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Nifedipine and Ritodrine in the Management of Preterm Labor: A Randomized Multicenter Trial

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Objective: **To compare the efficacy of nifedipine with ritodrine in the management of preterm labor.**

Methods: **One hundred eighty-five singleton pregnancies with preterm labor were assigned randomly to either ritodrine intravenously (n = 90) or nifedipine orally (n = 95). The principal outcome assessed was delay of delivery.**

Results: **Ritodrine was discontinued in 12 patients because of severe maternal side effects, and their results were excluded from further analysis. More women in the ritodrine group delivered within 24 hours (22 versus 11, P = .006), within 48 hours (29 versus 21, P = .03), within 1 week (45 versus 36, P = .009), and within 2 weeks (52 versus 43, P = .005) compared with those receiving nifedipine. There were significantly fewer maternal side effects in the nifedipine group. Apgar scores and umbilical artery and vein pHs were similar in both groups. The number of admissions to the neonatal intensive care unit (NICU) in the nifedipine group was significantly lower than in the ritodrine group (68.4 versus 82.1%, P = .04).**

Conclusion: **Nifedipine in comparison with ritodrine in the management of preterm labor is significantly associated with a longer postponement of delivery, fewer maternal side effects, and fewer admissions to the NICU. (Obstet Gynecol 1997;90:230–4. © 1997 by The American College of Obstetricians and Gynecologists.)**

Different tocolytic agents are used to inhibit preterm uterine contractions to postpone delivery. The most commonly used tocolytic agents are the beta-adrenergic agonists. Meta-analysis has shown that beta-adrenergic agents, especially ritodrine, are associated with a postponement of delivery of 24–48 hours.[1] Such a delay is not associated with a significant reduction in either preterm birth or perinatal morbidity and mortality.[1] Also, the Canadian Preterm Labour Group[2] concluded that ritodrine has no significant beneficial effects on perinatal mortality, prolongation of pregnancy to term, neonatal morbidity, or birth weight. Therefore, the clinical efficacy of beta-adrenergic agents is doubtful, while at the same time the use of these agents is associated with several side effects, limiting their use.[3,4] As a result, clinicians have looked for alternative agents.

Nifedipine, a dihydropyridine calcium entry blocker, is an effective smooth muscle relaxant with low toxicity and low teratogenicity.[4–8] Its use as a tocolytic agent has been restricted because of concerns regarding adverse effects on uteroplacental blood flow. Some animal studies[9,10] suggested that calcium channel blockers are associated with impaired uterine blood flow, which could result in fetal hypoxemia and acidemia. However, studies[6,11,12] in human pregnancies did not show any significant alteration in uterine blood flow with nifedipine.

Studies[4,6,8,13–17] comparing ritodrine with nifedipine in the management of preterm labor suggest a similar tocolytic efficacy but fewer maternal side effects and no adverse fetal side effects with nifedipine. We recently reported the results of a retrospective study[15] comparing ritodrine with nifedipine in the management of preterm labor, in which nifedipine was given in a dose up to 160 mg daily, which is much higher than reported previously. This high dose of nifedipine was not associated with adverse maternal or neonatal side effects. These results prompted us to initiate a multicenter randomized trial to compare nifedipine and ritodrine in the management of preterm labor. The main objectives of this study were to compare tocolytic efficacy and perinatal outcome and to assess maternal side effects.

Material and Methods

Between February 1, 1992, and February 1, 1995, patients admitted for preterm labor at the Free University Hospital Amsterdam, the Academic Medical Centre of the University of Amsterdam, and the Zuiderzee Hospital Lelystad, with gestational ages between 20 and

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33⅐ weeks, irrespective of the state of the membranes, were considered eligible for the study. The gestational age was based on the last menstrual period with a reliable menstrual history and/or an ultrasound before 20 weeks' gestation. The study was approved by the ethical committees of the three participating hospitals. Written informed consent was obtained from each patient.

Preterm labor was diagnosed as regular objective uterine contractions, at least one every 10 minutes during at least 1 hour, and/or rupture of the membranes. Changes in cervical status (dilation and/or effacement) were not obligatory for inclusion in the study. Vaginal examinations were performed only in patients with intact membranes. Exclusion criteria included multiple pregnancy, documented intrauterine infection, congenital anomalies of the fetus, a clinical diagnosis of (partial) abruptio placentae, severe fetal growth restriction, and any maternal contraindication for the use of beta-adrenergic drugs, such as diabetes mellitus, cardiovascular disease, hyperthyroidism, or severe preeclampsia.

