The influence of ritodrine alone or in combination with nifedipine on maternal cardiovascular side effects and pregnancy outcomes

M.J. Kim[1], I. Hwang[2], J.Y. Bae[2], W.J. Seong[2]

[1] Department of Obstetrics and Gynecology, Yeungnam University Hospital, Daegu
[2] Department of Obstetrics and Gynecology, Kyungpook National University Hospital, Daegu (Korea)

Summary

Objective: To compare the influence of ritodrine alone or in combination with nifedipine on maternal side effects and suppressing preterm labor. *Materials and Methods:* This retrospective study included 213 pregnancies with preterm labor (20–34 weeks) from May 2002 to April 2010 in Kyungpook National University Hospital in Daegu, Korea. Obstetric medical records were reviewed for both maternal characteristics and neonatal outcomes, including birth weight, Apgar score, admission to neonatal intensive care unit (NICU), ventilator support, and neonatal mortality. Maternal side effects such as tachycardia, pulmonary edema, and hyperglycemia were also reviewed. *Results:* Of 213 patients, 109 received ritodrine only and 104 were given ritodrine and nifedipine. There was no statistical difference between the two groups with regards to pregnancy outcomes and neonatal complications. Pregnancy prolongation over seven days was achieved more in the combination therapy group, with borderline statistical significance (59.6% *vs.* 72.1%, $p = 0.055$). Sixty-nine cases experienced maternal side effects; four cases were categorized as serious and 65 cases were mild. *Conclusion:* In the treatment of preterm labor, the combination regimen of ritodrine and nifedipine can be more effective than ritodrine alone for prolonging gestation over seven days. Moreover, as the combination did not cause severe maternal side effects, it may be considered as a safe and effective method to prolong gestation in patients with preterm labor.

Key words: Preterm labor; Pregnancy prolongation; Combination therapy; Ritodrine; Nifedipine.

Introduction

Acute tocolysis has the potential to delay preterm birth for 48 hours, the critical period for antenatal steroid administration and a transfer to tertiary center, or arrest an episode of preterm labor, thus delaying birth and improving neonatal outcome [1,2]. The β-sympathomimetic ritodrine has been studied as one of the most potent tocolytics in several randomized controlled trials since the 1970s [3, 4]. It acts by binding to β-2 adrenergic receptors on the myometrial cell membrane, which subsequently increases the levels of intracellular cyclic AMP and inactivates myosin light chain kinase [5]. To this day, ritodrine remains the first and only tocolytic FDA-approved for the treatment of preterm labor [6]. Because of this initial approval and acceptance by the medical community, ritodrine has been the most widely used as a first line tocolytic drug in Korea and Eastern Asia.

Calcium channel blockers, especially nifedipine, have gained popularity as tocolytic drug because of several reasons, such as the oral administration route, low incidence of maternal adverse effects, inexpensive cost, and variable options of formula and dosage.

There have been a few observational studies comparing the effect of ritodrine and nifedipine in spontaneous preterm labor, and nifedipine appears to be more effective than ritodrine in delaying birth at least 48 hours, and with fewer maternal and neonatal side effects [7,8]. However, very little is known about the combination of both tocolytics.

The authors performed this retrospective study to identify the safety and effectiveness of the ritodrine and nifedipine combination regimen for the purpose of gestation prolongation in patients with threatened preterm labor.

Materials and Methods

Women eligible for inclusion were those with a singleton pregnancy between 20 and 34 weeks of gestation, diagnosed with preterm labor defined as cervical changes and regular uterine contractions of four in 20 minutes or eight in 60 minutes. Exclusion criteria were rupture of membranes, cervical dilation over four cm at the time of admission, multifetal gestations, fetal growth restriction, preeclampsia, and incomplete medical records. In addition, women with diabetes mellitus, including gestational diabetes, thyroid diseases, and cardiovascular diseases, including hypertension, were also excluded.

Among 652 patients who were admitted with preterm labor pain from May 2002 to April 2010, 213 patients with singleton pregnancies who met the inclusion criteria, were selected and reviewed. Eligible subjects were managed with ritodrine only or ritodrine and nifedipine combination regimen. All medical records and laboratory tests were subsequently reviewed by two reviewers. Differences in interpretation were adjusted through an attempt to reach a consensus.

