Tocolytic Therapy for Acute Preterm Labor

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KEYWORDS

- Preterm labor • Tocolytic therapy • Magnesium sulfate
- Beta-mimetics • Calcium channel blockers
- Prostaglandin inhibitors • Oxytocin receptor antagonist

Preterm birth is the leading cause of perinatal morbidity and mortality and leads to significant health care costs annually. Despite numerous advances in the care of obstetrical patients, the incidence of preterm birth in the United States is at an all-time high and may be on the rise given current trends of advancing maternal age, maternal medical conditions, assisted reproductive technology, and multiple gestations.[1] Neonatal morbidity is strongly associated with gestational age at birth with adverse neonatal outcomes occurring in 77% of those born at 24 to 27 weeks' gestation compared with only 2% born at or beyond 34 weeks.[2] Therefore, prevention of preterm birth and its associated neonatal morbidity and mortality are major worldwide concerns and a significant focus for obstetrical research.

Certain maternal factors have been identified that increase the risk of preterm birth. African-American women have consistently higher rates of preterm birth ranging from 16% to 18% compared with 5% to 9% of Caucasian women.[3] Also, women with a prior history of preterm birth have a 2.5-fold increased risk of preterm delivery in a subsequent pregnancy,[4] although this risk may be reduced with progesterone supplementation.[5,6] Additional risk factors include low socioeconomic status, poor nutritional status, maternal medical conditions, extremes of maternal age, smoking, and history of cervical conization.

Preterm labor is thought to be a multifactorial process with an underlying infection as the initiating factor in at least 25% to 40% of preterm births.[3] Microorganisms within the upper genital tract cause activation of the immune response with production of inflammatory cytokines and prostaglandins that result in uterine contractions and weakening of the amniotic membranes. Despite this association between infection and preterm delivery, antibiotics have not been shown to decrease the risk for preterm birth.[7] Tocolytics have also not been shown to decrease the risk for

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preterm birth, but they have been shown to temporarily inhibit uterine contractions. In a systematic review including 18 randomized, controlled trials comparing a tocolytic versus placebo or no treatment for preterm labor, tocolysis decreased the risk of delivery within 48 hours and 7 days, but did not prevent preterm birth before 37 weeks.[8]

Given the short-term delay in delivery with tocolysis, the primary goal of tocolytic therapy is to allow administration of glucocorticoids to reduce the risk of the prematurity-related complications of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. In addition, a second goal of tocolytics is to allow for maternal transport to a facility capable of providing more advanced neonatal care. Tocolysis may be discontinued when these goals are met or when the maternal or fetal risk of pregnancy continuation or drug exposure outweighs the morbidity associated with preterm birth, generally around 34 weeks' gestation.[9] Contraindications to tocolysis include evidence of intra-amniotic infection, intrauterine fetal demise, lethal fetal anomalies, severe fetal growth restriction, preeclampsia, or nonreassuring fetal status. In this article, we review the various tocolytics used for preterm labor and examine their mechanisms of action, efficacy, dosing, and side effects.

MAGNESIUM SULFATE

Magnesium sulfate is the most commonly used tocolytic agent in the United States.[10] It was first evaluated for tocolysis in the 1970s.[11] Although the mechanism of action is not completely understood, it is thought to be related to its antagonistic action with calcium. A predominant portion (99%) of magnesium is intracellular, localized to bones, myocytes, nuclei, microsomes, and mitochondria. Of the 1% that is extracellular, 62% circulates ionized in the maternal serum.[12,13] Magnesium functions at the extracellular and intracellular levels, decreasing the availability of calcium by blocking membrane and intracellular calcium channels, which decreases myometrial contractility.[14,15]

Magnesium sulfate has failed to show benefit or superior efficacy to other tocolytics in multiple systematic reviews, yet it is still commonly used today. In a systematic review of 4 randomized trials evaluating the efficacy of magnesium sulfate compared with placebo or no therapy for preterm labor, there was no reduction in the frequency of delivery within 48 hours, 7 days, or before 37 weeks gestation. There was also not a reduction in the outcome of newborn birth weight of less than 2500 grams. In addition, no single study was able to show an improvement in the more common newborn morbidities of respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis.[16] Comparison of magnesium sulfate with other tocolytic regimens does not show magnesium to be more efficacious than other tocolytics. In this same systematic review, magnesium sulfate was compared with beta-mimetics, calcium channel blockers, and cyclooxygenase (COX) inhibitors in 15 studies. Magnesium sulfate did not show improved length of gestation or neonatal benefit compared with the other tocolytics.

