A Comparative Study of Ketorolac (Toradol) and Magnesium Sulfate for Arrest of Preterm Labor

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ABSTRACT

Background. We evaluated the efficacy and safety of ketorolac (Toradol).

Methods. In this prospective trial, 88 women in confirmed preterm labor at ≤32 weeks' gestation were randomized to receive magnesium sulfate given as an initial 6 g intravenous bolus followed by continuous infusion therapy (2 to 6 g/hr) or intramuscularly administered ketorolac (60 mg loading dose) followed by 30 mg every 6 hours for a maximum of 24 hours.

Results. The study groups were similar with respect to age, parity, cervical status, and gestational age on admission. Ketorolac was more rapid (2.71 hr ± 2.16) in the arrest of preterm labor than was magnesium sulfate (6.22 hr ± 5.65). No patient required discontinuance of either drug due to adverse effects. There was no difference in the incidence of neonatal complications between the two groups.

Conclusion. In gestations with preterm labor at <32 weeks, ketorolac appears to be an appropriate first-line tocolytic agent.

PRETERM BIRTH occurs in approximately 10% of all gestations and is the most important cause of neonatal mortality after congenital anomalies have been excluded, accounting for 75% of all neonatal deaths.[1] Beta sympathomimetics such as ritodrine hydrochloride and terbutaline have been widely used to treat preterm labor with variable results.[2] Infrequently, these agents can be associated with significant maternal side effects such as severe cardiopulmonary complications.[3] Consequently, magnesium sulfate has been adopted by many physicians because it has been shown to have similar efficacy as a tocolytic agent with fewer adverse maternal side effects.[4,5] Calcium channel blockers and prostaglandin synthetase inhibitors have been used as second-line drugs in selected clinical situations, usually when tocolysis has not been achieved with initial therapy.

As a group, prostaglandin synthetase inhibitors have been one of the most efficacious tocolytic agents,[6] with indomethacin being the most frequently used drug in this class for the treatment of preterm labor. Maternal side effects are minimal and include occasional gastrointestinal problems since dosing is usually by the oral or rectal route. Enthusiasm for these agents has been limited, however, by reports of rare but occasionally severe adverse fetal effects that include progressive oligohydramnios, narrowing of the ductus arteriosus with primary pulmonary hypertension at birth, necrotizing enterocolitis, and a possible increase in the incidence of neonatal intracranial hemorrhage.[7,8] These side effects have been observed almost exclusively in patients in whom the agents have been used for longer than 48 hours.[6-8]

The current study was designed to test the rapidity, efficacy, and safety of the short-term administration of a new intramuscular prostaglandin synthetase inhibitor, ketorolac (Toradol), compared with intravenous (IV) magnesium sulfate infusion as a first-line tocolytic agent in women with preterm labor.

MATERIALS AND METHODS

Patients with singleton and twin gestations admitted to the labor and delivery suite at the University of Mississippi Medical Center with confirmed preterm labor and intact mem-

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TABLE 1. Entry Variables

	Magnesium Sulfate (n = 43)	*Ketorolac (n = 45)*	P < .05
Age (yr)	22.7 ± 5.4	22.9 ± 5.1	NS
Gravidity	2.7 ± 1.5	2.8 ± 1.7	
Socioeconomic status			
Medicaid	95%	88%	NS
Race—black	69%	77%	NS
Multiparous	67%	77%	NS
Previous preterm delivery	30%	35%	NS

NS = Not significant.

branes between 20 and 32 weeks were eligible for this study. Preterm labor was defined as documented regular uterine contractions (≥12 in 60 minutes) in the presence of cervical effacement (>50%), cervical dilatation of ≥2 cm, or documented cervical change from a recent cervical examination. Patients were excluded from the study if they had ruptured membranes, cervical dilatation of >4 cm, significant maternal disease, or obstetric disorders, as well as maternal history of peptic ulcer disease, asthma, bleeding diathesis, thrombocytopenia, or sensitivity to nonsteroidal agents. Fetal exclusion criteria included fetal malformation, chorioamnionitis, oligohydramnios, fetal growth restriction, or non-reassuring fetal status. After signing the informed consent document, eligible women were randomized by pharmacy personnel who selected a sealed opaque envelope indicating either ketorolac or magnesium sulfate for tocolysis.

In the intrapartum unit, magnesium sulfate was given by IV infusion beginning with a 6 g bolus given over a 20-minute period, followed by continuous infusion therapy of 2 g/hr adjusted up to a maximum of 6 g/hr to achieve uterine quiescence (<4 contractions per/hr or irregular, subclinical contractions). Absence of uterine contractions for 2 hours prompted a slow tapering of magnesium sulfate over 3 to 4 hours until it was stopped. Ketorolac was given intramuscularly as an initial dose of 60 mg, followed by subsequent doses of 30 mg every 6 hours as needed to arrest uterine activity. Oral tocolysis was initiated in both groups with magnesium gluconate in a dosing regimen of 2 g every 4 hours after parenteral agents were discontinued. Patients were transferred from the labor and delivery suite to the antepartum ward usually 2 to 4 hours after oral tocolysis had begun, if continued uterine quiescence was observed. Oral magnesium gluconate was prescribed until 37 weeks' gestation was achieved.

