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ORIGINAL ARTICLE

Comparing Intratympanic Gentamicin with Methylprednisolone in Meniere's Disease with Non-Serviceable Hearing

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Abstract To compare the effectiveness of high dose fixed alternate day intratympanic gentamicin with methylprednisolone in the treatment of patients with unilateral, intractable Meniere's disease with poor hearing. Randomized single blind prospective parallel group trial in a tertiary referral centre. Twenty-two patients with definite unilateral Meniere's disease with average pure tone thresholds worse than 50 dB in the affected ear were enrolled. Eleven patients were treated with intratympanic buffered gentamicin and the other eleven were administered intratympanic methylprednisolone (both 4 injections, 40 mg/ml, on alternate days). Patients were assessed pre-intervention, 3 months post intervention and subsequently followed up for 2–4 years. Both groups of patients had significant control of vertigo, DHI scores and THI scores after treatment while the functional scores in the methylprednisolone group was not better than the pre- treatment scores in the long-term follow-up. 9 of 11(82%) patients in gentamicin group and 3 of 11(27%) patients in the methylprednisolone group achieved Class A vertigo control. The gentamicin group had better post intervention DHI scores ($p = 0.016$, 3 months and $p = 0.046$, long term) and Functional score ($p = 0.014$, 3 months and $p = 0.05$, long term). The hearing in both groups and THI scores, post intervention was similar between both groups. In patients with unilateral intractable MD with non-serviceable hearing, high fixed doses of both intratympanic gentamicin and methylprednisolone are effective in alleviating disease symptoms in long term follow-up. However, intratympanic gentamicin resulted in better control of vertigo, total DHI score and functional level scores than intratympanic methylprednisolone with no significant difference in hearing levels.
Trail Registration Number Clinical Trials Registry of India (CTRI- REF/2016/10/012363)

Keywords Meniere's disease · Intratympanic gentamicin · Intratympanic methylprednisolone · Vertigo · DHI

Introduction

Meniere's disease (MD) is an idiopathic syndrome of endolymphatic hydrops. Pathologically, the endolymphatic spaces in the membranous labyrinth are dilated due to excessive production of endolymph [5, 17, 22]. The classical symptoms described in MD are vertigo, tinnitus, hearing loss and aural fullness [10]. It is a long standing, disabling disorder of disequilibrium and hearing loss that affects daily living in patients. MD is usually unilateral but at times can affect both ears together or successively. The standard treatment of MD is conservative; lifestyle, diet modification and medications like diuretics and betahistine. When these measures fail, intratympanic injections of gentamicin or steroid are usually given as the next step [14]

Steroids are believed to act via an anti-inflammatory effect on the inner ear; generating a change in the ion and fluid homeostasis, control of aquaporin channels and causing an improvement in cochlear blood flow [16]. Methylprednisolone has better mineralocorticoid receptor

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binding properties than dexamethasone and achieves a higher concentration in the perilymph [12] Gentamicin meanwhile, is believed to be more vestibulotoxic, reducing the vestibular symptoms while preserving the hearing. It acts on the dark cells in the stria vascularis, reducing endolymph production and regulating ion production [3].

However, there is no consensus on the doses or protocol of intratympanic injections for intractable MD. Low dose and high dose regimes have been described and they differ between centres. Opinions are divided as to which therapy is more efficacious [1, 2, 12, 18, 20]. Some centres have used the titration/ on demand method as an indication to repeat a dose of gentamicin.

This study was undertaken to compare the efficacy of the 2 drugs when administered intratympanically in patients with intractable unilateral MD with non-serviceable hearing using the 4-dose alternate day regime. The comparison was made for control of symptoms, effects on hearing levels, quality of daily life and side effects.

Materials and methods

Patients presenting to the Audio-vestibular clinic of our institution from November 2016 to October 2018, who fulfilled the ICVD 2015 diagnostic criteria for definite Meniere's disease were considered for inclusion into the randomised control study. Prior clearance from our Institutional Review Board and Ethics Committee (IRB Min no- 10,222) was taken in accordance with the Helsinki declaration.

