Nationwide Survey of Intratympanic Steroids for the Management of Sudden Sensorineural Hearing Loss*

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ABSTRACT: **Background:** The currently accepted treatment for idiopathic sudden sensorineural hearing loss (ISSHL) is systemic steroids as first-line and intratympanic steroids as salvage therapy. Intratympanic (IT) treatment is applied worldwide in many different ways with no universally accepted protocol.

Objectives: To present the current disparity in ISSHL management and to discuss the necessity for establishing a common national protocol.

Methods: In 2014 we conducted a national survey by sending questionnaires on ISSHL management to otologists in every otolaryngology department in the country.

Results: The majority of otolaryngology departments (56%) admit patients with sudden sensorineural hearing. Almost two-thirds (61%) of departments recommend supplementary initial treatment in addition to systemic steroids. None of the medical centers offer intratympanic steroid treatment as primary therapy, but 94% offer this treatment as a salvage therapy. Fewer than half the medical centers (44%) consider the maximal period for intratympanic therapy to be 4 weeks since hearing loss appears. Almost half (48%) the departments use intratympanic steroids once every 5–7 days, usually in an ambulatory setting. Almost half (44%) the medical centers tend to use not more than four courses of IT steroids. In 44% of departments an audiogram is performed at the beginning and at the end of the intratympanic course.

Conclusions: Our results demonstrate a variability among Israeli medical centers in many aspects of intratympanic treatment. We believe this reinforces the need for a comparative international study in order to establish a standard protocol.

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KEY WORDS: idiopathic sudden sensorineural hearing loss (ISSHL), intratympanic steroids (IT), salvage, protocol

Idiopathic sudden sensorineural hearing loss (ISSHL) is a sudden decrease in sensorineural hearing sensitivity of unknown etiology [1] ISSHL is diagnosed when an audiometry confirms a 30-decibel (dB) hearing loss at three consecutive frequencies and no underlying condition has been identified [2]. Various theories explaining ISSHL have been proposed, including viral infection [3], vascular occlusion, breaks in labyrinthine membranes, immune-mediated mechanisms, and abnormal cellular stress responses within the cochlea. None of these hypotheses, however, have been convincingly proven in humans [4].

The treatment of patients with sudden sensorineural hearing loss remains varied among otologic centers. There is no universally accepted standard protocol. The currently accepted treatment for ISSHL is the use of systemic steroids [5], despite the conclusion of the most recent Cochrane meta-analysis which contends that the effectiveness of steroids in the treatment of sudden sensorineural hearing loss remains as yet unproven [6].

Haynes et al. [7] conducted a retrospective review of 40 patients who received an intratympanic injection of 24 mg/ml dexamethasone at one time, resulting in modest improvement in patients who failed systemic therapy. Ahn and colleagues [8] designed a prospective, randomized, controlled clinical trial involving 120 patients diagnosed with ISSHL. Patients randomized to the study group received intratympanic dexamethasone (0.3–0.4 ml of 5 mg/ml dexamethasone) plus systemic steroids (48 mg methylprednisolone), whereas patients randomized to the control group were administered systemic steroids alone. The researchers concluded that the addition of IT steroids to systemic steroids did not result in significant improvement in the treatment of ISSHL [8].

Rauch et al. [9] randomized 129 patients to receive either 60 mg/day oral prednisone for 14 days or 40 mg/ml of methylprednisolone intratympanic methylprednisolone with a dose given every 3 to 4 days by injection through the tympanic membrane over 2 weeks. Hearing level 2 months after treatment in patients with ISSHL showed that intratympanic treatment was not inferior to oral prednisone treatment [9]. In the protocol of Jung et al. [10] the study group was treated with a combination therapy of intravenous steroids (single dose of 10 mg IV dexamethasone daily for 5 days. The intravenous steroid was then continued for an additional 5 days at a daily dose of 5 mg) and intratympanic steroids (0.3 and 0.7 ml of 5 mg/ml dexamethasone). The control group received IV

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steroids alone. The findings of this study suggest that combination therapy results in higher hearing recovery rates when compared to treatment with systemic steroids alone, even in patients with severe hearing loss [10].

