Indian J Otolaryngol Head Neck Surg
(August 2022) 74(Suppl 1):S320–S325; https://doi.org/10.1007/s12070-020-02104-4

ORIGINAL ARTICLE

Low Dose Intratympanic Gentamicin in Ménière's Disease

Bini Faizal[1] · **Afsha Rajan**[1]

Received: 14 August 2020 / Accepted: 25 August 2020 / Published online: 1 September 2020

Abstract Intratympanic gentamicin has become an accepted standard of care for Ménière's disease. But there still exists controversies regarding the dosing protocol as well as the drug concentration for optimum control of vertigo and hearing preservation. To determine if 20 mg of intratympanic gentamicin administered once a month for a maximum of 2 months can alleviate intractable vertigo caused by definite Ménière's disease with hearing preservation. Once diagnosed with definite Ménière's disease as per AAO–HNS criteria, the patient was given 0.5 ml of 40 mg/ml intratympanic gentamicin. Follow-up was done at 1-month and 6-month post-treatment. If at 1-month review patient continued to have vertigo one more dose of intratympanic gentamicin was administered. Thirty-two patients were included in the study. Seventeen patients (53.1%) received one dose and 15 patients (46.9%) received two doses of intratympanic injection. We achieved an effective vertigo control of 59.4% and complete vertigo control rate of 53.1%. Worsening of symptoms was noted in 1 patient. Hearing was preserved in all patients except for one. Among the patients who attained effective vertigo control, 72.2% had dead labyrinth at 6-month cold caloric status. A single injection of 20 mg intratympanic gentamicin can alleviate intractable vertigo caused by definite Ménière's disease with hearing preservation. Non-responders may be given a second dose after one month. Intratympanic gentamicin is a simple, cheap treatment that can be carried out in an out-patient setting.

Keywords Injection · Intratympanic · Ménière's disease · Ménière's vertigo · Gentamicin

Introduction

In 1956, Schuknecht first introduced the use of intratympanic aminoglycosides (streptomycin) for Ménière's disease. The treatment was soon abandoned because of the resulting profound sensorineural hearing loss. It was almost two decades later in 1978 that Lange revived the therapy again and he suggested the use of gentamicin instead of streptomycin. Beck and Schmidt later brought about the modifications in the drug dosing and popularized the therapy [1].

In the present scenario, intratympanic gentamicin has become an accepted standard of care for Ménière's disease. But there still exists controversies regarding the dosing protocol as well as the drug concentration for optimum control of vertigo and hearing preservation. Transtympanic drug delivery can be categorized into different techniques like multiple daily dosing; weekly injections; low dose technique; continous microcatheter delivery or titration technique [1].

Low dose intratympanic gentamicin implies both lower drug concentration as well as the cumulative dose of gentamicin administered. It is evident that lower the dosage administered better the chance of hearing preservation. Low dose intratympanic gentamicin claims to control vertigo with single or maximum two doses. This protocol is more convenient and cheaper for the patient as well. Also, low dose intratympanic gentamicin finds applicability in

✉ Bini Faizal
binifaizal@aims.amrita.edu

Afsha Rajan
afsharajan@gmail.com

[1] Department of ENT, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeedham, Kochi, India

patients with mild sensorineural hearing loss and bilateral Ménière's disease as it promises superior hearing preservation as compared to the conventional dosing protocols.

Episodic vertigo in Ménière's disease is the most handicapping symptom in both active and elderly population. It hinders the quality of life of the patient. If the study shows any improvement in the symptom of vertigo with a potential hearing preservation it can be made use of in the treatment of Ménière's disease. Also, we aim to find the lowest possible dose for achievement of the same.

Materials and Methods

Selection and Description of Participants

A prospective observational study was conducted on thirty-two patients fulfilling both inclusion and exclusion criteria.

Objectives of the Study

To determine if 20 mg of injection Gentamicin administered via intratympanic route once a month for a maximum of 2 months can alleviate intractable vertigo caused by definite Ménière's disease. Another objective was to assess the safety of this regime in hearing preservation.