Standard administration doses for magnesium include a 4- to 6-g loading dose over 20 to 30 minutes followed by a continuous infusion of 2 g/h. Titration may be necessary depending on contraction frequency and tolerance of drug. It is contraindicated in women with myasthenia gravis and should be used in caution in the setting of renal insufficiency because it is excreted by the kidneys. Impaired renal function may quickly lead to toxicity at normal doses. In patients with renal insufficiency (serum creatinine $>$1.0 mg/dL), a loading dose is acceptable but the maintenance dose should be held or kept at 1 g/h.[17]

Maternal side effects, which range from mild to severe, are seen in up to 60% of exposed women and include flushing, nausea, blurry vision, headache, lethargy,

hypotension, and pulmonary edema.[18,19] Magnesium toxicity is related to serum concentration level. Loss of patellar reflexes may be the first clinical sign of toxicity followed by decreased urine output (<100 mL/4 h). Reflexes and urine output should be monitored closely during administration.[17] Although rare, respiratory depression and arrest can occur at levels above 10 to 12 mg/dL, so the medication should be stopped and serum level checked if there is clinical concern for toxicity.

Controversy around the effect of magnesium sulfate on the fetus and neonate has been cited in the literature. Magnesium has been shown to decrease fetal heart rate baseline and variability, but these do not have clinical significance.[20] Other studies have shown adverse neonatal effects from magnesium exposure. In a randomized, controlled trial by Lyell and colleages[19] comparing magnesium sulfate with nifedipine for tocolysis, infants exposed to magnesium had an increased rate of neonatal intensive care unit (NICU) admission and longer NICU stays. Other authors have suggested that magnesium sulfate slows gastrointestinal function and may lead to respiratory suppression.[21] Last, a Cochrane review of seven studies in 2002 found an increased risk for perinatal death with prenatal exposure to magnesium[22]; however, a more recent systematic review showed no increase in fetal or neonatal death before discharge for magnesium compared with any alternative tocolytic regimen or control group.[16]

Despite potential adverse neonatal effects, contrary evidence has suggested that prenatal exposure to magnesium may have a neuroprotective benefit. A randomized, controlled trial by Crowther and associates[23] evaluating the neuroprotective effect of magnesium given before preterm birth found an almost a 50% reduction in gross motor dysfunction (3.4% vs 6.6%) in the group treated with magnesium sulfate compared with placebo.[23] These findings were supported by Marret and co-workers,[24] who demonstrated a reduction in death or motor/cognitive dysfunction among the group receiving magnesium sulfate. In 2008, a randomized controlled trial by Rouse and coleageus[25] examined the role of magnesium sulfate for the prevention of cerebral palsy in 2241 patients. The study was conducted among women at gestational ages of 24 to 31 6/7 weeks who received a standard 6-g loading dose followed by a continuous infusion of 2g/h until the time of delivery. The study showed a 45% reduction in the overall rate of cerebral palsy (4.2% vs 7.3%) and in moderate or severe cerebral palsy (1.9% vs 3.5%) in the infants receiving magnesium.

Although it is widely used as a tocolytic agent, the literature does not support magnesium sulfate as being effective in withholding delivery for 48 hours, preventing preterm birth, or reducing the risk for neonatal morbidity. Given its association with the reduction in the rate of cerebral palsy, magnesium's best role seems to be as a neuroprotective agent for the fetus.

BETA-MIMETICS

The role of beta-mimetics for tocolysis has been explored since the 1970s.[26–28] Medications belonging to this class include terbutaline (Brethine), ritodrine (Yutopar), salbutamol, and hexoprenaline. Ritodrine is the only Food and Drug Administration-approved tocolytic medication, but it is no longer available in the United States.[17] Although beta-mimetics were initially commonly used, they have fallen out of favor secondary to their maternal and fetal side effects and a recent warning released in February 2011 by the US Food and Drug Administration. The US Food and Drug Administration placed a boxed warning on the drug's label stating that the medication should not be used for prolonged tocolysis (>48–72 hours) because of the potential for serious maternal cardiac toxicity and death.[29]

Beta-mimetics function as beta-adrenergic receptor agonists, relaxing smooth muscles, including the myometrium. Binding of the receptor activates a cascade of

intracellular reactions that affect adenyl cyclase and protein kinase. This cascade decreases the availability of intracellular calcium and the activity of myosin light-chain kinases, thus suppressing myometrial contractility.[30]

