

The effect of direct application of dexamethasone on the round window membrane in patients with sudden sensorineural hearing loss

Fatthi A. Abdel Baki^a, Ahmed A. Omran^a, Samir I. Asal^b, Khaled M. Hassan^a

^aDepartments of Otorhinolaryngology,

^bDepartment of Audiovestibular unit, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Correspondence to Khaled Mustafa Hasan Elsayed, Masters, Specialist at Departments of Otorhinolaryngology, Faculty of Medicine, University of Alexandria, Alexandria, 21131, Egypt; Tel: 002035557097; e-mail: Khaledsalmine035@gmail.com

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Objective

The aim of this study was to test the effect of direct application of dexamethasone on the round window (RW) after its adequate exposure following a transcanal approach in patients with sudden sensorineural hearing loss (SSNHL).

Study design

This investigation was designed to be a prospective cohort study.

Patients and methods

This study included eighteen adult patients with SSNHL who attended our outpatient clinic at Alexandria Main University Hospital between 1 July 2015 and 1 July 2016. Under general anesthesia the small tympanomeatal flap was elevated to visualize the RW. If it was fully exposed, dexamethasone (4 mg/ml) was applied directly over a piece of gel foam; if not fully exposed the overhang was removed first and then dexamethasone was applied. After 2 weeks, a repeat audiogram was taken in all patients in order to evaluate the efficacy of the treatment on their hearing ability.

Results

Post-treatment assessment revealed 50% of patients with variable levels of improvement, whereas 50% did not respond to the given treatment. Of the patients showing improvement, 16.7% had normal hearing levels restored. Thus, direct application of dexamethasone on the RW membrane after its adequate exposure may reverse the hearing deficits in a few patients with SSNHL.

Conclusion

There is a definitive improvement in hearing in patients with SSNHL on direct application of dexamethasone on the RW membrane after its adequate exposure in patients.

Keywords:

dexamethasone, round window, sudden hearing loss

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Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as a unilateral or bilateral sensorineural hearing loss of more than 30 dB affecting at least three consecutive frequencies and occurring over a maximum period of 72 h. The disorder has an estimated incidence of 5–20 persons per 100 000 [1].

In most patients with SSNHL, no specific cause is known; therefore, the disease is considered idiopathic. The causes of SSNHL are popularly theorized to be viral infection, inflammatory or immune-mediated reaction, vascular insufficiency, and intralabyrinthine membrane rupture. It was found that 10.2% of acoustic neuromas initially manifest with SSNHL. Mid-frequency and high-frequency hearing losses are more commonly associated with acoustic neuroma than is low-frequency loss [2,3].

Patients with SSNHL who do not undertake any treatment have recovery rates of 31–65%, whereas in

treated patients the recovery rate ranges from 35 to 89% [4].

According to Kim's criteria, the degrees of recovery are defined as follows: complete recovery, final hearing less than 25 dB and speech discrimination score (SDS) more than 90%; good recovery, final hearing 26–40 dB and SDS 75–90%; fair recovery, final hearing 41–55 dB and SDS 50–75%; slight recovery, final hearing 56–70 dB and SDS 25–50%; no recovery, final hearing more than 71 dB and/or SDS less than 25% [5].

Timing of therapy is an important factor in the prognosis of hearing recovery in SSNHL patients. Previous studies on SSNHL have found that

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patients seen within 1 month from onset of hearing loss experience a greater degree of improvement compared with patients seen later. Using more than one agent in the treatment regimen is common practice, and the choice of treatment regimens varies among clinicians [6,7].

Numerous drugs have been tested to improve the outcome in patients suffering from SSNHL, such as glucocorticoids that proved to have effect on the course of SSNHL by decreasing inflammation resulting from viral infection or from alteration of the immune response in the inner ear [8].

Intratympanic steroids can be administered at a high concentration into the inner ear, with no systemic side effects. Actual measurement and modeling of drug entry and dispersion suggests a concentration gradient exists from the base to the apex but sufficient amounts can reach the apical regions. Factors controlling this apical movement include the molecular weight, charge, concentration, amount injected, round window (RW) characteristics that impact the amount of drug entering, length of the cochlea, any intensive perilymph flow patterns, and speed of absorption into tissues at the base [9,10].

