PERSPECTIVE

Magnesium Sulfate for Preeclampsia

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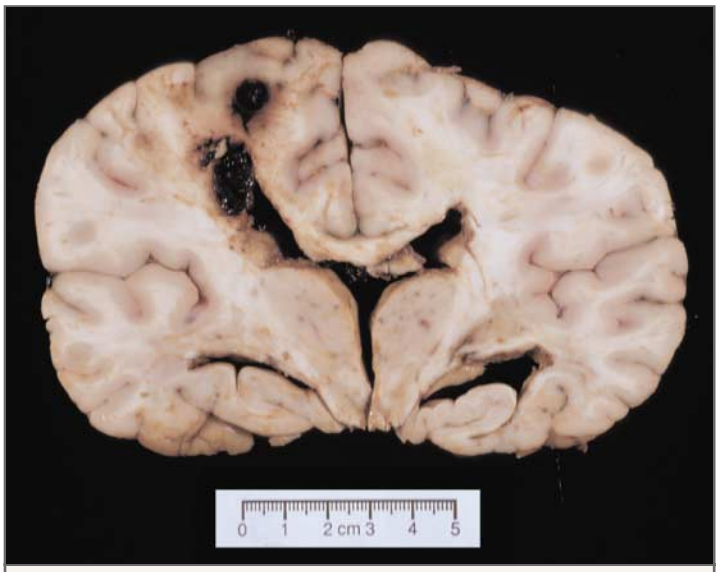
For centuries, practitioners of midwifery have feared the occurrence of convulsions during pregnancy because they carried a particularly grave prognosis for both mother and fetus. In 17th-century Paris, eclampsia was associated with a 50 percent maternal mortality rate. The seizures of eclampsia were distinguished from other types of seizures largely by the absence of a history of seizures before pregnancy. In 1776, Thomas Young of Edinburgh, Scotland, said, "If the woman has had these fits before, there is less danger to be apprehended from them." John Burns in Glasgow, Scotland, wrote in 1832 that "there is nothing either more difficult, or more mysterious, [than] the etiology of puerperal convulsions." He was an enthusiastic advocate of venesection, stating that successful treatment of eclampsia "requires instant, and generally a copious loss of blood" to prevent "fatal oppression of the brain, or extravasation of blood within the skull" (see Figure). By the end of the 19th century, bloodletting for eclampsia had generally been abandoned, replaced chiefly by expeditious delivery as the treatment of choice.

Eclampsia was noted to be associated with albuminuria in 1839 and with hypertension in 1897. These discoveries, coupled with the introduction of prenatal care in the first decade of the 20th century, led to earlier diagnosis of preeclampsia. Despite earlier diagnosis and safer cesarean operations, however, maternal mortality due to eclampsia in the United States remained at 25 to 30 percent through the first quarter of the 20th century. Success in treating tetanus with intraspinal magnesium sulfate in 1906 soon led to its intravenous use in women with eclampsia in Los Angeles. By 1929, the introduction of intramuscular magnesium sulfate treatment at the Chicago Lying-In Hospital was associated with a reduction in the maternal mortality rate from 36 percent to 7 percent. Subsequently, in large consecutive case series of patients with eclampsia in the United States from 1955 through the 1980s, maternal deaths were virtually eliminated among women treated empirically according to standardized protocols in which magnesium sulfate was the cornerstone of therapy.

The apparent success of such treatment in the United States was regarded skeptically in Britain, because magnesium was not a particularly efficacious anticonvulsant in other contexts and because its use in women with eclampsia had never been validated in randomized trials. A survey of British consultants, published in 1992, found that diazepam and phenytoin were the preferred anticonvulsants and that only 2 percent of consultants used magnesium in managing severe preeclampsia and eclampsia.[1] Lucas et al.[2] reported in the *Journal* that magnesium was superior to phenytoin for prophylaxis against seizures in a study of 2000 hypertensive women admitted to the labor suite at Parkland Hospital in Dallas. Magnesium was also superior to both diazepam and phenytoin for the prevention of recurrent eclamptic seizures among 1700 women in a study conducted in 23 centers in eight countries.[3] Most recently, in a comparison with placebo in the MAGPIE Trial, magnesium cut the risk of eclampsia among 10,000 women with preeclampsia by more than half.[4] It also reduced maternal mortality by half, but this effect failed to reach statistical significance by the traditional criterion of $P<0.05$.

There is now international consensus that magnesium is the treatment of choice for preeclampsia and eclampsia, but the mechanism underlying its salutary effect remains debatable. Although magnesium ion is a direct smooth-muscle relaxant at relatively high concentrations, it does not significantly reduce systemic blood pressure at the serum concentrations that are efficacious in treating preeclampsia. Under appropriate experimental condi-



Autopsy Specimen from a 40-Year-Old Woman with Severe Preeclampsia and Subarachnoid Hemorrhage.

Photograph courtesy of Dr. Umberto DeGirolami, Brigham and Women's Hospital, Boston.

tions, magnesium ion can depress the firing of cerebral cortical neurons. The concentrations of magnesium necessary to do so are slightly greater than those normally found in the brain and cerebrospinal fluid but cannot be achieved in the presence of an intact blood–brain barrier, even with sustained elevation of serum magnesium concentrations. Eclamptic seizures, however, are thought to result from local ischemia produced by severe cerebral vasospasm. In these circumstances, the blood–brain barrier might lose its integrity, permitting elevated concentrations of magnesium ion to diffuse into the brain from the blood. However, abnormal patterns on electroencephalograms — a common finding in patients with preeclampsia or eclampsia — do not correlate well with serum magnesium concentrations.

Could the efficacy of magnesium in preventing eclampsia be due to an entirely different mechanism — that is, a selective ability to improve cerebral vascular perfusion, thus reducing epileptogenic local ischemia? If so, a selective cerebral vasodilator should be even more effective than magnesium in treating preeclampsia. Yet in this issue of the *Journal*, Belfort et al. report that magnesium sulfate was clearly superior to the selective cerebral vasodilator nimodipine in reducing the risk of seizures in women with preeclampsia (pages 304–311). At the beginning of the 21st century, the mechanism of action of the simple magnesium ion in preeclampsia and eclampsia eludes precise definition, yet magnesium remains the standard of care.

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1. Hutton JD, James DK, Stirrat GM, Douglas KA, Redman CW. Management of severe pre-eclampsia and eclampsia by UK consultants. Br J Obstet Gynaecol 1992;99:554-6.
2. Lucas MJ, Leveno KJ, Cunningham G. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995;333:201-5.
3. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. Lancet 1995;345:1455-63.
4. The MAGPIE Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The MAGPIE Trial: a randomised placebo controlled trial. Lancet 2002; 359:1877-89.

CORRECTION

Magnesium Sulfate for Preeclampsia

Magnesium Sulfate for Preeclampsia . On page 276, the figure legend should have read ``Autopsy Specimen from a 40-Year-Old Woman with Severe Preeclampsia and Acute Intraparenchymal and Intraventricular Hemorrhage´´ rather than ``Autopsy Specimen from a 40-Year-Old Woman with Severe Preeclampsia and Subarachnoid Hemorrhage,´´ as printed.