Inclusion criteria: All patients between 18 and 80 years who were diagnosed as definite Ménière's disease (as defined by the Committee on hearing and equilibrium of the American Academy of Otolaryngology and Head and Neck Surgery Foundation (AAO–HNS)) with history of intractable vertigo of more than 12 months duration or breakthrough while on medical treatment (betahistine dihydrochloride/labyrinthine sedatives/diuretics) [2]. Patient should have no history of Ménière's disease in the contralateral ear and serviceable hearing should be present in the contralateral ear.

Exclusion criteria Patients with neuro-otological pathology in the contralateral ear, ipsilateral middle ear pathology or allergy to aminoglycosides were excluded.

Upon establishing the diagnosis of definite Ménière's disease pre-treatment assessment was done using six-point functional level scale score, cold caloric test, pure tone audiometry and speech discriminations score. Levels of disability were recorded using a six point functional level scale which helps in assessing the effects of episodic vertigo on daily activities [2]. Pure tone average of 500 Hz, 1 kHz, 2 kHz and 3 kHz were taken prior to and after intervention. A change of more than 10 dB in audiogram or $> 15\%$ in speech score was considered significant. Cold caloric test was done by Modified Kobrak's method. With the head tilted back at 60°, ice cold water irrigation is done (5 ml, 10 ml, 20 ml or 40 ml sequentially) and examined for nystagmus. While response to 5 ml was taken as normal, no response to 40 ml was taken as dead labyrinth. Response to irrigation for 5 ml to 40 ml of ice cold water was taken as hypoactive [3]. Gentamicin (0.5 ml of 40 mg/ml) was administered via intratympanic route through the inferior quadrant of tympanic membrane. Follow-up was done at 1 month and 6 months post injection. Six-point functional level scale score, cold caloric test, pure tone audiometry and speech discriminations score were repeated at each follow-up visit. If at the 1-month follow up patient continues to have vertigo one more dose of intratympanic gentamicin was administered. Vertigo control score was computed based on 6-month post injection vertigo spells per month. Vertigo control class was determined. Hearing status was assessed based on the pure tone audiometry and speech discrimination score results. Vertigo control class and hearing deterioration was documented as per AAO–HNS 1995 reporting guidelines [2].

Statistics

Based on the efficacy rate reported with low dose intratympanic gentamicin in an earlier publication and with 20% allowable error and 99% confidence minimum sample size came to 32 [4]. All statistical analysis was done using IBM SPSS Statistics 20 software. All the continuous parameters were expressed as Mean $\pm$ SD and all categorical variables were explained as either frequency or percentage. Pearson Chi square test and Fischer exact test were used for finding association between 6-month cold caloric test result with vertigo control and number of doses with vertigo control. Continuity correction test was used for finding association between change in caloric status and vertigo control. Wilcoxon signed rank test was used for comparing the average 6-point functional scale status at pre-treatment, 1-month review and 6-month review. Results were considered statistically significant if P value was < 0.05.

Results

In the present study the mean age group was 45.56 ± 13.04 years. Of the 32 patients studied, 15 patients i.e. 46.9% were females and 17 patients i.e. 53.1% were males. Nineteen patients (59.4%) had left sided Ménière's disease and thirteen patients (40.6%) had right sided Ménière's disease. One dose of intratympanic gentamicin was administered for 53.1% patients (n = 17) and 46.9% (n = 15) patients received two doses of intratympanic gentamicin (Table 1).

Seventeen patients (53.1%) achieved complete control of vertigo, 2 patients (6.3%) achieved significant control of

Table 1 Baseline characteristics of the study population

Characteristics	Study population (n = 32)	
	Mean	SD
Age (years)	45.56	13.04
Gender	Female (n, %)	Male (n, %)
	15 (46.9)	17 (53.1)
Side of disease	Left (n, %)	Right (n, %)
	19 (59.4)	13 (40.6)
Number of doses administered	Single dose (n, %)	Two doses (n, %)
	17 (53.1)	12 (46.9)

Vertigo class (n = 32)	Number	Percentage
A	17	53.1
B	2	6.3
C	6	18.8
D	6	18.8
E	1	3.1

Patient profile showing the vertigo class at the end of study period

vertigo, 6 patients (18.8%) achieved limited and insignificant control each and 1 patient (3.1%) had worsening of symptoms (Table 1). Hearing status was unchanged in all patients except one according to the pure tone audiometry. Hearing status remained unchanged in 96.8% of patients and worsening was observed in 3.2% patients with pure tone audiometry and speech discrimination score (Table 2).

