# Prophylactic nimodipine treatment and improvement in hearing outcome after vestibular schwannoma surgery: a combined analysis of a randomized, multicenter, Phase III trial and its pilot study

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**OBJECTIVE** In clinical routines, neuroprotective strategies in neurosurgical interventions are still missing. A pilot study (n = 30) and an analogously performed Phase III trial (n = 112) pointed to a beneficial effect of prophylactic nimodipine and hydroxyethyl starch (HES) in vestibular schwannoma (VS) surgery. Considering the small sample size, the data from both studies were pooled.

**METHODS** The patients in both investigator-initiated studies were assigned to 2 groups. The treatment group (n = 70) received parenteral nimodipine (1–2 mg/hour) and HES (hematocrit 30%–35%) from the day before surgery until the 7th postoperative day. The control group (n = 72) was not treated prophylactically. Facial and cochlear nerve functions were documented preoperatively, during the inpatient care, and 1 year after surgery.

**RESULTS** Pooled raw data were analyzed retrospectively. Intent-to-treat analysis revealed a significantly lower risk for hearing loss (Class D) 12 months after surgery in the treatment group compared with the control group (OR 0.46, 95% CI 0.22–0.97; p = 0.04). After exclusion of patients with preoperative Class D hearing, this effect was more pronounced (OR 0.38, 95% CI 0.17–0.83; p = 0.016). Logistic regression analysis adjusted for tumor size showed a 4 times lower risk for hearing loss in the treatment group compared with the control group (OR 0.25, 95% CI 0.09–0.63; p = 0.003). Facial nerve function was not significantly improved with treatment. Apart from dose-dependent hypotension (p < 0.001), the study medication was well tolerated.

**CONCLUSIONS** Prophylactic nimodipine is safe and may be recommended in VS surgery to preserve hearing. Prophylactic neuroprotective treatment in surgeries in which nerves are at risk seems to be a novel and promising concept.

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KEY WORDS facial nerve; cochlear nerve; nimodipine; hydroxyethyl starch; vestibular schwannoma; neuroprotection

ABBREVIATIONS AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; HB = House-Brackmann; HES = hydroxyethyl starch; ITT = intent to treat; RCT = randomized controlled trial; VS = vestibular schwannoma.

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The incidence of diagnosed vestibular schwannomas (VSs) has been estimated to range from 1-2/100,000/year;<sup>18</sup> VSs comprise 6%–8% of all intracranial tumors. Vestibular schwannomas most frequently present with hearing loss. Depending on the size of the tumor, facial nerve weakness may be additionally recognized. Other symptoms include tinnitus, vertigo, headache, facial numbness, and change in taste perceptions.<sup>5</sup> Possible options are wait and scan, radiotherapy, and microsurgery. In case of surgery, the objective should be complete tumor removal with preservation of facial and possibly cochlear nerve functions.<sup>18</sup> So far, application of neuroprotective strategies from basic research to clinical practice in neurosurgical procedures has been elusive.<sup>26</sup>

Nimodipine, a dihydropyridine calcium antagonist, reduces the risk of poor outcome and secondary ischemia after aneurysmal subarachnoid hemorrhage.<sup>4</sup> Besides preventing vasospasm, a neuroprotective effect of nimodipine has been proposed.17 The beneficial impact of nimodipine on protection and regeneration of nerve tissue is supported by animal experiments,<sup>1,6,10,13,15</sup> and it has been used in combination with hydroxyethyl starch (HES) by several retrospective and prospective clinical trials.<sup>3,19,20,27,28</sup> A pilot study showed superiority of prophylactic nimodipine compared with an intraoperative start or no treatment.<sup>19</sup> A Phase III trial with facial nerve function assessed 12 months after surgery as the primary outcome showed no significant results.<sup>22</sup> However, the risk for postoperative hearing loss was 2 times lower in the treatment group compared with the control group. Several factors are known to have an impact on the outcome of both the facial and cochlear nerves following VS surgery. Therefore, the efficacy of an additionally applied neuroprotective drug is difficult to quantify. However, it is possible to determine objectively the slightest alterations of hearing ability by pure-tone audiometry with speech discrimination. Considering the small sample size, the results of the only 2 analogously performed randomized controlled trials (RCTs) were pooled.

