

Neurovestibular Compensation following Ototoxic Lesion and Labyrinthectomy

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Abstract

Introduction Unilateral labyrinthectomy and intra-tympanic gentamycin have been employed in the treatment of Ménière's disease, but the efficacy of these techniques has not been well established.

Objective The objective of this study is to measure the time course of recovery from a unilateral labyrinthectomy either after ipsilateral topical treatment with gentamicin to the inner ear or without the previous insult.

Methods Twenty-nine adult Mongolian gerbils were randomized into two experimental groups. Group 1 ($n = 17$) received a right ear gentamicin drug-induced lesion by unilateral labyrinthectomy (UL). Group 2 ($n = 12$) only received a right unilateral labyrinthectomy lesion. We measured the horizontal vestibulo-ocular responses in gerbils before and after the lesion. The gerbils received an angular acceleration stimulus and their eye movements were recorded.

Results The gentamicin lesion resulted in a quicker recovery. Experimental groups underwent a similar time course of recovery. Statistical analysis showed no significant difference between the two groups. Both groups displayed adaptation to the lesion by day 21, but long-term compensation did not completely revert to the original pre-lesion state.

Conclusions In a lesion requiring both static and dynamic compensation as in UL, the need for a static compensation may alter pre-existing compensation from a previous dynamic insult and require a new compensation. A previous lesion and adaptation is not preserved for a second lesion and the subject has to re-compensate. Therefore, surgical treatment in Meniere's disease such as UL can be considered without prior gentamicin treatment. Static and dynamic compensations do not appear to be as independent as previous studies have suggested.

Keywords

- ▶ vestibuloocular reflex
- ▶ gerbils
- ▶ vestibular
- ▶ compensation

Introduction

Meniere's disease is a chronic illness that affects a substantial number of patients every year worldwide. The reported preva-

lence rates for Meniere's syndrome range from 3.5 per 100,000 to 513 per 100,000.^{1,2} The most disruptive symptom of Meniere's disease is intermittent/episodic vertigo, which can last from several minutes to a few hours, with positional vertigo in

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between and during attacks.^{1,3} Although there is currently no cure, numerous treatment options are used with the aim of reducing the severity and incidence of these attacks and chronic imbalance. More than 85% of patients with Meniere's disease improve by medical treatments and surgical procedures. In patients to whom vertigo becomes too disabling, ablative procedures, including chemical or surgical labyrinthectomy, are taken into consideration, which result in vestibular deafferentation of the inner ear with a very high rate of vertigo control. Additionally, vestibular nerve section is recommended as an effective treatment for very severe Meniere's cases.^{1,3-5}

Chemical labyrinthectomy is achieved by the use of intratympanic Gentamicin, which is known for its vestibulotoxic effects.^{5,6} This is a procedure in which Gentamicin is injected into the middle ear destroying the vestibular apparatus. Gentamicin, the longest acting aminoglycoside antimicrobial agent, is effective in decreasing the peripheral vestibular function which has been able to control vertigo in patients with Meniere's disease.^{3,7-10} Gentamicin causes damage and loss of calyceal afferents of type I vestibular hair cells in the semicircular canal ampullae and the otolith maculae; therefore, it reduces the sensitivity of the semicircular canals and otolith organs to rotational and transitional movements and, thus, affects dynamic function.^{3,9,11} This procedure is the initial surgical option in patients who are severely affected by the symptoms of Meniere's disease in whom medical management has failed.^{1,3,8,10}

Those patients whose disease progresses farther and who fail chemical labyrinthectomy by Gentamicin are then candidates for labyrinthectomy.^{3,6,8} Labyrinthectomy (surgical removal of the inner ear) is a procedure in which the balance/hearing apparatus of the inner ear is destroyed. Of note, the experimental model most commonly used to examine vestibular compensation is surgical unilateral labyrinthectomy (UL). Labyrinthectomy involves surgical exenteration of the labyrinth neuroepithelium in an attempt to eliminate vertigo and allow the central compensation process to take over.^{4,5} Hearing loss is inherent in this procedure and as such, it is indicated in patients with severe to profound symptoms with intractable vertigo. Additionally, because of its destructive nature, labyrinthectomy is performed unilaterally only.^{1,3}

UL induces a variety of postural and ocular motor deficits that can be divided into static signs (which are present in the absence of head movements) and dynamic signs (which are disorders of the vestibular reflexes during head movements).^{4,5,12} The static lesion causes loss of function of the spontaneous primary afferents to the ipsilateral vestibular nuclei, causing postural deficits. UL also leads to the dynamic loss of vestibulo-ocular (VOR) and vestibulo-spinal responses (VSR) due to the loss of function of the primary afferents and the central connection of the two labyrinths during head movements.¹² These procedures result in the highest rates of control of the vertigo attacks. Excellent vertigo control rates as high as 97% have been reported in the literature after labyrinthectomy. Also, there have been reports of the benefits and safety of surgical labyrinthectomy in elderly patients when carefully selected.^{4,5}

Overall, the evidence for each of these therapeutic modalities is somewhat lacking.^{1,3} One of the important areas is to

have a better understanding of the outcome of those patients undergoing UL as the primary treatment modality alone as opposed to those who initially undergo Gentamicin therapy and fail this treatment, hence requiring a second surgical intervention of UL. The focus of this study is to apply different insults to the vestibular system through Gentamicin treatment followed by UL as opposed to unilateral labyrinthectomy alone and to investigate the process of adaptation to these two insults. This adaptation process is important in recovery from neurological and otological diseases such as Meniere's disease. The main purpose of this study is to explore the differences in patient recovery from Gentamicin plus labyrinthectomy versus labyrinthectomy alone.

Method

Twenty-nine young adult Mongolian gerbils (were randomized into two experimental groups based on the type of lesion they received. In this study, we used adult Mongolian gerbils (*Meriones unguiculatus*) of both sexes weighing between 60–90 g. There were two experimental groups and one control group.

