

## Comparison the Efficacy of Intratympanic Injections of Methylprednisolone and Gentamicin to Control Vertigo in Unilateral Meniere's Disease

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### ABSTRACT

Meniere's disease (MD) is the most common form of endolymphatic hydrops with unknown etiology. Although various medical and surgical treatments have been introduced for this condition, there is still no definite cure for MD. The present study aims to comparatively evaluate the therapeutic effects of gentamicin perfusion and steroid therapy by methylprednisolone in controlling the vertigo among the unilateral MD patients. Twenty patients with unilateral MD patients were enrolled in this study according to the guidelines of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). The subjects who had not previously responded to the treatment for at least 3 months were included. Ten cases received injection of gentamicin solution. The gentamicin solution was injected under a microscope using a 25 needle. Likewise, 10 patients underwent intratympanic methylprednisolone injection 3 times a week. The response rate for the treatment of vertigo was evaluated based on AAO-HNS guidelines. After the intervention, tinnitus was observed in 45.5% of the gentamicin group, while in 54.4% of the methylprednisolone receiving group 54.4% ( $P>0.05$ ). Vertigo was controlled in 70% of the patients in the gentamicin group and 50% in methylprednisolone group (0.085). The reduction of PTA was significantly higher in patients received gentamicin, compared with the subjects received methylprednisolone ( $P=0.035$ ). Low-dose gentamicin may be a relatively safe and effective therapy in the treatment of intractable MD, providing superior vertigo control compared with intratympanic methylprednisolone.

**Key words:** Meniere's Disease, Methylprednisolone, Gentamicin, Vertigo.

### INTRODUCTION

Meniere's disease (MD), the most common form of endolymphatic hydrops, is a disease of the inner ear that is characterized by fluctuating sensorineural hearing loss, tinnitus, episodic vertigo, and aural fullness. MD is most commonly found among individuals aged between 40 to 60, with a preference for females and whites<sup>1</sup>. Based on the American Academy of Otolaryngology diagnostic criteria, MD is characterized by several complications, which are recurrent, well-defined

episodes of rotation or spinning with nystagmus which lasts between 20 min to 24 hrs. Vertigo attacks usually happen along with nausea, vomiting, or both. Progressive sensorineural hearing loss that is progressive and commonly unilateral<sup>2</sup>. There are a plethora of medical and surgical treatments for this disease. However, no definitive cure has been discovered yet. Some of the different remedies are changes in lifestyle, diet and diuretic therapy, steroid therapy, intratympanic gentamicin and methylprednisolone perfusion (ITGP and ITMP), pressure pulse treatment, endolymphatic sac

surgery and vestibular nerve section. Symptom therapy can be done using antiemetic, hypnotic and antidepressants<sup>2</sup>. Intratympanic gentamicin (ITG) and intratympanic steroids (ITSs), such as intratympanic methylprednisolone (ITMP), are the most commonly injected medications<sup>3</sup>.

In patients with intractable vertigo, destructive treatments are an option through ITGP. Gentamicin has destructive effects on both the vestibular and cochlear functions. Although the results of different studies are varied, gentamicin is known to be more toxic for vestibular apparatus than for the cochlear apparatus (4). In addition to the conventional medications for controlling pain and inflammatory and infections, new non-drug techniques have been developed recently for various disorders including tinnitus, vertigo, wound, and pain relieving<sup>5-7</sup>.

Anti-inflammatory and immunosuppressive effects of steroids are important in treatment of autoimmune hearing loss<sup>8</sup>. In humans, steroid receptors of inner ear are located in temporal bones. Among steroids, methylprednisolone has the best concentration profile used in the treatment of MD<sup>9</sup>. Gabra *et al.* showed in their study that ITG alleviates the symptoms more effectively than ITMP. Nevertheless, according to the study performed by Dodson *et al.* on short-term palliation of vertigo and other symptoms of MD ITSs can be efficient in short-term palliation of vertigo and other symptoms of MD<sup>10</sup>.

Menier's disease is an agonizing condition and oral medication almost not of much use. Moreover, the number of studies comparing the efficacy of gentamicin versus methylprednisolone are low and most of our information are from those of other countries. Therefore, in this study we aimed to compare the results of gentamicin perfusion with steroid therapy by methylprednisolone in controlling patients' vertigo.

