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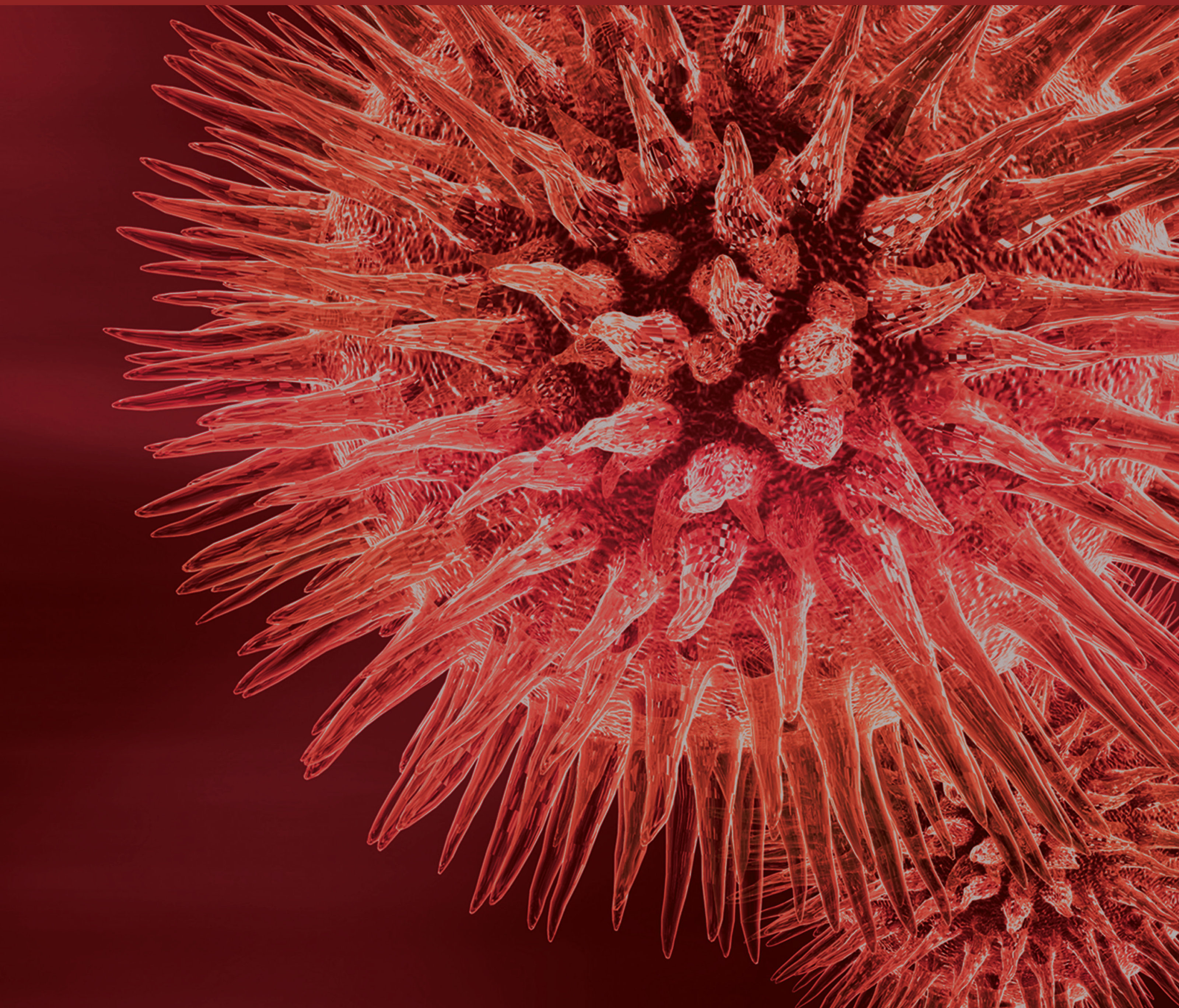
Otolaryngology, Head and Neck Surgery

Guest Editors: Mu-Kuan Chen, Robert L. Ferris, Peter Hwang, Tetsuya Ogawa, Michael Tong, and Tsung-Lin Yang



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Editorial

Otolaryngology, Head and Neck Surgery

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The medical fields of otolaryngology and head and neck are evolving rapidly. For the past years, much new knowledge and many techniques have been introduced into the basic researches and clinical practices of otolaryngology and head and neck for a comprehensive understanding of diseases and practical clinical applications. Just recall the recent development of many medical devices designed for enabling techniques and surgery, including the newly designed hearing aids and coagulative surgical instruments; the trend of newly developed technologies is likely to be a constant flow. In addition, many distinct diagnostic modalities and research approaches have also been invented to investigate the underlying phenomenon and mechanisms of diseases. The cornucopia of all novel technologies and approaches serve as important blessings for both doctors and patients in the fields of otolaryngology and head and neck. This special issue is to showcase the diversity and advances in recent progress that contributes to the different subspecialties of otolaryngology and head and neck surgery.

Recent advances both in basic and clinical studies have introduced new concepts and technologies to be applied in otolaryngology and head and neck surgery. In this special issue, several special topics regarding the applications of hearing devices and vestibular evoked myogenic potential, the surgical tools for potentiating the procedure of thyroidectomy, and identification of the novel therapeutic agents and underlying mechanism of head and neck cancer will be presented. One article of each field will be selected as the representative example of the progress. These articles will demonstrate the current advance of medical development in otolaryngology and head and neck surgery.

An article will discuss the role of screening of cognitive function in old adults because of the efficacy of using hearing aid assistance. Previous studies had found that hearing loss is associated with poorer cognitive function. This study examined cognitive function in elderly hearing aid users. The study investigated whether the screening cognitive function should be considered in the individuals with hearing impairment. On the other hand, for the adult patients with unilateral microtia and atresia, many devices of implantable hearing amplification have been created for hearing ability rehabilitation. An article in this special will give a comprehensive review of the development, the progress, and the technical advantages of the different types of implantable hearing devices available. After understanding the pros and cons of each specific type of devices, it is easy to make the clinical decision of recommending a device to match the need of patients.

Apart from the hearing ability, the vestibular function, another essential component of the 8th cranial nerve, has also drawn much attention of researchers and clinicians. An article included in this special issue will demonstrate the use of skull tap vestibular evoked myogenic potentials of diagnosing cerebellopontine angle tumor. The tap vestibular evoked myogenic potentials (tap VEMPs) are another method of inducing VEMPs by tapping method in contrary to the traditional one of using auditory stimulation. In the diagnosis and pretreatment evaluation of cerebellopontine angle tumor, the involvement and the extent of tumor are critical for the following treatments and can be clearly identified by clinical physiological examinations. In this article, the tap VEMPs could be successfully induced in some of the recruited patients. It shows a potential of clinical utility of combining both AC VEMP and tap VEMPs in the evaluation of patients suffering from cerebellopontine angle tumors.

With the innovation of many tools of basic research, the understanding of molecular and cellular mechanism has achieved a profound advancement in the head and neck cancer. An article in this special issue will address the importance of finding novel and potential therapeutic reagents that target the mitochondria-dependent pathway. Tanshinone IIA (Tan IIA) is an active phytochemical retrieved from the dried root of *Salvia miltiorrhiza* Bunge. It has been documented to be an antiproliferative reagent on various human cancer cells. This research aims to evaluate its role in nasopharyngeal carcinoma. By showing the effects of antiproliferation and apoptosis induction, Tan IIA is believed to be a potential candidate of exploring the anticancer drugs. On the other hand, bleeding is always a major concern in the procedure of thyroidectomy. Many distinct skills have been developed to control bleeding, and multiple devices and surgical instruments have been created to facilitate the hemostasis. Ligasure and bipolar thermofusion are two surgical tools that have been widely used to achieve hemostasis during thyroidectomy. In an article included in this special issue, the comparison between these two techniques will be addressed when more than 2122 lobectomies were performed within 8 years. The experience earned from the large patient population provides convincing evidence of using these distinct surgical tools for bleeding control of thyroidectomy.

The researches and development of new technologies and knowledge of the field of otolaryngology and head and neck surgery are committed to improving excellent medical care in all subspecialties to the patient groups worldwide. It is also committed to educating the health provider and investigators in the basics and the clinical practices of otolaryngology and head and neck surgery for the further progress in each subspecialty. The current knowledge and understanding have led to the exploration of new mechanism underlying the diseases and also development of novel therapies, surgical techniques, and tools to change the way of clinical practices. It is believed that the evolvement of medical researches and clinical health care may substantially improve the clinical outcomes and life quality of patients.

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Research Article

Screening of Cognitive Function and Hearing Impairment in Older Adults: A Preliminary Study

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Background. Previous research has found that hearing loss is associated with poorer cognitive function. The question is that when a hearing impairment is being compensated for by appropriately fitted monaural hearing aids, special precautions are still needed when screening cognitive function in older adults. *Objective*. This research examined cognitive function in elderly hearing aid users who used monaural hearing aids and whether the presence of a hearing impairment should be accounted for when screening cognitive function in these individuals. *Methods*. Auditory thresholds, sentence reception thresholds, and self-reported outcomes with hearing aids were measured in 34 older hearing aid users to ensure hearing aids were appropriately fitted. Mini-Mental State Examination (MMSE) results obtained in these participants were then compared to normative data obtained in a general older population exhibiting similar demographic characteristics. Stepwise multiple regression analyses were used to examine the effects of demographic and auditory variables on MMSE scores. *Conclusions*. Results showed that, even with appropriately fitted hearing aids, cognitive decline was significant. Besides the factors commonly measured in the literature, we believed that auditory deprivation was not being fully compensated for by hearing aids. Most importantly, screening of cognitive function should take into account the effects of hearing impairment, even when hearing devices have been appropriately fitted.

1. Hearing Loss and Cognitive Function

Besides hearing impairment, decline in cognitive functions is also commonly observed in the aging population. Recent studies showed that reduced auditory input due to a hearing impairment is also associated with greater declines in cognitive function in older adults than those without hearing loss.

Lin and colleagues [1] showed that older adults with hearing impairment would have a 24% increased risk for declines in cognitive function over time and may experience a 30 to 40% faster decline than those without a hearing loss. Furthermore, this decline was related to the degree of hearing loss measured at baseline. Lin [2] further reported that a mild to moderate hearing impairment in adults aged 60 to 69 years was associated with poorer executive function and psychomotor processing, while Lin et al. [3] reported that greater hearing loss in older adults was associated with not only lower scores in memory test, but also poorer mental status and executive function, such as shifting attention and inhabiting. Similar findings were reported by Wingfield and Tun [4] that those with a mild to moderate hearing loss had greater difficulties with recall, which could be a reflection that effortful listening took away resources available for storing information in working memory. Tay et al. [5] also found that, among adults of 50 years of age and over, those with a moderate to severe hearing loss exhibited slightly poorer Mini-Mental State Examination (MMSE) score than those with normal hearing. Results from Lindenberger and Baltes [6] and Schneider et al. [7] concur with these findings.

Various hypotheses have been proposed to explain this decline associated with hearing impairment. While there could be a common neuropathologic origin that underlies both hearing and cognitive decline, the hearing loss could possibly lead to a cycle of multimorbidity in different areas or may interact with other risk factors to accelerate cognitive declines [1]. The hearing impairment may also result in a deprivation of auditory inputs, leading to structural or functional changes related to cognitive function [8, 9]. Trying to fill in the gaps caused by missing speech information may result in a shortage of resources for information encoding and storage in an already reduced working memory in older adults [7, 9–11]. With greater hearing loss, speech understanding is more likely to be adversely affected. Speech understanding becomes effortful, resulting in withdrawal from social interactions, which could precipitate further cognitive declines [8]. Finally, some studies have shown that tests that are administered auditorily may show a cognitive deficit because older individuals are being disadvantaged by their disability [9]. One important question, therefore, is whether older adults with appropriately fitted hearing aids are able to demonstrate cognitive ability comparable to that of the general population when cognitive measures are being administered using verbal instructions.

2. Hearing Aid and Cognition

A search of the literature revealed only a small number of studies that had examined the effects of hearing aid use on cognitive function in the elderly population; findings were however inconclusive. For example, in a randomized control trial, Mulrow et al. [13] found that cognitive function measured on the Short Portable Mental Status Questionnaire (SPMSQ) improved after four months of hearing aid use in a group of older adults (mean age above 70 years, $n = 13$) with an average hearing loss of about 50 dB HL. Using the MMSE, Acar et al. [14] also showed significant improvement in cognitive function in a group of elderly subjects (mean age about 70 years) after three months of hearing aid use. However, because the cognitive function tests in both studies were administrated verbally prior to hearing aid fitting, the reduced cognitive function could have been confounded by the hearing disability.

While Lin [2] also found that the use of hearing aids was positively associated with cognitive function, Young Choi et al. [15] demonstrated significant changes in the total scores measured on the visual verbal learning test (VVLT) after six months of hearing aid use, compared to a control group of nonusers. Due to the small sample sizes, the findings in these studies should be interpreted with some caution.

On the contrary, other studies were not able to demonstrate improved cognitive function after six to 12 months of hearing aid use. Tesch-Römer [16] was not able to find changes in executive function and memory after six months of hearing aid use by those with a mild to moderate hearing loss. They attributed the lack of changes to subjects not being randomly assigned and six months of hearing aid use being too short to cause a significant change. In another study, Van Hooren et al. [17] evaluated cognitive function in terms of processing speed, reasoning, memory, knowledge, and verbal fluency after 12 months of HA use. No improvement was observed, compared to a control group of non-hearing aid users.

In a literature review of relevant studies, Kalluri and Humes [18] pointed out that there was a lack of strong evidence on the long-term effects of hearing aids on cognition. Furthermore, given that many older adults did not pursue intervention for 8 to 12 years after the first notice of a hearing impairment [17], a longer duration of hearing aid use is probably needed to demonstrate any effects of reversal of cognitive decline [16]. Among the majority of the studies, there was also a lack of information on whether amplification was well fitted and therefore it was uncertain whether the deficit in hearing had been appropriately compensated for.

Given the limitations associated with previous research, the present study controlled for the effects of hearing aids by documenting whether they have been appropriately fitted and administering the cognitive function tests with hearing aids at optimal settings. The subject sample was typical of the vast majority of hearing aid users in Hong Kong and in many developing countries, where, due to low income, they have opted for monaural hearing aids. They also exhibited poorer hearing than hearing device users in Western societies because Hong Kong Cantonese speakers were often not motivated to seek help until their hearing loss has exceeded 40 dB HL [18]. More severe hearing loss is related to distortion in hearing that could not be fully compensated for by the use of hearing aids and may precipitate greater declines in cognitive function [3]. The severity of hearing loss is such that the unaided side was also being deprived of auditory inputs. Thus, the characteristics of our subject sample were such that we expected to observe a decline in cognitive function. Our results on the cognitive function test were compared with norms obtained on the general older population with similar demographic characteristics [12]. Whether cognitive function was related to demographic (i.e., age and gender) and auditory variables (i.e., pure tone thresholds and speech reception thresholds) was examined. These results may have important implications on the screening and diagnosis of cognitive decline in those with a hearing impairment.

3. Methodology

3.1. Participants. A total of 34 hearing impaired elderly Cantonese speakers, aged above 60 years and exhibiting a bilateral mild to severe degree of hearing loss, regardless of the nature of the loss, were recruited. They were current users who had been wearing a monaural hearing aid for at least one year, to allow for adaption to amplification. Consecutive medical records at the Audiological Centers at the Prince of Wales Hospital (PWH) and Alice Ho Miu Ling Nethersole Hospital were reviewed for subject recruitment. Elderly individuals with reportedly poor physical or mental health, non-Cantonese speakers, and those not meeting the inclusion criteria were excluded.

Among the participants, 73.5% were married, 5.9% were single, 17.6% were widowed, and 2.9% were divorced/separated. In terms of other otologic conditions, 52.9% reported experiences of tinnitus, 21.2% had dizziness, and 32.4% had noise exposure. In terms of health issues, 8.8% reported having diabetes, 52.9% had high blood pressure, and

Table 1: Demographic variables of the subjects in the present study and the comparison reference population in Wong et al. [12].

Demographic variables	Present study	Wong et al. [12]
Age (years)	69.9 (5.6)	69.2 (7.2)
Gender (n)	15 male 19 female	20 female 20 male
Educational level (years)	7.3 (3.5)	7.3 (4.5)
Duration of hearing loss (years)	17.8 (16.5)	N/A
Duration of hearing aid use (years)	6.9 (4.3)	N/A

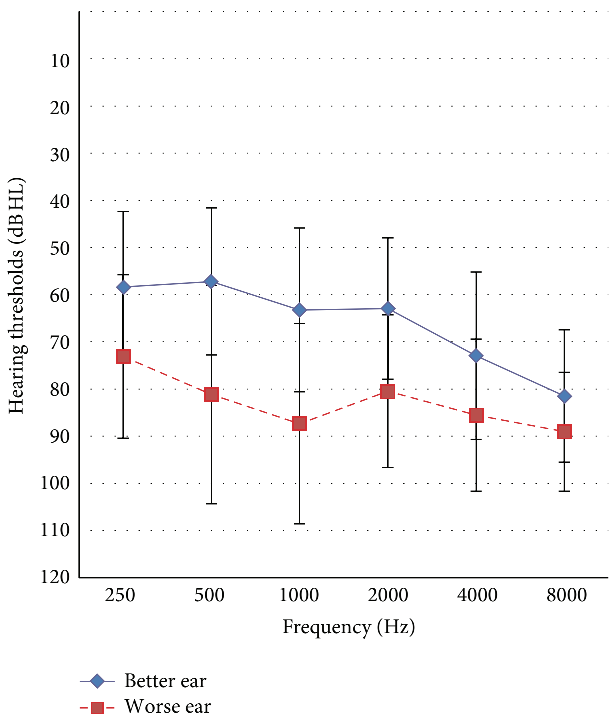

Figure 1: Audiometric thresholds are shown with standard deviations as error bars.

17.6% had heart problems but, overall, 88.2% of the participants reported average to good health; only 11.8% reported poor health. Participants were all community dwellers.

Table 1 shows other demographic information of the participants, suggesting that on average they had a lower secondary education. Without hearing aids, these subjects exhibited a hearing loss of 64.9 dB HL (SD = 15.2), averaged at 500, 1000, and 2000 Hz in the better ear and 80.7 dB HL (SD = 16.2) in the worse ear (see Figure 1). While on average participants had noted a hearing impairment for almost 17.8 years, they had only worn hearing devices for the past 6.9 years. In other words, they had waited for about 11 years before obtaining intervention. Table 1 also shows demographic characteristics of the normative sample for comparison with results obtained in the present study.

3.2. Materials and Equipment. All of the audiometric testing was conducted using a GSI 61 audiometer. Ear specific unaided air conduction thresholds at 0.25, 0.5, 1, 2, 4, and 8 kHz and ear specific bone conduction thresholds at 0.5, 1, 2, and 4 kHz were obtained in both ears using a TDH-49 headphone. Soundfield audiometric thresholds were obtained using warble tones at 250, 500, 1 k, 2 k, 3 k, and 4 kHz in both the aided and unaided conditions.