Adults with symptoms that fit into the diagnostic criteria of definite unilateral MD with a pure tone hearing average of 50 dB (at 500, 1000, 2000 and 3000 Hz) or worse in the affected ear, with complaints of persistent symptoms following medical therapy (Betahistine 48 mg) for at least 6 months duration and with no evidence of retrocochlear disease were taken. Patients with additional otological disorders, allergies to the proposed drugs and those who were unable to come for review following the intervention, were excluded from the study.

Patients were explained about the study in detail with the aid of a patient information booklet. A formal written consent was then taken from individuals willing to participate in the study, following which they underwent a thorough history and otoneurological examination. Baseline vertigo episodes per month along with the Dizziness Handicap Index [DHI] scores [8], Tinnitus Handicap Index [THI] scores [23] and the Functional Score [21] were noted.

The patients were randomised into one of two groups equally using block randomization technique, the first group received intratympanic gentamicin (ITG) 40 mg/ml and the second group received intratympanic methylprednisolone (ITMP) 40 mg/ml. Allocation concealment was done by sealed envelope method.

Procedure

Injections were administered in the out-patient department by the first author with the patient in supine position with head on a pillow turned towards the unaffected ear. After cleaning the ear with a solution of povidone-iodine, the tympanic membrane was examined under microscope. The injections were administered under microscopic guidance following topical anaesthetic application (10% lignocaine spray). Methylprednisolone 1 ml (40 mg/ml) OR 0.6 ml of gentamicin (40 mg/ml) buffered with 0.4 ml of sodium bicarbonate (8.4%) was taken in a 2 cc syringe and injected intratympanically using a 25gauge lumbar puncture needle. Around 0.8–1 ml of drug was injected into the middle ear through the anteroinferior/posteroinferior quadrant of the tympanic membrane.

The patients lay in this position for 20 min, without swallowing and talking, following which they were sent home and could continue with their daily activities. The injection was repeated every alternate day for a total of 4 injections.

Patients continued betahistine tablets 48 mg, once daily along with salt and caffeine restriction. They were also given vestibular rehabilitation therapy following the injections. Review was done after 3 months, where the DHI score, THI score and functional score were reassessed by an investigator who was blinded to the intervention received. The number of vertigo episodes, hearing symptoms and side effects if any were documented. They also underwent a pure tone audiogram. Thereafter, they were reviewed at regular intervals for a period ranging from 24 to 48 months, and reassessed by a 'blinded' investigator.

Statistical Methods

For normally distributed variables, the descriptive statistics of mean and standard deviation (SD) was presented. For the categorical data, the number and percentage were presented. The t-test was used to find the two-group difference. The non-parametric Mann–Whitney test was used to find the difference between the two groups. The histogram with summary values was used to test the hypothesis of normal distribution. The non-parametric Wilcoxon Signed Ranks Test was used to find the differences between pre- and post-treatment. All tests were two-sided at $\alpha = 0.05$ level of significance. Analysis was done using Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp).

Results

Twenty-two patients with intractable unilateral MD fulfilling the inclusion criteria were recruited for the study during this time period.

Eleven (7 men and 4 women) patients were treated with ITG, and eleven (6 men and 5 women) were treated with ITMP. The mean age was 44.36 years (SD = 10.70 years) in the ITG group while the mean age in the ITMP group was 42.27 years (SD = 7.7 years).

Clinical characteristics of the group is given in Table 1.

There was no statistical difference in the age, pre intervention pure tone audiogram, DHI, THI and functional scores between the two groups. The duration of follow-up in both the groups ranged from 24 to 48 months (mean being 36 months). At their last follow up, 8 of 11 patients in the ITMP group had stopped medications while 2 were taking betahistine at a reduced dose and 1 was taking medications for vestibular migraine. In the ITG group 10 had stopped betahistine and 1 was taking medications for concomitant vestibular migraine.

Immediate post injection side effects included pain (10 patients -ITMP group) and vertigo (4 patients-ITG group). One patient who received ITG suffered severe post injection vertigo following the last injection and required hospitalization for a day. However, at 3 months follow up he was vertigo free. Another patient complained of oscillopsia at his 3-month review which improved with vestibular rehabilitation exercises. One patient in the ITG group, developed symptoms on the opposite side at 6 months. One patient in the ITMP group had recurrence of severe symptoms and was given ITG at 22 months and not included in the subsequent analysis.

