for the trial. Preterm labor was successfully treated in 183 women. We excluded 11 women because they received additional tocolytic therapy including indomethacain (n = 8), nifedipine (n = 2), or nifedipine and indomethacin (n = 1), 11 women who completed 34 weeks of pregnancy before the intravenous treatment was stopped, and 16 women who had the suspected infection (Figure 1). Twenty-five women refused to participate in the study.

The final study sample included 120 women with singleton pregnancy and preterm labor. As none of the women were lost to follow up, the delivery and neonatal data on all women enrolled in the study were available for analysis.

Ethical Committee of the Hospital approved the study protocol and all women gave their written informed consent before the study.

Randomization

Pregnant women were enrolled in the trial once uterine quiescence had been achieved and randomized before the discontinuation of IV therapy. To receive oral maintenance treatment, the women had to be receiving <0.1 mg/min of

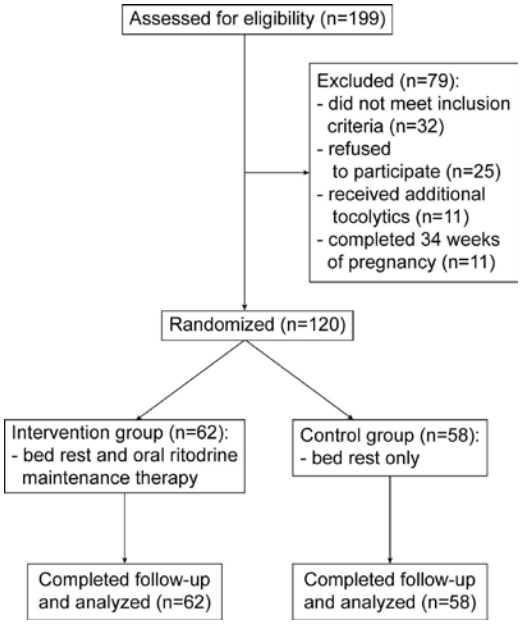

Figure 1. Flow diagram of the study.

ritodrine IV for at least 12-24 hours after the second dose of corticosteroids. We did not randomize women who had uterine contractions (painful, clinically palpable, or present on cardiotocography); cervical dilatation of ≥5 cm; clinical and laboratory signs of infection defined as offensive vaginal discharge on clinical examination, vaginal pH≥5, white blood cell count >16 × 10^9/L, and C-reactive protein (CRP)>10 mg/L; positive findings of microorganisms rather than normal vaginal flora on high vaginal swab, and any signs of fetal distress according to cardiotocography, Doppler assessment of blood flow in umbilical artery, and biophysical profile of <8.

Computer-generated random number tables were used for random assignment of the investigated treatment. Group assignments were placed in sealed, opaque, sequentially numbered envelopes. Women received either maintenance dose of oral ritodrine consisting of two 40-mg ritodrine sustained-release capsules three times a day (intervention group) or no treatment (control group), and were kept in hospital for 72 hours.

Follow up

All women were instructed to limit their physical activity and taught to recognize the signs and symptoms of preterm labor. After 72 hours, women were examined by the senior consultant (R.M.) and discharged from the hospital if symptom-free and without any change on clinical examination. All women were followed up weekly until the delivery in High Risk Obstetric Clinic. Compliance with the preterm labor instructions was emphasized at each visit. At discharge, the dose of ritodrine in the intervention group was reduced to one 40-mg sustained-release capsule three times a day. The treatment was completely discontinued after completed 34 weeks of pregnancy or in case of severe side effects, signs of chorioamnionitis, or fetal distress. The control group was discharged from hospital after 72 hours without any treatment.

Outcome measures

The primary outcome measure was the recurrence of preterm labor within 72 hours after discontinuation of IV treatment. Secondary outcome measures were incidence of preterm delivery before 37 weeks of gestation, incidence of early preterm delivery before completed 34 weeks of gestation, prolongation of pregnancy, birth weight, perinatal mortality, perinatal morbidity assessed at the admission to neonatal intensive care unit (NICU) and including Apgar score <7 after 5 minutes and the need for mechanical ventilation, mild maternal side effects (dizziness, tremor, tachycardia >110/min, or shortness of breath), and severe maternal side effects (pulmonary edema).

