SCHELLER et al. present a combined analysis of the only 2 randomized controlled trials (RCTs) of prophylactic nimodipine and hydroxyethyl starch (HES). In both trials, nimodipine was administered parenterally at 1–2 mg/hour starting the day before surgery and continuing for 7 postoperative days. In addition, 6% HES was given at 1 mg/hour for 2 hours prior to surgery and then continued at 2 mg/hour for the duration of treatment (7 days).

One year after surgery, despite larger tumor sizes in the treatment group, hearing preservation was achieved in 46% of the 55 treated patients and in only 25% of the 59 control patients. Some of the control patients were given nimodipine in response to altered values on intraoperative neurophysiological monitoring of the cochlear and facial nerve, with the concomitant potential to have diminished the overall magnitude of the observed nimodipine effect.

This study therefore presents limited evidence in a combined analysis that nimodipine and HES can improve hearing outcomes in the context of vestibular schwannoma (VS) surgery. Future research should focus on a better understanding of the nimodipine versus HES effect; the minimum required duration of therapy; whether starting nimodipine in response to monitoring changes would have a similar effect; and a better analysis of the economic argument for a prolonged inpatient parenteral course weighed against the patient-specific burden of worsened hearing.

Is there enough here to justify to insurers and patients that the regimen of treatment described is the proper course to take at this time in terms of improving hearing outcomes in VS surgery? An additional Phase III RCT of the aforementioned questions is an appropriate next step. The investigators may wish to focus on a more practical strategy of starting the nimodipine infusion in the preoperative area just prior to surgery, and continuing throughout the hospital course until discharge, with a minimum duration of therapy to be specified. It may not be practical or economically feasible for most patients to receive parenteral therapy for 7 days. Evidence for a minimum duration of therapy would be useful.

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Disclosures
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Response
Christian Scheller, MD
Department of Neurosurgery, University of Halle-Wittenberg, Halle (Saale), Germany

Prophylactic treatment with neuroprotective drugs prior to interventions in which nerve tissue is at risk seems to be a novel and promising concept. Besides dexamethasone there is a lack of neuroprotective substances available for use in clinical routine. However, I agree with the editorial that further clinical studies and further basic research are required.

So far basic research points to an underlying neuroprotective mechanism of nimodipine. In a surgery-like stress model based on Neuro2a cells we showed that nimodipine rescues these cells from stressor-induced cell death to different extents, in a dosage-dependent manner.
Significant evidence by RCTs for a clear neuroprotective efficacy and therefore a general recommendation of prophylactic nimodipine in VS surgery is still missing. The previously performed Phase III trial in 112 patients, a study in which facial nerve function 12 months after surgery was the primary outcome, showed no significant effects. However, the risk for postoperative hearing loss was 2 times lower in the treatment group compared to the control group (OR 0.49, 95% CI 0.18–1.30; p = 0.15), particularly in medium and large tumors (Koos III and IV). Therefore a continuation Phase III RCT with hearing preservation as the primary outcome in patients suffering from medium to large VSs and who have preoperative useful hearing ability is mandatory.

Nevertheless, the present combined analysis of the Phase III trial and its pilot study revealed a significantly lower risk for hearing loss in the treatment group for both the intent-to-treat and the subgroup analysis. Considering the fact that tumor size, preoperative nerve function, and the experience of the surgeon are the most influential factors for postoperative hearing ability, it is remarkable that the combined analysis showed an effect. Further detailed analyses showed that the results in both studies point in the same direction, which makes the combination of the data of the 2 studies appropriate. Considering that prophylactic nimodipine is safe, I recommend its administration in VS surgery to preserve hearing. Prophylactic administration was shown to be superior to an intraoperative start in response to monitoring changes.

The optimal pre- and postoperative duration of nimodipine treatment has to be clarified. Pharmacokinetic studies showed higher drug levels following parenteral compared to enteral nimodipine administration. An idea would be to start nimodipine parenterally and to continue its administration orally. This approach would not extend inpatient stay. Therapy costs of nimodipine treatment are assumed to be considerably lower compared to individual rehabilitation measures in patients suffering from reduced hearing or even hearing loss.

The neuroprotective effect of HES is questionable, because HES was administered for mild hemodilution, and basic research, animal experiments, and clinical trials conducted using nimodipine alone showed evidence of comparable neuroprotective efficacy. Considering the “Public Workshop: Risks and Benefits of Hydroxyethyl Starch Solutions” of the FDA, further studies that investigate neuroprotective prophylaxis in VS surgery should be performed with nimodipine alone.

References