

ORIGINAL ARTICLE

Evaluation of Two Procedures of Intratympanic Gentamicin Therapy in Meniere's Disease

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Objective: We investigated the effectiveness of two different procedures of intratympanic gentamicin therapy on the control of vertigo, hearing level, vestibular function, functional level and stability.

Method: Retrospective cohort analysis. Patients: 25 patients treated with intratympanic gentamicin administered by transtympanic injections or through a ventilation tube. All patients were treated by the same doctor. The questionable therapeutic effect of ventilation tubes was not taken into consideration. Main outcome basis: At inclusion and after two years of ending the treatment, the number of vertigo crises, unsteadiness, hearing level, vestibular function and functional level according to the 1995 criteria of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) were evaluated.

Results: Control of vertigo attacks was achieved in 88% of patients (classes A and B of the AAO-HNS). The treatment improved the patient functional level. 64% of patients reported unsteadiness that diminished gradually. Effectiveness controlling vertigo attacks was similar whatever procedure was used. We did not observe any relationship between hearing loss after treatment and the technique employed. The result of caloric excitability of the ear involved was observed in accordance with the procedure for gentamicin administration and with the classes of control of vertigo. It did not reach statistical significance in any case.

Conclusion: Gentamicin administration for intractable Meniere's disease is a relatively safe and effective treatment for the control of vertigo attacks no matter what procedure is used.

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Introduction

The majority of patients with Meniere's disease (MD) may be managed conservatively with medical therapy. Those who have symptoms refractory to medical management may benefit from surgery. Recently intratympanic gentamicin (IG) administration has gained widespread popularity. Different studies on the effectiveness of treatment with IG, including meta-analysis [1-3], document good results in the control of vertigo crises. At the beginning of use, the aim of IG treatment was to abolish vestibular function, hence the name of chemical labyrinthectomy. Later, good results

were observed with only partial annulment of vestibular function. For this reason, the quantity of gentamicin is limited at present to effective minimum [4-7]. Several methods of delivering gentamicin to the inner ear have been described in literature and no consensus has been reached as to which is the most effective. Controversy still exists regarding protocols that use multiple injections from the onset, as opposed to protocols that use multiple injections only if and when needed for recurrent vertigo. Furthermore, the security of administration with regard to the patient's hearing is not well established. [8-18]

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There are meta-analyses and review articles in the literature which compare the results on the control of vertigo and hearing level obtained through different application methods however we did not find any study comparing the results obtained by a *single* author using various techniques. The aim of this study was to verify the efficacy of intratympanic gentamicin application in the control of vertigo attacks using two techniques, and its effects on the auditory and vestibular function in patients with MD. The study also examined the effect of

treatment on balance and functional level as well as the results in the control of vertigo attacks in relation to hearing stages.

Materials And Methods

Type of study: Retrospective cohort.

Patients and inclusion criteria

We carried out a review of 25 patients (13 males and 12 females; Table 1) with definite MD in accordance with the American Academy of Otolaryngology-Head and

Table 1. Raw data.