Statistical analysis

Sample size calculation was performed with MaCorr sample size calculator (MaCorr Inc., Toronto, Ontario, Canada). The calculation was designed to detect at least 20% difference in the frequency of successful maintenance between

the ritodrine and control group. Successful maintenance was defined as no delivery or no administration of a new course of IV tocolytic treatment within the 72 hours after randomization. The confidence interval (CI) needed to detect 20% difference from the general level of accuracy (50%) in a representative sample of 100 women was 9.0%. After choosing 95% confidence level within the 9.0% CI, the sample size obtained was 119 participants.

The analysis was performed on intention-to-treat basis. The χ^2 and Fisher exact tests were used to evaluate categorical data where appropriate. Student *t* test was used to evaluate continuous variables. Comparison between the groups for IV ritodrine treatment was made with Wilcoxon signed-ranks test, whereas comparison of modified Bishop score and cervical dilatation was made with Cochran-Mantel-Haenszel test. Two-tailed statistical significance was set at $P<0.05$. Statistical analysis was performed with Statistical Package for Social Sciences version 11.0 (SPSS Inc., Chicago IL, USA).

Results

There were no significant differences between the two groups of women in their age, gestational age, and other demographic and relevant clinical characteristics (Table 1). Active treatment to prevent preterm labor had to be administered in 14 women included in the study (Table 2). There was no significant difference in the incidence of recurrent episode of preterm labor within 72 hours after discontinuation of ritodrine IV treatment between the group of women receiving maintenance ritodrine therapy in the form of sustained release preparations and their controls (Table 2). The secondary outcome measures, including the incidence of preterm and early preterm delivery, prolongation of pregnancy, birth weight, perinatal mortality, and perinatal morbidity were not significantly different in the two groups of women. However, significant differences were found in the frequency of some side effects of ritodrine. Among them, palpitations, tremor, and maternal tachycardia were the most prominent and significantly more frequent in the group of women on maintenance ritodrine therapy ($P<0.001$, Fischer exact test). There were no significant differences in other symptoms that could have been ascribed to side effects of ritodrine. There were no cases of maternal pulmonary edema as the most serious possible side effect of ritodrine (Table 2).

Discussion

We found no differences in the proportion of women who had to receive repeated course of IV tocolysis for treatment and prevention of preterm labor irrespective of the use of maintenance

Table 1. Maternal demographic and clinical characteristics at randomization

Characteristics	No. of women		*P**
	ritodrine (n = 62)	control (n = 58)	
Age (median, range; y)	29 (20-40)	29 (18-41)	0.829
Primiparous	32	39	
Multiparous	30	19	
Previous preterm delivery	6	2	0.317
Previous uterine surgery	0	1	0.973
Previous cervical surgery	1	1	0.505
Polyhydramnios present	1	1	0.505
Gestational age (mean±SD, completed weeks)	29 ± 3	30 ± 3	0.172
Cervical dilatation (median, range; cm)	1 (0-4)	1 (0-4)	0.655
Modified Bishop score (median, range)	1 (1-5)	1 (1-5)	0.505
Modified Bishop score ≥3	19	13	0.416
Intravenous ritodrine treatment (median, range; h)	72 (24-105)	48 (48-130)	0.052

*Student *t* test for age and gestational age; Fisher exact test for previous preterm delivery, uterine or cervical surgery, and polyhydramnios; Cochran-Mantel-Haenszel test for cervical dilatation and modified Bishop score (*http://www.mother-care.ca/bishop.htm*), χ^2 test for frequency of modified Bishop score ≥3; and Wilcoxson signed-ranks test for intravenous ritodrine treatment.

Table 2. Primary and secondary outcome measures in women with preterm labor treated with oral ritodrine maintenance therapy and their controls

Outcome measures	No. of women		*P*
	ritodrine (n = 62)	control (n = 58)	
Primary:			
new active treatment within 72 h	8	6	0.879†
Secondary:			
delivered within 72 h	0	1	0.973†
delivered before 34 weeks	3	1	0.682†
delivered before 37 weeks	13	7	0.288†
perinatal mortality	0	0	NA
prolongation of pregnancy (median, range; d)	54 (14-119)	58 (2-112)	0.434‡
CW at delivery (mean±SD)	37 ± 2	38 ± 1	0.252‡
birth weight (mean±SD, g)	3037 ± 573	3223 ± 423	0.862‡
Apgar ≤7 at 5 min	2	3	0.939†
NICU admission	4	3	0.927†
mechanical ventilation	1	1	0.519†
Maternal side effects:			
palpitations	47	23	<0.001§
tremor	28	5	<0.001§
tachycardia	39	11	<0.001§
shortness of breath	9	2	0.084§
dizziness	7	4	0.644†
hypotension	3	1	0.682†
fetal tachycardia	1	0	0.96†
pulmonary edema	0	0	NA