## MATERIALS AND METHODS

This was a randomized clinical trial study conducted on 20 patients with unilateral MD who were selected according to the guidelines of the

American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). They were divided into two groups of 10 patients. Subjects who had not previously responded to the treatment for at least 3 months were included. Subjects who suffered from bilateral Menière's disease, subjects who their infected organ was their only operational ear, subjects with CNS disorder, as well as subjects who preferred not to participate in the study were excluded from the study. All patients gave informed written consent to participate in the investigation. The study was approved by the ethical committee of Ahvaz Jundishapur University of Medical Sciences.

Patients underwent audiometry. For one group, the injectable solution of Gentamicin was prescribed in combination with sodium bicarbonate 8.4% with Gentamicin 80 mg vial (vial) (to normalize the pH, increase the drug absorption, and reduce the pain). This solution consisted of 27 mg Gentamicin per cc. Lidocaine was used for local anesthesia, at posterior superior part of the tympanic membrane, in the Semi Fowler's position. Then, the gentamicin solution was injected under a microscope using a 25 needle. For the other group, Methylprednisolone was injected 3 times a week, in the same manner. After 3 months, the patients filled the questionnaire and audiometry test was performed. The response rate for the treatment of vertigo was evaluated based on AAO-HNS guidelines.

The statistical analysis was carried out with statistical package SPSS (version 16) using Student t-test and Mann-Whitney tests for quantitative variables, and Chi-square and Fischer's exact tests for qualitative variables. The  $P < 0.05$  is considered statistically significant.

## RESULTS

Twenty patients with unilateral definite MD were included in the study. Ten patients (5 males) were treated with ITGP and 10 (3 males) with ITMP. The mean age was  $51.10 \pm 13.98$  years in the gentamicin group and  $46.10 \pm 7.98$  years in the ITMP group which was not statistically different ( $P > 0.05$ ). Of the ITG group, 19 patients received 1 injection and 13 received 2 injections. The

involvement of right ear was reported in 9 (45.0%) patients.

After the intervention the prevalence of tinnitus was 45.5% in the gentamicin group, while this rate was 54.4% in the patients who received methylprednisolone, which were not statistically different ( $P>0.05$ ). Totally, after the follow-up, using gentamicin can control the vertigo in 7 (70.0%) cases while, using methylprednisolone can control the vertigo attacks in 5 (50.0%) subjects. Of the ITGP group, at the follow-up, complete vertigo control (class A) was achieved in only one patient (10.0%) and substantial control (class B) in 6 (60.0%) patients. While, 3 (30.0) had no control of vertigo spells. In the ITMP group, 4 patients (40.0%) obtained complete control of vertigo (class A) and 1 (10.0%) good control (class B); 4 subjects (40.0 %) reported failure (class C) and one patient reported limited control (class D) (Fig. 1). However, there were slightly significant differences in response to treatment of vertigo between groups (0.085).

#### Hearing outcomes

In the ITGP group, the average of differences in pure tone average (PTA) values between before and after the treatment was 5.5

(SD, 3.6) dB. In addition, in ITMP group, the median of decreased in PTA was 0.0 (IQR, 1) dB before and after the treatment. Interestingly, the reduction of PTA was significantly higher in patients received gentamicin compare with subject received methylprednisolone ( $P=0.035$ ).

#### DISCUSSION

The etiology of MD remains unclear and it has exacerbations and remission courses with remissions, which make it hard to treat. In addition, the insignificant number of clinical trials on the treatment of MD makes evaluation of treatment difficult.

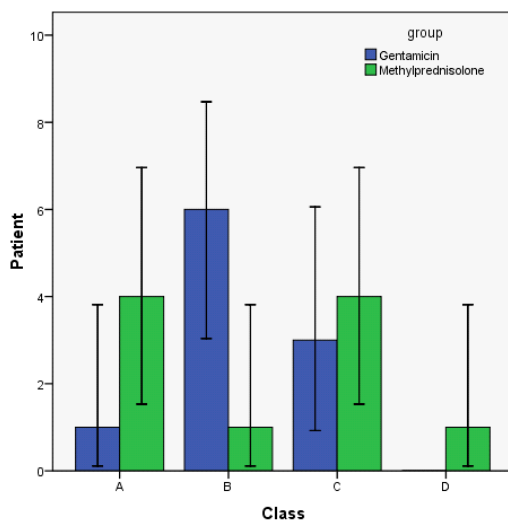
The current study compares hearing outcome and vertigo control in patients affected with MD receiving ITGP with those receiving ITMP. The risk of hearing decline and persistent dizziness from ITG remains a significant concern, particularly with the prescribing in high-doses. Therefore, it is important to monitor and control the adverse effects of intratympanic therapy such as vertigo. In this regard there are two main minimally invasive methods help to acquire optimum outcome: low-dose intratympanic gentamicin and steroids such as methylprednisolone.