Different types of RW can be distinguished: it may be very narrow, lengthened, or V-shaped; a pseudomembrane may be partially or completely ossified in the RWs entrance. Structures outside the niche and in the surrounding may show exostosis at its entrance [11].

The round window membrane (RWM) is the principal entry site for intratympanic drugs into the ear scala tympani. It is a semipermeable membrane that is lined on the middle ear with cuboidal epithelial cells joined by tight junctions and lined on the inner ear with mesothelial cells that are often intermittent. Between these lining layers are loosely organized collagen and elastic fibers, fibrocytes and fibroblasts, and occasionally blood vessels and nerve fibers. Although tight junctions join epithelial cells on the middle ear, molecules as large as 1 μm can pass through this layer into the inner ear either intercellularly or transcellularly via pinocytosis. Thus, the RWM provides little impediment to the movement of most drugs or other molecules into the inner ear [12].

Considering this, in order to broaden the studies in this line of research a prospective study was initiated in patients with SSNHL with the aim to evaluate whether the hearing loss can be improved by direct application

of dexamethasone on RWM after its adequate exposure.

Patients and methods

This study included eighteen patients of both sexes who had SSNHL and attended our outpatient clinic from 1 July 2015 to 1 July 2016 at Alexandria Main University Hospital. Informed consent was taken from patients after approval of committee. All drugs used in the research are approved by the Egyptian Ministry of Health.

- (1) Inclusion criteria: The following patients were eligible for inclusion:
 - (a) Adult patients fulfilling the criteria for SSNHL (loss of >30 db at three consecutive frequencies in pure-tone audiometry) within 3 days and attending our outpatient clinic within 1 month of onset with free MRI cerebellopontine angle.
 - (b) Patients:
 - (i) With contraindications to systemic corticosteroids (diabetes mellitus, hypertension, osteoporosis).
 - (ii) Who received systemic steroids before, with no improvement.
 - (iii) Who refused to take systemic steroids.
- (2) Exclusion criteria: The following patients were not eligible for inclusion:
 - (a) Patients who had otitis media with or without tympanic membrane perforation or cholesteatoma.
 - (b) Patients who suffered SSNHL more than 1 month earlier.

Methods

All patients were subjected to the following:

Preprocedural assessment

In the Otolaryngology Department each patient was subjected to full history-taking and to an otoscopic examination to verify the ear condition, which had to be free of any other pathology except the concurrent sensorineural hearing impairment.

In the Audiology Unit confirmation of the hearing impairment was verified by pure tone average (PTA) and tympanometry.

The PTA determines the mean threshold levels in air conduction and bone conduction along the frequency range of 250–8000 Hz. PTA refers to the average of hearing threshold levels at a set of specified frequencies: typically, 500, 1000, 2000, and 4000 Hz. The hearing threshold level for each patient was calculated as the

mean thresholds of 500, 1000, 2000, and 4000 Hz frequencies in air conduction curve.

According to Clark, the degree of hearing loss was classified as follows:

- (1) Minimal (15–25 dB).
- (2) Mild (26–40 dB).
- (3) Moderate (41–55 dB).
- (4) Moderately severe (56–70 dB).
- (5) Severe (71–90 dB).
- (6) Profound (>90 dB).

Procedure

Under general anesthesia the small tympanomeatal flap was elevated to visualize the RW. If it was fully exposed dexamethasone (4 mg/ml) was placed directly over a piece of gel foam; if not fully exposed the overhang was removed first and then dexamethasone was applied. A grommet tube was inserted to facilitate repeated injections on days 3, 7, and 10 from the start of the procedure.

Postprocedural assessment

PTA and speech audiometry were performed after 2 weeks.

Audiological assessment was carried out first (preliminary) when the assigned patient was admitted into the study, and then after 2 weeks.

Both PTA and tympanometry were performed each time in the same sound-proof booth, by the same examiner, and with the same tools, to minimize interpersonal evaluation errors. While recording the PTA, or the tympanometry, the patient might require retesting more than once for confirmation (test–retest reliability).

