Dissertation

Intratympanic triamcinolone acetonide as a salvage therapy for idiopathic sudden sensorineural hearing loss

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz"

Graz, February 2021 *Dr.med.univ. Alexandros Andrianakis eh*

Disclosures

Parts of this thesis have been published in the following two articles:

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Abbreviations and Definitions

3D-FLAIR	3-dimensional fluid-attenuated inversion recovery
AAO-HNSF	American Academy of Otorhinolaryngology – Head and Neck Surgery Foundation
ABR	Auditory brainstem response
ANOVA	Analysis of variances
CHL	Conductive hearing loss
CMV	Cytomegalovirus
CT	Computer tomography
dB	Decibel
e.g.	For example [exempli gratia]
et al.	And others [et alia]
GAORL-HNS	German Association of Otorhinolaryngology – Head and Neck Surgery
HBOT	Hyperbaric oxygen therapy
HINTS	Head impulse test, evaluation of a pathologic nystagmus, test of skew
HNE	4-hydroxy-2-nonenal
HSV	Herpes simplex virus
ISSNHL	Idiopathic sudden sensorineural hearing loss
ITS	Intratympanic Steroids
kHz / Hz	Kilohertz / Hertz
mg / ml / kg	Milligramm / Milliliter / Kilogramm
MRI	Magnetic resonance imaging
NIDCD	National Institute on Deafness and other Communication Disorders
PLF	Perilymphatic fistulas
PTA	Pure tone average
RCT	Randomised clinical trial
SAORL	Spanish Association of Otorhinolaryngology
SNHL	Sensorineural hearing loss
SRT	Speech recognition score
SSNHL	Sudden sensorineural hearing loss
TB	Temporal bone
TPSA	Topological polar surface area value
VEMP	Vestibular-evoked myogenic potential
VS	Vestibular schwannoma

vs.	Versus
VZV	Varicella zoster virus
WHO	World Health Organisation
WLOGP	Wildman and Crippen n-octanol/water partition log *P* coefficient
WRS	Word recognition score
CI	95% confidence interval
d	Cohen's measure of effect size for comparing two sample means
$D^{e.p.}$	Difference in empirical probability
F	Statistical test based on the Fisher distribution
f	Cohen's measure of effect size for comparing more than two sample means
f^2	Cohen's strength measure of association within a multiple linear correlation analysis
H_0	Null hypothesis
H_1	Alternative hypothesis
I^2	Higgin's measure of inconsistency in meta-analyses
M^{diff}	Mean difference
n	Subset case number
N	Total number of cases
p	Probability of significance in statistical hypothesis testing
P	Power of a statistical hypothesis test (1- *β)*
r	Estimate of the Pearson product-moment correlation coefficient
t	Statistical test based on the Student t-distribution
OR	Odds ratio
V	Cramer's strength measure of association between more than two categorical variables
α	Probability to false-negative reject the null hypothesis
β	Probability to false-positive accept the null hypothesis
ε	Greenhouse-Geisser's correction of degrees of freedom in case of violated sphericity
φ	Pearson's strength measure of association between two dichotomous variables
χ^2	Statistical test based on the Pearson Chi-square distribution

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Abstract in German

Einleitung

Die intratympanale Steroid Injektion (ITI) wird zunehmend als Reservetherapie bei primär-therapieresistentem Hörsturz eingesetzt. Es gibt keinen Konsens über das ideale ITS-Behandlungsprotokoll, was die Medikation, die Gesamtanzahl der Injektionen und die Intervalllänge betrifft. Die am häufigsten verwendeten Steroide sind Dexamethason und Methylprednisolon. Für Triamcinolonacetonid liegen nur begrenzte Daten vor. Seit der Einführung der ITI-Therapie an der Medizinischen Universität Graz im Jahr 2014 wird ein Protokoll, bestehend aus bis zu 3x intratympanalen Triamcinolonacetonid-Injektionen jeweils im Abstand von 1 Woche, verwendet. Im Januar 2020 wurde die Intervalllänge verkürzt und eine zusätzliche 4te Injektion in das Protokoll implementiert. Das vorliegende Dissertationsprojekt umfasste zwei Teile: Das primäre Ziel des ersten Teils war die Evaluierung der Wirksamkeit von intratympanalen Triamcinolonacetonid-Injektionen bei primär-therapieresistentem Hörsturz. Sekundäre Ziele waren die Ermittlung der Signifikanz der einzelnen Injektionen und die Identifizierung von Prädiktoren für den Ausgang der ITI-Reservetherapie. Das Ziel des zweiten Teils war das überarbeitete und das initiale Protokoll hinsichtlich ihrer Hörfunktions-Resultate zu vergleichen.

Material und Methoden

Im ersten Teil (= Kohortenstudie) wurden 152 primär-therapieresistente Hörsturz-Patienten, die zwischen Januar 2014 und August 2019 bis zu 3x ITI mit Triamcinolonacetonid im Abstand von 1 Woche erhielten, retrospektiv untersucht. Die primäre Zielgröße war die absolute Hörverbesserung durch die ITI-Behandlung. Sekundäre Zielgrößen waren eine klinisch signifikante Hörverbesserung (>10 dB), der Grad an Hörgenesung und die Genesung in einen Hörgerät-tauglichen Hörfunktionsbereich (≤50 dB). Die Signifikanz jeder einzelnen Injektion wurde bestimmt, indem der Anteil am gesamten Ausmaß der Hörverbesserung durch die einzelnen Injektionen berechnet und verglichen wurde. Prädiktoren für den Ausgang der ITI-Reservetherapie wurden mit Hilfe einer multiplen linearen Regressionsanalyse identifiziert. Im zweiten Teil (= Fall-Kontroll-Studie) wurden 32 primär-therapieresistente Hörsturz-Patienten, die zwischen August 2019 und Dezember 2020 bis zu 4x ITI im Abstand von 2-4 Tagen erhielten, retrospektiv eingeschlossen. Diese Patienten wurden 1:1 mit Probanden aus der Kohortenstudie gematcht. Die Resultate der Hörverbesserung zwischen dem revidierten und

dem ursprünglichen ITI-Behandlungsprotokoll wurden anhand derselben Zielgrößen wie in der Kohortenstudie verglichen.

Ergebnisse

In der Kohortenstudie verbesserte sich die mittlere Hörfunktion durch die ITI-Reservetherapie um 15.9 ± 18.9 dB. 52.6% der Patienten hatten eine klinisch signifikante Hörverbesserung. Eine vollständige und teilweise Hörgenesung wurde von 9.9% bzw. 48% der Patienten erreicht. 23.9% der Patienten mit einer Hörgerät-untauglichen Hörfunktion kehrten durch die ITI-Reservetherapie in einen Hörgerät-tauglichen Hörbereich zurück. Die erste der drei ITI erbrachte die größte Hörverbesserung. Behandlungsverzögerung, der Grad an Hörverbesserung durch die primäre Therapie und der Schweregrad des Hörverlusts wurden als prognostische Faktoren für den Ausgang der ITI-Reservetherapie identifiziert. In der Fall-Kontroll-Studie führten beide ITI-Protokolle zu einer statistisch signifikanten Abnahme der Hörschwellen (p<0.05). Das ursprüngliche Protokoll verbesserte die mittlere Hörfunktion um 12 ± 11.7 dB (p<0.001, d=1, P=99%). Die Hörschwellen sanken bei Patienten mit dem überarbeiteten Protokoll um durchschnittlich 13.4 ± 19.1 dB (p<0.001, d=0.7, P=98%). Eine klinisch signifikante Hörverbesserung wurde bei 18 Patienten (58,1 %) mit dem ursprünglichen Protokoll und bei 14 Patienten (41,9 %) mit dem überarbeiteten Protokoll festgestellt. Es fanden sich keine statistisch signifikanten Unterschiede in sämtlichen Zielgrößen zwischen den Protokollen (p>0.05).

Schlussfolgerung

Triamcinolonacetonid führte zu ähnlich signifikanten Resultaten im Vergleich zu früheren Studien, in denen Dexamethason und Methylprednisolon verwendet wurden. Daher stellt Triamcinolonacetonid einen wirksamen Kandidaten für die ITI-Reservetherapie des Hörsturzes dar. Lange Behandlungsverzögerung, geringe Hörverbesserung durch die primäre Therapie und ein hoher Schweregrad des Hörverlusts sind mit einer schlechteren Prognose der Hörerholung assoziiert. Beide ITI-Protokolle führten zu einer ähnlich signifikanten Hörverbesserung. Diese Ergebnisse weisen darauf hin, dass ein kürzeres Injektionsintervall nicht zu besseren Hörergebnissen führt. Darüber hinaus könnten weniger ITI-Injektionen die Kosten und die physische sowie psychische Belastung der Patienten reduzieren und das Risiko einer persistierenden Trommelfellperforation verringern, bei gleichbleibender Effizienz.

Abstract in English

Introduction

Intratympanic steroid (ITS) injections are increasingly used as salvage treatment for idiopathic sudden sensorineural hearing loss (ISSHNL). No consensus exists on the ideal ITS treatment protocol regarding medication, total injection count and interval length. The widely used corticosteroids are dexamethasone and methylprednisolone. There are limited data for triamcinolone acetonide as medication for this treatment modality. Since the initiation of ITS treatment at the Medical University of Graz in 2014, a protocol consisting up to 3x intratympanic triamcinolone acetonide injections at 1-week intervals has been used. In January 2020, the protocol was revised by shortening the interval length and implementation of an additional 4th injection. The present dissertation project included two parts: The primary objective of the first part was to evaluate the efficacy of triamcinolone acetonide as medication for ITS salvage treatment of ISSNHL. Secondary objectives were the evaluation of the significance of each individual injection, and the identification of plausible predictors for ITS hearing improvement. The aim of the second part was to compare the revised and initial ITS protocols on hearing outcome.

Materials and Methods

In the first part (= cohort study), 152 patients diagnosed with ISSNHL between January 2014 and August 2019, who failed to response sufficiently to primary systemic corticosteroid therapy, and who received up to 3x ITS injections at 1-week intervals as a salvage treatment, were retrospectively reviewed. The primary outcome measure was the absolute hearing improvement by ITS salvage treatment. Secondary outcome measures were a clinically significant ITS hearing improvement (>10 dB), grade of hearing recovery, and recovery into a serviceable hearing range (≤50 dB). The significance of each individual injection was determined by calculating and comparing the amount of hearing improvement due to each particular injection. Predictors for ITS salvage treatment outcome were identified by using a multiple linear regression analysis. In the second part (= case-control study), 32 primary-refractory ISSNHL patients who received up to 4x ITS injections every 2-4 days between August 2019 and December 2020, were retrospectively enrolled. These patients (= revised-protocol group), were 1:1 matched to subjects out of the cohort study (= initial-protocol group).

Hearing outcomes between the revised and initial ITS salvage treatment protocols were compared by using the same outcome measures as in the cohort study.

Results

In the cohort study, patients improved in mean hearing function by 15.9 ± 18.9 dB due to salvage treatment with intratympanic triamcinolone acetonide injections. 52.6% of the patients had a clinically significant ITS hearing improvement. A complete and partial hearing recovery were achieved from 9.9% and 48% of the patients, respectively. 23.9% of the patients with an unserviceable hearing level returned by ITS salvage treatment into a serviceable hearing range. The first of the three ITS injections yielded the greatest hearing improvement. Prognostic outcome factors turned out to be treatment delay, degree of primary systemic hearing improvement and severity of initial hearing loss. In the case-control study, both ITS salvage treatment protocols resulted in a statistically significant decline in hearing thresholds (p<0.05). The initial protocol improved patient's hearing function by 12 ± 11.7 dB (p<0.001, d=1, P=99%). Hearing thresholds decreased by 13.4 ± 19.1 dB in the revised-protocol group (p<0.001, d=0.7, P=98%). A clinically significant hearing improvement was seen in 18 patients (58.1%) in the initial-protocol group, and in 14 patients (41.9%) in the revised-protocol group. There were no statistically significant differences in all hearing outcome measures between protocol groups (p>0.05).

Conclusion

Triamcinolone acetonide in ITS salvage treatment of ISSNHL resulted in similar significant hearing outcomes compared to previous studies using commonly applied corticosteroids, namely, dexamethasone and methylprednisolone. Therefore, triamcinolone acetonide constitutes an effective candidate for the ITS treatment of ISSNHL. Longer treatment delays, lower hearing improvement by primary systemic treatment, and higher severity of hearing loss were associated with poorer prognoses of hearing recovery. Both ITS protocols resulted in a similar significant hearing recovery. These results indicate that a shorter injection interval does not lead to better hearing outcomes. Moreover, the usage of fewer ITS injections may reduce costs, physical/mental stress of the patients and lower the risk of persistent tympanic perforations, while maintaining similar treatment efficacy.

Foreword

Sudden sensorineural hearing loss (SSNHL) represents a current issue of debate and research in the otolaryngologic field. SSNHL is an alarming symptom that frequently initiates an urgent consultation to a physician. Despite the low incidence, it is contemplated as one of the most abundant emergencies in otolaryngologic clinical practice. This medical condition manifests as abrupt, mostly unilateral hearing loss in sensorineural nature and may be accompanied by frightening symptoms like vertigo and tinnitus. The severity of hearing loss can widely range from mild to total deafness (3). The spontaneous hearing recovery have been estimated with a range of 32% up to 65% (4,5). Various factors, such as severity of hearing loss, older age, treatment delay or presence of vertigo, have been displayed to influence the prognosis of recovery (4–7). Up to 90% of the cases deems idiopathic (ISSNHL) following detailed investigation, and are ascribed to vascular, infectious or immune-mediated etiologies (8–10). Broad consensus exists on the diagnostic management of ISSNHL (3). On the contrary, treatment of ISSNHL points out more debated among clinicians. The variety of potential etiologies, diversity in research definitions and outcome measures, wide heterogeneity of hearing loss degree, and its natural evolution make evidence-based practice difficult. A large number of different therapeutic regiments, based on the suggested pathophysiological mechanism, have been proposed. At the present time, systemic corticosteroids are commonly used as primary treatment worldwide (11). According to a recently updated Cochrane review, systemic corticosteroids as therapy of ISSNHL cannot be confirmed as effective, neither be proven as ineffective (12). On behalf of even a slightly likelihood of hearing improvement, the clinical practice guidelines by the American Academy of Otorhinolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) propose systemic corticosteroids as an option for initial therapy of ISSNHL (3).

