JNS

ATLAS

CLINICAL ARTICLE

J Neurosurg 125:1277–1282, 2016

Stability of hearing preservation and regeneration capacity of the cochlear nerve following vestibular schwannoma surgery via a retrosigmoid approach

Christian Scheller, MD,[1,2] Andreas Wienke, PhD,[3] Marcos Tatagiba, MD,[4] Alireza Gharabaghi, MD,[4] Kristofer F. Ramina, MD,[4] Oliver Ganslandt, MD,[5] Barbara Bischoff, MD,[5] Cordula Matthies, MD,[7] Thomas Westermaier, MD,[7] Gregor Antoniadis, MD,[8] Maria Teresa Pedro, MD,[8] Veit Rohde, MD,[9] Kajetan von Eckardstein, MD,[9] Thomas Kretschmer, MD,[10] Johannes Zenk, MD,[6] and Christian Strauss, MD[1]

[1]Department of Neurosurgery, University of Halle-Wittenberg; [2]Translational Centre for Regenerative Medicine (TRM), University of Leipzig; [3]Institute of Medical Epidemiology, Biostatistics, and Informatics, University of Halle-Wittenberg; [4]Department of Neurosurgery, University of Tübingen; [5]Department of Neurosurgery, University of Erlangen-Nuremberg; [6]Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen-Nuremberg; [7]Department of Neurosurgery, Würzburg University Hospital; [8]Department of Neurosurgery, Bezirkskrankenhaus Günzburg, University of Ulm; [9]Department of Neurosurgery, University of Göttingen; and [10]Department of Neurosurgery, Evangelisches Krankenhaus, University of Oldenburg, Germany

OBJECTIVE The purpose of this research was to examine the stability of long-term hearing preservation and the regeneration capacity of the cochlear nerve following vestibular schwannoma (VS) surgery in a prospective study.

METHODS A total of 112 patients were recruited for a randomized multicenter trial between January 2010 and April 2012 to investigate the efficacy of prophylactic nimodipine treatment versus no prophylactic nimodipine treatment in VS surgery. For the present investigation, both groups were pooled to compare hearing abilities in the early postoperative course and 1 year after the surgery. Hearing was examined using pure-tone audiometry with speech discrimination, which was performed preoperatively, in the early postoperative course, and 12 months after surgery and was subsequently classified by an independent otorhinolaryngologist using the Gardner-Robertson classification system.

RESULTS Hearing abilities at 2 time points were compared by evaluation in the early postoperative course and 1 year after surgery in 102 patients. The chi-square test showed a very strong association between the 2 measurements in all 102 patients ($p < 0.001$) and in the subgroup of 66 patients with a preserved cochlear nerve ($p < 0.001$).

CONCLUSIONS There is no significant change in cochlear nerve function between the early postoperative course and 1 year after VS surgery. The result of hearing performance, as evaluated by early postoperative audiometry after VS surgery, seems to be a reliable prognosticator for future hearing ability.

Clinical trial registration nos.: 2009-012088-32 (clinicaltrialsregister.eu) and DRKS 00000328 ("AkNiPro," drks-neu.uniklinik-freiburg.de/drks_web/)

http://thejns.org/doi/abs/10.3171/2015.10.JNS15926

KEY WORDS vestibular schwannoma; cochlear nerve; hearing; regeneration

Vestibular schwannomas (VSs) account for 6%–8% of all intracranial tumors. Treatment options for VS include microsurgical removal or stereotactic radiosurgery (SRS).[12] The goal of modern VS surgery is total tumor removal with preservation of facial and cochlear nerve function.[11] So far, the stability of hearing preservation and the regeneration potential of the cochlear nerve after VS surgery have been analyzed retrospectively.[2,3,8,12,17] Long-term follow-ups after SRS showed serviceable hearing rates in 44 patients with VS at 1, 3, 5, 7, and 10 years of 80%, 55%, 48%, 38%, and 23%, respectively.[2] In contrast, a majority of 103 patients with preserved hearing follow-

ABBREVIATIONS SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

SUBMITTED April 23, 2015. **ACCEPTED** October 22, 2015.
INCLUDE WHEN CITING Published online January 29, 2016; DOI: 10.3171/2015.10.JNS15926.