The Cantonese Hearing In Noise Test was used to measure speech recognition in quiet and in three noise conditions [19]. The noise conditions were (1) speech front (SF), where speech and noise were both presented from the front speakers; (2) noise on the hearing aid side (N-HA), where speech was from the front and noise was from the side where the hearing aid was worn; and (3) noise on the non-hearing aid side (N-NA), where speech was from the front but noise was being presented on the side where a hearing aid was not worn. The speech was adjusted adaptively, based on the correctness of the responses. For testing in noise, the noise level was fixed at 65 dB(A). The speakers were placed at one meter away from the center of the head of the subjects. The HINT system was used to present the stimuli and score the responses. A sentence recognition threshold (SRT) in quiet was defined as the signal level, in dB(A), where a participant is able to repeat 50% of the sentences correctly. A SRT in noise was defined as the signal-to-noise ratio (in dB S/N), where the participant is able to repeat 50% of the sentences correctly. Aided and unaided SRTs were obtained. Audiological assessment and the CHINT were conducted in a sound treated room at the Audiology Centre of the PWH that met the ANSI S3.1-1991 standard for maximum permissible ambient noise levels.

Participants also filled in the Chinese version of the International Outcome Inventory of Hearing Aid (IOI-HA) to evaluate self-reported outcomes with hearing aids in seven domains: usage, benefit, residual activity limitation, satisfaction, residual participation restriction, effects of the hearing impairment on significant others, and quality of life [20]. A maximum score of 5 is possible for each domain, which indicates the best outcomes possible with amplification.

The audiological assessment, SRTs, and IOI-HA were administered to ensure that the hearing aids were fitted properly and provided optimal outcomes. The MMSE was conducted to assess cognitive function [21]. The MMSE evaluates cognitive function in the following domains.

(1) "Orientation to time" measures the participant's sense of date and time, to yield a maximum score of five points.

(2) "Orientation to place" evaluates the patient's sense of location, to yield a maximum score of five points.

(3) "Registration" accesses the ability to repeat a short list of common items and a maximum score of three points is possible.

(4) "Attention and calculations" evaluates arithmetic ability by having the patient count backward from 100 using a step size of 7; a maximum score of five is possible.

(5) "Recall" evaluates whether the individual is able to recall the items from "Registration," to yield a maximum score of three.

(6) "Language" measures whether the patient could name two common objects; a maximum score of two points is possible.

(7) "Repetition" involves having the individual repeat a short phrase; one point is given for a correct response.

(8) "Complex Commands" involves having the individual follow instructions to perform a task or draw, to yield a maximum score of six points.

The total MMSE score ranges from 0 to 30 and the MMSE took less than 10 minutes to be completed. The Cantonese version of the MMSE [22] was administered with the hearing aids of the participants adjusted to a level optimal for speech understanding in a quiet sound treated room.

3.3. Procedures. Research ethics were approved by the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (CREC) (Ref. number CRE-2013.481). Informed consent was obtained at the start of the data collection process. Demographic data, including age, gender, marital status, educational level, hearing and otological history, and medical history, were documented. Electroacoustic measurements were conducted on the hearing aids to ensure they were in proper working order. Hearing aids were adjusted once to settings optimal for speech understanding, prior to administering tests. Hearing assessments, cognitive assessments, and the IOI-HA were then administered in random orders. The testers took special care (e.g., repetition, speaking at a slower rate, and enunciating each word clearly) to ensure that the test instructions were heard clearly. The whole test procedure took approximately two hours. To avoid fatigue, breaks were given to subjects after one hour of assessment or upon their request. A transportation allowance of HKD 200 (or USD 25) was provided.

4. Results

Soundfield pure tone average hearing thresholds improved significantly from 62.7 dB HL (SD = 13.6) unaided to 41.8 dB HL (SD = 7.3) aided; $t(31) = 11.3$; $P < .001$; Cohen's $d = 2.4$. With hearing aids, a significant improvement, with small to large effect sizes, in SRTs obtained in quiet and in all three noise conditions was noted (see Table 2). The improvement in SRT was the greatest when the noise was presented to the side of the nonaided ear and speech was from the front (N-HA condition).

Results from the IOI-HA are reported in Figure 2 and suggest that these subjects used hearing aids for an average of about 4 to 8 hours per day. The ratings for other items ranged from 3.71 to 4.09, out of a maximum of 5, suggesting that these participants were on average obtaining quite a lot of benefit, were experiencing slight difficulty with hearing, and thought that hearing aids were worth the trouble, that hearing difficulties had affected their life slightly, and that significant others were only slightly bothered by the hearing impairment. The ratings on quality of life were lower (mean rating of 3.24, out of a maximum of 5), suggesting that hearing aids have made their enjoyment of life slightly to quite a lot better.

Table 1 shows that the demographic characteristics of the subjects in the current study are quite similar to those obtained on the general older population in Hong Kong, providing justification for their results to be compared. Table 3 shows the results from the MMSE. An independent samples t-test revealed a significant difference in MMSE total scores; $t(72) = -3.18$; $P < .005$; Cohen's $d = .72$. Domain scores could not be compared because of a lack of normative data.

As MMSE total scores were lower among those with hearing impairment and using hearing aids, we attempted to explore whether cognition was related to demographic and auditory variables. These variables included age, gender, aided soundfield average hearing thresholds, duration of hearing loss, duration of hearing aid use, and aided SRTs obtained in quiet and in noise as a composite score. The noise

Table 2: Mean sentence reception thresholds (SRTs) and the standard deviations (in brackets). Paired sample t-tests were conducted to compare SRTs obtained in the aided and unaided conditions; statistically significant differences between aided and unaided SRTs were found in all test conditions ($^{*}P < .001$, 2-tailed).

Test conditions	Unaided	Aided	t-statistics	Cohen's d
Quiet (dB A)	68.9 (9.9)	59.7 (10.3)	6.0*	1.05
Noise front (NF) (dB S/N)	8.9 (4.7)	6.0 (4.7)	5.6*	.77
Noise on the hearing aid side (N-HA) (dB S/N)	8.3 (6.4)	6.4 (5.2)	2.9*	.36
Noise on the non-hearing aid side (N-NA) (dB S/N)	8.2 (5.5)	4.6 (5.7)	4.0*	.62

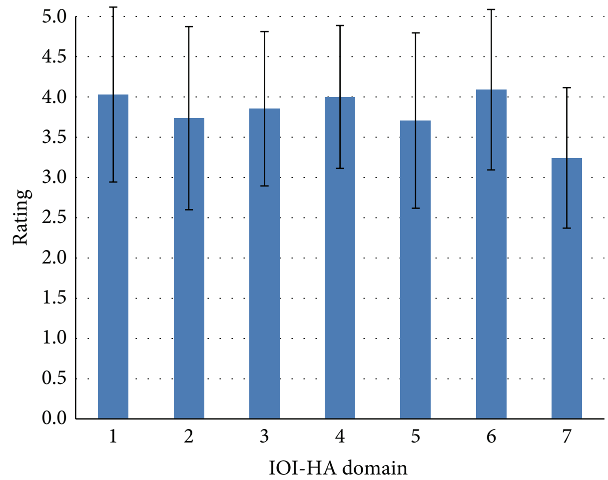

Figure 2: Mean IOI-HA ratings are shown with standard deviations as error bars. The respective domains are 1 = usage, 2 = benefit, 3 = residual activity limitation, 4 = satisfaction, 5 = residual participation restriction, 6 = effects of the hearing impairment on significant others, and 7 = quality of life. A maximum rating of 5 indicates best outcomes with the respective domain.

Table 3: Results on the MMSE from the present study and the comparison reference population in Wong et al. [12].

	Present study	Wong et al. [12]
Orientation to time	4.8 (.50)	N/A
Orientation to place	4.7 (.65)	N/A
Registration	2.8 (.53)	N/A
Attention and calculations	3.7 (1.69)	N/A
Recall	1.6 (1.12)	N/A
Language	1.9 (.17)	N/A
Repetition	.97 (.17)	N/A
Complex Commands	5.5 (.66)	N/A
Total score	26.4 (3.09)	28.2 (1.5)

composite SRT was calculated using the following formula: [(noise front SRT × 2) + noise hearing aid side SRT + noise non-hearing aid side SRT]/4 [19]. Stepwise multiple regression analyses were conducted with these as auditory variables and MMSE total and domain scores as dependent variables. Table 4 shows the results and indicates that only five of the eight MMSE domains were predicted by one of the auditory variables, with small to medium effects sizes. That is, Orientation to time and place could be predicted by noise composite SRT; aided soundfield thresholds predicted scores on Registration and Complex Commands. Duration of hearing aid use contributed to scores on Repetition. Other regression models were not significant.

5. Discussion

Overall, results from audiological assessment and the CHINT suggest that hearing aids brought significant benefits in terms of improving sensitivity to sounds and speech reception. Results from the IOI-HA also revealed that participants were using their hearing aids consistently and reported very positive outcomes with the hearing aids. In fact, patient records showed that their hearing aids were adjusted to the satisfaction of the users and further adjustment was not needed. Thus, we were ensured by these results that the hearing aids had been appropriately fitted.

Results obtained on the MMSE showed slight but significant decline in overall cognitive function (with moderate to large effect size) among the subject population. Interestingly, out of the eight domains measured on the MMSE, auditory factors (duration of hearing aid use, aided noise composite SRTs, and aided soundfield thresholds) predicted the scores on five MMSE domains that required understanding of the verbal instructions. Auditory or demographic variables did not predict scores measured on Attention and calculations, Recall, or Language. Nonetheless, these findings suggested that hearing and cognition are intricate aspects of the aging process.

While the current study could not delineate which of the hypotheses mentioned above made greater contribution to the results, we would elaborate on three issues here. First, there was deprivation of auditory inputs in the participants. As mentioned above, the users waited an average of 11 years before they obtained hearing aids. The long-term deprivation in auditory inputs prior to hearing aid fitting might not be fully reversible even with the use of hearing aids. Similarly, monaural hearing aid use might have resulted in the unaided ear being deprived of auditory inputs. Although it would be difficult to control the duration of the wait to get intervention, future research could compare cognitive outcomes between monaural and binaural users.

Second, one could argue that more gain could be provided to further optimize the hearing. Although the participants felt that their hearing aids were fitted appropriately, aided hearing thresholds obtained in the soundfield were improved to 42 dB HL, which meant that some of the weaker signals were not audible. When the hearing disability is not being fully compensated for, the efforts spent on understanding conversations may result in fewer resources being left for storing information [23]. Listening in noise is particularly difficult when extra resources have to be allocated to make up the missing speech information that was being masked. However, increasing gain was not considered appropriate among the participants, as patient records showed that they were not able to tolerate further increase in gain.

Finally, we could not rule out the possibility that some participants might have difficulties understanding the verbal instructions. While there were several measures to ensure optimal understanding of the instructions during cognitive testing, it would be difficult to rule out the possibility that some instructions were not heard clearly. As discussed above, auditory factors seemed to influence scores on the MMSE domains that required understanding of the verbal instructions, although the effect sizes are only small to medium. Schneider and Pichora-Fuller [8] also found that when visually administered cognitive tests were used, hearing impairment did not relate to reduction in cognitive function and therefore should be used as much as possible when screening and diagnosing cognitive decline. Future studies should therefore utilize cognitive measures that minimize the need to listen.

5.1. Implications on Clinical Practice. The present and previous researches have shown that hearing aid users tend to wait a long time before they take up hearing devices [17]. As hearing loss is related to cognitive declines [3], it would be crucial for doctors, healthcare workers, and others who work closely with older adults to encourage them to try hearing aids early. We hope that the use of hearing devices could at least slow down, if not arrest, this decline. A longitudinal study is required to examine the progression of cognitive function and provide evidence to the use of hearing devices. In addition, as mentioned above, clinicians should be aware of the implication of a hearing impairment on cognitive function even when appropriate monaural hearing devices are worn.

Emerging evidence is showing that hearing aid users with poorer cognitive function are less able to take advantage of more advanced signal processing algorithms that are supposed to aid speech understanding. These may include noise reduction and compression with short time constants

Table 4: Results from stepwise linear regression analysis. The dependent variables (DV) included age, gender, aided soundfield average hearing thresholds, duration of hearing loss, duration of hearing aid use, and aided speech reception thresholds (SRTs) obtained in quiet and in noise as a composite score. Only models with statistical significance are listed with their dependent variables and variables entered into the model (EV).

Models tested	R square	F-statistics	Beta	t-statistics	Cohen's f^2
DV: Orientation to time EV: noise composite SRT	.21	7.2^{*}	−.47	-2.7^{*}	.27
DV: Orientation to place EV: noise composite SRT	.16	5.2^{*}	−.41	2.3^{*}	.19
DV: Registration EV: aided soundfield thresholds	.27	9.9^{***}	.52	3.1^{***}	.37
DV: Complex Commands EV: aided soundfield thresholds	.24	8.1^{**}	−.48	-2.8^{**}	.32
DV: Repetition EV: duration of hearing aid use	.33	12.8^{***}	−.58	-3.6^{***}	.49

Note: $^{*}P < .05$, $^{**}P < .01$, and $^{***}P < .005$.

and directional microphones [23–26]. Therefore, Lunner et al. [23] argued that hearing aid fitting should be individualized to release working memory resources, in order to maximize hearing potentials. While a "cognition-driven signal-processing" hearing aid has yet to become a reality, clinicians should not assume that all older individuals would be able to benefit from these algorithms.

In Hong Kong, it is uncommon for individuals with hearing impairment to receive aural rehabilitation, other than the fitting of amplification devices. Via a meta-analysis, Chisolm and Arnold [27] have shown that auditory perceptual training could enhance short-term outcomes with hearing aids. Furthermore, cognitive training has also been shown to improve cognitive function [28] and Kwok et al. [29] were able to show similar training effects, as well as improvement in mental health among community-dwelling Chinese older adults in Hong Kong. Knowing that hearing loss may have concomitant effects on cognition, clinicians and policy makers should consider adding these components to intervention.

We reported findings from a preliminary study and they are somewhat limited by the small sample size. However, the results will help us plan follow-up studies that address the imminent issues. A larger scale study is being carried out in our laboratory to examine the application of several cognitive tests in the subject population. The current study took a cross-sectional view of cognitive function in a general hearing aid user population; a carefully planned longitudinal study would hopefully help establish a causal relationship between the long-term use of hearing aids that are appropriately fitted and cognitive function. Learning about whether hearing aid use could reverse or arrest the progression of cognitive decline is essential for clinicians to make evidenced based recommendation on early hearing aid use. It will also be interesting to find out whether other invention options, such as the use of binaural hearing aids and perceptual and cognitive training, could improve cognitive function to a level commensurate with that of the general older population.

6. Conclusion

Overall, the present study showed that while appropriately fitted monaural hearing aids could partially make up for the hearing disability and improve speech understanding, the use of hearing aids may not fully compensate for the decline in cognitive function associated with hearing loss. Therefore, when screening cognitive function, the presence of a hearing impairment should be accounted for. In particular, ensuring audibility of signals and perhaps the use of cognitive function tests that employ visual presentation of stimuli should be used. We have also identified a few research areas where greater understanding on the relationship between cognition and hearing impairment would improve the clinical management of older patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

A Tutorial on Implantable Hearing Amplification Options for Adults with Unilateral Microtia and Atresia

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Background. Patients with unilateral atresia and microtia encounter problems in sound localization and speech understanding in noise. Although there are four implantable hearing devices available, there is little discussion and evidence on the application of these devices on patients with unilateral atresia and microtia problems. *Objective.* This paper will review the details of these four implantable hearing devices for the treatment of unilateral atresia. They are percuteaneous osseointegrated bone anchored hearing aid, Vibrant Soundbridge middle ear implant, Bonebridge bone conduction system, and Carina fully implantable hearing device. *Methods.* Four implantable hearing devices were reviewed and compared. The clinical decision process that led to the recommendation of a device was illustrated by using a case study. *Conclusions.* The selection of appropriate implantable hearing devices should be based on various factors, including radiological findings and patient preferences, possible surgical complications, whether the device is Food and Drug Administration- (FDA-)/CE-approved, and the finances. To ensure the accurate evaluation of candidacy and outcomes, the evaluation methods should be adapted to suite the type of hearing device.

1. Introduction

Difficulties in sound localization and speech understanding in noise have been underestimated in adults with unilateral atresia [1]. The amplification options for atretic canal patients are limited; this is because conventional amplification is not a treatment option due to the absence of an external ear canal. In addition, the cosmetic concerns of a conventional bone conduction hearing aid often lead to a relatively low compliance rate. Implantable hearing aids have been developed recently as alternative treatment options to fill in these gaps.

There are four commercially available implantable hearing devices available as rehabilitative options for patients with unilateral microtia and atresia. They are

(a) Percutaneous osseointegrated bone anchored hearing aid (p-BAHA), for example, Cochlear BAHA by Cochlear Bone Anchored Solutions AB and Ponto by Oticon Medical AB, Sweden;

(b) Vibrant Soundbridge (VSB) middle ear implant system (MED-EL, Innsbruck, Austria);

(c) BoneBridge bone (BB) conduction system (MED-EL, Innsbruck, Austria);

(d) Otologics MET Carina fully implantable hearing device (FIHA) (Otologics LLC, Boulder, CO, USA).

All of these devices need to be implanted surgically. These devices are expected to benefit patients with moderate to severe hearing, regardless of their type of hearing loss, that is, sensorineural, conductive, or mixed. However, these devices differ in terms of the sound transmission pathway, and some, such as the FIHA, are suitable for adults only.

1.1. The Percutaneous Bone Anchored Hearing System (p-BAHA). The bone anchored hearing aid (BAHA) was first introduced in 1977 as an alternative hearing rehabilitation option for patients with conductive hearing loss. Later developments expanded the indications to include single-sided deafness and mixed hearing loss. The BAHA hearing system incorporated the concept of osseointegration discovered by Professor Brånemark, enabling improved comfort and fine sound quality. It represented a major milestone in the evolution of bone conduction hearing amplification [2]. Two commercially available systems of the BAHA hearing devices include the Cochlear BAHA by Cochlear Bone Anchored Solutions AB or the Ponto by Oticon Medical AB, Sweden. These devices are FDA-approved for children of the age of 5 and above; for younger children, a BAHA soft band will be applied.

The surgical procedure for the BAHA is relatively simple in comparison with other implantable devices. BAHA is placed in the mastoid bone. Local anesthesia could be used for the majority of the adult cases. The most obvious benefit for the BAHA system is its surgical simplicity; it bypasses the outer and middle ear pathology and stimulates the inner ear effectively via direct bone conduction, which is particularly well suited for patients with aural atresia. However, despite years of technological advancement, the problem of postoperative periabutment wound infection has remained at approximately 5%, which results in a significant negative impact on the clinical application.