# **Methods**

#### **Trial Design**

A combined analysis using the raw data from the only 2 RCTs of prophylactic nimodipine and HES in VS surgery conducted so far was performed retrospectively. Treatment, follow-up, and data acquisition were identical in both studies. However, expert review was different between the studies (see *Outcomes, Follow-Ups, and Blinding*).

Both the pilot study and the multicenter trial were investigator-initiated trials conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The multicenter trial was approved by the German Competent Authority. The study protocols had been positively reviewed by the ethics committees of the University of Halle-Wittenberg (multicenter trial) and the University of Ulm (pilot study), and all local review boards of the participating institutions. All patients gave informed consent prior to inclusion. No changes to methods were made after the trials were started. The multicenter study (n = 112) was an open-label, 2-armed, randomized, Phase III trial with blinded expert review (performed 2010–2013). Design and sample size planning were based on the data of the single-center pilot study (n = 30, performed 2004–2006), which was randomized as well. The aim of both studies was to investigate the efficacy and safety of prophylactic parenteral nimodipine and HES treatment in VS surgery. Parenteral administration of nimodipine for several days requires the use of a central line. It was not considered ethical to impose this on control patients. Therefore a blinded design was not used.

#### **Study Participants**

Adults 18 years of age or older with an indication for VS surgery were included. Reasons for exclusion were contraindications against nimodipine or HES, surgery for recurrent VS, pregnancy and lactation period, neurofibromatosis Type 2, tumor inoperability, and participation in other clinical trials within the last 30 days. Considering that facial nerve function 12 months after surgery was the primary outcome of the multicenter trial, preoperative facial nerve function Grade VI according to the House-Brackmann (HB) grading scale was an additional exclusion criterion.<sup>17</sup>

#### Surgical and Neuroprotective Interventions

The pilot study was performed at a single center. Seven German university hospitals participated in the multicenter trial. The aim of all surgeries done by experienced surgeons was to preserve facial and cochlear nerve functions and to achieve gross-total resection via a retrosigmoid approach. Intraoperative neurophysiological monitoring including brainstem auditory evoked potentials, continuous facial nerve electromyography, and direct facial nerve stimulation was used in all surgeries, and histopathological examinations were performed. One hundred forty-two patients were randomly assigned to treatment (n = 70) and control groups (n = 72), respectively. Neuroprotective prophylaxis was started the day before surgery and was continued until the 7th postoperative day. The medication consisted of parenteral nimodipine (1-2 mg/hour; Nimotop, Bayer) and HES 6% (aiming at a hematocrit between 30% and 35%; Voluven 6%, Fresenius Kabi) and was preoperatively administered via a peripheral venous catheter with a dose of 1 mg/hour for 2 hours. Thereafter the dose was increased to 2 mg/hour.

In the treatment group, 2 patients were not treated 1 day before surgery but before skin incision. In 11 patients the duration of nimodipine and HES therapy was reduced and in 2 patients the therapy was prolonged. Thirty-three patients tolerated the full dose of 2 mg/hour. Symptomatic hypotension with headaches or dizziness was observed in 28 patients, resulting in a dose reduction to 1 mg/hour. These symptoms were dose dependent and reversible. A strict lower blood pressure limit together with a dose reduction was not defined in asymptomatic patients. When intraoperative monitoring indicated deterioration of facial or cochlear nerve functions, the intraoperative start of the neuroprotective therapy was permitted in the control group because of its beneficial effect in previous studies.<sup>2,19,20,27,28</sup> An intraoperative start was documented in 26 patients in the control group. These 26 patients also received a full 7-day course of treatment. The HES was given according to schedule in 48 patients. The duration of HES treatment was reduced in 13 patients.