ing VS surgery experienced stability of preserved hearing at the 5-year follow-up.[17] The purpose of the present study was to examine the stability of hearing preservation and the regeneration capacity of the cochlear nerve following VS surgery in 112 patients in a prospective, randomized multicenter Phase III trial.[13]

Methods

A prospective, open-label, 2-armed, randomized multicenter Phase III trial with blinded expert review was performed from January 2010 to April 2012 to investigate the efficacy of prophylactic parenteral nimodipine treatment in VS surgery (clinical trial registration nos. 2009-012088-32 [www.clinicaltrialsregister.eu] and DRKS 00000328 ["AkNiPro," drks-neu.uniklinik-freiburg.de/drks_web/]).[13] This investigator-initiated trial had been positively reviewed by the local ethics committee of each center. The study enrolled patients 18 years of age or older who harbored a VS. The main exclusion criteria were contraindications against nimodipine treatment, Grade VI preoperative facial nerve function according to the House-Brackmann grading scale, surgery for recurrent VS, and neurofibromatosis Type 2.[5] Gross-total resection via a retrosigmoid approach with preservation of facial and cochlear nerve function was the goal of each procedure performed by experienced surgeons at 7 German university hospitals. Intraoperative neurophysiological monitoring including brainstem auditory evoked potentials, continuous facial nerve electromyography, and direct facial nerve stimulation were used in all surgeries. The diagnosis of VS was confirmed histopathologically in all patients. For the present investigation both treatment groups were pooled to compare hearing abilities in the early postoperative course and 1 year after surgery. No data regarding the contralateral side were evaluated.

Outcomes, Follow-Up, and Blinding

Cochlear nerve function was determined by pure-tone audiometry and speech discrimination, which was performed preoperatively, in the early postoperative course (between the 3rd and 7th postoperative day), and 12 months after surgery, and was analyzed by an independent otorhinolaryngologist and classified using the Gardner-Robertson scale.[4] Tumor size (according to the Koos grading system) and extent of resection were evaluated on the basis of axial contrast-enhanced T1-weighted MRI performed preoperatively and 3 months after surgery.[6]

Statistical Methods

Cochlear nerve function in the early postoperative course in comparison with the findings 1 year after surgery were analyzed using the chi-square test in the total study population and in the subgroup of individuals with a preserved cochlear nerve; p values less than 0.05 were considered significant.

Results

Participant Flow

A total of 112 patients were enrolled. Nine patients dropped out for the following reasons: withdrawn consent (n = 5), no surgery performed (n = 1), meningioma (n = 1), trigeminal schwannoma (n = 1), and death (n = 1). In 1 patient cochlear nerve function information for the early postoperative course was missing. Therefore, 102 patients were suitable for statistical analysis (Fig. 1). Morphological preservation of the cochlear nerve was achieved in 66 patients (65%).

Baseline Data

The mean age of the 102 patients was 49 years and in the series with preserved cochlear nerve it was 47 years. Fifty-seven patients in the total series and 35 patients in the series with a preserved cochlear nerve were female. The percentage distributions of tumor sizes in the total series were 2% for Koos Grade I, 33% for Koos Grade II, 41% for Koos Grade III, and 24% for Koos Grade IV and in the patients with a preserved cochlear nerve they were 3% for Koos Grade I, 42% for Koos Grade II, 44% for Koos Grade III, and 11% for Koos Grade IV. The percentage distributions of preoperative hearing (according to the Gardner-Robertson classification system) in the total series were 35% for Grade I, 28% for Grades II and III, 5% for Grade IV, and 5% for Grade V and in the group with a preserved cochlear nerve they were 42% for Grade I, 29% for Grade II, 24% for Grade III, 2% for Grade IV, and 3% for Grade V. Preoperative facial nerve function was intact (House-Brackmann Grade I) in 99 patients overall and 64 patients with a preserved cochlear nerve and mildly impaired (House-Brackmann Grade II) in 3 patients overall and in 2 patients with a preserved cochlear nerve (Table 1). Extent of resection in the group with preserved cochlear nerve was documented as complete in 61 patients and as subtotal (3–10 mm) in 5 patients.