1.2. The Vibrant Soundbridge Middle Ear Implant. An alternative to p-BAHA is the Vibrant Soundbridge middle ear implant system (VSB) (Med-El, Innsbruck, Austria). The Vibrant Soundbridge (VSB) is a direct-drive, partly implantable middle ear hearing device which was approved by the FDA in 2000. It is intended for patients of the age of 3 and above with a mild to severe degree of hearing loss, with their bone conduction thresholds at or not worse than 65 dBHL across frequencies.

The VSB system is comprised of two parts, namely, an internal component of the VSB called the Vibrating Ossicular Prosthesis (VORP) and an external audio processor (AP). The VORP consists of an internal coil, a magnet to hold the Amadé audio processor over the implant, a demodulator, the conductor link, and the floating mass transducer (FMT). The VORP is implanted by a surgical procedure in which the FMT is attached to a vibratory structure in the middle ear either via a round window approach (round window vibroplasty (RWV)) or via ossicular chain coupling [3]. Intraoperative electrocochleography is needed to locate the best orientation of the floating mass transducer. The details of the electrocochleography procedure are available in the guidelines written by Radeloff and colleagues [4]. The AP is about 1.2 inches in diameter and contains a microphone, which picks up sounds and converts them into electrical signals that can be transmitted across the skin to be received by the implanted internal receiver of the VSB.

Benefits from the VSB device include, firstly, the provision of a unilateral stimulation to the atretic ear, which is beneficial for those with unilateral hearing loss. Secondly, there is no pin tract problem as in BAHA. In addition, the patient's satisfaction with the sound quality and the improvement in speech intelligibility are higher and could be sustained even after five to eight years of implant use [5, 6]. However, because the VSB surgery involves the manipulation of the fragile ossicle bones, there are therefore possible risks of surgical trauma and irreparable sensorineural deafness. Other potential complications include postsurgical displacement of the implant due to development of scar tissues, taste disturbance, or damage to the chorda tympani nerve [5–7]. Lastly, magnetic resonance imaging (MRI) is contraindicated in patients with VSB device.

1.3. The Bonebridge Bone Conduction Implant. The Bonebridge (BB) (Med-EL; Innsbruck, Austria) is another feasible option for children at age of 5 years and above who have conductive, mixed hearing loss or single-sided deafness with bone conduction thresholds at 45 dBHL or better at 0.5, 1, 2, and 3 kHz. It is a semi-implantable bone conduction implant hearing device consisting of an external audio processor (AP) worn behind the ear and a bone conduction implant (BCI) positioned surgically under the skin. The acoustic signals are recorded by the microphones of the AP, which converts sounds into electrical signals, and these are then transferred to the BCI. The BCI then converts the electrical signals to mechanical vibrations on the mastoid bone and thus the inner ear is stimulated via bone conduction.

Several advantages have been noted with the BB. Firstly, the BB offers a bilateral stimulation that is similar to the BAHA. Thus, it is especially beneficial for those with bilateral hearing loss in that they will need to wear only one device to achieve desirable outcomes. Secondly, the BB does not require a good middle ear structure for the coupling of the device; thus it is suitable for patients with middle ear pathologies and who are not feasible for VSB implantation. Thirdly, the risks associated with the use of MRI are reduced, compared to the VSB. The BB allows MRI to be done up to 1.5 Tesla.

Although the BB seems to be a better device in terms of surgical complications and the application of MRI, compared to the VSB, the BB system is still pending FDA approval in the United States' market. Thus, the BB system may not be considered as a reimbursable item by a third party (e.g., healthcare insurance). Other disadvantages of the BB include possible postsurgical displacement of the BCI and extrusion of the implant, although this is uncommon. Lastly, the BB provides bilateral stimulation and thus may not be desirable when hearing in the other ear is normal; this is because there is a possible risk of signal interference to the normal contralateral ear. Careful assessment of individual preferences and preoperative trial on potential candidates with the Apollen bone conduction hearing aid provided by MED-EL could be helpful to determine its suitability before surgery is performed.

1.4. The Carina Fully Implantable Hearing Aid (Carina FIHA). The Carina implantable hearing aid, developed by Otologics LLC (Boulder, CO, USA), was initially developed as a semi-implantable middle ear transducer (MET) but is now a fully implantable hearing device. The Carina device consists of the implant, the programming system, the charger, and the remote control. The implant itself contains the electronics which contain the microphone, battery, magnet, digital signal processor, and connector. The system utilizes a microphone located beneath the skin that picks up acoustic signals, which are then amplified and converted into an electrical signal. The signal is sent down the lead and into the transducer and the ossicular stimulator is coupled directly with the ossicular chain or the round window [8].

The Carina is considered to be another viable option for adults with moderate to severe hearing loss of conductive, sensorineural, or mixed etiologies. The device is CE-marked for sale and currently is still in the clinical trial stage, and therefore it has not been cleared for marketing by the FDA in United States. Three advantages of the Carina device include the following: (1) among the four devices discussed in this paper, the Carina is cosmetically the most appealing because no external processor can be seen; (2) it is easy to use; and (3) unilateral stimulation is provided. This device is thus suitable for adults with unilateral hearing loss such as unilateral congenital atresia. Siegert et al. investigated the surgical and audiological outcomes of Carina FIHA on five adults with either unilateral or bilateral congenital aural atresia [8]. All patients indicated no intra- or postoperative complications. Audiologically, all five patients demonstrated an average improvement of aided soundfield thresholds of approximately 35 dBHL with the Carina device. This provides the conclusion that the Carina device offers a new option for patients with congenital atresia [9].

However, there are several drawbacks of using the Carina device as follows: (1) it is not suitable for children and teenagers under 18 years of age; (2) the surgery is difficult to perform and it requires general anesthesia for about three hours; (3) revision surgery is required for battery change and future upgrade; (4) it is MRI-incompatible; (5) it is the most costly of all the MEIs; and (6) postoperative deterioration in hearing thresholds has been reported. Local experience in Hong Kong, with the application of the Carina device on five adults with sensorineural hearing loss, indicates a general drop of pure tone air conduction thresholds in all subjects postoperatively, at an average of 9 dB across the 250–8,000 Hz frequencies. A few cases also indicated a drop in bone conduction thresholds of about 10–15 dBHL [9]. Thus, preoperative counseling of the pros and cons of using a Carina device is suggested [9].

2. Candidacy

A candidate who has unilateral atresia must meet various criteria in order to be considered for implantation. In general, three types of considerations should be given: (1) the nature of the hearing loss, (2) patient preferences, and (3) issues related to practical usage.

In terms of the nature of the hearing loss, the patient should be selected according to the following criteria (see Figure 1 for the clinical decision making process).

(a) The air conduction hearing thresholds must fall within the manufacturer's suggested criteria, that is, not more than a moderate to severe degree of hearing loss, except for the FIHA, where bone conduction thresholds are used as one of the selection criteria. While the BAHA and the BB would allow hearing loss up to 45 to 55 dB HL, the VSB and the Carina would fit a hearing loss of up to 70 to 80 dB HL.

(b) The bone conduction threshold should be stable.

(c) Whether the middle ear structure would allow the coupling of the transducer.

(d) There should be an absence of retrocochlear pathology and auditory processing disorders.

(e) The unaided speech intelligibility should be better than 50% to 60%. However, there is no speech discrimination requirement for the BB device.

In regard to patient preferences, patient should understand the following factors (see Figure 1).

(a) The device is only for those who have do not receive satisfactory benefit from conventional bone conduction hearing aids or there is a cosmetic concern.

(b) There is limited evidence available for some of these devices.

(c) Only the BAHA and Carina are FDA- and/or CE-approved for conductive hearing loss and are eligible for reimbursement by third parties. Otherwise, the patient should be willing to pay for the device (i.e., VSB and BB).

(d) While local anesthesia is used for implanting the BAHA, general anesthesia surgical procedures are recommended for other devices and there are risks associated with the surgery.

(e) At the moment, the fact is only the BAHA and BB is MRI conditional, BB can have MRI up to 1.5 Tesla, while as long as the Baha sound processor is removed for the MRI procedure, a patient can have MRI up to 3 Tesla. The use of MRI is contraindicated with the VSB and Carina. The patient should understand that there could be issues with MRI assessment in the future.

In regard to the usage of implantable devices, the patient should be informed about the following.

(a) Due to normal hearing in the good ear, the benefits from amplification may be limited (e.g., amount of functional gain, speech intelligibility improvement).

(b) Due to bilateral stimulation by the implant, there could be a distortion of hearing.

(c) There could be implications related to long-term reliability of the device and other complications (e.g., skin overgrowth, extrusion of device, and device failure rate).

(d) Cosmetic appearance could be a concern with the BAHA.

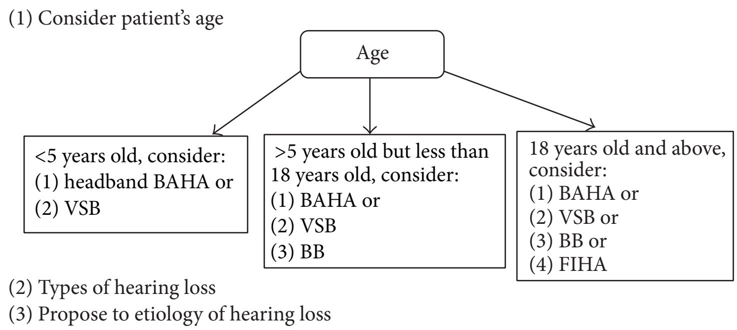

Figure 1: Flow chart on the clinical decision making process for implantable hearing devices.

3. Special Considerations in the Evaluation of an Atretic Ear

The consideration of an appropriate hearing device involves the examination of hearing thresholds. However, there are issues in regard to the measurement of air conduction thresholds in an ear with microtia and atresia because the calibration of the earphone is based on a normal physiologic pathway of air conduction. The volume of the ear under a supra-aural earphone is estimated to be about 6 cm^3. However, this assumption cannot be made in cases of malformed external ear structures. Difficulties in establishing valid air conduction thresholds would also mean that we are not able to establish posttreatment advantages in air conduction thresholds. Thus, other types of outcome measures, such as soundfield thresholds measures, should be used.

When evaluating soundfield thresholds, the involvement of the good contralateral ear should be minimized, in order to obtain the true thresholds. When speech intelligibility is measured, the clinician should also consider whether the objective is to demonstrate the effects of implantation on hearing in the poor ear only (implant ear) or binaural hearing. In the former case, the good ear should be plugged and muffed to prevent its participation so that whether appropriate amplification has been provided to the poor ear can be verified. However, if the latter objective is desired, then the individual should be tested binaurally, without the good ear being plugged and muffed. Because of the good ear, it is likely that benefits in speech intelligibility will not be demonstrated if both speech and noise are being presented from the front loudspeaker. In other words, the effects of amplification may not be readily observable unless there is a spatial separation of speech and noise.

With the other ear having normal hearing, the benefits from an implant in the atretic ear are expected to be minimal. Thus, the above objective measures (e.g., soundfield air conduction testing and speech intelligibility evaluation) might not be effective in demonstrating benefits. Self-reports of aided benefit and satisfaction should be obtained to evaluate the outcomes.

4. Case Study

Background. K.C. is a 23-year-old man presenting with a unilateral microtia with congenital complete bony external auditory canal atresia on the right side, as confirmed by using a computer tomography (CT) scan. The malleus and incus had fused together and were found attached to the bony atretic plate. The stapes, oval window, and round window appeared normal on a CT scan. His major complaints were poor sound localization and speech understanding difficulties on the right side, especially in the presence of background noise. The unaided audiogram for K.C. was indicated in Figure 3.

Figure 2: The Vibrant Soundbridge (VSB) implantable hearing device. The VSB system is comprised of two parts: the internal component is called the vibrating ossicular prosthesis (VORP) and the external component is an audio processor (AP). The VORP consists of a receiver coil, a magnet to hold the Amadé audio processor over the implant, a demodulator, the conductor link, and the floating mass transducer (FMT). The receiver coil sends the sound signal from the audio processor to the demodulator or electronics package. The demodulator demodulates the signal so that it can be converted into signals that will drive the FMT. The conductor link just sends these signals to the FMT. Adapted from marketing materials on the VSB, with permission of MED-EL, Innsbruck, Austria.

While both the VSB and Carina would be good choices, the VSB was chosen because K.C. was worried about possible future revision surgery in the case of a battery recharge problem. The VSB was an appropriate option for his right ear because CT scan findings showed that his stapes, oval window, and round window were normal and that therefore VSB could provide a unilateral stimulation to his right ear. Y.H. was counseled regarding the risks and benefits of the VSB (Figure 2). The surgery was performed in October 2012.

Surgical Monitoring. The operation was done under general anesthesia with facial nerve monitoring. The skin incision and soft tissue handling were such that the patient may need to undergo plastic reconstruction of the pinna at a later

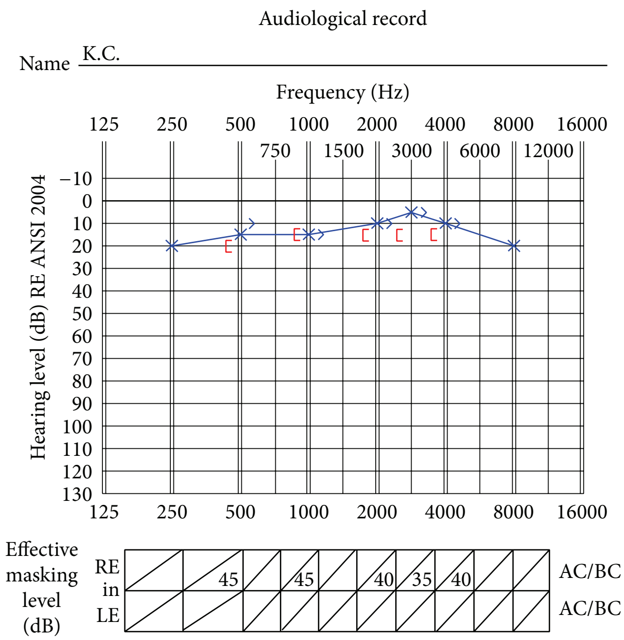

Figure 3: Unaided audiogram before surgery.

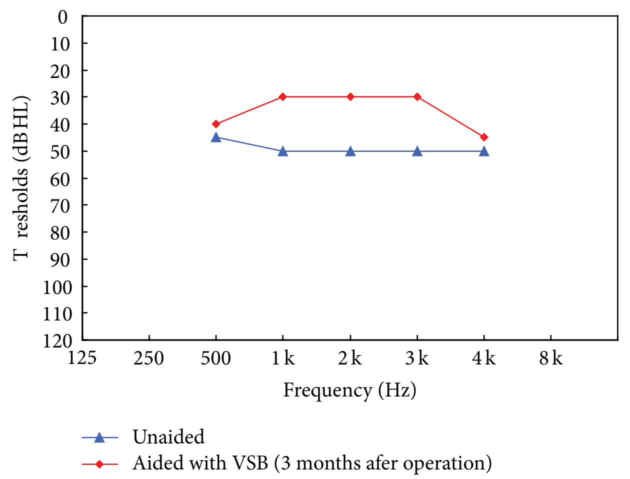

Figure 4: Unaided (U) and aided (A) soundfield audiogram obtained 3 months after the implantation of VSB in the right ear. Thresholds were measured with the warble tone signals presented from the poor ear (at 90 degree azimuths). The left (nonimplant) ear was plugged and muffed during testing.

stage. Mastoidectomy was performed and access to the round window was achieved by removing atretic plate, malformed malleus and incus. The round window membrane needed to be fully exposed and this was performed by careful removal of bony overhang at the round window niche by a diamond burr. To ensure that the round window membrane will not be damaged by the FMT, a layer of perichondrium was placed on the round window membrane. To allow placement of the FMT in the round window niche, the titanium clip was removed. The FMT was carefully orientated and rested on the round window area. An extra perichondrium was put onto the FMT body to provide further stability.

Facial nerve monitoring is essential in this surgery for identifying any abnormal course of facial nerves and for avoiding facial nerve injury. Compound action potential (CAP) thresholds were examined during electrocochleography (ECochG) intraoperatively to determine the best site of the FMT placement as well as to evaluate the function of the implant system. With the electrodes placed on the promontory (active), vertex (reference), and forehead (ground), an increased CAP amplitude was observed with the FMT, and the goal was to achieve the best CAP thresholds possible.

Device Fitting. The device was activated eight weeks after the surgery. This wait was required for wound healing both internally and externally. Based on the unaided soundfield hearing thresholds obtained from the implanted ear, the Amadé audio processor (MED-EL; Innsbruck, Austria) was programmed with the Connexx 6.11 software equipped with the Symfit database Rev.5.0. The default desired sensation level (DSL I/O) fitting formula was applied. Although the NAL/NL1 fitting formula is also available, it has not been modified to yield gain targets appropriate for a direct-drive device. When the aid was first switched on, the patient was not able to tolerate the prescribed gain. However, verification of the VSB device gain was difficult because the VSB is not an acoustic device. It is not possible to perform real ear measurements; soundfield aided thresholds, sentence reception thresholds (SRTs), and self-reports were obtained to evaluate the outcomes. K.C. returned for a fine-tuning session two weeks after device activation to ensure that he was listening at most comfortable levels as well as obtaining benefits from the device. Informal feedback on sound tolerance was obtained.

Results. Change in residual hearing was evaluated by comparing the preoperative unaided bone conduction thresholds to the postoperative bone conduction thresholds. The results revealed no obvious change at any frequency. Figure 4 presents unaided air and bone conduction thresholds before the surgery. The hearing thresholds were maintained after surgery. In addition, there were no postoperative complications observed or reported by K.C. after surgery.

Verification of the Implantable Hearing Device Performance. One of K.C.'s chief preimplant complaints was his difficulty in picking up the signals from the right ear. In order to assess the aided benefits with the implant, aided soundfield thresholds were measured with warble tone signals presented at 90 degree azimuths, with the left ear both plugged and muffed. With the VSB set at the most comfortable listening level, it was also shown that VSB offered functional gains of 5 to 20 dB across the frequencies from 500 Hz to 4 kHz, when compared with the unaided thresholds (Figure 4). The amount of functional gain was less than that (45.5 dB) reported by Frenzel et al. [10]. However, the gain could not be adjusted to a higher volume setting because of intolerance. Aided thresholds ranged from 35 to 50 dBHL, which is slightly worse than those reported in the literature [10].