Over the past two decades, the local corticosteroid treatment of ISSNHL through direct application into the tympanic cavity has been increasingly situated in the center of research. The theoretical benefits of intratympanic steroid therapy (ITS) relies on eluding the blood-brain barrier to gain a higher drug concentration in the perilymph fluid and further to bypass the systemic side effects of corticosteroids (13). Numerous systematic reviews and meta-analyses investigated the effectiveness of ITS treatment for ISSNHL, either as primary therapy in combination with systemic corticosteroids or as salvage therapy (14–23). As primary treatment, intratympanic and systemic corticosteroids seem to result in similar hearing outcome (14–17). Available data on the efficacy of combined therapy over systemic therapy appear more equivocal (19–22). The greater part of randomised clinical trials (RCT)

investigating ITS as salvage treatment demonstrated somewhat the propensity to achieve better hearing outcomes (14,16,18,23). Therefore, the AAO-HNSF recommends to offer ITS treatment as second-line therapy to those patients with incomplete recovery after primary treatment (3).

For the present, a generally used ITS treatment protocol does not exist. The most effective corticosteroid for ITS treatment remains unclear (3). Commonly used corticosteroids for ITS treatment are methylprednisolone and dexamethasone (24–26). Recent experimental studies indicated that methylprednisolone and dexamethasone do not possess ideal pharmacokinetic properties for local inner ear therapy, and suggested that triamcinolone acetonide constitute a more appropriate candidate for local treatment of hearing disorders (27). However, there are extremely limited data of the clinical efficacy of triamcinolone acetonide as medication for ITS treatment of ISSNHL (28). Regarding application technique, steroids can be delivered into the tympanic cavity by intratympanic injection, transtympanic instillation through a ventilation tube or by sustained-released drug carrier devices. The most applied delivery technique is the intratympanic injection. This method has the advantages to be less invasive, safer and more cost efficient than the others (29). Therefore, the AAO-HNSF currently recommends intratympanic injection as the main delivery technique. However, no consensus exists on the ideal protocol for ITS injections (3). Only a few studies investigated different interval lengths between injections and total count of injections per patient (30–34).

At the Department of Otorhinolaryngology, Medical University of Graz, triamcinolone acetonide has been used for ITS salvage treatment since its initiation in January 2014. Thenceforth, a paradigm of up to 3x ITS injections at 1-week intervals has been utilised as recommended in the first clinical practice guidelines by the AAO-HNSF (35). Aiming to improve the hearing outcomes of our ISSNHL patients, we recently have shortened the interval length to 2-4 days and implemented an additional 4^{th} injection, in accordance to the current AAO-HNSF guidelines (3).

We aimed in the present dissertation project to 1.) evaluate the clinical efficacy of triamcinolone acetonide as medication for the ITS salvage treatment of ISSNHL and to 2.) compare the hearing outcomes of the revised ITS protocol with shortened intervals and an additional 4^{th} injection to our previously 1-week interval ITS protocol.

1 Introduction

1.1 Idiopathic Sudden Sensorineural Hearing Loss

1.1.1 Definition

Hearing loss is the complete or partial loss of the hearing function and is typically classified as conductive hearing loss (CHL), sensorineural hearing loss (SNHL), and mixed hearing loss (simultaneous presence of CHL and SNHL). CHL occurs due to an abnormality of the conductive elements of the auditory system including: the auricle, external ear canal, tympanic membrane and the middle ear cavity with its auditory ossicles. Sensorineural elements of the ear comprise the cochlea, auditory nerve and the higher parts of the central auditory system. Damage or impairment of these sensorineural elements, result in SNHL.

SSNHL is characterised by rapid-onset hearing loss of cochlear or retro-cochlear origin. This medical condition was first described by De Kleyn (36) in 1944. Currently, there is still no internationally standardised definition of SSNHL. The most commonly used definition of SSNHL in literature is provided by the National Institute on Deafness and other Communication Disorders (NIDCD). The NIDCD defines SSNHL as a sudden decline in hearing function of at least 30 decibels (dB) in three or more consecutive frequencies (Figure 1), developing within a time period of three days and often accompanyied by debilitating comorbidities including tinnitus, ear fullness and/or dizziness (37). Recent guidelines by the AAO-HNSF endorsed the universally usage of the NIDCD definition in terms of generalisation for future research. However, in clinical practice, the audiometric criteria of the NIDCD definition may be extended to events of SSNHL less than 30 dB (3). As a rationale for an alternative definition, a SSNHL of 25 dB affecting the human speech frequencies would likely anxious and frustrate a person with normal hearing ability (38). The Spanish Association of Otorhinolaryngology (SAORL) therefore acknowledged in their Madrid consensus statement: a sudden hearing loss in sensorineural nature of 20 dB in less than three connected frequencies occurring within a 12 hour-window as an incomplete SSNHL (39).

Finally, idiopathic sudden sensorineural hearing loss (ISSNHL) is considered as SSNHL in the absence of an identifiable cause following a decent investigation. This situation appears in up to 90% of all patients affected by SSNHL (8–10). The remaining cases with a clear explicable cause are specified as non-idiopathic SSNHL.

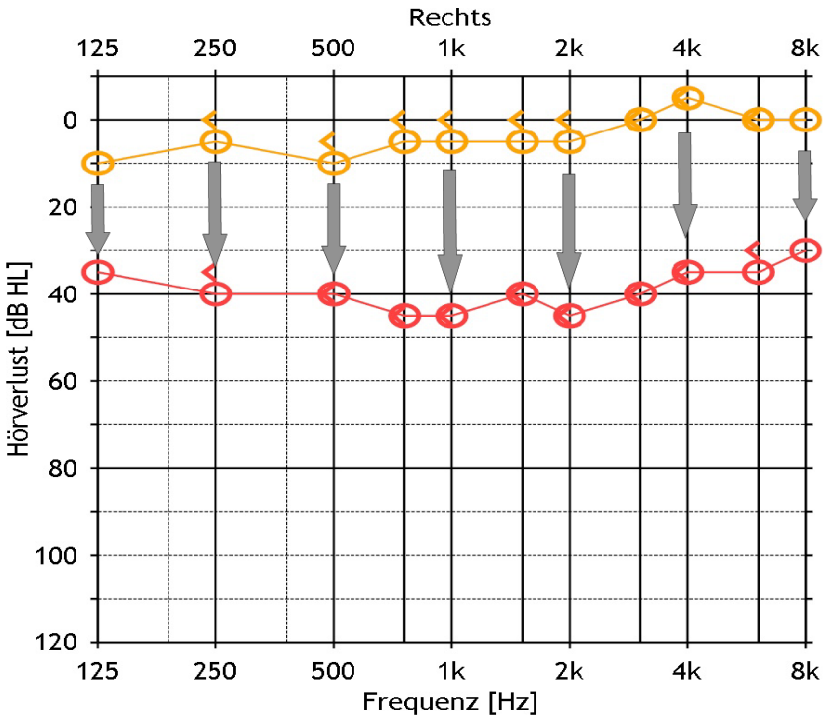

Figure 1: Audiometric criteria of ISSHL (yellow line: baseline hearing threshold, red line: post-morbid hearing threshold)

1.1.2 Epidemiology

The estimated incidence of ISSNHL ranges between 5 to 160 cases per 100.000 inhabitants per year according to prior reports (5,40–43). The by far most cited annual incidence rate of ISSNHL in literature is 5 to 20 per 100.000 people, noted in an epidemiologic report by Byl in 1984 (5). There are a few more recent studies focusing on the epidemiology of ISSNHL (40–43).

Teranishi et al. analysed the collected data from four nationwide surveys between 1972 and 2001, addressing otolaryngologists at hospitals all over Japan gathering clinical data of treated patients diagnosed with sudden hearing loss. The assembled quantity of patients was then used to approximately calculate the annual incidence of the disease. The authors observed a rise in the annual incidence rate throughout the 30 evaluated years, increasing from 3.9 per 100.000 in 1972 to 27.5 per 100.00 people in 2001 (40). A German study group enquired in otolaryngologic offices in Dresden, the number of medicated ISSNHL patients in the year 2004. The total city population served as denominator for the annual incidence estimation. The authors calculated an incidence rate of 160 per 100.000 inhabitants per year, by far the highest published incidence rate of ISSNHL. They assumed that the immense greater incidence rate

compared to the available data from other studies is a result of a higher awareness of the medical condition, larger number of patients seek medical attention and an improved health-care system (41).

The above-mentioned reports are survey-based studies obtaining incidences through localised samples and medical records from selected hospitals or medical offices. Such a study design may introduce selection bias. A more sufficiently accurate methodology of discovering epidemiological features of a disease are cross-sectional studies. ISSNHL is a relatively infrequent medical condition; hence, an extensive sample size is wanted to obtain precise epidemiological characteristics. Currently, two studies upon ISSNHL with population-based cross-sectional design exist (42,43). Alexander and Harris examined medical records from a huge health claims database, covering data of over 60 million people. All new cases of ISSNHL during 2006 and 2007 were analysed. The authors determined over the 2-year study duration the estimated incidence of ISSNHL in the United States as 27 per 100.000 people annually, with approximately 66.000 new occurrences per year (42). Wu et al. analysed data from the National Health Insurance program database of Taiwan, providing inpatients medical demands of over 20 million people. Patients newly diagnosed with ISSNHL during an almost 5-year period from 1998 to 2002 were identified. The annual incidence rate in Taiwan increased from 6.4 per 100.000 people in 1998 to 10.2 per 100.000 people in 2002. However, all the published incidences of ISSNHL are likely to be an underestimate, since many patients with spontaneous hearing recovery within the first days after onset, never see a physician (44).

Overall, the annual incidence rates rise with increased age. Alexander and Harris reported a steadily enlarged incidence with extending age, with a peak of 70 per 100.000 in the age group 65 and older (42). Similarly, the study from Taiwan found a continuously rising age-specific incidence with the highest incidence of 23.1 per 100.000 in those patients aged over 70 years (43). Teranishi et al. observed the greatest incidence rate of 58 per 100.000 in the age group 60 to 64 and a subsequently decrease in incidence in patients older than 65 years (40). Klemm et al. found a bimodal incidence peak in the 4^{th} and 6^{th} decade of life (41). Pediatric ISSNHL occurs very infrequently. In the study by Wu et al. there were 3.7% of all patients diagnosed with ISSNHL aged under 18 years with an incidence rate of 1.3 per 100.000 children. A few smaller, retrospective studies reported that 3.3% to 10.9% of patients with ISSNHL are pediatric cases (45–47).

In general, ISSNHL seems to appear nearly equal in sex distribution. Alexander and Harris found a male-to-female incidence ratio of 1.07 to 1.0 with a slightly predominance for elderly men (42). These findings are in line with the Taiwan study in which the male-to-female ratio

was identified as 1.14:1 (43). Contrarily, Klemm et al. reported a gender distribution of 1.22:1 with female predominance (41).

Universally agreement exists that elderly patients have a poorer chance for a hearing remission. Younger patients were found in numerous trials to have a better prognosis for hearing recovery and absolute hearing improvement compared to older patients (4–7,10,48,49). Interestingly, Byl noted a worse prognosis for hearing recovery in patients less than 15 years old, similar to patients with an age of over 60 years (5). It appears that sex does not have a prognostic impact on hearing recovery (5–7).

1.1.3 Etiology

In approximately 10% of the patients, an appropriate evaluation will distinguish a definite etiology of SSNHL, such as neoplasm or Menière's disease. In about 20% to 40%, coexisting clinical disorders are possibly causative related to SSNHL. The leftover of cases are assumed in the end as idiopathic (9). Many hypotheses of the underlying pathophysiological mechanism of ISSNHL have been suggested. The mainly suspected causes are: viral infections, vascular phenomena, membrane rupture and immune-mediated mechanisms (50):

1.1.3.1 Viral infections

Many viral infections have been associated with ISSNHL. Possible etiopathogeneses of virus-induced ISSNHL relies on direct injury of the cochlea or auditory nerve, the reactivation of dormant viruses within the spiral ganglion, and the indirect damage of inner ear tissues due to a systemic viral infection that result in pathologic immune responses within the labyrinth (51). The idea of viral infections causing ISSNHL remains popular for several reasons:

40% of all congenitally developed cases of hearing loss are due to viral infections, especially: cytomegalovirus (CMV), rubella and herpes simplex virus (HSV). Infections with the measles and mumps virus are well-documented diseases that can be accompanied with SNHL. Reactivation of inherent varicella zoster virus (VZV) inside the geniculate ganglion, lead to herpes zoster oticus which is typically characterised by: sudden peripheral facial nerve paralysis, vesicular exanthema on the external ear, vertigo, otalgia and SSNHL (52). The similarity in sudden hearing loss onset between this disorder and ISSNHL may support the viral hypothesis of ISSNHL (38).

Results of serologic studies investigating the relationship between viral infections and ISSNHL seems to be controversial (53–58). Such studies are commonly based on seroconversion or increased serum levels of specific antibodies. The group of Herpesviridiae are deemed as the most potential viral cause of ISSNHL. Representatives of this virus family have been disclosed serologically in the majority of people in particular showing seroconversion in more than 90% of adults for: HSV, VZV, Ebstein Barr virus, human herpes virus and in 70% for CMV. Therefore, the only hypothetical mechanism of causation from these viruses in most of the cases can be the reactivation. Serologic methods may not accurately diagnose virus reactivation; thus, making such a study design potentially biased (50). A more recent study detected anti-mumps acute- IgM antibodies in ISSNHL patients, and assumed that only 1% of all cases are due to an asymptomatic mumps infection (59). A different approach to investigate serologically the viral theory was performed by Pitkäranta and Julkunen. The authors were not able to identify in ISSNHL patients a higher level of interferon-α/β-inducible MxA protein or detectable interferon-α activity, both diagnostic blood markers for general viral infections. Consequently, their results contradicted the association between viral infections and ISSNHL (60).

A number of experimental trials in an animal model investigated the effect of direct pathogenic virus injection into the cochlea on hearing function, and changes in inner ear tissues (61–66). Hearing dysfunction, extensive damage of the sensorineural auditory elements, leukocytic infiltration and bleeding within the cochlea were found in various of these trials (61–63). Furthermore, Stokroos et al. medicated HSV infected guinea pigs with an antiviral agent in addition to steroids, and reported a better hearing outcome and less severe cochlea degeneration in comparison to the control group with steroid monotherapy (64). On the contrary, some other trials failed to observe major pathogenic impact following virus injection into the labyrinth (65,66).

