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Intratympanal gentamicin in Meniere's disease: Effects on individual semicircular canals

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ABSTRACT

Objective: In this retrospective study the aim of the authors was to examine the effect of gentamicin on the individual semicircular canals after low dose, single injection intratympanal gentamicin therapy in Meniere's disease.
Methods: Data of 32 patients treated between 2011 and 2015 were collected. The high frequency, high acceleration vestibuloocular reflex (VOR) gain was measured in the individual semicircular canals using video head impulse test immediately before the first intratympanal gentamicin instillation and approximately two months later.
Results: In all cases 'AAO-HNS Class A' vertigo control could be attained at least for several months. In 13 cases only one instillation was necessary. In the other 19 cases the attacks returned after a few months. In 11 cases the injection had to be repeated a second time, in 4 cases 3 injections, in 2 cases 4, in 1 case 5 injections and in another 6 injections were necessary. The initial VOR gain was normal in all cases and two months after one injection it decreased in average by 40% in a highly significant manner. However, there were cases in which, although the patients became free of attacks, the gain values remained normal.
Conclusion: It was possible to demonstrate a significant correlation between the gain decrease of the individual canals. There was no prognostic correlation between the initial gain decrease after the first injection and the necessity of further injections. Gain values also decreased slightly but significantly in the lateral and posteriors canals on the contralateral, untreated side, possibly because of the missing disfacilitation from the treated side.

1. Introduction

In the last few years it has been demonstrated, that in Meniere's disease (MD) it is possible to prevent vertigo attacks by mild inhibition of peripheral vestibular function using intratympanic gentamicin (ITPG) injection [1,2]. By infrequent administration of single ITPG injections it is possible titrate the desired vestibular inhibition and the side effects (such as hearing loss) can be held on an acceptably low level [3,4]. Based on two randomised, controlled trials a Cochrane review found that intratympanal gentamicin seems to be effective against vertigo compared to placebo [5]. It has been shown that a single dose of ITPG markedly reduced AVOR gains for the semicircular canals on the treated side [4,6]. According Carey et al. [4] it does not cause complete hair cell destruction allowing the preservation of baseline afferent discharge on the treated side. Hirvonen et al. [7] showed that, at least in chinchilla, a single intratympanic gentamicin injection causes partial damage and loss of vestibular hair cells, particularly type I hair cells or their calyceal afferent endings, does not damage the afferent spike initiation zones, and preserves enough hair

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cell synaptic activity to drive the spontaneous activity of vestibular afferents.

The mild peripheral inhibition seems to be well suited to inhibit vertigo attacks without causing symptoms of chronic vestibular insufficiency, which occurs sometimes (in 15%: [8]) after vestibular neurectomy or labyrinthectomy.

Although in the last four years it has been possible to measure the vestibulo-ocular reflex gain (VOR gain) in individual semicircular canals using the three-dimensional video-head impulse test, reports on the effect of the drug on the individual semicircular canals are scarce. In several early studies magnetic search coils were used [4,6,9] and we found two recent studies carried out using video head impulse testing [10,11].

In 2004 we adopted the single injection strategy at our department and during the last 12 years we treated 117 MD patients because of intractable vertigo attacks with good results [12,13]. Since 2012 we have been measuring the VOR gain using video head impulses before and after the ITPG-therapy. In this retrospective study our aim was to assess the effects of the successful ITPG-therapy on the individual semicircular canals on the treated and on the intact side, respectively. We also wanted to determine if the long-term effectiveness of the ITPG therapy can be predicted by the degree of initial VOR gain inhibition after the first injection.

2. Materials and methods

Cases with the diagnosis "definite Meniere's disease [14]" were collected from the period between November 2011 and May 2015. Before data collection permission has been obtained from the Ethical Commission of Lower Austria (GS4-EK-4/319-2015). Cases were included if admission occurred after 1st August, 2012 and all follow up examinations were completed before 30th May, 2015.

Inclusion criteria were: adults over 18 years of age; final diagnosis: "definite Meniere's disease [14]"; results of video head-impulse testing done before and two months after ITPG injection were available. Exclusion criteria: missing results of follow up examination. ITPG injection was done basically as recommended by Carey et al. [4] and as documented in Refs. [12,13]. Briefly, the middle ear was filled with an unbuffered gentamicin solution (gentamicin sulfate, Sandoz, 40 mg/1 ml) after myringotomy. The gentamicin was held in the middle ear (the patients are laying in the lateral horizontal position and instructed not to swallow) for one hour. The effect of this injection develops over several days and lasts usually at least for several months. Should the vertigo spells recur (usually in form of weak attacks) a second (or a third or fourth etc.) injection can be given.