Stability of Hearing Preservation and Regeneration Capacity of the Cochlear Nerve

Hearing preservation was achieved in 34 of 102 patients (Table 2). In 9 patients, hearing ability changed between the early postoperative course and 1 year after surgery. An improvement of 1 class according to the Gardner-Robertson scale was observed in 4 patients and an improvement of 2 classes in 1 patient. Four of these patients were treated prophylactically with nimodipine. A deterioration of 1 class was documented in 2 patients and a deterioration of 2 classes in another 2 patients. Three of these patients were treated prophylactically with nimodipine. Three patients with preserved hearing in the early postoperative course (2 with Gardner-Robertson Class III and 1 with Gardner-Robertson Class IV hearing) lost hearing on the operated side during follow-up (Tables 3 and 4). Table 5 shows the postoperative hearing with respect to the tumor sizes and extent of resection.

There was a very strong association between hearing abilities in the early postoperative course and 1 year after surgery for both patient groups, the 102 patients overall ($p < 0.001$), and in the 66 patients with a preserved cochlear nerve ($p < 0.001$). Prophylactic nimodipine had no impact on the stability of hearing preservation. Changes in hearing abilities were observed in both groups.

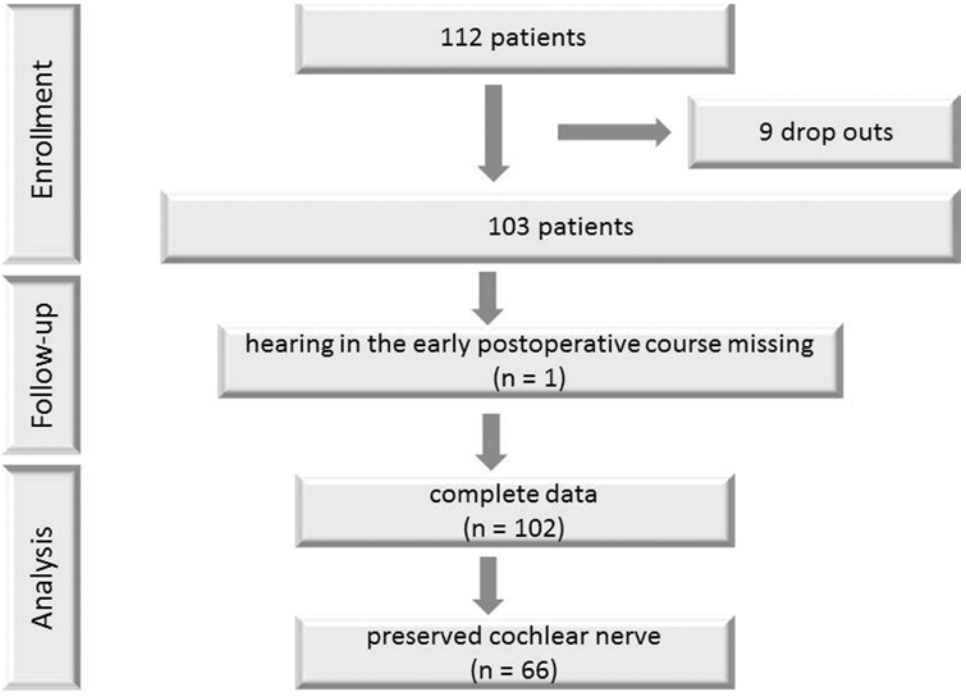

FIG. 1. Participant flow diagram.

Facial nerve function 1 year after surgery was significantly (p = 0.014) better (House-Brackmann Grade I or II compared with House-Brackmann Grade III–VI) in the group with preserved hearing. As expected, tumor sizes were significantly (p = 0.004) smaller (Koos Grade I and II compared with Koos Grade III and IV) in patients with preserved hearing (Table 2).

TABLE 1. Baseline data

Variable	All Patients (n = 102)	Patients w/ Preserved Cochlear Nerve (n = 66)
Age in yrs		
Mean	49	47
Range	18–75	18–75
Sex		
Female	56%	53%
Male	44%	47%
Koos grade		
I	2	2
II	34	28
III	42	29
IV	24	7
GR class		
I	35	28
II	29	19
III	29	16
IV	5	1
V	4	2
HB grade		
I	99	64
II	3	2

GR = Gardner-Robertson; HB = House-Brackmann.

Discussion

This is the first prospective, randomized, multicenter Phase III trial investigating the stability of hearing preservation and the regeneration potential of the cochlear nerve after VS surgery. Although there was a very strong association between hearing abilities in the early postoperative course and 1 year after surgery for both patient groups (i.e., the group viewed as a whole and the group with a preserved cochlear nerve), a limitation of the current study is that long-term stability of preserved hearing longer than 1 year after VS surgery remains unclear.