As early as 1954, Lindsay and colleagues observed in ISSNHL patients diagnosed with measles or mumps, histopathological cochlea atrophy and attributed it to viral origins (67,68). Subsequently, several histopathologic studies reported virus-associated cochlea degeneration in postmortem human temporal bones of patients who suffered from ISSNHL during their lifetime (69–72). However, a critical review of these reports concluded that there is insufficient proof of a direct viral causation due to the lack of detection of virus particles and viral antigens within the cochlea. Moreover, an indication was made that in many cases the diagnosis of the viral infection is based on self-reports by the subjects and therefore may be incorrect.

Furthermore, the author stated that miscellaneous entities such as genetic mutations, trauma or ototoxic agents can result in comparable histopathological findings (50).

A systemic review and meta-analysis of RCTs revealed that the addition of antiviral agents to systemic corticosteroids in the primary treatment of ISSNHL shows no significant clinical benefits for the patients. This conclusion argues against the concept of a viral etiology (73,74).

Some of the above discussed studies do support indirectly the theory of viral causation. By contrast, there are also data against this hypothesis. The direct verification of the relationship between virus infections and ISSNHL displays as very challenging for a few reasons, such as the inaccessibility of inner ear tissues during life or technical limitations. Since there is no direct proof of evidence for a viral cause at the present time, the theory of virus-induced ISSNHL remains a matter of debate (50).

1.1.3.2 Vascular phenomena

The auditory sense organ is supplied by a terminal artery, namely the labyrinthine artery or internal auditory artery. The labyrinthine artery is usually a branch of the anterior inferior cerebellar artery, which originates consistently from the basilar artery. Rarely it derives from the posterior inferior cerebellar artery. The labyrinthine artery is an end artery and supplies besides the cochlea, also the vestibular organ. The audio-vestibular organs show an extensive energy demand due to its intense metabolism. The solely supply by the labyrinthine artery without any compensating collateral vessels, makes the cochlea especially sensitive to blood flow disruptions (75).

Perlman et al. obstructed in experimental animals temporarily the blood flow to the cochlea, which induced consecutive hearing loss. The authors observed irreversible hearing dysfunction when the blood supply of the inner ear interrupts for more than 30 minutes. A following histopathologic investigation of the temporal bones revealed a fibrosis and consequently ossification of the labyrinth (76). The majority of the studies focusing on postmortem histopathological cochlea changes in ISSNHL patients recognised barely fibrosis and ossifications in the labyrinth (69–72). A more recent study evaluated the cochlea histopathology of human temporal bones from ISSNHL patients and from subjects with normal hearing function which have undergone surgical procedures and showed postoperative hearing loss. Because the auditory nerve has been undamaged in these patients, the hearing loss was ascribed to vascular impairment during surgery. The authors identified in the surgery group in six out of seven samples, signs of fibrosis and ossification in the cochlea, while none

of the ISSNHL samples presented typically vascular-related histopathological changes, which disagrees with the vascular theory (77).

Various recent magnetic resonance imaging (MRI) studies on ISSNHL noted that the use of new imaging sequences can identify, and possibly differentiate intra-labyrinthine abnormal findings. According to these studies, the detection of high signal intensity in the cochlea on both T1-weighted and 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR), agrees with the existence of methemoglobin indicating intra-labyrinthine hemorrhage. On the other hand, the presence of hyperintensity only in the 3D-FLAIR sequences is consistent with an elevated protein level within the membranous fluid due to a damaged blood-labyrinth barrier, suggesting an acute inflammatory process within the cochlea (78–81). A current systematic review and meta-analysis on these studies determined a labyrinth abnormality in 29% of all included ISSNHL patients. Of these cases, 79% and 21% are presumed to have an acute inflammation within the cochlea and an intra-labyrinthine hemorrhage, respectively (82).

Thrombophilia is one out of the proposed vascular mechanisms to cause ISSNHL. A number of studies were unsuccessful to identify a causative association between ISSNHL and thrombophilic genomic polymorphisms involving gene mutations of factor V Leiden, prothrombin G20210A and methylene-tetrahydrofolate reductase C677T (83–85). Increased serum levels of fibrinogen may precipitate thrombosis by rising blood density and inducing endothelial dysfunction. In an animal study, high concentration of serum fibrinogen resulted in reduced cochlea perfusion and hearing dysfunction (86). However, a meta-analysis of clinical studies evaluating the correlation between ISSNHL and serum fibrinogen revealed that hyperfibrinogenemia is not associated with the development of ISSNHL (87). Another systemic review and meta-analysis investigated the role of platelet parameters in the etiopathogenesis of ISSNHL. The authors failed to identify a clear significant link between platelet parameters and ISSNHL (88). Pregnancy may cause ISSNHL due to its well-known increased risk of thrombosis. However, a recent longitudinal cohort study found no significant differences in annual occurrences of ISSNHL between pregnant and postpartum females (89).

Involvement of traditional cardiovascular risk factors in the development of ISSNHL have been widely discussed over the past decades. Numerous trials found higher rates of dyslipidemia, Diabetes mellitus type 2, hypertension and obesity in ISSNHL patients compared to healthy controls, while a direct proof of a causative relationship remains uncertain (90–94). Considering the high prevalence of these medical conditions in industrialised nations, further investigations are needed to justify their impact in the development of ISSNHL (95).

1.1.3.3 Membrane ruptures

The theory of membrane rupture was introduced by Simmons in 1968, and is generally based on an abrupt break of the cochlear membranes due to rapid pressure shifts within the labyrinth (96). Many potential causes of membrane rupture have been reported (96–98). Simmons observed in a few patients, a sudden onset of hearing loss immediately after physical activity or performing a Valsalva maneuver. He speculated that these factors may have increased rapidly the intracranial blood or cerebrospinal fluid pressure and induced subsequently a break of the intra-labyrinthine membranes, such as Reissner's membrane or tectorial membrane (96). A histopathological examination of two postmortem human temporal bones from ISSNHL patients supported this hypothesis by discovery of ruptures within the Reissner's membrane (99). Fee added perilymphatic fistulas (PLF) to Simmons theory once he surgically notified ruptures in the oval window membrane in patients with ISSNHL, ensuing physical head trauma (97). Goodhill found in patients who suffered from ISSNHL following barotrauma, ruptures in both oval and round window membrane, and differentiated explosive and implosive PLF. The pathophysiological mechanism of explosive PLF relies on sudden elevated cerebrospinal fluid pressure forwarding through the cochlear aqueduct or the internal auditory meatus to the labyrinthine membranes. Implosive PLF originates due to an increased middle ear pressure bulging the cochlea membranes into the labyrinth. Both routes may lead to loss of perilymphatic fluid through the emerged ruptures (98). However, the greater part of ISSNHL patients do not provide a recent history of trauma or intense physical activity (4). Hence, it is difficult to argue in the majority of cases in favor for the membrane rupture theory. Moreover, the majority of histopathological studies on postmortem temporal bones of ISSNHL patients have not found evidence for cochlear membrane ruptures (69–71).

It is further hypothesised that PLF and intra-cochlear membrane break may occur spontaneously. Shelton and Simmons reported in their Stanford Experience that 15 out of 65 ISSNHL patients with surgically validated PLF presented no trauma history of any kind, prior external/internal pressure changes or previously undergone middle ear surgery (100). The pathophysiological process behind the theory of spontaneous membrane ruptures has not yet been established. Suggested mechanisms include an imbalance of electrolytes in the cochlear fluids, pathological changes in the elasticity of the labyrinthine membranes, and abnormal pathways of basilar membrane vibration (4).

Definite identification of PLF appears to be very challenging. There is no trustworthy, clinical feature to predict this entity. The surgical approach to the middle ear space is the common practice to diagnose a presumed PLF. Surgical evidence of a PLF is mainly based on the

visualisation of fluid in the round window niche, and direct detection of cochlear window breaks (101). According to a nationwide survey in the United States in 1991, approximately half of the performed exploratory tympanotomies confirmed a supposed PLF (102).

However, some anatomical conditions must be taken into consideration. The tympanic promontory usually protrudes to some degree over the round window membrane and therefore allows infrequently the full inspection of the round window membrane (13). A surgical reduction of the overhanging bony prominence, aiming for a sufficient observation of the membrane, may cause fluid leak by itself (101). Another anatomical aspect that must be taken into account are fibrous plugs covering the round window niche. Such false membranes may be misdiagnosed as PLF (13).

1.1.3.4 Immune-mediated mechanisms

The proposed immunological involvement as causative factor for ISSNHL is based on the cross-reaction theory, and the so-called sympathetic labyrinthitis. According to the cross-reaction theory, recognition of inner ear antigens results in an irreversible damage of cochlear tissue by autoantibodies targeting these antigens. The hypothesis of sympathetic labyrinthitis suggests that antibodies and activated T-cells attack a prior damaged labyrinth produced by miscellaneous reasons like hypoperfusion or infections (103).

Because of the blood-labyrinthine barrier, the auditory sense organ has been regarded to be free from immune cells. Recently, numerous cells of the innate immune system, such as macrophagen or dendritic cells have been identified in the lymphatic sac of the cochlea, suggesting that the endolymphatic sac is the prime location for the immune defense in the labyrinth. These cells identify usually pathogenic microorganisms and initiates the innate immune response by releasing inflammatory cytokines like IL-1β and TNF-α. The released inflammatory mediators lead to a recruitment of antibodies and cytotoxic T-cells targeting the external antigens. It is hypothesised that lymphocytes originate from the peripheral blood system, proceeds through the spiral modiolar vein into the labyrinth, and surpass the blood-labyrinthine barrier. According to the sympathetic labyrinthitis theory, exposed proteins in inner ear tissue caused by infections or hypoperfusion, may be recognized as antigens, and further inducing self-damage of the cochlea by lymphocytes. The cross-reaction theory relies on the recent identification of autoantibodies targeting specific inner ear antigens. Up to now, several molecule structures of the cochlea, such as cochlin or heat shock protein 70, have been identified as potential inner ear antigen. Despite the discovery of cochlear damage due to

pathologic immune-mediated responses, the precise underlying pathophysiological process has still not been established (103–105).

However, immune-mediated SNHL involves in more than 80% of cases both ears, develops rapidly progressive rather than abrupt, occurs mainly in middle aged women, appears often secondary to other autoimmune diseases, shows a very high recovery rate, and responds sufficiently to immunosuppressive agents even after months, quite unlike to the clinical presentation of ISSNHL. Therefore, immune-mediated SNHL and ISSNHL are nowadays generally distinguished as separate entities (103,104). The role of detectable autoantibodies against inner ear antigens in patients with typical clinical presentation of ISSNHL remains unclear.

1.1.4 Clinical Presentation

1.1.4.1 Laterality

SSNHL occurs nearly exclusively unilateral. It is generally reported that less than 4.9% of all SSNHL cases presents a bilateral involvement. Bilateral appearance of SSNHL is usually associated with systemic conditions rather than being idiopathic in nature. According to a current systematic review and meta-analysis in which 103 cases were included, bilateral SSNHL is causative related to ototoxic agents in 29.1%, neoplasia, vascular accidents and autoimmune diseases in 16.5%, various systemic infections in 10.7%, idiopathic origin in 5.8%, iatrogenic injury in 3.9% and trauma in 1%. Bilateral SSNHL seems to be linked with a higher severity of hearing loss. Approximately half of the cases showed profound hearing impairment while a mild degree of hearing loss was seen only in 2.9%. Hearing improvement in bilateral SSNHL appears to be frustrating. Nearly half of the patients achieved no significant hearing improvement, whereas complete and partial hearing recovery was reported solely in 21.4% and 26.2% of the cases, respectively. Approximately half of the patients received systemic corticosteroids as therapy, with a treatment response of a bit more than 50%. In cases of corticosteroid treatment, the highest rate of hearing recovery was found in identified vascular accidents and autoimmune diseases (106).

Some patients with unilateral SSNHL experience a subsequent involvement of the contralateral side, resulting ultimately in bilateral SSNHL. Xenellis et al. therefore differentiate this condition as sequential bilateral SSNHL, and compared it to cases with solely unilateral or bilateral affliction. Sequential bilateral SSNHL was defined when the consecutive involvement of the opposite ear appears within 3 days. The authors documented 7 cases of sequential

bilateral SSNHL, 11 cases of simultaneous bilateral SSNHL and 232 cases of unilateral SSNHL. All patients were treated equally with systemic corticosteroids. With regard to the identified etiology, autoimmune diseases were the most common cause in simultaneous bilateral SSNHL, whereas idiopathic cause was the prevalent type in sequential bilateral and unilateral SSNHL. Unfortunately, potential retro-cochlear pathologies were not evaluated through generally recommended MRI; hence, results of the causative origin may be incorrect. However, the authors found statistically significant differences between the entities concerning initial hearing loss and hearing recovery. Simultaneous bilateral SSNHL showed a higher severity of hearing loss and a worse treatment outcome compared to sequential bilateral and unilateral SSNHL. The authors concluded that sequential bilateral SSNHL and simultaneous bilateral SSNHL present diverse clinical features and should be distinguished as separate conditions (58).

1.1.4.2 Accompanying symptoms

The appearance of ISSNHL can often be attended by co-existing symptoms. Common co-occurring morbidities are aural fullness, tinnitus and vertigo (3).

1.1.4.2.1 Aural fullness

Aural fullness is a very frequent co-existing morbidity in ISSNHL. More than 80% of the patients report an ear fullness coming along with ISSNHL. Solely few detailed investigations upon this subject matter exists (107,108). According to Sakata et al., presence of ear fullness sensation seems to be not associated with the audiogram slope of ISSNHL (107). Contrarily, another study found a significant higher prevalence of ear fullness in cases affecting the lower frequencies. The authors additionally proposed that a lack of pressure compensation among the labyrinth membranes may be a potential cause for these findings (108). Both studies agreed that there is no relationship between co-presenting sense of fullness and the initial severity of ISSNHL. Hearing improvement was greater in positive ear fullness cases compared to cases without sense of ear fullness. With regard to convalescence, vanishing of co-presenting sensation of fullness was clearly correlated to a greater hearing improvement. Patients with regressed sense of ear fullness showed in comparison to patients with a persistent feeling of ear pressure, a significant higher decrease in hearing thresholds. Therefore, the authors assumed the occurrence and the convalescence of accompanying ear fullness sensation as prognostic factors for the hearing recovery in ISSNHL events (107,108).