- **Experimental group 1:** Right ipsilateral topical gentamicin treatment followed by unilateral labyrinthectomy ($n = 17$)
- **Experimental group 2:** Only right unilateral labyrinthectomy (no drug treatment) ($n = 12$)
- **Control group:** Two animals underwent bilateral gentamicin treatments. These animals were controls to test the efficacy of the gentamicin drug therapy. This group was expected to have a complete loss of VOR following the bilateral lesion.

All procedures were performed by the same researcher and all techniques were approved by the institutional ACUC and conformed to the *Guide for the Care and Use of Laboratory Animals* (NIH Publication No. 86–23, revised 1996). The animals were euthanized by an overdose of sodium pentothal at the end of the experiments or in the case of a bolt implant failure.

A- Experimental Design

In the first part of this study, the drug gentamicin was used to induce insults to the vestibular system and in the second part of this study, surgical Unilateral Labyrinthectomy (UL) was performed to remove the neuroepithelium of the vestibular labyrinth.

A.1- Head Bolt Implantation: To restrain the head when recording the eye movements, first a head bolt was surgically implanted into the skull of the gerbils. The head could then be positioned in a way that the horizontal semicircular canals are horizontal to the ground and perpendicular to the axis of rotation when the gerbil is in the experimental apparatus. To place the head bolt, the gerbils were anesthetized with isoflurane (1–2%) by a custom mask.

They were then placed in the stereotaxic device. The eyelashes, whiskers, and head were shaved to clear the area for surgery and the subsequent VOR experiments. A dorsal incision was made and the skull bones were exposed. The

periosteum and neck muscle insertions were scraped away. Then, the head bolt was secured to the skull by small stainless steel screws ($0 \times \frac{1}{8}$ FFILL #303SS Self/Tap Screws) and hydrophilic cyanoacrylate adhesive (Prism 4541, Loctite Medical Devices, Henkle, IL, USA) followed by dental acrylic. Several layers of glue and dental acrylic were applied. This glued the skull, screws, and head bolts firmly together. The gerbils were then given a three-day recovery time after surgery before the experiments were initiated.

A.2- Gentamicin Injection: After the recovery period and three control VOR runs (only for the gentamicin group or experimental group 1) the animal was again anesthetized with inhaled 1–2% isoflurane. Then, the right mastoid bulla was opened and a 1 mm fenestration was made in the vestibule to facilitate diffusion of gentamicin into the perilymphatic space. The middle ear and/or mastoid was flooded with the pharmaceutical in solution (27mg/ml gentamicin solution buffered with HCO_3) for 15 minutes. After the surgery, all gentamicin treated animals demonstrated a slight head tilt in the first 24 hours.

A.3- Surgical Unilateral Labyrinthectomy: For all labyrinthectomies (experimental groups 1 and 2) a second surgery was also performed under isoflurane anesthesia. Using a diamond burr, the bulla and the vestibule were exposed and all the pigmented neuroepithelium cells (semicircular canals and the otolith) were removed by fine forceps and otologic hooks. For animals in experimental group 1, the neuroepithelia was preserved at the time of labyrinthectomy for histological analysis, which showed destroyed hair cells. The bulla and the vestibule were then packed with ofloxacin (0.3% Floxin otic, Daiichi Pharmaceuticals, Montvale, NJ, U.S.A.) soaked gelfoam and the soft tissues were closed. All UL animals demonstrated a slight head tilt and spontaneous nystagmus in the first 24 hours.

A.4- Vestibular Compensation: Lesions to the vestibular system create an imbalance to which the brain has to adjust. A reliable method for interpreting the brain's ability to adapt to these changes is to introduce a stimulus and then measure the VOR response after the lesion. Vestibular compensation is the process of recovery from these lesions. In prior studies, static and dynamic mechanisms in VOR compensations have been defined. Static symptoms are defined as postural deficits and spontaneous nystagmus in the absence of head movements, and dynamic symptoms are dynamic vestibular reflexes during the head movement.^{13–15}

A.5- Vestibulo-Ocular reflex (VOR) Measurement: In these experiments, the gerbils received a sinusoidal angular acceleration stimulus and their VOR responses were recorded by infrared Video-Oculography (VOG). The two quantities used in measuring VOR were phase and gain. The gain is the ratio of the amplitude of the response (eye velocity) to the amplitude of the stimulus (head velocity). We averaged the eye and the head velocity over multiple cycles and calculated the gain and phase by comparing the averaged head and eye sine waves. The phase shift is the time difference between the stimulus amplitude and the response amplitude. Horizontal VOR gain in humans is 1; hence, the head and the eye velocity are similar but completely out of phase. In gerbils, the horizontal VOR gain is ~ 0.78 .^{16,17}

B- Experimental Apparatus

The apparatus used for these experiments has been previously described in detail by Kaufman (\rightarrow Fig. 1).¹⁶ It is a platform in a light-tight drum mounted on a yaw motor with the gerbil's head placed at the center of the axis of rotation. The eye position and movements were recorded by infrared VOG and the signals were processed using an ISCAN