For comparing the 6-month cold caloric test response and vertigo control class, active and hypoactive response on 6-month cold caloric test have been combined since the number of patients in each group was comparatively less. In patients who had achieved complete or significant control of vertigo 72.2% patients had a dead labyrinth on cold caloric test at 6-month follow up, and it was found to be hypoactive and active in 22.2% and 5.6% patients respectively. In patients who did not achieve adequate control of vertigo (Vertigo class C, D and E), 41.7% patients had an active labyrinth on cold caloric test at 6-month follow up and 33.3% patients had a hypoactive labyrinth. Dead labyrinth was seen in 25% of the patients. This is found to be statistically significant using Chi square test ($P = 0.024$) (Table 3).

Table 2 Hearing status 6 months post injection—pure tone audiometry and speech discrimination score

Pure tone audiometry	Number	Percentage
Unchanged	30	96.8
Worsened	1	3.2
Total	31	100

Status of hearing at 6 months showing unchanged hearing status in 30 patients

Of the 17 patients who achieved adequate control of vertigo, 14 patients (73.7%) required only 1 dose of intratympanic gentamicin and 3 patients (23.1%) required 2 doses of intratympanic gentamicin. Fifteen patients in whom vertigo control was insignificant, one dose of intratympanic gentamicin was administered in 5 patients (26.3%) and 2 doses were administered in 10 patients (76.9%). Patients who received single dose of intratympanic gentamicin were found to have better vertigo control than patients who received two doses. This found to be statistically significant using Chi square test ($P = 0.014$) (Table 4).

Median of six-point functional score at pre-treatment, 1-month and 6-month follow up are 2, 1.5 and 1 respectively. When comparing the pre-treatment with 1-month review, pre-treatment with 6-month review and 1-month with 6-month review six-point functional level scale score was found to be reduced. This was found to be statistically significant (Wilcoxon signed rank test) with P value of < 0.001, < 0.001 and 0.025 respectively (Table 5).

On comparing achievement of effective vertigo control with the change in cold caloric status at 6 months follow-up as compared to pre-treatment status, 71.4% of the patient who had change in caloric status had achieved effective vertigo control and 28.6% patients did not. Of the patients who did not have change in caloric status 56.2% achieved effective vertigo control and 43.8% did not have significant control of vertigo. However, the results were not statistically significant. The results were calculated using continuity correction test ($P = 0.631$) (Table 6).

Discussion

Medical management of Ménière's disease is often ineffective in reducing or eliminating symptoms permanently. For many patients with incapacitating symptoms, intratympanic instillation of gentamicin has proved considerably more successful. The application of a low dosage of gentamicin is a new frontier in treatment for Ménière's disease and is favoured more than the surgical options. This low dosage is known to cause minor damage to the cochlea, and post-treatment follow-up have confirmed the long-term success of the therapy approach.

In our study we aimed to study the treatment outcome of low dose intratympanic gentamicin in intractable Ménière's disease and to assess the safety of this regime in hearing preservation. As calculation of the vertigo control score using vertigo spells/month 2 years post-treatment was not feasible considering the study period of our study, the post-treatment vertigo spells/month

Table 3 Relationship of vertigo control with 6-month follow-up cold caloric status

6-month cold caloric test status	Vertigo control class A/B		Vertigo control class C/D/E	
	Number	%	Number	%
Active	1	5.6	5	41.7
Hypoactive	4	22.2	4	33.3
Dead	13	72.2	3	25
Total	18	100	12	100
P value	0.024			

Table showing active labyrinth in one patient with vertigo control class A/B and in 5 patients in the class C/D/E

Table 4 Relationship of vertigo control class with number of doses administered

Number of doses	Vertigo control class A/B		Vertigo control class C/D/E	
	Number	%	Number	%
1 dose	14	73.7	5	26.3
2 doses	3	23.1	10	76.9
P value	0.014			

Fourteen patients had good control of vertigo with a single dose

were taken as the number of spells/month in the immediate 6 months post injection. The same calculation was adopted in another study done by Kasemsuwan et al. citing the same reasons [5]. Tinnitus was not evaluated at the follow-up visits and hence effect of gentamicin on tinnitus was not assessed.

