Intratympanic Gentamicin as a Treatment for Drop Attacks in Patients With Meniere's Disease

Article *in* The Laryngoscope · September 2014

DOI: 10.1002/lary.24716

3 authors:

Lucas Moura Viana
University of Brasília
10 PUBLICATIONS **32** CITATIONS
SEE PROFILE

Fayez Bahmad
University of Brasília
54 PUBLICATIONS **216** CITATIONS
SEE PROFILE

Steven D Rauch
Harvard Medical School
110 PUBLICATIONS **2,643** CITATIONS
SEE PROFILE

The Laryngoscope

Intratympanic Gentamicin as a Treatment for Drop Attacks in Patients With Meniere's Disease

Lucas M. Viana, MD; Fayez Bahmad Jr., MD, PhD; Steven D. Rauch, MD

Objectives/Hypothesis: Vertigo attacks in most cases of Meniere's disease (MD) are successfully treated with lifestyle changes and medication. However, approximately 6% of patients with MD develop drop attacks (DAs), a potentially life-threatening condition. Traditional treatment for DAs has been surgical labyrinthectomy. The objective of this study was to assess the effectiveness of intratympanic gentamicin for DAs in patients with MD.

Study Design: Retrospective charts review.

Methods: All charts were reviewed from Meniere DA patients at our hospital during the 10-year period from 2002 to 2012 who had been treated with intratympanic gentamicin and had been followed for at least 1 year afterward.

Results: Twenty-four ears fulfilled inclusion criteria. The time for manifestation of DAs varied from 1 to 20 years after diagnosis (mean 10 years). A total of 83.3% of ears with intractable MD and DA achieved complete symptom control of DAs after the first intratympanic gentamicin cycle and 95.8% after the further injections. Among patients with no DA recurrence by the end of the study follow-up, the symptom-free interval varied from 12 to 120 months (mean: 43.5 months). All 15 patients with ≥ 24 months follow-up were still free of DAs. Elevated or absent vestibular evoked myogenic potential thresholds were more common in DA than in contralateral ears, and hearing loss was not a major complication of the treatment.

Conclusion: Intratympanic gentamicin treatment appears to be a long-lasting and effective treatment for MD with DAs.

Key Words: Meniere's disease, drop attack, intratympanic gentamicin.

Level of Evidence: 4.

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

Meniere's disease (MD) is an inner ear disorder characterized by episodic vertigo, fluctuating hearing loss, tinnitus, and aural fullness.[1] A small percentage of patients with MD—as many as 6%—develops drop attacks (DAs).[2,3] They were first described by Tumarkin in 1936 in patients with MD who have sudden falls that occur without warning, loss of consciousness, or any other concomitant neurologic symptoms or sequelae.[4]

Treatment of MD is most effective for the control of vertigo symptoms. The vast majority of cases are treated with lifestyle changes and medication. Despite these measures, invasive treatment is indicated if the patients still present incapacitating vertigo. These treatments include intratympanic steroids or gentamicin injections, endolymphatic sac surgery, transmastoid labyrinthectomy, or vestibular neurectomy to achieve control of vestibular symptoms.[5] Because DAs are potentially life-threatening—and because sac surgery and intratympanic steroids have only modest success rates—DAs have traditionally been treated with labyrinthectomy or vestibular neurectomy.

Schuknecht first described intratympatic therapy with aminoglycosides in 1957.[6] Subsequently, the use of intratympanic gentamicin (ITG) has become popular for the treatment of incapacitating vertigo and DAs. This therapy is based on the relatively selective vestibulotoxicity of the medication to control vertigo symptoms with relatively less risk of damage to hearing.

It has long been theorized that DA are due to pathology in the otolith organs. Calzada et al. showed in post-surgical human specimens that the otolithic membrane is damaged in patients with DAs.[7] They also demonstrated that there is a higher incidence of otolithic membrane changes in patients with MD and delayed endolymphatic hydrops compared with patients without hydrops, suggesting that the underlying pathophysiology in DAs results from injury to the otolithic membrane of the saccule and utricle, resulting in free-floating otoliths and atrophy. Both animal and human studies support the notion that gentamicin could be an effective treatment for DA by ablation of otolith organ hair cells. Topical application of gentamicin in guinea pigs has shown dose-dependent damage to the neuroepithelium of ampular crista and the macula of otolithic.[8,9] Keene et al. studied histopathological findings in a case of gentamicin sulfate-induced hearing loss and vertigo in an anephric patient undergoing hemodialysis.[10] In addition to cochlear findings, their study of the sensory neuroepithelium of the

From the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary (L.M.V., S.D.R.), Boston, Massachusetts, U.S.A; and the Faculty of Health Sciences, University of Brasilia (L.M.V., F.B.), Brasilia, Distrito Federal, Brazil.