Of 213 patients, 109 received ritodrine only and 104 were given ritodrine and nifedipine in combination. Cervical cerclage was performed in patients with a history of repetitive preterm births or a second trimester pregnancy loss, or patients with a short cervi

Revised manuscript accepted for publication November 25, 2013

Table 1. — *Maternal baseline characteristics and pregnancy outcomes.*

	Ritodrine (N=109)	Ritodrine and nifedipine (N=104)	*p*-value
Age (years)	30.5±3.9	30.2±4.6	NS
Multiparity	55(51%)	58(56%)	NS
GA at admission (days)	209.8±26.8	209.6±27.8	NS
< 28 weeks	32	31	
≥ 28 weeks	77	73	
Prior preterm birth	16(15%)	14(14%)	NS
Cervical cerclage	13(12%)	17(16%)	NS
Cervical length (mm)	14±9	16±7	NS
Duration of ritodrine (days)	11.2±14.8	12.5±15.2	NS
Leukocytosis (> 15,000/mm3)	11(10%)	8(8%)	NS
CRP (mg/dL)	1.1±2.8	0.9±1.5	NS

GA: gestational age. Values are given as number and mean ± SD.
NS: not significant; $p < 0.05$: significant.

cal length (< 25 mm) after previous cervical surgery (e.g. loop electrical excision procedure). Patients belonging to the ritodrine only group received an intravenous infusion of ritodrine in Hartman solution at a rate of 0.2 mg/min. The dose was increased by 0.2 mg every 20 minutes until uterine contractions were suppressed, intolerable side effects appeared, or a limit dose of two mg/min was achieved. In the combination group, intravenous ritodrine was also used as the first line regimen with the same protocol, and oral nifedipine was added with an initial loading dose of 30 mg and a maintenance dose of 30 mg every six hours when preterm labor could not be controlled with ritodrine only.

Neonatal outcomes, including birth weight, Apgar score, admission to neonatal intensive care unit (NICU), ventilator treatment, and neonatal mortality rate, were obtained. Obstetric medical records were also reviewed to evaluate changes in preterm labor pain patterns before and after the tocolysis, and to note the presence of any maternal side effects. The authors classified adverse events in terms of severity (severe or mild) by using the definition of the Council for International Organizations of Medical Sciences [9]. According to the council, a serious adverse event refers to certain side effects which can result in death or a life-threatening condition, persistent or critical disability or incapacity, lead to a congenital anomaly, require admission to a hospital, or prolong an existing hospital stay. Based on this definition, any of the following could be serious adverse events: severe hypotension (systolic blood pressure < 90 mmHg and > 20% drop compared with baseline values), severe dyspnea (oxygen saturation < 90% or respiration rate > 30/minute), pulmonary edema, abnormal electrocardiogram (ECG), myocardial infarction, anaphylactic shock, admission to the intensive care unit, or maternal death. Mild adverse events were defined as those that led to cessation of tocolytic therapy (such as tachycardia, nausea, dizziness, and headache) but did not meet the criteria for a serious adverse event. Cervical length was measured with transvaginal ultrasonography by using Voluson 730 Expert or Accuvix XQ at the time of admission.

Maternal hematological laboratory tests, such as white blood cell count (WBC), C-reactive protein (CRP), and electrolytes, were checked at the time of admission and at three-day intervals during the admission period. Maternal chest radiography and ECG were also obtained at seven-day intervals. Statistical analyses were performed by using SPSS 12.0. Differences of each value were considered as statistically significant if the p value was < 0.05. Statistical inferences were based on Student's t-tests and chi-square tests.