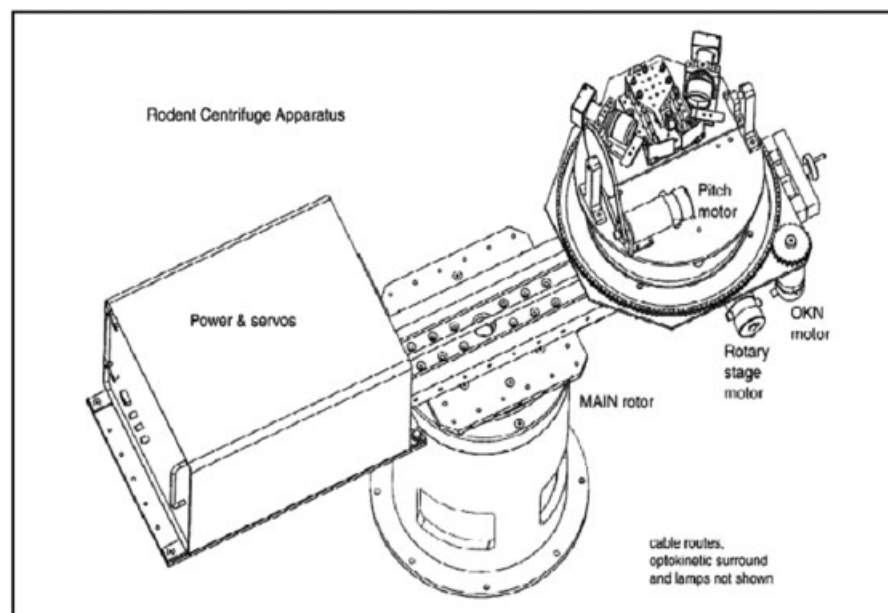


Fig. 1 Centrifuge schematic composed of: the main earth vertical rotor, the eccentric earth vertical rotor, a pitch or roll platform of 30° where the animal and the camera are located, and a horizontal optokinetic drum.

Table 1 Centrifuge testing protocol for horizontal VOR

Test	Motor1	Amp	MaxVel	Frequency (Hz)	Cycles	Lights
hVOR	ECC	23.87	30	0.2	10	No
hVOR	ECC	47.75	60	0.2	10	No
hVOR	ECC	71.62	90	0.2	10	No
hVOR	ECC	9.55	30	0.5	20	No
hVOR	ECC	19.1	60	0.5	20	No
hVOR	ECC	28.65	90	0.5	20	No
hVOR	ECC	4.775	30	1	30	No
hVOR	ECC	9.55	60	1	30	No
hVOR	ECC	14.32	90	1	30	No
hVOR	ECC	9.55	30	0.5	20	Yes
hVOR	ECC	19.1	60	0.5	20	Yes
hVOR	ECC	28.65	90	0.5	20	Yes

Abbreviations: Amp, amplitude; ECC, eccentric; hVOR, horizontal vestibulo-ocular reflex; MaxVel, maximum velocity; VOR, vestibulo-ocular reflex.

system (RK-426). Two 50 mm lenses (1:1.8, V5018) and monochrome cameras (model 20A6981, Videology Imaging Solutions) were located lateral to the gerbil on a turntable and an image of the eye was reflected on an infrared dichroic mirror. This helped the pupils to be observed while preserving the gerbil's field of view. Pupil movements were tracked using a pupil light sink method and two television monitors captured the left and right eye images from the ISCAN cameras. The researcher then recorded VOR in infrared light, with a wavelength of 920 nm, produced by infrared diodes placed in front of the camera lens on the optic axis of the measured eye. Since infrared is not in the gerbil's visible spectrum, the field of vision appears dark to the gerbil. Topical pilocarpine was used, when necessary, to constrict the animal's pupil, facilitating the eye movement recording. Eye rotation was measured using the geometric relationship of eye radius to the two dimensional translation detected by the camera. A small wide-edge camera provided a view of the gerbil, which was displayed on a small television monitor.

C- Experimental Protocols

Horizontal angular acceleration stimulus of 30, 60, and 90°/sec at frequencies of 0.2, 0.5, and 1 Hz were applied to the gerbils while recording their horizontal VOR (hVOR) both before and after the lesions at specific times. Twelve sinusoidal yaw patterns at these 3 frequencies and 3 velocities were recorded with and without lights (→Table 1). Custom software, Data Store and Motion Control, written in LabView programming language (National Instruments, Austin, TX) were used to record the data and each session took ~20 minutes.

For the gentamicin group, VOR testing was performed pre-lesion (3 controls) and at day 1, 3, 7, 14, and 21. For all the UL animals, VOR testing was done pre-lesion, post-lesion after 3 hour, 6 hour, 9 hour, 12 hour, 24 hour, day 3, day 7, day 14, and day 21 (→Table 2).

D- Data Collection and Analysis

We used three custom software programs (Data View, View Events, Unit Rates) also written in Laboratory View to convert eye position data acquired by VOG to gain and phase shift. Using these programs, we averaged the eye velocity and stimulus velocity across 10–30 cycles depending on the frequency used. Next, the stimulus and response best-fit curve (sine waves) for each stimulus velocity at each of the mentioned frequencies was obtained. We then used this data to calculate the gain and phase shift values for each frequency and velocity of the left eye left head movements (L eye L head), left eye right head movements (L eye R head), right eye left head movements (R eye L head), and right eye right head movements (R eye R head). During the analysis, specific attention was given to excise data with significant background noise or poor eye signal. The first cycles of each set of data were also discarded. Comparisons across groups were made using T-Test analysis with the Statistical Package for Social Sciences (SPSS) version 21.

Results

Control Experiments

Three pre-lesion Horizontal VOR recordings on three separate days were done for each animal. The gain values were consistently above 0.5 and the animals responded better to higher frequencies and velocities. The average raw gain and phase shift values for the left and right eyes are outlined in →Tables 3 and 4 ($n = 29$). All data was normalized using these averaged pre-lesion values for all animals. This was done to account for any asymmetries between the left and right sides or in data collection. Bilateral gentamicin lesion in two gerbils indicated no VOR response by day 3 (data not shown). This demonstrated the effectiveness of this drug, hence confirming its ability to eliminate the dynamic

Table 2 VOR schedule

Groups	pre-lesion	pre-lesion	pre-lesion	3 hours	6 hours	9 hours	12 hours	Day 1	Day 3	Day 7	Day 14	Day 21
Experimental Group 1: <i>Gentamicin (1st Lesion)</i>	VOR control 1	VOR control 2	VOR control 3	–	–	–	–	VOR	VOR	VOR	VOR	VOR
Experimental Group 1: <i>UL (2nd Lesion)</i>	VOR control 1	VOR control 2	VOR control 3	VOR	VOR	VOR	VOR	VOR	VOR	VOR	VOR	VOR
Experimental Group 2: <i>UL alone</i>	VOR control 1	VOR control 2	VOR control 3	VOR	VOR	VOR	VOR	VOR	VOR	VOR	VOR	VOR

Abbreviations: UL, unilateral labyrinthectomy; VOR, vestibulo-ocular reflex.

response. The VOR response did not return to normal for these animals, but slight improvements were observed by day 21.