Editor's Note: This Manuscript was accepted for publication April 9, 2014.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Lucas M. Viana, MD, Ed Dr Crispim SMHN Quadra 2 Bloco C Sala 515 ASA NORTE, Brasilia, Distrito Federal, Brazil 70710-149. E-mail: lucasmvianaorl@gmail.com

DOI: 10.1002/lary.24716

cristae and maculae disclosed ototoxic injury in the form of vacuoles, along with clubbing of the sensory cells.

At our institution, we began using ITG for intractable MD in 1994. Encouraged by the high success rate, in 2002 we began offering it as an option to treat DA patients. As part of the surgical informed-consent discussion, each patient was told that the success rate of DA control and duration of control were uncertain. If this uncertainty was unacceptable to the patient, transmastoid labyrinthectomy was offered as an alternative.

All patients who experience a relapse of DA after ITG treatment are advised to have labyrinthectomy. There are many studies showing good control of vertigo with low rates of hearing damage from ITG for intractable MD patients.[11,12] However, there are scant data regarding the effectiveness of ITG for control of DA in patients with MD. Therefore, the objective of this study was to retrospectively review the effectiveness of ITG injection for the treatment of patients with MD and DA.

MATERIALS AND METHODS

This retrospective chart review study was approved by our institutional review board.

Patients

We reviewed charts from all Meniere patients at our hospital who had DA, had been treated with ITG, and had been followed for at least 1 year afterward. MD patients without DA or $<$ 1-year follow-up were excluded from the study. MD was diagnosed according to standard criteria.[1]

Methods

ITG: The affected ear was anesthetized at two sites—one anterosuperior and one posterosuperior—using topical phenol 90% solution in 10% water. One mL of gentamicin sulfate solution (40 mg/mL; pH 6.4) was warmed briefly in a bead sterilizer to prevent a caloric effect and then drawn into a 1-cc tuberculin syringe, which was then fitted with a 22-gauge spinal needle. The anterior anesthetized site was punctured as an air vent, and the entire 1 mL of gentamicin solution was injected into the middle ear via the posterior anesthetized site. Air bubbles and then excess gentamicin solution were flowed out of the vent site. The patient remained supine, with the head rotated slightly to the untreated side, for 1 hour.

Patients each received a single injection of ITG, as described above, and were monitored for 1 month. If the patient showed no symptoms of deafferentation (manifesting as persistent subjective disequilibrium and/or a newly positive head thrust sign on the treated side) or the Meniere's attacks continued, the patient underwent another injection of gentamicin, which was considered as part of the same cycle. The repeat ITG dosings with 3 months of the initial dose were all considered part of one "cycle" of treatment. However, if retreatment was administered after 3 months, it was considered a new cycle.

Most patients underwent pure tone audiometry, cervical vestibular-evoked myogenic potential (cVEMP), and magnetic resonance imaging of the brain. In order to maximize follow-up data collection, patients were contacted by telephone.

Data Analysis

The collected data were plotted in an Excel spreadsheet. Descriptive demographic statistics were tabulated. A Kaplan-Meier time-to-event curve was constructed for all individuals using GraphPad Prism (version 6.0c; GraphPad Software, Inc., La Jolla, CA) to assess the follow-up after ITG injections. The cVEMP thresholds were compared between the affected and unaffected ears, and the *P* value was calculated using the Fisher's exact test.

RESULTS

We reviewed the charts of 320 consecutive ITG-treated patients from a total of 3,450 MD patients seen from 2002 to 2012 to identify the subset of those with DA. All patients with DAs were treated with ITG. None of the patients declined that treatment, and none of the patients went directly to labyrinthectomy. Twenty-three patients (12 females, 11 males; 41–80 years of age) fulfilled inclusion criteria. The follow-up period ranged from 1 to 10 years. In six patients, the right ear was affected; in 16 patients, the left ear was affected. In one patient, both ears were affected (cases 8 and 9). The results for all patients are summarized in Table I. The duration of disease in the patients varied from 4 to 24 years (mean 15.5 years). The time for manifestation of DA varied from 1 to 20 years (mean 10 years) from the beginning of symptoms. In keeping with the widely held notion that DAs are a characteristic of late-stage MD, pretreatment audiometry showed advanced hearing loss in 91.3% of affected ears.