In the current study, 17 patients (53.1%) received single dose of intratympanic gentamicin and 15 patients (46.9%) received 2 doses of intratympanic gentamicin. We achieved an effective vertigo control rate of 59.4% and complete control of vertigo was achieved in 53.1% of the patients. Hearing was preserved in 31 patients (96.8%) and worsening of hearing was seen in only 1 patient (3.2%). In a meta-analysis conducted by Chia et al. comparing the various dosing regimens, complete vertigo control rate of 66.7% was recorded with low dose regime which is comparable with our study. Worsening of hearing was seen in 23.7% patients [6]. Casani et al. also conducted a study comparing the high dose and low dose regime. In their study, 35 patients were included in the high dose regime where in total 6 injections were administered (twice a day for 3 days) and the 42 patients in low dose group received 1–2 injections. 40 mg/ml gentamicin was used. They reported vertigo control rates of 71.4% and 55% for the high dose and low dose groups respectively. Hearing status deterioration was mentioned in 37% patients in the high dose category and 12% in the low dose category [7]. The vertigo control rate was comparable with our study but we achieved better hearing preservation.

But there are other studies which report higher vertigo control with low dose regimen. Study done by Gode et al. using single shot of gentamicin (16 mg/ml) reported

Table 5 Comparison of pre-treatment vs 1-month and 6-month follow-up six-point functional level scale score

6-point functional level scale (n = 32)	Median	Minimum	Maximum
Pre-treatment	2	1	4
1 month	1.5	1	3
6 months	1	1	3

6 point functional scale score	Pretreatment-1 month review	Pretreatment- 6 month review	1 month review- 6 month review
P value	< 0. 001	< 0.001	< 0.025

The comparison of vertigo between pre treatment status and post treatment status at 1 month and 6 months show statistically significant improvement

Table 6 Comparison of change in cold caloric test response with vertigo control achieved

Cold caloric status change	Vertigo control class A/B		Vertigo control class C/D/E	
	Number	%	Number	%
Present	10	71.4	4	28.6
Absent	9	56.2	7	43.8
P value	0.631			

Good vertigo control class was seen post treatment in 19 patients; with 10 patients having active labyrinth

complete vertigo control in 80% patients and hearing preservation in 100% of the patients [8]. Driscoll et al. also administered single dose of gentamicin (40 mg/ml) and attained a complete control of vertigo in 84% of the patients and significant hearing loss was not seen in any of the patients. They do mention hearing deterioration in high frequency in all but one patient (average − 7.5 dB [4]. Quaranta et al. administered 2 doses of 0.5 ml 20 mg/ml gentamicin and attained a vertigo control rate of 93% and hearing deterioration was mentioned in only 7% of the patients. On further administering two more doses they were able to control vertigo in all patients [9].

Long term follow-up of patients revealed that failure of treatment usually occurs in the first few months of treatment and once controlled rarely recur [8]. Postema et al. also mentions that there was not much difference in the immediate post-therapy period between the gentamicin and placebo group indicating that better vertigo control was achieved in long-term follow up [10]. The probable reason for lower rate of vertigo control in our study, might be because of the methodology adopted to calculate numeric value of the vertigo control class (post-treatment vertigo spells/month in immediate 6 months post-injection was taken for calculation).