Ultrasonography was done on all study subjects to confirm fetal gestational age and to assess the amniotic fluid volume. On admission, cervicovaginal cultures were obtained for group B streptococcus, chlamydia, and gonorrhea. All patients received 12 mg of betamethasone intramuscularly, which was repeated 24 hours later in an attempt to enhance fetal pulmonary maturity. Reassessment of the amniotic fluid volume 48 hours after treatment initiation was done on all women who received ketorolac.

Statistical analysis was done, using the Student's *t* test for comparison of interval and ratio data. These variables were expressed as mean ± standard deviation. Categoric and ordinal data were analyzed using the chi-square test. If an expected cell value was <5, the Fisher's Exact Test was used. In all cases, a two-tailed test for significance was used. A $P < .05$ or a confidence interval not containing one was deemed statistically significant. Sample size was estimated for a two-tailed test, assuring a success rate (70%) of tocolysis within 4 hours in the test group and 40% in the control group. Using a power of 80% and a significance of $P = .05$, 42 patients would be required in each group.

RESULTS

A total of 88 patients were randomized in this trial; 43 received magnesium sulfate, and 45 were treated with ketorolac. Seven eligible patients did not participate. Four declined entry to the study, one began bleeding and

TABLE 2. Obstetric Characteristics

Variable	*Magnesium (n = 43)*	*Ketorolac (n = 45)*	P < .05
Admission gestational age (wk)	29.4 ± 2.8	28.8 ± 3.0	NS
Contraction frequency on admission (number/hr)	14.3 ± 2.1	15.1 ± 2.6	NS
Cervical dilatation on admission (cm)	2.0 ± 1.0	1.9 ± 1.0	NS
Cervical effacement on admission (%)	55.0 ± 15.5	57.50 ± 18.8	NS
Cervical dilatation on transfer (cm)	2.0 ± 0.9	1.9 ± 1.1	NS
Cervical effacement on transfer (%)	54.3 ± 13.4	57.8 ± 16.4	NS
Gestational age at delivery	34.8 ± 4.3	34.9 ± 3.6	NS

NS = Not significant.

TABLE 3. Short-term Treatment Characteristics

	Magnesium (n = 43)	*Ketorolac (n = 45)*	P *Value*
Time to uterine quiescence (hr)	6.22 ± 5.65	2.7 ± 2.16	.0003
Recurrent preterm labor in hospital	5	3	NS
Delivery during current admission	3	1	NS
Readmission for preterm labor	9	6	NS
Preterm delivery (<37 weeks)	7	4	NS

was found to have a placental abruption, and two had advanced cervical dilatation (>4 cm) before treatment. The demographic and obstetric profile of these women was not different from those who participated in the study. Table 1 shows no difference between the groups in the entry variables such as age, ethnicity, socioeconomic standing, or previous obstetric experience.

Obstetric factors are described in Table 2. Both groups revealed similar findings in gestational age and contraction frequency at presentation, as well as cervical examination at entry or after treatment. There were no cases of chorioamnionitis in either group and both treatment modalities had four patients each who were positive for illicit drugs. The gestational age at delivery of the women was not different in those women who received magnesium compared with women treated with ketorolac. In contrast, there was a statistically significant difference between the two groups in the time required to achieve uterine quiescence (Table 3). Ketorolac (2.71 hr ± 2.16) was superior to magnesium sulfate (6.22 hr ± 5.65) in the prompt arrest of uterine activity, since more than twice as much time was required for magnesium sulfate to achieve the same effect ($P < .0003$). No more than two injections of ketorolac were required in any patient (1.2 ± 0.4 doses), and only seven women needed a second dose. The number of women having recurrent preterm labor and/or delivery during the current hospitalization or those with readmission for preterm labor as well as delivery before 37 weeks always were more common in the magnesium study arm, but it was never statistically significant (Table 3).

Among those treated with ketorolac, there was no significant change in the amniotic fluid volume after treatment (–1.65 ± 3.38 cm change on amniotic fluid index). In fact, 35% of patients showed a slight increase after treatment, confirming that there was essentially no significant change in the amniotic fluid volume as a result of the short-term treatment with ketorolac. No women had oligohydramnios (AI <5.0 cm) after therapy with the test drug. No adverse maternal effects were noted in either group. Side effects of magnesium sulfate such as flushing were noted in only a few women, and the drug was not discontinued or reduced. Patients treated with ketorolac did not have allergic reaction, gastrointestinal upset, or bleeding complications, but a few had mild nausea without vomiting.