Table 2. — *Pregnancy outcomes and neonatal complications of both groups.*

	Ritodrine (N=109)	Ritodrine and nifedipine (N=104)	*p*-value
GA at delivery (days)	237.3±28.7	237.8±29.0	NS
Birthweight (g)	2207±776	2319±800	NS
1-min Apgar <7	39(36%)	42(40%)	NS
5-min Apgar <7	11(10%)	14(13%)	NS
NICU admission	63(58%)	62(60%)	NS
Ventilator treatment	22(20%)	23(22%)	NS
>7 days	14	11	NS
≤7 days	8	12	NS
Neonatal death	4(4%)	9(9%)	NS

GA: gestational age. Values are given as number and mean ± SD.
$p < 0.05$: significant.

Table 3. — *Maternal side effects during the usage of tocolytics.*

	Ritodrine (N=109)	Ritodrine and nifedipine (N=104)	*p*-value
Total adverse effect	33	36	NS
Serious adverse effect			
Severe dyspnea	1	0	
ECG abnormality	2	1	
Pulmonary edema	0	0	
Mild adverse effect			
Palpitation, tachycardia	19	10	
Chest tightness	19	23	
Headache	1	3	
Nausea	0	2	
Tremor	7	4	
Hot flush	3	0	
Toxic erythema	2	2	
Hyperglycemia	2	0	
Hypokalemia	0	0	

Tachycardia was defined as heart rate over 120/min.
Values are given as number of patients. $p < 0.05$: significant.

Results

Table 1 shows baseline demographic characteristics of this study. There were no differences between the two groups in maternal age, parity, gestational age, cervical length, cerclage or not, serum WBC count, and CRP. In the combination regimen group, the period of nifedipine treatment was 8.3 ± 12.3 days, and the dose was 41.7 ± 22.8 mg/day (mean ± standard deviation). Ritodrine and nifedipine were combined for 5.9 ± 10.7 days.

As shown in Table 2, there was no statistical difference between the two groups in either pregnancy outcomes or neonatal complications, such as birth weight, NICU admission rate, Apgar score, and neonatal mortality. Neonatal mortality was mainly caused by extreme preterm birth.

Table 3 represents adverse events, which were found in 69 patients. Four cases were categorized as serious events,

Table 4. — *Pregnancy prolongation after the usage of tocolytics.*

Pregnancy prolongation	Ritodrine (N=109)	Ritodrine and nifedipine (N=104)	*p*-value
48 hours	90 (82.6%)	93 (89.3%)	NS
<28 weeks	24/32	27/31	
≥28 weeks	66/77	66/73	
7 days	65 (59.6%)	75 (72.1%)	0.055
<28 weeks	20/32	22/31	
≥28 weeks	45/77	53/73	

Values are given as number of patients (%); $p < 0.05$: significant.

and 65 cases were mild. One patient experienced severe dyspnea without pulmonary edema and recovered after application of an oxygen mask. Three patients showed abnormal change of ECG after administration of tocolytics. In all patients, myocardial infarction was ruled out because serum cardiac enzyme levels were within the normal range. All patients who experienced adverse events recovered without persistent disability or incapacity. There was no intrauterine fetal death. No differences were found between the two groups with regard to mild side effects. The rate of pregnancy prolongation over 48 hours was not different between the two groups (Table 4). Pregnancy prolongation over seven days was achieved more frequently in the combination therapy group, though with borderline statistical significance (59.6% *vs.* 72.1%, $p = 0.055$). When patients were subgrouped by gestational age at the time of enrollment (< 28 and ≥ 28 weeks of gestation), there was no difference in pregnancy prolongation between the two groups.

Discussion

Meta-analyses have shown that β-sympathomimetics, especially ritodrine, are associated with a delay of delivery of 24 hours, 48 hours, and seven days. However, such delay has not been associated with a significant reduction in either perinatal mortality or morbidity [10,11]. Due to the high incidence of side effects of β-sympathomimetics, the search for better drugs has become an important issue in preterm labor research. The oxytocin receptor antagonist atosiban newly appeared as a tocolytic in 2000. However, despite the clear advantage in the lack of relevant side effects of this new agent, perinatal mortality and morbidity still have not been modified. It is also expensive and is not yet FDA-approved; therefore, its worldwide use has limitations [12].

