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MAIN ARTICLE

Long-term effects of intratympanic methylprednisolone perfusion treatment on intractable Ménière's disease

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Abstract

Objective: This study aimed to investigate the long-term efficacy of intratympanic methylprednisolone perfusion treatment for intractable Ménière's disease.

Methods: A retrospective analysis of 17 intractable Ménière's disease patients treated with intratympanic methylprednisolone perfusion was performed. Treatment efficacy was evaluated according to the American Academy of Otolaryngology–Head and Neck Surgery criteria. Short and long-term control or improvement rates were calculated after 6 and 24 months, respectively.

Results: Sixteen patients were followed for more than two years. Short- and long-term vertigo control rates were 94 per cent and 81 per cent, respectively; short- and long-term functional activity improvements were 94 per cent and 88 per cent, respectively. The pure tone average was 53 ± 14 dB before treatment, and 50 ± 16 dB at 6 months and 52 ± 20 dB at 24 months after intratympanic methylprednisolone perfusion. Tinnitus was controlled or improved in five patients over the two-year follow-up period.

Conclusion: Intratympanic methylprednisolone perfusion can effectively control vertigo and improve functional activity in intractable Ménière's disease patients with good hearing preservation. It may therefore be a viable alternative treatment for intractable Ménière's disease.

Key words: Ménière's disease; Methylprednisolone; Perfusion; Tympanum

Introduction

Ménière's disease is a common inner-ear disorder typically characterised by recurrent vertigo, fluctuant hearing loss, tinnitus and aural fullness.[1] Idiopathic endolymphatic hydrops is thought to be associated with Ménière's disease, although its true pathogenesis remains unknown. Of all the disease symptoms, vertigo represents the most severe functional barrier for patients. Thus, Ménière's disease treatments have primarily targeted the control of vestibular dysfunction. However, 15 per cent of Ménière's disease patients are unresponsive to conventional medication and psychotherapy aimed at treating this symptom.[2] Intractable Ménière's disease is diagnosed when patients have been unresponsive to conventional vertigo treatment strategies for more than six months.[3] One treatment option for intractable Ménière's disease is tympanic perfusion therapy using aminoglycoside antibiotics (i.e. gentamicin) or steroids (i.e. methylprednisolone or dexamethasone).[1,2,4] Tympanic aminoglycoside administration therapy was initially used by Schuknecht in 1957 for vertigo associated with intractable Ménière's disease, and has gradually been adopted in clinical practice since.[1,4–6] However, tympanic gentamicin administration is associated with hearing loss as a side effect in 10–30 per cent of patients, despite having greater efficacy than steroids for controlling vertigo.[1,4–7] Therefore, intratympanic aminoglycoside perfusion is typically reserved for patients without serviceable hearing.[1,3,5] In contrast, tympanic steroid administration is considered the first treatment option for intractable Ménière's disease.[4] In a two-year retrospective study, intratympanic methylprednisolone administration dramatically reduced the number of vertigo spells in more than 90 per cent of intractable Ménière's disease patients in whom hearing was preserved.[8] An inner-ear pharmacokinetics study has revealed higher drug concentrations in inner-ear tissue with intratympanic steroid use (methylprednisolone, dexamethasone or hydrocortisone) compared with systemic administration. Furthermore, methylprednisolone was reported to reach a higher concentration and to

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remain longer in the perilymph compared with either hydrocortisone or dexamethasone.[9]

The present study included 17 intractable Ménière's disease patients whose vertigo was not controlled after conventional medication and psychotherapy; this severely impacted their daily activity. These patients were treated with daily intratympanic methylprednisolone perfusion. The outcome in 16 patients that were followed up for at least two years is presented.

Materials and methods

Clinical inclusion criteria

The criteria for Ménière's disease diagnosis were published by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) in 1995.[10] This study recruited patients who had failed conventional medical treatments (sedatives (e.g. diazepam), dehydration agent, vasodilator, vestibular suppressants (difenidol hydrochloride), systemic glucocorticoid administration, immunosuppressants and vitamins) and psychotherapy for more than six months; they were therefore considered to have intractable Ménière's disease.[3] Symptoms included recurrent vertigo (more than one spell per month for six months immediately prior to enrollment), intermittent or continuous tinnitus, and aural fullness with fluctuating sensorineural hearing loss (SNHL). The age range was from 28 to 65 years. Patients were excluded if they also suffered from other organ-specific or systemic disease, dropped out voluntarily during the treatment course, or were lost to follow up. Patients who enrolled in the study were hospitalised and underwent intratympanic intubation and daily perfusion with 20 mg methylprednisolone (0.5 ml volume; Pfizer, New York, New York, USA), along with a daily intravenous injection of 105 mg Ginkgo biloba extract and 0.5 mg methylcobalamin, for 10 consecutive days. Eleven patients simultaneously received 125 ml per day of 20 per cent mannitol intravenously.