DAs were controlled in 20/24 (83.3%) of ears after the first treatment (Fig. 1). Of the four remaining cases with no response, cases 1, 4, and 24 underwent three, two, and one more cycles, respectively, with complete remission of DA (95.8%) (Fig. 2). Case 3 is still under assessment for further treatment. Among patients with no DA recurrence by the end of the study follow-up, the symptom-free interval varied from 12 to 120 months (mean: 43.5 months). All 15 cases with $\geq$ 24 months follow-up were still free of DA. The other cases were not seen after 24 months follow-up because the study finished before that time.

By the end of the ITG treatment, six cases were considered as a partial response; that is, although they no longer had DA, they had recurrence/persistence of typical Meniere vertigo attacks. Among those cases, two underwent labyrinthectomy, and the other four cases were undecided about further treatment.

Prior to ITG treatment, cVEMP responses were absent in 32% % of affected ears, and thresholds were elevated in 64% of affected ears compared to 8% ($P = 0.0005$) and 33% ($P = 0.0004$), respectively, in the unaffected ears of our subjects. Pre-ITG and post-ITG audiograms were available for 15 patients. Four patients showed hearing threshold shift $>$ 10dB at 0.5 kHz and 1.0 kHz, and three patients showed threshold shift $>$ 10dB at 2 kHz and 4 kHz, respectively.

DISCUSSION

We retrospectively reviewed the outcome of ITG treatment for DA in 24 ears of 23 patients with MD. The time for manifestation of DA varied among the patients from 1 to 20 years after diagnosis (mean 10 years). In this study, 83.3% of ears with intractable MD and DA

TABLE I.
Summary of the Results for Each Case After Intratympanic Gentamicin.

Patient	Sex	Age	Side	No. Doses	No. Cycles	ITG Results		Labyrinthectomy	Pretreatment Hearing	
						After First ITG	After Last ITG		Pure Tone Average (dB)	Discrimination Score (%)
1	Male	73	Left	4	4	NR	CR	NO	66.25	44
2	Male	43	Left	6	3	PR	PR	YES	66.25	40
3	Female	45	Left	2	1	NR		NO	53.75	12
4	Female	67	Left	3	3	NR	CR	NO	58.75	24
5	Male	65	Left	2	1	CR		NO	77.5	28
6	Male	54	Left	3	2	PR	CR	NO	–	–
7	Male	68	Left	1	1	CR		NO	66.25	46
8	Female	72	Left	1	1	CR		NO	56.25	58
9	Female	72	Right	1	1	CR		NO	53.75	68
10	Female	44	Left	1	1	CR		NO	67.5	48
11	Male	41	Left	6	2	PR	CR	NO	52.5	70
12	Female	51	Left	1	1	PR		NO	52.5	58
13	Male	55	Right	1	1	PR		NO	50	86
14	Female	47	Right	1	1	CR		NO	68.75	52
15	Female	60	Left	1	1	CR		NO	33.75	92
16	Female	45	Left	1	1	PR		NO	66.25	34
17	Male	80	Right	2	1	PR		NO	61.25	68
18	Male	62	Right	1	1	CR		NO	33.75	90
19	Female	69	Left	2	2	PR	CR	NO	56.25	22
20	Female	60	Right	1	1	PR		YES	71.25	56
21	Male	50	Right	1	1	CR		NO	62.5	38
22	Female	60	Left	1	1	CR		NO	66.25	10
23	Female	54	Left	4	1	CR		NO	51.25	36
24	Male	56	Left	2	2	NR	CR	NO	58.75	48

Each case represents one patient, except cases 8 and 9, which represent the left and the right side of the same patient, respectively.
= no data available; blank = no further treatment; CR = complete remission; ITG = intratympanic gentamicin; NR = no response; PR = partial remission; Pure-tone average is 0.5K, 1K, 2K, and 4 KHz.

achieved complete symptom control of DAs after the first ITG cycle—and 95.8% after further injections. Among patients with no DA recurrence by the end of the study follow-up, the symptom-free interval varied from 12 to 120 months (mean: 43.5 mos). All fifteen patients with-$\geq$24 months follow-up were still free of DA.