Data were fed into a computer and analyzed using IBM SPSS software, version 20.0. Qualitative data were described using number and percentage. Significance of the obtained results was judged at the 5% level. The following tests were used: the χ^2 -test for categorical variables, to compare between different groups; and the Fisher exact or Monte Carlo correction (correction for χ^2 when >20% of the cells have expected count <5).

Results

Out of the 18 patients in this study, 11 (61.1%) were male and seven (38.9%) were female. Among the 11 male patients five (71.4%) recovered and six (54.5%) did not, whereas out of the seven female patients two (28.6%) recovered and five (45.5%) did not.

The age group of the patients ranged from 19.5 to 56.5 years, with a mean±SD of 44.17±10.61 years. Hearing recovery was experienced by patients less than 40 (range: 19.5–40) years, whereas patients more than 40 (range: 40–56.5) years failed to recover their normal hearing.

All five patients with no risk factors (27.8%) recovered; of the four patients who were diabetic (22.2%) one recovered and three did not; of the eight patients who were hyperlipidemic (44.4%), two recovered and six did not; the only hypertensive patient also recovered.

Regarding the associated symptoms with hearing loss (HL), four patients had no associated symptoms (22.2%) and all recovered; the four patients who had tinnitus (22.2%) also recovered; of the 10 (55.6%) patients with vertigo, only one recovered and nine did not (Table 1).

It was found that the sex of the patient had no statistically significant effect on hearing recovery, whereas the effect of age, risk factors, and associated symptoms on hearing recovery was statistically significant.

The two patients who attended the hospital during the first week of HL (22.2%) recovered; the four patients who came within 1–2 weeks (44.4%) also recovered; of the four patients who came within 2–3 weeks, one (11.2%) recovered and three did not; and of the eight patients who came within 3–4 weeks, two recovered and six did not. It was found that the duration of disease (from its onset to initiation of treatment) did not have a statistically significant effect on hearing recovery (Table 2).

Table 1 Distribution of total cases according to sex, age, risk factors, and associated symptoms (N=18)

	n (%)
Sex	
Male	11 (61.1)
Female	7 (38.9)
Age (years)	
Minimum–Maximum	19.50–56.50
Mean±SD	44.17±10.61
Median	41.75
Risk factors	
Free	5 (27.8)
Diabetes mellitus	4 (22.2)
Hyperlipidemia	8 (44.4)
Hypertension	1 (5.6)
Associated symptoms	
No	4 (22.2)
Tinnitus	4 (22.2)
Vertigo	10 (55.6)

Regarding the reported degree of hearing impairment, among the 18 patients the only one who presented with mild SNHL recovered (11.2%); the four patients who presented with moderate SNHL (44.4%) and the two patients who presented with moderate to severe SNHL (22.2%) also recovered; of the five patients who presented with severe SNHL, two patients recovered (22.2%) and three did not, whereas the six patients who presented with profound SNHL did not recover (66.7%). It was found that the degree of hearing loss (db) had a statistically significant effect on hearing recovery (Table 3).

With regard to the audiogram that patients presented with, the five patients with ascending audiograms (55.6%) and the two with flat audiograms (22.2%) recovered; of the five patients who presented with descending audiograms, two (22.2%) recovered and three (33.3%) did not; none of the six patients who presented to us with profound audiograms recovered (66.7%). It was found that the configuration of the audiogram at the time of presentation had a

statistically significant effect on hearing recovery (Table 4).

Concerning the endoscopic view of RW, the two patients in whom RW was fully exposed recovered (22.2%); the only patient in whom we found a secondary membrane also recovered (11.2%). Of the seven patients in whom we found an overhanging niche, four recovered (44.4%) and three (33.3%) did not. Among the eight patients in whom we found both a secondary membrane and an overhanging niche, two (22.2%) recovered and six (66.7%) did not. Thus, the endoscopic view of RW did not have a statistically significant effect on hearing recovery (Table 5 and Fig. 1).

Discussion

SSNHL is an otologic emergency that has the possibility of high spontaneous recovery; all studies indicate that early initiation of treatment will lead to good prognosis.