The intratympanic injection of glucocorticoids for sudden sensorineural hearing loss was pioneered by Silverstein and co-workers [11] and Parnes et al. [12]. Despite the publication of a rapidly growing number of reports on the treatment results of the intratympanic application of glucocorticoids for sudden sensorineural hearing loss [13] over recent years, there continues to be a general lack of high quality intratympanic steroid therapy data. In 2012, the American Academy of Otolaryngology (AAO) published clinical practice guidelines for sudden sensorineural hearing loss, summarizing that intratympanic steroids are most often used as salvage therapy and are recommended as initial treatment only to patients who either cannot tolerate systemic steroid therapy or are refractory to it [2]. A variety of treatment methods were applied in these guidelines, including but not limited to different methods of delivery, different types and doses of steroids, and varied frequency of treatment.

The objective of the present study was to present the different ISSHL management methodologies in all 18 Ear, Nose and Throat (ENT) departments in Israel and to discuss the necessity and possible effectiveness of a common international protocol. Our search of the professional literature did not yield a similar survey of a comparable number of medical institutions, except for one national survey in Spain which dealt with ISSHL management generally and found significant disparity in the diagnostic means and treatments for sudden deafness [14].

PATIENTS AND METHODS

This study did not require the permission of an ethics committee since the data were collected from physicians reporting, generally, on their daily work. No personal patient data were used in this research.

In 2014, a national survey was conducted in all 18 Israeli medical centers. Questionnaires were sent to a senior otologist in each ENT department regarding ISSHL treatment indication, treatment frequency, methods of delivery, drugs and dosages, and post-procedure management. All 18 departments replied to the survey and acknowledged following the American Academy of Otolaryngology guidelines, whereby idiopathic sudden sensorineural hearing loss is diagnosed if audiometry confirmed a 30-decibel (dB) hearing loss at three consecutive frequencies and no underlying condition was identified [2]. Only one of these departments did not perform intratympanic treatment due to the absence of a consolidated protocol. The results presented in this article relate to the remaining 17 departments.

RESULTS

The first part of the survey referred to the initial management of patients with sudden hearing loss. The majority (56%) of ENT departments hospitalize patients with sudden sensorineural hearing loss. The remainder do not. The medical centers that offer hospital care tend to hospitalize for 6 days on average (SD = 1.8).

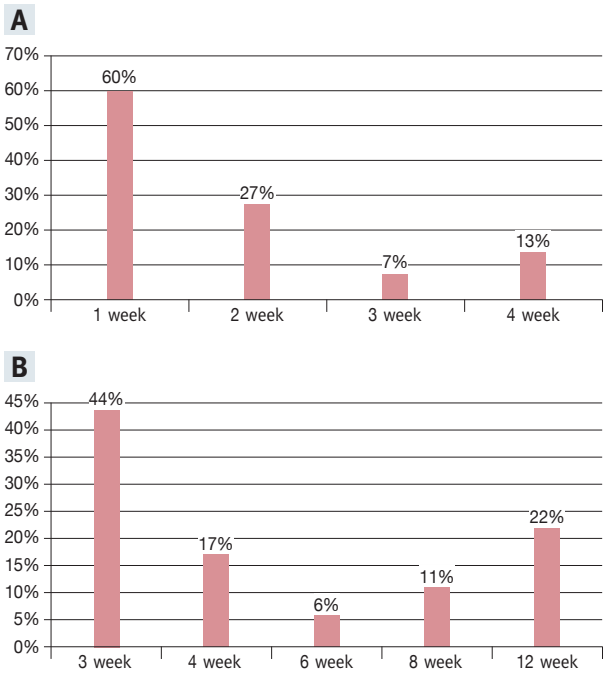
Almost two-thirds (61%) of ENT departments recommend supplementary initial treatment in addition to systemic steroids. Almost one-quarter (28%) of all ENT departments prescribe inhalations of carbogen (a mixture of 95% oxygen with 5% carbon dioxide) on top of steroids, while 6% prescribe vitamin E and 6% prescribe proton pump inhibitors. As for the treatment of primary steroids, we found that ENT departments offer treatment for up to 28 days on average (SD = 9.5) from onset of sudden hearing loss. None of the medical centers offers intratympanic steroid treatment as a primary therapy, but 94% offer intratympanic treatment as a salvage therapy for ISSHL.