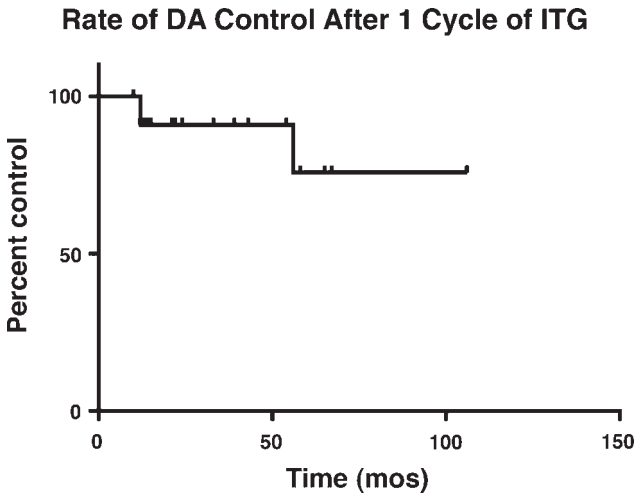

Fig. 1. Kaplan-Meier curve for all individuals after first ITG cycle: Twenty out of 24 ears had no more drop attacks.
DA = drop attack; ITG = intratympanic gentamicin; mos = months.

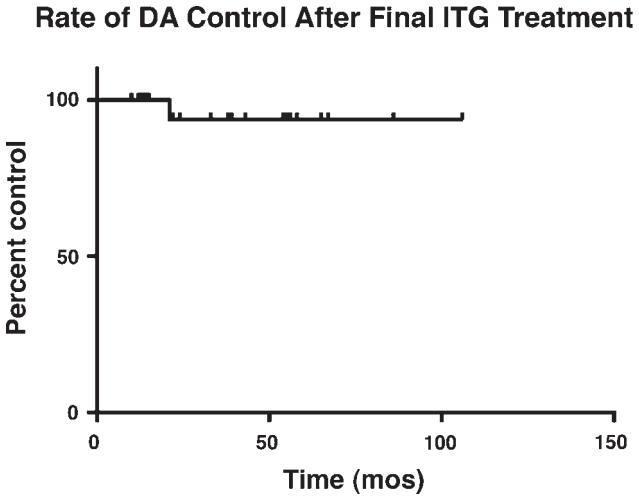

Fig. 2. Kaplan-Meier curve for all individuals after final treatment: Twenty-three out of 24 cases had complete remission of DAs.
DA = drop attack; ITG = intratympanic gentamicin; mos = months.

DAs are typically seen in patients with severe and long-lasting MD.[13] In this case series, they developed on average 10 years after the onset of disease. DAs are thought to arise from mechanical stimulation of the utricle and/or saccule, which might activate vestibulospinal pathways and trigger the symptom. The attacks are characterized by the instantaneous onset of short-lasting, often profound, loss of balance during which patients may suddenly fall but remain conscious.[4] Timmer et al.[14] demonstrated that cVEMP thresholds—a measure of saccular function—were markedly more likely to be elevated or absent in DA ears than in regular Meniere ears. Our results confirmed these findings, showing that VEMP thresholds were undetectable in 32% of DA affected ears compared to 8% of unaffected ears.

Ours is not the first report of ITG for the treatment of DA in Meniere patients. Previous studies have shown success rate of control of DAs in 60%[15] and 100% of Meniere patients.[16] Those studies have assessed all severe cases of Meniere's patients who had undergone either surgical or clinical treatment previously, whereas this study only focuses on intractable MD patients with DA with no surgical treatment previously. A meta-analysis of ITG results across several different treatment protocols, performed by Chia et al., demonstrated significantly better complete and effective (96.3%; $P < 0.05$) vertigo control by the titration method (as used in the present study) compared with other methods. No significant difference in profound hearing loss was found between groups. [17] In the present study, the high rate of vertigo control of 95.8% by the end of the treatment was in agreement with these earlier studies. Because DAs are so dangerous, it is considered imperative to offer a reliable and highly successful treatment. Whereas a prospective study with placebo or no-treatment control group might be methodologically rigorous, it is obviously unethical. In the present study, we have follow-up data of ≥ 24 months, as recommended by the Meniere reporting criteria of the American Academy of Otolaryngology–Head and Neck Surgery,[1] in 15 of 24 treated ears, with no relapses observed after 24 months. All relapses in our study population occurred before 24 months of follow-up. This raises the hope that those patients who do not show early relapse may have a durable benefit of this treatment.

Indications for ITG treatment are similar to indications for surgical labyrinthectomy; that is, intractable vertigo symptoms despite aggressive medical management with diet, diuretics, and vestibular suppressants. Whereas most patients with severe or advanced MD have poor hearing, this is not always the case. Because significant hearing loss is seen in only a minority of ITG cases, this treatment is particularly appropriate in cases of DAs with only mild to moderate hearing loss. To date, in our clinic we recommend surgical labyrinthectomy or vestibular neurectomy after the ITG treatment failure. In some cases, however, patients would rather undergo additional cycles of gentamicin, for example, cases 1, 2, 4, 6, 11, 19, and 24 (Table I).