In the magnesium group, four neonates had acute respiratory distress syndrome (ARDS); of these, three also had a patent ductus arteriosus (PDA). One neonate with ARDS and a PDA also had evidence of paraventricular leucomalacia on ultrasonography done several days after birth. This neonate was born at 30 weeks' gestation and had a birth weight of 1,100 g. In the ketorolac group, two neonates had ARDS—one also had a PDA and the other had an asymptomatic grade II intraventricular hemorrhage. The mother of the latter neonate received one injection of ketorolac for tocolysis, and delivery occurred 12 days after treatment was given. Delivery occurred at 28 weeks' gestational age and the birth weight was 1,000 g.

DISCUSSION

Zuckerman, in 1974,[9] was the first to describe the tocolytic effect of the antiprostaglandin drug—indomethacin—in the treatment of preterm labor. Many investigators have published subsequent studies showing the efficacy of prostaglandin synthetase inhibitors to arrest preterm labor. Early reports showed a marked improvement in the tocolytic effect of indomethacin compared with a placebo.[10] Two separate trials compared the efficacy of indomethacin with ritodrine[11] and indomethacin with magnesium sulfate.[12] In both trials, similar efficacy was noted, but fewer maternal adverse effects were recorded with indomethacin compared with beta agonists; no difference in neonatal outcome was observed.

The current prospective trial is the first study to use the antiprostaglandin ketorolac as a tocolytic agent. This drug was chosen to ascertain if parenteral administration might result in more rapid uterine quiescence and to assess if short-term administration might reduce fetal side effects. Indomethacin is gener-

ally given rectally for initial dosing, and serum levels may be unpredictable. Magnesium sulfate requires 20 to 30 minutes for initial IV dosing and continued monitoring of magnesium concentrations in the serum or indirectly by physical examination (urine output, respiratory depression, deep tendon reflexes) is recommended. This may be cumbersome and could be potentially dangerous, particularly during maternal transport.

Although efficacious in arresting preterm labor, neonatal complications have been reported with the use of antiprostaglandin agents. These adverse effects include oligohydramnios, necrotizing enterocolitis, intraventricular hemorrhage, and narrowing of the ductus arteriosus, which can lead to neonatal pulmonary hypertension. Most of the adverse fetal effects have been reported with maternal administration of such drugs for more than 48 to 72 hours.[6] In utero, circulating prostaglandins maintain the patency of the ductus arterious.[8] Potentially, the most serious in utero complication is ductal constriction, and this has been most commonly detected with prolonged administration (>72 hours) of the drug, particularly when given at gestational ages >32 weeks.[6,7] Sensitivity of the ductus arteriosus to prostaglandin synthetase inhibitors increases after 32 weeks, with more than 50% of fetuses showing ductal constriction as compared with 5% to 10% of fetuses at earlier gestations.[7,8] Premature constriction of the ductus arteriosus also may lead to fetal and neonatal pulmonary hypertension and can result in persistent fetal circulation at birth. Fetal echocardiography has been used by some investigators to detect ductal constriction and early tricuspid regurgitation may herald the onset of this untoward effect and warrant discontinuance of the drug.[13] Serial fetal echocardiography does not appear to be indicated with drug treatment for <72 hours and was not done in this study.[14]

Fetal renal function may also depend on an established level of circulating prostaglandins, and oligohydramnios is another well-documented side effect of prostaglandin synthetase inhibitors.[7] Decreasing fetal urine output has been noted within 5 hours of maternal administration of indomethacin and is probably mediated through the potentiation of antidiuretic hormone activity on the fetal kidney.[15] This problem is usually a transient event and is reversible with discontinuance of the medication.[15] There is still controversy surrounding the possibly increased risk of intracranial hemorrhage necrotizing enterocolitis due to the use of these agents. Prostaglandin synthetase inhibitors do affect platelet function but studies have been inconclusive regarding the risk of bleeding.[7] While we found none of these detrimental fetal/neonatal effects, our study population was too small to have expected many of these complications to occur. Obviously, further studies are needed, but a common finding in those with adverse neonatal effects was the prolonged use of these agents (>48 to 72 hr).

Since prostaglandin synthetase inhibitors have tocolytic efficacy that is comparable or superior to other agents[6,10-12] and because short-term use for <48 hours are of little risk to the fetus at less than 32 weeks' gestation, parenteral ketorolac appears to be a viable alternative for acute tocolysis since it more rapidly leads to uterine quiescence without increasing maternal/fetal adverse effects. Should subsequent studies corroborate our finding that ketorolac is an effective, safe tocolytic agent, its dosing form and rapid onset of action may potentially deem this drug superior to magnesium, since antiprostaglandin drugs have been shown to be effective for tocolysis placebo control trials. This may especially be the case for patients with preterm labor ≤32 weeks' gestation when rapid, safe, and effective tocolysis for maternal transfer is required.

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