Original Article
Intratympanic dexamethasone injections for refractory Meniere’s disease

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Abstract: Intratympanic injections or titration is a potential medical therapeutic strategy for patients with incurable inner ear diseases. Dexamethasone represent an attractive steroid source in intratympanic steroids strategies in the treatment of inner ear disorders. Here, we evaluated the effectiveness of intratympanic dexamethasone injections (IDI) in outpatients with refractory Meniere’s disease (MD). Vestibular function measured by Vestibular Ocular Reflex (VOR) gain and caloric test revealed that 21 outpatients out of 43 (48.8%) had complete sufficient vertigo control, while 9 (20.9%) of them were attached to fundamental manipulation. Out of the 13 remaining outpatients, 4 (9.3%) had a limit control and 9 had less modification. Therefore, 5 of 9 received re-treatment with IDI and 2 of 9 patients were administered ablative treatment with gentamicin. Meanwhile, audiology data suggested that 3 (7.0%), 4 (9.3%), 32 (74.4%), 4 (9.3%) patients were attached to the level of A, B, C, D, respectively. Furthermore, the symptom of tinnitus in 5 outpatients vanished, 21 (48.8%) diminished, 10 (23.3%) invariable, 7 (16.3%) aggravated. In 4 of 24 cases (16.7%), aural fullness disappeared after IDI, when the aural fullness was alleviated in 11 cases (45.8%) even intensive in 9 patients (37.5%). Together, our results demonstrate that intratympanic dexamethasone injection, as an effective therapeutic strategy for refractory Meniere’s disease, could either be used for cascade therapy preoperation or used for patients who couldn’t accept the surgery.

Keywords: Meniere’s disease, refractory, dexamethasone, intratympanic injections, intratympanic dexamethasone injections (IDI), sensorineural hearing loss (SNHL), tinnitus, aural fullness, gentamicin, intratympanic gentamicin injections

Introduction
Meniere’s disease, first described by Prosper Meniere in 1861 [1], is a long-term, progressive inner ear disorder characterized by episodic vertigo, fluctuating sensorineural hearing loss (SNHL), tinnitus, and aural fullness [2]. Meniere ascribed the pathology to inner ear challenging the prevailing opinions at the time that those combinations of system caused by disorders of the central nervous system called cerebral congestion. The primary histopathological theory of MD is endolymphatic hydrops [3-6]. Although the potential mechanisms underlying MD are not completely understood, the pathology in MD is generally attributed to [7] autoimmune mechanisms [8-11], viral infection postulated to have relatively affinity to the inner ear such as the neurotropic viruses, herpes simplex virus (HSV) types 1 and 2 [12, 13], varicella zos-
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py preoperation for its high responsiveness, and prompt treatment. Its mechanism of mode is not yet fully understood. Several studies on IT steroids for MD showing that steroids, in addition to its anti-inflammatory effects, can affect ion and fluid homeostasis of the inner ear to stabilize the vascular endothelium [20-24]. Finally, cochlear blood flow [25, 26] may be positively affected by topical application of steroids [27, 28]. Clinical trials and meta-analyses suggested that dexamethasone might have a beneficial effect on patients with Meniere's disease, especially on the temporary relief of vertigo without destroying vestibular function [29-31]. Nevertheless, there is still a few well-conducted, controlled, double-blind randomized prospective clinical trials on the application of dexamethasone in Meniere's disease.

The goal of this study was to evaluate the effects of clinically administration of dexamethasone for MD and to determine that IDI could either be used for cascade therapy preoperation or used for patients who couldn’t accept the surgery. Ultimately, we aimed to document the role of autoimmune in MD.

Materials and methods

Ethics

The subject's written informed consent was obtained to participate in the study according to the Changsha guidelines and approved by the ethical committee of the Second Xiangya Hospital, Central South University. The entire experiment procedure is shown in the schematic diagram in Figure 1.

Subjects

This is a retrospective study from February 2007 to April 2011 including 43 outpatients (27 left ear, 16 right ear) at the department of Otolaryngology Head and Neck Surgery, the Second Xiangya Hospital, Central South University (Changsha, China) and with a clinical diagnosis of definite unilateral MD according to the diagnostic scale of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). According to these criteria, definite unilateral Ménière's disease must meet the following criteria: 1) 2 or more definitive spontaneous episodes of vertigo lasted for 20 minutes or longer, 2) audiometrically documented hearing loss on at least 1 occasion, 3) tinnitus or aural fullness in the treated ear, and 4) other causes excluded [13]. We selected outpatients (29 males, 14 females) with no response to normal oral medicine beyond 1 year. They suffered vertigo attacks at least 1 time every month and accompanied by SNHL and tinitus during the last 6 months. All of those patients, aged from 29 years to 75 years (median 43.5 years), had been suffering MD for an average of 3.6 years. Simultaneously, their pathogenesis lasted for an average of 3.6 years (1.2-4.6 years). All of the patients were followed-up for 18 months for treatment studies in MD. When patients agreed to participate in the study, they were informed that they must provide information about the frequency and duration of episodes of vertigo, hearing loss, tinnitus and aural fullness they had experienced.