Unilateral Gentamicin Lesion

Seventeen gerbils underwent right middle ear gentamicin-induced dynamic lesions. The VOR time points testing included day 1, 3, 7, 14, and 21. Depending on the signal quality, data from at least 10 animals was obtained at each specific time point for all frequencies and velocities, with most reaching the maximum n . The bias velocity (a measurement of static dysfunction) averaged for all frequencies and velocities are depicted in ► **Fig. 2**. The animals that underwent gentamicin lesion did not show any bias velocity. The ones with UL post gentamicin lesion showed some bias velocity in day 1, but the group that experienced the UL-only lesion had the most bias velocity, which also subsided in the first day.

The normalized gain versus time graph of the gerbils with gentamicin lesion for 0.5 Hz frequency at 60°/sec is depicted in ► **Fig. 3**. The gains decreased to the lowest value in the first 24 hours, at which point they started to increase as the animals began to compensate for the insult. As shown in the Figure, the compensation for the head movements toward the contralateral side of the lesion (left) was slightly more than the ipsilateral side during the first 7 days, but the two even out by day 21. The gains reach ~79–86% of the original gains with half cycles ranging 80–82% for the left eye and 79–86% for the right eye. (Note: The 0.5 Hz frequency at 60°/sec was chosen here due to its signal clarity and the best possible stimulus response best-fit curves in data analysis.)

Unilateral Labyrinthectomy

Twelve gerbils underwent right hemi-labyrinthectomy lesions. The VOR time points for the UL experiments were 3 hours, 6 hours, 9 hours, 12 hours, day 1, 3, 7, 14, and 21. Again, depending on the signal quality, we obtained data from at least 5 animals at each specific time point for all frequencies and velocities, with most reaching the maximum n . As depicted in ► **Fig. 2**, the UL-only animals showed a bias velocity on the first day, unlike the gentamicin animals, but this velocity started to decline after the first day post lesion. The normalized gain versus time graph of the gerbils with UL lesion for 0.5 Hz frequency at 60°/sec is shown in ► **Fig. 4**. The gains decreased at 3 hours and 6 hours, reaching their lowest value at 24 hours, at which point they began to increase again. As previously described and depicted in the Figure, the compensation for the head movements toward the contralateral side of the lesion (left) was slightly more than the ipsilateral side (right) during the first 7 days. The compensation is not as evident as that seen in the gentamicin animals, as the gains reach ~31–59% of the original gains, with half cycles ranging 31–56% for the left eye and 41–59% for the right eye.

Unilateral Labyrinthectomy Post-Gentamicin Lesion

After recovery from the gentamicin lesion (day 21), twelve gerbils underwent a second lesion (UL). This was done to indicate whether or not the prior compensation was beneficial for the second lesion compensation. The animals with the

Table 3 Normal left eye VOR responses pre-lesion, $n = 29$ (data given as mean \pm SD)

Frequency (Hz)	Vel (deg)	Phase	Gain Left Eye	Gain Left Eye	Gain Left Eye
			Full Cycle	L Head	R Head
0.2	30	0.89 \pm 4.5	0.67 \pm 0.20	0.76 \pm 0.15	0.65 \pm 0.30
0.2	60	-1.4 \pm 3.1	0.68 \pm 0.24	0.76 \pm 0.2	0.61 \pm 0.27
0.2	90	-3.1 \pm 3.5	0.64 \pm 0.22	0.73 \pm 0.21	0.63 \pm 0.3
0.5	30	-8.4 \pm 2.9	0.76 \pm 0.22	0.83 \pm 0.27	0.7 \pm 0.26
0.5	60	-11.3 \pm 4.2	0.76 \pm 0.24	0.83 \pm 0.22	0.7 \pm 0.28
0.5	90	-12.7 \pm 7.3	0.70 \pm 0.2	0.68 \pm 0.19	0.66 \pm 0.25
1	30	-23.4 \pm 6.4	0.79 \pm 0.26	0.76 \pm 0.28	0.8 \pm 0.28
1	60	-21.6 \pm 5.0	0.72 \pm 0.29	0.71 \pm 0.28	0.73 \pm 0.33
1	90	-21.4 \pm 4.7	0.74 \pm 0.24	0.71 \pm 0.3	0.75 \pm 0.22
0.5 light-on	30	-14.0 \pm 15.5	0.92 \pm 0.19	0.94 \pm 0.25	0.79 \pm 0.41
0.5 light-on	60	-11.6 \pm 3.5	0.92 \pm 0.21	0.93 \pm 0.25	0.90 \pm 0.19
0.5 light-on	90	-11.6 \pm 3.9	0.86 \pm 0.24	0.9 \pm 0.25	0.83 \pm 0.25

Abbreviations: L Head, left head movement; R Head, right head movement; Vel (deg), velocity degree; VOR, vestibulo-ocular reflex.