In the current case, we had aimed to present the results to demonstrate both the effects of amplification on the

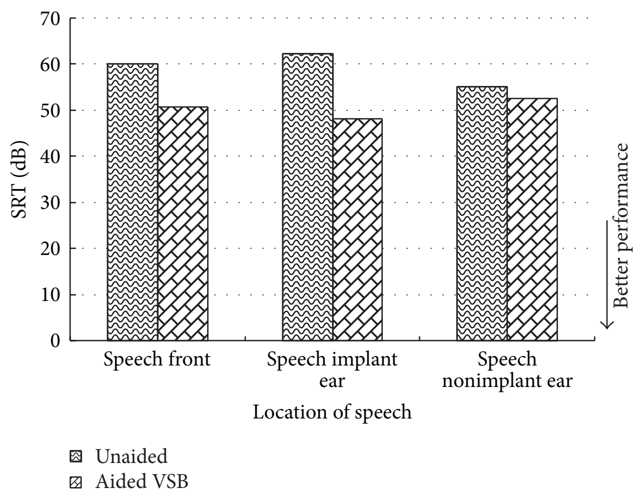

Figure 5: Speech reception thresholds (SRT) obtained in quiet using the Cantonese version of the Hearing In Noise Test (CHINT). SRTs were obtained unaided and aided at 3 months after activation of the VSB.

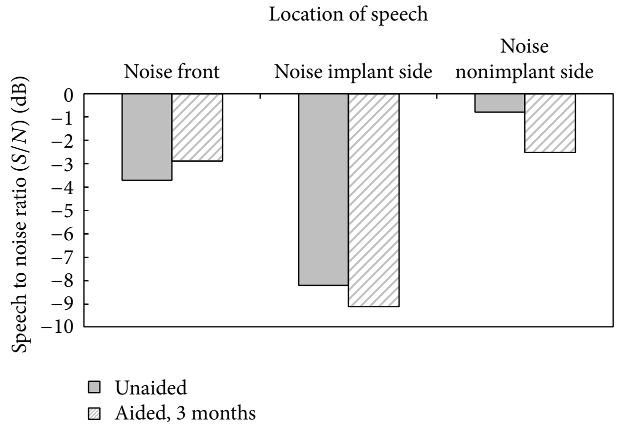

Figure 6: Speech reception thresholds (SRT) obtained in noise using the Cantonese version of the Hearing In Noise Test (CHINT). SRTs were obtained unaided and aided at 3 months after activation of the VSB.

poor ear and binaural hearing. Speech reception thresholds (SRTs) were measured 3 months after implantation, when acclimatization, if any, would have been completed. With the good ear plugged and muffed, the SRT of the poor ear improved to 50.8 dB (A) in quiet, suggesting that although the VSB implant improved understanding of moderately soft speech, the benefit has not been optimized for soft speech. These results are consistent with findings in aided soundfield thresholds. SRT was −0.4 dB (A) in noise, thereby suggesting no improvement from the unaided condition. Thus, the implant improved the audibility of signals but not the S/N for 50% intelligibility when listening in noise.

With binaural hearing in quiet, there was a slight elevation of SRT (0.8 to 3.8 dB) when compared to the unaided conditions (Figure 5). However, any changes smaller than 3.1 dB are within the confidence interval for test and retest [11], and therefore they could not be regarded as significant from a statistical point of view.

In noise, as shown in Figure 6, the use of the VSB implant did not improve binaural squelch in the noise front condition; that is, the SRT did not improve compared to unaided, probably because the gain of the implant was low and thus did not yield true binaural hearing. When the noise was on the nonimplant side (good ear), the use of an implant-assisted speech reception (and thus SRT) improved to −2.5 dB S/N. Compared to when unaided, the patient was better able to take advantage of the spatial separation of speech and noise when noise was moved from the front to the implant side, resulting in an improvement of 6.2 dB in SRT. Overall, however, the changes in SRTs were small and could not be regarded as significant.

Self-reported aided benefit and satisfaction were measured with the two Chinese versions of the abbreviated profile of hearing aid benefit (APHAB) and the satisfaction with amplification in daily life (SADL) [12, 13]. The global score on the APHAB was 52 (with 100 indicating the greatest benefit) and on the SADL it was 4.29 (with 5 indicating the greatest satisfaction). Y.H. was satisfied with the VSB middle ear implant in his right ear, although the benefits were reportedly only moderate. However, these findings are not unexpected, given that the contralateral ear exhibits normal hearing ability. The patient also reported good sound quality and comfort and he accepted the appearance of the aids as was often reported in previous studies [10]. Y.H. used the VSB for approximately 4 to 5 hours per day, primarily for his part-time work and for communication at home. His ability to hear the signals from the right ear (the poor ear) reportedly improved his localization ability, despite the distorted interaural phase and time differences due to the use of a hearing device in one ear.

5. Discussion

Overall, there are many practical concerns when making clinical decisions on the selection of an appropriate implantable device for an adult with unilateral atresia. One of the most important questions to ask is the age of the patient (see Figure 1). The second question will be the types of hearing loss and thirdly it would be the etiologies of hearing loss.

For microtia patient with pure conductive hearing loss, the underlying cause is likely due to malformed ossicles; then the option of VSB surgery should only be considered after radiological studies where an appropriate coupling is possible. The options of BAHA and BB do not have this constraint. However, the clinician should be aware that both the BAHA and BB provide bilateral stimulations and thus they may introduce interference to the contralateral ear. In contrast, the VSB and Carina FIHA provide a unilateral stimulation of the worse ear. Skin tract problem of BAHA must be thoroughly discussed. Also the VSB and FIHA are neither MRI-incompatible nor FDA-approved, and the potential candidates should be well informed of the risks including worsening of hearing loss and implant failure before they opt for a relatively difficult operating procedure in VSB and FIHA.

Regarding the cost, the FIHA is the most expensive in comparison with the VSB and BB. Thus, preoperative counseling of the risks and benefits of each device is important.

6. Conclusion

Despite the lack of high-level evidence about these devices, the selection of appropriate implantable hearing devices should be based on various factors, including radiological findings and patient preferences. In addition, surgical complications, whether the device is FDA-/CE-approved, and the finances should be considered. To ensure the accurate evaluation of candidacy and outcomes, the evaluation methods should be adapted to suit the type of hearing device.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Tanshinone IIA Induces Apoptosis in Human Oral Cancer KB Cells through a Mitochondria-Dependent Pathway

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Tanshinone IIA (Tan IIA), an active phytochemical in the dried root of *Salvia miltiorrhiza* Bunge, has shown an antiproliferative activity on various human cancer cell lines including nasopharyngeal carcinoma cells. However, the effects of Tan IIA on human oral cancer cells are still unknown. This study aimed to investigate the antiproliferative effects of Tan IIA on human oral cancer KB cells and explored the possible underlying mechanism. Treatment of KB cells with Tan IIA suppressed cell proliferation/viability and induced cell death in a dose-dependent manner through sulforhodamine B colorimetric assay. Observation of cell morphology revealed the involvement of apoptosis in the Tan IIA-induced growth inhibition on KB cells. Cell cycle analysis showed a cell cycle arrest in G_2/M phase on Tan IIA-treated cells. The dissipation of mitochondrial membrane potential observed by flow cytometry and the expression of activated caspases with the cleaved poly (ADP-ribose) polymerase under immunoblotting analysis indicated that Tan IIA-induced apoptosis in KB cells was mediated through the mitochondria-dependent caspase pathway. These observations suggested that Tan IIA could be a potential anticancer agent for oral cancer.

1. Introduction

The incidence of oral cancer increases annually with the epidemiology of oral and oropharyngeal cancer, grouped together, as the sixth most common cancer worldwide [1]. It is estimated that about 275000~300000 people will be diagnosed with oral cancer annually [1, 2]. The management of oral cancer is complex and challenging. The majority of treatment includes surgery alone for very early stage patient, surgery with adjuvant concurrent chemoradiotherapy or radiotherapy alone, neoadjuvant chemotherapy followed by surgery and adjuvant concurrent chemoradiotherapy in locally advanced disease, and chemoradiotherapy alone in certain status like inoperative cases [3–8].

With many choices of treatment available, the role of chemotherapy is moving toward a more prominent position. The compounds extracted from the natural sources have been introduced into the chemotherapy of head and neck cancers. Taxanes including paclitaxel, the ingredient in the Pacific yew tree, and docetaxel, an extract of European yew tree, are cytotoxic agents that interfere with the microtubule structure and cause the pause of cell division [9, 10]. Paclitaxel and docetaxel have been used as chemotherapy agents to treat squamous cell carcinoma of the head and neck in selected patients with survival benefits in clinical practice [11–13].

Danshen, the dried root of *Salvia miltiorrhiza* Bunge, has been used for the treatment of coronary artery diseases and cerebrovascular diseases in traditional Chinese medicine. Tanshinone IIA (Tan IIA), a diterpene quinonic compound from the extractable ingredient of Danshen, has shown its ability to protect from H_2O_2-induced cell death in cardiac myocytes and macrophage [14, 15]. In addition, Tan IIA was reported to have the growth inhibitory effects and induced apoptosis on various cancer cell lines [16–19]. These studies indicated that Tan IIA could induce cell death through activation of selective members in caspase family and trigger the mitotic arrested cells to enter apoptosis [16, 17]. Yang et al. also pointed out that Tan IIA caused the release of cytochrome c, the loss of mitochondrial membrane potential, and subsequently the apoptosis of the EAhy926 human endothelial cells [19]. However, the effects of Tan IIA on human oral cancer cells are still unclear. This study was designed to investigate the cytotoxic effects of Tan IIA on human KB cells and discussed the possible underlying mechanism. Our data showed that Tan IIA may have the potential to become a novel agent of chemotherapy for oral cancer.

2. Materials and Methods

2.1. Reagents. Tanshinone IIA (Tan IIA) was purchased from Herbasin Co., Ltd. (Shenyang, China) and dissolved in pure grade dimethyl sulfoxide (DMSO). Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum, penicillin, streptomycin, and 3, 3′-dihexyloxacarbocyanine iodide ($DiOC_6$) were purchased from Gibco/Invitrogen (Carlsbad, CA, USA). The protein assay kit was obtained from Bio-Rad (Hercules, CA, USA). Antibodies to caspase-3, caspase-9, poly-(ADP-ribose) polymerase (PARP), and β-actin were purchased from Cell Signaling Technology, Inc. (Beverley, MA). PVDF membrane and chemiluminescent substrates for horseradish peroxidase (HRP) were purchased from Millipore (Bedford, MA, USA). Unless otherwise indicated, all other chemicals employed in this study were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

2.2. Cell Culture. The human oral squamous carcinoma KB cells were from ATCC (Manassas, VA, USA). The cells were cultured in DMEM supplemented with 10% fetal bovine serum, 100 units/mL penicillin, and 100 μg/mL streptomycin at 37°C in one atmosphere with 5% CO_2.

2.3. Cytotoxicity Assay. KB cells (8×10^3 cells/well) were seeded in 96-well plate and grew overnight. Various concentrations of Tan IIA (0, 5, 10, 20 and 25 μg/mL) were added and incubated for 24, 48, and 72 hours. The cell viability was determined by sulforhodamine B (SRB) colorimetric assay at different time periods.

For SRB colorimetric assay, 10% wt/vol trichloroacetic acid was added to each well and the cells were then washed by tap water after 60 minutes. After dehydration, the plates were incubated in 0.4% SRB and then washed by 1% acetic acid after 15 minutes. Subsequently, 10 mM Tris buffer (pH 10.5) was added to dissolve precipitates. Finally, the optical density at 492 nm was measured to determine the cell viability.

2.4. Determination of Apoptosis and Morphologic Changes. KB cells treated with different concentrations of Tan IIA (0, 5, 10, and 20 μg/mL) were incubated. At indicated time points (24 and 48 hours), the cells were fixed with 4% paraformaldehyde for 15 minutes at room temperature and kept incubating overnight at 4°C. Then, the plates were washed twice with phosphate-buffered saline (PBS) and nuclei were stained with 100 ng/mL Hoechst for 15 minutes in the dark. Following three times of tap water washing, the cells were examined under a fluorescence microscope. Cells with rough surface and dark stained nuclei with fragmented chromosome were considered as apoptotic cells. The apoptotic cells were counted for each sample.

2.5. DNA Cell Cycle Analysis. For the cell cycle analysis, the cellular DNA content was detected by flow cytometry. KB cells were plated in 6-well plates and incubated with Tan IIA (0, 5, and 10 μg/mL) for 24 and 48 hours. The cells were harvested by centrifugation, washed with PBS, and fixed in 70% ethanol at −20°C overnight. Then, the cells were washed twice by ice-cold PBS and incubated in PBS containing 4 μg/mL of propidium iodide, 0.1 mg/mL RNase A, and 0.1% Triton X-100 at room temperature for 1 hour in the dark. Finally, the cell cycle was analyzed with flow cytometry (Beckman FC500, San Diego, CA, USA).

2.6. Measurement of Mitochondrial Membrane Potential. KB cells were plated in 12-well plates and treated with different concentrations of Tan IIA (0, 5, and 10 μg/mL) for 24 hours. The harvested cells were washed twice with PBS, resuspended in 10 μM of 3,3′-dihexyloxacarbocyanine iodide ($DiOC_6$), and incubated at 37°C for 30 minutes. Subsequently, the cells were analyzed with flow cytometry (Beckman FC500, San Diego, CA, USA).

2.7. Western Blot Analysis for PARP and Caspase Activity. After incubation with Tanshinone IIA (0, 5, 10 and 20 μg/mL) for 24 hours, KB cells were harvested and washed with cold PBS. Then, cell pellets were lysed in ice-cold RIPA buffer containing 20 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM Na_2 EDTA, 1 mM EGTA, 1% NP-40, 1% sodium deoxycholate, 2.5 mM sodium pyrophosphate, 1 mM β-glycerophosphate, 1 mM Na_3VO_4, and 1 μg/mL leupeptin for 5 minutes. The supernatants were collected by centrifugation at 11,752 g for 10 minutes at 4°C. The protein concentration was measured using the Bradford protein assay (Bio-Rad, Hercules, CA, USA). Proteins were electrophoretically separated on 8% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gels and transferred to PVDF membrane. Membranes were supplemented with 5% nonfat dry milk and PBS containing 0.1% Tween-20 at room temperature for 1 hour. Then, membranes were incubated with diluted primary antibody against caspase-3, caspase-9, PARP, and β-actin at 4°C with gentle shaking overnight. After washing with PBST for three times, membranes were incubated with the appropriate horseradish peroxidase-conjugated secondary antibody at room temperature for 1 hour. Rewashing with

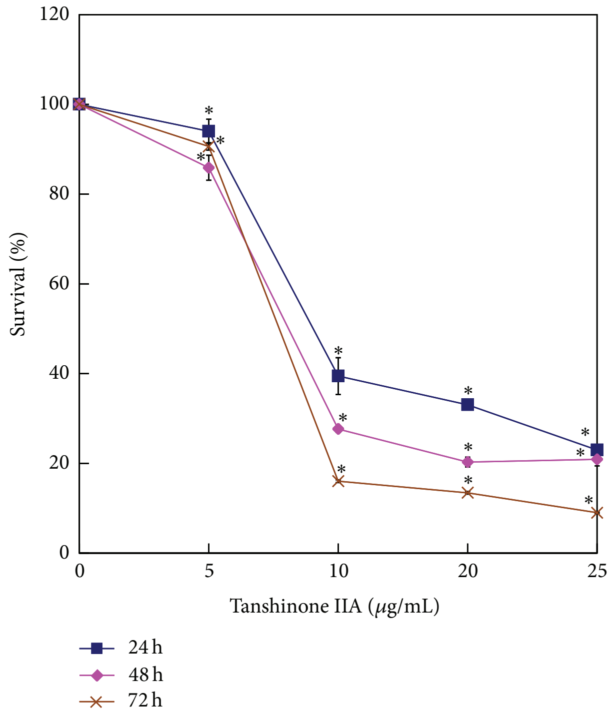

Figure 1: Effect of Tan IIA on KB cell proliferation. KB cells were treated with different concentrations of Tan IIA (0, 5, 10, 20, and 25 μg/mL) for 24, 48, and 72 hours. The cell cytotoxicity and viability were detected by SRB colorimetric assay. Values are the mean ± SD of 3 independent experiments. $*$ indicates $P < 0.05$.

PBST for three times, the blots were visualized using chemiluminescent detection reagents and autoradiographic film (Eastman Kodak Co., Rochester, NY, USA).

2.8. Statistical Analysis. Data were presented as the mean ± standard deviation (SD). Student's t-test was used for comparison among different groups. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Tanshinone IIA Inhibited Cell Growth and Caused Apoptosis of Oral KB Cells. To examine the cytotoxicity of Tan IIA on KB cells, the cells were evaluated by SRB colorimetric assay. The dose-dependent growth inhibitory effects were observed (Figure 1). The survival rates of 94.0%, 39.5%, 33.1%, and 23.0%, respectively, compared with that in non-Tan IIA-treated cells were detected after treatment with different concentrations of Tan IIA (0, 5, 10, 20, and 25 μg/mL) for 24 hours. More than 90% of cells were killed with 25 μg/mL of Tan IIA administration for 72 hours. The cytotoxic effects also became obvious as time passes when 10 μg/mL of Tan IIA was added for 24, 48, and 72 hours; the survival rates were 39.5%, 27.7%, and 16.0%, respectively. Furthermore, nuclear morphological changes during apoptosis were observed using Hoechst staining assay (Figure 2(a)). After treatment of Tan IIA (0, 5, 10, and 20 μg/mL), the apoptotic rates were 4.4%, 5.7%, 42.2%, and 93.9%, respectively, at 24 hours and 2.7%, 7.6%, 92.7%, and 98.6%, respectively, at 48 hours (Figure 2(b)). With higher dose and longer time period of administration, the apoptotic cells with shrunken and condensed nuclei became more prominent. Taken together, Tan IIA did induce oral KB cell death in a dose-dependent manner.

3.2. Tanshinone IIA Arrested KB Cells in G_2/M Phase. To evaluate the effect of Tan IIA on cell cycle progression, the cell cycle distribution was determined through flow cytometry analysis. After treatment with 10 μg/mL of Tan IIA for 24 and 48 hours, there was an accumulation of cells in G_2/M phase, while the cells in G_0/G_1 phase decreased compared with that in non-Tan IIA-treated cells (Figure 3). Moreover, the appearance of sub-G_1 population indicated a proportion of apoptotic cell. The results suggested that Tan IIA-induced cell death might be involved in the induction of G_2/M phase arrest and apoptosis.

3.3. Tanshinone IIA Induced the Loss of Mitochondrial Membrane Potential. The loss of mitochondrial membrane potential ($\Delta\Psi$m) has been regarded as one of the early events in the apoptotic pathway, which can trigger the release of cytochrome c and other apoptogenic molecules after induction by various stimuli [20, 21]. To detect the change of the mitochondrial membrane potential, we used a mitochondria-specific and voltage-dependent dye, $DiOC_6$, to stain the cells and then analyzed them through flow cytometry. As shown in Figure 4, KB cells treated with 10 μg/mL of Tan IIA for 24 hours underwent the disruption of the mitochondrial membrane potential. Around 20% of the treated cells lost their mitochondrial membrane potential.