Vertigo

Of the eleven patients in the ITG group, 9 achieved Class A control, 1 Class B and 1 was Class C (this patient had dizziness associated with headaches along with photophobia and phonophobia). In the ITMP group, 3 patients achieved Class A control, 5, Class B and 2, Class C. The patient who received ITG subsequently, achieved substantial vertigo control and was Class B (Fig. 1).

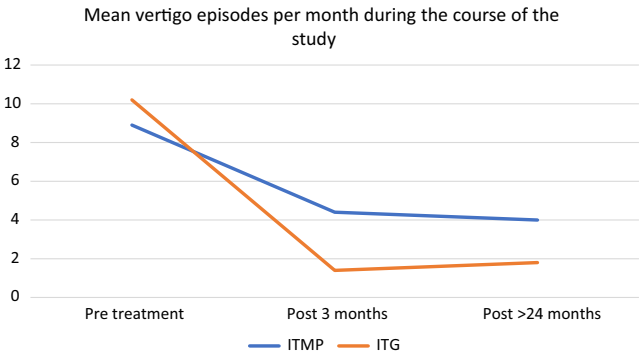

Fig. 1 Mean vertigo episodes per month; pre- injection, early post treatment and late post treatment in the 2 groups

Within the ITG group, there was a significant fall in the total DHI score post injection at 3 months as well as long term, along with a statistically significant decrease in each of the sub component scores of DHI viz, DHI *physical* score, DHI *emotional* score and DHI *functional* score (Table 2).

Within the ITMP group also, there was a significant decrease in the total DHI post injection at 3 months as well as long term with a statistically significant decrease in the DHI *emotional* score and DHI *functional* score, while the DHI *physical* score change was not significantly different compared to the pre -treatment values (Table 2).

Between the two groups, when comparing the pre- and post-injection (3 months) DHI scores, there was a statistically significant improvement in the DHI total score, the DHI *emotional* score and the DHI *functional* score in the ITG group. The change in the DHI *physical* score between the 2 groups was not statistically significant (Table 3). In the long-term, when DHI scores were compared between groups, DHI total score was significantly better in the ITG group but individual sub-components did not show significant difference (Table 4).

The Kaplan Meier plot shows the median time for good control of symptoms status is 4 years (95%CI: 3, 5) in the study population (Fig. 2).

Tinnitus

In both the groups, the THI scores improved significantly and patients experienced decreased handicap due to their tinnitus at 3 months as well as in the long term (Table 2).

On comparing the THI scores between the 2 groups the difference was not statistically significant at both 3 months as well as in the long term (Tables 3 and 4).

Table 1 Comparison of treatment groups

		Gentamicin	Methylprednisolone
Side affected	Left	7	5
	Right	4	6
Duration of Symptoms	< 1yr	1	0
	1–5yr	7	7
	> 5 yrs	3	4

Table 2 Comparison of outcome measures Pre- and Post-injection within the two treatment groups ITG and ITMP (Wilcoxon signed ranks test)

Title	Group		*n*	Median PTA	*P* value
Avg. PTA	ITG	Pre	11	58.75	0.959
		post 3 months	11	53.75	
	ITMP	Pre	11	56.25	0.014
		Post 3 months	11	51.25	
				Median score	
DHI Total	ITG	Pre	11	58	0.003
		3 Months	11	8	
		> 24 months	11	0	0.003
	ITMP	Pre	11	30	0.003
		3 Months	11	8	
		> 24 Months	10	7	0.005
DHI Physical	ITG	Pre	11	10	0.004
		3 Months	11	6	
		> 24 months	11	0	0.004
	ITMP	Pre	11	4	0.089
		3 Months	11	4	
		> 24 Months	10	5	0.41
DHI Functional	ITG	Pre	11	24	0.003
		3 Months	11	2	
		> 24 Months	11	0	0.003
	ITMP	Pre	11	14	0.005
		3 Months	11	2	
		> 24 Months	10	4	0.008
DHI Emotional	ITG	Pre	11	22	0.005
		3 Months	11	0	
		> 24 Months	11	0	0.003
	ITMP	Pre	11	12	0.003
		3 Months	11	0	
		> 24 Months	10	0	0.005
THI Grade	ITG	Pre	11	3	0.004
		3 Months	11	1	
		> 24 Months	11	1	0.004
	ITMP	Pre	11	3	0.010
		3 Months	11	1	
		> 24 Months	10	1	0.005
Functional score	ITG	Pre	11	3	0.003
		3 Months	11	1	
		> 24 Months	11	1	0.004
	ITMP	Pre	11	3	0.006
		3 Months	11	1	
		> 24 Months	10	2.5	0.49