All patients underwent complete otological examination with tympanometry and audiologic evaluation such as pure-tone audiometry, acoustic immittance, auditory brain stem response (ABR). Neurologic examination including spontaneous gaze-evoked nystagmus, head thrust test and standard caloric test were also performed. Hearing staging for each patient with definite MD was defined as the mean of three-tone average of 0.5, 1 and 2 kHz according to the AAO-HNS criteria: stage 1, #25 dB; stage 2, 26-40 dB; stage 3, 41-70 dB; 4, stage 4, 71-75 dB. Episodes of vertigo were characterized by their frequency and duration as previously described [32], and episodes of vertigo lasting less than 20 minutes or the sensation of instability usually observed in these patients were not considered in this study. In addition, the protocol of diagnosis included an examination by temporal bone CT and MRI to exclude other possible causes of neurological symptoms.

Figure 1. Complete study procedure.
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The IT steroid injection procedure was performed in the outpatient clinic under a binocular microscope after informed consent was obtained from the patient just as previously described [33, 34]. With the patient supine and the head turned to the opposite side, the local anesthesia of the posterosuperior quadrant of the tympanic membrane was first offered by Glycerinum phenolis (5%) tampon. Approximately 1ml dexamethasone solution (5 g/L) was loaded into a 1-mL syringe with a long 25-gauge needle attached on it. A needle hole was made in the anesthetized area for air to escape during the middle ear injection, while another hole was made for intratympanic injection. One patient received a total of 17.5 mg usually in a volume of 0.3-0.8 ml injected into the tympanic once daily for 5 days consecutively sufficient to fill the space or at least cover the round-window niche. After the injection, the head was placed slightly lower than the body, and the subject was instructed to lie in the supine position with the head turned 45 degrees toward the contralateral side, keeping the treated ear up and not swallow for 30 minutes in order to assure enough time for the buffer to interact with the inner ear completely through round-window niche. Majority of patients were asked to complete Caloric and quantitative Head thrust test before and after each treatment.

Outcome assessment

In the following clinical appointments, vertigo, tinnitus and aural fullness control was monitored by the subject’s report of the frequency and severity of any vertigo attacks that occurred since the last treatment. Efficacy in recovery of SNHL throughout the study was assessed by pure-tone audiometry performed preoperation and postoperation for 10 days, 1 month, 3 months, 6 months, 1 year, 18 months from the end of the treatment. If there were no vertigo attacks reported, then no further therapy was recommended at that time. If there were any vertigo attacks but the patient was satisfied with a sufficient reduction in the episodic vertigo compared with what they had experienced before IDI, then further IDI was continued. However, if the subject felt that the effect of the last IDI was negligible or unsatisfied, then IT gentamicin injection or ablative surgery was recommended.

Caloric tests

Caloric tests were performed using a temperature switch irrigation technique for 30 and 44 °C. The water was irrigated for 40 minutes in total 400 ml. The results were evaluated by the frequency of the nystagmus beats during the culmination period of the response. Horizontal eye movements were observed and the slow-phase of nystagmus was analyzed for unilateral weakness and directional preponderance was determined by conventional formulas. An ice water caloric test was performed when there was no response to warm or cold irrigation in the affected ear. If nystagmus was noted in response to the ice water test, the patient was turned from supine to prone to see if nystagmus reversed direction.

Results

Clinical features

The clinical features of the patients with unilateral definite MD in the study are shown in Table 1. Forty-three patients (14 females and 29
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Males) aged from 29 to 75 years (median 43.5 years) were treated with IDI. All of them had been suffering for an average course of 3.6 years. The afflicted parts of 27 patients were in the left ear while the other 16 patients in the right ear. Hearing stage referring to the best ear were on Stages 3 and 4. Simultaneously, unilateral SNHL was found in those 43 subjects since the air conduction loss ranged from 32.5 to 82.5 dB HL (median 51 dB HL) was observed. The hearing curve analysis demonstrated that 22 of 43 patients showed upward-sloping curve in which low frequencies were more commonly affected when 19 of 43 patients showed flat configuration. In addition, high frequencies of the remaining 2 patients were affected showing downward-sloping curve. They suffered vertigo attacks at least 1 time every month and disrupting by SNHL, tinnitus and aural fullness during the last 6 months.