3.4. Tanshinone IIA Induced the Activation of Caspase-3, Caspase-9, and PARP. It is known that the apoptotic intrinsic pathway is initiated by intracellular stress, which dissipates transmembrane potential of mitochondrial membrane and results in the release of proapoptotic factors, including cytochrome c [20, 21]. The increased level of cytochrome c in the cytosol results in the initiation of caspase-9 and caspase-3 and the subsequent activation of PARP and induces the morphological changes of the dying cell [20–26]. In this signaling pathway, the specific PARP, a biochemical characteristic of apoptosis, mainly depends on the activation of caspase-3 [27]. In our study, western blot analysis was used to determine the effect of Tan IIA on caspase proteins and PARP. After exposure to different concentrations of Tan IIA (0, 5, 10, and 20 μg/mL) for 24 hours, cellular proteins were lysed and immunoblotting was performed. Figure 5 showed the activated subunits of caspase-9 with the decreased expression of procaspase-3 in Tan 20 group; a 116 kDa PARP was also cleaved to an 89 kDa fragment. The results suggested that Tan IIA-induced KB cell death was involved in the activation of caspase-3 and caspase-9 and the cleavage of PARP.

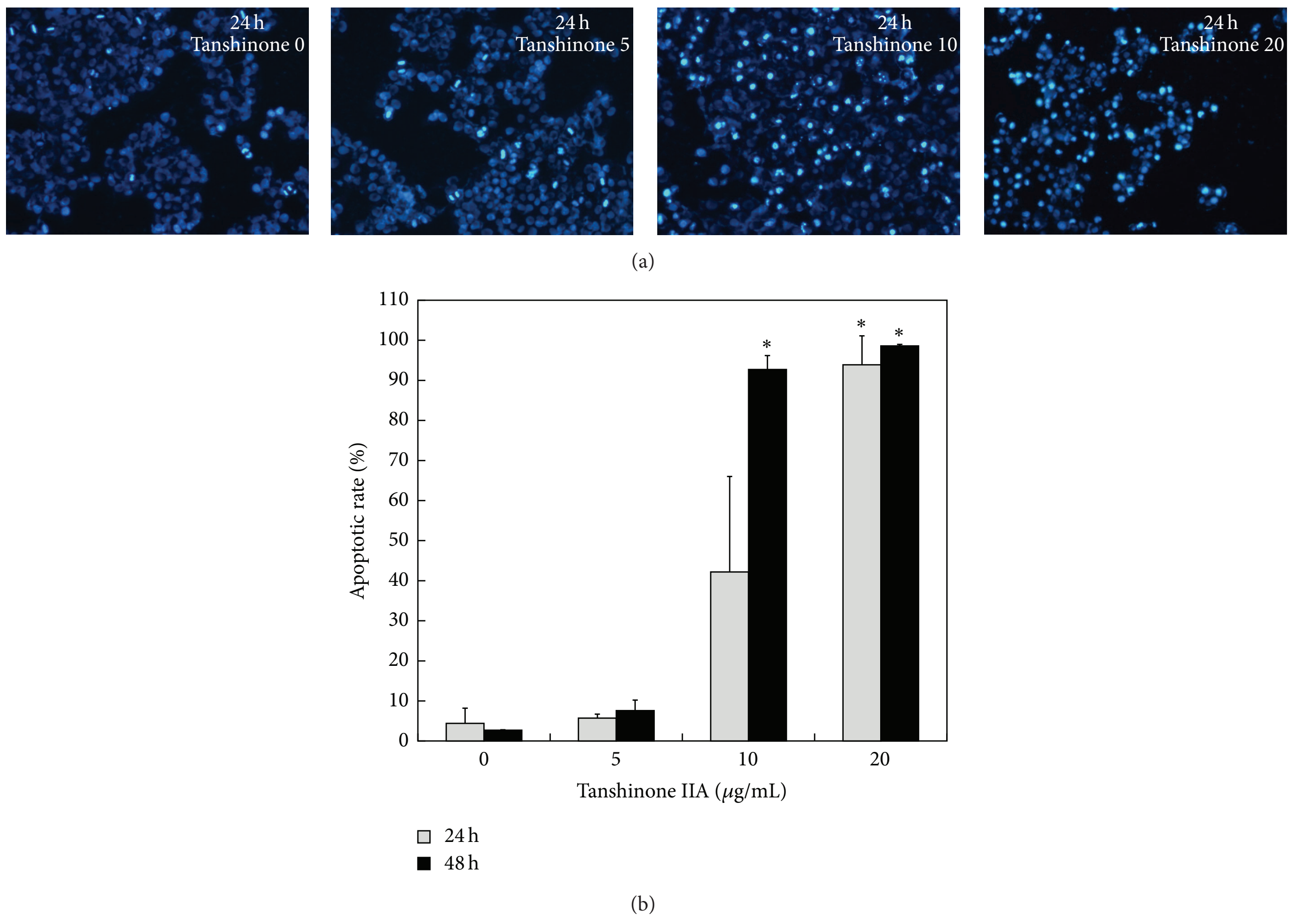

Figure 2: Assessment of nuclear morphological changes of KB cells exposed to Tan IIA. KB cells were treated with various contractions of Tan IIA (0, 5, 10, and 20 μg/mL) for different time periods. (a) After 24 hours, cells stained with Hoechst and exhibiting shrunken, condensed nuclei with fragmented chromosomes under fluorescent microscope were identified as apoptotic cells. (b) Apoptotic rates were calculated. The points are the mean ± SD of 2 independent experiments. $*$ indicates $P < 0.05$.

4. Discussion

Tanshinone IIA (Tan IIA) is one major component of the dried root of *Salvia miltiorrhiza* Bunge. It acts as two faces in the biological and pharmacological effects. Some studies showed that Tan IIA is correlated with protection from cell death in cardiac myocytes and macrophage [14, 15]. However, others reported that Tan IIA has cytotoxic effects on several cancer cells [16–19]. The effects of Tan IIA on human oral cancer cells still remain unknown. The goal of this study is to investigate whether Tan IIA shows the anticancer effects on human oral cancer KB cells and to explore the possible underlying mechanism. Our findings indicate that Tan IIA inhibits cell proliferation, stops cell cycle progression, and induces apoptosis through the intrinsic mitochondrial pathway.

Apoptosis, one type of programmed cell death, is a well-defined self-suicide process counteracting tumor growth. Many chemotherapy drugs produce antitumor effects by triggering the apoptosis through a variety of molecular mechanisms [28]. As the natural phytochemicals have been increasingly employed as chemotherapy agents, we examined the cytotoxic effect of Tan IIA on KB cells and assessed the possible application of this ancient herbal medicine as a novel agent for treatment of oral cancer. In the present study, we demonstrated a naturally extracted Tan IIA inhibited the proliferation and viability of KB cancer cells in a dose-dependent manner using SRB colorimetric assay. More than 90% of cells were killed after administration with 25 μg/mL of Tan IIA for 72 hours (Figure 1). Like studies mentioned above, Tan IIA did possess antiproliferative effects on human cancer cells. Furthermore, the cellular morphology was observed using Hoechst staining; those with shrunken and condensed fragmented chromosomes were identified as apoptotic cells (Figure 2(a)). Significant apoptosis developed when KB cells were treated with Tan 10 for 48 hours or Tan 20 for 24 and 48 hours (Figure 2(b)). Our results confirmed the involvement of apoptosis in response to Tan IIA in a dose-dependent manner.

Normal cell cycle progression is critical in regulating the cell proliferation and cell division. A dysregulation of the cell cycle that makes the cells undergo uncontrolled cell growth

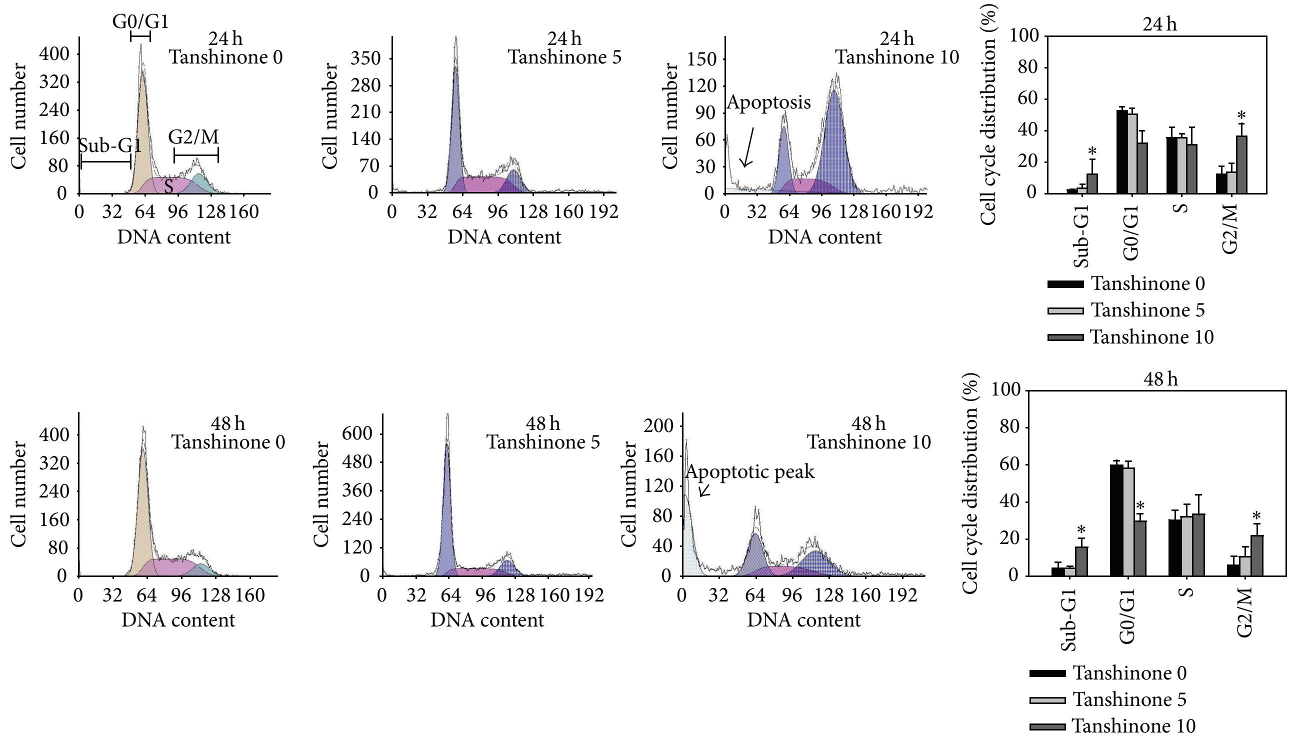

Figure 3: Effect of Tan IIA on cell cycle of KB cells. KB cells were treated with Tan IIA (0, 5, and 10 μg/mL) for 24 and 48 hours. Harvested cells were stained by propidium iodide and analyzed by flow cytometry. Values are the mean ± SD of 4 independent experiments. $*$ indicates $P < 0.05$.

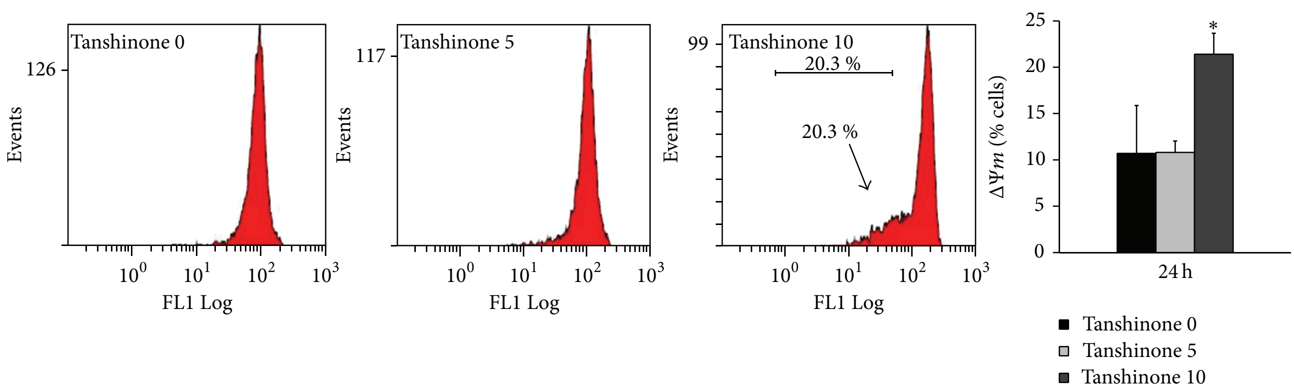

Figure 4: Influence of Tan IIA on the mitochondrial membrane potential ($\Delta\Psi$m) of KB cells. KB cells were treated with Tan IIA (0, 5, and 10 μg/mL) for 24 hours. After $DiOC_6$ staining, the changes of the mitochondrial membrane potential were measured using flow cytometry. Values are the mean ± SD of 4 independent experiments. $*$ indicates $P < 0.05$.

can result in the development of cancer. There are now more anticancer drugs that abrogate the cell cycle checkpoints and make the apoptosis develop [29, 30]. Thus, to target the errors of cell cycle regulation in cancer cells is considered a potential strategy for control of tumor growth. Previous studies showed that Tan IIA could arrest the nasopharyngeal carcinoma cell line (CNE-1) and human hepatocellular carcinoma cells (SMMC-7721) in G_0/G_1 phase, while other studies reported that human erythroleukemic cell line (K562) and HeLa cells were arrested in G_2/M phase [16, 17, 31, 32]. When the cell cycle is arrested, there comes an opportunity for cells to undergo either a repairing mechanism or the apoptotic cascade. Prolonged mitotic arrest induced by microtubule-interfering agents such as taxol and vincristine had been proved to make cells enter apoptosis [33, 34]. Zhou et al. had found that Tan IIA arrested HeLa cells in mitosis through disrupting the mitotic spindle and triggered the apoptosis [17]. Our data indicated that Tan IIA caused the decrease of KB cells in G_0/G_1 phase, an accumulation in G_2/M phase and an appearance in sub-G_1 proportion (Figure 3). Thus,

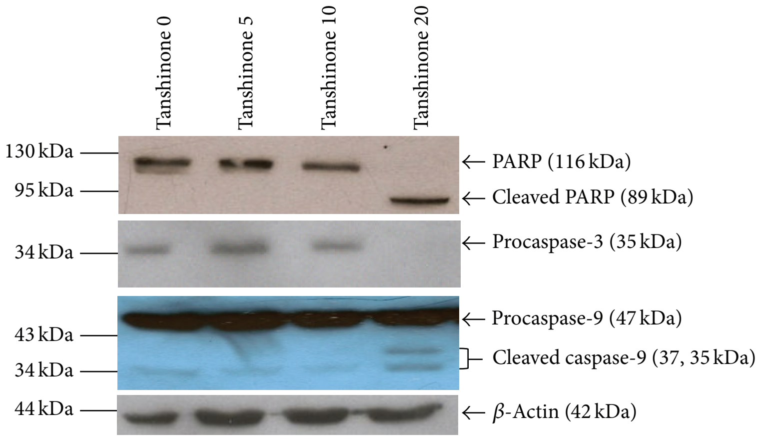

Figure 5: Effect of Tan IIA on caspase proteins and PARP of KB cells. Lysates of the KB cells treated with Tan IIA (0, 5, 10, and 20 μg/mL) for 24 hours were subjected to an immunoblot analysis with antibodies against caspase-3, caspase-9, and PARP. β-actin was served as the loading control.

treatment of KB cells with Tan IIA induced G_2/M phase arrest of cell cycle and the apoptosis indicating that Tan IIA might arrest cell cycle progression and lead to apoptosis.

Apoptotic signaling processes tightly regulated by many antiapoptotic and proapoptotic molecules have been divided into extrinsic and intrinsic pathways. In the intrinsic mitochondrial apoptotic signaling, *Bcl-2* has been identified as an apoptotic inhibitor and Bax protein inhibits the function of *bcl-2*. The apoptotic proteins, Bak and Bax, are key components that initiate mitochondrial dysfunction; an increased *Bax/Bcl-2* ratio disrupts the mitochondrial membrane potential [35–37]. The loss of mitochondrial membrane potential is one of the characteristic biochemical changes in apoptosis. Yang et al. pointed out that Tan IIA caused the decrease in mitochondrial membrane potential of the EAhy926 human endothelial cells [19]. We observed that Tan IIA treatment led to the dissipation of mitochondrial membrane potential in partial KB cancer cells (Figure 4). Thus, a mitochondrial response was involved in the Tan IIA-induced apoptotic pathway of KB cancer cells. The loss of mitochondrial membrane potential results in the release of cytochrome c and other apoptogenic proteins from the mitochondria to cytosol. Consequently, the interaction between cytochrome c, apoptosis protease-activating factor 1, and ATP/dATP forms the apoptosome which activates caspase-9. The activation of caspase-9 causes the cleavage of caspase-3, a critical executioner of apoptosis. Subsequently the activated caspase-3 cleaves the substrates including PARP, ultimately leading to apoptosis [20–27]. Therefore, we evaluated the effect of Tan IIA on caspase proteins and PARP in KB cancer cells. Western blot analysis showed that Tan IIA treatment resulted in the activation of caspase-9, the triggering of caspase-3, and the cleavage of PARP in the KB cancer cells (Figure 5). Several studies also indicated that caspase-9, caspase-3, and PARP were associated with the Tan IIA-induced apoptosis on the cancer cell lines [16, 17, 19]. Taken together, Tan IIA treatment led to the initiation of the intrinsic mitochondrial pathway and the activation of downstream caspase-3 in apoptosis of human oral cancer KB cells.

5. Conclusion

In conclusion, our study shows that Tan IIA suppresses the cell growth, arrests cells in G_2/M phase, and induces the apoptotic cell death of human oral cancer KB cells. In addition, we find that Tan IIA induces the apoptosis of KB cells through mitochondrial-dependent pathway in which the loss of mitochondrial membrane potential and the activation of caspase-9 and caspase-3 are involved, though other routes may be associated with the apoptotic events and need further investigation. Data obtained from our study indicate that Tan IIA could be a potential anticancer agent for oral cancer.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Research Article

Bipolar Thermofusion BiClamp 150 in Thyroidectomy: A Review of 1156 Operations

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Objectives. To compare the bipolar thermofusion BiClamp 150 with conventional ligature techniques for thyroid gland surgery, and report the advantages/disadvantages of both techniques. *Methods*. In this retrospective comparative study, all thyroid gland operations performed in the ENT Clinic Faculty Hospital Ostrava from 2006 to 2013 were included (1156 operations, 2122 lobes). Patients were categorized into two groups according to the type of vessel sealing method used, group I (BiClamp, $n = 819$ operations) and group II (conventional ligature, $n = 337$ operations). The number of revision surgeries due to wound hematoma was recorded as a bleeding event. Statistical analysis of the complication rate (bleeding rate, recurrent nerve palsy) and time of duration was performed. *Results*. The rate of revision surgery performed due to postoperative wound hematoma was significantly lower in group I (15/819, 1.83%) compared with group II (14/337, 4.15%) ($P = 0.022$). There was no statistically significant difference in the frequency of recurrent laryngeal nerve palsy between groups I and II ($P = 0.36$). The average surgery time was significantly shorter in group I ($P < 0.001$). *Conclusion*. Bipolar thermofusion BiClamp is an effective vessel sealing method that leads to a significant reduction in postoperative wound bleeding rates and reduces surgical time compared with conventional vessel ligature.