Procedure

The treatment protocol was approved by the Ethics Committee of Nanjing Drum Tower Hospital, Nanjing University Medical School. All patients were informed of the potential risks associated with intratympanic perfusion before providing consent. Details of the tympanostomy catheter insertion and drug perfusion were previously reported.[11]

Efficacy assessment and follow up

After discharge, patients were followed up once per month for the first six months, and then once every six months for at least two years. Follow-up assessments included monitoring the effects of treatment on vertigo, tinnitus, hearing loss and functional activity. Treatment efficacy for vertigo, hearing loss and functional activity was evaluated according the AAO-HNS criteria of 1995.[10] The short-term improvement rate was calculated from functional scores obtained six months before and six months after treatment. The long-term improvement rate was calculated from functional scores obtained two years after and six months before treatment. The vertigo severity scale comprised classes A–F, defined according to AAO-HNS criteria.[10] The vertigo control rate (as a percentage) was calculated by dividing the number of patients in classes A and B by the total number of patients and multiplying by 100.[1,12] Hearing improvement was defined as a greater than 10 dB reduction in the pure tone average (PTA; i.e. the mean of thresholds at 0.25, 0.5, 1, 2 and 4 kHz). The functional disability scale comprised levels 1–5, defined according to AAO-HNS criteria.[10] The rate of functional activity improvement (as a percentage) was calculated by dividing the number of patients achieving levels 1–3 by the total number of patients and multiplying by 100.

Statistical analyses

All statistical data were analysed using IBM SPSS Statistics software version 17.0 (Chicago, Illinois, USA) and expressed as means ± standard deviation. Ménière's disease symptom presentation before and after treatment were compared using the Student's *t*-test, Mann–Whitney U test or Fisher's exact test. The Mann–Whitney U test was used when data were non-normally distributed. Group data were expressed as frequencies. A p value of less than 0.05 was considered statistically significant.

Results

From January 2008 to November 2011, 17 patients clinically diagnosed with unilateral intractable Ménière's disease were treated with intratympanic methylprednisolone perfusion over a 10-day period. Of these, 16 were followed up for more than 2 years, while 1 patient was followed up for only 6 months. Of the total 17 patients, 11 were male and 6 were female. The left ear was affected in 11 patients (6 male and 5 female) and the right ear in 6 (5 male and 1 female). The average patient age was 51 ± 9 years. The mean vertigo course was 6 ± 4 years and the PTA was 53 ± 14 dB before intratympanic methylprednisolone perfusion treatment (Table I). According

TABLE I
INTRACTABLE MD PATIENT DEMOGRAPHICS*

Parameter	Pre-IMP (n)
Sex (M:F)	11:6
Ear side (L:R)	11:6
Average age† (yr)	51 ± 9
Vertigo course† (yr)	6 ± 4
Pure tone average† (dB)	53 ± 14

*n=17. †Data are presented as the means ± standard deviation. MD = Ménière's disease; IMP = intratympanic methylprednisolone perfusion; M = male; F = female; L = left; R = right; yr = years

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TABLE II
EFFECT OF IMP ON VERTIGO CONTROL

Post-IMP (mth)	Patients (*n*)	Class*					Control rate (%)	χ^2 value	*p* value
		A	B	C	D	F			
6	17	13	3	0	1	0	94	3.50	0.174
24	16	10	3	0	1	2	81		
36	10	5	2	1	0	2	70		

*There were no patients in class E. IMP = intratympanic methylprednisolone perfusion; mth = months

to the AAO-HNS criteria of 1995,[10] 12 patients were at stage 3 (PTA = 41–70 dB) and 5 were at stage 2 (PTA = 26–40 dB) before treatment. All patients had received conventional medication and psychotherapy for six months prior to treatment.

Vertigo control

Ten patients were followed up for more than three years, while six were followed up for two years. Vertigo was controlled in most patients (Table II). According to AAO-HNS criteria, vertigo control rates for the first six months (short-term) and two years (long-term) following treatment were 94 per cent and 81 per cent, respectively. Although the short-term control rate seems better than the long-term rate, the difference was not significant. Of the 10 patients who were followed up for 3 years, vertigo was completely controlled (class A) or sub-controlled (class B) in 7 (Table II).