PTA– pure tone audiogram, DHI– Dizziness Handicap Inventory, THI– Tinnitus Handicap Scale, ITG– Intratympanic gentamicin, ITMP– Intratympanic Methylprednisolone

Table 3 Comparing of outcome measures Post 3 months injection between ITG and ITMP groups (MANN WHITNEY TEST)

	Group	*N*	Median (IQR)	*P* value
Avg. PTA	ITG	11	53.75(47.7–100)	0.357
	ITMP	11	51.25(47.5–57.5)	
DHI Total	ITG	11	8 (6–10)	0.016
	ITMP	11	8 (0–34)	
DHI Physical	ITG	11	6 (2–6)	0.094
	ITMP	11	4 (0–10)	
DHI Functional	ITG	11	2(0–4)	0.004
	ITMP	11	2 (0–10)	
DHI Emotional	ITG	11	0 (0–2)	0.038
	ITMP	11	0(0–10)	
THI Grade	ITG	11	1 (1–1)	0.159
	ITMP	11	1 (0–3)	
Functional score	ITG	11	1 (1–2)	0.014
	ITMP	11	1 (1–3)	

PTA− pure tone audiogram, DHI− Dizziness Handicap Inventory, THI−Tinnitus Handicap Scale, ITG− Intratympanic gentamicin, ITMP− Intratympanic Methylprednisolone

Table 4 Comparing of outcome measures at end of the Study(Mean 36 Months, Post Injection) between ITG and ITMP groups (MANN WHITNEY TEST)

	Group	*N*	Median (IQR)	*P* value
DHI Total	ITG	11	0(0–2)	0.046
	ITMP	10	7(0–18)	
DHI Physical	ITG	11	0(0–2)	0.09
	ITMP	10	5(0–10)	
DHI Functional	ITG	11	0(0–0)	0.06
	ITMP	10	2(0–4)	
DHI Emotional	ITG	11	0(0–0)	0.52
	ITMP	10	0(0–0)	
THI Grade	ITG	11	1(1–1)	0.48
	ITMP	10	1(1–1)	
Functional Score	ITG	11	1(1–2)	0.05
	ITMP	10	2.5(1–3)	

Hearing Loss

Within the ITG group, the *median* 4 frequency, pure tone average (PTA) pre injection was 58.75 dB and post injection it was 53.75 dB. However, this difference was not statistically significant ($p = 0.959$) (Table 2).

In the ITMP group the *median* 4 frequency PTA pre injection was 56.25 dB, while post injection it was 51.25 dB. This was statistically significant ($p = 0.014$) with post treatment hearing levels better than pre-treatment (Table 2).

Of the eleven patients in the ITG group, four patients developed worsening of hearing (two developed profound hearing loss- their pre-treatment PTA average hearing was 60-65 dB) The *mean* PTA pre injection in the ITG group was 61.59 dB while post injection *mean* PTA was 64.35 dB. The *mean* change in hearing was a worsening of 14.66 dB across the group.

Of the eleven patients in the ITMP group, one patient had a decrease in hearing by 3.75 dB post injection while another had worsening in hearing by 1.75 dB. The *mean* pre injection PTA in the ITMP group was 56.7 dB while