*Abbreviations: RR – risk ratio; SD – standard deviation; CW – completed weeks of pregnancy; NA – not applicable.
†Fischer exact test.
‡Student *t* test.
§χ^2 test.

oral ritodrine therapy. Furthermore, maintenance ritodrine therapy did not delay the delivery, nor were there differences found in adverse pregnancy outcomes. Holleboom et al (1) obtained different results, although their study design, outcome measures, and the number of women included in the trial were very similar to ours. There are two possible explanations for these differences. The first may lie in the fact that, in contrast to Holleboom et al (1), we excluded women with multiple pregnancies from our sample. These women are more likely to have preterm labor and the possibility of recurrence of preterm labor in them may be higher. Therefore, it is possible that the maintenance therapy in women with multiple pregnancies may be of some benefit. The second explanation may be related to infection. As the infection is the most common cause of preterm labor, we excluded 16 women before the randomization because of suspected infection on high vaginal swab, increased white blood cell count, or increased C-reactive protein values. It was not specified if the women with suspected infection were excluded from the trial by Holleboom et al (1).

The well-known maternal and fetal side effects of ritodrine (5,7,11-13) were also found in our trial. However, there were no severe side effects and only a single case of fetal tachycardia, potentially related to ritodrine use, was reported in the study group. The fetal heart rate of 180 beats/min was found on a routine clinical examination and resolved spontaneously after 30 minutes. The oral ritodrine maintenance treatment had to be discontinued in 6 of 62 women due to maternal side-effects. Among them, treatment was discontinued in 2 women during the initial hospital stay (48-72 hours after discontinuing IV treatment). None of the 6 women needed new active treatment with IV ritodrine and only one delivered before term at 35 completed weeks. The side effects may reduce the compliance of women taking oral ritodrine. Despite the presentation of empty blisters at each clinical visit, we suspect that many women might not be following the protocol for oral ritodrine therapy.

The efficacy of oral maintenance tocolytic therapy after successful arrest of preterm labor remains controversial (1,4-6,14,15). This question is not limited to the use of a specific drug as the data are the similar for ritodrine, terbutaline, magnesium sulfate, and calcium channel blockers (1,16-18). A meta-analysis might not provide conclusive results because, according to Meirowitz et al (6), such an analysis is not possible due to the small number of properly designed trials and inconsistent definitions of outcome variables. Sanchez-Ramos et al (5) concluded that maintenance tocolysis does not reduce the incidence of recurrent preterm labor. Similar conclusion by the Cochrane Collaboration points to the need for a well-designed, large, randomized trial to evaluate the efficacy of oral tocolytics in improving perinatal outcome (19).

Ritodrine in IV preparations and oral forms is still widely used drug mostly because of its low cost (20). Recent survey in Australia and New Zealand has shown that the first-choice drug for tocolysis were beta-adrenergic agents, followed by nifedipine, and that maintenance tocolysis was used by a third of obstetricians participating in the survey (8). Oral maintenance preparations after successful arrest of preterm labor are incorporated in most of the protocols (1,21,22). This is against currently available results of meta-analysis showing that oral maintenance treatment offers no advantages over placebo during the latency phase of for a recurrence rate of preterm labor and delivery (12,18).

Oral maintenance therapy results in significant cost for a national health system as well as unnecessary use of the drugs that may potentially have the harmful effects for the pregnant women and her unborn baby. Despite the fact that regime of oral administration of ritodrine was found to be relatively safe and harmless, there are reports of serious complications including dizziness, nausea, and tremors as the most common; cases of pulmonary edema have also been reported (23).

There are several possible limitation of our trial. First, it was not double-blind. However, it would be very difficult to perform such a trial due to strong side effects of ritodrine preparations. Monitoring patient compliance after hospital discharge also proved difficult. Furthermore, it was difficult to diagnose accurately preterm labor on the basis of the symptoms and clinical findings. Ultrasound assessment and fibronectin values were not used in all cases. However, this was a pragmatic trial aiming to test the hypothesis in routine everyday clinical practice.

We believe that, despite our findings and findings of other studies, some clinicians will continue to use the maintenance tocolytics, mostly to reduce maternal (and obstetrician's) anxiety (24). However, if clinically and laboratory parameters are not suggestive of infection, there is no need for additional maintenance ritodrine therapy in women singleton pregnancies who have had an episode of threatened preterm labor and are successfully treated with intravenous tocolytic therapy.

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