Table 2 Relation between hearing recovery and duration of the disease from its onset to start of treatment (weeks) (N=18)

Duration from onset to treatment (weeks)	Hearing recovery [n (%)]		χ^2	MC P
	Recovery (n=9)	No recovery (n=9)		
Total				
Within 1	2 (22.2)	0 (0.0)		
1-2	4 (44.4)	0 (0.0)		
2-3	1 (11.2)	3 (33.3)	8.137*	0.035 [†]
3-4	2 (22.2)	6 (66.7)		

MC, Monte Carlo. * $P \leq 0.05$, statistically significant.

Table 3 Relation between hearing recovery and degree of hearing loss

Degree of hearing loss	Hearing recovery [n (%)]		χ^2	MC P
	Recovery (n=9)	No recovery (n=9)		
Total				
Mild	1 (11.2)	0 (0.0)		
Moderate	4 (44.4)	0 (0.0)	12.582*	0.003 [†]
Moderate to severe	2 (22.2)	0 (0.0)		
Severe	2 (22.2)	3 (33.3)		
Profound	0 (0.0)	6 (66.7)		

MC, Monte Carlo. * $P \leq 0.05$, statistically significant.

Table 4 Relation between hearing recovery and shape of the audiogram (N=18)

Shape of audiogram	Hearing recovery [n (%)]		χ^2	MC P
	Recovery (n=9)	No recovery (n=9)		
Total				
Ascending	5 (55.6)	0 (0.0)		
Flat	2 (22.2)	0 (0.0)		
Descending	2 (22.2)	3 (33.3)	12.810*	0.001 [†]
Profound	0 (0.0)	6 (66.7)		

MC, Monte Carlo. * $P \leq 0.05$, statistically significant.

The present study was conducted to test the effect of direct application of dexamethasone on the RW after its adequate exposure through a transcanal approach in SSNHL patients.

These results were consistent with those of Byl [13] who performed a limited ‘meta-analysis’ of studies published before 1984 and identified 200 male and 191 female patients (a male-to-female ratio of 1.05 : 1). He found increasing incidence with increasing age, with a peak incidence of 47/100 000 in patients 45 years and older.

The increase in the incidence of SSNHL with increasing age may be due to differences in the etiology between younger and older patients. Vascular events causing SSNHL may be more common in the elderly and in men because of the increased prevalence of underlying cardiovascular disease among them [14].

Results of the current study were consistent with those of Bogaz *et al.* [15], who found that tinnitus was present in 92.1% of patients, and they had statistically significantly higher rates of recovery compared with the group without tinnitus. It is assumed that the presence of tinnitus after cochlear injury would indicate that hair cells are viable.

Vertigo is a negative predictive factor for hearing recovery after SSNHL. The extent of the labyrinthine

lesion might correlate with the severity of cochlear damage, and the likelihood of hearing recovery tends to reduce as the degree of labyrinthine involvement increases. These results are in agreement with those of Ben-David *et al.* [16], who said that vertigo is associated with poor prognosis after SSNHL.

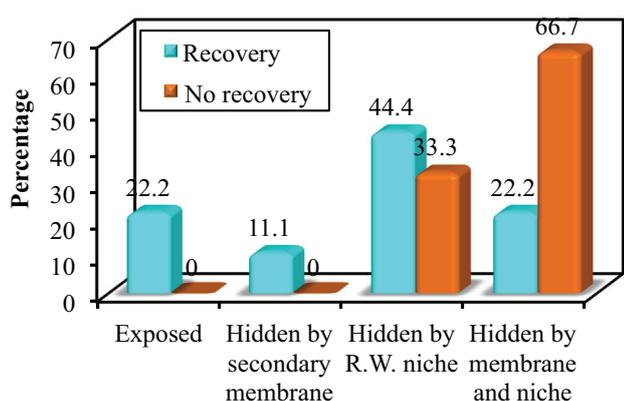
Results of the current study were consistent with those of Marcucci *et al.* [17], who thought that hypercholesterolemia may contribute to the clinical event of SSNHL, thus indirectly supporting the hypothesis of a vascular occlusion in the pathogenesis of the disease. But they were inconsistent with the findings of Ullrich *et al.* [18], who found that hyperlipidemia is not of major pathological importance in SSNHL.