#### Outcomes, Follow-Ups, and Blinding

In both studies facial and cochlear nerve functions were documented at defined time points (preoperative, during the inpatient stay, and long term [mostly 1 year after surgery]). For both trials facial function was documented photographically at rest and in motion, as described by House and Brackmann.8 Photographs were evaluated by the investigators for the pilot study and in a blinded fashion by a neurologist for the multicenter trial, and were classified using the HB grading scale. Hearing ability was determined by pure-tone audiometry with speech discrimination in both studies. Speech audiograms were analyzed by the investigators for the pilot study and in a blinded fashion by an otorhinolaryngologist for the multicenter trial, and the audiograms were classified using the "Committee on Hearing and Equilibrium Guidelines for the Evaluation of Hearing Preservation in Acoustic Neuroma (vestibular schwannoma)" of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS).16

Tumor size (according to the Koos grading system) and extent of resection were evaluated by the investigators for the pilot study and in a blinded fashion by a neuroradiologist on the basis of axial contrast-enhanced T1-weighted MRI studies performed preoperatively and 3 months after surgery for the multicenter trial.<sup>11</sup>

Side effects, concomitant medication, and comorbidity were documented descriptively in both studies. Because possible hypotension is a known side effect of nimodipine, blood pressure was carefully monitored.

Based on the results of the pilot study, facial nerve function 12 months after surgery compared with its function before surgery was assessed as the primary outcome in the multicenter trial. Secondary outcomes were cochlear nerve function 12 months after surgery and adverse events. There were no amendments to the trial protocols.

#### **Sample Sizes**

Based on the findings of the single-center pilot study including 30 patients (i.e., the assumption of 50% worsening of the facial nerve function in the control group and of 15% worsening in the treatment group), the sample size of the multicenter trial was determined.

A 2-sided chi-square test with continuity correction, a significance level of 5%, and a power of 95% revealed that 50 patients per group would be required. Considering a 10% expected dropout rate, the final sample size was fixed at 56 patients per group. There was no interim analysis planned or performed.

#### **Randomization Procedure**

Participants in the multicenter study were enrolled and assigned to intervention by the investigator of each trial site by using an online randomization tool, whereas the participants in the pilot study were allocated by drawing lots. For generation of the random allocation sequence the software SAS 9.1, procedure "plan" with block randomization, created at the Coordination Centre for Clinical Trials (Koordinierungszentrum für Klinische Studien [KKS]), University of Halle-Wittenberg, Germany, was used. The trial center was responsible for blocking.

#### **Statistical Methods**

The raw data of both the pilot and the multicenter studies were pooled and analyzed together. Both studies were planned with a fixed sample size and no interim analysis. The ITT analysis was performed with all patients in both studies, which means that all patients were analyzed as randomized. Preservation of the facial and cochlear nerve function 1 year after surgery in comparison with the preoperative findings was analyzed by logistic regression to allow adjustment with respect to tumor size and extent of resection. Tumor size and extent of resection show a relative imbalance in the distribution between the treatment and control groups despite a proper randomization procedure, with larger tumors in the treatment group (Table 1). Odds ratios and their 95% confidence intervals were determined and binary outcomes were analyzed using Fisher's exact test.

# **Results**

# Participant Enrollment

A total of 142 patients were enrolled and randomly assigned to the treatment group (n = 70) or the control group (n = 72). An ITT analysis regarding hearing preservation was performed in 141 patients, because postoperative hearing was absent in 1 patient. For detailed analysis of hearing preservation, 15 patients who received treatment and 13 patients in the control group had to be excluded. Particularly, preoperative hearing loss (Class D) was observed in 7 patients of the treatment and in 6 patients of the

TABLE 1. Pooled data	of the multicenter	rtrial and	the pilot	study
analogous to the flow	diagram			

Tx Group, n = 55	Control Group, n = 59
48 ± 13.3	48 ± 12.6
31 (56.4)	34 (57.6)
24 (43.6)	25 (42.4)
5 (9.1)	3 (5)
15 (27.3)	29 (49.2)
24 (43.6)	18 (30.5)
11 (20)	9 (15.3)
20 (36.4)	19 (32.2)
19 (34.6)	18 (30.5)
16 (29)	22 (37.3)
52 (95)	56 (95)
3 (5)	3 (5)
	$Tx Group, n = 55$ $48 \pm 13.3$ $31 (56.4)$ $24 (43.6)$ $15 (27.3)$ $24 (43.6)$ $11 (20)$ $20 (36.4)$ $19 (34.6)$ $10 (29)$ $52 (95)$ $3 (5)$

Tx = treatment.