Of the patients who achieved effective control of vertigo, 72.2% patients were found to have dead labyrinth on 6-month follow up cold caloric test indicating that complete vestibular ablation was needed for better vertigo control. This was found to be statistically significant ($P = 0.024$). These findings were similar to the study by Gode et al. where both VEMP and caloric test were significantly correlated with an improvement in general dizziness status [7]. Chia et al. also found that there was a higher rate of complete vertigo control with complete vestibular ablation than with partial ablation [6]. There are several studies indicating that total lateral canal caloric areflexia is not necessary in order to make the vertiginous attacks disappear [1, 11]. In our study also 1 patient with active labyrinth and 4 patients with hypoactive labyrinth on 6-month post-treatment cold caloric test had achieved effective control of vertigo. Study done by Chung et al. mentions similar canal paresis rates in both multiple and single gentamicin injection groups, 88% and 85% respectively inferring that canal areflexia can be attained with single dose regimen [12].

In our study on comparing the vertigo control rate and change in caloric test status post-treatment as compared with pre-treatment 71.4% who had change in status had achieved effective vertigo control but 56.2% who did not have change in status also achieved effective vertigo control. But the results obtained were not statistically significant ($P > 0.05$). In a prospective study done by Horri et al. (once daily injections for 3 days) they had concluded that induction of vestibular damage in injected ear is essential for control of vertigo [13].

Our study also reports better vertigo control with single dose intratympanic gentamicin than two doses ($P = 0.014$). Though this is in contraindication with the generally accepted theory that more the dosage, better the vertigo control, it is possible that the patients receiving two doses never responded to treatment at all. Probable assorted reasons for the same have been cited in literature e.g. inflammation of middle ear mucosa leading to altered permeability of round window membrane, presence of a second membrane over the round window hindering permeability [1]. However, Yoon et al. suggested tympanotomy and direct application of injection Gentamicin over round window when intratympanic instillation failed. Labyrinthectomy and vestibular neurectomy may be tried in failed cases [14]. Another advantage described by Wu Li is a reduction in the number of drop attacks along with control of vertigo (Class A) in 84.6% of their patients with a single dose [15]. The treatment may be extended to bilateral cases also without much risk to hearing [16].

When comparing the median of pre-treatment and 1-month and 6-month follow-up six-point functional level scale, statistically significant reduction was noted indicating satisfactory control of vertigo resulting in significant improvement in the patient's disability status. Similar results were seen in studies done by Gode et al. and Driscoll et al. [4, 8]. This goes on to validate that intratympanic gentamicin provided significant relief of disability resulting from vertigo spells.

Study Limitations

A 2-year follow up was beyond the scope of the study hence vertigo control score was not calculated according to the AAO–HNS guidelines which might have resulted in lower vertigo control rates. Recurrence of vertigo after attaining complete control was not assessed. Delayed effects of gentamicin on hearing status could not be assessed as long term follow up was not possible. Effect on intratympanic gentamicin on tinnitus was not assessed.

Conclusion

A single injection of 20 mg intratympanic gentamicin can alleviate intractable vertigo caused by definite Ménière's disease. Hearing preservation was possible with this regime proving its safety. Non-responders may be given a second dose after one month. Treatment protocols with less frequent administration of gentamicin appear to have a lower risk of hearing loss than those involving more frequent administration of the drug. Partial ablation of vestibular apparatus with gentamicin is a more appealing option than its surgical counterparts. Its application can be extended to patients with mild sensorineural hearing loss and bilateral Ménière's disease. Intratympanic gentamicin is a simple, cheap treatment that can be carried out in an out-patient setting.

Acknowledgements Professor Sundaram, Head of Biostatistics, Amrita Institute of Medical Sciences, Kochi for statistical analysis. Professor Dr Prem, Department of Audiology, Amrita Institute of Medical Sciences, Kochi.

Author Contributions Bini Faizal: Responsible for the conception of the work, drafting and revision for intellectual content. Afsha Rajan: Drafting of the work, analysis and interpretation of data.

Funding All authors have not received any funding for this work.

Compliance with Ethical Standards

Conflict of interest No conflict of interest declared.

Ethical Approval The study protocol was reviewed and approved by the Institutional Ethics Committee of our institute, and they were in accordance with the ethical standards laid down in the Declaration of Helsinki.

Informed Consent All interventions and investigations were done with informed consent of the patient.