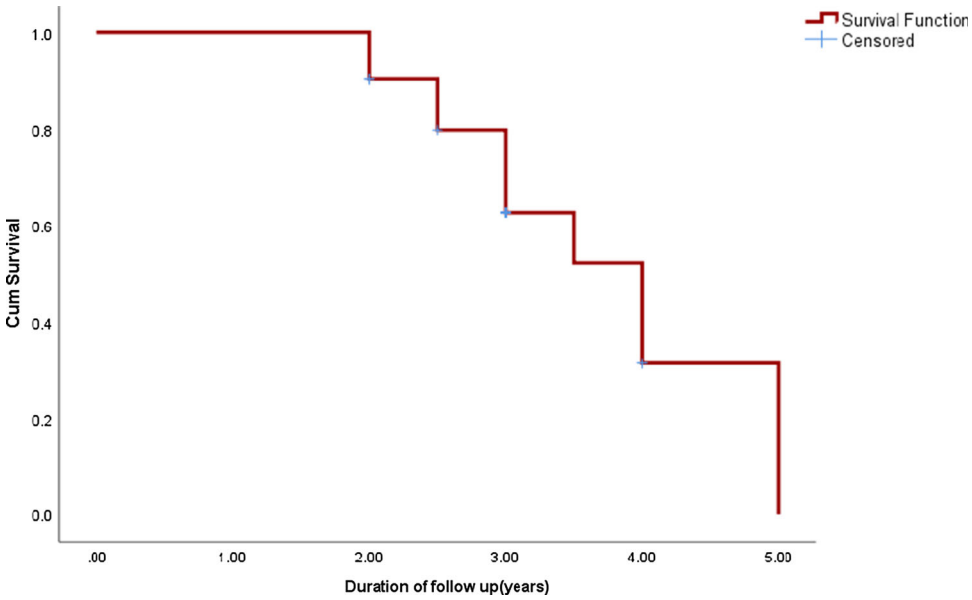

Fig. 2 Kaplan Meier plot showing the median time for good control of vertigo (Class A and Class B)

post injection *mean* PTA was 50.91. The *mean* change in hearing was an improvement by 6.69 dB.

There was no significant difference in hearing change between the 2 groups post intervention. ($p = 0.365$) (Table 3).

Functional Score

Of the twenty-two patients, fourteen patients reported a functional score of 1 at 3 months (6 from ITMP group, 8 from the ITG group). In both the groups, the change in functional score post injection was found to be statistically significant at 3 months, however in the ITMP group this was not sustained in the long-term follow-up (Table 2).

On comparing the 2 groups, improvement in functional score was significantly better in the ITG group at both the 3 month and long term follow up when compared to the ITMP group (Tables 3 and 4).

Discussion

MD is a debilitating disorder that affects work, activities of daily life, leisure, family relationships and sleep. Persistent episodes of vertigo affect the patients' ability to enjoy a fruitful life [24]. While hearing loss and tinnitus are also a cause for concern, vertigo continues to be the main symptom that affects all aspects of an individual's life.

Intratympanic medications have been used in the management of intractable MD, although there are no standardised protocols describing the use and duration of IT injections. In our institution we have used the 4 injection (alternate day) protocol. This is a high dose gentamicin protocol and we have reserved this regime for patients with non-serviceable hearing.

We have compared the outcomes with respect to vertigo control, number of vertigo episodes, tinnitus, hearing loss and patient functionality in those with unilateral MD that have received ITG with those receiving ITMP. There are very few studies that have studied outcomes comparing these 2 drugs [6, 15]. In the study by Patel et al., 60 patients with unilateral MD were recruited to receive either methylprednisolone (62.5 mg/ml) or gentamicin (40 mg/ml), 2 injections intratympanically 2 weeks apart and followed up for 2 years. The audiological criteria in these patients were not specified. They found both methylprednisolone and gentamicin giving significant relief from vertigo episodes [15]. When these patients were followed up for a time period of 70 months, they found no difference between the 2 treatment [6]. A study by Casani et al. report a 90% substantial control(Class A or Class B) of vertigo at 2 year follow up in patients who received gentamicin compared to a 61% rate in those that received IT dexamethasone [2].They used a low dose gentamicin protocol which was titrated against the appearance of vestibular dysfunction on the treated side. Martin and Perez reported vertigo control of 83.1% on using gentamicin with only 15.5% patients noted to have decrease in hearing. They also used a weekly dose of gentamicin titrated to the appearance of vestibular dysfunction [11].

In our study, we had 9 of the ITG group achieve Class A control in the long term, 1, Class B and 1, Class C. The patient who had Class C control also had vestibular migraine and this contributed to the dizzy spells. In the ITMP group we had only 3 patients who had Class A control, while 5 had Class B and 2 had Class C. One lady

required gentamicin injection at 22 months after the ITMP treatment for recurrent vertigo but managed to achieve Class B control at 42 months evaluation. Patients with MD can have simultaneous vestibular migraine symptoms and those who fulfill independent criteria for both disorders are designated as MDVM in recent literature. A separate assessment of therapeutic outcomes for MDVM needs to be developed. These require management of both disorders separately as the treatments do not overlap [9, 13, 19].