Vestibular function was evaluated by Glycerol test and Caloric test. 29 patients respond positively in Glycerol test. However, 14 patients gave no response in Glycerol test. At the same time, among the total, 34 patients respond positively in Caloric test, vestibular function deceased slightly in 23 patients and 11 patients' vestibular function impaired severely. The vestibular function can be evaluated through the Table 2.

Regarding the efficiency of the IDI group, if no vertigo attacks were reported, no further therapy was recommended. Otherwise, further treatment with IDI was scheduled. Consequently, majority of subjects performed with IDI received relatively efficient vertigo control except for 9 of them. They were classified as failures after the pre-treatment. Therefore, 5 of 9 received re-treatment with IDI and 2 of 9 patients were administered ablative treatment with gentamicin. 2 of 9 patients were scheduled for endolymphatic sac decompression.

Vertigo

After 18 months follow-up period, vestibular function measured by Vestibular Ocular Reflex (VOR) gain and caloric test revealed that 21 outpatients out of 43 (48.8%) had complete sufficient vertigo control (class A), while 9 (20.9%) of them were attached to substantial manipulation (class B). Out of the 13 remaining outpatients, 4 (9.3%) had a limited control and 9 had less modification. As aforementioned, 5 of 9 received re-treatment with IDI and 2 of 9 patients were administered ablative treatment with gentamicin. 2 of 9 patients were scheduled for endolymphatic sac decompression. The ablative procedure used after the failure of IT steroid, gave good results in term of vertigo control (Table 3).

Hearing function

In patients with unilateral Meniere's disease, hearing function deteriorated as the disease progressed, fortunately, no further hearing loss was reported after the IDI injection. Meanwhile, pure-tone audiometry data suggested that 3 (7.0%), 4 (9.3%), 32 (74.4%), 4 (9.3%) patients were attached to the level of A, B, C, D, respectively (Table 4).

Tinnitus

Among all of the 43 patients complained suffering from the tinnitus, 5 of them reported that the symptom vanished. Furthermore, the tinnitus diminished in 21 (48.8%) patients and invariable in 10 (23.3%) patients. Nevertheless, the tinnitus in 7 of 43 (16.3%) patients aggravated after IDI.

<table>
<thead>
<tr>
<th>Table 3. Results of vertigo attacks</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete control</td>
<td>21</td>
<td>48.8</td>
</tr>
<tr>
<td>Substantial control</td>
<td>9</td>
<td>20.9</td>
</tr>
<tr>
<td>Limited control</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>No exact response</td>
<td>9</td>
<td>20.9</td>
</tr>
</tbody>
</table>

Note: Vestibular function results: 21 outpatients out of 43 (48.8%) had complete sufficient vertigo control (class A), while 9 (20.9%) of them were attached to substantial manipulation (class B). Out of the 13 remaining outpatients, 4 (9.3%) had a limited control and 9 had less modification.

<table>
<thead>
<tr>
<th>Table 4. Results of hearing function</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>3</td>
<td>7.0</td>
</tr>
<tr>
<td>Level B</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>Level C</td>
<td>32</td>
<td>74.4</td>
</tr>
<tr>
<td>Level D</td>
<td>4</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Note: Hearing function results: pure-tone audiometry data suggests that 3 (7.0%), 4 (9.3%), 32 (74.4%), 4 (9.3%) patients were attached to the level of A, B, C, D, respectively.
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Aural fullness

Twenty-four of 43 patients complained that they were disrupted by aural fullness except for the remaining nineteen patients. They never stated suffering from aural fullness. In 4 of 24 cases (16.7%), aural fullness disappeared after IDI. The aural fullness was alleviated in 11 cases (45.8%) even intensive in 9 patients (37.5%).

Exclusion criteria

We excluded patients with vestibular migraine, benign paroxysmal positional vertigo, vestibular neuritis, head trauma, ear surgery, recurrent infection of the middle ear, acoustic schwannoma and any known cause mimicking MD, according to the diagnostic scale of the AAO-HNS.

Discussion

The major findings of this study were as follows: IDI, as an effective therapeutic strategy for refractory Meniere's disease, could either be used for cascade therapy preoperation or used for patients who couldn't accept the surgery. As yet, several studies have already devoted into detecting the effects of IDI on Meniere's disease [30, 35-37]. Our data are in line with those previously published results in addition to the following parts: First, few investigations had been focus on the subjects that had also undergone medical therapy for at least 1 year. Second, our results demonstrates the relation between the effects of IDI and the surgery for Meniere's disease, that is to say, IDI can be used for cascade therapy preoperation.