1.1.4.2.2 Tinnitus

The cognition of an auditory stimulus in lack of a matching exogenous sound, also known as tinnitus, is a quite prevalent symptom that accompanies ISSNHL events. It is reported that a co-existing tinnitus occurs in 62% up to 93% of all ISSNHL cases (4,48,93,109,110). Numerous trials evaluated the prognostic association between accompanying acute tinnitus and ISSNHL with inconsistent results. Some studies identified the occurrence of acute tinnitus as positive prognostic factor for hearing recovery (48,109), while others failed to detect any prognostic association between co-existing tinnitus and ISSNHL (93,110).

However, a persistent tinnitus might have a significant negative influence on a patient's quality of life. A recent study; therefore, evaluated in ISSNHL patients their everyday life's burden due to secondary and persistent tinnitus through the validated tinnitus handicap inventory – a questionnaire covering functional, psychological and social aspects. 90% of the 283 included patients presented a new occurrence of tinnitus. Approximately two-third of the tinnitus cases were reported as being either mild or moderate in terms of severity. Cases with low-frequency involvement showed a more intense tinnitus. The severity of secondary tinnitus was not associated neither with the profundity of initial hearing loss nor with the degree of hearing recovery. The prognosis of tinnitus appeared to be independent from profundity of primary hearing impairment or audiogram pattern. 79% of the tinnitus cases showed a significant decrease of tinnitus related handicap. This improvement in a patient's quality of life was significantly correlated with the reduction of hearing impairment (111).

1.1.4.2.3 Vertigo

Vertigo is compared to aural fullness and tinnitus a less frequently seen accompanying symptom in ISSNHL events, with an incidence rate ranging from approximately 30% to 60%. (4,5,8,10). The co-occurrence of this symptom may be causative related with the anatomical and phylogenetical juxtaposition of cochlea and vestibular organs. Presence of vertigo in patients with ISSNHL has been generally correlated to a worse prognosis of hearing recovery. Numerous articles upon this relationship have been published. A current systematic review and meta-analysis summarised the findings of studies focusing on the prognostic association between co-existing vertigo and ISSNHL. The article included a total sample size of 4814 cases. 35.5% of these patients experienced a sensation of co-presenting dizziness or vertigo while the remaining 64.5% showed no signs of a disequilibrium. The authors found a clearly

significant association regarding hearing recovery between patients, with and without vertigo. Patients with secondary vertigo achieved a clinically significant hearing recovery in 42%, whereas patients without co-presenting vertigo had a clinically significant hearing recovery rate of 60%. However, this article has not identified the intensity of vertigo or the activity of the peripheral vestibular organ. The magnitude of co-existing vertigo in ISSNHL events can diverge widely among patients. Moreover, it should be differentiated if the peripheral vestibular system is intact or manifest a dysfunction (112).

According to Rauch, an event of ISSNHL with co-existing vertigo shall be distinguished as two distinct clinical entities, namely, labyrinthitis or cochleovestibular dysfunction and ISSNHL with vestibulopathy. These two conditions may rely upon separate pathophysiological processes. Cochleovestibular dysfunction consists of a unilateral ISSNHL and an acute unilateral peripheral vestibulopathy. In this condition, hearing loss is usually more severe and barely responses to corticosteroids. Furthermore, the peripheral vestibular system presents a dysfunction and the feeling of vertigo is more intense and lasts longer. Contrarily, unilateral ISSNHL with vestibulopathy shows generally a less excessive sensation of vertigo with a shorter time period of presence. Therefore, it is conducive to perform a vestibular assessment in ISSNHL cases with accompanying vertigo in order to differentiate between these two clinical manifestations (113).

Apparated assessment of the peripheral vestibular system includes inter alia the vestibular caloric stimulation, ocular and cervical vestibular-evoked myogenic potential (VEMP). The vestibular caloric stimulation assesses the function of the lateral semicircular canal. Together with oVEMP, which evaluates the utricular activity, they investigate the function of the superior vestibular nerve. cVEMP expresses the function of the saccule and thereby the capacity of the inferior vestibular nerve. Yu and Li conducted a systematic review and meta-analysis of studies investigating instrument-based cochleovestibular integrity in ISSNHL patients, with and without vertigo. A bit more than 50% of the patients with vertigo showed a vestibular dysfunction, whereas approximately 25% of the non-vertigo group presented some kind of vestibule lesion. Furthermore, the authors subdivided 4 different patterns of labyrinth dysfunction according to the location of lesion. The most prevalent pattern of labyrinth dysfunction was the lateral semicircular canal, followed by the saccule, utricle and cochlea solely. Patients with vestibular dysfunction had a worse prognosis for hearing recovery compared to the patients with intact integrity of the vestibular system (114).

1.1.4.3 Severity of hearing loss

The degree of hearing impairment can be assessed by pure-tone audiometry and is generally displayed with the 4-frequencies pure-tone average (PTA) in dB hearing level. The 4f-PTA represents the arithmetic mean of the hearing thresholds at the frequencies of the human speech, including 0.5, 1, 2 and 4 kilohertz (kHz). The term PTA will be used equally to 4f-PTA in the current thesis. The severity of hearing loss is widely classified according to the dB level of the PTA. The World Health Organisation (WHO), defines 4 different grades of bilateral hearing impairment including: mild: 26-40 dB, moderate: 41-60 dB, severe: 61-80 dB and profound to deafness: >80 dB (115). Few authors may have used the classification of the WHO in order to describe the profundity of hearing loss in ISSNHL patients. However, there is no standardised severity classification of unilateral hearing loss. Presumptively, the most commonly used severity classification of ISSNHL include: mild: 20 – 40 dB, moderate: 41 – 70 dB, severe: 71-90 dB and profound: > 90 dB (22):

In 2010, the global burden disease study revised the current WHO classification of hearing impairment and additionally involved a separate category for disabling unilateral hearing loss, which is defined as hearing loss of more than 35 dB in the worse ear, with a hearing threshold of less than 20 dB in the normal ear. The revision included the decrease of the normal hearing function threshold from 25 dB to 20 dB and the implementation of a 15 dB step as grading system, resulting in 6 different classes of hearing impairment. According to the revised WHO classification, the PTA severity types of hearing loss can be differentiated between: mild: 20 - 35 dB, moderate: 35 - 49 dB, moderately severe: 50 - 64 dB, severe: 65 - 79 dB, profound: 80 – 94 dB and complete deafness: > 94 dB (116):

Some authors applied the hearing classification system provided by the Committee on Hearing and Equilibrium of the AAO-HNSF in order to describe the severity of hearing loss in ISSNHL events (117,118). The AAO-HNSF hearing classification system involves, besides the basic hearing loss degree assessed by pure-tone audiometry, also the functional hearing handicap measured by speech audiometry and expressed as word recognition score (WRS) (117). The AAO-HNSF classifies a serviceable and a non-serviceable hearing function. A serviceable hearing level renders a patient as candidate for conventional hearing amplification, whereas a patient with a non-serviceable hearing function will usually not profit from conventional hearing devices (3). According to the Committee on Hearing and Equilibrium of the AAO-HNSF, hearing function can be differentiated into four different types based on PTA and WRS level (117):

- Type A: ≤ 30 dB and ≥ 70% WRS
- Type B: > 30 dB, ≤ 50 dB PTA and ≥ 50% WRS
- Type C: > 50 dB and ≥ 50% WRS
- Type D: any level of dB and < 50% WRS

Type A and Type B correspond to a serviceable hearing function while Type C and Type D indicate a non-serviceable hearing level. The usage of the AAO-HNSF classification system for characterisation of the hearing loss severity in ISSNHL events, might be convenient because the current clinical practice guidelines included this format into their recommended definition of the different degrees of hearing recovery (3). However, an internationally standardised system of hearing impairment severity in ISSNHL patients is essential for a good comparison among future studies.

An additional issue to concern is that the determined severity of hearing impairment at initial consultation after symptom onset must not be equal to the precise degree of hearing loss due to ISSNHL. Some patients may have had already some extent of hearing impairment on the affected ear before the onset of ISSNHL. The assessed level of PTA at the primary visit may; therefore, not always reflect the exact degree of hearing loss owing to ISSNHL. In most cases, a pre-morbid audiogram is not available in order to assess the level of the hearing function before the onset of ISSNHL. In these situations, the opposite healthy side can be used to determine the baseline hearing function of the affected ear. Thus, the difference between the baseline hearing function and the severity of hearing impairment at initial consultation represents approximately the degree of hearing loss in ISSNHL events. A requirement for this calculation is a presumed symmetrical hearing capacity before the onset of ISSNHL. In cases of a reported unequal hearing function before symptom onset and a lack of an available pre-morbidity audiogram, the precise extent of hearing loss in ISSNHL cannot be determined accurately.

Various trials identified in ISSNHL cases a significant prognostic association between the severity of initial hearing loss and hearing improvement. Presumptively, a high profundity of hearing loss seems to be one of the greatest negative predictors for hearing recovery (4–7,49,109,110).

1.1.4.4 Pattern of hearing loss

ISSNHL can be divided into subtypes with regard to the audiogram pattern. The subtypes are usually distinguished by the affected frequencies in addition, with the degree of hearing loss. In general, low-frequencies comprise ≤ 0.5 kHz, mid-frequencies consist 0.5 - 2 kHz and high-frequencies involves ≥ 2 kHz (119). A standardised classification of the audiogram characteristics in ISSNHL events does not exist. A frequently used pattern of the audiogram shape is the subjective categorisation into: ascending (low-frequency hearing loss, figure 2A), cup-shaped (mid-frequency hearing loss, figure 2B), descending (high-frequency hearing loss, figure 2C), flat (hearing loss over all frequencies, figure 2D) and total deafness (figure 2E). Based on the objective evaluation, various audiometric criteria for these subtypes have been applied (4–6,119).

Affection of lower frequencies has been generally associated with a better prognosis for hearing recovery (4,6,7,49).

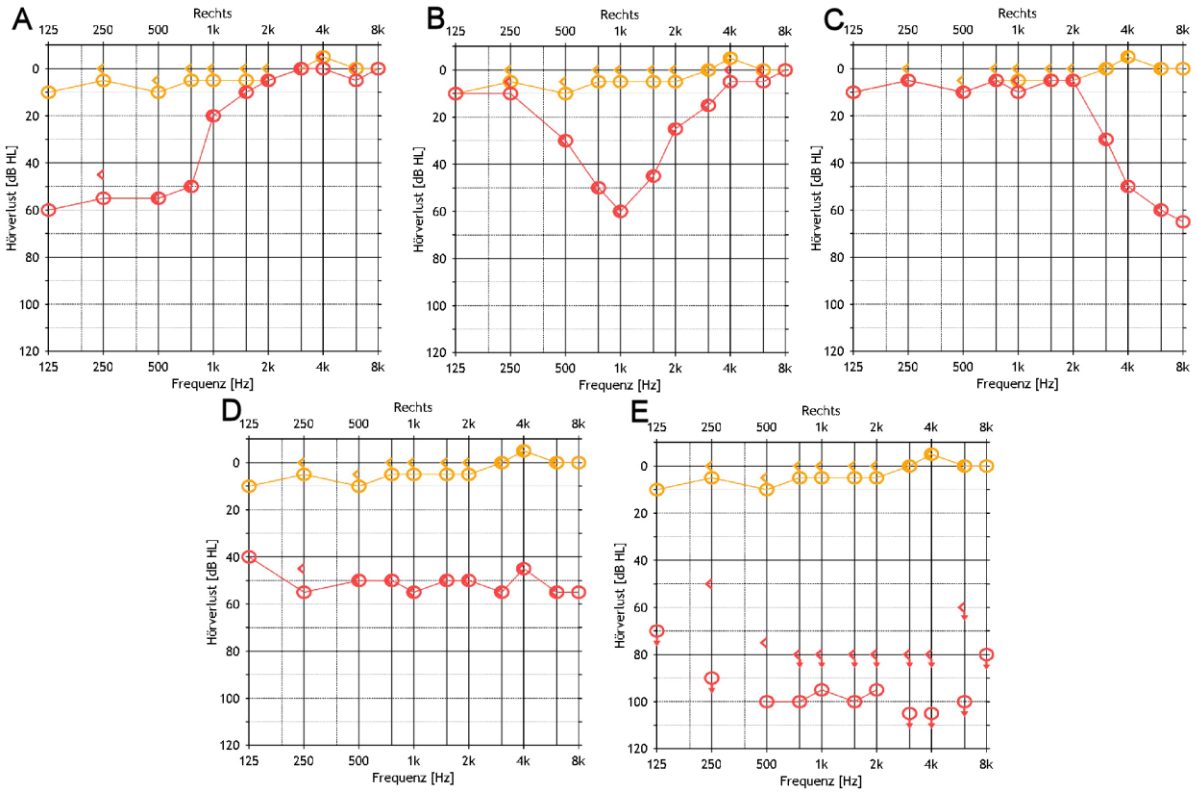

Figure 2: Audiometric patterns of ISSNHL

1.1.4.5 Natural hearing recovery

Some patients affected by ISSNHL may recover spontaneously without any treatment. Hearing recovery in ISSNHL due to its natural evolution have been reported with an incidence rate ranging between 31% to 68%. (4,6,120–122). However, definition of recovery varies among these studies. Moreover, some studies did not distinct between complete and partial recovery (120,121).

Only two prospective controlled trials with a higher level of evidence evaluated the natural evolution of untreated ISSNHL patients (4,120). Mattox and Simmons reported a natural complete hearing remission in 35% out of 28 cases. Additionally, 43% achieved spontaneously an absolute hearing gain of at least 30 dB (4). Wilson and colleagues observed in 52 untreated patients a natural hearing recovery of 58%. Unfortunately, they missed to distinguish between complete and partial recovery (120). A few more, non-controlled or retrospective studies with a lower level of evidence have been published upon non treated ISSNHL cases (6,121,122). Weinaug et al. found in 63 untreated patients, a natural hearing improvement of 89% with a fully hearing remission of 68% (122). Chen and colleagues determined retrospectively the natural hearing recovery in 52 untreated subjects as 31% (121). Nosrati-Zaronoe and co-workers analysed in a retrospective manner the clinical findings of ISSNHL patients gathered in a Swedish national database. Out of 208 patients, 44% were not treated with any kind of therapy. Of these patients, 28% showed a hearing improvement of more than 30 dB and 36% presented an absolute hearing gain between 10 dB to 30 dB. With regard to hearing remission, 47% achieved a partial recovery and 17% regained their normal hearing function (6).