FIG. 1. Participant flow diagram for the study of prophylactic nimodipine and hearing outcome after VS surgery. CPA = cerebellopontine angle.

control group. All reasons for exclusion are shown in Fig. 1. Accordingly, 55 (79%) patients in the treatment group and 59 (82%) patients in the control group were suitable for detailed hearing analysis. For analysis of facial nerve function, patients with preoperative Class D hearing were not excluded. Facial nerve function 12 months after surgery was not documented in 8 patients. Therefore, ITT analysis for facial nerve preservation was conducted in 134 patients.

#### Patient Recruitment

For the pilot study a consecutive series of 30 patients was randomized and allocated to the treatment (n = 14) and the control group (n = 16) between 2004 and 2006. The multicenter trial was performed from January 2010 to February 2013. Recruitment was planned to occur within 2 years, from January 2010 (first patient in) to December 2011. The last patient had been included ahead of schedule in April 2011 (last patient in) and follow-up examinations were completed in February 2013 (last patient out).

#### **Baseline Data**

Both treatment and control group were comparable in age, sex, and preoperative cranial nerve functions. However, both groups differed regarding tumor sizes (Table 1). In the treatment group, more moderately large and large to giant-sized tumors (Koos III and IV: 63.6%) than small and medium-sized tumors (Koos I and II: 36.4%) were observed. In contrast, the distribution of tumor sizes in the control group was 54.2% of Koos I and II and 45.8% of Koos III and IV tumors.

Extent of resection was also different between groups, with complete removal in 47 (85%) patients of the treatment group and in 45 (76%) patients of the control group. Capsule remnants (1–3 mm) were observed in 6 (11%) patients in the treatment group and in 12 (20%) patients in the control group, and subtotal removal (> 3–10 mm) in 2 patients in each group.

#### **Outcomes and Estimation**

#### Hearing 1 Year After Surgery

Despite larger tumor sizes in the treatment group, hearing preservation (AAO-HNS Class A–C) was achieved in 25/55 (46%) of all patients in the treatment group, compared with 15/59 (25%) of the control group. Results of Fisher's exact test were significant (p = 0.03). Analysis of hearing preservation in Classes A and B showed similar results: 11/55 (20%) in the treatment group versus 9/59 (15%) in the control group (p = 0.34). Postoperative excellent hearing (Class A) was observed in 5/55 (10%) of the treatment group and in 3/59 (5%) of the control group (p = 0.48). Hearing preservation (Class A–C) in patients with Koos IV tumors was achieved in 2/11 (18%) in the

	Koos Grade for Tumor Size				
Group	I	II		IV	Total
Тх					
HB grade, n = 61					
1&11	100% (5/5)	94% (16/17)	89% (24/27)	58% (7/12)	85% (52/61)
1–111	100% (5/5)	94% (16/17)	100% (27/27)	83% (10/12)	95% (58/61)
AAO-HNS class, n = 55					
A	0 (0/5)	0 (0/15)	21% (5/24)	0 (0/11)	10% (5/55)
A & B	0 (0/5)	33% (5/15)	25% (6/24)	0 (0/11)	20% (11/55)
A–C	80% (4/5)	67% (10/15)	38% (9/24)	18% (2/11)	46% (25/55)
Control					
HB grade, n = 63					
1&11	67% (2/3)	90% (26/29)	85% (17/20)	46% (5/11)	79% (50/63)
I–III	100% (3/3)	100% (29/29)	100% (20/20)	73% (8/11)	95% (60/63)
AAO-HNS class, n = 59					
A	0 (0/3)	7% (2/29)	6% (1/18)	0 (0/9)	5% (3/59)
A & B	33% (1/3)	17% (5/29)	17% (3/18)	0 (0/9)	15% (9/59)
A-C	33% (1/3)	35% (10/29)	22% (4/18)	0 (0/9)	25% (15/59)