The efficacy of beta-mimetics as a tocolytic has predominately involved studies that compared ritodrine with another tocolytic agent or placebo. In a Cochrane meta-analysis of 11 randomized trials of beta-mimetics versus placebo for preterm labor, beta-mimetics decreased the risk of delivery within 48 hours and showed a trend toward reduction in delivery within 7 days, but there was no reduction in preterm birth or neonatal morbidity.[31] Based on the available literature, beta-mimetics do not seem to be a superior tocolytic than other medications. When beta-mimetics were compared with nifedipine in a large meta-analysis of 16 trials, beta-mimetics were not as effective as nifedipine in reducing the risk of delivery within 7 days or before 34 weeks gestation. They were also less effective at reducing the risk for neonatal respiratory distress syndrome.[32] In another review of 5 studies comparing beta-mimetics with magnesium sulfate, beta-mimetics were not associated with reducing delivery at any interval (within 48 hours, 7 days, or before 37 weeks) or in reducing low birth weight infants.[16]

Terbutaline is the most commonly used beta-mimetic for preterm labor in the United States and it is generally administered as a subcutaneous injection. Given its off-label use, the dosing may vary, but, most commonly, 0.25 mg is given subcutaneously and may be repeated in 15 to 30 minutes if there is inadequate response. Total dosing in 4 hours should not exceed 0.5 mg. Common maternal side effects secondary to beta-mimetics include tachycardia, tremor, dyspnea, chest discomfort, palpitations, and hyperglycemia.[8,33] These side effects may be unpleasant to the patient and often result in discontinuation of treatment. More rare side effects include pulmonary edema and myocardial ischemia, but these may be related to other confounding factors, like fluid overload, infection, preeclampsia, or underlying cardiac disease. With prolonged use of beta-mimetics, tachyphylaxis may develop.

Given the known side effects, this class of medication is contraindicated in patients with known cardiac disease or poorly controlled diabetes. It should be withheld if maternal heart rate increases to more than 120 beats/minute or the patient experiences significant symptoms such as dyspnea or chest pain.

Beta-mimetics cross the placental barrier and may lead to fetal effects. Side effects include fetal tachycardia in response to maternal tachycardia and neonatal hypoglycemia linked to maternal hyperglycemia.[34] In addition, question has been raised linking beta-mimetics to an increased risk of neonatal intraventricular hemorrhage,[35,36] although this has been refuted in other studies.[37–39]

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are typically used in the treatment of hypertension, angina, and coronary artery disease and exert their effect by preventing reuptake of calcium ions via the voltage-dependent calcium channels. The resultant decrease in intracellular calcium leads to inhibition of actin and myosin interaction and, therefore, decreased myometrial contractility.[1,40] Given their ability to relax smooth muscle, calcium channel blockers, in particular nifedipine, are widely used tocolytic agents.

A recent systematic review and meta-analysis of 26 randomized, controlled trials evaluated nifedipine (Procardia) compared with other tocolytics, placebo, or no treatment in the management of preterm labor. To date, no placebo-controlled trials of nifedipine have been published. When compared with beta-mimetics, nifedipine showed a significant reduction in the risk of delivery within 7 days of initiation of treatment (37% vs 45%) as well as a reduction in rate of delivery before 34 weeks

(48% vs 62%). When nifedipine was compared with magnesium sulfate, there was no overall difference in delivery within 48 hours or before 34 or 37 weeks' gestation. This meta-analysis also revealed a significant improvement in neonatal outcomes with nifedipine tocolysis including a reduction in the rate of the common neonatal morbidities of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Nifedipine was also associated with fewer NICU admissions and shorter NICU stays.[32]

There are numerous dosing regimens for tocolysis with nifedipine discussed in the literature with most using oral capsules. Initial loading doses range from 10 to 40 mg followed by 10 to 20 mg every 4 to 6 hours, with the dose titrated based on contraction pattern.[32,40] Nifedipine is usually well-tolerated with minimal cardiovascular alterations.[41] In a meta-analysis, nifedipine was less likely to result in maternal side effects when compared with other tocolytics such as beta-mimetics or magnesium sulfate.[32] The majority of maternal side effects with nifedipine are related to relaxation of endothelial smooth muscle, which leads to peripheral vasodilation. Maternal symptoms often include nausea, flushing, headache, dizziness, and palpitations. Peripheral vasodilation leads to a compensatory rise in heart rate and stroke, volume which increases cardiac output, allowing for maintenance of blood pressure in women with no underlying cardiovascular disease. Rare but more serious maternal side effects include pulmonary edema, hypoxia, myocardial infarction, atrial fibrillation, and severe hypotension.[40] Calcium channel blockers should be used with caution in conjunction with magnesium sulfate as cases of cardiovascular collapse have been reported.