Another issue examined in the survey was the treatment schedule. The majority (60%) of ENT departments require one week of treatment prior to deciding that primary treatment with systemic steroids has failed. In the remaining departments, primary treatment failure is defined as having occurred 2 weeks (27%), 3 weeks (7%), or 4 weeks (13%) after the completion of system steroid use. Fewer than half the medical centers (44%) consider 4 weeks as the maximal period since onset of hearing loss for salvage intratympanic therapy. The other departments offer intratympanic salvage therapy after 3 weeks (17%), 6 weeks (22%), 8 weeks (11%), or 12 weeks (6%) [Figure 1]. There were no uniform criteria of failure of primary systemic steroid therapy among medical departments. The physicians usually considered subjective complaints and objective audiogram findings before starting IT injections.

The frequency of intratympanic steroid treatment for patients with ISSHL varies among departments. Intratympanic steroids are used by 43% of the ENT departments either once every 5–7 days or once every 1–2 days, usually in an ambulatory setting, while 14% of the departments treat with intratympanic steroids once every 4–5 days. Almost half (44%) the medical centers tend to use no more than four courses of intratympanic steroids. The other centers have a different maximal number of intratympanic courses: 5 (17%), 6 (11%), 7 (22%), and 14 courses (6%) [Figure 2].

The most common intratympanic steroid delivery method is injection (76%), while 18% of departments treat through a ventilation tube, and one department (6%) uses LASER to puncture the tympanic membrane. Local anesthesia applied to the tympanic membrane before intratympanic delivery varies as well. Lidocaine hydrochloride 2% with epinephrine, phenol, percutaneous lidocaine (EMLA®, AstraZeneca, UK), and 10% lidocaine spray (Xylocaine®, AstraZeneca, UK) are

Figure 1. [A] Time period after which therapy is considered a failure. **[B]** Time interval during which departments offer intratympanic salvage therapy



used equally in different departments (40%). Tetracaine is less commonly used for local anesthesia (7%). Several medical centers that use a ventilation tube do not offer anesthesia for subsequent intratympanic treatments (7%).

Both residents and senior ENT physicians usually perform the procedure (72%). In a minority of departments (28%), intratympanic delivery is done by senior physicians only. Audiometric exams are performed as part of the diagnosis of sudden sensorineural hearing loss as well as during treatment courses. One department (6%) performs a hearing exam only at the time of diagnosis. In half the medical centers, audiometric exams are performed before each intratympanic administration, and in 44% of departments an audiogram is also performed at the end of the intratympanic course.

Finally, we inquired about the type of corticosteroid therapy and the doses given. The majority of ENT departments (89%) use dexamethasone and only two departments (11%) use methylprednisolone for intratympanic treatments. Regarding dosage, there is great diversity among physicians. Dexamethasone is commonly used at a dosage of 20 mg/ml, although in some hospitals a lower dosage of 1–10 mg/ml is administered. Methylprednisolone is also used at dosages of 20 mg/ml and 40 mg/ml [Figure 3]. For all parameters we did not find differences among primary, secondary, or tertiary medical centers.

Figure 2. [A] Frequency of intratympanic steroid therapy. **[B]** Maximum number of intratympanic steroid treatments