Table 4 Normal right eye VOR responses pre-lesion, $n = 29$ (data given as mean \pm SD)

Frequency (Hz)	Vel (deg)	Phase	Gain Right Eye	Gain Right Eye	Gain Right Eye
			Full Cycle	L Head	R Head
0.2	30	1.5 \pm 4.1	0.60 \pm 0.19	0.53 \pm 0.25	0.67 \pm 0.16
0.2	60	-0.99 \pm 3.3	0.61 \pm 0.21	0.52 \pm 0.27	0.70 \pm 0.17
0.2	90	-5.0 \pm 5.2	0.59 \pm 0.20	0.53 \pm 0.21	0.66 \pm 0.18
0.5	30	-7.1 \pm 5.0	0.64 \pm 0.16	0.59 \pm 0.19	0.68 \pm 0.16
0.5	60	-9.2 \pm 4.2	0.63 \pm 0.18	0.55 \pm 0.20	0.71 \pm 0.18
0.5	90	-14.6 \pm 5.9	0.56 \pm 0.20	0.54 \pm 0.23	0.59 \pm 0.19
1	30	-19.5 \pm 7.2	0.59 \pm 0.20	0.62 \pm 0.21	0.60 \pm 0.23
1	60	-22.1 \pm 7.4	0.65 \pm 0.18	0.64 \pm 0.19	0.68 \pm 0.22
1	90	-23.6 \pm 4.7	0.68 \pm 0.17	0.69 \pm 0.18	0.64 \pm 0.24
0.5 light-on	30	-12.3 \pm 3.1	0.89 \pm 0.19	0.84 \pm 0.18	0.91 \pm 0.26
0.5 light-on	60	-12.0 \pm 2.0	0.88 \pm 0.15	0.86 \pm 0.16	0.88 \pm 0.18
0.5 light-on	90	-17.7 \pm 16.3	0.83 \pm 0.21	0.81 \pm 0.28	0.86 \pm 0.20

Abbreviations: L Head, left head movement; R Head, right head movement; Vel (deg), velocity degree; VOR, vestibulo-ocular reflex.

UL post-gentamicin lesion showed some bias velocity on day 1, as previously described (\blacktriangleright Fig. 2). \blacktriangleright Fig. 5 shows the Gentamicin, UL alone, Gent + UL animals at each half cycle for 0.5 Hz at 60°/sec velocity. The gentamicin compensation and gains were significantly above the gains for UL and Gent + UL groups. Data analysis showed no significant difference between the UL and Gent + UL groups at each time point ($p \geq 0.05$).

Discussion

Meniere's disease (endolymphatic hydrops) is a disorder of the inner ear that results in various degrees of damage to the

vestibular end organ, causing asymmetric input to the brain. This will disrupt the resting tone of the vestibular system and will manifest itself as vertigo, dizziness, and disequilibrium.^{2,3,18} Normally, the brain tends to compensate for this asymmetry, however, the vestibular end organ which is subject to recurrent insults in this disease will make the central compensation difficult to achieve.^{2,3} Several medical and surgical remedies have been offered to patients with Meniere's disease over the past 150 years. The plethora of medical and surgical therapies signifies that no one effective treatment is available for these patients; however, in about 10–20% of patients, surgical treatment is necessary.^{2,5} Surgical procedures aim at controlling the vertigo spells so

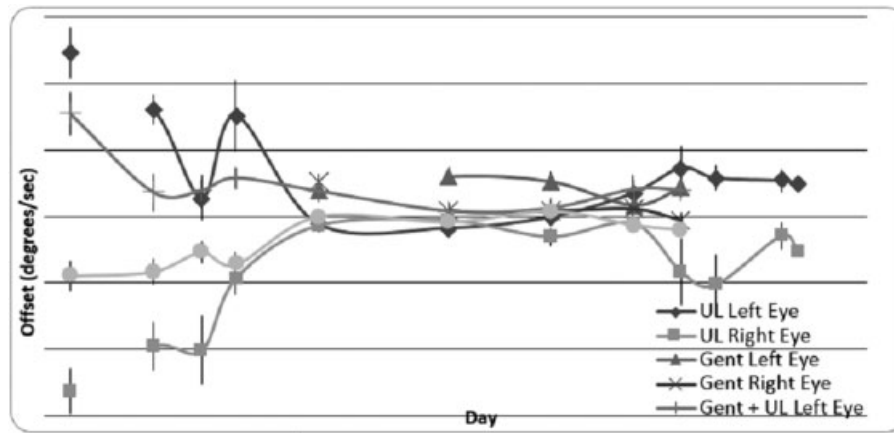


Fig. 2 Bias velocity averaged for all frequencies and velocities (x-axis: logarithmic scale). Abbreviation: UL, unilateral labyrinthectomy.

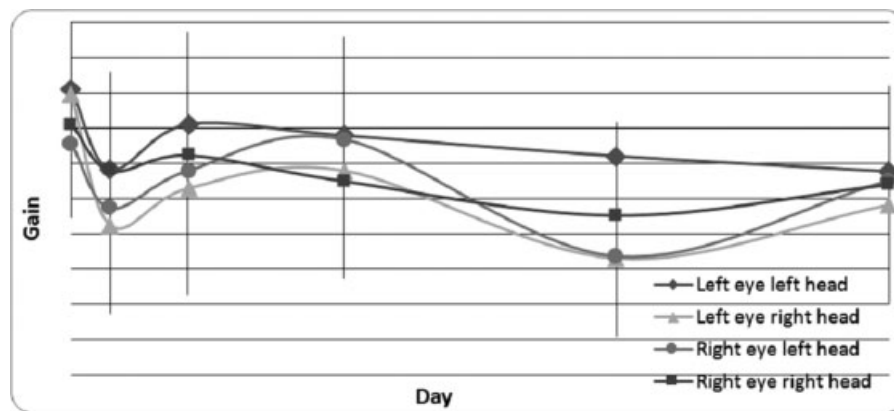


Fig. 3 Gentamicin lesion at 0.5 Hz and 60° /sec depicting gain values over time.

the central compensation can take place and consist of labyrinthectomy either chemical or surgical.⁵

In a unilateral labyrinthectomy or a drug-induced lesion, the input from the semicircular canals and otolith to the vestibular nuclei is lost or changed and the vestibular system has to compensate.^{12,15,18} As previously described, unilateral labyrinthectomy is a static and dynamic lesion in which postural deficits, head tilting, spontaneous nystagmus in the absence of head movements, and spinning around the vertical axis toward the side of the lesion are observed. On the other hand, a gentamicin drug-induced lesion is a dynamic lesion in which vestibular reflexes during the head movement (translational VOR and rotational VOR) are affected.^{7,12,19}

As a common practice, the initial surgical option in patients with severe Meniere's symptoms who didn't respond to the medical treatment is chemical labyrinthectomy, such as gentamicin drug-induced lesion^{1,3,8,10} and if the chemical labyrinthectomy couldn't stop the progress of the disease, then surgical labyrinthectomy is considered. Furthermore, vestibular neurectomy (VN) is one of the most widely used treatments for very severe Meniere's disease.^{3,8} Since the effectiveness and recovery of these two types of labyrinthectomy (chemical and surgical), separately or combined, is not well understood,^{1,3} we undertook this study to determine

whether the preservation of resting discharge, which reduces the static imbalance after a labyrinthectomy, allows for a quicker dynamic compensation and whether dynamic recovery after the gentamicin lesion is preserved with subsequent labyrinthectomy, which causes loss of the remaining static function.

