



Intratympanic mixture gentamicin and dexamethasone versus dexamethasone for unilateral Meniere's disease

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ABSTRACT

Objective: This study aimed to determine the effectiveness of an intratympanic (IT) injection of a mixture of gentamicin and dexamethasone compared with intratympanic dexamethasone (ITD) for controlling vertigo and protecting the hearing level of Meniere's disease patients who have persistent vertigo attacks, despite medical treatment.

Methods: Thirty eight patients with intractable Meniere's disease were included in this study.

Twenty-one patients were treated with IT mixture gentamicin and dexamethasone injection; seventeen patients were treated with ITD. Pre- and post-treatment audiograms were compared with pure-tone averages. Control of vertigo was classified according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) vertigo control index.

Results: In the mixture group single IT injection was administered in 18 patients (85.7%), 2 injections were administered in 2 patients (9.5%) and 3 injections were administered in one patient (4.8%). In the ITD group IT injection was performed 3 times (days 1,3,5) at intervals. The mean number of intervals per patient was 3,41 (range 1–6).

Two years after IT treatment there was better control of vertigo in mixture group than in ITD group; 81% of mixture group and 70,6% of the ITD group achieved satisfactory control of vertigo ($p = 0,0286$). Audiology results of mixture group showed 20 patients (95,24%) with unchanged hearing and 1 patient (4,76%) with only 10-decibel deteriorated hearing. There was no worsening of hearing in the ITD group.

Conclusion: The results of this study showed that an IT injection of a mixture of gentamicin and dexamethasone in intractable Meniere's disease cases is more effective than ITD for vertigo control.

1. Introduction

Meniere's disease (MD) is an idiopathic chronic inner ear disease associated with attacks of disabling vertigo, progressive hearing loss and tinnitus [1]. The initial treatment for MD consists of a low-salt and caffeine-free diet, diuretics, vasodilator drugs and symptomatic therapy for the nausea [2]. In cases resistant to this therapy, several surgical strategies have been attempted, including endolymphatic sac decompression and vestibular nerve transection. However, reliable evidence of their efficacy is scarce for these surgeries [3].

Recently, intratympanic (IT) steroid or gentamicin treatments have been increasing. Unfortunately, one of the side effects of gentamicin is that it usually increases the risk of sensorineural hearing loss [2]. Several publications have reported that the serum immunocomplexes are significantly elevated in patients with MD, which supports the idea

that MD is an autoimmune disease [4]. Moreover, the efficacy of steroid treatments in MD cases may be due to their anti-inflammatory and immunosuppressive effects [5].

Aminoglycoside antibiotics were first used intramuscularly to perform chemical labyrinthectomies in 1948 due to their vestibulotoxic effects [6]. In 1957, the IT use of aminoglycoside drugs was described by Schuknecht to protect against their systemic side effects [7]. IT gentamicin can cause damage to the endolymph-secreting vestibular dark cells, which may lead to a reduction in the endolymph and an improvement in the MD symptoms. However, gentamicin is both a vestibulotoxic and cochleotoxic drug. Gentamicin-induced hearing loss can range from 0% to 75%, depending on the dose and frequency of administration [8].

A meta-analysis conducted by Chia et al. found that there was an average hearing loss rate of 25% due to IT gentamicin [9]. In general, IT

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injections of gentamicin are more efficient than IT steroids in controlling MD symptoms [10,11].

Although several studies have detailed the vertigo control effects of IT gentamicin and steroids, to our knowledge, no study to date has described the clinical use, efficacy and safety profile of an IT injection of a mixture of gentamicin and dexamethasone for the management of MD.

Based on the abovementioned information, the aim of this study was to compare the efficacy of IT injections of combined gentamicin and dexamethasone and ITD in controlling vertigo during the first 2 years following its administration. Additionally, the role of dexamethasone in decreasing the risk of hearing loss due to the gentamicin was determined.

2. Materials and methods

2.1. Study population and inclusion criteria

This retrospective study included 38 patients with unilateral MD. The inclusion criteria consisted of adult patients with unilateral definitive MD with recurrent vertigo attacks refractory to a low-salt diet and medical treatment for at least one year. The diagnosis was based on the guidelines of the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) for MD [12]. None of the patients were subject to Tumarkin's otolithic crisis.