After inclusion, women were assigned randomly to either oral nifedipine or intravenous (IV) ritodrine. Randomization was carried out separately in each hospital by the hospital pharmacist using sealed opaque envelopes. Because it is controversial whether tocolysis is useful in patients with preterm labor and ruptured membranes, random assignment was done stratified for gestational age (under 25, 25–27, 28–31, and 32 or more weeks) and for state of the membranes (intact or ruptured).

Ritodrine was administered IV according to the protocol of Holleboom et al,[18] consisting of a fixed loading dose, after which the infusion rate is determined by the time lag after which tocolysis is established. The infusion rate was kept unchanged for at least 3 days unless contractions recurred, in which case infusion was readjusted to the rate that had achieved tocolysis. Depending on the clinical condition, the IV dose of ritodrine was decreased progressively after 3 days and eventually was stopped. After stopping IV ritodrine, two of the three hospitals continued treatment with oral ritodrine (ritodrine retard) 40 mg three times daily until 34 weeks, and one hospital did not. In the case of recurrent preterm contractions, IV ritodrine was administered again. Intravenous and/or oral ritodrine was continued until a gestational age of 34 weeks.

Tocolysis with nifedipine was initiated with a 10-mg capsule. Patients were instructed to crush the capsule between their teeth to facilitate sublingual absorption. If uterine contractions persisted after 15 minutes, a second dose of 10 mg was given. If contractions still persisted after the second dose of 10 mg, two additional capsules could be given again in intervals of 15 minutes. Thus, the maximum dose of nifedipine in the 1st hour was 40 mg. Depending on the tocolytic effect of the nifedipine capsules administered in the 1st hour, a maintenance dose of 60–160 mg of slow-release nifedipine was used per day. Depending on the clinical condition, nifedipine was decreased progressively after 3 days. The patients were kept on a minimum maintenance dose of 20 mg of slow-release nifedipine three times daily until a gestational age of 34 weeks, at which time the medication was stopped.

The study protocol did not allow a therapeutic crossover. Because we were interested primarily in comparing the tocolytic efficacy of both drugs, we decided to include only patients who received only the tocolytic agent to which they had been assigned. Consequently, an intention-to-treat analysis was considered not appropriate.

Indomethacin was used in both groups as a second-line tocolytic agent when contractions did not cease after the maximum dose of nifedipine or ritodrine was reached. The maximum dose was 300 mg per day for 3 consecutive days. All patients received steroids to promote fetal lung maturation. The maternal side effects analyzed semiquantitatively during the first 3 days of tocolysis were tachycardia, chest pain, nausea, vomiting, tremor, flushes, sweating, dizziness, anxiety, and headache.

The research hypothesis was that nifedipine was more successful than ritodrine in delaying delivery up to the end of the 1st week. Based on a 25% difference, we calculated the sample size to be 85 in each group to have a power of 90%, with $\alpha = .05$. Analysis of variance was used to compare gestational age at starting tocolysis and at delivery. Survival analysis was applied to analyze delay of delivery. Student t tests were used to compare differences between the two groups. $P < .05$ was considered statistically significant.

Results

One hundred eighty-five women with singleton pregnancies and preterm labor were enrolled, 90 assigned to ritodrine and 95 to nifedipine. The groups were similar with respect to maternal age, gestational age, parity, state of the membranes, and dilation of the cervix (in those with intact membranes) (Table 1). Ritodrine administration was stopped in 12 patients after a mean (± standard deviation [SD]) of 4 ± 2.8 days because of severe maternal side effects, such as nausea, vomiting, tachycardia, anxiety, and headache; these patients were treated subsequently with nifedipine. These 12 patients were excluded from the final analysis in which the tocolytic efficacy of the two agents was compared. The

Table 1. Clinical Characteristics

Characteristic	Ritodrine	Nifedipine
Intact membranes	$N = 61$	$N = 68$
Maternal age (y)	29.8 ± 5.0	28.7 ± 5.8
Gestational age (wk)	29.5 ± 2.3	28.8 ± 2.8
Nulliparity	34 (55.7%)	39 (57.4%)
Multiparity	27 (44.3%)	29 (42.6%)
Cervical dilation (cm)	1.8 ± 2.2	1.5 ± 2.1
Ruptured membranes	$N = 29$	$N = 27$
Maternal age (y)	29.3 ± 5.6	28.3 ± 4.6
Gestational age (wk)	29.3 ± 2.3	28.8 ± 2.1
Nulliparity	16 (55.2%)	12 (44.4%)
Multiparity	13 (44.8%)	15 (55.6%)

Data are presented as mean ± standard deviation or *n* (%).