Relationship of Head Movement with the Side of Lesion

Mainly, the rotational VOR in different animals has been investigated in previous studies.^{20–24} These studies have shown that VOR gains are considerably decreased with head rotations toward the lesion side compared with the contralateral side, and this is more pronounced at higher velocities.^{12,25} This finding was also substantiated in the present study, with higher gains and better compensations with head movements toward the contralateral side of the lesion.

In previous studies using our VOR measurement technique, a rotational VOR asymmetry in normal gerbils has been noted.^{12,16,17} To account for this asymmetry and alleviate poor signal data, all data were normalized. Also, we used both full cycle and half cycle analysis in this study, giving it an advantage for comparison of the left and right side head rotations. As mentioned previously, we also noted the VOR

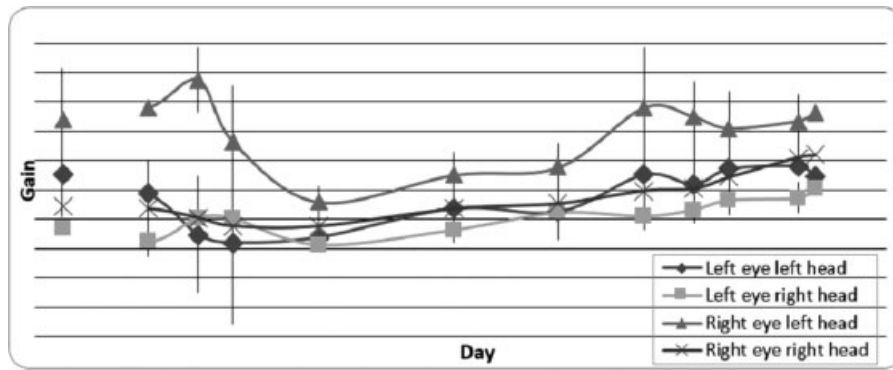


Fig. 4 UL lesion at 0.5 Hz and 60° /sec depicting gain values over time (x-axis: logarithmic scale).

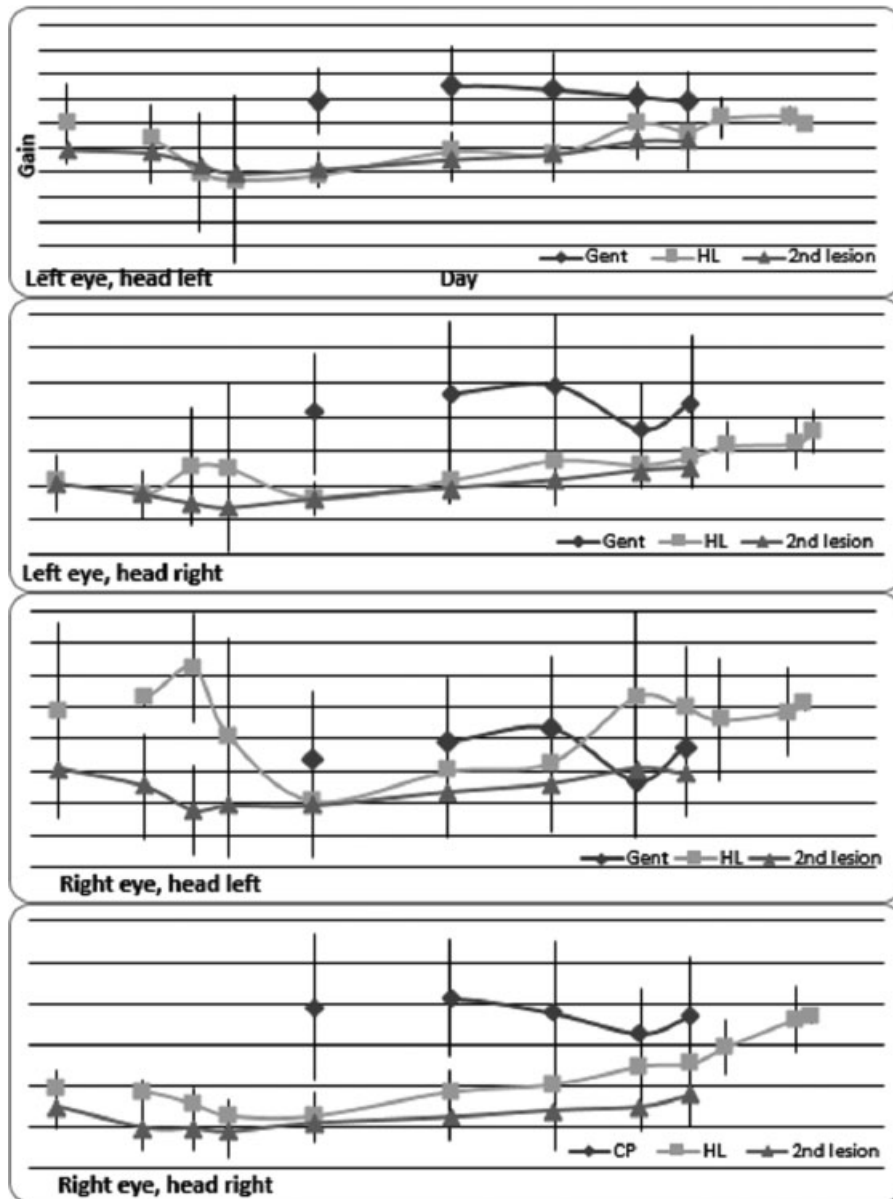


Fig. 5 VOR gain vs. time for gent, UL, and gent + UL groups at 0.5 Hz and 60° /sec (x-axis: logarithmic scale).