1. Introduction

The success of thyroid gland surgery depends on meticulous hemostasis in the operative field; otherwise, there is a possibility for numerous complications to occur, ranging from worsened wound healing due to hematoma to massive life-threatening hemorrhage [1]. Recurrent laryngeal nerve (RLN) damage is another possible complication of this type of surgery, occurring in 0.8–2.5% of all lobes operated on according to the literature [1].

Hemostasis during thyroidectomy can be performed by classic suture ligature (clamp-and-tie technique) or by electrocoagulation. Both methods are frequently used to control bleeding [2]. During the past few years, a variety of energy-based techniques for vessel sealing have been introduced [2–5]. For example, there is a harmonic scalpel that uses vibration energy [2]. Another novel technique for vessel sealing is bipolar thermofusion of tissue, for example, the frequently used marketed product, LigaSure [4, 5]. In our department, we use another marketed product BiClamp 150 (ERBE) that is specially designed for thyroidectomies.

The goal of our current study was to compare the bipolar thermofusion system, BiClamp 150, with the conventional clamp-and-tie technique for use during thyroid gland surgery in the terms of its effectiveness in hemostasis, safety in relationship with possible RLN damage, and possible shortening of the operation time.

2. Material and Methods

2.1. Study Design. During the period from September 2006 to June 2013, we retrospectively evaluated all 1156 thyroid gland operations performed in the ENT Clinic Faculty Hospital Ostrava. All patients who underwent a thyroid procedure were eligible for inclusion. The aim of this study was to compare the effectiveness of hemostasis and safety of the bipolar thermofusion system, BiClamp 150 in thyroid gland surgery with the conventional clamp-and-tie technique. The indications for surgery included all kinds of thyroid pathology (benign and malignant tumors of the thyroid gland

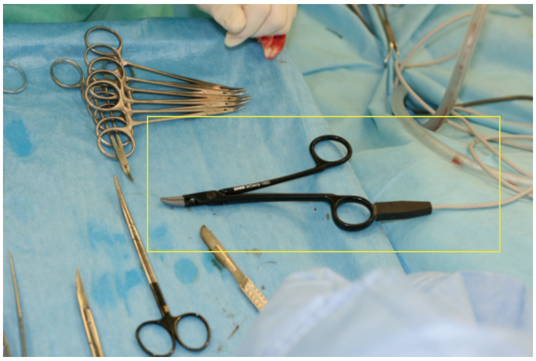

Figure 1: BiClamp manipulator.

and parathyroid tumors with thyroid extension, multinodular goiter, thyroiditis lymphomatosa, and others), including reoperative thyroid surgery due to residual thyroid tissue. Extent of surgery was considered to be total thyroidectomy and hemithyroidectomy, including extirpation of residual thyroid tissue in reoperative surgery. In the case of malignancy with lymph node involvement, block neck dissection was performed concurrently. We also included operations of the parathyroid gland with thyroid extension and hemithyroidectomy performed in our cohort. All operations were performed under general anesthesia, with the patient lying on their back and the head extended backwards. In all patients, before closure negative suction drain was placed and compression bandage was applied. Drain was removed on second postoperative day.

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. Written consent was obtained from all patients before the initiation of surgery.

2.2. Division of Patients and Rating. The patients were divided into two groups according to the type of vessel sealing used during the surgery. In group I, the bipolar thermofusion system, BiClamp 150, was used to seal the superior and inferior thyroid vessels and lateral thyroid veins. Conventional bipolar coagulation was used in smaller vessels. In this group, conventional ligature was not used at all. In group II, a conventional clamp-and-tie technique was used for ligating of the superior and inferior thyroid vessels and lateral thyroid veins. Smaller vessels were coagulated using conventional bipolar coagulation.

The number of revision surgeries due to wound hematoma was a parameter of hemostasis effectiveness for each group in our cohort. In this study, perioperative blood loss was not taken as a parameter due to wide spectrum of diagnosis operated. The number of permanent RLN palsies was a parameter of the safety of surgery. Only recurrent palsy lasting more than one year after the surgery was considered in the ratio of the number of palsies to the number of lobe operations. The duration of surgery was evaluated as a parameter of time saving. We did not evaluate possible hypocalcaemia after thyroid gland surgery in this cohort.

2.3. Bipolar Thermofusion with BiClamp 150 (ERBE). Bipolar thermofusion BiClamp 150 (ERBE Elektromedizin GmbH, Teubingen, Germany, www.erbe-med.com) is a tool specifically designed for thyroid surgery. It works on the principle of bipolar thermofusion of tissue. Low-voltage energy is strong enough to seal vessels of up to 7 mm in diameter on the basis of collagen fiber fusion [3]. The handpiece is shaped like forceps and is easily used to grasp and coagulate the vessel. It is useful for tissue preparation as well (Figure 1). After placing the handpiece into the proper position on the vessel and pushing the pedal, electrocoagulation starts. The process ends with acoustic signals from the processing unit, after the vessel is sealed and it is possible to cut it. An automatic stop function prevents heat injury from the surrounding tissues. Another advantage of the instrument is the possibility of resterilization. It should not be used in the area of the RLN due to the potential risk of injuring the nerve from the dispersion of heat. The tool is not suitable for coagulation of very small vessels because forceps tips of BiClamp are thicker than conventional bipolar coagulation tips. Encrusted coagulations could adhere to the forceps tips and there is danger of damaging the vessel when the forceps are withdrawn.

2.4. Statistical Analysis. The χ^2 test for 5% significance was used to analyze differences in revision surgery rates and recurrent nerve palsy rates between groups I and II, with $P < 0.05$ considered statistically significant. For analysis of the duration of the operation, nonparametrical two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for 5% significance. Stata software (version 10) was used for all statistical calculations.

3. Results

During the period from September 2006 to June 2013, there were 819 (1522 lobes) thyroid gland surgeries in group I (BiClamp). In group II (conventional ligature), there were 337 thyroid gland surgeries (600 lobes). The male to female ratio was 1/5.4.

In group I, the ratio of revisions to surgery was 15 to 819 (1.83%). In group II, revision due to bleeding was performed 14 times in 337 surgeries (4.15%). The total postoperative bleeding rate was 2.51%, and all revisions were performed within 24 hours after surgery. The ratio of revisions to surgery was significantly lower in group I (BiClamp) compared with surgery with conventional ligature ($P = 0.022$).

RLN palsy was observed in 22/1522 (1.45%) lobes in group I and 12/600 (2.0%) in group II. No significant difference between groups was observed ($P = 0.36$).

The average ± standard deviation duration of total thyroidectomy was 89.6 ± 27.6 minutes in group I and 122.9 ± 37.7 minutes in group II (Table 1). The average duration of surgery was decreased by 25.99% (Figure 2). The difference in time saving in group I was statistically significant compared with group II ($P < 0.001$).

Table 1: Duration of surgery in minutes according to extent of the surgery.

Group	BiClamp N	BiClamp Median (min)	BiClamp Mean (min)	Ligature N	Ligature Median (min)	Ligature Mean (min)	P value*
TTE	679	90	89.66	263	120	122.90	<0.001
TTE + BND	26	137.5	145.08	9	165	171.67	0.144
HTE	114	60	63.12	65	75	82.63	<0.001
Total	**819**	**82**	**87.72**	**337**	**120**	**116.44**	**<0.001**

HTE: hemithyroidectomy; TTE: total thyroidectomy; BND: bloc neck dissection.
*Two-sample Wilcoxon rank-sum (Mann-Whitney) test.

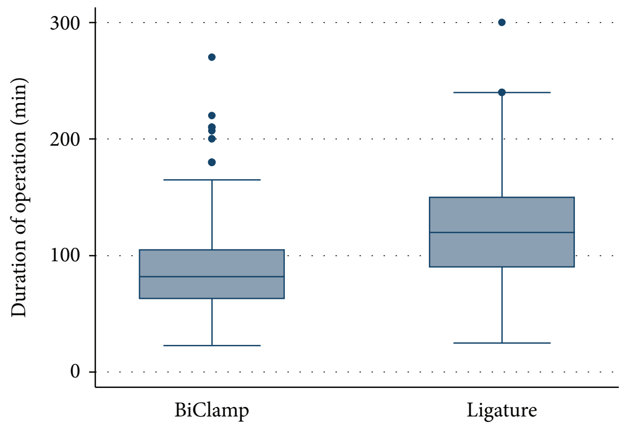

Figure 2: Duration of surgery in minutes for group I (BiClamp) and group II (ligature).

4. Discussion

In the past few years, novel methods of vessel sealing without using conventional ligature have emerged [2–6]. In addition to spray coagulation or harmonic scalpel, there is also the principle of bipolar tissue thermofusion as used by BiClamp 150 [3]. In our department, this system is frequently used in thyroid gland surgery. Traditionally, use of electrosurgical bipolar thermofusion systems spread to head and neck surgery from abdominal surgery and gynecology [4]. A randomized study by Silva-Filho in 45 patients with vaginal hysterectomies showed shorter operative times, faster recovery, lower perioperative blood loss, and less pain with the bipolar vessel sealing system compared with conventional sutures [4]. However, since 2003 several studies have reported successful usage of bipolar vessel sealing systems in thyroidectomy [5–7]. In his comparable study of 155 patients, Franko et al. emphasize that LigaSure bipolar electrosealer, when used as the primary means of hemostasis during thyroidectomy, significantly reduced mean operative times, whereas the rates of perioperative complications were unchanged [5]. Lachanas et al. obtained similar findings during thyroid surgery with LigaSure in 72 consecutive patients. There was a mean reduction in operative time of 23 minutes compared with previous surgical thyroid procedures when a bipolar vessel sealing system was not used [6]. Manouras et al. compared the outcome of thyroidectomy using an electrothermal bipolar vessel sealing system (n = 148), the harmonic scalpel (n = 144), and classic suture ligation techniques (n = 90). Compared with the classic technique, surgical time was reduced by about 20% when a bipolar sealer or harmonic scalpel was used. The 3 groups were similar in terms of perioperative complications, hospital stay, and thyroid gland pathology [7].

Data in the literature show rates of about 1.72–4.2% postoperative bleeding that require revision of thyroidectomy wounds [8–10]. In a study of 30,142 thyroid gland operations, Promberger et al. observed postoperative bleeding in 1.7% [8]. Risk factors identified were older age, male sex, extent of the resection, bilateral procedure, and operations for recurrent disease. The risk of postoperative bleeding doubled during bilateral thyroid surgery compared with unilateral surgery, occurring in 2.0% of bilateral operations compared with 1% of unilateral operations [8]. A high frequency of total thyroidectomy (663/819 in group I, 250/337 in group II) in our cohort is probably one of the factors that influenced the higher frequency of postoperative bleeding (the number of vessels treated is doubled during total thyroidectomy). Morton et al. identified a postoperative systolic blood pressure of greater than 150 mmHg as a major significant factor associated with an increased risk of hemorrhage following thyroid surgery [9]. Finally, the method of vessel sealing influenced the postoperative bleeding rate. Saint Marc et al. in his prospective study of 200 patients found that 1 patient in the LigaSure group (n = 100) and 2 patients in the clamp-and-tie group (n = 100) required revision surgery due to hematoma. Despite this, the authors considered LigaSure to be as safe as the clamp-and-tie technique [11]. Franko et al. obtained similar results. One patient in each group (LigaSure group, n = 85, clamp-and-tie group, n = 70) developed neck hematoma requiring surgery [5]. In our cohort, bipolar thermofusion during surgery decreased the frequency of postoperative bleeding during surgery compared with classical vessel ligature (clamp-and-tie method). The frequency of wound revision due to bleeding was significantly lower in the thyroid surgery with use of BiClamp compared with conventional ligature ($P = 0.022$).

We did not observe any statistically significant difference in the frequency of RLN palsies based on the method of vessel sealing (BiClamp, conventional ligature) ($P = 0.36$). BiClamp has not been used in the area of the RLN because it is not recommended by the manufacturer due to possible heat dispersion and injury of the nerve. In this area only conventional bipolar coagulation was used in BiClamp group. The incidence of RLN paresis in the literature is 0.8–2.5% of all lobes operated, with higher rates occurring in older patients [1, 12–14]. Our findings are in agreement with these.

According to the literature, bipolar thermofusion could reduce the duration of surgery [5–7]. Franko et al. observed significantly shorter times when hemostasis was achieved with a bipolar electrosealing device (LigaSure, $n = 85$, 110 ± 33 minutes) compared with conventional ties ($n = 70$, 130 ± 37 minutes, $P < 0.001$) [5]. Manouras et al. found that surgical time was reduced significantly by about 20% when the bipolar vessel sealer or harmonic scalpel was used compared with the classic technique (93 ± 12.5 versus 74.3 ± 14.2 and 73.8 ± 13.8 minutes). Such findings were also shown in our cohort. In group I (BiClamp) we found a 26% time reduction compared with group II (conventional ligature) ($P < 0.001$). However, the BiClamp bipolar vessel sealing system is reusable compared to single-use manipulators such as the harmonic scalpel. This decreases the cost of surgery and may justify use of a bipolar vessel sealing system in ENT departments.

5. Conclusion

The bipolar thermofusion BiClamp is an effective and safe method for vessels sealing during thyroidectomy, including sealing of the main thyroid vessels. BiClamp may achieve statistically significant reductions in the frequency of postoperative bleeding compared with conventional vessel ligature. Using bipolar thermofusion also leads to significant reductions in operative time.

Conflict of Interests

The authors declare that there is no actual or potential conflict of interests in relation to this paper. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this paper.

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Research Article

Clinical Use of Skull Tap Vestibular Evoked Myogenic Potentials for the Diagnoses of the Cerebellopontine Angle Tumor Patients

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Objective. To document our experiences using a new skull tapping induced Vestibular Evoked Myogenic Potentials (tap VEMPs) technique combined with standard Auditory Vestibular Evoked Myogenic Potentials (AC VEMPs) for advanced clinical assessment of cerebellopontine angle tumor (CPAT) patients. *Design and Study Sample.* Three patients were selected in order to highlight observations shown in a larger patient population and to show the variability of the findings. Both tap VEMPs and AC VEMPs were acquired from the sternocleidomastoid muscle (SCM) with EMG-based biofeedback and monitoring. *Results.* The usefulness of VEMPs was demonstrated, indicating the presence of a tumor and contributing additional information as to the involved nerve bundles in two out of the three cases. *Conclusion.* Due to the sensory organ dependency and related innervations differences, acquiring both AC VEMPs and tap VEMPs is likely to increase the probability of diagnosing CPATs and provide more information on the involved vestibular nerve bundles. This study demonstrates the feasibility of the possible expansion and combination of tap VEMPs and AC VEMPs techniques into a clinical diagnostic battery for advanced assessment of CPAT patients and its contribution as a guideline for the use of tap VEMPs in general.

1. Introduction

Vestibular Evoked Myogenic Potentials (VEMPs) are one of the most recent methods added to the vestibular organ test battery. Although the initial reports of the VEMPs can be dated back to the early 1935 [1], the current highly used method based on the myogenic activity recordings from the sternocleidomastoid (SCM) muscle was introduced by Colebatch et al. [2, 3]. Sound evoked cervical VEMPs rapidly gained the attention of both researchers and clinicians, resulting in numerous publications describing the clinical and research potential of VEMPs. Additional research extended the VEMP stimulation from auditory to skull tapping [4], bone conduction vibrations [5, 6], and galvanic stimulation [7, 8]. In addition to the SCM muscle, a variety of muscles were also shown to produce VEMPs, such as masseter [9], gastrocnemius, tibialis anterior, biceps femoris, quadriceps [10], and extraocular muscles [11, 12].

Auditory cervical approach is currently the most investigated VEMP acquisition method. The current consensus on the sensory organ responsible for the Auditory Cervical VEMPs (AC VEMPs) is the saccule [13, 14]. Saccular origin suggests that the inferior vestibular nerve functional integrity is essential in the generation of AC VEMPs as the majority of the sacculus innervation is carried by this nerve [15–18]. More recently, skull tapping VEMPs (tap VEMPs) have been heavily investigated by various authors. The tap VEMPs are proposed to generate a more complex stimulation paradigm described as containing two different mechanisms, one resulting in an ipsilateral inhibitory activity on the SCM and the second acting bilaterally producing a response with a polarity which is opposite for the two SCM muscles [19]. Although it is still not clear which part of the vestibular organ is responsible for the tap VEMPs, the utricle has been designated to be the origin of the unilateral and bilateral components [19–22]. However, the vibrations conducted via bone are propagated to a large region on the skull and may stimulate other parts of the vestibular organ. Therefore, skull tapping is a more complex stimulus type, likely to result in activation of multiple sensors on both sides of the head bilaterally activating the superior and inferior vestibular nerves [23, 24]. Evidence strongly suggests that tap VEMPs, to a significant extent, are dependent on superior bundle of vestibular nerve; they are more often affected in patients with vestibular neuritis (which usually affects only the superior vestibular nerve), in contrast to AC VEMP [25]. It has been also reported that the tap VEMPs can be recorded despite selective section of the inferior vestibular nerve [26], indicating that tap VEMPs strongly rely on the superior vestibular nerve [23].

Initial tap VEMP studies were performed by using a manually controlled reflex hammer attached to a triggering mechanism [4]. Skull tapping via reflex hammer is prone to deliver varying amount of momentum with each individual hit to the test subject, thus causing variability in the response. Later studies used mechanically controlled vibration and impact generating devices for skull tapping in order to standardize the amount of momentum delivered with each tap [23, 27, 28]. These devices are generally held by hand against the impact site on the skull. The forces delivered by these devices are also prone to variability as the position on the head and the hand position are likely to change during the recordings. The major source of variability in VEMP recordings is shown to be the contraction level of the muscle that is used as the electromyelography (EMG) source. It has been shown that the VEMP amplitude is directly related to the strength of the background SCM muscle activity and is absent at rest [3, 29, 30]. In general, during VEMP recordings, the subject is asked to push the head against a structure to ensure a certain amount of contraction in the cervical muscles [3] or asked to lie in supine position lifting their heads up [4] or asked to turn their heads away from the stimulus [31]. Although the abovementioned methods for muscle contraction can help to maintain muscle activity, none can be used to guarantee a constant EMG activity range. To overcome this problem, EMG-based biofeedback methods were developed to increase the cooperation of the subjects so that the subject can monitor and correct the contraction level of the muscle. In this approach, a muscle activity value is calculated from the rectified EMG signals and displayed to the subject as feedback [21, 32].

