

Does magnesium sulfate prevent neonatal brain injury?

Mittendorf R, Dambrosia J, Pryde P, et al. Transactions of the sixty-ninth annual meeting of the Central Association of Obstetricians and Gynecologists. *Am J Obstet Gynecol.* 2002;186:1111-1118.

OBJECTIVE Prior research has shown a reduced risk for cerebral palsy and other neurologic defects among premature infants exposed antenatally to magnesium sulfate.

METHODS AND RESULTS Over 16 months, 149 gravidas between 24 and 34 weeks' gestation in active labor were randomized to magnesium tocolysis, "other" tocolysis, "neuroprotective" magnesium, or placebo. In the tocolytic groups, 37 singletons and 9 pairs of twins were born to mothers administered magnesium via a 4-g bolus followed by an hourly infusion of 2 to 3 g, and 41 singletons and 5 pairs of twins were born to women receiving ritodrine, terbutaline, indomethacin, or nifedipine, at the discretion of the attending physician. In the preventive groups, 28 singletons and 1 pair of twins were randomized to a 4-g bolus of magnesium (without further infusion), and 27 singletons and 1 pair of twins were exposed to placebo.

Umbilical cord blood was collected at delivery to determine serum ionized magnesium levels, and neonatal cranial ultrasound scans were performed. Of 165 infants examined, 37 experienced neonatal intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy, and/or death; those infants had higher umbilical cord magnesium levels.

The researchers concluded that the use of magnesium was associated with a higher risk of adverse perinatal outcome.

WHO MAY BE AFFECTED BY THESE FINDINGS? Infants exposed to magnesium.

EXPERT COMMENTARY Mittendorf et al recom-

mend "abandoning magnesium for use as routine tocolytic therapy," but they fail to offer sufficient evidence to warrant such a conclusion.

For example, maternal and cord blood samples were obtained on only half of the population. And while placental cultures were obtained, the results were not reported.

Many potentially important differences between the groups were not explicated in this study. Instead, data are presented for the combined groups and divided into adverse versus no adverse outcomes. For instance, 101 of 142 patients for whom data are reported had preterm premature rupture of membranes, but we don't know how many fell into either the tocolytic or preventive arms of the study.

The distribution of gestational ages in the 2 separate trials was not revealed—only that 42 of the 147 participants were at less than 28 weeks' gestation. In addition, the use of betamethasone was roughly equivalent in both the adverse and no adverse outcome groups. Presumably, a higher proportion of women in the tocolytic arm were able to receive the full 24 hours of treatment than in the neuroprotective arm. Further, the rate of steroid use was available for only 135 of the 149 women. Since steroids have been shown to decrease the rate of intraventricular hemorrhage, this particular issue needs to be more clearly explored.

Finally, for both the tocolytic and preventive groups, results were reported as composite adverse outcomes. As such, an infant who died with an intraventricular hemorrhage had 2 adverse events. This method of counting may be misleading.

BOTTOM LINE This study does not support the conclusion that tocolytic use of magnesium should be limited to controlled trials. Rather, we should await the results of 2 large, randomized magnesium trials before deciding to

halt the use of magnesium. Until then, it is appropriate to continue judicious use of tocolytics to allow for steroid administration and effectiveness.

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New options in emergency contraception: A WHO study

von Hertzen H, Piaggio G, Ding J, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet*. 2002;360:1803-1810.

OBJECTIVE Two 0.75-mg doses of levonorgestrel administered 12 hours apart and a single 10-mg dose of mifepristone are both effective emergency contraception (EC) options, prior research has shown. Researchers for this World Health Organization (WHO) study compared the efficacy and side-effects profile of these regimens, as well as a third, previously untested alternative: a single 1.5-mg dose of levonorgestrel.

METHODS AND RESULTS The evidence presented here, from randomized blinded trials, shows that a single 1.5-mg dose of levonorgestrel is as effective as 2 doses of 0.75 mg taken 12 hours apart. The findings of this study, and others like it, also indicate that efficacy continues for up to 5 days—not the 72 hours to which we have limited EC use in the past.^{2,3} The WHO group also found that the progesterone antagonist mifepristone (“RU 486”) is not a better EC than levonorgestrel.

WHO MAY BE AFFECTED BY THESE FINDINGS?

Sexually active women.

EXPERT COMMENTARY This study simplifies the postcoital contraceptive regimens established by Yuzpe decades ago and still in use today.¹

We can now tell patients seeking EC, “Take these 2 tablets (of 0.75-mg levonorgestrel) together as soon as possible up to 5 days after unprotected intercourse.” This off-label instruction is firmly supported by evidence from the current study, as well as other trials.^{2,3} (Although the extended therapeutic opportunity demonstrated in this study applies specifically to EC with levonorgestrel, it presumably also holds true for older, less-effective forms of EC, like birth-control pills containing levonorgestrel and estrogen.)

Unfortunately, FDA approval may come slowly. If this simpler levonorgestrel regimen is accompanied by advance prescription and direct pharmacy access (as in the states of Alaska, Washington, and California), it could lead to a reduction in abortion rates beyond that already achieved with the expanded use of EC and other contraceptives.

Although mifepristone remains an effective EC option, it is more expensive than levonorgestrel and unlikely to be considered for over-the-counter use because of its additional abortifacient actions. Levonorgestrel, on the other hand, is inexpensive and has a long history of safety.

BOTTOM LINE Levonorgestrel is an effective, economical alternative to mifepristone for EC, and a single 1.5-mg dose is a viable option. ■

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