One patient experienced mild vertigo two months after treatment. Two patients experienced severe vertigo and received an intratympanic gentamicin injection 12 or 18 months after receiving intratympanic methylprednisolone perfusion. However, in both patients, vertigo was recalcitrant to treatment. A hearing loss of 29 dB (PTA aggrevation from 34 dB to 63 dB) was detected in one of these patients after three gentamicin injections (20 mg per injection at 40 mg/ml, at 10 day intervals). This patient then received tympanic injections of 0.5 ml dexamethasone (5 mg/ml, once per week) and oral betahistine mesilate (6 mg, three times a day). Vertigo was controlled (improved from severe to mild) and a 30 dB hearing improvement (PTA improvement from 63 dB to 33 dB) was observed one month after two intratympanic dexamethasone injections. Another patient had sub-controlled vertigo (class B) and no significant change in hearing at the two-year follow up after intratympanic gentamicin injection. One patient received a second intratympanic methylprednisolone perfusion treatment two years after the initial treatment because of recurrent vertigo and hearing loss. In this patient, vertigo episodes had markedly decreased six months after the second treatment.

Functional activity improvement

Before intratympanic methylprednisolone perfusion, functional impairment was noted in four patients (functional level 5) and nine patients had reduced their working hours from full to part time because of vertigo (functional level 4; Table III). Shortly after this treatment, there was a significant improvement in daily functional activity in 13 patients, all of whom had no vertigo recurrence and had returned to full-time work. One patient presented with vertigo recurrence two months after intratympanic methylprednisolone perfusion. However, his vertigo gradually improved and he was able to perform his daily activities normally after three months. Three patients reduced their working hours from full to part time because of mild vertigo. Improvements in functional activity are summarised in Table III. According to AAO-HNS criteria, intratympanic methylprednisolone perfusion resulted in a short-term (6 months) functional activity improvement rate of 94 per cent and a long-term (24 months) functional activity improvement rate of 88 per cent. The short-term improvement rate was higher than the long-term improvement rate, and there was a significant difference between the rates calculated for the three sampling intervals ($\chi^2 = 28.00$, $p = 0.000$; Table III).

Hearing loss and tinnitus control

In this study, 12 patients presented with clinical stage 3 hearing loss and 5 presented with stage 2 hearing

TABLE III
POST-IMP FUNCTIONAL ACTIVITY OF INTRACTABLE MD PATIENTS

Post-IMP (mth)	Patients (*n*)	Level					Improvement rate (%)	χ^2 value	*p* value
		1	2	3	4	5			
0	17	0	1	3	9	4	–	28.00	0.000
6	17	13	2	1	1	0	94		
24	16	9	3	2	2	0	87		

IMP = intratympanic methylprednisolone perfusion; MD = Ménière's disease; mth = months

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TABLE IV
COMPARISON OF HEARING CHANGES OF INTRACTABLE MD PATIENTS AFTER IMP

Post-IMP (mth)	Patients (n)	Stage				χ^2 value	p value
		1	2	3	4		
0	17	0	5	12	0	2.00	0.368
6	17	1	5	10	1		
24	16	1	5	8	2		

MD = Ménière's disease; IMP = intratympanic methylprednisolone perfusion; mth = months

loss (according to AAO-HNS criteria) prior to intratympanic methylprednisolone perfusion treatment.[10] In two patients, improved PTA (by more than 10 dB) was observed six months after intratympanic methylprednisolone perfusion. However, only one patient still had an improved PTA two years after treatment. Hearing loss of greater than 10 dB was observed in one patient with no vertigo recurrence during four years of follow up. The PTA for these 12 patients was 53 ± 14 dB before treatment, 50 ± 16 dB 6 months after treatment and 52 ± 20 dB 2 years after treatment. Thus, a significant improvement in PTA ($t = -2.476$, $p = 0.025$) after six months had returned to the pre-treatment baseline after two years ($t = 0.000$, $p = 1.000$). However, there were no significant differences in clinical stage, based on hearing changes at the 6- and 24 month follow up ($p > 0.05$; Table IV). Tinnitus was controlled in three patients and improved in 2 patients at the 24 months follow up, and in no patient had tinnitus worsened over this interval.

Side effects and complications

A major side effect for all patients was a burning pain sensation in the ear and pharyngeal area after each perfusion. However, the pain was tolerable and alleviated within 0.5–1 hours. Tympanic membrane perforations healed in most patients within two to four weeks of catheter removal; however, in one patient, it did not heal within four years. In one patient, catheter extrusion occurred on the eighth day of the perfusion procedure; thus, the treatment period was reduced by two days. In another patient, progressive SNHL in the low frequency range was observed in the affected ear, accompanied by mild dizziness, one year after intratympanic methylprednisolone perfusion. Middle-ear infection was not observed in this patient group.