A patient was excluded from this study if they had any of the following: received previous IT gentamicin or corticosteroid treatments, bilateral MD, undergone ear surgery, chronic otitis media, a retrocochlear pathology diagnosis, and peripheral or central vestibular syndromes. All patients treated with ITD from January 2012 to February 2014 or with a mixture of gentamicin and dexamethasone injection from March 2014 to February 2016. Ethical approval was obtained, and written consent was provided by all of the patients, after the benefits and risks of the treatment were explained.

Seventeen patients (5 men and 12 women) aged 37–71 years old (mean 49,2) treated with ITG and 21 patients (11 men and 10 women) aged 37–69 years old (mean 52.4 years) treated with IT mixture of gentamicin and dexamethasone.

The patient evaluation included obtaining a detailed medical history, an otoscopic examination, audiological testing and magnetic resonance imaging in order to rule out the possibility of a retrocochlear lesion.

2.2. Forms and scales used in this study

A MD form was designed to record the name, sex, age, disease duration, frequency of attacks, affected ear side and average hearing level.

2.3. Treatment protocol

The IT injections were performed in an office setting using a microscope. A 10% lidocaine spray (Xylocaine; AstraZeneca, Cambridge, UK) was applied three times from the external auditory canal onto the tympanic membrane 20 min before the IT injection. The lidocaine spray was aspirated from the tympanic membrane prior to the injection. During the procedure, each patient was placed in a supine position with their head turned 45° to the opposite side. Using a 22-gauge needle, 0.5 ml of a 1 to 1 mixture of a gentamicin and dexamethasone solution (containing 27 mg/ml of the gentamicin base and 40 mg/ml of the dexamethasone base) was injected. After the injection, the patient maintained their head position for at least 30 min, and they were told to avoid swallowing in order to prevent opening the eustachian tube. Each patient returned for weekly follow-up examinations during the course of the treatment protocol. Audiological and bedside tests were performed during each follow-up examination. No further medical therapy

was recommended to those patients who reported no attacks since the IT injection. If there were vertigo attacks 3 weeks after the first IT injection, the patient was offered another IT injection, but if the patient was satisfied with the treatment, no further injections were administered.

In the ITD group we used the same procedure. Using a 22-gauge needle, approximately 0.5 ml dexamethasone solution (40 mg/ml) was injected. All 17 patients received 3 injections at intervals (on days 1, 3 and 5).

2.4. Audiometric investigation

An audiological assessment was performed using a sound-proof cabin. Hearing impairment was assessed according to the patient's speech discrimination scores (SDSs) and pure tone averages (PTAs) at 500, 1000, 2000 and 3000 Hz. A change of 10 dB or more in the PTA or 15% or more in the SDS was considered to be clinically significant. These tests were performed before the procedure and at each of the follow-up visits after the IT injection.

2.5. Vertigo evaluation

Each patient was monitored for at least 2 years after the termination of the treatment. In order to evaluate the vertigo control, the AAO-HNS has a specific elaborate and updated method. The number of episodes of vertigo during the 6 months before treatment with IT therapy was compared with the number of episodes 18 to 24 months after treatment were divided and multiplied by 100 to obtain a numerical value. According to this numeric score, patients were grouped into 6 classes: Class A (numeric score 0) represents elimination of vertigo, Class B (numeric score 1–40) is reduction of episodes of vertigo to 40% or less of the pretreatment frequency, Class C (numeric score 41–80) is reduction of episodes to 41% to 80% of pretreatment frequency, Class D (numeric score 81–120) is a change in episodes of vertigo by 81% to 120% of pretreatment frequency, Class E (numeric score 120) is an increase in episodes of vertigo by > 120% when compared with pretreatment frequency, Class F in which a new treatment was performed as a result of disability. A functional level score was determined for each patient from reading the description of each level given in the 1995 AAO–HNS guidelines.

2.6. Statistical analysis

Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA) used for the data analysis. Data was shown as mean $\pm$ standard deviation. Paired Student's *t*-test or independent *t*-test was used to compare the differences between the groups, where appropriate. Pearson's chi-square test was used for the categorical data. A *p* value < 0.05 was considered statistically significant.

3. Results

A total of 37 patients received IT applications; 21 from the mixture and 17 from the dexamethasone group. Baseline characteristics did not differ between two groups (Table 1). Mean disease duration was 4,5 years (range 1–8 years) in the mixture group and 4 years in the dexamethasone group. According to the clinical results obtained at 2 years follow-up, complete control of vertigo (class A) was seen in 12 patients (57,15%) in the mixture group and 5 (29,4%) in the dexamethasone group. Substantial control (class B) was seen in 5 patients (23,8%) in the mixture group and 7 (41,2%) in the dexamethasone group. No control of vertigo (class F) was seen in 4 patients (19,05%) in the mixture group and 5 (29,4%) in the dexamethasone group (Table 2). The long-term (after 24 months) satisfactory vertigo control rate (class A + B) was 81% in the mixture group and %70,6 in the dexamethasone group, with a statistically significant difference

Table 1
Demographics and baseline characteristics.