Facial nerve function was evaluated according to the HB system, and cochlear nerve function according to the Committee on Hearing and Equilibrium Guidelines for the Evaluation of Hearing Preservation in Acoustic Neuroma (vestibular schwannoma); referred to throughout as the AAO-HNS class (see Monsell et al.).

treatment group, whereas all patients (9/9) in the control group lost hearing (p = 0.48). Postoperative excellent hearing preservation (Class A or A and B) was not achieved in patients with Koos IV tumors in either group. As shown in Table 2, there was a tendency for a better outcome for hearing in the treatment group as compared with the control group in all subclasses (Class A–D on the AAO-HNS scale, and Koos classification).

#### Facial Nerve Function 1 Year After Surgery

The rate of facial nerve preservation of HB Grade I–III was 95% in both groups. There was a small but not significant tendency for more HB Grade I and II findings in the treatment group (85%) as compared with the control group (81%) (p = 0.48). For Koos IV tumors the treatment group showed higher preservation rates of HB I and II (58%) and of HB I–III (83%) as compared with the control group (HB I and II: 46%, HB I–III: 73%). However, these differences were not significant (HB I and II: p = 0.68, HB I–III: p = 0.64) (Table 2).

The ITT analysis revealed that the risk for postoperative hearing loss (AAO-HNS Class D) was 2 times lower in the treatment compared with the control group (OR 0.463, p = 0.04). After exclusion of patients with preoperative Class D hearing, this effect was more pronounced (OR 0.38, p = 0.016). Preservation of cochlear nerve function after VS surgery depends on tumor size,<sup>1</sup> and is achieved in 57% of patients with tumor size of < 1 cm, in 33% of patients with tumor size of 1–2 cm, and in only 6% of patients with tumor size of > 2 cm.<sup>16</sup> Because tumor size and extent of resection were different between groups, multiple logistic regression analysis was additionally performed. The risk for hearing loss was 4 times lower in the treatment group compared with the control group (OR 0.25, p = 0.003) when adjusted for tumor size. Postoperative facial nerve functions were excellent (HB I and II) in most patients in both groups. However, results of both ITT and logistic regression analysis (adjusted for tumor size and extent of resection) were not significant, but suggested a possible beneficial effect in preventing deterioration of facial nerve function to HB IV–VI (OR 0.77, 95% CI 0.32–1.85 [p = 0.56], and OR 0.55, 95% CI 0.19–1.60 [p = 0.27]). Further detailed analyses show that the results in both studies point in the same direction, which makes combining the data of the 2 studies appropriate (Table 3).

# **Adverse Effects of Treatment**

Neither of the studies was discontinued due to adverse events caused by the study medication. No drug-induced mortality or serious adverse events were observed in either study. One patient of the control group (multicenter trial) died of unknown reasons several weeks after surgery. Study medication was administered to this patient from the 1st until the 6th postoperative day because intraoperative monitoring pointed to deterioration of cranial nerve functions. Hypotension was the only significantly differing adverse effect between the treatment and the control group, which was dose-dependent and reversible. Hypotension was observed in 28 of 55 (51%) patients in the treatment group and in only 6 of 59 (10%) patients in the control group (p < 0.001). All other adverse events did not significantly differ between both groups (Table 4). Following the start of nimodipine infusion no patient experienced local pain in the area of peripheral venous catheter.

# Discussion

# Limitations of the Study

The raw data of the only 2 RCTs of prophylactic ni-

Analysis	OR (Tx vs control group)	95% CI	p Value
Risk for hearing loss (Class D)			
ITT analysis (n = 141)*	0.463	0.222-0.967	0.040
Not adjusted (n = 114)	0.380	0.173-0.838	0.016
Adjusted for tumor size	0.250	0.099-0.626	0.003
Adjusted for tumor size & for extent of resection	0.255	0.100-0.652	0.004
Adjusted for tumor size, for extent of resection, & pilot study	0.246	0.095-0.639	0.004
Risk for facial nerve deterioration (HB IV–VI)			
ITT analysis (n = 134)*	0.771	0.322-1.849	0.561
Not adjusted (n = 123)	0.679	0.266-1.729	0.417
Adjusted for tumor size	0.546	0.194-1.538	0.252
Adjusted for tumor size & for extent of resection	0.547	0.187-1.598	0.270
Adjusted for tumor size, for extent of resection, & pilot study	0.559	0.190-1.641	0.290

TABLE 3. Logistic regression adjusted for tumor size and extent of resection for facial and cochlear nerve functions 1 year after surgery

GR = Gardner-Robertson.