Discussion

Over the last 20 years, tympanic glucocorticoid administration has become a widely accepted clinical treatment for Ménière's disease. Tympanic glucocorticoid perfusion therapy was first used by Itoh and Sakata, with demonstrated efficacy associated with a low risk of hearing loss.[12] Glucocorticoids infiltrate into the inner ear through the round window membrane and improve Ménière's disease symptoms by forming glucocorticoid–hormone receptor complexes in the vestibular maculae and cochleae. These interactions induce immunosuppressive and anti-inflammatory responses, enhance blood flow, and prevent ischaemia. They may also alter the ion (e.g. sodium and potassium) flux to maintain electrolyte balance and provide endolymphatic stabilization? in the inner ear.[8,13,14]

In the present study, intractable Ménière's disease was treated with intratympanic methylprednisolone perfusion. The resulting long-term vertigo control and functional activity improvement rates were greater than 80 per cent, which is similar to the vertigo control rate obtained by dexamethasone perfusion or injection.[2,8,15,16] However, the vertigo control rate achieved with intratympanic methylprednisolone perfusion in the present patient group is significantly higher than that previously reported following tympanic steroid injection (62.5 mg/ml methylprednisolone, once per week for three weeks).[1,5,6] This result suggests that daily perfusion improves treatment efficacy. An inner-ear pharmacokinetics study revealed that the maximal methylprednisolone concentration in the perilymph occurs 2 hours after intratympanic injection and that a high concentration is maintained for 6 hours, before a gradual decline to baseline levels within 24 hours.[9] Therefore, daily administration is needed to maintain a high drug concentration in the inner ear. Furthermore, intratympanic catheter-mediated steroid perfusion avoids repeated penetration of the tympanic membrane.[11]

Despite positive effects on vertigo control, similar treatment strategies employing intratympanic gentamicin perfusion have resulted in significant hearing loss.[1,5,6] The intratympanic methylprednisolone perfusion treatment strategy described herein effectively controlled vertigo associated with Ménière's disease in the context of hearing preservation. In fact, a significant improvement in short-term PTA was observed following this treatment. However, no significant hearing improvement was observed during long-term follow up. This result may be attributed to the low pre-treatment hearing levels documented in this patient group, suggesting intractable pre-existing damage to the auditory system; over 70 per cent (12 out 17) of the patients were assigned to hearing stage 3 prior to treatment. Progressive low frequency hearing loss was observed in only one patient. Progressive low frequency SNHL is one of the characteristics of Ménière's disease.[17] It may therefore may be attributable to the natural course of Ménière's disease progression (i.e. resulting from spiral ganglion neurodegeneration in the cochlea) rather than to the adverse effects of intratympanic methylprednisolone perfusion.[8,18] The results of this and previous studies suggest that tympanic steroid perfusion treatment may be preferable for treating intractable Ménière's disease while minimising SNHL.[19]

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Tinnitus improvement was also observed following intratympanic methylprednisolone perfusion: in five patients, tinnitus was either controlled or significantly improved. A similar improvement was previously reported in 48 per cent of patients following tympanic dexamethasone perfusion treatment.[15] However, a much higher tinnitus control rate (more than 70 per cent, with 81 per cent of patients free of vertigo spells) has been documented in Ménière's disease patients after three consecutive methylprednisolone injections.[8] Six out of seven patients diagnosed with 'cochlear endolymphatic hydrops' (i.e. Ménière's disease without vestibular involvement) had better tinnitus control. However, the present study did not include any cochlear endolymphatic hydrops patients. These results suggest that the pathological status of the inner ear may be an important factor influencing treatment efficacy.

