



Original Article

Selective Window Application of Gentamicin+ Dexamethasone in Meniere's Disease

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OBJECTIVE: The purpose of the study is to prevent hearing loss when using intratympanic (IT) gentamicin for intractable Meniere's disease.

MATERIALS and METHODS: It is a retrospective case review study. Twenty five patients who had definite Meniere's disease and had either selective window application or weekly IT gentamicin were included into the study. First group (selective) had dexamethasone on the round window and gentamicin on oval window during exploratory tympanotomy procedure. The second group had IT gentamicin at weekly intervals. The degree of caloric weakness (CW), average hearing level in low pitch (HLP) (250, 500, 1000, 2000 Hz) and high pitch (HHP) (4000, 6000, 8000 Hz) were compared before and after treatment. The need for further treatment was noted.

RESULTS: In the first group, the average HLP was increased from 51.6±7dB to 52.2±5.6 dB. The average HHP was increased 41.96±20.2 dB to 47.2±18.3 dB after treatment. The CW changed from 37.6±23.9 % to 54.6±30.6 %. In the second group, the average HLP was increased from 56.3±10.5 dB to 61.65±18.3 dB. The average HHP was increased 59.05±17.4 dB to 69.4±21.98 dB after treatment. The CW changed from 45.8±22.3% to 71.53±29.63 %. Both methods had statistically significant increase in caloric weakness. But only IT gentamicin led a significant hearing loss in HHP.

CONCLUSION: The use of dexamethasone and gentamycin via different windows in the middle ear is safe and effective method for Meniere's disease in the short term. Application of dexamethasone protects not only the hearing cells but vestibular cells also.

KEYWORDS: Meniere's disease, intratympanic gentamicin, intratympanic dexametasone

INTRODUCTION

Meniere's disease is characterized by rotatory vertigo, hearing loss, tinnitus, and fullness of the ear. Its prevalence has been estimated as 190/100,000 in the American population^[1]. Most of the patients respond to medical treatment. Intratympanic (IT) treatment options are good alternatives in patients that do not respond to medical treatment. It has been shown that medications administered into the middle ear pass into the inner ear through oval and round windows, in very high concentrations^[2]. IT gentamicin application has been widely accepted in Meniere's disease because of the dominant vestibulotoxic effect of the agent^[3, 4]. The mechanism of action has been supposed to be destruction of the dark cells to decrease endolymph secretion and /or vestibular sensory cells, and a reduction in the sensation of vertigo^[5, 6]. In addition to its effects on the target organ, gentamicin may exert a toxic effect on the cochlear sensory cells, also. The rate of hearing loss has been reported between 0% and 75% in clinical IT applications, depending on the dose and frequency of application^[7].

A number of methods have been employed to make IT gentamicin application more safer and manageable. A piece of gelfoam soaked in gentamicin was directly put on the round window in order to standardize the dose and duration of the agent given^[8]. Some others covered the round window with connective tissue, then administered IT gentamicin^[9, 10]. The agent was administered together with dexamethasone in order to decrease harmful effects of the aminoglycosides^[4]. It was speculated that the toxic effects of the aminoglycosides could be prevented in this way.

Despite all those efforts, IT gentamicin application still carries the risk for hearing loss. A new method is needed in which vertigo is prevented and hearing is preserved with only a single intervention.

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A new application was planned to administer gentamicin with dexamethasone to decrease the risk for hearing loss, since it has been known that dexamethasone prevents reactions causing cell death. However, administration of two drugs simultaneously into the middle ear would cause a decrease in the vestibulotoxic effect. Therefore, we planned to control absorption of the agents from the oval and round windows. Oval and round windows were used for application of dexamethasone and gentamicin separately but at the same time. The results were compared with control group treated with weekly administration of IT gentamicin.

MATERIALS and METHODS

In this study, we retrospectively analyzed the files of 25 patients with definite Meniere’s disease, who had IT gentamicin with two different methods. Patients selected the method according to their will, after we explained the situation and all possible side effects. All had signed an informed consent about the procedure. Meniere’s disease was diagnosed according to the 1995 diagnostic criteria of American Academy of Otorhinolaryngology. The ethical approval of the study was obtained from the institutional committee (No:60116787-020/37).

The patients who had been followed up in the “vertigo outpatient clinic” for a long time had had complete blood count, pure tone audiogram, vestibule-ocular tests, vestibulospinal tests, and caloric test on their admission. On follow up, their audiograms repeated time to time. Temporal magnetic resonance imaging was obtained for differential diagnosis in patients with unilateral hearing loss.