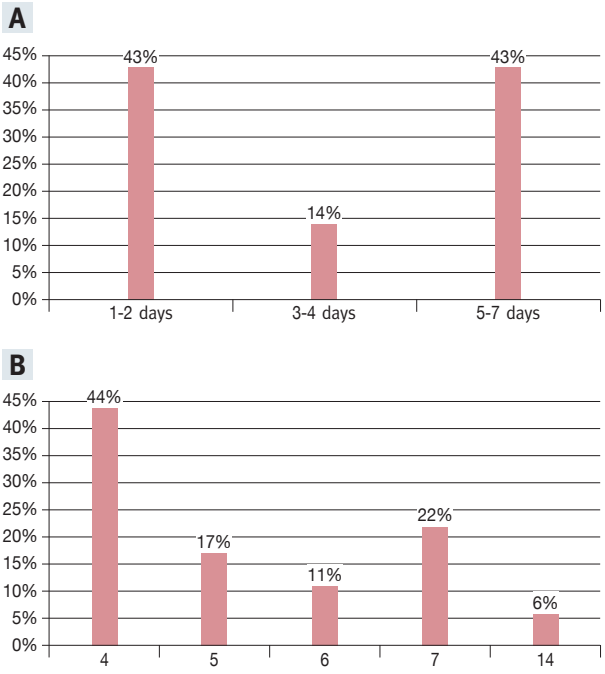
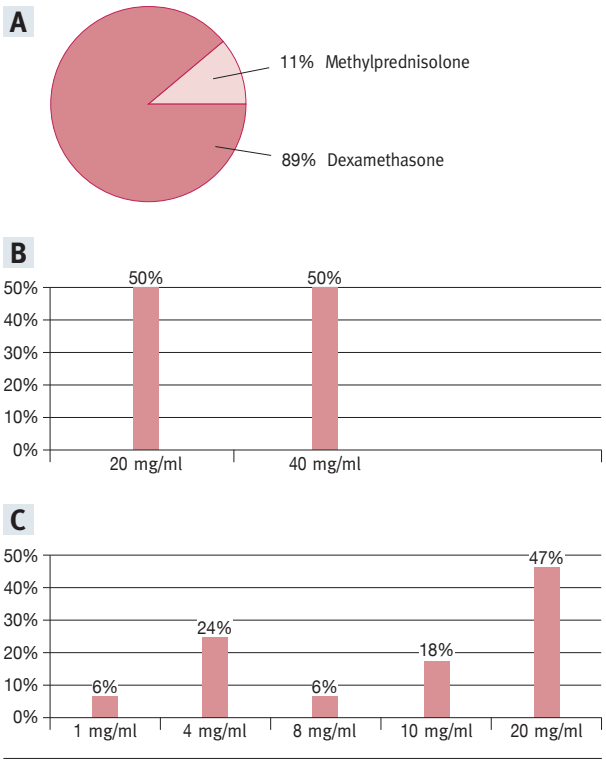


Figure 3. [A] Type of steroids used. **[B]** Methylprednisolone dosage used. **[C]** Dexamethasone dosage used



DISCUSSION

Since the first series of publications on intratympanic steroid application by Silverstein et al. [11] and Parnes et al. [12], a large number of small series without controls and usually retrospective in nature have shown inconsistent results for intratympanic steroid use [8,15-17]. Recently, several comprehensive meta-analyses were published in an attempt to determine the efficacy of this treatment for the management of ISSHL. According to updated databases, it was shown that intratympanic steroid therapy, given as a primary treatment, appears to produce equivalent results when compared to treatment with high-dose oral prednisone therapy. As a salvage therapy, intratympanic steroids offer a mild degree of additional improvement in hearing recovery. Rauch at el. [9] in a prospective, randomized trial found no difference in outcome between oral or trans-tympanic administration, unless the presenting hearing loss is profound and then oral administration trended to be superior [9,18-21]. Because of this inconsistency, intratympanic therapy is indeed given worldwide, but with no uniform protocol or guidelines.

There is a growing body of evidence that combination therapy as initial treatment is more effective than primary steroid therapy alone for ISSHL. Combination therapy exhibited better outcomes in pure tone average improvement than systemic steroids alone, especially in cases with severe–profound initial hearing loss. Combination therapy also showed advantages in recovery rate [10,21]. In this context, one should remember the possible complications of IT steroids, such as transient dizziness, injection pain, a burning sensation, increasing tinnitus, post-injection vertigo, tongue numbness, and a small perforation of the eardrum [22].