Subject	Age	Sex	Ear	DDST	DM	Doses	Stage pre	Baseline			18-24 months after first treatment			HT Pre-post	CT Post-pre
								FV	HT	FL	FV	HT	FL		
1	32	F	R	3	GIVT	5	3	0,8	57,5	3	0,3	56,3	2	1,25	<30
2	60	M	L	9	GIVT	5	3	2,2	63,8	5	1,7	77,5	2	-13,75	<30
3 *	52	M	R	3	GIVT	7	3	2	65	4	0,7	62,5	2	2,5	NP
4	42	M	L	4	GIVT	5	3	1,8	55	4	0	42,5	1	12,5	40
5	36	F	L	16	GIVT	5	3	2,2	77,5	4	0	70	1	7,5	<30
6	55	F	R	18	GIVT	3	4	1	75	4	0	66,3	1	8,75	47
7	51	M	L	4	GIVT	5	3	1	68,8	3	0	67,5	1	1,25	30
8	44	F	L	3	GIVT	5	3	1,3	52,5	4	1	62,5	4	-10	<30
9*	55	M	R	4	GIVT	5	3	0,3	67,5	5	0	72,5	1	-5	60
10	43	M	L	3	GIVT	5	3	0,7	68,8	3	0,2	58,8	2	10	100
11	45	F	R	2	GIVT	5	3	1,3	70	5	0	57,5	1	12,5	NP
12	47	M	R	7	GIVT	7	3	1,3	58,8	4	0	63,8	1	-5	32
13*	51	M	L	21	DII	3	4	2,8	73,8	4	ST	56,3	5	17,5	NP
14	44	F	L	2	DII	3	2	1,5	26,3	4	0	18,8	1	7,5	NP
15	45	F	L	1	DII	2	2	5,7	35	5	0	40	1	-5	<30
16	55	F	L	3	DII	1	4	0,8	73,8	4	0	78,8	1	-5	NP
17	68	F	R	17	DII	2	3	1,8	61,3	4	0	80	1	-18,75	NP
18	64	M	L	4	DII	1	4	6,7	77,5	5	0,3	83,8	2	-6,25	NP
19	48	M	R	6	DII	2	3	3,7	42,5	4	0	48,8	1	-6,25	NP
20	66	M	R	2	DII	2	4	1,3	73,8	4	0	62,5	4	11,25	100
21	60	F	R	21	DII	1	3	2	62,5	4	0,3	63,8	2	-1,25	<30
22	49	M	R	19	DII	3	3	5,7	67,5	5	0	71,3	1	-3,75	<30
23	33	F	L	2	DII	2	3	3	60	5	1,2	53,8	2	6,25	100
24 *	60	F	L	8	DII	1	3	5,2	67,5	6	0,7	71,3	3	-3,75	<30
25	64	M	R	3	DII	1	3	4,3	41,3	4	0	43,8	1	-2,5	<30

* Patients undergoing two cycles of treatment. DDST: duration of disease at start of treatment (in years).

DM: delivery methods. DII: direct intratympanic injection. GIVT: gentamicin injection through a ventilation tube.

Doses: number of doses. Stage pre: stage of MD measured through level of hearing before beginning treatment according to the AAO-HNS criteria.

FV: frequency of vertigo, average of definitive episodes per month in the previous 6 months (baseline) or 18-24 months after first treatment.

HT: hearing thresholds, pure tone average 0.5, 1, 2 and 3 kHz. FL: functional level. HT pre-post: hearing threshold pre-posttreatment change in dBs. CT pot-pre: caloric test change posttreatment-pretreatment.

ST Surgical Treatment.

NP: not performed. NV: not valid

Neck Surgery AAO-HNS^[19], all of them, suffered from incapacitating MD. The average age of the patients was $50,7 \pm 9,9$ years (range, 32–68 years). The history of MD (years of evolution since the onset of the disease up to the time of the IG) ranged from 12 months to 21 years.

The criteria for inclusion of patients in IG treatment were: 1) the history of MD lasted for more than 12 months 2) previous medical treatment with low salt diet, diuretics and betahistine had shown no benefit 3) there were no symptoms suggestive of MD in the contralateral ear 4) causes other than MD of the symptoms or complaints were excluded 5) alternatives to participation in the protocol were discussed with each patient before enrolment 6) the patients gave their informed consent for treatment.

The Hospital Institutional Review Board approved the study.

Patient evaluation

All patients were followed up for at least 2 years. They were asked to annotate all crisis of vertigo suffered on a card. Following the AAO-HNS criteria we considered only definite crises of vertigo (spontaneous rotational vertigo lasting at least 20 minutes).