A recent meta-analysis including only RCTs, evaluated the hearing improvement in ISSNHL patients who received some kind of placebo therapy as control group. The authors identified a mean absolute hearing gain of 14.3 dB for the placebo-treated cases. Hearing recovery rates were not calculated, probably due to a lack of reporting or different definitions of recovery (123).

A further large multi-center RCT, not included in the above mentioned meta-analysis, found in ISSNHL patients receiving some form of placebo therapy, a complete and partial hearing recovery rate of 53.8% and 28.8%, respectively (124).

1.1.4.6 Prognostic factors

As pre-discussed, many factors have been associated as prognostic factors for hearing recovery. In conclusion, the most frequently reported predictors for a better prognosis of hearing remission are:

- Lower severity of initial hearing loss (4–7,49,109,110)
- Younger age (5–7,10,48,49)
- Earlier start of treatment (5–7,49,109)
- Presence of co-existing vertigo and/or vestibular dysfunction (112,114)
- Affection of lower-frequencies (4,6,7,49)

1.1.5 Diagnostics

Broad consensus exists among national guidelines on the diagnostic management of ISSNHL (3,39,125). The diagnostic pathway is based on the distinction between the different kinds of hearing loss and on the identification of potential underlying conditions. The by far most comprehensive and cited guidelines on ISSNHL are provided by the AAO-HNSF. The current AAO-HNSF guidelines include the following diagnostic recommendations (3):

- History taking and physical examination – Strong recommendation
- Audiometric assessment – Recommendation
- Routine laboratory examinations – Strong recommendation against
- Routine computed tomography (CT) – Strong recommendation against
- Evaluation of retro-cochlear pathologies with MRI or auditory brainstem response (ABR) – Recommendation

1.1.5.1 History taking and physical examination

Sudden hearing loss can be a consequence from both, impairment of the conductive auditory elements and of the sensorineural auditory elements. Moreover, frequent co-presenting symptoms, including aural fullness and tinnitus, can occur in both kinds of hearing loss. Therefore, a fundamental diagnostic aspect at the first consultation is to distinguish between sudden CHL and SSNHL, as both conditions diverge completely in terms of further diagnostic, treatment and prognosis. Patient's medical history, an otologic -focused physical examination and a following audiometric assessment are the required parts for an accurate distinction of these two entities (3).

Physicians should obtain a thorough general and otologic history from consulting patients by reason of a SSNHL. Essential factors of a patient's anamnesis are: the evolution of hearing loss onset, unilateral or bilateral appearance, history of fluctuating or recurrent hearing loss, evaluation of the hearing function before symptom onset, history of recent trauma of any kind, existing medical conditions, undergone otologic surgeries, recent intake of ototoxic agents, presence of typical otologic symptoms including otalgia, otorrhea, vertigo, tinnitus and aural fullness, neurologic and other systemic symptoms (3).

Assessment of systemic and neurologic symptoms is mandatory in order to rule out a medical emergency such as hypertensive crisis or stroke. Presence of severe dizziness and vertigo together with SSNHL may be caused by a vascular occlusion in the area of the anterior inferior cerebellar artery. In such cases, a quick clinical examination by using the HINTS test is obligatory (13). The HINTS test was established by Kattah et al. and comprises: the horizontal head impulse test (HI), evaluation of a pathologic nystagmus (N), and the test of skew (TS). Compared to early MRI, a normal head impulse test, a central nystagmus and a positive skew deviation show together a higher sensitivity to distinguish between central and peripheral origin in the acute vestibular syndrome (126). If the HINTS test forecloses a central etiology, a following apparated vestibular examination should be performed to evaluate the function of the peripheral vestibule organs.

The otologic-focused physical examination includes: the direct inspection and palpation of the external ear, the otoscopic visualisation of the external acoustic meatus, and the tympanic membrane and optionally, tuning fork tests. For instance, vesicular exanthema on the auricle and/or external ear canal displays a strong indicator for herpes zoster oticus as sudden hearing loss cause. Ear-microscopic evaluation can identify etiologies of CHL, such as external ear infection, impacted ear wax or several middle ear diseases. However, otoscopic signs of CHL do not exclude automatically the occurrence of SSNHL. Thus, a following audiometric

assessment is essential for a precise diagnosis. In absence of an early available audiometry, a tuning forks test may support the preliminary identification of SSNHL (3). Solely one trial compared in SSNHL patients tuning fork findings with the results of audiometric examination. In this RCT, in which 250 ISSNHL patients without CHL were included, the Weber test showed a sensitivity of 78% with a 99% agreement between lateralised cases and audiometric results (127).

1.1.5.2 Audiometric assessment

Audiometric examination is essential to verify ISSNHL. As already discussed, the most frequently used audiometric criterion for the diagnosis of ISSNHL, is a sudden decline in hearing function of at least 30 dB in three or more consecutive frequencies developing within 72 hours (37). For this definition, it is required to ascertain the pre-morbid hearing capability of the affected ear. In most cases, a previous audiometric examination is not available in the patient's medical records for a direct comparison. A generally applied approach is to use the hearing thresholds of the contralateral, healthy side, in order to determine the baseline hearing function of the affected ear. An assumption for this practice is the symmetric hearing function before the onset of hearing loss. This information should therefore always be obtained during patient's medical history taking (3).

According to the AAO-HNSF and SAORL, the essential parts of the audiometric examination in ISSNHL events are pure-tone audiometry, speech audiometry and immittance measurement (3,39). The German Association of Otorhinolaryngology – Head and Neck Surgery (GAORL-HNS), stated in their guidelines from 2014 that speech audiometry may be beneficial in particular cases (125). However, it must be emphasised that the German guidelines are currently in revision and that the American and Spanish guidelines have recently been updated (both in 2019). Consistency exists on the performance of otoacoustic emissions as expedient examination (3,39,125).

In our opinion, the main component of the audiometric assessment is the pure-tone audiometry as it is mandatory for the diagnosis of ISSNHL. Physicians should audiometrically confirm ISSNHL as soon as possible due to the fact that an early start of treatment seems to be a positive prognostic factor for hearing recovery (5–7,49,109). The AAO-HNSF recommends to perform a pure-tone audiometry within two weeks since hearing loss onset (3). Pure-tone audiometry is a behavioral and subjective test to determine the basic hearing function of an individual. It evaluates pure-tone hearing thresholds, which are defined as the minimum

required sound level to perceive a pure tone stimulus at a specific frequency. Pure-tone thresholds are measured in dB-hearing level. 0 dB in the hearing level scale represents the average hearing threshold of young healthy adults with normal hearing function. Pure tone hearing thresholds are generally measured bilaterally and separately for air conduction and for bone conduction. Hearing thresholds are computed from 0,125 to 8 kHz at octave skips with additionally semi-octave intervals if required. The universally pure-tone audiometric parameter is the PTA. It represents the arithmetic mean of the hearing thresholds at specific frequencies within the human speech (128).

Speech audiometry examines the functional auditory ability of an individual to perceive speech stimuli. This diagnostic evaluation is especially relevant in incompletely recovered cases, who may profit from hearing amplification after ISSNHL: The AAO-HNSF implicated for that reason speech audiometric parameters in their recommended assessment of hearing outcome (3). Obtained parameters by speech audiometry are the speech recognition threshold (SRT) and the WRS. The SRT constitutes the lowest intensity level at which the patient is capable to correctly repeat at least 50% of presenting spondee words. The SRT of people with a normal hearing function averages 18.5 dB sound pressure level. The difference between this normal value and the evaluated SRT is classified as speech hearing loss. This parameter corresponds approximately to the calculated PTA. The SRT serves to estimate a suitable intensity level for suprathreshold speech recognition testing and to cross-check the validity of pure tone hearing. The WRS is a suprathreshold value for speech recognition. Suprathreshold testing determines how precisely speech is recognised at a normal conversational level. The WRS reveals the percentage of correct repeated monosyllabic nouns presented at a suprathreshold level. The generally used intensity level for WRS testing is 65 dB sound pressure level. At this intensity level, a person with normal hearing abilities is able to recognise for sure 100% of the presented items. The Freiburg speech intelligibility test has been established in the past decades as gold standard for speech audiometry in German-speaking countries. The Freiburg test comprises 10 clusters of 10 binary numbers and 10 clusters of 20 one-syllable words. The Freiburg test shows several deficiencies, like the use of old-fashioned words, lack of test material equivalence or the imbalance in phonemics, and has been vastly criticised for that in the past. On that account, many other German-language speech tests have been devised, such as the Göttingen sentence test or the Oldenburg sentence test. However, none of the alternatives adjusts all the disadvantages of the Freiburg test. Thus, the Freiburg test remains with its widespread use the German-language standard speech test in clinical practice (128).

Immittance diagnostics involves tympanometry and the stapedius reflex test. Both tests can be used to investigate the middle ear integrity and to exclude air conduction impairment (3). Tympanometry is generally recommended as immittance measurement. Stapedius reflex testing needs high-intensity stimuli which can be very discomforting for ISSNHL patients and may even induce further hearing impairment. Therefore, this procedure should solely be performed if necessary, and if so, not in the acute or subacute phase of the condition (3,39,125).

Otoacoustic emissions as a diagnostic tool in ISSNHL can be applied in order to support the differentiation between sensory and neural origin in patients with at least moderate hearing loss (3). Additionally, the early detection of otoacoustic emissions following ISSNHL appears to be a positive predictor for a greater hearing recovery (129).

1.1.5.3 Laboratory examinations

Strong consistency exists on the laboratory assessment as a part of the diagnostic pathway of ISSNHL. Guidelines recommend to not execute routine laboratory test batteries (3,39,125). In this context, the term “routine” stands for a universally performance of laboratory examinations in the absence of regarding the clinical characteristics of the patient. Particular laboratory parameters might support the recognition of the etiology of SSHL in selected cases where the patient’s anamnesis, medical history, and/or physical examination provide a strong causative hint. However, the majority of trials investigating the usefulness of laboratory testing are either small case series or observational studies with a low level of evidence. Furthermore, there is insufficient evidence that any laboratory test result would lead to an adjustment of the disease management or to a greater recovery of the hearing function. Moreover, the consequences of false-positive test results may include a psychological burden for the patient or financial costs for the health-care system due to redundant consecutive investigations. Therefore, it is recommended to consider specific laboratory examinations solely in appropriate cases (3,13).

1.1.5.4 Computed tomography

The AAO-HNSF stated in their clinical practice guidelines, a strong recommendation against the routine performance of immediate CT in patients with supposed diagnosis of ISSNHL following an appropriate neuro-otological investigation (3). This recommendation is mainly based on the American College of Radiology appropriateness criteria © of imaging in hearing loss and/or vertigo. According to these criteria, a CT of the head, regardless of the use of

contrast, is usually not appropriate as initial imaging modality in cases of acquired SSNHL due to its preponderance of harm over benefit (130). The benefits-harm assessment of initial CT imaging in presumptive ISSNHL involves the high radiation exposure, possible side events of intravenous contrast and the lack of support for the differential diagnosis. However, the AAO-HNSF specifies clearly that their recommendation implies solely those SSNHL cases in which initial evaluation (patient's medical history taking and physical examination) failed to identify a potential cause for sudden hearing loss. In some specific situations, initial CT imaging may be appropriate. If SSNHL is accompanied with focal neurological symptoms, a contrast-enhanced CT of the head may be appropriate to rule out a stroke and transient ischemic attack. For SSNHL patients with a recent history of head trauma, an initial head CT may be appropriate to exclude a temporal bone fracture or a large vestibular aqueduct syndrome. SSNHL cases with history and otoscopic signs of chronic middle ear diseases may need an initial CT of the temporal bone to foreclose a tympanogene labyrinthitis. CT as diagnostic imaging modality for SSNHL may also be obtained in other circumstances such as systemic bone diseases or conditions which make the patient ineligible for MRI, e.g. pacemakers (3).

1.1.5.5 Evaluation of retro-cochlear pathologies with MRI or ABR

It is universally recommended that all SSNHL cases, regardless of their hearing recovery, should be evaluated for retro-cochlear pathologies (3,39). Retro-cochlear pathologies can be described as textural lesions of the vestibulocochlear nerve and the central auditory system. These conditions, especially vestibular schwannomas (VS), have been identified as the underlying cause for SSNHL in a small percentage of the cases (9). Diagnostic modalities for the evaluation of retro-cochlear pathologies are ABR and MRI (13). Nowadays, MRI is the advised diagnostic tool and ABR should be performed solely when a MRI is not possible to obtain. An ideal time frame for the MRI cannot be provided precisely due to the lack of enough published data. The AAO-HNSF stated that SSNHL patients should undergo a MRI within an acceptable period of time (3). According to the SAORL, a MRI should be done within the first two weeks since the disease's onset (39).

ABR measures evoked electrical potentials originating from the central auditory pathways in response to an external auditory click stimulus. The responded potentials are typically recorded as five waves, namely Jewett I to V, of which each wave corresponds to an anatomical structure of the central auditory system. VS or other masses can debilitate the conduction of the auditory action potentials due to its juxtaposition to the auditory nerve. This impairment can then be seen as prolonged latency of the waves III and V in comparison to the

healthy side (13). A meta-analysis which included 3.314 patients with surgically confirmed VS, examined the sensitivity and specificity of ABR measurement as a diagnostic tool for VS. ABR could correctly detect a VS in 93.4% of the cases. According to a size-related subgroups analysis, VS greater than 1 cm were correctly recognized in 95,6% whereas the sensitivity for VS with a size smaller than 1 cm quantified merely 85.6%. The specificity of ABR for VS was determined as 82% (131). However, there are some limitations to take into consideration in this context. The sensitivity of ABR corresponds to the severity of hearing impairment, which means that VS in SSNHL patients with a less severe hearing impairment have a higher probability to be overseen. Additionally, ABR cannot be obtained in cases with a hearing impairment of 80 dB in the frequency range of 2 to 4kHz (132). Another issue to consider when choosing ABR as diagnostic modality for SSNHL is that each pathological ABR result must either way be confirmed by a MRI. Furthermore, a non-pathological ABR test result does not exclude a VS automatically. In these cases, an extensive follow-up testing is required and in events of progressive hearing loss or new occurrence of ABR abnormalities, a MRI is a-fortiori indispensable (3). Moreover, a MRI can provide, in contrast to ABR, supplementary facts other than the simple presence of VS (13). In summary, ABR as a diagnostic tool for evaluation of retro-cochlear pathologies in SSNHL should be considered solely for patients with contraindications against MRI and for elderly patients who are unlikely to undergo surgical treatment due to a small cochlear or retro-cochlear tumor (3).