There are several obvious advantages to ITG over surgical labyrinthectomy. Pyykkö et al. have shown that ITG is a relatively safe and effective way to treat bilateral MD when the symptoms can be localized to one ear.[18] Furthermore, ITG treatment is done in the outpatient setting without admission and without risk of the complications accompanying surgery. The relatively long time to DA relapse seen in the Kaplan-Meier curves (Figs. 1 and 2) makes it clear that all DA cases that achieve initial symptom relief with ITG must followed for years to monitor for possible future relapse.

CONCLUSION

This study has shown that the time for manifestation of DA varied among the patients from 1 to 20 years after diagnosis (mean 10 years). ITG treatment reached an 83.3% initial DA control rate—and a 95.8% control rate after further injections. Furthermore, the average symptom-free interval was 43.5 months. The number of elevated and absent cVEMP threshold was higher in DA ears, and hearing loss was not a major complication of the treatment. ITG treatment is a long-lasting and effective treatment for MD patients with DA.

BIBLIOGRAPHY

1. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's Disease. American Academy of Otolaryngology–Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg* 1995;113:181–185.
2. Black F, Effron M, Burns D. Diagnosis and management of DAs of vestibular origin: Tumarkin's otolithic crisis. *Otolaryngol Head Neck Surg* 1982; 90:256–262.
3. Baloh R, Jacobson K, Winder T. DAs with Meniere's syndrome. *Ann Neurol* 1990;28:384–387.
4. Tumarkin A. The otolithic catastrophe: a new syndrome. *BMJ* 1936;1:175–177.
5. Rauch, SD. Clinical hints and precipitating factors in patients suffering from Meniere's Disease. *Otolaryngol Clin N Am* 2010;43:1011–1017.
6. Schuknecht HF. Ablation therapy in the management of Meniere's disease. *Acta Otolaryngol Suppl* 1957;132:1–42.
7. Calzada AP, Lopez IA, Ishiyama G, Ishiyama A. Otolithic membrane damage in patients with endolymphatic hydrops and DAs. *Otol Neurotol* 2012;33:1593–1598.
8. Watanuki K, Stupp HF, Meyer-zum-Gottesberge A. Toxic effects of gentamycin upon the peripheral vestibular sensory organs. *Laryngoscope* 1972;82:363–371.
9. Demarco RC, Rossato M, de Oliveira JA, Hyppolito MA. Histological effects of intratympanic gentamicin on the vestibular organ of guinea pigs. *J Laryngol Otol* 2011;125:357–362.
10. Keene M, Hawke M, Barber HO, Farkashidy J. Histopathological findings in clinical gentamicin ototoxicity. *Arch Otolaryngol* 1982;108:65–70.
11. Manrique-Huarte R, Guillen-Grima F, Perez-Fernandez N. Treatment of Meniere's disease with 'on-demandÇ intratympanic gentamicin injections. *Otol Neurotol* 2011;32:461–465.
12. Wasson J, Upile N, Pfleiderer A. Intratympanic gentamicin treatment for unilateral Meniere's disease: long-term follow-up of a proven regime. *J Laryngol Otol* 2013;127:20–24.
13. Black FL, Effron MZ, Burns DS. Diagnosis and management of DAs of vestibular origin: Tumarkin's otolithic crises. *Otolaryngol Head Neck Surg* 1982;90:256–262.
14. Timmer, FCA, Zhou G, Rauch, et al. Vestibular evoked myogenic potential (VEMP) in patients with Meniere's disease with DAs. *Laryngoscope* 2006;116:776–779.
15. Kaasinen S, Pyykko I, Ishizaki H, Aalto H. Intratympanic gentamicin in Meniere's Disease. *Acta Otolaryngol* 1998;118:294–298.
16. Odkvist LM, Bergenius J. DAs in Meniere's disease. *Acta Otolaryngol Suppl* 1988;455:82–85.
17. Chia, SH, Gamst AC, Anderson JP, Harris JP. Intratympanic Gentamicin Therapy for Meniere's Disease: A Meta-analysis. *Otol Neurotol* 2004; 25: 544–552.
18. Pyykko I, Ishizaki H, Kaasinen S, Aalto H. Intratympanic gentamicin in bilateral Meniere's disease. *Otolaryngol Head Neck Surg* 1994;110:162–167.