The pathology of Meniere's disease is still unknown; however, previous studies had proposed that viral infections and autoimmune processes may play a role in the induction of the disease. Since last century, Ryan [38] postulated that Meniere's disease might be an immune-mediated or even an autoimmune condition. Many studies have demonstrated that they have extracted circulating antibodies against antigens in bovine inner ear of patients with Meniere's disease such as anti-heat shock protein 70 (HPS70) antibody, tumour necrosis factor (TNF)-alpha, antinuclear antibody (ANA), and erythrocyte sedimentation rate (ESR) and so on [8, 32, 39-42]. Moreover, several studies had found a higher prevalence of systemic AD as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) within patients with MD [10, 43, 44]. Immune response plays a role in the activity and progression of MD, as reported in studies on inner ear disorders showing that B lymphocytes are related with hearing loss and CD8+ T lymphocytes with persistence of vertigo similar to the founds of results in previous studies [45-47].

Although a number of studies pointed out that viral infection has long been recognized as the pathological correlate of Meniere's disease since 1930s [48, 49], viral invasion of the endolymphatic sac is impeded through immunological mechanisms under normal conditions [50]. Those findings support the hypothesis that viral infections and autoimmune processes may be important in the development of Meniere's disease.

Steroid therapy has commonly been used in Meniere's disease [51]. Diagnosis of autoimmune inner ear disorders is still largely based on the response to steroid therapy. It is believed that the mode of action of steroid therapy in MD, in addition to its anti-inflammatory effects on the labyrinth likely caused by the immune mechanism, probably protects neural tissues from ischemic injury and affects sodium and fluid transport to stabilize the vascular endothelium. Satyanarayana demonstrated for the first time that steroid regulates Na+ absorption and osmotically couple water flux to ameliorate the inner ear dysfunction during the treatment of MD [22, 52].

To date, steroid has been generally administered orally or intravenously in clinical used to investigate the effect of steroid on inner ear disorders. We are all aware that the pharmacokinetics of enteral or the total body absorption is followed by a considerably decelerated bioavailability. Therefore, intratympanic injections, as a substitute way of traditional treatments, including intratympanic injection of steroid and intratympanic injection of gentamicin appeared with minimal side effects related (mainly the tympanic membrane perforation and inflammatory in middle ear) [53]. Patients accepted IDI as the first option whose responsiveness is high and provide temporary relief of vertigo for preserving the structures of the inner ear so that inner ear damage may be reversible.
However, it would be prudent for us to choose intratympanic gentamicin injection for a worsening of hearing and word recognition [54-56]. Gentamicin leads to direct damage to the sensorineural epithelium of the labyrinth, thus affecting vestibular and cochlear function which is also the likely mechanism through which gentamicin provides prompt treatment effects [57, 58].

The current study was conducted to determine whether IDI is efficient enough so that ablative treatments were subsequently avoided. If patients do not respond to the IDI, intratympanic gentamicin injection or surgery can be given. In the present investigation, the total 43 outpatients chose IDI at the time of initial treatment. Since most of them received an effective vertigo control in addition to 9 patients had less modification, 5 of 9 received re-treatment with IDI and 2 of 9 patients were administered ablative treatment with gentamicin. 2 of 9 patients were scheduled for endolymphatic sac decompression. Vestibular function measured by Vestibular Ocular Reflex (VOR) gain and caloric test revealed that 21 outpatients out of 43 (48.8%) had complete sufficient vertigo control, while 9 (20.9%) of them attached to fundamental manipulation. Of the 13 remaining outpatients, 4 (9.3%) had a limit control and 9 had less modification. Meanwhile, audiology data suggests that 3 (7.0%), 4 (9.3%), 32 (74.4%), 4 (9.3%) patients attached to the level of A, B, C, D, respectively; Furthermore, the symptom of tinnitus in 5 outpatients vanished, 21 (48.8%) diminished, 10 (23.3%) invariability, 7 (16.3%) aggravated. All of the results mentioned above suggests that IDI makes a perfect effect on MD which is similar to the previous studies [30, 59].

There are also some limitations or side effects to this study. Although the IDI can achieve vertigo control by improving the autoimmune status to some extent, it can’t modify the fundamental mechanism of endolymphatic hydrops [60, 61]. Additionally, 1 of 43 cases occurred tympanic membrane perforation in case of the humble tympanic membrane before IDI. The perforated tympanic membrane was repaired by adipose tissues posterior of the ear.

Together, our results demonstrates that intratympanic dexamethasone injections, as an effective therapeutic strategy for refractory Meniere’s disease, could either be used for cascade therapy preoperation or used for patients who couldn’t accept the surgery [62, 63]. Additional multicentre studies should confirm the effectiveness of IDI in MD.

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Disclosure of conflict of interest

None.

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