The DHI Scale qualifies the effects of giddiness with respect to *physical* handicap, *emotional* wellbeing and daily *functionality* [8]. Both ITG and ITMP showed significant improvement in DHI scores (*physical* handicap, *emotional* wellbeing and daily *functionality*) in the early post treatment periods. When it came to the DHI score pre- and post- injection, there was a statistically significant advantage of ITG over ITMP in the total score as well as in the *emotional* and *functional* sub scores at 3 months and the total score at long term follow up. In the absence of vertigo, patients reported better daily functionality and social interactions. They were willing to participate in community activities, as vertigo was no longer a restricting factor. Imbalance and post injection giddiness caused by ITG settled completely with vestibular rehabilitation exercises and no patients in the ITG group had a significant disability in the long term. All patients were told to continue their betahistine 48 mg daily, at the time of intervention, but at the last follow up no patients in the ITG group was on betahistine, while only 1 was on medications for vestibular migraine. However, in the ITMP group, 2 were still taking betahistine at a reduced dose and 1 was taking medications for vestibular migraine.

Most studies have reported improvement of vertigo only with respect to number of vertigo episodes and not the DHI scores [2, 11]. However, Patel et al. and Harcourt et al. reported no difference between the methylprednisolone and gentamicin groups with regard to the long term DHI scores[6, 15].

Although, the overall mean PTA in the ITG group dropped by 14.66 dB after injection and mean PTA in the ITMP group improved by 6.69 dB, there was no significant change in hearing, when pre- and post-injection audiograms were compared between the groups ($p = 0.365$). Six out of twenty-two patients had worsening in hearing, four of whom had received ITG. Of these, 2 patients had profound loss of hearing post injection, their pre intervention hearing level was an average of 60-65 dB. Both these patients did not report serious disability in hearing when compared to pretreatment status. As this study included only those with poor hearing, this change did not seem to impact their quality of life as evidenced by overall DHI and functional scores. Other studies have also reported a negligible change in hearing after ITG via different regimes [2–4]. Martin and Perez, in their study assessing hearing loss following ITG injections, have reported that patients who had no change in hearing, had an overall poorer control of vertigo and required another course of injections [11].

Tinnitus however continued to be a symptom for most of our patients irrespective of the injection they received. While both groups reported a significant improvement in the THI scores after treatment, both early and in the long-term follow-up, the difference in THI scores between the groups were not significant. Literature also reports great variation in tinnitus control rates, from 0.4 to 47.9% [7]. Most patients also reported an improved tolerance to tinnitus and they were able to function despite the presence of tinnitus. The THI aims to assess the effect of tinnitus on daily functioning and not just the presence or absence thereof. A low score (Grade 1) is reported not as the absence of tinnitus, but rather, tinnitus which is slight; with no interference with sleep or daily activities [23]. We note that in the absence of vertigo episodes, tinnitus failed to be a cause of concern for most patients.

Functional scale score assesses the patient's overall functionality, not just during attacks and can be used to compare pre-treatment to post treatment functionality [21]. In our study, both groups had a significant improvement of their functional scores as 3 months. While the ITG group continued to show this improvement even in the long term follow up, the ITMP group did not have this improvement.

Limitations

Preparations of Methylprednisolone and Gentamicin being differently constituted as well as the requirement to add a buffer solution to Gentamicin made blinding of the drugs impossible. The post treatment assessment was however performed by a blinded assessor.

As the inclusion criteria was quite specific, we could recruit limited patients in the time frame of the study.

Conclusion

In patients with unilateral intractable MD with non-serviceable hearing, the 4-dose alternate day regime of both ITMP and ITG are effective in alleviating disease symptoms with regards to vertigo control, DHI score and THI score in the early post intervention follow up. However, ITG resulted in better improvement in total DHI score, DHI functional score and DHI emotional score, better functional level scale and better vertigo control rate than ITMP in the long term with no significant worsening of hearing. Hence, in patients with unilateral intractable MD and poor hearing,

high dose of ITG may be advocated for better disease control.

Author Contributions Institution where the study was carried out: Christian Medical College, Vellore, India.

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Declarations

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Institution (IRB Min no- 10222).

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