Since the late 1980s, MRI has been established as gold-standard for retro-cochlear pathology diagnosis in SSNHL (13). Pathological MRI findings that are causative associated with SSNHL have been reported with a range of 4.4% to 12.5%. Out of these, VS is the most prevalent pathology (133–135). VS shows in SSNHL cases an overall incidence rate of approximately 4% (13). However, the likelihood of incidental abnormalities that are not linked with SSNHL represents a significant disfavor of the high-resolution MRI (3). For instance, a study reported that 46% of the 57% overall abnormality rate were not directly related to SSNHL (133).

MRI should be carried out, as possible, on a 3-Tesla scanning machine. The imaging field should include the temporal bones (TB) with special attention on the labyrinth, the internal auditory canal and the cerebellopontine angle (136). Inappropriate MRI imaging, such as a head MRI instead of a TB MRI, use of thick layers or missed attention to the aforementioned anatomical structures, may often lead to a misdiagnosis of pathologies, especially small and intra-labyrinthine VS (13). There are few TB MRI protocols that can be applied. The protocol that will be used often hinges on the accessible technological material and the radiological expertise (3). Traditionally, protocols are based on the evaluation of cochlear and retro-

cochlear tumors, demyelinating processes and central vascular phenomena as potential origin of SSNHL (39). A very frequently performed protocol due to its common disposability is the gadolinium-enhanced TB MRI protocol. If available, this protocol should involve heavily T2-weighted 3D steady state free precession – gradient echo sequences and T1-weighted 3D fast spin echo sequences (3). Some researchers reported a similar high sensitivity for VS of non-enhanced gradient echo sequences but with the beneficial addition to be more economical, and to avoid potential possible side effects of contrast (137). However, unenhanced MRI sequences may fail to recognise other retro-cochlear lesions than VS. More recent applied imaging techniques are concepted to gain more knowledge of the pathophysiological processes behind ISSNHL (39). Some authors have recommended to routinely include 3D-FLAIR sequences in the TB MRI protocol because they may identify intra-labyrinthine abnormalities, such as hemorrhage, inflammation or intra-cochlear VS and therewith may support the etiological clarification of ISSNHL. However, these sequences are currently not widespread among clinicians and it has yet not established how those novel imaging techniques may change the clinical and therapeutic management of ISSNHL (136).

1.1.6 Treatment

Based on the suggested pathophysiologic processes causing ISSNHL, a variety of different therapies has been tried in the past. Commonly prescribed drugs were corticosteroids, antiviral agents, vasodilators and rheologic substances. In addition to these agents, a large number of other medications have been suggested (3) – to name a few: vitamin C (138), dietary elements [e.g., Zinc (139)], N-acetylcysteine (140), Co-enzyme Q10 (141). Other used treatment modalities are hyperbaric oxygen therapy (HBOT), and surgically sealing of the labyrinthine membranes (101,142).

In terms of viral infections as suggested cause of ISSNHL, the aforementioned experimental animal-based data, results of serologic studies and histopathological findings may have led some researches to apply antiviral agents as therapy of ISSNHL. To date, four RCTs have investigated the efficacy of antiviral agents as treatment for ISSNHL (143–146). These four trials were incorporated into the Cochrane review by Awad et al., published in 2012 (147). A total of 257 patients were included in this review. All four studies compared the effectiveness of antiviral agents (acyclovir or valacyclovir) in addition to systemic corticosteroids against systemic corticosteroids only. Three of the trials were conducted placebo-controlled and double-blinded. These three studies had a very low risk of overall bias (143,144,146). The 4th study showed a high risk of bias due to missing information regarding randomisation,

allocation, blinding and exclusion of patients (145). All included trials demonstrated no significant benefit of the additional use of antiviral agents as treatment of ISSNHL (147). In addition, one of the studies observed antiviral agents-related side effects, including insomnia, nervousness and weight gain (144). Therefore, the AAO-HNSF, SAORL and GAORL-HNS recommend that physicians should not prescribe antiviral drugs as treatment of ISSNHL due to its preponderance of harm over benefit (3,39,125).

One of the commonly proposed cause of ISSNHL is ischemia of the auditory sense organ. By reason of etiological indices from experimental and histopathological studies, researchers have tried for the treatment of ISSNHL some substances which are supposed to enhance the blood flow, namely vasodilators and rheologic agents. In 2009, Agarwal and Pothier conducted a Cochrane review upon this subject matter (148). The authors could incorporate in their review solely three RCTs with a total sum of 189 patients (149–151). All included trials showed a high risk of bias due to a low methodological quality. The applied vasodilators and rheologic agents in these trials were prostaglandin E1, naftidrofuryl and carbogen. Because of the small sample sizes and the considerable heterogeneity between the trials regarding methodology, outcome assessment, type, dosage, and duration of the used rheologic treatment, the authors were not able to prove the effectiveness of vasodilators (148). Further applied rheologic agents including pentoxyfylin (152), *Ginkgo biloba* (153), calcium antagonists (154), volume expanders (155), defibrinogenating agents (156) and anticoagulants (157), could not be proven as effective neither. Considering the lack of efficacy and the potential adverse events, such as allergic reactions, bleeding, hypotension, or arrhythmias, there is a universal recommendation against the usage of vasodilators and rheologic agents in the treatment of ISSNHL (3,39,125).

Following the arise of the membrane rupture theory, surgically sealing of the labyrinthine membranes with soft tissue has been suggested in some areas, especially Germany, as therapy option for ISSNHL (39). The basic principle of this practice is to stop the drainage of the perilymphatic liquid. Performance of exploratory tympanotomy and sealing of the cochlear windows in ISSNHL cases is controversially debated in the otolaryngological society. The generally used diagnostic indicators to carry out this procedure are a high grade of hearing loss, intense vertigo or the failure of conventional treatment (101). Several studies reported a beneficial audiological effect of this therapy (142,158). However, all these trials are retrospective observations with small sample sizes and absence of an appropriate comparison group (12). Hence, there is a lack of clear evidence for the efficiency of exploratory tympanotomy and sealing of the cochlear windows as therapeutic option in ISSNHL cases. The performance of this treatment procedure has therefore decreased in the recent years.

Exploratory tympanotomy and sealing of the labyrinthine windows should be reserved for ISSNHL cases with at least profound hearing impairment where the patient's history reveals a solid hint for PLF (102). The AAO-HNSF did not mention this treatment modality within their guidelines (3). The German guidelines only stated that a diagnostic tympanotomy can turn into a useful therapy option, when a PLF is surgically validated (125). The SAORL recommends sealing of the labyrinthine membranes solely in cases when a PLF is highly suspected (39).

In similarity to rheologic agents, the rationale of HBOT in the therapeutic management of ISSNHL is based on cochlear ischemia as proposed etiology of ISSNHL. HBOT allows for enhanced oxygen delivery to the auditory sense organ, which is especially sensitive to blood flow disruptions due to its solely supply by the internal auditory artery without any compensating collateral vessels. During HBOT, patients are exposed in typically rooms to 100% oxygen at an ambient pressure higher than the atmospheric level. There is a variety in existing HBOT protocols regarding daily exposure time (45 - 120 minutes), used pressure (1.5 - 2.5 atmospheric absolute pressure) and total count of sessions (15 – 25 visits) (159). The American Undersea and Hyperbaric Medical Society recommends a HBOT regiment consisting of 10 to 20 sessions of 100% oxygen at a 2 - 2.5 atmospheric absolute pressure for 90 minutes (160). An updated Cochrane review from 2007 included 7 RCTs (392 pooled patients) investigating the efficacy of HBOT as primary treatment of ISSNHL. All included studies showed methodological flaws resulting in a high risk of overall bias. The nature of the control group differed substantially between trials (pharmaceutical agents, sham treatment or no treatment). Due to insufficient reports and a variety of used outcome measures, only restricted meta-analyses were possible. The authors concluded that there is limited evidence of the efficacy of HBOT as primary treatment modality for ISSNHL. Furthermore, patients with a mild degree of hearing loss and a treatment delay more than two weeks, were less likely to recover (159). A further RCT compared the efficacy of HBOT alone against HBOT concomitantly to corticosteroids as primary treatments. Both therapy modalities improved the hearing function significantly and no difference in hearing outcome between the therapy modalities was found (161). In 2018, Rhee et al. conducted a systematic review and meta-analysis including 19 studies with a total sum of 2401 patients (three RCTs, two prospective trials, 14 retrospective trials), which investigated the effect of HBOT in addition to corticosteroids vs. corticosteroids alone, either as primary treatment (12 studies) or as salvage treatment (seven studies). The authors reported an overall significant benefit of the additional HBOT with a pooled odds ratio of 1.61 (*CI:* 1.05-2.44) and 1.43 (*CI:* 1.20-1.67) for complete and any hearing recovery, respectively, and a weighted mean difference in absolute hearing improvement of 8.7 dB (*CI:* 5.05-12.43). With respect to subgroups analyses, additional HBOT

was more beneficial when given as salvage treatment. Moreover, the concomitant treatment resulted in a greater hearing recovery in patients with initial severe and profound hearing loss (≥70 dB) (162). It must be noted that the heterogeneity of the overall meta-analysis was extensively high (I^2=79%). Seven of the nine subgroups analyses showed a heterogeneity of I^2>50%, especially the significant results stated by the authors. Hence, the findings of this meta-analysis should be interpreted with caution (163). Nevertheless, a further systematic review, published recently in 2020 by the experts of the American Undersea and Hyperbaric Medical Society (164), reported similar findings as Rhee et al. (162). It seems that HBOT may result in the greatest hearing improvement when given as an adjunct. Despite its relative safe adverse-events profile, HBOT may cause in rare occasions side effects including eustachian tube dysfunction, ear-, sinus- and lung-barotrauma, claustrophobia, worsening of cataracts and oxygen poisoning. Moreover, HBOT is very cost-effective and time-consuming. Taken the pre-discussed lack of clear evidence for efficacy and the harm/cost assessment into consideration, the American guidelines on ISSNHL provided the following statements: Physicians may offer HBOT concomitantly to corticosteroids as an option, either as primary treatment within 14 days since hearing loss onset or as salvage treatment within four weeks since hearing loss onset (3). Similarly, the European Committee for Hyperbaric Medicine recommends HBOT as an adjunct to medical therapy when initiating within two weeks after the occurrence of ISSNHL. Moreover, they stated that it is appropriate to offer ISSNHL patients HBOT as additional treatment if they present between two and four weeks since hearing loss onset, especially to those with severe and profound degree of hearing loss (165).

Sufficient data regarding the efficacy of other medications, such as vitamins or minerals, as treatment option of ISSNHL are lacking. Recommendations for their usage are therefore not available (3). Researchers are consistently seeking for new effective agents as treatment option of ISSNHL. In experimental animal-based trials, insulin-like growth factor-1 (IGF-1) has been attributed otoprotective effects against cochlea damage by ischemia and ototoxic agents (166,167). Following small pilot trials (168), a larger multi-center RCT was conducted to evaluate the clinical efficacy of IGF-1 as salvage treatment option for ISSNHL. In this trial, hearing outcomes between 62 patients, receiving intratympanic applied IGF-1 interpolated in gelatin hydrogel, and 58 patients who were treated with 4x intratympanic dexamethasone injections within one week, were compared. The authors failed to find a significant difference in hearing recovery (>10 dB) between the groups. However, there was a trend towards significance favoring IGF-1 (66.7% vs. 53.6%, p=0.109) (169). Another promising agent for the treatment of ISSNHL might be AM-111 (brimapitide) (3). AM-111 is an inhibitor of the JNK stress kinase, which plays a fundamental role in the sensory cell apoptosis after mechanical

and chemical stress reactions within the cochlea (170). Researchers have experimentally demonstrated that AM-111 possess otoprotective effects (171,172). In 2019, results of an AM-111 phase-3 trial were published (173). In this multi-center, double-blind, placebo-controlled, three-arm RCT, 256 ISSNHL patients received either AM-111 at 0.4 mg/ml or 0.8 mg/ml or a placebo. AM-111 was impregnated into a hyaluronic acid gel and delivered intratympanically. The primary efficacy parameter was the absolute hearing improvement in dB PTA, assessed at the 4-weeks follow up visit. In the overall analysis, the authors failed to find a significant difference between the three treatment arms (0.4 mg/ml AM-111: 38.4 dB, 0.8 mg/ml AM-111: not-specified in the article, placebo: 33.8 dB, p=0.226). Subgroups analyses revealed that solely 0.4 mg/ml AM-111 resulted in a significantly higher hearing improvement than placebo in patients with profound hearing loss (42.7 dB vs. 26.8 dB, p=0.018), whereas no significant differences between groups were found in patients with severe hearing loss. The authors related these findings to experimental evidence showing that the JNK pathway is activated only at a higher severity of cochlear damage (174). To conclude, AM-111 at 0.4 mg/ml may be an effective treatment option for ISSNHL patients with a profound degree of hearing loss. At the moment of this writing, AM-111 is commercially not yet available (173).