On the other hand, nifedipine is a very familiar and widely used calcium channel blocker. It reduces the intracellular entrance of calcium through the slow channel, producing an inhibition of contractile activity of nonpregnant, pregnant, and postpartum myometrium. It also reduces the amplitude and frequency of contractions and the basal myometrial tone, and it acts more strongly in pregnant than in non-pregnant women. The mean half-life in pregnant women is short (81 min); therefore, its effect is reversible [13, 14]. It was introduced as an antihypertensive drug, but its hypotensive effect is mild in normotensive pregnant patients. Many reports have evaluated the efficacy of nifedipine as a tocolytic agent. A large-scale systematic review, which included 12 randomized controlled trials with a total of 1,029 participating women, compared the efficacy of nifedipine with that of ritodrine. Nifedipine was found to be more effective than ritodrine in prolongation of pregnancy beyond seven days and was also much less likely to cause maternal side effects. Furthermore, nifedipine can be administered orally and is also cost-effective [15].

However, little is known about combinations of tocolytics. There have been only a few reports about combination of tocolytics, such as β-sympathomimetics with magnesium sulfate, or β-sympathomimetics with atosiban [16,17]. To the best of the present authors' knowledge, there was no prior study on the combination of ritodrine and nifedipine in patients presenting with threatened preterm labor, although there were several animal and in vitro studies. There was a rat model study by Gallagher *et al.*, which showed that the combination of two drugs was more effective in inhibition of labor than a single agent [18]. Hajagos-Toth *et al.* studied the uterus-relaxing effects of β-sympathomimetics with nifedipine on rats and the human myometrium, and showed that the effect of nifedipine was tripled by the addition of β-sympathomimetics [19]. Doret *et al.* reported on a rat model study that used ritodrine, atosiban, and nicardipine, and proved the ritodrine and nicardipine combination regimen had a good inhibitory effect on myometrial contractility (78.5%), although the effect of the ritodrine and atosiban combination regimen was slightly better (88.9%) [20].

The results obtained in this study showed that ritodrine and nifedipine combination regimen could be more effective than ritodrine alone for prolonging gestation over seven days in the treatment of preterm labor, although of borderline statistical significance. Moreover, the combination did not induce severe maternal side effects, such as myocardial infarction and pulmonary edema. Therefore, the present authors propose that combination tocolytic therapy, specifically ritodrine and nifedipine, can be considered as a safe and effective method to prolong gestation in patients with preterm labor, though no improvements were found in neonatal outcomes.

Many obstetricians have general concerns about pulmonary edema or severe cardiovascular side effects while using β-sympathomimetics or calcium channel blockers for preterm labor. However, as shown in the present study, maternal side effects of the combination regimen did not exceed the side effects of the ritodrine only regimen.

Despite the present results, careful observation of pregnant women who receive tocolytic therapy, especially those

with multiple pregnancies or undergoing steroid therapy, must continue. Close hemodynamic control and patient selection is mandatory to avoid severe side effects. Moreover, despite many reports on the use of nifedipine, this drug has not been licensed for use in pregnancy. In the present worldwide context of litigation, this fact should also be considered [21].

In conclusion, the present authors found that ritodrine and nifedipine in combination did not lead to a higher incidence of serious adverse side effects than ritodrine alone, and the combined regimen could be considered for prolonging pregnancy.

References

[1] Higby K., Xenakis E.M., Pauerstein C.J.: "Do tocolytic agents stop preterm labor? A critical and comprehensive review of efficacy and safety". *Am. J. Obstet. Gynecol.*, 1993, *168*, 1247.

[2] Cotton D.B., Strassner H.T., Hill L.M., Schifrin B.S., Paul R.H.: "Comparison of magnesium sulfate, terbutaline and a placebo for inhibition of preterm labor: a randomized study". *J. Reprod. Med.*, 1984, *29*, 92.

[3] Wesselius-de Casparis A., Thiery M., Yo le Sian A., Baumgarten K., Brosens I., Gamisans O., *et al.*: "Results of double blind, multicentre study with ritodrine in premature labour". Br. Med. J. 1971, *3*, 144.

[4] Walters W.A., Wood C.: "A trial of oral ritodrine for the prevention of premature labour". *BJOG*, 1977, *84*, 26.