VEMPs stand out as a promising tool in clinical practice as they are noninvasive and easy to acquire with low time and instrumentation cost. Additionally, when acquired together AC VEMPs and tap VEMPs may be used as a tool to identify the functional integrity of inferior and superior vestibular nerves.

Despite large amount of research on VEMPs and constant development of the instrumentation and methods for the clinical usage, VEMPs and in particular tap VEMPs are still not well established clinically due to a number of issues. Some of these issues are lack of a standardized tap VEMP specific device, limited or no quantification on the delivered force and instantaneous EMG activity, lack of clinical experience, sensitivity, specifications, and also lack of established clinical protocol for the use of tap VEMPs.

In this paper, our main goal is to establish a clear, repeatable protocol for the clinical assessment of CPAT cases, geared by the recent developments in the objective vestibular functional evaluation methods, particularly the complimentary use of AC VEMPs and tap VEMPs in daily clinical practice. In our department VEMPs are part of a routine testing on various vestibular problems, particularly on patients with cerebellopontine angle tumors (CPAT). In this study, we present results of AC VEMP and tap VEMP recordings acquired with the use of a new prototype automated skull tapping device (Intelligent Hearing System Inc., Miami, FL) that can be stabilized on the skull using a headband that ensures a fixed placement and contact pressure. Additionally, an EMG standardization method integrated into the acquisition software is used to further minimize the variability of the AC VEMP and tap VEMP recordings. This paper describes our findings on 3-case examples from a growing patient data pool which will be presented in the future.

2. Material and Methods

2.1. Clinical Investigation Protocol. In our department, when a patient is identified as a potential CPAT case, our general protocol is to conduct a diagnostic battery on the patient by following a diagnostic procedure for vestibular or acoustic schwannoma [33] using the standard tests with the complimentary addition of AC VEMPs and tap VEMPs. The order of the tests in the following list reflects the escalation in the diagnosis towards a CPAT case.

(1) Patient history.

(2) Otoscopy.

(3) Audiological assessment (particularly for signs of compression reflecting the involvement of other nerves that share the same trajectory in the auditory canal [34–36]) that involves pure tone audiometry, speech discrimination test, impedance audiometry with stapedius reflex, and auditory brainstem response (ABR).

(4) Examination of the patients by acquiring auditory and skull tapping VEMPs according to the protocol that will be described in detail below. Due to the sensory organ dependency and related innervations differences, as mentioned above, recording both the AC VEMPs and tap VEMPs further increases the potential of identification of the affected nerve bundles. For instance, in cases where no or reduced AC VEMPs are observed but tap VEMPs are present, a nonfunctional inferior bundle but a functioning superior vestibular nerve can be estimated.

(5) The magnetic resonance imaging (MRI) with gadolinium enhancement is currently viewed as the most accurate diagnostic tool for VIII nerve schwannoma capable of identifying tumors as small as 3 mm in size. On the other hand it is quite costly and it is

not performed at the early stages of the diagnostics procedure. In many countries, where health services are rationed, a clear indication of tumor presence is necessary for scheduling an early MRI appointment. The MRI is performed if tests described above indicate the high suspicion of the CPAT according to cross-check rule. In MRI tumor size, location in the internal auditory canal (which part of the canal) and brainstem compression if present are described. This information is very helpful in consideration of surgery approach which depends on the size and location of the tumor and the degree of hearing loss.

(6) Clinical and electrical examination of the facial nerve is performed to test the facial nerve involvement.

(7) Surgical referral.

While the MRI provides information on tumor presence and its size and location in the internal auditory canal (which part of the canal) that are essential for the surgeon, it does not provide information about which nerve bundles are involved in the process. The information provided by ABR and AC VEMPS and tap VEMPs together is very useful for a surgeon due to the relationship of cochlear and vestibular nerves in the internal auditory canal. The vestibulocochlear nerve divides into individual nerves in the lateral aspect of the internal auditory canal: cochlear nerve more anteriorly and both vestibular nerves superior and inferior more posteriorly [34–36]. The facial nerve courses anterior like cochlear nerve but remains more superior to it. The nerves all together rotate 90 degrees in their course from the fundus of the internal auditory canal to the cerebellopontine angle, so that the cochlear nerve rotates from anterior to posterior but stays most inferior [34]. As the vestibulocochlear nerve divides into individual nerves, the presence of a tumor can be reflected by malfunctions of these nerves depending on which nerve the compression occurs.

2.2. Acquisition of AC VEMPs and tap VEMPs. All VEMP recordings were conducted using surface electrodes placed on the skin above SCM muscle. The positive electrodes were placed bilaterally on the midpoint of the SCM muscle measured between the points where the muscle was connected to the mastoid and the sternum. The negative electrodes were positioned on the sternum and the SCM junction. The ground electrode was placed laterally on the zygomatic bone so that the placement of the skull tapper on the forehead was possible for tap VEMP recordings.

All VEMPs were acquired using SmartEP evoked potential acquisition system on the IHS USB Box platform (Intelligent Hearing Systems, Inc., Miami, FL). Recordings were performed with sampling period of 400 ms with 5K amplification filtered using a 6 dB per octave band pass filter with highpass cutoff set at 30 Hz and lowpass cutoff set at 1500 Hz. The AC VEMPs were collected by averaging 128 sweeps and tap VEMPs were acquired averaging 64 sweeps. Less number of sweeps was used for the tap VEMPs as skull tapping was found to generally generate larger amplitude responses compared to the auditory counterpart. For each recording site and type two sets of recordings were made which were later averaged to increase the signal to noise ratio. The two sets of recordings were used to monitor the repeatability of the recorded signals. The AC VEMPs were evoked by 5000 ms long 500 Hz tone bursts conditioned by an exact Blackman window delivered via ER3a ear insert phones (Etymotic Research, Inc., Elk Grove Village, IL) at 100 dBnHL. The tap VEMPs were evoked by a prototype skull tapping device produced by Intelligent Hearing Systems Corp. The skull tapper was composed of an electromagnetic push type mechanism automatically controlled by the software to deliver a controlled force with a hit onset detection mechanism. The piston of the tapper was held at the same position for 100 ms following the hit at the surface interfacing the skull to ensure a unidirectional force delivery. The delivered force was measured to be 10.5 N using a commercially available artificial mastoid device (type 4930) Bruel & Kjær (Nærum, Denmark). Details on the skull tapper device will be described in a separate article. A stimulation rate of 3.1/s was used for both VEMP recording types. The recording system uses an EMG-based biofeedback monitoring method to minimize the variation in the SCM muscle contractions and thus the variation in the amplitude of VEMPs. This method is based on continuous monitoring of pre- and poststimulus EMG activity. In this method two conditions had to be fulfilled for a window of a recording cycle to be accepted into the average: (a) the root means squared (RMS) EMG activity had to fall into a range set by the user (generally minimum at 50 μV and maximum at 150 μV RMS), and (b) the poststimulus activity should not exceed a user set artifact rejection value. If both cases were satisfied an illustration of a smiling face was shown on the monitor to the patient (this would indicate to the patient that the SCM muscle contraction was sufficient for recording and that he/she should stay in this position to complete the set of recordings). In addition, a green bar showing the actual EMG RMS levels was also presented. When any of the conditions was not met the smiling face was replaced by an upset face and the EMG bar color was turned to red. A secondary feedback indicator box that contained a red and a green LED light was also present. Both indicators were used to increase the patient cooperation with the SCM muscle contraction and minimize the muscle fatigue.

The skull tapper was placed on the skull at three locations: (a) at the midline on the forehead, (b) behind the left ear on the mastoid process, and (c) behind the right ear on the mastoid process. The stabilization of the skull tapper was ensured using an adjustable head band.

The recordings were performed with the patients comfortably resting in a supine position and lifting the head up towards midline. The patients were directed to just lift the head, with no shoulder and abdominal muscle activity if possible. During all recordings a researcher was present at all times directing the patient to increase or decrease the lift of the head or the turn movement to stay in the selected RMS EMG levels using the biofeedback monitor for guid ance.

Three different types of recordings were conducted with AC VEMPs (two repetitions each):

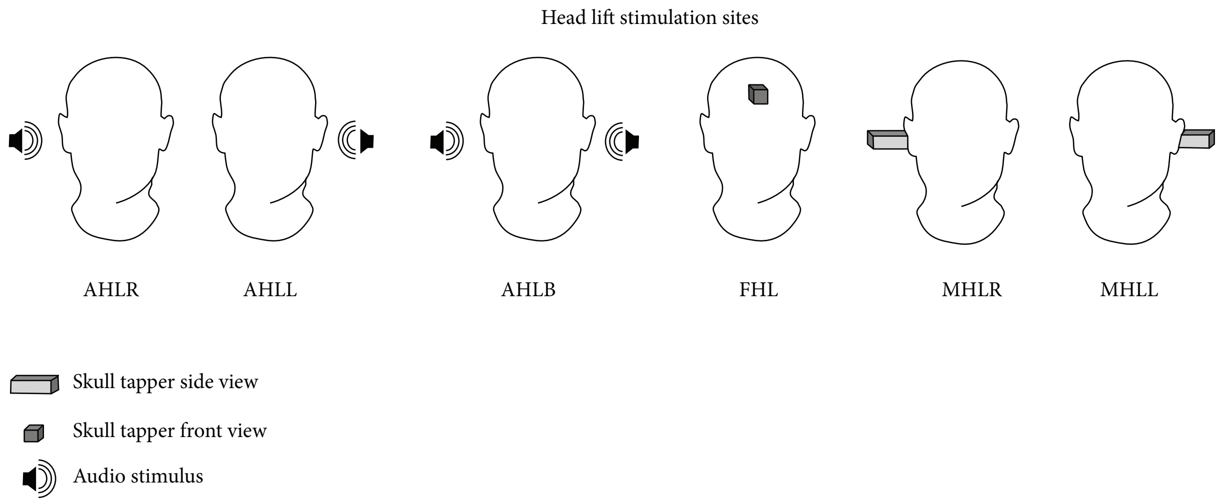

Figure 1: The stimulus presentations sites for the head lift recordings made for acoustic and skull tap VEMPs. Abbreviations in the illustration indicate the stimulus type and direction as follows: (1) head lift stimulus delivered to the right ear (AHLR); (2) head lift stimulus delivered to the left ear (AHLL); (3) head lift stimulus delivered to both ears (AHLB); (4) forehead head lift (FHL); (5) mastoid head lift skull tapper located at right (MHLR); (6) mastoid head lift skull tapper located at left (MHLL).

(1) head lift stimulus delivered to the left ear (AHLL),
(2) head lift stimulus delivered to the right ear (AHLR),
(3) head lift stimulus delivered to both ears (AHLB).

Three different types of recordings were conducted for the skull tapping evoked VEMPs (two repetitions each) with skull tapper located at

(1) forehead head lift both sides recorded (FHLB),
(2) mastoid head lift skull tapper located at left (MHLL),
(3) mastoid head lift skull tapper located at right (MHLR).

Therefore a total of 12 recordings were conducted for each patient (6 total types with two repetitions) before and after the surgical intervention as shown in Figure 1.

The recorded responses were normalized according to the prestimulus (base) EMG RMS calculations. Normalized values were used to assess the asymmetry ratios (AR) between the left and right side measurements. The usefulness of the normalization of AR measurements is still under debate [37]. The following equation (1) was used for the asymmetry ratio, where the A_L is the amplitude measure from the left side recording between the first positive and first negative peak and similarly A_R is the amplitude measured on the right side. Corrected AR of up to 35% is considered normal [38]:

$$\text{Asymmetry Ratio} = 100\left|\frac{(A_L - A_R)}{(A_L + A_R)}\right|. \quad (1)$$

During the course of this study additional VEMP recordings were made where the SCM contraction was sustained via the head turn to the sides. In this paper we only present the results and the details of the head lift data as we found the head turn method to be unreliable when analyzed via asymmetry ratio approach. We prefer and advocate the head lift approach as it is much easier to control and identify if a patient's head is symmetrically lifted or not. For this reason we believe that the VEMPs recorded via head lift are less prone to be affected by the orientation differences of the vestibular organs during the recording sessions compared to head turn with the current instrumentation limits. Additional feedback monitoring of the 3D positioning of the head by using additional means such as gyroscopes and/or accelerometers could help to minimize this variability.

2.3. Participating Patients Details

Patient Number 1. Patient number 1 was a 43-year-old man who suffered from slight tinnitus and slight hearing loss in his right ear with no vestibular problems prior to admission. Audiological tests revealed a small high-frequency sensorineural hearing loss on the right side with pure tone average (PTA) for 3 and 4 kHz = 35 dBHL. The speech discrimination score at 60 dB was almost normal (80%, scored 100% at 70 dB). Impedance audiometry revealed normal middle ear function and normal stapedius reflex thresholds on both sides. Normal response to click stimulus at 90 dBnHL was present on the left side in ABR but on the right side ABR showed retrocochlear abnormality. Vestibular caloric test and videonystagmography showed normal responses on both sides with no central vestibular disorders. Details on the VEMP recordings will be described in the Results section. MRI revealed a tumor in the internal auditory canal; the tumor was 12 × 9 mm in size. Clinical and electrical examination (using electromyography) of the right facial nerve revealed its normal function.

Middle fossa approach was chosen for the surgery attempting to preserve the hearing. The tumor appeared to arise from cochlear nerve and was attached to other nerves in the internal auditory canal.

Patient Number 2. Patient number 2 was a 51-year-old woman. Prior to the admission, she complained about tinnitus and hearing loss in the right ear with some symptoms of right facial nerve paresis. Pure tone audiometry revealed sensorineural hearing loss on the right side with PTA for 0.5 and 1 kHz = 30 dBHL and for 2 and 4 kHz = 57.5 dBHL, and the speech discrimination score at 60 dB was 30% for the right ear. Normal middle ear function was proved with tympanometry but stapedius reflexes were missed. Normal response to click stimulus at 90 dBnHL was present on the left side in ABR and no reproducible waves on the right. Vestibular caloric test and videonystagmography revealed aflexia on the right side with no central vestibular abnormalities and normal function on the left. Clinical and electrical examination (electromyography) of the right facial nerve revealed its abnormal function. Details on the VEMP recordings will be described in the results section. MRI showed a 4 × 9 mm tumor in the right internal ear canal.

Middle fossa approach was selected to increase the possibility of hearing preservation. The tumor seemed to arise from superior vestibular nerve but involved the inferior one as well.

Patient Number 3. Patient number 3 was a 26-year-old woman whose main complaint was tinnitus on the left side. At the admission she stated not having any other hearing or vestibular problems. Auditory testing revealed normal hearing in both ears in all audiometric frequencies with the pure tone average for 0.5, 1, 2, and 4 kHz = 2.5 dB and speech discrimination score at 60 dB was 100%. Impedance audiometry revealed normal results. Auditory brainstem response showed normal reproducible waves on both sides. Vestibular caloric test and videonystagmography showed normal responses on both sides with no central vestibular disorders. Left facial nerve function was normal. VEMPs will be discussed in the Results section. Due to the patient's history of asymmetric tinnitus and young age it was decided to perform MRI. The MRI revealed a tumor in the internal auditory canal; the tumor was 7 × 5 × 15 mm in size.

For the surgery middle fossa approach was selected for the hearing preservation. The tumor seemed to arise from superior vestibular nerve.

This study is a part of a retrospective-prospective project that was approved by the Ethics Committee Review Board at the Medical University of Warsaw, where the VEMPs recordings have been conducted. The project conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

3. Results

Table 1 shows AC VEMP and tap VEMP results with values for P1 latencies and corrected amplitudes of the responses along with corrected asymmetry ratios. Figure 2 presents the results of the preoperative (preop) recordings acquired by both VEMP techniques. Figure 3 shows the change observed between the preop and postoperative (postop) responses recorded from the ipsilateral side to the tumor.

Patient Number 1. In this patient, highly large corrected asymmetry ratio (AR) values for AC VEMPs (AHLB AR = 47.59%; AHLL versus AHLR AR = 45.43%) were observed. Values lower than 35% are considered normal [38] and we used them as referral. In close inspection of the waveforms from the contralateral side, one can easily see that the left side stimulation produced much smaller activity on the right side, where the right side stimulation did not produce a similar activity on the left side (Figure 2).

The tap VEMPs were symmetric for the forehead (FHLB AR = 19.15%) and for the mastoid skull tapping results recorded from the ipsilateral side SCM (right MHLR versus left MHLL AR = 16.84%).

The postop responses were compared with the preop data (Figure 3). The AC VEMPs results showed that P1 and N1 disappeared when the ear ipsilateral to the tumor was stimulated. In the bilaterally stimulated recordings, we observed the preservation of these peaks to an extent. Considering the surgical cut of the ipsilateral inferior bundle, the preservation of the peaks suggested the contribution of the contralateral side. Forehead placement tap VEMPs showed a reversal in the recorded P1-N1 peak complex. In all of the above recordings the later waveforms observed between 25 and 60 ms range which are generally regarded as cochlear in origin [24, 39] did not display a major change.

Patient Number 2. Patient number 2 medical history, along with unilateral sensorineural hearing loss, poor speech recognition, ABR, VNG, and facial nerve EMG results, pointed to impaired function of VIII and VII nerves on the right side.

In AC VEMPs we observed drastic differences between left and right side responses (AHLB AR = 43.49%). The right side auditory stimulation failed to generate a response where the left side stimulation evoked a robust response (Figure 2).

Skull tapping the forehead and each mastoid resulted in large ARs (FHLB AR = 57.60%; MHLR versus MHLR AR = 61.32%). Upon visual inspection of ipsilateral responses, the initial parts of the waveform morphology (P1-N1 region) were different (Figure 2.).

In the postop preop comparison (Figure 3), there were no significant changes in any of the responses recorded ipsilateral to the tumor in neither of the VEMP techniques for P1 and N1 peaks, suggesting that both bundles had total functional loss before the surgery. Additionally, similar to the first patient, late waveforms did not display a significant change.

Patient Number 3. In patient number 3, all audiological VNG and VEMP tests were within normal limits. Due to patient's young age and history of tinnitus on the left side this suggested that there might be a retrocochlear problem.

No asymmetry was observed in the AC VEMPs (AHLB AR = 16.62%; AHLR versus AHLL AR = 19.95%) and tap VEMPs (FHLB AR = 17.18%; MHLR versus MHLL AR = 19.29%). The mastoid ipsilateral tap VEMP recordings showed high similarity. In this case, both AC VEMP and

Table 1: Auditory and skull tap VEMP head lift results.