The AAO-HNS criteria were used to quantify the control of vertigo: the number of definite spells of vertigo during the 6 months previous to treatment with intratympanic gentamicin was compared with the number of episodes 18 to 24 months after treatment.

The AAO-HNS Functional Level Scale (FLS) were used to reflect how MD affects the patient's activities. The FLS is a 6-point scale that evaluates the patient's overall function or current status, and it offers an objective measure of the patient's state at any given time.

Patients underwent a complete neurotologic examination, audiogram, and bithermal caloric test before the start and after completion of the treatment. Data were compared between baseline and follow-up (i.e., after 18–24 months) to identify potential changes in either hearing or caloric test. Audiometric findings were reported in terms of the PTA calculated from the readings at four frequencies (0.5, 1, 2, and 3 kHz). According to the AAO-HNS, hearing was considered to have improved when PTA decreased by 10 dB or more, and was considered worse when PTA increased by 10 dB or more; changes in PTA between these intervals were considered to be unchanged.

Caloric tests were performed using 150 ml of water, irrigating the external ear canal for 30 seconds with cold (30°C) and warm (44°C) water. The nystagmus maximum slow-phase velocity was used to evaluate the outcome of caloric response on the basis of percentage of changes in the ear with MD before and after treatment. Changes were considered relevant when they were of the 30% or more.

Treatment protocol

We used a solution of 40 mg/mL of gentamicin sulphate diluted in a final concentration of 26,7 mg/mL and buffered in sodium bicarbonate to obtain a 6,4 pH level^[20]. Gentamicin was administered in 12 patients by a middle ear ventilation tube and 13 cases by direct intratympanic injection. In all procedures local anaesthesia of the tympanic membrane was achieved by application of a cottonoid soaked in 10% lidocaine spray.

1. Gentamicin injected through a middle ear ventilation tube (GIVT): The middle ear ventilation tube was introduced 2 weeks before the start of therapy. During the 7 following days 0.4–0.8 mL of gentamicin sulphate were injected daily into the middle ear with a small needle through the ventilation tube. During the procedure, each patient lay supine with the head turned 45° to the opposite side in order to continually bathe the round window with the gentamicin solution. After the injection, the patient maintained this head position for at least 30 minutes. Complete otoneurologic evaluation and PTA measurement were carried out before each gentamicin administration. Treatment end points were determined by subjective complaints of imbalance, hearing loss, spontaneous nystagmus, post-head-shaking nystagmus or a head-thrust sign (corrective eye movement following a rapid head thrust in the horizontal plane). If any of these symptoms or signs occurred, no further gentamicin was injected. Otherwise, the treatment continued for one week.

2. Direct Intratympanic Injection (DII): A paracentesis was performed in the inferior part of the tympanic membrane and 0.4–0.8 mL of gentamicin were injected. The patient's position and resting time were the same as in GIVT technique. If no symptoms or signs of gentamicin effect were recognizable, the injection was repeated a maximum of three times over a period of 15 days, on days 1, 8, and 15. In 4 patients only one application of gentamicin was necessary, 6 patients required two injections and the remaining 3 were given three injections.

We considered performing a second cycle if the frequency of attacks persisted at least three months after ending the first cycle of treatment. The 4 cases that needed a second cycle were treated with DII. One patient was treated with ablative surgery after failed gentamicin treatment.

Statistical analysis

All results were summarized as counts and relative frequencies (percentages). Distributions were compared with Chi-squared statistic tests using exact methods if expected frequencies were lower than 5. All analyses were performed using SPSS 15 statistical software package and $p < 0.05$ was considered to be statistically significant.

Results

Effectiveness: Frequency of vertigo

Using the criteria for control of vertigo defined by the AAO-HNS, the results (Table 2) showed complete control of vertigo spells in 15 patients (60%; class A of the AAO-HNS criteria), good control in 7 patients (28%; class B), moderate control in 2 patient (8%; class C), and no control in 1 patient (4%; class F). 4 cases needed a second cycle of gentamicin treatment to achieve those results. Bad results persisted in one patient after the second cycle and decided to undergo ablative surgery. The differences in the control of vertigo between the two procedures for gentamicin administration were not statistically significant. The control of vertigo classes according to the history of MD showed better results in the cases with less years of evolution, but the differences were not statistically significant.