This study is a cross-sectional survey of 18 medical centers in Israel regarding the variability of treatment for idiopathic sudden sensorineural hearing loss. Our objective was to demonstrate the disparity in ISSHL management and to discuss the necessity for establishing a common international protocol. Our group conducted a national survey by sending questionnaires on ISSHL management to otologists in every otolaryngology department in Israel. Surprisingly, the majority (56%) of otolaryngology departments admit patients with ISSHL, and 61% recommended supplemental initial treatment in addition to systemic steroids, including carbon, vitamin E, and proton pump inhibitors. These additional therapies have minimal validated research to support their use. Interestingly, none of the centers use combination therapy (systemic steroids + simultaneous intratympanic steroid therapy) for the treatment of ISSHL. Furthermore, none of the medical centers offers intratympanic steroid treatment as primary therapy, although 94% offer this treatment as a salvage therapy. Additionally, we demonstrated a great deal of variability among Israeli medical centers in many aspects of intratympanic salvage treatment, including the criteria for failure of primary systemic steroid therapy, the method of injection, and the dosage of intratympanic steroid to be used. It is clear from the survey that intratympanic steroids are offered after failure of systemic treatment in nearly all ENT departments and, in practice, currently represent the standard treatment for patients with persistent sudden sensorineural hearing loss. The results, which reflect local practice, are generalizable to other settings where practice patterns/reimbursement policies are different.

Moreover, there are medicolegal issues in the management of sudden sensorineural hearing loss that are often raised. As maintained in the AAO guidelines, considering the profound impact of ISSHL on quality of life, even the small likelihood of hearing improvement justifies the administration of steroids [2].

Patients with persistent hearing loss may require all possible treatments, including intratympanic steroids. Based on the results of this survey which reflect common practice throughout Israel, intratympanic steroid treatment is offered as salvage therapy. Although intratympanic treatment is widely used and in some centers is considered to be the standard of care, with no agreed-upon protocol or guidelines each department offers its own procedure for management of ISSHL.

In conclusion, after 30 years of intratympanic steroid treatment experience, it emerges from the literature that intratympanic steroid treatment is an acceptable therapeutic tool as a salvage treatment for ISSHL. That said, intratympanic treatment is applied worldwide in many different ways with no unified protocol that can be followed. This survey demonstrates the variability among medical centers and emphasizes the need for a comparative national study in order to examine the effectiveness of one method over another.

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Capsule

Cognitive aging and memory

A poor ability to recollect details about past events is part of normal brain aging. This is often attributed to depleted efficacy of encoding processes. Reduced selectivity of brain regions sensitive to a specific class of stimuli, a phenomenon called neural dedifferentiation, is thought to play a role. **Koen** and fellow-researchers investigated neural dedifferentiation in old and young subjects during memory encoding and whether this could predict subsequent recollection. Objects and scenes were chosen because they selectively engage distinct cortical regions. Only one of these regions showed neural dedifferentiation that correlated with age. An outcome from neuropsychological tests also correlated with subsequent memory performance. However, this correlation was age invariant. Neural differentiation is thus associated with two independent factors: age and cognitive performance.

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Capsule

Translation control of the immune checkpoint in cancer and its therapeutic targeting

Cancer cells develop mechanisms to escape immunosurveillance, among which modulating the expression of immune suppressive messenger RNAs is most well-documented. However, how this is molecularly achieved remains largely unresolved. **Xu** and group developed an in vivo mouse model of liver cancer to study oncogene cooperation in immunosurveillance. The authors show that MYC overexpression (*MYCTg*) synergizes with *KRASG12D* to induce an aggressive liver tumor leading to metastasis formation and reduced mouse survival compared with *KRASG12D* alone. Genome-wide ribosomal footprinting of *MYCTg*;*KRASG12* tumors compared with *KRASG12D* revealed potential alterations in translation of mRNAs, including programmed-death-ligand 1 (PD-L1). Further analysis revealed that PD-L1 translation is repressed in *KRASG12D* tumors by functional, non-canonical upstream open reading frames in its 5' untranslated region, which is bypassed in *MYCTg*;*KRASG12D* tumors to evade immune attack. They also show that this mechanism of PD-L1 translational upregulation was effectively targeted by a potent, clinical compound that inhibits eIF4E phosphorylation, eFT508, which reverses the aggressive and metastatic characteristics of *MYCTg*;*KRASG12D* tumors. Together, these studies reveal how immune-checkpoint proteins are manipulated by distinct oncogenes at the level of mRNA translation, which can be exploited for new immunotherapies.

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