The fetal effects of calcium channel blockers are related to its peripheral vasodilative effects and risk of maternal hypotension which can lead to hypoperfusion of the uterus and placenta. Therefore, monitoring of maternal blood pressure and avoidance of calcium channel blockers in women at high risk for hypotension (cardiovascular disease, multiple gestations) are recommended.

PROSTAGLANDIN INHIBITORS

Indomethacin (Indocin), a nonselective COX inhibitor, is the most widely used prostaglandin inhibitor to treat preterm labor. Prostaglandins are known to play a crucial role in the onset of labor through the formation of gap junctions in the myometrium that increase intracellular calcium and facilitate myometrial contractility. Prostaglandin inhibitors function as tocolytics through inhibition of the COX enzyme responsible for converting arachidonic acid to prostaglandins.

Indomethacin has been shown to be an effective tocolytic agent. In addition, it is easy to administer, inexpensive, and has minimal maternal side effects. A 2005 Cochrane review of COX inhibitors for treating preterm labor evaluated 13 trials with a total of 713 women.[42] Indomethacin was shown to be effective when compared with placebo at reducing preterm birth before 37 weeks in 1 trial that included 36 women. In addition, there was a significant increase in gestational age by 3.5 weeks and birth weight of 716 g in 2 trials of 67 women compared with placebo. Despite these findings, there was no difference in perinatal mortality or morbidity, including respiratory distress syndrome or intraventricular hemorrhage. In this same review, 3 trials of 168 women evaluated indomethacin compared with other tocolytic agents, including beta-mimetics and magnesium sulfate. A similar reduction in preterm birth before 37 weeks was seen without any difference in overall perinatal mortality. Selective COX-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx) have also been compared with indomethacin with no appreciated difference in maternal or neonatal outcomes.

For tocolytic therapy, indomethacin is generally administered as a loading dose of 50 to 100 mg orally or 50 mg rectally followed by 25 to 50 mg every 6 hours for 48 hours.[43] Maternal side effects are primarily related to the gastrointestinal tract and include nausea, vomiting, gastroesophageal reflux, and gastritis. In addition, platelet dysfunction may occur with use of prostaglandin inhibitors. Selective COX-2 inhibitors have fewer gastrointestinal side effects; however, they are associated with increased cardiovascular risks and, therefore, should be used with caution. Overall, studies have shown that prostaglandin inhibitors are better tolerated and have a lower discontinuation rate owing to side effects than other tocolytics such as beta-mimetics and magnesium sulfate.[42,44]

The usefulness of prostaglandin inhibitors as tocolytics is limited by their effects on the fetus, primarily premature closure of the ductus arteriosus and oligohydramnios. Long-term use of indomethacin is associated with premature closure of the ductus arteriosus in 25% to 50% of pregnancies and results in oligohydramnios in 5% to 70% of pregnancies. A retrospective study of 124 women receiving prolonged indomethacin ($\geq$48 hours) reported the incidence of ductal constriction to be less than previously reported at 6.5% with reversal of constriction 24 to 48 hours after discontinuation of therapy.[45] In addition, the incidence of ductal constriction is reported to be dependent on gestational age at the time of use with increased risk of premature closure at later gestational ages ($>$31 weeks).[46,47] When used for a short duration ($<$48 hours), the incidence of oligohydramnios is low. In a study of 61 women before 34 weeks' gestation, the incidence of oligohydramnios was only 3.3% with return to normal amniotic fluid volume within 24 hours of discontinuation.[48] Indomethacin has been linked to other adverse neonatal outcomes, including necrotizing enterocolitis, intraventricular hemorrhage, and cardiac, pulmonary, and renal abnormalities, although these associations were not supported in a more recent meta-analysis of randomized and observational studies.[49] Although concern for fetal side effects of indomethacin may limit prolonged use, it seems to be a safe and effective tocolytic when used for a short period of time.