[5] Simhan H.N., Caritis S.N.: "Prevention of preterm delivery". *N. Engl. J. Med.*, 2007, *357*, 477.

[6] Merkatz I.R., Peter J.B., Barden T.P.: "Ritodrine hydrochloride: a β-mimetic agent for use in preterm labor. II. Evidence of efficacy". *Obstet. Gynecol.*, 1980, *56*, 7.

[7] Tsatsaris V., Papatsonis D., Goffinet F., Dekker G., Carbonne B.: "Tocolysis with nifedipine or β-adrenergic agonists: a meta-analysis". *Obstet. Gynecol.*, 2001, *97*, 840.

[8] Van De Water M., Kessel E.T., De Kleine M.J., Oei S.G.: "Tocolytic effectiveness of nifedipine versus ritodrine and follow-up of newborns: a randomised controlled trial". *Acta Obstet. Gynecol. Scand.*, 2008, *87*, 340.

[9] Venulet J., Bankowski Z.: "Harmonising adverse drug reaction terminology: the role of the Council for International Organizations of Medical Sciences". Drug Saf., 1998, *19*, 165.

[10] The Canadian Preterm Labor Investigators Group: :Treatment of preterm labor with the β-adrenergic antagonist ritodrine". *N. Engl. J. Med.*, 1992, *327*, 308.

[11] Gyetvai K., Hannah M.E., Hodnett E.D., Ohlsson A.: "Tocolytics for preterm labor: a systematic review". *Obstet. Gynecol.*, 1999, *94*, 869.

[12] The worldwide Atosiban versus β-agonists Study Group: "Effectiveness and safety of the oxytocin antagonist atosiban versus β-adrenergic agonists in the treatment of preterm labour". *BJOG*, 2001, *108*, 133.

[13] Ulmsten U., Andersson K.R., Wingerup L.: "Treatment of premature labor with the calcium antagonist nifedipine". *Arch. Gynecol.*, 1980, *229*, 1.

[14] Fenakel K., Lurie S.: "The use of calcium channel blockers in obstetrics and gynecology: a review". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1990, *37*, 199.

[15] King J.F., Flenady V., Papatsonis D., Dekker G., Carbonne B.: "Calcium channel blockers for inhibiting preterm labour: a systematic review of the evidence and a protocol for administration of nifedipine". *Aust. N. Z. J. Obstet. Gynaecol.*, 2003, *43*, 192.

[16] Coleman F.H.: "Safety and efficacy of combined ritodrine and magnesium sulfate for preterm labor: a method for reduction of complications". *Am. J. Perinatol.*, 1990, *7*, 366.

[17] Shim J.Y., Park Y.W., Yoon B.H., Cho Y.K., Yang J.H., Lee Y., *et al.*: "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". *BJOG*, 2006, *113*, 1228.

[18] Gallagher L.A., Gautieri R.F.: "Influence of a combination of ritodrine and nifedipine on the isolated rat uterus". *Res. Commun. Chem. Pathol. Pharmacol.*, 1992, *75*, 3.

[19] Hajagos-Tóth J., Kormányos Z., Falkay G., Pál A., Gáspár R.: "Potentiation of the uterus-relaxing effects of β-adrenergic agonists with nifedipine: studies on rats and the human myometrium". *Acta Obstet. Gynecol. Scand.*, 2010, *89*, 1284.

[20] Doret M., Mellier G., Gaucherand P., Saade G.R., Benchaib M., Frutoso J., *et al.*: "The in vitro effect of dual combinations of ritodrine, nicardipine and atosiban on contractility of pregnant rat myometrium". *BJOG*, 2003, *110*, 731.

[21] Lamont R.F.: "Reply to article by King JF et al". *Aust. N. Z. J. Obstet. Gynaecol.*, 2004, 44, 275.

Address reprint requests to:
W.J. SEONG, M.D.
Division of Obstetrics,
Department of Obstetrics and Gynecology,
Kyungpook National University Hospital,
Daegu, 700-721 (Korea)
e-mail: wjseong@knu.ac.kr