We identified 32 cases with MD treated at our department between August 2012 and May 2015 (15 men, 17 women, 11 on the right side, 21 on the left). In all cases only one side was affected and the contralateral side showed normal VOR gain. In 6 cases only the horizontal semicircular canal (SCC) was measured (the tool for the measurement of the vertical canals was not available that time), in the remaining 26 cases all three SCC could be measured before and after therapy. Average age at the time of the first injection was 57 years (min.= 39; max. = 81). Follow up VOR gain measurement occurred in average after 63 days (min. = 31; max. = 77). All patients had been having frequent attacks for months at least for five months before therapy. As a measure of the activity of the symptoms we use the number of attacks during the last two weeks. We did not administer ITPG-injection unless the patients had at least two attacks in the last two weeks.

All examinations, except audiometry were done by the same experienced examiner (B.B.). During data acquisition the following parameters were collected retrospectively: date of admission and of the first measurements, age and sex of the patients, gain of the different semicircular canals as measured by video-head-impulse test at approximately 160 °/s head velocity on the day of ITPG injection and at the follow-up examination, which occurred approximately after two months. vHIT-Test was carried out using Otometrics ICS Impulse Otosuite Vestibular V 1.2. Gain-values were determined using the average value of software-calculated individual gain values of separate impulses with a velocity between 140–180 °/s. In order to filter out artefacts, the presence of corrective saccades in the time period up to 200 ms after the impulse was considered obligatory for the validation of decreased gain values. The result of the vHIT was considered pathological in the horizontal canal if the gain was under 0.8. In the case of the vertical canals the VOR gain under 0.7 was pathological (as established in our laboratory after having measured 35 normal values and determining average ±2 standard deviation). Audiometry was done using Interacoustics Equinox Affinity Suite AC440. Statistics were done using Graphpad Prism® Software.

3. Results

In all cases 'AAO-HNS Class A' [14] vertigo control could be attained at least for several months. In our experience [13], ITPG-injection is typically followed by a 3–5 days latency without any effect, during which sometimes even attacks occur. Then the attacks cease and unsteadiness develops, which lasts for 2–3 weeks. In 13 cases only one instillation was necessary. Although in this paper we only analyse the effects of the first ITPG injection, we mention here that in the other 19 cases the attacks returned after several months. Out of these, in 11 cases the injection had to be repeated a second time, in 4 cases 3 injections, in 2 cases 4, in 1 case 5 injections and in another 6 injections were necessary. The initial VOR gain in the horizontal canal was normal (greater than 0.8) in all cases. Anterior canal gain was lower than normal in three cases and the posterior canals gain was decreased in one case before the first injection. The following analysis describes the effects of the first injection. VOR gain measured two months after the first injection decreased in average by 40% in a highly significant manner (Fig. 1 and Table 1). However, there were cases in which, although the patients became free of attacks, the gain values remained normal.

On the contralateral side after the injection the VOR gain values decreased slightly but significantly in the horizontal and posterior canals and there was no significant difference in the

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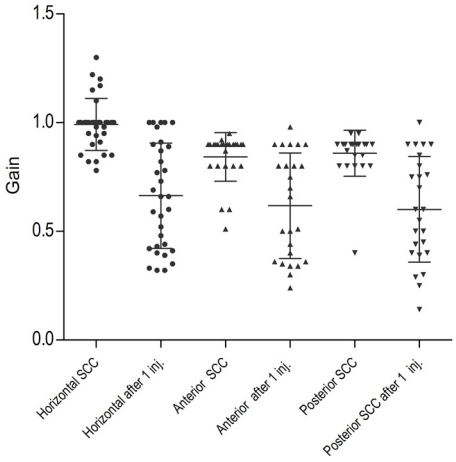

Fig. 1. VOR gain of the individual canals before and after the first ITPG injection (horizontal lines: average ± SD; details see Table 1).