OXYTOCIN RECEPTOR ANTAGONIST

Given the overall limited efficacy of traditional tocolytic therapy, many European nations have explored the use of an oxytocin receptor antagonist atosiban (Tractocile). Atosiban, in theory, should have limited systemic maternal effects because of its site-specific action on myometrial cells in the uterus and myoepithelial cells in mammary glands, the only known locations of oxytocin receptor expression. Atosiban is a synthetic peptide that functions by blocking oxytocin from binding to its receptor and by downregulating the number of oxytocin receptors, thus decreasing myometrial contractility.[50,51]

Like other tocolytics, there is uncertainty about the efficacy of atosiban as a first-line tocolytic agent. In a meta-analysis that included 2 randomized, controlled trials that compared atosiban with placebo, a small but significant increase in women undelivered at 48 hours was seen in the atosiban group.[52] This result, however, was not seen in a 2005 Cochrane Review of oxytocin receptor antagonists for inhibiting preterm labor.[53] Atosiban was not shown to delay delivery for 48 hours, prevent preterm birth, or improve neonatal outcomes. Atosiban has also not been shown to be superior to other tocolytics. Two small studies have compared atosiban and nifedipine and did not show a difference in efficacy between the 2 medications.[54,55] Given their limited sample sizes, a larger randomized study would be necessary to better compare treatment superiority. Atosiban has been compared with beta-mimetics in

large, randomized, controlled trials in Europe, with no difference in tocolytic effectiveness at 48 hours or 7 days or in neonatal outcomes.[56,57]

Atosiban is administered as a continuous intravenous infusion with a loading dose of 6.75 mg followed by a maintenance dose of 300 μg/min for 3 hours, and then 100 μg/min for up to 48 hours.[57]

Studies of atosiban show limited side effects on both mother and fetus. When administered intravenously, it achieves a rapid maternal plasma steady state followed by a high clearance rate, with an estimated half-life of 18 minutes.[58] In addition, studies suggest that atosiban crosses the placenta in a limited fashion and does not seem to accumulate in the fetal circulation.[59] Unlike some tocolytics, atosiban does not alter maternal or fetal cardiovascular parameters in animal models, making it a very tolerable drug.[60] The most commonly cited maternal adverse reactions to atosiban include headache, nausea, and vomiting (8%–12%).[61] These adverse effects are more common during the loading period of the drug and decrease significantly during the maintenance period of the infusion.[62] In terms of overall maternal side effects, studies comparing atosiban with nifedipine and beta-mimetics favor atosiban.[54–56,61]

Questions have been raised about higher rates of death among infants exposed to atosiban. In a study by Romero and colleageus[63] that included 583 infants, more women were unexpectedly randomly allocated to receive atosiban as opposed to placebo before 26 weeks' gestation (10% vs 5%). There were more fetal–infant deaths in the group receiving atosiban (4.5% vs 1.7%). Seven of the 10 infant deaths in the atosiban group were among babies weighing less than 650 g; therefore, extreme prematurity may have played a significant role in the adverse neonatal outcomes in this group.[63,64] Given the increased infant deaths in the atosiban group, the US Food and Drug Administration has not approved the use of this drug for tocolysis in the United States.[30]

SUMMARY

The pathophysiology leading to preterm labor is not well understood and often multifactorial; initiating factors include intrauterine infection, inflammation, ischemia, overdistension, and hemorrhage.[3] Given these different potential causes, directing therapy for preterm labor has been difficult and suboptimal. To date, no single drug has been identified as successful in treating all of the underlying mechanisms leading to preterm labor. In addition, the methodology of many of the tocolytic studies is limited by lack of sufficient patient numbers, lack of comparison with a placebo, and inconsistent use of glucocorticoids. The limitations in these individual studies make it difficult to evaluate the efficacy of a single tocolytic by meta-analysis. Despite these limitations, the goals for tocolysis for preterm labor are clear: To complete a course of glucocorticoids and secure the appropriate level of neonatal care for the fetus in the event of preterm delivery.

The literature demonstrates that many tocolytic agents inhibit uterine contractility. The decision as to which tocolytic agent should be used as first-line therapy for a patient is based on multiple factors, including gestational age, the patient's medical history, common and severe side effects, and a patient's response to therapy. In a patient at less than 32 weeks gestation, indomethacin may be a reasonable first choice based on its efficacy, ease of administration, and minimal side effects. Concurrent administration of magnesium for neuroprotection may be given. At 32 to 34 weeks, nifedipine may be a reasonable first choice because it does not carry the fetal risks of indomethacin at these later gestational ages, is easy to administer, and has limited side effects relative to beta-mimetics.

In an effort to review a commonly faced obstetrical complication, this article has provided a summary of the most commonly used tocolytics, their mechanisms of action, side effects, and clinical data regarding their efficacy.

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