Patient	Analyzed parameter	Head lift: Auditory: AHLB: Response from left SCM	Response from right SCM	AR (%)	AHLL: Response from left SCM	AHLR: Response from right SCM	AR (%)	Tapping forehead: FHLB: Response from left SCM	Response from right SCM	AR (%)	Tapping mastoids IPSI responses: MHLL: Response from left SCM	MHLR: Response from right SCM	AR (%)
1	P1 latency (ms)	13.20	13.40		13.40	14.20		13.20	14.40		14.00	14.40	
	Corr. amplitude	**25.56**	**9.08**	**47.59***	**22.96**	**8.62**	**45.43***	**36.24**	**24.59**	**19.15**	**33.67**	**23.97**	**16.84**
2	P1 latency (ms)	14.00	13.60		14.60	NR		14.40	15.20		17.20	15.60	
	Corr. amplitude	**13.14**	**5.18**	**43.49***	**23.51**	**NR**		**33.22**	**8.94**	**57.60***	**38.19**	**9.16**	**61.32***
3	P1 latency (ms)	12.60	12.80		12.80	13.00		14.00	13.60		14.40	13.20	
	Corr. amplitude	**10.19**	**14.14**	**16.26**	**19.62**	**29.40**	**19.95**	**44.88**	**31.72**	**17.18**	**58.23**	**39.40**	**19.29**

AHLB: head lift stimulus delivered to both ears; AHLL: head lift stimulus delivered to the left ear; AHLR: head lift stimulus delivered to the right ear; FHLB: Forehead Head Lift skull tapper located at forehead; MHLL: Mastoid Head Lift skull tapper located at Left; MHLR: Mastoid Head Lift skull tapper located at Right; P1: positive peak; corr. amplitude: corrected amplitude; SCM: sternocleidomastoid muscle; AR: Asymmetry ratio; NR: no response. Abnormal results of corrected asymmetry ratios (AR% > 35%) and no response results (NR) are marked with ∗.

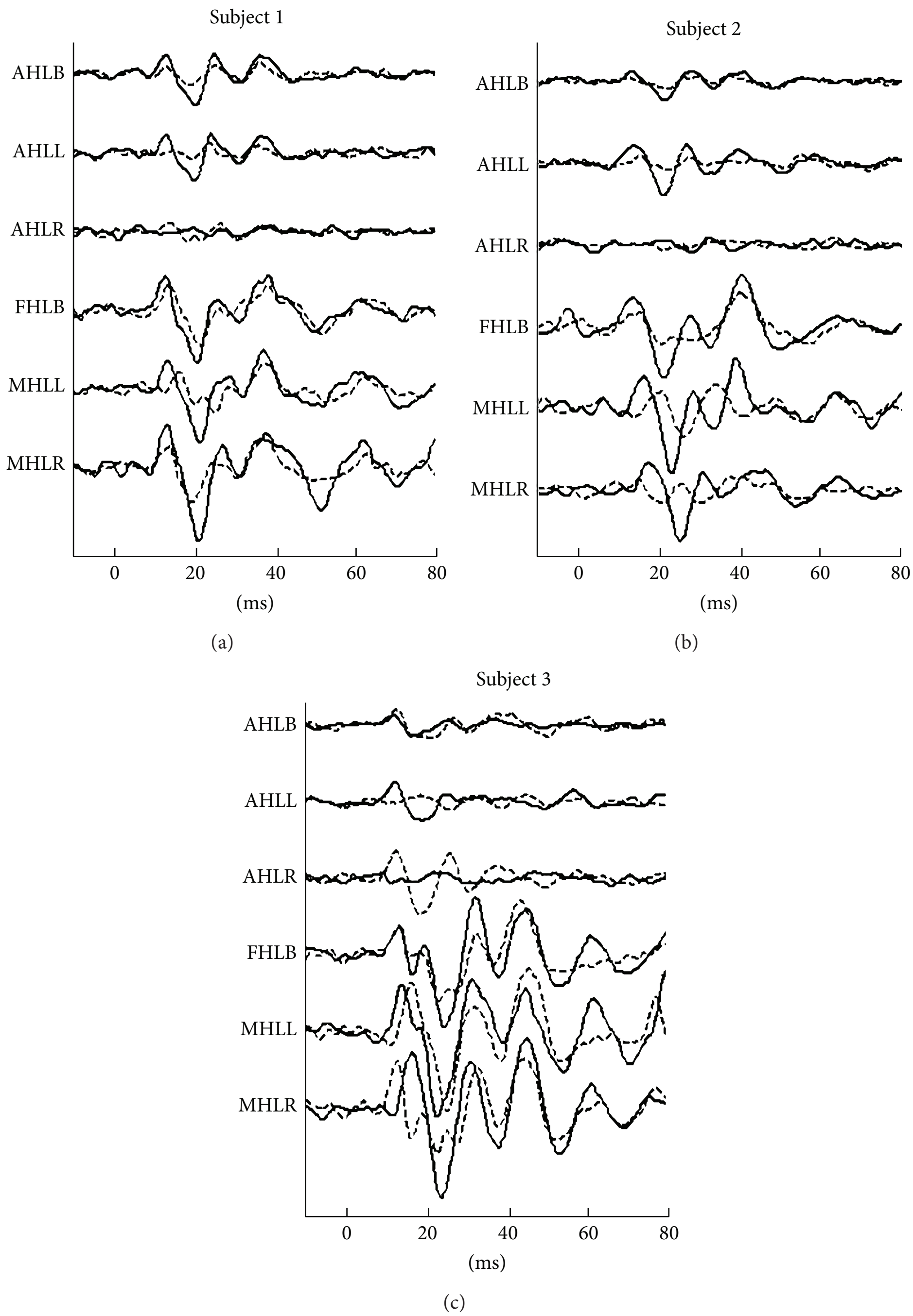

Figure 2: VEMP waveforms recorded from all 3 subjects. All the waveforms are normalized according to prestimulus EMG activity. In this figure left side recordings are plotted as solid lines while right side recordings are plotted as dashed lines. Abbreviations are used in this figure as follows. AHLB: auditory head lift both ear stimulation recorded bilaterally; AHLL: auditory head lift left ear stimulation recorded bilaterally; AHLR: auditory head lift right ear stimulation recorded bilaterally; FHLB: head lift recording tapper located at forehead recorded bilaterally; MHLL: head lift recording tapper located at left mastoid recorded bilaterally; MHLR: head lift recording tapper located at right mastoid recorded bilaterally.

tap VEMP results failed to point to a tumor presence. The MRI showed a tumor in the left internal auditory canal (7 × 5 × 15 mm). During the surgical intervention, the tumor was identified as arising from the superior vestibular nerve.

In the postop versus preop comparison (Figure 3) of the head lift AC VEMP recordings, no significant change on the tumor side was found when both ears were stimulated. However, significant difference was shown when the stimulation was at the side of pathology. For the tap VEMP,

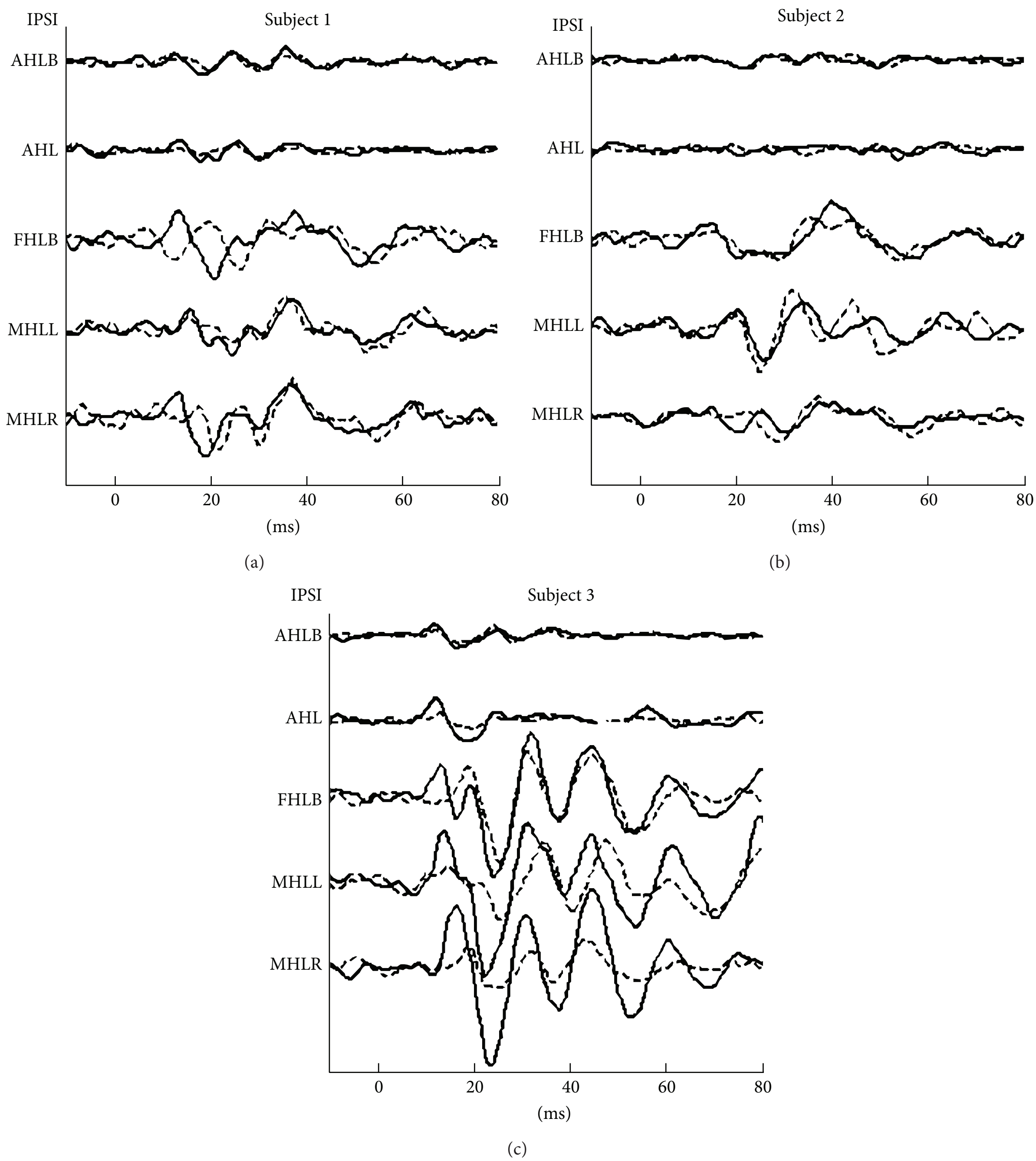

Figure 3: Preop (solid lines) and postop (dashed lines) VEMP waveforms recorded ipsilateral to the pathology from all 3 subjects. All the waveforms are normalized according to prestimulus EMG activity. Abbreviations are used in this figure as follows where ipsilateral indicates the location in return to the pathology location. AHLB: ipsilateral auditory head lift recording with both ears stimulated; AHL: ipsilateral auditory head lift recording in return to ipsilateral stimulation; FHLB: ipsilateral head lift recording tapper located at forehead; MHL: ipsilateral head lift recording tapper located at left mastoid recorded bilaterally; MHLR: head lift recording tapper located at ipsilateral mastoid.

P1 peak could not be identified in any of the recordings and N1 peak amplitudes were diminished in all recordings except for the forehead placement where N1 latency and amplitude were preserved. In general, more variability in latency and amplitude was also present for the later waves as well.

4. Discussion

In today's audiovestibular clinical practice a large number of tests are available to determine the functionality of the audiovestibular system. The selection and the use of these tests are mostly limited by their selectivity, practicality, and costs. The rapid development of VEMP related research and our recent experience with AC VEMPs and tap VEMPs have led us to use VEMPs as an integral part of our diagnostic battery. In our department we routinely use the cervical VEMPs due to the longer history; thus there is larger amount of accumulated research on cervical VEMPs. Currently we are also investigating the use of relatively newer approach of ocular VEMPs and adding it to our collected data set. Although the recent research on ocular VEMPs has been encouraging for clinical usage, the technique has to still be refined to be used as a routine test. The cervical VEMPs are easy to acquire and can be efficiently used with quantification methods for ongoing muscle activity monitoring such as the one used in this study where acceptance and rejection muscle activity regions are used. Our near feature plan is to include the ocular VEMPs recording in our routine diagnostic tests ensuring that the adaptation of the muscle activity quantification methods we use is properly utilized.

Our results showed that the VEMP recordings were not only capable of identifying the CPAT but were also able to contribute additional information of involved nerve bundles in first patient. The observed abnormal audiological findings strongly suggested the initial diagnosis of vestibular schwannoma. The MRI pointed to the presence of a tumor located in the right internal auditory canal. VEMP results also supported the presence of a tumor, additionally pointing to the inferior vestibular nerve involvement. The surgery report described the tumor to be arising from cochlear nerve and to be attached to the other nerves in the internal auditory canal. The cochlear nerve is located closer to the inferior bundle of the vestibular nerve [34–36] and compression on the inferior nerve therefore was affecting the AC VEMPs results but not altering the proper function of the superior vestibular nerve (AR in tap VEMPs within normal limits [38]).

For the second patient, the audiological results along with VNG and VEMP results strongly suggested the tumor presence in the internal auditory canal which was supported by the MRI findings. The surgeon described the tumor arising from superior vestibular nerve involving the inferior bundle as well. During the surgery, the tumor was found to be bigger than initially described by the MRI, which was performed a few months before. As routinely done prior to the surgery, the other tests, including VEMPs, were performed to decide on the surgical approach and determine the possibility for hearing preservation. In this case, the tumor affected the function of all the nerves in the internal auditory canal. Our conclusion from the AC VEMP and tap VEMP findings was the involvement of both the inferior and superior nerves. The VEMPs were successful in pointing out both the tumor presence and the involvement of both of the vestibular nerves. An interesting observation was that the left and right responses recorded during both right side and left side auditory stimulation were highly similar, suggesting that the whole response seen in AHLB might have been driven by the left ear.

The third patient was a particularly interesting case because all tests performed along with AC VEMPs and tap VEMPs proved to be not helpful in the diagnosis of the vestibular schwannoma. Although the tumor was arising from the superior vestibular nerve, the tap VEMP failed to indicate presence of the tumor similar to the rest of the clinical tools, suggesting a normal function. In this case only the MRI was sensitive enough to show the tumor. The MRI was performed due to the history of the patient, her young age, and our experience in vestibular schwannoma cases. The reason why the recorded tap VEMPs were not able to detect the pathology is a good question to investigate.

We observed that the mastoid placement of the skull tapper created additional challenges. It was extremely difficult to replicate the same conditions when the skull tapper was placed on a surface of the mastoid region. Due to the 3-dimensional shape of the mastoid area, it was very difficult to maintain a steady 3D relation between the head and the skull tapper hit axis (thus with the vestibule axis) especially when tapper is moved from one side to the other. As with the current setup there was no chance of monitoring the relation between the skull tapper hit direction and the vestibular organs and it was not possible to limit the introduced variability. In the light of these observations (although we acquired data with skull tapper positioned at mastoids on both sides and described the results of the responses acquired from the ipsilateral SMCs), we preferred to relay and advocate the usage of the forehead stimulation results due to the limits of currently available instrumentation. The directional information revealed by the mastoid placement is complex and has to be carefully analyzed. For general clinical implementation additional safeguards are required. An additional feedback mechanism describing the orientation relation between the tapper and gravity, such as a gyroscope, could be helpful in minimizing the variability and thus could be useful in producing equivalent directional force delivery to each side when skull tapper is moved from left to right.

5. Conclusions

In this paper we introduced our efforts in adding the AC VEMPs and tap VEMPs to expend the clinical diagnostic tests used for advanced assessment in CPAT patients, hoping that it will serve as a guideline for other clinicians interested in utilizing tap VEMPs.

The patients presented in this study were selected to point out different results we observed among a larger patient population. The findings from the larger population group will be presented in a more detailed follow-up subsequent paper. The main goal of this paper was to focus on the protocol used and point at the variability in the findings.

In two of three presented cases AC VEMPs and tap VEMPs together proved to be helpful in establishing the diagnosis of CPAT providing more information on the tumor affected bundle of vestibular nerve (superior or inferior or both). Performing only AC VEMPs or only tap VEMPs would have provided insufficient information about the tumor and the vestibular nerve bundle involvement. In the third case, VEMPs failed to identify the vestibular schwannoma, which was clearly shown in MRI scans. In this case, our medical intuition and expertise with CPAT patients prompted us to perform MRI. Due to the high cost of MRI, it is typically not performed at the early stages of the diagnostics procedure in many countries. Once other tests indicate the possible presence of the CPAT an MRI is conducted.

Providing AC VEMPs and tap VEMPs to the available test battery in the assessment of CPAT is likely to improve the diagnostic process by providing more information on the involved vestibular nerve bundles. In addition, this information might be used later during the surgery. In many cases the MRI is not performed very short before the surgery. Usually it is performed earlier during the diagnostic process. The surgery takes place sometime after. As mentioned before, the MRI is quite costly and usually is not performed again if not much time passed. However, the ABR, AC VEMPs, and tap VEMP, once performed in diagnostic proceeding, might be repeated short before the surgery to clarify the presence along with possible compression characteristics of the tumor on the vestibular and/or auditory nerves. This combined information, from earlier MRI scans and latest electrophysiological tests, serves the surgeons as a guideline in their surgical approach and during tumor removal. It provides very useful information for the surgeon in making a decision about additional intraoperative monitoring of hearing. In our department intraoperative monitoring is routinely used in every CPAT surgery and many other ear surgeries, but intraoperative hearing monitoring is not routinely performed in most of the other clinics. In addition, the details from electrophysiological tests about the involved nerve bundles are useful in patients counseling and informing them on more realistic possible outcomes of the surgery like hearing preservations possibilities and a risk of hearing loss during the surgery, a risk of facial nerve paresis, and vertigo symptoms after the surgery.

Abbreviations

ABR: Auditory brainstem response
AS: Asymmetry ratio
CPAT: Cerebellopontine angle tumor
ECochG: Electrocochleography
EEG: Electroencephalography
EMG: Electromiography
MRI: Magnetic resonance imaging
PTA: Pure tone average
RMS: Root means squared
SCM: Sternocleidomastoid
VEMP: Vestibular Evoked Myogenic Potential
AC VEMP: Auditory Vestibular Evoked Myogenic Potential
tap VEMP: Skull tapping induced Vestibular Evoked Myogenic Potential.

AC VEMPs Three Types of Recordings

AHLL: Head lift stimulus delivered to the left ear
AHLR: Head lift stimulus delivered to the right ear
AHLB: Head lift stimulus delivered to both ears.

tap VEMPs Three Types of Recordings with Skull Tapper

FHLB: Forehead head lift both sides recorded
MHLL: Mastoid head lift skull tapper located at left
MHLR: Mastoid head lift skull tapper located at right.

Conflict of Interests

The authors declare the following: Dr. Erdem Yavuz is a Research Scientist at Research and Development, Intelligent Hearing Systems Inc., and Dr. Rafael Delgado is the Executive Vice President and Director of Research and Development, Intelligent Hearing Systems Inc. The authors declare no other conflict of interests related to this paper.

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