The control of vertigo classes was also ascertained in accordance with stage of MD measured through hearing level before beginning treatment, following the AAO-HNS. Results were better in patients in

stages 1 and 2 than in patients in stages 3 and 4, but the differences were not statistically significant ($p=0.19$).

Functional level Scale

The quality of life according to the Functional Level Scale of the AAO-HNS showed a shift from a lower level (4/5/6) to a higher level (1/2/3) in 22 patients (88 %; table 1).

Unsteadiness after Intratympanic Gentamicin Treatment

Patients were asked to report any feeling of unsteadiness or lightheadedness in the posttreatment period. We evaluated the patients that received only one cycle treatment because these symptoms can change when the patient receives a second cycle. 16 patients (64%) experienced unsteadiness (minimum 4 days and maximum 720 days). Patients were exposed to a systematic balance-training program and unsteadiness diminished gradually. Age showed no influence on the duration of instability. No statistical significance was observed.

Hearing outcome

PTA before and the treatment for each patient is presented in Table 1. PTA remained unchanged in 18 patients (72%); it improved in 4 patients (16%; maximum 17,5 dB); and it worsened in 3 patients (12%; maximum 18,7 dB). With regard to patients who received a second cycle of treatment, PTA did not

Table 3. Duration of unsteadiness (days) and age of patient (years). Number of cases. One case was not evaluated.

GIVT / DII	<60 year	>= 60 year
0 days	6/3	0/1
4-30 days	5/2	1/2
31-90 days	0/1	0/1
> 90 days	0/1	0/1

Table 2. Control of vertigo classes applying the AAO-HNS criteria. The number of definite episodes of vertigo 18 to 24 months after treatment. GIVT: Gentamicin Intratympanic through a Ventilation Tubes. DII: Direct intratympanic Injection.

Class	GIVT	DII	Outcome after two cycles of treatment
A	7 (28%)	8 (32%)	15 (60%)
B	3 (12%)	4 (16%)	7 (28%)
C	2 (8%)	0	2 (8%)
E	0	0	0 (0%)
F	0	1 (4%)	1 (4%)

Table 4. Results of hearing function. Pure tone average (PTA) after treatment compared to PTA before treatment. Patients (%). Unchange: changes in PTA were < 10 dB. Loss: PTA increases ≥ 10 dB after treatment. Improvement: PTA decreases ≥ 10 dB after treatment. DII: direct intratympanic injection. GIVT: gentamicin injection through middle ear ventilation tube.

	Unchange	Loss	Improvement	Average Loss	Average Improvement
DII	10 (76,9%)	1 (7,7%)	2 (15,4%)	5,8 dB (max 18,7 min 1,2)	10,6 dB (max 17,5 min 6,3)
GIVT	7 (58,3%)	2 (16,6%)	3 (25%)	8.4 dB (max 13,7 min 5)	7.0 dB (max 12,5 min 1,2)

change in 3 patients (75%) and it worsened in 1 patients (25%) after the second cycle. Fewer patients suffer hearing loss and the mean of hearing loss was inferior in the group treated with DII than in the group treated with GIVT (Table 4). Average change was more favourable for DII than for GIVT, but it did not reach statistical significance.

Caloric Excitability after Intratympanic Gentamicin Treatment

In 8 cases the caloric test could not be performed after treatment because the patients refused further testing. In 8 cases a reduction of the caloric excitability of the involved ear ($\geq 30\%$) was observed after the first treatment; we performed the caloric test irrigating with water at 0°C in 3 out of these 8 cases observing a 100% reduction of the caloric excitability. Caloric reaction remained unchanged in 9 cases (Table 1). The differences in the caloric test results before and after treatment of the involved ear, were ascertained in accordance with procedure for gentamicin administration and with control of vertigo classes. The results did not reach statistical significance in any case.