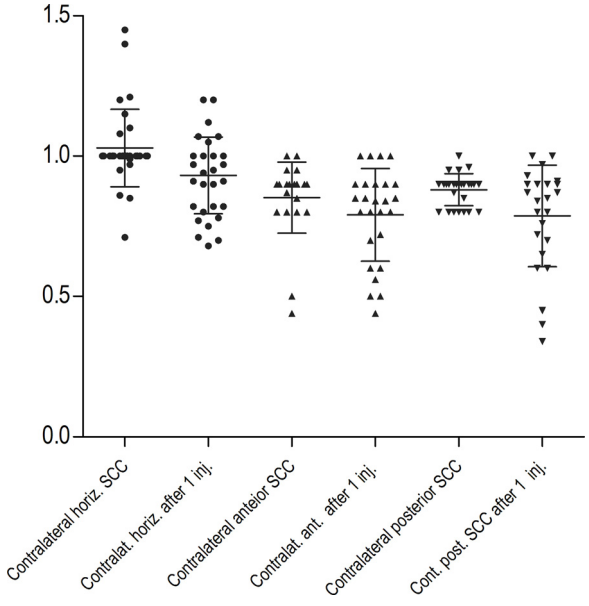

Fig. 2. VOR gain of the individual canals on the untreated (contralateral) side before and after the first ITPG injection (horizontal lines: average ± SD; details see Table 2).

anterior canals before and after on the untreated side (see Fig. 2 and Table 2).

When the relationship of gain decrease between the individual semicircular canals was calculated after the first injection (anterior and posterior canal against the lateral) it was possible to demonstrate a significant correlation between the individual canals.

To measure the significance of the correlation between the horizontal canal gain and anterior and posterior canal gain respectively, a two-tailed non-parametric correlation calculation (Spearman) was carried out (number of pairs 26). Between the horizontal and anterior canal gains the Spearman 'r' was 0.54, $p < 0.005$ (value summary **); between the horizontal and posterior canal gains the Spearman 'r' was 0.74, $p < 0.0001$ (value summary ***). Values of a linear regression fit between horizontal-anterior SCC gains: slope = 0.55; y intercept (when X =0) = 0.26; R square = 0.32; p value = 0.0034. Linear regression fit between lateral-posterior SCC gains: slope = 0.71, y intercept (when X = 0) = 0.12; R square 0.53; p value < 0.0001. Thus, the lateral and posterior canal gain decrease correlated very strongly, the correlation between the lateral and anterior canal was less strong but still significant (Fig. 3).

Next we compared the lateral canal gain values after one injection in two groups. The first group consisted of patients who became symptom free after one injection, the second of those, who needed two or more injections. Average gain decrease in the first group with only one injection was: mean (±SD) = 0.66(±0.26) (n = 13). In the group with more injections: mean (±SD) = 0.67(±0.24) (n = 19). Since we did not assume Gaussian distribution, the Mann–Whitney test was carried out: the result was not significant, (two-tailed p value: 0.9). Thus there was no significant difference between the two groups concerning the gain decrease after the first injection (Fig. 4).

4. Discussion

In our material in all cases 'AAO-HNS Class A' [14] vertigo control could be reached at least for several months. It has been described in the literature that the vertigo spells may cease after ITPG and that the attacks may return necessitating a repeated injection [4,15,16]. Two months after the first injection the VOR gain decreased highly significantly in all three canals on the treated side. Similar results have been reached by Marques et al. [10], who found that the VOR gain decreased to 0.5–0.7 after single ITPG. In our material, although the average inhibition was also around this value, in many cases the gain remained normal and in spite of this, the attacks ceased. In fact, a closer inspection of Fig. 1 reveals two rather distinct groups in all three semicircular canals, one in which the gain did not change much after one ITPG injection and another, in which the gain decreased approximately by 40%. We did not find a statistical difference between the groups with decreased versus normal gains after the first injection with regard to the necessity

Table 1
Statistical details before and after one ITPG on the treated side.

	Average VOR gain	±SD	p (two tailed Wilcoxon matched-pairs signed rank test)
Horizontal SCC before the first injection (n = 32)	0.99	0.2	
Horizontal SCC after the first injection (n = 32)	0.66	0.24	p < 0.0001
Anterior SCC before the first injection (n = 26)	0.84	0.11	
Anterior SCC after the first injection (n = 26)	0.62	0.24	p = 0.0002
Posterior SCC before the first injection (n = 26)	0.86	0.11	
Posterior SCC after the first injection (n = 26)	0.61	0.24	P = 0.0001

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Table 2
Statistical details before and after one ITPG on the untreated side.