- **The long-term efficacy of intratympanic methylprednisolone perfusion on intractable Ménière's disease was investigated**
- **Most patients maintained vertigo control over a two-year follow up**
- **The treatment controlled intractable Ménière's disease, with good hearing preservation**

Immunological abnormalities may also be associated with the Ménière's disease pathology. Elevated immunoglobulin G (IgG) and circulating immune complex levels, autoimmune responses to type II collagen, focal inflammation with intraepithelial mononuclear cell invasion (endolymphatic sacitis), and IgG and autoantibody deposits in the endolymphatic sac have been observed in Ménière's disease patients.[1,8] Therefore, the beneficial effects of intratympanic steroids could be due to their anti-inflammatory and immunosuppressive effects. Steroids can also improve ionic homeostasis regulation by modulating potassium transport, which may reduce Ménière's disease progression by reducing damage to the intra-cochlear barrier.[16]

Conclusion

Intratympanic methylprednisolone perfusion appears to be an effective treatment strategy for intractable Ménière's disease that ameliorates the symptoms of vertigo, tinnitus and reduced functional activity. Short-term hearing improvement and long-term hearing preservation were also observed. Future studies, for example a double-blinded, randomised clinical trial to compare the efficacy of intratympanic perfusion of steroid versus gentamycin (especially in stage 3 intractable Ménière's disease patients), should provide greater clarity about how Ménière's disease staging and inner-ear pathological status affect intratympanic methylprednisolone perfusion treatment efficacy.

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References

1 Gabra N, Saliba I. The effect of intratympanic methylprednisolone and gentamicin injection on Ménière's disease. *Otolaryngol Head Neck Surg* 2013;**148**:642–7
2 Boleas-Aguirre MS, Lin FR, Della Santina CC, Minor LB, Carey JP. Longitudinal results with intratympanic dexamethasone in the treatment of Ménière's disease. *Otol Neurotol* 2008;**29**:33–8
3 Kitahara T, Fukushima M, Uno A, Imai T, Ohta Y, Morihana T *et al*. Long-term results of endolymphatic sac drainage with local steroids for intractable Meniere's disease. *Auris Nasus Larynx* 2013;**40**:425–30
4 Sajjadi H, Paparella MM. Meniere's disease. *Lancet* 2008;**372**:406–14
5 Pullens B, van Benthem PP. Intratympanic gentamicin for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2011;(**16**):CD008234
6 Casani AP, Piaggi P, Cerchiai N, Seccia V, Franceschini SS, Dallan I. Intratympanic treatment of intractable unilateral Meniere disease: gentamicin or dexamethasone? A randomized controlled trial. *Otolaryngol Head Neck Surg* 2012;**146**:430–7
7 Sajjadi H. Medical management of Ménière's disease. *Otolaryngol Clin North Am* 2002;**35**:581–9
8 Herraiz C, Plaza G, Aparicio JM, Gallego I, Marcos S, Ruiz C. Transtympanic steroids for Ménière's disease. *Otol Neurotol* 2010;**31**:162–7
9 Parnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. *Laryngoscope* 1999;**109**:1–17
10 Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium guidelines on for the diagnosis and evaluation of therapy for Meniere's disease. *Otolaryngol Head Neck Surg* 1995;**113**:181–5
11 She W, Dai Y, Du X, Yu C, Chen F, Wang J *et al*. Hearing evaluation of intratympanic methylprednisolone perfusion for refractory sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2010;**142**:266–71
12 Itoh A, Sakata E. Treatment of vestibular disorders. *Acta Otolaryngol Suppl* 1991;**481**:617–23
13 Rupprecht R, Reul JM,Van Steensel B, Spengler D, Söder M, Berning B *et al*. Pharmacological and functional characterization of human mineralocorticoid and glucocorticoid receptor ligands. *Eur J Pharmacol* 1993;**247**:145–54
14 Smith PJ, Cousins DJ, Jee YK, Staynov DZ, Lee TH, Lavender P. Suppression of granulocyte macrophage colony stimulating factor expression by glucocorticoids involves inhibition of enhancer function by the glucocorticoid receptor binding to composite NF-AT/activator protein-1 elements. *J Immunol* 2001;**167**:2502–10
15 Garduño-Anaya MA, Couthino De Toledo H, Hinojosa-González R, Pane-Pianese C, Ríos-Castañeda LC. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Ménière's disease, a two-year prospective, placebo-controlled, double-blind, randomized trial. *Otolaryngol Head Neck Surg* 2005;**133**:285–94
16 Phillips JS, Westerberg B. Intratympanic steroids for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2011;(**6**):CD008514
17 Belinchon A, Perez-Garrigues H, Tenias JM, Lopez A. Hearing assessment in Menière's disease. *Laryngoscope* 2011;**121**:622–6
18 Semaan MT, Zheng QY, Han F, Zheng Y, Yu H, Heaphy JC *et al*. Characterization of neuronal cell death in the spiral ganglia of a mouse model of endolymphatic hydrops. *Otol Neurotol* 2013;**34**:559–69
19 Peterson WM, Isaacson JE. Current management of Ménière's disease in an only hearing ear. *Otol Neurotol* 2007;**28**:696–9

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