Table 2. Prolongation of Pregnancy

Delivery	Ritodrine*	Nifedipine*	*P*
Intact membranes	$N = 54$	$N = 68$	
Within 24 h	17 (31.5%)	7 (10.3%)	.003
Within 48 h	20 (37.0%)	13 (19.1%)	.03
Within 1 wk	27 (50.0%)	19 (27.9%)	.01
Within 2 wk	32 (59.3%)	24 (35.3%)	.008
Within <34 wk	35 (64.8%)	30 (44.1%)	.04
Within <37 wk	40 (74.1%)	39 (57.4%)	.055
Ruptured membranes	$N = 24$	$N = 27$	
Within 24 h	5 (20.8%)	4 (14.8%)	.57
Within 48 h	9 (37.5%)	8 (29.6%)	.55
Within 1 wk	18 (75.0%)	17 (63.0%)	.35
Within 2 wk	20 (83.3%)	19 (70.4%)	.27
Within <34 wk	23 (95.8%)	23 (85.2%)	.35
Within <37 wk	24 (100%)	27 (100%)	1.00

* Data are presented as *n* (%).

mean (± SD) gestational age at delivery of these 12 patients was 33.1 ± 4.4 weeks and the mean (± SD) birth weight was 1908 ± 567 g.

Thus, the study groups consisted of patients receiving only the tocolytic agent for which they had been randomized. Analysis by means of survival analysis curves (Figure 1) demonstrated a highly significant difference between the two groups (Wilcoxon [Gehan] test = 13.027; df = 1; $P < .001$). More women in the ritodrine group than in the nifedipine group delivered within 24 hours (22 versus 11, $P = .006$), within 48 hours (29 versus 21, $P = .03$), within 1 week (45 versus 36, $P = .009$), and within 2 weeks (52 versus 43, $P = .005$).

The groups with intact and ruptured membranes also were analyzed separately, and these results are shown in Table 2. The mean delay of delivery from randomization to delivery in the group with intact membranes was 39.2 days (95% confidence interval [CI] 30.7, 47.6) in the nifedipine group and 22.1 days (95% CI 14.9, 29.3) in the ritodrine group ($P = .003$). In the group with ruptured membranes, the mean delay of delivery was 15.1 days (95% CI 7.9, 22.3) in the nifedipine group and 7.2 days (95% CI 3.2, 11.2) in the ritodrine group ($P = .056$).

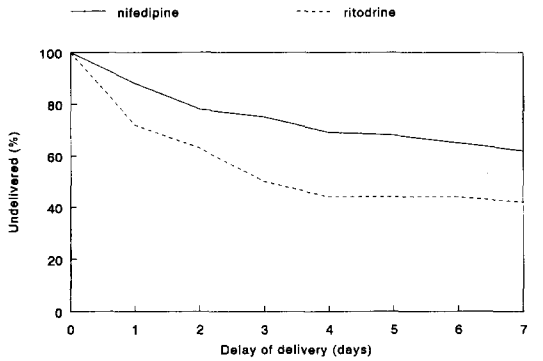

Figure 1. Survival curves of patients delivered until the end of the 1st week after initiation of tocolysis. Wilcoxon (Gehan) test = 13.027; df = 1; $P < .001$.

Although one hospital in this study did not give oral ritodrine after IV treatment had been stopped, there were no statistically significant differences between the three hospitals in delay of delivery. The number of patients receiving additional indomethacin was 20 (25.6%) in the ritodrine group and 26 (27.4%) in the nifedipine group, a nonsignificant difference ($P = .86$). The mean (± SD) total indomethacin dose overall was very low: 116 ± 37 mg in the ritodrine group and 119 ± 40 mg in the nifedipine group ($P = .80$). Overall perinatal outcome is shown in Table 3.