Intratympanic T gentamicin was administered to the patients diagnosed with Meniere’s disease according to following criteria:

1. A follow up period of at least one year,
2. No response to medical treatment (diuretics, betahistine),
3. Unilateral hearing loss, with a good hearing in the opposite ear,
4. Moderate or worse sensorineural hearing loss in the affected ear,
5. Dynamic patient with normal vision and no alcohol addiction (no age limits),
6. No drug allergies or idiosyncrasy.

Intratympanic Gentamicin Application

1. Direct injection method: We used commercially available gentamicin 2 mL ampul (40 mgr/mL) (I.E. Uluagay, Turkey). Following surface anesthesia, approximately 1 mL of buffered gentamicin solution (30.7 mg/mL) was injected directly into the middle ear using a 25-27 G spinal needle when the patient was lying on his/her back, and his/her head slightly turned towards the opposite side. The patient was asked not to gulp, and he/she stayed at this position for half an hour. This procedure was performed once a week, for three weeks. Pure tone audiogram was performed just before each gentamicin application, and 3 doses were completed if there was no hearing loss. Treatment was stopped when hearing loss appeared. A repeat caloric test was performed 2 weeks after completion of the treatment.

2. Selective window method: In this procedure, the tympanomeatal flap was elevated under local anesthesia, and oval and round windows were examined. First, a piece of gel foam soaked in dexamethasone was placed on the round window until the level of the round window niche, then pieces of gel foam soaked in gentamicin (4 mg/mL)

were placed on the oval window, all around the stapes footplate. Then, the tympanomeatal flap was put into place. Pure tone audiometry and caloric test were repeated 3 months later.

Statistical Analysis

Two groups were compared for mean low (250, 500, 1000, 2000 Hz) and high (4000, 6000, 8000 Hz) frequency hearing thresholds, bithermal caloric test results, and vertigo control. Intergroup comparisons of the parametric variables were done with t test, and intergroup comparisons of the non-parametric variables were done with Mann Whitney U test. Intragroup pre- and post-procedure comparisons were done with Wilcoxon test. PASW (Statistical Package for the Social Sciences version 18 Inc.; Chicago, IL, USA) program was used for statistical analysis.

RESULTS

A total of 25 patients with definite Meniere’s disease, 13 females and 12 males, were included in the study. The mean age of the study group was 47.8±10.7 years. Fifteen of 25 patients were administered IT gentamicin, and 10 of 25 had the selective window procedure. There were no differences between two groups for age, gender, the type of the hearing curve, mean follow up period, or caloric weakness (p>0.05). The high frequency pure tone thresholds were better in the selective window procedure group (p<0.05) (Table 1).

Pre- and post-treatment comparisons revealed that the mean low frequency threshold did not change, however there were significant increases in the mean high frequency threshold and caloric weakness after treatment in IT gentamicin group (p<0.01). In selective window procedure group, only the increase in caloric weakness was significant (p<0.05) (Table 2). The number of patients that had hear-

Table 1. Pretreatment comparison of demographic characteristics and test results of two groups

	IT gentamicin	Selective	Significance
Age	47.8±12.6	48±7.5	p>0.05
Female / Male	9/6	4/6	p>0.05
Mean low-pitch hearing threshold (dB)	56.3±10.5	51.6±7	p>0.05
Mean high-pitch hearing threshold (dB)	59.05±17.4	41.96±20.2	p<0.05
Caloric weakness (%)	45.8±22.3	37.6±23.9	p>0.05
Follow up (months)	17.4±9.9	19.4±2.8	p>0.05

IT: intratympanic; dB: decibel

Table 2. Intragroup comparisons of the pre- and post-treatment test results

IT gentamicin	Before	After	Significance
Mean low-pitch hearing threshold (dB)	56.3±10.5	61.65±18.3	p>0.05
Mean high-pitch hearing threshold (dB)	59.05±17.4	69.4±21.98	p<0.01
Caloric weakness (%)	45.8±22.3	71.53±29.63	p<0.01

Selective window procedure	Before	After	Significance
Mean low-pitch hearing threshold (dB)	51.6±7	52.2±5.6	p>0.05
Mean high-pitch hearing threshold (dB)	41.96±20.2	47.2±18.3	p>0.05
Caloric weakness (%)	37.6±23.9	54.6±30.6	p<0.05

IT: intratympanic; dB: decibel

Table 3. Number (n) of patients classified according to level of hearing loss or caloric weakness after treatment

	IT Gentamicin	Selective	Significance
n of patients who had more than 10 dB low pitch difference (Decreased / Increased)	4/1	0/1	p>0.05
n of patients who had more than 10 dB high pitch difference (Decreased/ Increased)	6/0	2/1	p>0.05
% of patients who had 10-20% caloric decrease	13%	10%	p>0.05
% of patients who had 20-50% caloric decrease	27%	40%	p>0.05
% of patients who had more than 50% caloric decrease	27%	10%	p>0.05
n of patient with recurrence of vertigo attack	2 (13%)	2 (20%)	p>0.05

IT: intratympanic; dB: decibel

ing loss more than 10 dB and a caloric weakness more than 50% was higher in the IT gentamicin group, but the difference between two groups was not significant ($p>0.05$) (Table 3).