	Average VOR gain	±SD	p (two tailed Wilcoxon matched-pairs signed rank test)
Contralateral horiz. SCC before the first injection (n = 32)	1.03	0.14	
Contralateral horiz. SCC after the first injection (n = 32)	0.93	0.14	p = 0.0008
Contralateral anterior SCC before the first injection (n = 26)	0.85	0.13	
Contralateral anterior SCC after the first injection (n = 26)	0.79	0.17	n.s. p = 0.1
Contralateral posterior SCC before the first injection (n = 26)	0.88	0.16	
Contralateral posterior SCC after the first injection (n = 26)	0.79	0.18	p = 0.039

of further injections; in other words, the gain change after the first injection did not give any prognostic information as to the necessity of further injections. This was already observed by Murofushi et al. [8], who noted that ITPG may be effective even if the patients do not have acute unilateral vestibular deafferentation after several gentamicin injections given on consecutive days. Nguyen et al. [6] found that greater reductions in AVOR gain corresponded to lower rates of vertigo after ITPG treatment. However, in their group of patients the difference in caloric unilateral weakness did not reach statistical significance between patients who were vertigo-free and those who experienced recurrent vertigo. In these results the vertigo rates after the injection were considered (we did not assess this variable) but not the necessity of a next injection. The authors mentioned that greater AVOR gain reduction may predict lower vertigo rates, but not necessarily lower rates of retreatment with ITPG and that the inclusion of vertigo occurring after 1 year might explain the lack of correlation between AVOR gain and vertigo control. All these results differ from the experience of Marques et al. [10], who found that if the horizontal canal VOR gain was higher than 0.8 after treatment, this was associated with the need for a second gentamicin injection.

Why might repeated injection be necessary? de Waele et al. [17] found that in roughly one-third of the patients, after initially losing their caloric responses and displaying refixation saccades to head impulse tests recovered within 2 years after intratympanic gentamicin injection. Judged by these results, recovery of hair cell function may play a role in the recurrence of symptoms. Our success rate (measured by the number of necessary single dose ITPG injections) was similar to that of Nguyen et al. [15], who found that in 54% only one injection was necessary (in our material 40%). In their material a second injection was given in 21% of all cases (in our cases 34%), in 5% a third injection was needed (in our material in 13%).

When the relationship of gain decrease between the individual semicircular canals was calculated after the first injection (anterior and posterior canal against the horizontal) it was possible to demonstrate a significant correlation between the individual canals. The horizontal and posterior canal gain decrease correlated very strongly, the correlation between the lateral and anterior canal was less strong but still significant. We have not found similar calculations for the effect of ITPG in Meniere's disease in the literature. Our group published similar statistics concerning the involvement of different semicircular canals in vestibular neuritis [18]. In this study the VOR gain decrease measured by head impulse test was correlated in the acute phase of vestibular neuritis between the individual semicircular canals and a correlation could be shown between gain decrease in the anterior and horizontal canals but no such correlation could be demonstrated between the horizontal and inferior SCCs. We contributed this to the anatomy of innervation: the anterior and horizontal SCC canals are innervated by superior branch of the vestibular nerve and the inferior branch is separated from them anatomically. Comparing this to the effect of gentamicin there is a difference: the effect on the horizontal canal correlated better with the posterior canal, the anterior canal showed only looser correlation. We speculate here that this reflects the anatomical proximity of the horizontal and inferior canal ampullae to the round window; the anterior canal ampulla is further away from the round window (for an excellent, freely available three dimensional reconstruction see Fig. 1A of Ref. [19]).

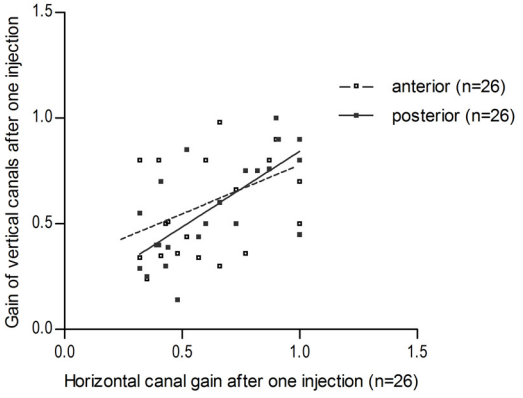

Fig. 3. Correlation of horizontal canal gain versus vertical canal gain values after one injection.