In light of the natural hearing recovery and unknown etiology of ISSNHL, none of the treatments have been directly proven as effective. However, the most accepted and prescribed therapy are corticosteroids due to its balance in their benefits-harm and cost assessment. Corticosteroids as a treatment option are separately discussed in the sections 1.6.3 and 1.6.4. The most comprehensive guidelines on ISSNHL, provided by the AAO-HNSF, stated the following treatment recommendations (3):

- Corticosteroids as primary treatment – Option
- Intratympanic corticosteroids as salvage treatment – Recommendation
- HBOT, in addition to corticosteroids, as primary treatment – Option
- HBOT, in addition to corticosteroids, as salvage treatment – Option
- Antiviral drugs and vasoactive/rheologic agents – Strong Recommendation against
- Other pharmaceutical agents – No comment due to insufficient evidence
- Surgically sealing of the labyrinthine membranes – Not specified

1.1.6.1 Outcome assessment

An issue that arises in this context is how to measure and quantify the outcome of the therapy. Clearly, the adequate method for assessing the efficacy of a treatment for ISSNHL is the comparison of the respective audiometric examinations before and after the therapy. The nearly universally used audiological examination is the pure-tone audiometry. In this case, the PTA serves as the reference parameter. Although there are different versions of the PTA, depending on how many frequencies are involved in the calculation (3f-PTA, 4f-PTA, 5f-PTA, 6f-PTA, 9f-PTA). Presumptively, the most commonly applied variant is the 4-frequency PTA, including the frequencies of the human speech (500 Hz, 1 kHz, 2 kHz, 4 kHz). However, dynamics in the very low (125 Hz, 250 Hz) and high frequencies (6 kHz, 8 kHz) are not covered by this parameter; hence, the results might be biased in ISSNHL cases where these frequencies are mainly affected. The 9-frequency PTA, which covers the complete audiometric range, may therefore, represent a more accurate parameter. Though, Plontke et al. compared the different PTA variants and concluded that the PTA choice does not have a significant influence on the treatment outcome of ISSNHL patients. Several authors further defined, according to the frequency range, separately a low-, mid- and high tone PTA. However, these parameters do not comply with the audiometric criteria of ISSNHL (≥ three affected frequencies) (175). Nevertheless, frequency-specific PTAs may provide supplementary information when calculated additionally for subgroups. The selection of the PTA type probably hinges on the available audiometric equipment, which usually automatic calculates a predefined variant. An interesting alternative was made by Burschka et al. In their calculation of the PTA, only those frequencies with a hearing loss of at least 15 dB compared to the baseline function were incorporated. By using this so-called “affected PTA”, solely frequencies that are actually afflicted will be analysed (153). However, affected frequencies with 10 dB hearing loss would be overlooked in this case and the mean hearing loss severity would be subsequently miscalculated. Moreover, delayed hearing loss in initial “unaffected” frequencies would further not be covered by the affected PTA. Another factor that must be taken into account is the test limit of the used audiometric equipment. If the hearing threshold is above the limit of the audiometric device, the test limit will be “dummy coded” as hearing threshold. Varying test limits may influence the calculated absolute hearing improvement. A higher dummy coded hearing threshold allows for a higher amount of potential hearing improvement. For instance, patients with a dummy coded PTA of 130 dB are in principle able to improve 30 dB more than patients with a dummy coded PTA of 100 dB, despite potentially equal hearing capability (175).

A further frequently applied audiometric examination is the speech-audiometry. The reference parameter for this method is the WRS. However, an unbiased inter-individual comparison of WRS findings appears challenging. Several test conditions have the ability to confound the result of speech-audiometry including: type of voice presentation (recorded vs. live), environment setting (noise vs. quite), intensity level of presentation and characteristics of the used test material, (e.g.; word list length, words choice). Moreover, particular languages differ considerable in their phonemics. The AAO-HNSF recommends to measure WRS at a 20-30 dB suprathreshold intensity level by using recorded test material consisting of ideally 50-words lists (3).

In 2017 at the Ear-Nose-Throat World Congress by the International Federation of Oto-rhino-laryngological Societies, specialists upon ISSNHL from all over the world gathered together and drafted an international consensus statement on treatment management of ISSNHL. In this statement, the specialists proposed that the absolute evolution of pure-tone hearing thresholds should be used as the primary outcome measure for a few reasons: absolute hearing improvement as a continuous variable provides much more information than categories of hearing improvement. The presence of a significant hearing improvement and the grade of hearing recovery, both categorical variables, should therefore be considered as secondary outcome parameters. Moreover, pure-tone hearing thresholds are independent of the subject's language; hence, making them comparable internationally. Absolute change of WRS should therefore serve as a secondary outcome parameter to provide further important information regarding functional hearing capability. Similar to pure-tone hearing thresholds, significant evolutions of WRS can be determined as a further secondary outcome measure (11).

In this context, significant refers to clinically significant rather than statistically significant. A hearing improvement may have statistical significance without being meaningful in a clinically way. However, several definitions of a clinically relevant hearing improvement have been suggested. In any case, the result must exceed the test-retest reliability of the examination method, in order to potentially consider it as clinically relevant (175). The test-retest reliability of pure-tone audiometry has been determined as 5 dB (176,177). So, this value is definitely not appropriate to serve as a clinically significant criterion. The next audiometric step is usually 10 dB. A change of at least 10 dB in pure-tone hearing thresholds is therefore generally considered as clinically relevant. Although, since 10 dB does not far surpass the value of reliability, some authors employed 15 dB, 20 dB or even 30 dB as criterion for clinical relevance. Nevertheless, the ISSNHL specialists advocated the usage of the 10 dB cut-off

(3,11,175). Concerning WRS, clinically meaningful improvements should be assessed by using Thornton's and Raffin's binomial distribution table rather than fixed values. WRS follow a binomial distribution, which means that the distribution of WRS is larger in the middle (50%) of its possible range (0%-100%), than at the edges. A fixed significance value (e.g., 15%) may cause an incorrect result, especially at the range extremes. Moreover, the substantial impact of word list length must be considered. The variance of WRS decreases with increasing word list length. These influencing factors are covered by Thornton's and Raffin's binomial distribution table. The authors evaluated separately for a 10-, 25-, 50- and 100-words list the upper and lower 95% critical interval limits of each WRS percentage score (0-100%). When comparing intra-individual WRS scores, the post-treatment value has to surpass the upper limit of the 95% critical interval of the pre-treatment value so that the improvement of speech recognition can be deemed as significant. For example, in case of an initial WRS of 40% for a 25-words list, the post-treatment WRS must exceed 64% in order to consider this improvement as clinically significant (3,178).

Another aspect that needs to be considered is the pre-morbid hearing level. Patients with an initial normal hearing function have a broader range of possible absolute hearing improvement than patients with a certain degree of pre-morbid hearing impairment. Furthermore, an absolute hearing improvement of 20 dB, for instance, may result in different benefits for different patients: a patient with a pre-morbid normal hearing function will benefit certainly more from an absolute 20 dB hearing improvement than a patient with a pre-morbid mean hearing threshold of 50 dB. Therefore, in addition to absolute parameters, relative parameters should also be utilised. A shortcoming of relative outcome parameters is the requirement of the baseline hearing function. In the vast majority, a pre-event audiometric evaluation is not available. Therefore, it is recommended to consider the contralateral hearing level as baseline, unless a pre-morbid asymmetric hearing was present. In such cases, relative outcome parameters cannot be assessed accurately. When a pre-morbid asymmetric hearing was present, some authors proposed to apply age-related normalised hearing thresholds (DIN EN ISO 7029) as a baseline to compare with (179).

Relative parameters include the relative hearing improvement and the grade of hearing recovery. The relative hearing improvement can be calculated by the following formula (3,175):

(pre-treatment PTA – post-treatment PTA) / pre-treatment PTA – contralateral PTA) x 100%.

Concerning grades of hearing recovery, a variety of classifications has been proposed. The most prominent are the Wilson's criteria (120), Siegel's criteria (180), and the classification provided by the Japanese Ministry of Health, Labor and Welfare (181). Grades and definition

of recovery differs considerably between these classifications, making direct comparisons among studies difficult. However, these categories do not regard the patient's functional hearing ability. The AAO-HNSF; therefore, incorporated WRS and distinction of serviceable hearing levels into the preferred Wilson criteria and recommends the following hearing recovery classification (3):

- *Complete recovery*: Improvement to within 10 dB PTA and 10% WRS of the contralateral side
- *Partial recovery* is defined in two ways, based on the patient's initial hearing level after ISSNHL onset and before start of treatment:
    - Serviceable hearing level (≤50 dB PTA and ≥50% WRS): improvement of >10 dB PTA or ≥ 10% WRS
    - Unserviceable hearing level (>50 dB PTA and <50% WRS): recovery into a serviceable hearing range
- *No recovery*: any hearing improvement of <10 dB PTA

1.1.6.2 Follow-up

The first follow-up visit should take place immediately after completion of primary treatment, in order to evaluate treatment outcome and to identify those patients who might benefit from a second-line therapy due to insufficient hearing recovery. If a subsequent salvage therapy is carried out, a second short-term follow-up at the conclusion of treatment should be performed. The vast majority of hearing recovery occurs within the first weeks since onset of ISSNHL. In approximately 80%-90% of the patients with delayed recovery, total hearing improvement is completed at the 1-month follow-up. The remaining 10%-20% still achieve a certain degree of hearing improvement within the next two months. A very small percentage of patients exhibit a slightly additional improvement in hearing function within three to six months since ISSNHL onset. The proportion of delayed hearing improvement after six months is negligible (182,183). It is therefore recommended to schedule a long-term follow up within six months after hearing loss onset, based on two reasons: first, to capture delayed hearing recoveries and second, to identify those patients, who might need audiologic rehabilitation and other supportive measures, e.g., hearing amplification devices (3).

1.1.6.3 Systemic corticosteroids

Corticosteroids as treatment of ISSNHL has been employed for over 40 years and still maintain the standard therapy for this hearing disorder. The rational basis was certainly their known anti-inflammatory activity, although in the 1970s where this therapy option was introduced, it was not even known whether the inner ear exhibits glucocorticoid receptors at all. Years later, researchers could demonstrate the presence of glucocorticoid receptors in the inner and outer auditory hair cells, spiral ligament and neurons of the spiral ganglion. The specific mechanisms of corticosteroids within the cochlea in the event of ISSNHL, remains uncertain. Their use in the treatment of ISSNHL is widely relied upon their ability to relieve inflammations and edemas. However, besides their anti-inflammatory and immunosuppressive properties, corticosteroids impact several other metabolic processes within the ear, including the maintenance of the blood-labyrinth barrier integrity, endolymph ion homeostasis, cochlear blood flow and inhibition of the apoptosis of impaired auditory hair cells (184).

Despite extensive prescribing, the effectiveness of corticosteroids in the treatment of ISSNHL remains unproven. The first evidence is provided by the hallmark study of Wilson et al., conducted in 1980 (48). In this double-blind, placebo-controlled RCT, 33 patients, who were treated with oral corticosteroids, were compared to 34 patients, receiving a placebo. A third group consisting of 52 patients, who did not participate in the study, served as a non-treated control group. The hearing outcome was assessed at the 4-week and 3-month follow up visit. The authors reported a significant difference in recovery rate (complete + partial) between the treatment and placebo groups (61% vs. 32%) and concluded the efficacy of corticosteroids. However, there were some major issues resulting in a high risk of bias. First, due to the recruitment of subjects from two independent clinics, an extensive heterogeneity in the total study population can be found: patients received differed kinds of corticosteroids (methylprednisolone or dexamethasone) at varying concentrations over different durations. Second, the baseline characteristics (age, presence of vertigo, audiogram pattern, group size) differed considerably between groups, indicating an inadequate randomisation. Third, there was insufficient information regarding allocation concealment and blinding. Finally, the non-treatment control group had a recovery rate of 58% - similar to the steroid group. Nevertheless, the study by Wilson et al. was included in the Cochrane Review upon this subject matter. The Cochrane Review was first conducted in 2006 and recently updated by Wei et al. in 2013. After the last update, more than 300 potentially relevant articles were reviewed and solely two further RCTs fulfilled the eligibility criteria and were included (12). In the double-blind RCT by Cinamon et al., published in 2001, 41 patients were allocated to 4 treatment arms: 1 mg/kg/day of oral prednisolone, carbogen inhalation, room air inhalation or placebo. The interventions were

performed for five consecutive days and hearing outcomes were evaluated at day 6 and at a long-term follow up. The authors failed to find a significant difference in all hearing outcome measures between the treatment groups (185). Similar to Wilson et al., the study showed extensive methodological flaws causing a high probability for bias (12). The third included study was conducted more recently in 2012 by Nosrati-Zarenoe et al. In this double-blind, multi-center RCT, the authors compared hearing outcomes of 47 patients, who were treated with 60 mg/day prednisolone for three days and a following oral taper for five days, against 46 patients, who received a placebo. The efficacy criterion for corticosteroids was defined as an absolute hearing improvement of >10 dB greater than placebo. The study hypothesis could not be confirmed as the mean difference in hearing improvement between the prednisolone and placebo groups was -0.9 dB (25.5 dB vs. 26.4 dB, p=0.863) at day 8, and 3.9 dB (39 dB vs. 35.1 dB, p=0.484) at day 90, respectively (186). Likewise, there were too many shortcomings in the study to ensure a high quality. The authors of the Cochrane Review concluded that systemic corticosteroids as treatment of ISSNHL cannot be confirmed as effective, neither be proven as ineffective, due to several reasons: The overall quality of the included trials was low. Furthermore, there was a large heterogeneity between the trials, which did not allow any pooling of the findings. Moreover, it is difficult to ascertain the exact proportion of hearing improvement due to corticosteroids in consideration of the highly variable spontaneous hearing recovery. Finally, the sample sizes of the RCTs were small. The Cochrane Review authors demonstrated that approximately 1000 patients would be necessary in order to identify a 10% significantly higher hearing recovery rate with corticosteroids, if the spontaneous hearing recovery is assumed to be 60% (12). Same conclusions were stated in an independent systematic review and meta-analysis by Conlin and Parnes (73,74).

A variety of systemic corticosteroid protocols for the treatment of ISSNHL exists. Sufficient data of direct comparisons between different protocols are lacking in literature. The used drugs are prednisone, methylprednisolone and dexamethasone. Systemic corticosteroids are widely administered in low or medium doses for several days up to a few weeks with a following taper course (3,13). Presumptively, the most frequently applied regiment is 60 mg/day prednisone (11). Considering the varying anti-inflammatory potencies of the corticosteroids, the equivalent dosages are 48 mg/day methylprednisolone and 10 mg/day dexamethasone. These dosages are currently recommended by the AAO-HNSF, with a duration of 7 to 14 days and a subsequent similar long taper course (3). The SAORL advocates the usage of 1 mg/kg/day prednisone or 1 mg/kg/day methylprednisolone for five days and a following dose reduction every five days until a total treatment period of 25 days is reached (39). Systemic corticosteroids can be applied by the intravenous or per-oral route. A recommendation

concerning the systemic application method is not specified in the American guidelines (3). However, the by far most common used method of application is certainly per-oral. Nevertheless, experimental, animal-based trials have demonstrated higher corticosteroid concentrations in the perilymph when administered intravenously rather than per-orally (187). This might be the reason why the SAORL stated in their ISSNHL guidelines that physicians may apply corticosteroids by the intravenous route in cases of severe or profound hearing loss (39). A few studies evaluated the effect of high-dosed corticosteroids as treatment of ISSNHL. A double-blind RCT compared an extremely high-dosed and short-termed protocol consisting of 300 mg/day dexamethasone for three days to a standard dosed regiment (70 mg prednisolone on day 1 with following reduction of 10 mg per day). No significant differences in hearing outcomes between the dosage groups were reported. Similar findings were observed from another trial that applied a 500 mg/day methylprednisolone pulse-therapy (188). Contrary, some retrospective studies supported the utilisation of high-dosed corticosteroids as treatment of ISSNHL (189,190). Furthermore, Niedermayer et al. obtained perilymph samples of patients undergoing a stapedotomy, who received preoperatively either 125 mg or 250 mg intravenous prednisolone. The latter group showed a significantly higher corticosteroid concentration in the perilymph, whereas the 125 mg group had similarly low values as a control group, whose subjects got a placebo (191). Based on these reports, the German guidelines recommends 250 mg/day methylprednisolone (or an equivalent dosage of other corticosteroids) for three consecutive days as primary treatment of ISSNHL. From an endocrinological aspect, a taper course may not be necessary in case of a short-term, high-dose corticosteroid administration (125). However, the evidence for the superiority of high-dosed regiments is low. A large multicenter, triple-blind, three-armed RCT (HODOKORT study), which is currently ongoing, aims to address this lack of evidence (192).