	Mixture group (n: 21)	Dexamethasone group (n: 17)
Age	52,4	49,2
Sex		
Female	10	12
Male	11	5
Ear laterality		
Right	11	7
Left	10	10
Disease duration (years)	4,47 (1–8)	4 (1–10)

Table 2
Control of vertigo by IT treatment in patients followed up for 2 years.

Vertigo control (class)	2-year follow-up (n)	
	Mixture group	Dexamethasone group
A	12	5
B	5	7
C	–	–
D	–	–
E	–	–
F	4	5

($p = 0,0286$).

The number of injection per group was compared statistically and showed a significant advantage for mixture over dexamethasone ($p < 0,0001$). The mean number of total mixture IT injections per patient was 1,19 (range 1–3). A single injection was performed on 18 patients, 2 injections were performed on 2 patients and 3 injections were performed on one patient. In the dexamethasone group the mean number of intervals per patient was 3,41 (range 1–6 intervals, 3–18 injections). A single (3 injection), 5 and 6 interval was performed on one patient, 2 interval were performed on 2 patients, 3 interval were performed on 8 patients and 4 interval were performed on 5 patients.

Audiology results of mixture group showed 20 patients (95,24%) with unchanged hearing and 1 patient (4,76%) with only 10-decibel deteriorated hearing. There was no worsening of hearing in the ITD group. Mean PTA pretreatment was 55.04 dB (SD 16.67 dB) and 44.52 (SD 19,39) for the mixture and ITD groups, respectively; after 2 year, the PTA was 57.19 dB (SD 16,28; mixture group) and 44,70 (SD 19,39; ITD group). The hearing changes of patients from pretreatment to 2-year follow-up are displayed in Table 3. No patients developed TM perforations. Mixture IT injections were well tolerated. None of the patients had an interruption of treatment due to a sign of cochlear or vestibular toxicity. In case of treatment failure, in our study group, no patient was treated with surgical labyrinthectomy or vestibular neurectomy. No serious adverse effect was observed.

Table 3
Hearing levels before and 2 years and long-term after IT treatment.

Hearing level	Pretreatment	2-year follow-up
Mixture group		
PTA	55,04 (SD 16,67)	57,19 (SD 16,25, $p > 0,05$)
Stage 1 (PTA $\leq$ 25 dB)	1	1
Stage 2 (PTA 26–40 dB)	3	2
Stage 3 (PTA 41–70 dB)	14	15
Stage 4 (PTA $>$ 70 dB)	2	2
Dexamethasone group		
PTA	44,52 (SD 19,39)	44,70 (SD 19,94, $p > 0,05$)
Stage 1 (PTA $\leq$ 25 dB)	2	2
Stage 2 (PTA 26–40 dB)	7	7
Stage 3 (PTA 41–70 dB)	6	6
Stage 4 (PTA $>$ 70 dB)	2	2

4. Discussion

Intratympanic gentamicin administration has become a widely accepted means of managing symptoms in MD. IT gentamicin treatment for MD is an office procedure that can be well-tolerated by patients, that does not necessitate hospitalization. On the other hand, the risk of sensorineural hearing loss due to gentamicin injection is the disadvantage [13]. Although there are a number of articles regarding the IT gentamicin injection, there is no consensus as to which interval would be the best to apply in terms of low incidence of sensorineural hearing loss [13]. In the first years of IT gentamicin applications, multiple daily injections were used to be able to create to total ablate the vestibular labyrinth [11]. Some authors suggested just 1 or 2 gentamicin injections with a similar effectiveness for vertigo control and with a lower risk for major side effects [14,15]. Another weekly interval study demonstrated good control of vertigo and low incidence of sensorineural hearing loss [16]. Zhai et al. reported that in their both experimental animals and human study low-dose 3-week interval titration injection technique had a relatively high vertigo control with a low risk of vertigo control. They showed that in the cochlea, the greatest uptake of gentamicin occurred in cochlear outer hair cells at 3 days and was retained for at least 3 weeks following transtympanic injection [17].