These results were consistent with those of Chang *et al.* [19], who found that patients with low-frequency or mid-frequency hearing loss have higher rates of recovery in comparison with patients with flat or sloping-down audiometric profiles. Our results are also in agreement with the findings of Fu *et al.* [6], who found that patients seen within 1 month from onset of hearing loss experience a greater degree of improvement than those patients seen later.

There are a lot of variations in the selection of the drug (dexamethasone vs. methylprednisolone) and the dose and concentration of steroid administered, as well as in the timing, frequency, and total number of injections. For the first time, Silverstein *et al.* [20] showed that intratympanic steroid therapy was effective in the treatment of SSNHL. The Silverstein *et al.* [20] microwick is composed of polyvinyl acetate and is 1 mm in diameter and 9 mm in length. It is small enough to be inserted through a ventilation tube. Its applications in inner ear disease treatment, including Meniere’s disease, SSNHL, and autoimmune inner ear disease, have been documented since 1999.

Loader *et al.* [21] treated patients primarily with intravenous steroids (500 mg prednisolone) for a minimum of 3 days. Patients who did not experience remission (change <10 dB) underwent an enaural tympanotomy under general anesthesia. After

Figure 1



Relation between hearing recovery and endoscopic view of round window (RW) (N=18)

Table 5 Relation between hearing recovery and endoscopic view of the round window (N=18)

Endoscopic view of round window	Hearing recovery [n (%)]		χ^2	MCp
	Recovery (n=9)	No recovery (n=9)		
Exposed	2 (22.2)	0 (0.0)	4.626	0.124
Hidden by secondary membrane	1 (11.2)	0 (0.0)		
Hidden by round window niche	4 (44.4)	3 (33.3)		
Hidden by membrane and niche	2 (22.2)	6 (66.7)		

MC, Monte Carlo. *P≤0.05, statistically significant.

visualization of the oval niche and RW, the promontory bone around both windows was delicately scraped with a microhook to stimulate blood flow. Then the fascia was harvested preauricularly and soaked in triamcinolone suspension (1 ml of 40 mg/ml), laced with fibrin glue, and subsequently placed on the stapedial footplate and in the RW niche. With the soaked fascia lying across the oval and round niches for a long period of time postoperatively, containing high concentrations of steroid (being firmly held in position by the lacing of fibrin glue), it seems logical that steroid loss through the Eustachian tube caused by swallowing would be reduced. The additional application of fascia to the oval niche (and not only to the RW) aims to maximize the absorption of steroid into the inner ear by maximizing the surface area available for resorption. Salt *et al.* [22] have shown a high absorption of locally applied drugs to the stapes. A total of 13/25 (52%) patients exhibited recovery: marked recovery (>30 dB) could be seen in eight patients, and normal recovery (10–30 dB) in five patients. Twelve (48%) patients showed no improvement [21].

Hyaluronic acid has been shown in animal studies to increase the permeability of the RW membrane without cochlear ototoxic effects. The simultaneous use of dexamethasone and hyaluronic acid would be expected to increase RWM permeability such that the concentration of dexamethasone in the perilymph (and possibly in the endolymph) would increase, thus increasing the availability and activity of dexamethasone in the inner ear structures. Hyaluronic acid may not only increase the permeability of the RWM but may also influence the distribution of dexamethasone within the inner ear. Gouveris *et al.* [23] found that intratympanic injection of dexamethasone/hyaluronic acid resulted in a significant improvement in hearing in patients with SSNHL. In our study we did not use any facilitating agent with dexamethasone.

Conclusion

The present study was performed on 18 patients with confirmed SSNHL. Otological examination and audiological investigations were conducted preoperatively; exploration of RW was done in all patients endoscopically. It was found that there was statistically significant improvement in hearing threshold in 50% of patients, but that depended on factors other than the endoscopic view of RW, which was either exposed, hidden by a secondary membrane, niche, or both. These factors were degree of hearing loss, onset of treatment, shape of audiogram, associated symptoms, and associated risk factors (diabetes mellitus, hyperlipidemia).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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