Our study proves that gentamicin was more effective than methylprednisolone in control of vertigo attacks (70.0% vs. 50.0%); however, this superiority was slightly significant.

Regarding the hearing outcome, there was significant difference between the two groups in terms of PTA evolution.

There are few prospective randomized controlled studies with 2 year follow-up have compared the effect of ITG with intratympanic steroids (dexamethasone, ITD) in MD (10, 11). Casani and Piaggi reported a vertigo control rate of 93.5% and 61% in the ITG and ITD groups, respectively<sup>10</sup>. They also suggested that low-dose ITGP prescription would have led to a better outcome than ITDP in the control of vertigo attacks and hearing deterioration<sup>10</sup>.

In other control trial study by Ren *et al.*<sup>12</sup>



**Fig-1** Number of patients belonging to vertigo classes treatment with intratympanic gentamicin and intratympanic methylprednisolone. Error bars represent the 95% confidence interval

were evaluated the efficacy of intratympanic injection of dexamethasone in patients with MD. They reported that the rate of complete vertigo control was 48.8% and the symptom of tinnitus was treated in 60% of patients. Comparing with our study, the success rate of both methylprednisolone and gentamicin was higher than dexamethasone the control of vertigo.

Parnes *et al.*<sup>13</sup> investigated the efficacy of intratympanic injections of short, intermediate and long acting corticosteroids including hydrocortisone, methylprednisolone, and dexamethasone, respectively.

They pointed that the inner ear concentrations of intratympanic methylprednisolone injection were higher than dexamethasone, as it reached at the highest level after 2 hrs of injection and its level remained for 6 hrs; while in case of dexamethasone the inner ear concentration was vanished after 6 hours. It should be noted that these studies did not compare the hearing outcome of ITGP and ITMP for patients with severe hearing loss only; therefore, the comparison with our study may be not appropriate for this group.

Huon *et al.* reviewed 14 studies about the controversy in various ITG dosing methods in MD. In the reviewed articles gentamicin concentration was ranged from 12 to 80 mg/ml in fixed or titration schedules. With a review of 14 studies published over a 16-year period, patients (N = 599) required an average number of 2.1 treatments to achieve 87.5% rate of substantial control. Miller *et al.* (14) has suggested that the optimum dose for prescribing gentamicin is 26.7 mg/ml at 3-week intervals until symptoms are vanished. This dosing

strategy would guarantee a balance between the potential acquirement for multiple injections and the possibility of the ototoxicity from strategies that are more aggressive<sup>3</sup>.

Our study has some limitations. First, because of its historical character, it is more difficult to analyze qualitative data such as disability score assessment. In addition, only a 3-month follow-up was considered since many patients did not present at their appointments later on, which limited our observations. We had only 20 subjects in two groups at baseline, so we used Mann-Whitney and Fischer exact test for comparing the changes and prevalence between groups. Certainly, our study sample was small and the possibility of type I error is bigger.

Although ITG and ITI of steroids were largely investigated separately, this is one of the first studies in the literature to compare methylprednisolone as an intratympanic steroid injection with ITG in the treatment of MD. Since all treatments used in MD are empirical, this approach is clinically relevant so as to establish an algorithm adapted to each case<sup>15</sup>.

## CONCLUSION

Keeping in mind the limitations of this study, we could state that our results cannot serve as the basis for generalized treatment recommendations. However, we can conclude that intratympanic delivery of low-dose gentamicin can be considered a relatively safe and effective therapy in the treatment of intractable MD, providing superior vertigo control, compared with ITMP (70.0% vs 50.0%). Furthermore, it is associated with higher incidence of hearing impairment.

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