\* The numbers of patients for the ITT analyses are lower than the overall total of 142 because postoperative hearing was absent in 1 and facial nerve function was not documented in 8.

modipine in VS surgery that have been published so far were pooled and retrospectively analyzed. Both studies were performed analogously, and the inclusion criteria were identical. Therefore, the selection of both studies for a combined analysis is scientifically justified to develop a more correct estimate of the effect magnitude. Because none of the patients in either of the published studies was excluded for ITT analysis, a selection bias appears very unlikely. However, a blinded expert review was not performed in the patients (n = 30) in the pilot study, which could result in some evaluation bias. Considering that the assessment of pure-tone audiometry with speech discrimination is clearly defined and that it is possible to determine the slightest alterations of hearing ability, this bias is expected to be small.<sup>16</sup> Although several factors have impact on the outcome after VS surgery, the neuroprotective effect of an additionally administered medication is measured objectively.

#### **Sample Sizes and End Points**

The pilot study showed promising results for both facial and cochlear nerve preservation with the use of prophylactic nimodipine and HES in VS surgery. Sample size planning for the multicenter trial was determined based on the assumption of 50% worsening of the facial nerve function in the control group and of 15% worsening in the treatment group. In retrospect, this rate is too high, resulting in an insufficient number of patients for the multicenter trial with facial nerve function as primary outcome. Furthermore, it could not be expected at that time that the medication would have stronger effects on hearing preservation. In retrospect, hearing would have been more suitable for the primary end point.

# **Cochlear Nerve**

Both ITT and additional analysis revealed a significant effect of prophylactic nimodipine and HES on hearing preservation (AAO-HNS Class A–C) 1 year after surgery. Most likely due to the small number of cases, there was not

a significant result for cochlear nerve preservation of Class A or Classes A and B.

### **Facial Nerve**

There were no significant results. However, ITT and additional analysis (adjusted for tumor size and extent of resection) pointed to a potential beneficial effect in preventing deterioration of facial nerve function to HB IV–VI.

#### **Study Medication**

This work was based on a series of studies with nimodipine and HES treatment in VS surgery, each forming the basis for the next. First, a beneficial effect of the intraoperative start of nimodipine and HES for hearing preservation was reported in 2001,<sup>3,27</sup> and was later also noticed for facial nerve outcome.<sup>20,28</sup> The concept of a prophylactic administration of nimodipine and HES arose from these observations.<sup>19,22</sup> Considering the positive effect of prophylactic nimodipine and HES on hearing preservation in the presented combined analysis gives rise to the following questions. Because pharmacokinetic studies of prophylactically administered nimodipine in skull base surgery showed that parenteral nimodipine produces higher drug levels and has a higher neuroprotective efficacy as compared with enteral administration, parenteral nimodipine seems to be superior.<sup>23,24</sup> However, the optimal preoperative duration and the optimal dosage remain unclear and should be further investigated, especially because continuously administered parenteral nimodipine can produce variable serum levels.<sup>21</sup>

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.<sup>1,3,6,7,9,10,12–15,25,29</sup> Considering the "Public Workshop: Risks and Benefits of Hydroxyethyl Starch Solutions" of the FDA, potential risks of HES administration cannot be excluded. Further studies of neuroprotective prophylaxis in VS surgery should be performed with nimodipine alone.