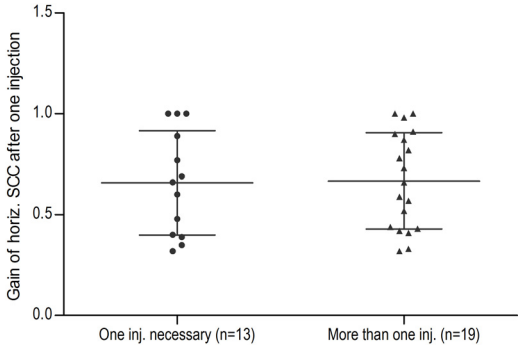

Fig. 4. Horizontal canal gain values after one injection in the group patients, who needed one injection, and in the group with two or more injections.

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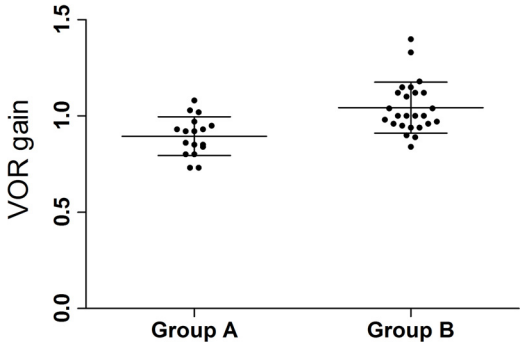

Fig. 5. Contralateral lateral canal VOR-gain values two months after vestibular neuritis (Group A: low gain on the affected side; Group B: normal gain on the affected side).

We found that two months after the first ITPG the VOR gain on the intact (contralateral) side also decreased slightly but significantly in the posterior and horizontal SCCs as measured by head impulse test. There was a similar tendency also in the anterior canal, but this did not reach a significant level. We have not found any analysis of the VOR gain on the contralateral side after ITPG in the literature. However, it is possible to compare these results to the above mentioned patient group suffering from vestibular neuritis.

In Fig. 5 the contralateral horizontal canal VOR gain values are shown (previously unpublished data, other details see Ref. [17]) two months after the acute vestibular neuritis. Group A consisted of cases, in which two months later the VOR gain has not normalized (as was the case in approximately every second patient, with an average gain of 0.45); in Group B cases were included, in which the VOR gain normalized as measured by head impulse test two months after the acute symptoms. There is a highly significant difference (as tested by two tailed unpaired t test; $p = 0.0003$). Average VOR gain in Group A = 0.89 (±SD: 0.1); in Group B = 1.04 (±SD:0.13). Apparently, if the VOR gain is decreased on the affected side, the contralateral gain decreases slightly but significantly, at least after two months with the advent of the central compensation; contralateral VOR gain behaving similarly in this regard after gentamicin and vestibular neuritis. This phenomenon has also been described by Weber et al. [20] after vestibular neuritis and after unilateral surgical vestibular deafferentation. The authors explained this phenomenon by the push–pull cooperation between the horizontal semicircular canal pair. In normals, during a head impulse, mainly the excitation of afferents from the ipsilateral canal drive the VOR, but also the disfacilitation (diminishing inhibition arriving from the contralateral side through the commissural inhibitory fibers) augments the gain of the reflex. If, during head impulses to the intact side, the disfacilitation coming from the affected (ITPG-treated) side is missing or less, the VOR to the contralateral, intact side will be less than in normal subjects.

5. Conclusion

In summary, we conclude that ITPG constitutes an effective method for controlling intractable MD. In our material before single ITPG injection the initial VOR gain was normal in all cases and two months after one injection it decreased in average by 40% in a highly significant manner. There were cases in which, although the patients became free of attacks, the gain values remained normal. It was possible to demonstrate a significant correlation between the gain decrease of the individual canals. The lateral and posterior canal gain decrease correlated very strongly, the correlation between the lateral and anterior canal was less strong. This we interpreted as a sign of the anatomical relation and distance between the round window and the canal ampullae. There was no prognostic correlation between the initial gain decrease after the first injection and the necessity of further injections. Gain values also decreased slightly but significantly in the lateral and posteriors canals on the contralateral, untreated side, this possibly because the missing disfacilitation from the treated side.

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