Late hearing loss is a known phenomenon following VS surgery. However, its exact incidence and pathophysiological mechanisms have yet to be determined.[11] Late hearing loss was observed in 3 patients in the current study (3%). These findings concur with those in the retrospective study of Wang et al.[17] A majority of their 103 consecutive patients with preserved hearing after microsurgical treatment of VS using the middle fossa approach experienced stability of their preserved hearing at the 5-year follow-up. In contrast, the retrospective study of Chee et al. including 30 patients with tumors smaller than 2 cm following excision via a retrosigmoidal approach showed that over time serviceable hearing deteriorated from 76.6% in the early postoperative course to 56.7% in the late postoperative period (average follow-up period of 113.6 months).[3] Shelton et al. reported significant deterioration of hearing in 14 of 25 patients following a middle fossa approach for

TABLE 2. Hearing preservation and facial nerve function with respect to tumor sizes*

HB & Koos Grades	Hearing Preservation Immediately Postop (n = 34)	No Hearing Preservation Immediately Postop (n = 68)
Preop HB grade		
I	34	65
II	0	3
1-yr postop HB grade		
HB Grade I	28	41
Koos grade		
I	1	0
II	15	16
III	11	17
IV	1	8
HB Grade II	4	9
Koos grade		
I	0	0
II	2	0
III	2	6
IV	0	3
HB Grade III	1	13
Koos grade		
I	0	1
II	0	1
III	0	6
IV	1	5
HB Grade IV	1	3
Koos grade		
I	0	0
II	1	0
III	0	0
IV	0	3
HB Grade V	0	2
Koos grade		
I	0	0
II	0	0
III	0	0
IV	0	2

* Values are number of patients.

VS resection with a mean follow-up time of more than 8 years. Only 1 of the 14 patients had a similar hearing loss in the contralateral ear.[14] Tucci et al. showed in 5 of 17 patients either a significant increase in pure-tone average or a significant decrease in speech recognition over 1.5–8 years.[16] To summarize, existing retrospective literature has revealed divergent results concerning stability of hearing preservation rates following VS surgery. The prospective data of the presented study support the assumption that preserved hearing after VS surgery remains stable at least between the early postoperative course and 1-year follow-up. Secondary deterioration of hearing rates after SRS is well recognized. Carlson et al. reported Kaplan-Meier estimated rates of serviceable hearing at 1, 3, 5, 7, and 10 years following SRS of 80%, 55%, 48%, 38%, and 23%, respectively. Nakamizo et al. showed that the long-term preservation of serviceable hearing after VS surgery was achieved in 86% (5 years) respectively in 72% (7 years) of patients.[10] Secondary deterioration of hearing therefore appears to be slightly more prevalent after SRS compared with its onset after surgery.[2] Long-term risks for hearing deterioration following surgery or SRS of VS have not been defined so far, and the diverging results of retrospectively performed studies highlight that further data from prospective trials are mandatory.[17]

TABLE 3. Comparison between the immediately postoperative outcomes and 1 year after surgery in the entire group (n = 102)*

HB Grade	1 Yr Postop GR Class†				
Immediately Postop	I	II	III	IV	V
I	**5**	1	0	0	0
II	1	**8**	0	0	0
III	0	3	**14**	0	2
IV	0	0	0	**1**	2
V	0	0	1	0	**64**

* There was a very strong association between hearing abilities in the early postoperative course and 1 year after surgery ($p < 0.001$, chi-square test).
† Boldface type indicates no change of GR classification.