Discussion

Most studies have achieved control of vertigo in more than 85% of the patients treated with intratympanic gentamicin, whatever protocol or technique they used [1,2,7,11,21-23]. Nevertheless, there is clearly no consensus on some questions. Blakley et al [3], observed in a literature review that there is no pattern of hearing loss or control of vertigo as a result of the method of medication delivery employed (injection through tympanostomy tubes, catheters through the tympanic membrane or needle injections through the tympanic membrane). We observed complete control of vertigo attacks in 60% (class A) of our patients and effective control in the 88% (classes A and B). 16% of the cases needed two cycles of treatment in order to obtain these results. We used two techniques of administration and various protocols, and

efficacy in the control of vertigo was similar in all of them. Since time intervals between injections in the two treatment protocols were not homogeneous, we were not able to analyse the relevance of the total dose of gentamicin in the control of vertigo at the time.

In our study the control of vertigo according to the AAO-HNS classes did not reach statistical significance in relation to the history or the stage of MD. We did not find any other studies that took this relationship into consideration.

The quality of life according to the Functional Level Scale of the AAO-HNS showed a shift from a lower level (4/5/6) to a higher level (1/2/3) in 88% of cases, rendering a positive effect of the treatment on quality of life. These results are in accordance with data reported in literature [4,5,9,12,13].

Sixty-four percent of patients reported feelings of unsteadiness (mean 84 days) in the posttreatment period that diminished gradually with a systematic balance-training program, without any influence of the age of the patient on the duration of unsteadiness. Boleas et al [24], observed that 15,5 % of patients treated with intratympanic gentamicin complained of chronic unsteadiness persisting five years after ending the treatment and there was no significant reduction in disability for them. In any case, the patient should be warned of possible unsteadiness when considering this treatment.

We observed greater hearing loss in cases treated with GIVT than in cases treated with DII, but the differences did not reach statistical significance. The safety of the administration with regard to the patient's hearing is not well established in literature. [3,5,6]

It is pharmacologically plausible that administration of repeated doses of gentamicin over a short period of time will enhance tissue saturation and increase the likelihood of both vestibular ablation and cochleotoxicity. However, genetic susceptibility to aminoglycosides may also play a role in facilitating ototoxicity [25].

It was possible to study the influence of treatment on caloric excitability in 17 patients after the first treatment. 8 cases showed a reduction of the caloric excitability of the ear treated ($\geq 30\%$) compared to the pretreatment test. In 9 cases caloric reaction remained unchanged. The results of caloric excitability of the involved ear were ascertained studied in accordance with procedure for gentamicin administration and with classes of control of vertigo, and did not reach statistical significance in any case. The fact that there appears to be no relationship between caloric excitability and the classes of control of vertigo, may indicate that complete ablation of the caloric response is not mandatory for a successful treatment of MD with gentamicin^[3,11,13]. Gentamicin may relieve vertigo due to its toxic effects on the dark cells and the stria vascularis of the labyrinth without causing any changes in the vestibular function^[9].

Treatment of Meniere's disease with only transtympanic ventilation tubes was proposed^[26]. Despite this there is not enough evidence to draw a conclusion and the procedure seems to have a placebo effect.^[27, 28, 29]. Therefore, the questionable therapeutic effect of ventilation tubes has been dismissed in this study.

In conclusion, according with our results, gentamicin administration for intractable Meniere's disease is a relatively safe and effective treatment for the control of vertigo attacks no matter what procedure is used. However it is necessary to continue investigating a larger number of cases to be able to assess the different procedures and to know better what signs or symptoms represent the point at which the efficacy of gentamicin is most adequate without it producing any secondary effects.

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