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Nifedipine versus ritodrine for suppression of preterm labor Comparison of their efficacy and secondary effects

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Abstract

Objectives: To compare the efficacy of nifedipine and ritodrine in prolonging pregnancy beyond 48 h, 1 week and 36.0 weeks and to evaluate maternal side effects and adverse perinatal outcome.
Study design: Non-blinded, randomized controlled trial. Eighty patients with singleton pregnancies admitted for preterm labor with intact membranes between 22 and 35 weeks of gestation were included in the study. Preterm labor was defined as the persistence of at least two symptomatic uterine contractions within a 10 min period during 60 min after admission and despite bed rest.
Results: Forty women received oral nifedipine and forty intravenous ritodrine. Two patients, one from each group, were excluded because of loss to follow-up after discharge. Therefore, 39 women in the nifedipine and the ritodrine groups, respectively, were evaluable for the final analysis. Baseline characteristics were comparable in both groups. The percentage of initial response, the speed of onset of action and the rate of successful treatment within 48 h were significantly better in the ritodrine group. However, prolongation of pregnancy beyond 7 days and 36 weeks of pregnancy was similar with a significantly lower rate of side effects in the nifedipine group.
Conclusions: In this small trial, ritodrine provided more effective tocolysis within the first 48 h than nifedipine at the doses used in this study, although with a significantly higher rate of side effects.

Keywords: Preterm labor; Tocolytics; Nifedipine; Ritodrine

1. Introduction

Preterm delivery occurs in 7–9% of all births and has even increased recently [1]. Moreover, the most frequently associated condition with neonatal mortality and morbidity, excluding congenital malformations, is also preterm delivery. Neurological and sensorial deficiency rates are especially high in newborns of less than 31–32 weeks [2,3]. Although primary prevention would be ideal, the efforts in this direction have not been successful so far, probably because of multifactorial social, behavioral and biological etiology [4].

When preterm uterine contractions are present, but especially when cervical conditions are modified, it is essential to start treatment to postpone delivery unless there are signs of intrauterine infection or fetal distress. The most commonly used tocolytic agents are beta-adrenergic agonists. Meta-analyses have shown that beta-adrenergic agents, especially ritodrine, are associated with a postponement of delivery of 24, 48 h and 7 days. However, such a delay has not been associated with a significant reduction in either perinatal mortality or morbidity [5,6]. The great incidence of usually mild but potentially severe side effects of beta-sympathicomimetics has led to the search for better drugs. The oxytocin receptor antagonist, atosiban, appeared in the tocolytic scenario in the year 2000. Nonetheless, despite the clear advantage in the lack of relevant side effects

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with its use, perinatal mortality and morbidity have not been modified with this new agent [7] and the high cost of this antagonist limits its widespread use. Therefore, financial costs must be taken into account, thereby restricting the use of atosiban to hemodynamic high risk patients and thus, justifying the wise use of other tocolytics.

Nifedipine is a calcium-channel blocker drug (type II calcium blockers). It acts by reducing the intracellular entrance of calcium through the slow channel (or L type) producing an inhibition of contractile activity of non-pregnant, pregnant and postpartum myometrium. Nifedipine reduces the amplitude and frequency of contractions and the basal myometrial tone and is more active in pregnant than in non-pregnant women. The mean half-life in pregnant women is short (81 min) and, therefore, its effect is reversible. It was introduced as an antihypertensive drug but its hypotensive effect is mild in normotensive pregnant patients [8,9].

In the last 20 years many reports have evaluated the use and efficacy of nifedipine as a tocolytic agent. The latest systematic review includes 12 randomized controlled trials with a total of 1029 participating women. Ten compared its efficacy with ritodrine and all found nifedipine to be more effective than ritodrine in prolonging pregnancy beyond 7 days and much less likely to cause maternal side effects [10].

2. Materials and methods

Pregnant women with singleton pregnancies admitted for preterm labor with intact membranes between 22 and 35 weeks of gestation were eligible for the study. Preterm labor was defined as the persistence of at least two symptomatic uterine contractions within a 10 min period during 60 min after admission and despite bed rest.

Exclusion criteria were: cervix dilatation greater than 5 cm, polyhydramnios, fetal anomalies, signs of fetal distress, suspected intrauterine infection or growth restriction, contraindication for the use of beta-sympathomimetic drugs and previous treatment with tocolytics in the present gestation.

Biochemical and hematological blood tests and an electrocardiogram were performed. Patients with a clinical contraindication for the use of beta-adrenergic drugs or nifedipine were excluded.

Informed consent was obtained before randomization from eligible subjects. The study protocol was approved by the hospital's Ethics and Research Committee.

Women were allocated into two groups by opening a series of sealed, opaque, consecutively numbered envelopes that were sequentially selected. There was a 1:1 randomization ratio. Women were randomly assigned to receive either ritodrine or nifedipine. Clinicians were not blinded to the study group in which the women were allocated.

Women assigned to the nifedipine group received an initial oral loading dose of 30 mg (10 sublingual and 20 mg oral) and a maintenance oral dose of 20 mg every 6 h. Treatment was discontinued if no uterine contractions occurred within a 48 h period [11]. Women allocated to the ritodrine group received an intravenous infusion at a rate of 100 mcg/min. The initial dose was increased 50 mcg every 20 min until uterine contractions were suppressed or intolerable side effects appeared or a limit dose of 350 mcg/min was achieved. The lowest effective tocolytic dose was maintained during 2 days, followed by oral therapy with a dose of 10 mg/6 h. After discharge, no maintenance tocolytic treatment was indicated. If uterine contractions reappeared, relapse was diagnosed and treatment was repeated as indicated above.

Initial response was defined if uterine contractions were suppressed within 2 h of tocolytic treatment. Otherwise, treatment failure was considered and women received the drug indicated in the other study arm. If the second tocolytic was not effective, the woman was excluded from the analysis and indometacin was added. An ''escape phenomenon'' was considered on relapse of uterine contractions after their suppression before discontinuation of the treatment. In this case, an extra dose of 10 mg of sublingual nifedipine was added or ritodrine was increased as previously indicated. If contractions were not suppressed, a failure of treatment was considered and the patient was changed to the other treatment arm as referred above.

Maternal blood pressure and heart rate were monitored every 20 min until a stable dose was achieved and every 4 h thereafter. Daily hydric balance was performed and blood parameters (cell blood count, glycemia, ionogram) and hepatic and renal function) were monitored every 24 h. Clinical signs and symptoms of intolerance to the drugs used were assessed every 6 h.

Continuous fetal heart rate and uterine contraction monitoring was carried out during the first 12 h and until uterine contractions disappeared. Afterwards, fetal heart rate and uterine contractions were monitored every 12 h during hospital admission.

At delivery, several neonatal parameters, such as weight, Apgar's score, umbilical arterial and vein pH values and presence of hyperbilirrubinemia were determined. Neonatal complications such as hemorrhage or infections were recorded.

Outcome measurements were successful tocolysis at 2 h, at 48 h and at 7 days. Prolongation of gestation from admission to hospital to delivery and the number of preterm deliveries before 36 weeks (252 days) of gestation were also assessed.

The data collected were processed with Filemaker pro II for Macintosh database. Statistical analysis was performed using Stat View 512 for Macintosh. Differences were considered statistically significant when the p value was <0.05. For comparison of categorical variables the Chi-square test was used with Yate's correction when appropriate. For comparison of mean values, the Student's t-test for independent samples was used.