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gain asymmetry after the lesion with the gains for rotation toward the lesion side being lower (→Figs. 3 and 5).

Static versus Dynamic Compensation

With a gentamicin lesion, the static function is unaffected; hence, the animals did not show any bias velocity. But with UL lesions, in which both the static and dynamic function are compromised, the bias velocity was observed on day 1, after which it subsided due to compensations.^{6,12,16,26,27} Previous studies with canal plugging of the semicircular canals (a dynamic lesion affecting the rotational VOR but not the translational VOR) had shown that the bias velocity is greater on day 1 in animals with UL post unilateral canal plugging (UCP) versus those undergoing UL alone. In this study, however, the bias velocity was actually higher for the gerbils that underwent UL alone versus those with UL post gentamicin.^{6,9,12,27–29} This finding indicates that the dynamic compensation after the initial lesion might have facilitated the static compensation needed in the second lesion, making the static dysfunction or the bias less than expected. This finding implies that the static and dynamic lesions are not as independent as previously described. This result could also be due to the nature of the dynamic insult received by the gerbils. The UCP is a dynamic lesion that only affects the rotational VOR and not the translational VOR since it has an exclusive effect on the canals, but gentamicin destroys the hair cells in the semicircular canal ampullae and the otolith maculae, affecting both translational and rotational VOR. Since UCP does not affect translational VOR, but UL affects both the translational and rotational VOR, a previous insult affecting both the translational and rotational VOR, such as gentamicin, might facilitate the second lesion including both the translation and rotation.

Gentamycin Effectiveness

The gerbils compensated more quickly from the gentamicin lesion as opposed to the UL lesion. This is again due to the fact that gentamicin does not affect the static function; hence, the lesion is not a complete lesion.^{3,4,6,9,12,16,29} To test the effectiveness of this drug, two control animals with bilateral gentamicin were studied; we observed no VORs after the third day post lesion in both, indicating the drug therapy was effective and our interpretation is reasonable.

Rotational vs Translational VOR

In a previous study by Newlands et al comparing UCP and UL, UCP compensation was more complete than UL. In that study, the authors specified that since UCP only affects the rotational VOR and UL affects both rotational and translational VOR, the early compensation of the UCP could be due to the fact that the rotational VOR is somehow connected to translational VOR.¹² If adding the otolith (linear) dynamic dysfunction prior to subsequent UL does not assist compensation to the UL as prior UCP seemed to do, this study implies that it is the otolith function that: 1) could represent a vestibular framework anchor (often attributed to the vector of gravity), and 2) complicates the recovery process and, therefore, supports the idea of entwinement between

the rotational and translational systems. Translational VOR is not as well understood as rotational VOR, and due to its organization and complexity, it is not well studied in laterally eyed animals like gerbils.^{12,30,31}

Gentamycin Followed by UL vs UL Alone

A major investigation in this study was a comparison between UL alone versus a post gentamicin UL lesion. The gerbils were given a period of 21 days compensation to the original gentamicin lesion. After this period, they were insulted with a second lesion which was a UL. This was done to understand whether this period of compensation to the eliminated dynamic function could have an advantage in the second lesion. We believed that by having the compensatory inhibitory effect from the contralateral side on the ipsilateral side of the lesion after the first insult, the loss of static excitation from the ipsilateral side after the second lesion would be complemented. However, the gain values for the gerbils with post gentamicin UL lesions were similar to those with UL-only lesions and we observed no statistically significant differences between the two groups. This can be explained again by the fact that the dynamic and static functions are not as independent as previously perceived. A dynamic compensation is not a complete compensation and not preserved for a lesion eliminating both static and dynamic functions. Even though there are some inhibitory effects from the contralateral side after the first lesion, perhaps this inhibition is not enough to compensate for the loss from the ipsilateral side in the second lesion.^{6,9,12,15,16,29}

Conclusions

The current study evaluates whether the preservation of resting discharge in a gentamicin lesion allows for a quicker dynamic compensation in a UL and if dynamic recovery after the gentamicin lesion is preserved with subsequent UL. The hypothesis tested was that pre-treatment with gentamicin will speed up dynamic compensation as measured by VOR. Based on the data and analysis, this hypothesis cannot be confirmed. In a lesion requiring both static and dynamic compensation as in UL, the need for a static compensation may alter pre-existing compensation from a previous dynamic insult and require a new compensation. Consequently, a previous lesion and adaptation is not preserved for a second lesion and the subject has to re-compensate as if the first lesion had not occurred. Static and dynamic compensations are not as independent as perceived and linear dynamic VOR complicates the recovery process, supporting a link between the rotational and translational dynamic systems.

This study's findings represent no difference in patient recovery from gentamicin plus labyrinthectomy versus labyrinthectomy alone treatment for Meniere's disease. This finding represents more freedom in treatment options of Meniere's if the intratympanic chemical injection fails. Hence, if a patient with Meniere's disease fails conservative medical treatments, surgical treatment such as UL can be considered without doing a prior gentamicin treatment. The vestibular system is a complex system affected by diseases such as

Meniere's and neurovestibular compensation is a key in treating such diseases, but major challenges still remain in understanding how the compensation process works.