In this study, a single injection of mixture IT dexamethasone and gentamicin was found to be sufficient in most patients. If necessary applications were repeated three weeks later like described Zhai et al. [17].

There are 3 studies in the literature about the application of aminoglycoside drugs and steroids to the middle ear. One of them is an animal study, and one is a drug application with the exploration of the middle ear [18,19]. In another study, a mixture of streptomycin and dexamethasone was used clinically [20].

Ardıç et al. performed gentamicin and dexamethasone in the middle ear by surgical intervention in a clinical trial. They protected the round window with a piece of gel foam soaked in dexamethasone and placed a piece of gel foam soaked in gentamicin to the oval window. The vertigo control rate was found as 80%, and a high-frequency hearing loss > 10 dB was found only in 2 patients and 1 patient had 11 dB hearing loss when the mean of all frequencies were taken into consideration [18]. Despite the high degree of vertigo control, surgical intervention is a disadvantage.

In a recent compared animal study with albino rats Güneri et al. reported that single intratympanic injection of dexamethasone and gentamicin combination led to significant preservation of the hearing thresholds of rats in contrast to single intratympanic gentamicin application [19].

Shea et al. used a combination of IT streptomycin and dexamethasone injection for MD. The hearing changes and vertigo control outcomes of 393 cases of mixture streptomycin/dexamethasone IT injection were searched retrospectively. All patients underwent one or more 3-day treatments consisting of daily intratympanic mixture injections (streptomycin + dexamethasone) (24 mg/ml) plus 16 mg of intravenous dexamethasone. In their study, 78,9% of patients had adequate vertigo control after one mixture IT injection, 94% after two and 98% after three. Clinically significant hearing loss was detected in 62 (15.7%) patients and hearing loss was severe in 20 (5%) of those patients [20]. Shea et al. injected streptomycin with dexamethasone [20]. Although there is currently the most frequently used aminoglycoside antibiotic gentamicin in MD treatment, there is no data in the literature about the use of gentamicin and steroid combination in human form as an intratympanic injection.

The results of this study demonstrates IT mixture gentamicin and dexamethasone shows a higher effective control of vertigo in patients with MD when compared with ITD. In the mixture group; 21 intractable MD patients treated with IT mixture gentamicin and dexamethasone, long-term (after 24 months) satisfactory vertigo control rates were 81%. Twelve patients (57,15%) had full vertigo control (class A), 5 patients

(23,8%) had substantial control (class B). Clinically significant hearing loss was seen in only one patient in our study. Dilution of gentamicin with dexamethasone reduces the amount of gentamicin injected. Dexamethasone in the mixture to reduce the degree of vertigo as well as gentamicin-related hearing loss is likely to prevent. We recommend a combined injection of gentamicin with steroids instead of gentamicin alone in MD treatment because satisfactory vertigo control over 80% of our study results can be achieved and hearing is better preserved.

There are some limitations in our work. In a study by Shea et al., the combination of intratympanic streptomycin and dexamethasone was administered to 299 MD patients [20]. In our study, there are 21 MD patients in the mixture group. Combined gentamicin and dexamethasone activity should be investigated in larger series of MD patients. All patients treated in this study had unilateral Meniere's disease. In bilateral Meniere's disease, the effect of intratympanic combined treatment on hearing should be investigated in future studies. In our study, vertigo control rates of mixture IT gentamicin and dexamethasone group were better than the ITG group. Further studies are needed to determine whether the intratympanic application of mixture IT gentamicin and dexamethasone results in better outcomes than IT gentamicin alone. In our study, gentamicin and dexamethasone were mixed at a ratio of 1/1. Only 1 patient had a decrease in hearing. In future animal studies, the ratio of gentamicin in the mixture and the frequency of application should be determined so that the best application to protect the hearing can be determined.

5. Conclusion

IT gentamicin injection still carries the risk for hearing loss. Dexamethasone prevents reactions causing cell death. Separately both intratympanic dexamethasone and gentamicin are effective in reducing the symptoms of Meniere's disease. The combined use of dexamethasone and gentamicin may increase the success of treatment with a synergistic effect. In addition, the use of dexamethasone can prevent the hearing loss due to the use of gentamicin. Combination of IT gentamicin and dexamethasone did not cause any serious or unusual adverse effect and it is an office procedure, safe and well-tolerated therapy. It can be used for patients with Meniere's disease who do not respond to medical therapy.

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Declaration of Competing Interest

No conflict of interest was declared by the authors.

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