#### TABLE 4. Adverse events in 114 patients with VS

Adverse Events	Tx Group, n = 55	Control Group, n = 59
Mild		
Nausea*	29	29
Headache*	21	15
Hypotension*	28	6
Pain	10	14
Insomnia	7	6
Dizziness	8	5
Urinary tract infection	0	3
Hypokalemia	3	0
Nystagmus	2	1
Acidosis	2	0
Muscle tension	1	1
Blood sugar level increased	1	1
Depression	1	1
Taste disorder	1	1
Pulmonary problems	1	1
Eye inflammation	1	1
Hypertension	0	1
Fever	1	0
Mood swing	1	0
Hyponatremia	0	1
Thrombophlebitis	1	0
Potassium deficiency	0	1
Late facial nerve paresis	0	1
ALT increase*	1	0
GGT increase*	1	0
Tachycardia*	1	0
Allergic reaction*	1	0
Serious		
CSF fistula	3	4
Meningitis	2	0
Thrombosis	0	1
Intraop air embolism	1	1
Bilat pulmonary embolism	1	0
Intraop cerebellar swelling	1	0
Hydrocephalus occlusus	1	0
Subdural hematoma	1	0
Cerebellar infarction	1	0

ALT = alanine aminotransferase; GGT =  $\gamma$ -glutamyl transpeptidase.

\* Potentially caused by nimodipine.

# Intraoperative Start of Medication in the Control Group

The evidence of effectiveness of the neuroprotective medication was probably negatively influenced by the permission for an intraoperative start of nimodipine and HES in 26 patients in the control group when intraoperative monitoring pointed to a deterioration of facial or cochlear nerve function. However, the pooled analysis showed significant results for hearing preservation (even in ITT analysis). Without that permission, the therapeutic effect would have been even stronger. Therefore, and because of the missing comparability of the treatment group (with both eventful and uneventful intraoperative monitoring) and the "true" control group (with uneventful intraoperative monitoring and therefore no expected postoperative deterioration of facial or cochlear nerve function), a further subgroup analysis would not have been appropriate.

### Generalizability of the Findings

Several retrospective and prospective clinical trials have pointed to a beneficial effect of nimodipine on longterm outcome of cranial nerve functions following VS, laryngeal, and maxillofacial surgery.<sup>3,9,12,14,19,20,22,25,27,28</sup> The beneficial effect of nimodipine treatment for the protection and regeneration of nerve tissue is also supported by animal experiments.<sup>1,6,10,13,15</sup> Additionally, basic research points to an underlying neuroprotective mechanism of nimodipine.<sup>3,7,29</sup> In principle, prophylactic treatment with neuroprotective drugs prior to interventions in which nerve tissue is at risk seems to be a novel and promising concept.

# Conclusions

The combined analysis shows the efficacy and safety of prophylactic parenteral nimodipine treatment for hearing preservation in VS surgery. This observation suggests an unknown neuroprotective effect of nimodipine, which should be investigated in basic research. Hearing and, consequently, communication ability, is a major factor determining the quality of life.<sup>18</sup> Additionally, social and rehabilitation costs may be reduced when preservation of hearing ability can be achieved by prophylactic neuroprotective treatment. Therapy costs of nimodipine treatment are assumed to be considerably lower compared with individual rehabilitation measures in patients suffering from reduced hearing or even hearing loss. A continuation Phase III RCT with hearing preservation as the primary outcome in patients with preoperative useful hearing ability is planned to confirm the results of this pooled analysis.

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# Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Scheller, Strauss. Acquisition of data: Scheller, Tatagiba, Gharabaghi, Ramina, Ganslandt, Bischoff, Engelhorn, Matthies, Westermaier, Antoniadis, Pedro, Rohde, von Eckardstein, Kretschmer, Steighardt. Analysis and interpretation of data: Scheller, Wienke, Zenk, Kornhuber, Richter. Drafting the article: Scheller. Critically revising the article: Tatagiba, Barker, Strauss. Approved the final version of the manuscript on behalf of all authors: Scheller. Study supervision: Scheller.

# Supplemental Information

### **Online-Only Content**

Supplemental material is available with the online version of the article.

Protocol. https://thejns.org/doi/suppl/10.3171/2016.8. JNS16626.

Statistical Analysis Plan. https://thejns.org/doi/suppl/10.3171/2016.8.JNS16626.

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