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References

- Sajjadi H, Paparella MM. Meniere's disease. *Lancet* 2008; 372(9636):406–414 10.1016/s0140-6736(08)61161-7
- Tassinari M, Mandrioli D, Gaggioli N, Roberti di Sarsina P. Ménière's disease treatment: a patient-centered systematic review. *Audiol Neurootol* 2015;20(3):153–165 10.1159/000375393
- Sharon JD, Trevino C, Schubert MC, Carey JP. Treatment of Ménière's Disease. *Curr Treat Options Neurol* 2015;17(4):341 10.1007/s11940-015-0341-x
- Pullens B, Verschuur HP, van Benthem PP. Surgery for Ménière's disease. *Cochrane Database Syst Rev* 2013;2:CD005395 10.1002/14651858.CD005395.pub3
- Ghossaini SN, Wazen JJ. An update on the surgical treatment of Ménière's diseases. *J Am Acad Audiol* 2006;17(1):38–44
- De Beer L, Stokroos R, Kingma H. Intratympanic gentamicin therapy for intractable Ménière's disease. *Acta Otolaryngol* 2007;127(6):605–612 10.1080/00016480600951475
- Lyford-Pike S, Vogelheim C, Chu E, Della Santina CC, Carey JP. Gentamicin is primarily localized in vestibular type I hair cells after intratympanic administration. *J Assoc Res Otolaryngol* 2007; 8(4):497–508 10.1007/s10162-007-0093-8
- Harner SGDC, Driscoll CL, Facer GW, Beatty CW, McDonald TJ. Long-term follow-up of transtympanic gentamicin for Ménière's syndrome. *Otol Neurotol* 2001;22(2):210–214
- Lange G, Maurer J, Mann W. Long-term results after interval therapy with intratympanic gentamicin for Ménière's disease. *Laryngoscope* 2004;114(1):102–105 10.1097/00005537-200401000-00018
- Perez N, Martín E, García-Tapia R. Intratympanic gentamicin for intractable Meniere's disease. *Laryngoscope* 2003;113(3): 456–464 10.1097/00005537-200303000-00013
- Hirvonen TPML, Minor LB, Hullar TE, Carey JP. Effects of intratympanic gentamicin on vestibular afferents and hair cells in the chinchilla. *J Neurophysiol* 2005;93(2):643–655
- Newlands SDDS, Dara S, Kaufman GD. Relationship of static and dynamic mechanisms in vestibuloocular reflex compensation. *Laryngoscope* 2005;115(2):191–204
- Shinder ME, Perachio AA, Kaufman GD. VOR and Fos response during acute vestibular compensation in the Mongolian gerbil in darkness and in light. *Brain Res* 2005;1038(2):183–197 10.1016/j.brainres.2005.01.043
- Shinder ME, Perachio AA, Kaufman GD. Fos responses to short-term adaptation of the horizontal vestibuloocular reflex before and after vestibular compensation in the Mongolian gerbil. *Brain Res* 2005;1050(1–2):79–93 10.1016/j.brainres.2005.05.029
- Mantokoudis G, Schubert MC, Tehrani AS, Wong AL, Agrawal Y. Early adaptation and compensation of clinical vestibular responses after unilateral vestibular deafferentation surgery. *Otol Neurotol* 2014;35(1):148–154 10.1097/MAO.0b013e3182956196
- Kaufman GD. Video-oculography in the gerbil. *Brain Res* 2002; 958(2):472–487
- Watanabe S, Hattori K, Koizuka I. Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. *Auris Nasus Larynx* 2003;30(Suppl):S29–S34
- van Sonsbeek S, Pullens B, van Benthem PP. Positive pressure therapy for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2015;3:CD008419 10.1002/14651858.CD008419.pub2
- Dara S. Neurovestibular compensation in gerbils following unilateral three canal plug and unilateral labyrinthectomy. *International Space University* 2003
- Ushio M, Minor LB, Della Santina CC, Lasker DM. Unidirectional rotations produce asymmetric changes in horizontal VOR gain before and after unilateral labyrinthectomy in macaques. *Exp Brain Res* 2011;210(3–4):651–660 10.1007/s00221-011-2622-2
- Beraneck M, McKee JL, Aleisa M, Cullen KE. Asymmetric recovery in cerebellar-deficient mice following unilateral labyrinthectomy. *J Neurophysiol* 2008;100(2):945–958 10.1152/jn.90319.2008
- Sadeghi SG, Minor LB, Cullen KE. Dynamics of the horizontal vestibuloocular reflex after unilateral labyrinthectomy: response to high frequency, high acceleration, and high velocity rotations. *Exp Brain Res* 2006;175(3):471–484 10.1007/s00221-006-0567-7
- Lewis RF, Haburcakova C, Gong W, Makary C, Merfeld DM. Vestibuloocular reflex adaptation investigated with chronic motion-modulated electrical stimulation of semicircular canal afferents. *J Neurophysiol* 2010;103(2):1066–1079 10.1152/jn.00241.2009
- Lasker DM, Hullar TE, Minor LB. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. III. Responses after labyrinthectomy. *J Neurophysiol* 2000;83(5): 2482–2496
- Mao Y, Chen P, Li L, Huang D. Virtual reality training improves balance function. *Neural Regen Res* 2014;9(17):1628–1634
- Dieringer N. Activity-related postlesional vestibular reorganization. *Ann N Y Acad Sci* 2003;1004:50–60
- Koizuka I. Adaptive plasticity in the otolith-ocular reflex. *Auris Nasus Larynx* 2003;30(Suppl):S3–S6
- Harrod CG, Baker JF. The vestibulo ocular reflex (VOR) in otoconia deficient head tilt (het) mutant mice versus wild type C57BL/6 mice. *Brain Res* 2003;972(1–2):75–83
- Wu IC, Minor LB. Long-term hearing outcome in patients receiving intratympanic gentamicin for Ménière's disease. *Laryngoscope* 2003;113(5):815–820 10.1097/00005537-200305000-00009
- Shimizu N, Wood S, Kushihiro K, Yanai S, Perachio A, Makishima T. Dynamic characteristics of otolith ocular response during counter rotation about dual yaw axes in mice. *Neuroscience* 2015; 285:204–214 10.1016/j.neuroscience.2014.11.022
- Yoder RM, Taube JS. The vestibular contribution to the head direction signal and navigation. *Front Integr Neurosci* 2014;8:32 10.3389/fnint.2014.00032