As already mentioned, 12 patients were excluded from the study because of severe maternal side effects. Even after excluding these 12 patients, the number of patients with side effects was significantly higher in the ritodrine group (33 versus 18, χ^2; $P < .001$) as compared with the nifedipine group. In the group of patients with side effects, the mean (± SD) number of side effects in ritodrine-treated women was significantly higher (4.18 ± 2.14 versus 2.06 ± 1.0; $P < .001$), compared with those receiving nifedipine. No nifedipine-treated women

Table 3. Perinatal Outcome

	Ritodrine ($N = 78$)	Nifedipine ($N = 95$)	*P*
Gestational age (wk)	32.1 ± 4.1	33.4 ± 4.5	.046
Birth weight (g)	1870 ± 847	2120 ± 920	.07
Umbilical artery pH	7.23 ± 0.13	7.26 ± 0.08	NS
Umbilical vein pH	7.30 ± 0.10	7.32 ± 0.07	NS
Perinatal death	6 (7.7%)	7 (7.4%)	NS
RDS	31 (39.7%)	23 (24.2%)	.03
Admission to NICU	64 (82.1%)	65 (68.4%)	.04

NS = not significant; RDS = respiratory distress syndrome; NICU = neonatal intensive care unit.

Data are presented as mean ± standard deviation or *n* (%).

had side effects of such severity that it was necessary to discontinue medication.

Discussion

Since the late 1970s, nifedipine has been known to relax the pregnant and nonpregnant uterus.[19,20] The first study on nifedipine in the management of preterm labor was reported by Ulmsten et al[21] in 1980; in all patients, nifedipine stopped uterine activity and delayed delivery. In a second study, Ulmsten[13] showed that nifedipine was associated with a postponement of delivery for more than 3 days in 80% of the study patients. In the first reported randomized trial, Read and Wellby[8] compared the tocolytic efficacy of nifedipine with ritodrine and no treatment, with 20 subjects in each group. They found nifedipine to be significantly more effective than ritodrine and no treatment and also to be associated with fewer side effects than ritodrine. In subsequent randomized studies, Ferguson et al,[4] Meyer et al,[6] and Kupferminc et al[14] all found nifedipine to have a tocolytic efficacy similar to that of ritodrine. The dose of nifedipine used in these earlier trials was lower than in our study. Read and Wellby[8] gave an initial loading dose of 30 mg of nifedipine and a maximum maintenance dose of 20 mg every 8 hours for 3 days. Ferguson et al[4] gave an initial maximum loading dose of 40 mg of nifedipine and a maximum maintenance dose of 20 mg every 4–6 hours. Meyer et al[6] gave an initial loading dose of 30 mg of nifedipine and a maximum maintenance dose of 20 mg every 6 hours. Kupferminc et al[14] gave an initial loading dose of 30 mg of nifedipine and a maximum maintenance dose of 20 mg every 8 hours. We found nifedipine to be more effective than ritodrine in postponing delivery, a difference that probably is related to the higher dose of nifedipine used in our study.

The survival analysis shows that at 48 hours (which is relevant because it permits use of steroids to promote fetal lung maturation), 77.9% of the nifedipine patients remained undelivered compared with 62.8% in the ritodrine group ($P = .03$). At the end of the 1st week after randomization, 62.1% remain undelivered with nifedipine compared with 42.3% with ritodrine ($P = .009$). In our study, the major gain was reached in the group with intact membranes. Preterm labor is a difficult diagnosis in patients with intact membranes. Apparently, the clinical diagnosis in the study was firm, despite the fact that changes in cervical status were not obligatory for entering the study. In the group with intact membranes, almost 60% of the ritodrine-treated patients were delivered within 2 weeks of randomization, and nearly 75% delivered before 37 weeks' gestation.

The use of tocolytic agents in patients with preterm premature rupture of the membranes (PROM) is controversial. However, many hospitals in Europe and the United States use these agents in the management of preterm labor whether the membranes are intact or ruptured to gain time for steroids to promote fetal lung maturation.[22] Therefore, in our study, patients were stratified not only for gestational age but also for intact or ruptured membranes. Comparison of the subgroups with ruptured membranes shows a tendency for better results in the nifedipine group, but because of the small numbers, it is impossible to draw definite conclusions.

Ferguson et al,[4] Meyer et al,[6] and Kupferminc et al[14] all found nifedipine to be associated with significantly fewer maternal side effects as compared with ritodrine, and our results concur. The higher efficacy of nifedipine and the lower incidence of maternal side effects are not the only advantages. The lower neonatal intensive care unit admission rate with nifedipine is probably the most relevant finding. Nifedipine has the ease of oral administration. Other theoretical advantages are the (relative) lack of influence on maternal cardiac output and carbohydrate metabolism, which is in contrast with the beta-adrenergic agents.[23] In addition, nifedipine does not interfere with the interpretation of fetal heart rate tracings as does ritodrine, which may be important in the timely diagnosis of an intrauterine infection in patients with preterm PROM.

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