Cranial nerve regeneration potential after VS surgery appears to differ largely. It is well known that facial nerve function can regenerate between the early postoperative course and 1 year after surgery. Arriaga et al. reported a series of 515 patients who had undergone VS surgery and analyzed the rate of acceptable facial nerve function (House-Brackmann Grades I–IV) at 3 postoperative time points. Facial nerve function differed significantly at those time points ($p < 0.001$), reaching its highest functional level at least 1 year after surgery.[1] In contrast, the results of the presented study revealed no differences between the cochlear nerve function in the early postoperative course and 1 year after surgery pointing to a lack of regenerative potential of the cochlear nerve. Reasoning for this is only speculative and possibly multifactorial. However, there is a distinct anatomical difference between the cochlear and the facial nerve. Lang reported different lengths for the cen-

TABLE 4. Comparison between the outcomes immediately postoperative and 1 year after surgery in patients with a preserved cochlear nerve (n = 66)*

HB Grade	1 Yr Postop GR Class†				
Immediately Postop	I	II	III	IV	V
I	**5**	1	0	0	0
II	1	**8**	0	0	0
III	0	2	**11**	0	2
IV	0	0	0	**1**	2
V	0	0	1	0	**32**

* There was a very strong association between hearing abilities in the early postoperative course and 1 year after surgery ($p < 0.001$, chi-square test).
† Boldface type indicates no change of GR classification.

TABLE 5. Postoperative hearing with respect to tumor size and extent of resection in the 66 patients with a preserved cochlear nerve

Koos Grade & GR Class	No. of Patients	Extent of Resection
Koos Grade I		Complete (n = 2)
GR class		
I	0	
II	1	
III	0	
IV	0	
V	1	
Koos Grade II		Complete (n = 25), remnant of 3–10 mm (n = 3)
GR class		
I	1	
II	7	
III	7	
IV	1	
V	12	
Koos Grade III		Complete (n = 27), remnant of 3–10 mm (n = 2)
GR class		
I	5	
II	3	
III	4	
IV	0	
V	17	
Koos Grade IV		Complete (n = 7)
GR class		
I	0	
II	0	
III	1	
IV	0	
V	6	

tral myelin segment between the facial (2.05 mm) and the vestibulocochlear (10 mm) nerves.[7] In contrast to cochlear nerves, which might already be dysfunctional or nonfunctional facial nerves still function when they are already severely flattened and spread out by the tumor. Intraoperative damage to the central myelin portion of the vestibulocochlear nerve is therefore more likely, resulting in a missing functional recovery and disturbs signal transmission in the complete cochlear nerve or in individual neurons.[8] Deceleration of signal transmission in individual cochlear neurons impairs the temporal coherence of the impulses, thus affecting speech discrimination.[9] Additional reasons might be differences between motor and sensory nerves and different blood supplies. Damage to the internal auditory artery results in loss of function of the cochlea and of acoustic evoked potentials including wave I.

Nevertheless, an analysis of published literature on hearing preservation following VS surgery including 62 studies and a total of 998 patients showed that the follow-up in these studies ranged from 6 months to 7 years.[15] Considering the results of the presented prospective trial the average duration of studies investigating hearing preservation following VS surgery should be standardized.

Conclusions

There is no significant change of cochlear nerve function between the early postoperative course and 1 year after VS surgery. The result of hearing performance, as evaluated by early postoperative audiometry studies after VS surgery seems to be a reliable prognosticator for future hearing ability.

Acknowledgments

We thank Monika Göttlich, Jenny Hampel, Melanie Querfurt, Cornelia Seiffert, and Christin Zöller, study nurses, for administrative contributions and assistance in performing this study.

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Disclosures

Support for this study was provided by Bayer Health Care, Germany, the German Federal Ministry of Education and Research (BMBF 1315883), the Wilhelm-Roux-Program (FKZ 19/07, FKZ 23/26) of the University Halle-Wittenberg, Germany, and the Acoustic Neuroma Brain Tumor and Interest Group, Switzerland.

Author Contributions

Conception and design: Scheller. Acquisition of data: Scheller, Tatagiba, Gharabaghi, Ramina, Ganslandt, Bischoff, Matthies, Westermaier, Antoniadis, Pedro, Rohde von Eckardstein, Kretschmer. Analysis and interpretation of data: Scheller, Zenk, Strauss. Drafting the article: Scheller, Strauss. Critically revising the article: Scheller, Strauss. Reviewed submitted version of manuscript: Scheller. Approved the final version of the manuscript on behalf of all authors: Scheller. Statistical analysis: Wienke. Administrative/technical/material support: Strauss. Study supervision: Scheller, Strauss.

Correspondence

Christian Scheller, Department of Neurosurgery, Martin-Luther University of Halle-Wittenberg, Ernst-Grube-Str. 40, 06097 Halle (Saale), Germany. email: christian.scheller@medizin.uni-halle.de.