



Which tocolytic agents are most likely to delay delivery and improve neonatal outcomes?

Prostaglandin inhibitors and calcium channel blockers are most likely to delay delivery and improve neonatal outcomes in the setting of preterm labor, according to this systematic review and network meta-analysis of 95 randomized, controlled trials.

Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *BMJ*. 2012;345:e6226. doi:10.1136/bmj.e6226.

► EXPERT COMMENTARY

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This statistical tour de force on the topic of tocolytic therapy attempts to determine which agents are most effective at delaying delivery. The analysis is not a typical meta-analysis but what the investigators refer to as “network meta-analysis,” the distinction being that the latter makes an assumption of consistency because all relevant data are compared, including treatments that may no longer appear to be effective or relevant. This distinction may be a bit too esoteric for most clinicians, me included.

Details of the trial

Investigators identified 95 randomized, controlled trials of tocolytic therapy.

The probability of delivery being delayed by 48 hours was greatest with prostaglandin inhibitors (odds ratio [OR], 5.39; 95%

confidence interval [CI], 2.14–12.34), followed by magnesium sulfate (OR, 2.76; 95% CI, 1.58–4.94), calcium channel blockers (OR, 2.71; 95% CI, 1.17–5.91), beta mimetics (OR, 2.41; 95% CI, 1.27–4.55), and the oxytocin receptor blocker atosiban (OR, 2.02; 95% CI, 1.10–3.80), compared with placebo.

No class of tocolytic was superior to placebo in reducing the incidence of neonatal respiratory distress syndrome.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

I plan to continue my current practice of employing indomethacin or nifedipine as first-line, short-term tocolytic therapy in conjunction with administration of magnesium sulfate for fetal neuroprotection, when appropriate.

I give a starting dose of indomethacin of 50 to 100 mg (orally or rectally), with a maintenance dose of 25 mg orally every 4 hours or 50 mg every 6 hours, not to exceed 48 consecutive hours of treatment.

For nifedipine, I give 20 to 30 mg orally, which can be repeated in 2 hours, if necessary. The maintenance dose is 10 to 20 mg orally every 4 to 6 hours, not to exceed 180 mg/day or 72 consecutive hours of treatment.

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The author reports no financial relationships relevant to this article.

FAST TRACK

Prostaglandin inhibitors and calcium channel blockers were most likely to be ranked in the top 3 classes of medication for the outcomes of a 48-hour delay in delivery, lower risk of respiratory distress syndrome and neonatal mortality, and fewer maternal side effects

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Side effects that required a change of medication were significantly more common with beta mimetics (OR, 22.68; 95% CI, 7.51–73.67), magnesium sulfate (OR, 8.15; 95% CI, 2.47–27.70), and calcium channel blockers (OR, 3.80; 95% CI, 1.02–16.92), compared with placebo.

Prostaglandin inhibitors and calcium channel blockers were the agents most likely to be ranked in the top three classes of medication for the outcomes of a 48-hour delay in delivery, lower risk of respiratory distress syndrome and neonatal mortality, and fewer maternal side effects.

Strengths and limitations

The major strength of this analysis is its inclusion of trials from the world literature.

Weaknesses include the:

- lack of practice standardization in many trials
- inclusion of many trials that used composite or secondary analysis
- inability to control for the inclusion of magnesium sulfate in more recent trials, when it was classified as a neuroprotective agent and not a tocolytic
- inclusion of studies involving drugs unavailable in the United States.

The investigators also made some decisions about which trials to include and exclude that could have confused the picture. For example, they excluded trials that used combination drug therapy for tocolysis. As

a result, the use of magnesium sulfate as a neuroprotective agent could have confounded the results if it was not recorded as a tocolytic when used in conjunction with another tocolytic.

The most recent practice bulletin from the American College of Obstetricians and Gynecologists addresses this point when it cautions practitioners about developing guidelines for concurrent tocolytic use when employing magnesium sulfate for fetal neuroprotection.¹ The practice bulletin also confirms Level A evidence for the use of beta-agonists, calcium channel blockers, or nonsteroidal anti-inflammatory drugs for short-term tocolysis, effectively summarizing current clinical practice and agreeing with the conclusions of Haas and colleagues.

Overall, Haas and colleagues affirm current practice, concluding that prostaglandin inhibitors (eg, indomethacin) and calcium channel blockers (eg, nifedipine, nicardipine) delay delivery and improve short-term neonatal outcomes, whereas beta-agonist therapy was not considered to be as preferable, largely due to its maternal side effect profile. In addition, it is difficult to decipher the relative contributions of the drugs described in this investigation to neonatal and maternal side effects. ❌


Reference

1. Committee on Practice Bulletin–Obstetrics; American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 127: Management of preterm labor. *Obstet Gynecol.* 2012;119(6):1307–1317.



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