The mean number of the injections was 2.4 (1-4) in IT gentamicin group. During follow up, vertigo recurred in 2 patients in IT gentamicin group, and one dose of IT gentamicin was administered to those patients. Vertigo attacks were also recurred in two patients who had selective window procedure. They had additional one dose of IT gentamicin (Table 3).

There was no correlation of the number of injections with hearing loss or caloric weakness in the IT gentamicin group.

DISCUSSION

Use of IT gentamicin or dexamethasone is an accepted treatment option in patients with Meniere's disease that do not respond to medical treatment. IT gentamicin is more effective than IT dexamethasone for vertigo control [11]. However, its use is limited in patients with good hearing thresholds due to probability of hearing loss after treatment. IT gentamicin success is changing between 73-100% for vertigo control and results hearing loss between 0-75% of the patients according to the protocol used [7].

First, decreasing the frequency of application was tried in order to overcome this handicap. Probability of hearing loss is smaller in weekly applications [12]. As a matter of fact, recent protocols recommended use of a single dose during vertigo attack (on demand) rather than a standard regimen. The vertigo control rate was reported as 96.5% without any hearing loss [13].

Controlling the place and the amount of the absorption of the drug is another option. A piece of gel foam soaked in gentamicin (26.7 mgr/mL) was put in front of the round window after cleaning this area, and vertigo control was reported as 75%, but hearing loss appeared in 10% of the patients [8]. On the opposite, the round window was protected with a piece of connective tissue, and then IT gentamicin (80 mg/mL) was administered twice a week [10]. This technique resulted in a vertigo control rate of 91%, and a hearing

loss rate of 27%. Kalberg et al. [14] protected the round window with a piece of gel foam soaked in normal saline, and placed a piece of gel foam soaked in gentamicin (30 mg/mL) to the oval window. The vertigo control rate was found as 88% without any hearing loss. In our study, we used the same method, but we used dexamethasone. After a mean follow up period of 19 months, we found the vertigo control rate as 80%, and a high frequency hearing loss more than 10 dB was found only in 2 patients. When the mean of all frequencies was taken into consideration, there was 11 dB loss in one patient (10%) in selective window procedure group. However, 4 patients in direct injection group (26%) had more than 10 dB hearing loss when the mean of all frequencies were taken into consideration.

Some studies investigated the rate of absorption of the drugs into the inner ear through oval and round windows. Different drugs had different results [15,16]. It was reported that application of gentamicin to oval window caused more vestibulotoxicity and hearing loss in Guinea pigs [17]. This was supposed to be due to more absorption of gentamicin through the oval window. Selective absorption has been confirmed by a number of studies. King et al. [16] estimated that the rate of gadolinium absorption in the region of stapes was more than 90%. Salt et al. [15] showed that trimethylphenylammonium (TMPA) marker was absorbed at a rate of 65% from the round window. Placing gentamicin to the oval window caused a mean increase of 17 ± 22.6 in the caloric weakness. However, this increase was found as 25.7 ± 26.2 when gentamicin was administered directly to the middle ear. Less vestibulotoxicity in selective application shows that dexamethasone placed in round window not only protected the cochlear cells, but also the vestibular cells. Application of gel foam soaked with drugs provides a longer stay of the drug in the middle ear, and access of the drug until the cochlear apex [18]. This situation seems to be true for the drugs placed to both windows.

Use of IT aminoglycosides and steroids is not new. Shea et al. [19] used IT low-dose streptomycin/ high-dose dexamethasone mixture plus intravenous dexamethasone combination for 3 days in Meniere's disease patients, and found the vertigo control rate as 88%, and hearing loss rate as 15.7%. It has been known that corticosteroids pass into the inner ear and attach to their own receptors. Those receptors have been shown predominantly in the spiral ligament, and then organ of Corti and stria vascularis in the human inner ear [20]. Ion homeostasis, immune suppression, and free radical scavenging effects of those agents made them to be used to protect cochlea, particularly in ototoxic drug use and acoustic trauma [21]. The results of this study suggest that dexamethasone has a protective effect for gentamicin toxicity.

In conclusion, applying dexamethasone and gentamicin simultaneously to different windows prevents vertigo at a high rate, and causes high frequency hearing loss only in only a small percent of the patients. Long term results of this promising treatment option should be obtained to determine whether it could take place in the treatment protocol of Meniere's disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Pamukkale University School of Medicine (No:60116787-020/37).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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