References

1. Carey J (2004) Intratympanic gentamicin for the treatment of Ménière's disease and other forms of peripheral vertigo. Otolaryngol Clin N Am 37(5):1075–1090 **(PMID: 15474112)**
2. HEARING CO, Balkany TA, Gates GA, Goldenberg RA, Meyerhoff WL, House JW et al (1995) Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. Otolaryngol Head Neck Surg 113(3):181–185 **(PMID: 7675476)**
3. Paparella MM, Shumrick DA (1980) TExtbool of otolaryngology, vol 3. WB Saunders Company, Philadelphia
4. Driscoll CL, Kasperbauer JL, Facer GW, Harner SG, Beatty CW (1997) Low-dose intratympanic gentamicin and the treatment of Ménière's disease: preliminary results. Laryngosc 107(1):83–89 **(PMID: 9001270)**
5. Kasemsuwan L, Jariengprasert C, Chaturapatranont S (2006) Transtympanic gentamicin treatment in Ménière's disease: a preliminary report. J Med Assoc Thail 89(7):979 **(PMID: 16881430)**
6. Chia SH, Gamst AC, Anderson JP, Harris JP (2004) Intratympanic gentamicin therapy for Ménière's disease: a meta-analysis. Otol Neurotol 25(4):544–552 **(PMID: 15241234)**
7. Casani AP, Cerchiai N, Navari E, Dallan I, Piaggi P, Sellari-Franceschini S (2014) Intratympanic gentamicin for Ménière's disease: short- and long-term follow-up of two regimens of treatment. Otolaryngol Head Neck Surg 150(5):847–852 **(PMID: 24477826)**
8. Gode S, Celebisoy N, Akyuz A, Gulec F, Karapolat H, Bilgen C, Kirazli T (2011) Single-shot, low-dose intratympanic gentamicin in Ménière disease: role of vestibular-evoked myogenic potentials and caloric test in the prediction of outcome. Am J Otolaryngol 32(5):412–416 **(PMID: 20851502)**
9. Quaranta A, Scaringi A, Aloidi A, Quaranta N, Salonna I (2001) Intratympanic therapy for Ménière's disease: effect of administration of low concentration of gentamicin. Acta Otolaryngol (Stockh) 121(3):387–392 **(PMID: 11425206)**
10. Postema RJ, Kingma CM, Wit HP, Albers FWJ, Van Der Laan BFAM (2008) Intratympanic gentamicin therapy for control of vertigo in unilateral Menière's disease: a prospective, double-blind, randomized, placebo-controlled trial. Acta Otolaryngol (Stockh) 128(8):876–880 **(PMID: 18607963)**
11. Stokroos R, Kingma H (2004) Selective vestibular ablation by intratympanic gentamicin in patients with unilateral active Ménière's disease: a prospective, double-blind, placebo-controlled, randomized clinical trial. Acta Otolaryngol (Stockh) 124(2):172–175 **(PMID: 15072419)**
12. Chung W-H, Whan Chung K, Ho Kim J, Cho Y-S, Hwa HS (2007) Effects of a single intratympanic gentamicin injection on Ménière's disease. Acta Otolaryngol (Stockh) 127(sup558): 61–66 **(PMID: 17882572)**
13. Horii A, Saika T, Uno A, Nishiike S, Mitani K, Nishimura M et al (2006) Factors relating to the vertigo control and hearing changes following intratympanic gentamicin for intractable Ménière's disease. Otol Neurotol 27(6):896–900 **(PMID: 16788414)**
14. Rah YC, Han JJ, Park J, Choi BY, Koo JW (2015) Management of intractable Ménière's disease after intratympanic injection of gentamicin. Laryngosc 125(4):972–978. https://doi.org/10.1002/lary.25009
15. Wu Q, Li X, Sha Y, Dai C (2019) Clinical features and management of Meniere's disease patients with drop attacks. Eur Arch Otorhinolaryngol. https://doi.org/10.1007/s00405-018-5260-5
16. Gayathri H, Rao SS (2016) Low dose intratympanic gentamicin for control of intractable vertigo. Indian J Otol 22:110–118. https://doi.org/10.4103/0971-7749.182284