Despite their unproven efficacy, systemic corticosteroids are the most frequently prescribed treatment for ISSNHL. The administration of corticosteroids may be accompanied by potential adverse events that can affect many organs of the body. Common side effects of systemic corticosteroid use in healthy individuals include: insomnia, irritability, weight gain, and gastrointestinal upset. They may also lead to a worsening of pre-existing underlying conditions, such as hypertension, diabetes mellitus or glaucoma. However, the risk of severe side effects is very low, as these mainly appear when the medication is taken for a longer period of time. The commonly occurring adverse events during the usually 2-weeks treatment duration, such as insomnia, nervousness/restlessness or hypertension, are short-termed, self-resolving and/or manageable. Considering the lack of clear evidence for efficacy and the potential for adverse events, the AAO-HNSF concluded in their ISSNHL guidelines a balance in the benefit-

harm assessment (3). In light of the current available evidence, it may be acceptable for physicians to follow a wait-and-see strategy initially, as the majority of natural hearing recovery occurs within the first days since hearing loss onset (4). On the other side, several studies determined treatment delay as predictor for a poorer hearing improvement (6,7,49,109). Some researchers, however, attributed this association to a “sham-effect”: patients, who consulate a physician several days after hearing loss onset, may have already improved in hearing function by a certain degree due to the natural course of the disease (193). Nevertheless, persistent hearing loss after ISSHNL may dramatically impair a patient’s quality of life. Therefore, the AAO-HNSF suggests systemic corticosteroids as a treatment option for ISSNHL within two weeks of symptom onset (3). In any case, the patients should be informed comprehensively regarding the disease and the therapy should be arranged in agreement with the patient.

1.1.6.4 Intratympanic corticosteroids

Over the past decades, the local inner ear treatment by direct drug application into the middle ear has been increasingly situated in the center of research. This treatment modality is being used for a variety of inner ear disorders including: ISSNHL, Menière’s disease, autoimmune-mediated hearing loss, acute/chronic tinnitus, noise-induced hearing loss and ototoxicity-related hearing loss. In 1996, Silverstein et al. were the first to use ITS as therapy of ISSNHL (194). The rational basis for the ITS treatment of ISSNHL is the same as for systemic corticosteroid therapy: reduction of inflammation and edema, maintaining the blood-labyrinth barrier integrity and endolymph ion homeostasis, enhancing the cochlear blood flow and inhibition of the apoptosis of impaired auditory hair cells (3,184).

The local treatment has the following advantages by comparison with the systemic therapy: bypassing the blood-labyrinth barrier, avoiding a first-pass metabolism and preventing systemic adverse events (13). Bypassing the blood-labyrinth barrier and avoiding a first-pass effect result in a higher drug concentration in the perilymph. In a pioneering experimental trial by Parnes et al. conducted in 1999, guinea pigs received corticosteroids either by the systemic or intratympanic route. Perilymph samples were taken at different time points after the administrations, and the corticosteroid concentrations within the inner ear fluid were measured. The intratympanic application yielded a significantly higher drug concentration in the perilymph (187). Further experimental, animal-based trials reported similar findings (195). This evidence was confirmed in a human setting as well. During cochlea surgery, Bird and colleagues compared the corticosteroid concentrations in perilymph and blood plasma samples between patients with preoperative intratympanic or intravenous corticosteroid administration. The

authors observed that intratympanic administration of 4 mg dexamethasone and 40 mg methylprednisolone provides an 88x and 127x times higher steroid concentration in the perilymph and a 40x and 16x times lower steroid concentration in the blood plasma, respectively, compared to the usually medium-dosed systemic administration (196,197). Even after a high-dosed systemic application (1 mg/kg methylprednisolone), the intratympanic route led to a 33x fold higher drug concentration in the perilymph (196).

The corticosteroid has to be applied in the tympanic cavity in order to pass into the inner ear. There are three methods of drug delivery for the ITS treatment, namely: intratympanic injection, transtympanic instillation through a ventilation tube and sustained-released drug carrier systems (29). During intratympanic injection, the tympanic membrane is punctured by a 22 to 27-gauge spinal needle and the medication is subsequently injected into the middle ear cavity (15). Instead of needle perforation, a myringotomy, made by an ear-drum knife or a CO^2-laser, may be utilised. An average injection amount of 0.4 to 0.8 ml is recommended (3). In our experience, the middle ear cavity should be nearly completely filled (approximately 0.7 ml). Otherwise, an exceeding volume may produce a too high middle ear pressure, resulting in a backflow of the medication. The second method, transtympanic instillation, requires the insertion of a ventilation tube. The medication is then instilled through the tube into the tympanic cavity. This method has the advantage that the patient can self-administer the drug by using ear drops. However, it remains debatable how much of the medication actually enters the middle ear. Moreover, the risk for a tympanic membrane perforation is higher (29). The third delivery method are sustained drug release devices. This technique also needs the insertion of a ventilation tube. The drug carrier system can then be placed through the tube at the round window niche. Available devices are the Silverstein MicroWick and microcatheters (e.g., *μ*-Cath and e-Cath). The Silverstein MicroWick consists of polyvinyl acetate and has a size of 1 mm in diameter and 9 mm in length. The medial wick end touches the round window membrane and the lateral wick end is located at the external ear canal. Similar to the second method, the patient is instructed to daily self-administer the medication into the external ear canal. Thereby, the device allows for a near-continuous drug perfusion into the cochlea. Round window catheters administer the medication continuously by using a pump system. The cartridge of the pump that is filled with the medication is attached outside the ear. The tip of the microcatheters is anchored in the bone of the round window niche. The microcatheters usually contain two separate lumens. Through the first lumen, the medication is administered by the micropump at a continuous rate to the catheter tip, where the drug enters the inner ear through small orifices at the tip end. The second lumen serves for the drainage. Sustained-released devices allow for a continuous drug delivery; however, they are high in cost, time-

consuming and at greater risk for adverse events due to their invasiveness, especially the microcatheters (198). Intratympanic injection is the most preferred delivery technique for several reasons: this method has the advantages to be less invasive, safer and more cost efficient than the others. Moreover, there is no clinical evidence for the superiority of transtympanic instillation and sustained-released drug delivery over intratympanic injection (29). Therefore, the AAO-HNSF recommends intratympanic injection by needle perforation as the main delivery technique for ITS treatment of ISSNHL (3).

Following the intratympanic application, the drug entry into the inner ear happens via passive diffusion through the round window membrane and stapes footplate. The round window membrane consists of three layers: an external cuboid epithelium that is part of the middle ear mucosa, an intermediate layer composing of connective tissue (collagen, elastic fibers) and an internal squamous epithelium facing the scala tympani. The stapes footplate covers the oval window that represents the entrance to the scala vestibuli. With respect to the round window membrane, the stapes footplate is composed of the same three layers. The physical barrier between the tympanic cavity and the perilymph is provided mainly by the outer epithelial layer, due to its intrinsic properties. The round window membrane is deemed as the primary location for the inner ear entry. For a long time, the stapes footplate has not been considered as potential passage into the inner ear, though, recent research refuted this assumption. Nevertheless, the exact contribution of the two membranes on the inner ear drug entry remains uncertain (198,199). In experimental guinea pigs, a drug passage into the apex of the cochlea via the bony otic capsule was observed (200). However, the human bony otic capsule is far thicker than those of rodents; hence, it is highly unlikely that this route of entry appears in humans (199).

Both, round window membrane and stapes footplate, constitute semi permeable boundaries between middle and inner ear. The ability of pharmaceutical agents to passively diffuse through semi permeable membranes depends on certain chemical properties including: molecular weight, polarity and lipophilicity. Two parameters can be used to quantify these properties: The Wildman and Crippen n-octanol/water partition log *P* coefficient (WLOGP) describes the lipid solubility. The topological polar surface area value (TPSA) gives the sum of present polar molecules. This parameter also takes the molecular weight into account. Drugs which are lipophilic (high WLOGP), and contain small, less polar molecules (low TPSA), diffuse readily through semi permeable boundaries. Contrary, drugs which are less soluble in lipids (low WLOGP), and have large, very polar atoms (high TPSA), do not pass slightly through

biological membranes. The individual molecular properties of the corticosteroids play; therefore, an important role in the local treatment of ISSNHL (27).

Anatomical circumstances and physiological processes of the middle ear have a significant impact on ITS treatment. In the normal state, the tympanic cavity is air-filled with an ambient pressure. The presence of a corticosteroid fluid in the tympanic cavity represents an abnormal state. The middle ear possesses several physiological mechanisms to remove liquids, drugs and foreign bodies. The mucosa covering the tympanic cavity contains a highly dense vascular and lymphatic network. The vasculature and lymphatic system absorb drugs by passive diffusion. Furthermore, the mucosa is able to soak up fluids through transport channels. In an upright position, the medication drains off passively towards the eustachian tube into the pharynx. Motile cilia of the respiratory epithelium, which can be found in the ventral parts of the tympanic cavity, drive the drug actively to the eustachian tube. Finally, experimental data indicated that drugs are already metabolised in the middle ear at a certain level. Other factors, such as the degree of petrous bone pneumatisation may also influence the drug elimination from the middle ear (27,198,199). For the ITS administration, patients should be placed in the supine position with the head titled 45 degrees to the unaffected ear. After the application, it is recommended to stay in this position for 15 to 30 minutes and avoid speaking, swallowing and head movements, in order to maintain the medication in the middle ear cavity and prevent rapid drug lost through the eustachian tube (3).

In terms of middle ear kinetics, another factor that should be considered is the mixture of the intratympanic applied medication. Pharmaceutical corticosteroid formulations, which are approved for the intravenous, intramuscular, intradermal or intraarticular application, are being used as “off label” for the ITS treatment. The majority of commercially available corticosteroid formulations are solutions, due to their polarity (27). Solutions are rapidly eliminated from the tympanic cavity, due to several reasons (198,199): solutions typically contain a high amount of sodium and chloride, which have been related to a higher absorption to the vascular system of the middle ear (201). Moreover, solutions are easily cleared away to the eustachian tube by the motile cilia of the middle ear mucosa. On the contrary, the application of suspensions creates a “depot effect”, resulting in a longer drug residence time in the tympanic cavity (202). The duration that the drug remains in the tympanic cavity, has a substantial impact on the subsequent drug concentration within the inner ear. The longer the drug residence time in the middle ear, the higher the drug entry into the inner ear (27,199).

Recent research in the local treatment of hearing disorders has shifted to timed-release drug delivery formulations. In such novel delivery systems, the active agent is typically embedded

in hydrogels or suspensions composed of various polymers. The polymers prolong the residence time of the drug in the tympanic cavity by overcoming the physiologic drug elimination mechanisms of the middle ear and further enable a controlled drug release over a preconfigured duration. The exact operating principle of the polymer system concerning drug incorporation and release, depends on its mechanical and chemical properties. A variety of polymer classes has been investigated as vehicle for the inner ear drug delivery. In principle, polymers can be divided into natural and synthetic polymers. Evaluated natural polymers include gelatin, hyaluronic acid, alginate and chitosan. Synthetic polymers that have been used for the local inner ear treatment are typically poloxamer-based. A prominent representative is poloxamer 407. This substance has served as vehicle for several drugs in the local treatment of various neuro-otological disorders. For instance, OTO-104, a micronized dexamethasone loaded poloxamer 407 hydrogel formulation for local treatment of Meniere's disease, is currently in the clinical drug development (phase 3). Such novel delivery formulations will potentially play in the future an important role in the local treatment of ISSNHL (198,199).

The entry rate of the drug into the cochlea can further be enhanced by adding specific chemical agents to the medication (198,199). Benzyl alcohol, a preservative commonly included in commercially available drug formulations, has been shown to enhance the drug entry rate from the middle ear into the perilymph (203). Another experimental trial observed, that the addition of various detergents and solvents, including saponin, N-methyl-2-pyrrolidone and dimethylsulfoxide, significantly increased the inner ear drug entry (204). A further investigation identified histamine as perilymph entry enhancer (205). Although, it remains unknown whether or not these specific agents are ototoxic. These uncertainties need to be clarified before such agents can be used clinically. Moreover, their utilisation is hindered in principle by extensive interindividual variance due to inconsistencies in the inherent characteristics of the middle ear membranes. Besides the chemical enhancement, mechanical manipulations have been determined to increase the permeability of the round window membrane (199). Experimental studies reported that creating microperforations in the round window membrane by microneedles led to an enhanced permeability (206). However, it has been identified that even microperforations result in significant perilymph loss to the middle ear, which may cause further hearing loss. (199,207). Another trial demonstrated that suction near the round window membrane enhanced its permeability (203). However, nearby suction would be very uncomfortable for the patient and its clinical benefit remains uncertain. To conclude, mechanical manipulations as method to increase the inner ear drug entry are currently not suitable for the clinical setting (199).

After the intratympanic applied drug migrates through the round window membrane and stapes footplate, it enters the perilymph fluid inside the basal turns of the respective scales. The dispersion of the medication within the total perilymph space operates primarily via passive diffusion. As the perilymph exhibits typically a slow inherent volume flow, solely a negligible proportion of inner ear drug distribution is due to this process. The drug spreads from the cochlea base along its two and a half turns of the respective scales to the apex of the cochlea. The velocity of passive diffusion declines non-linear with increasing distance. Immediately after the inner ear entry, the elimination (or clearance) of the drug initiates. The inner ear drug loss is mostly due to active metabolism. Further elimination processes include loss to the vascular system and the cerebrospinal-perilymph exchange. Because of the non-linear passive diffusion and drug clearance, the concentration of the drug decreases along the cochlea turns – a concentration gradient results. The less, or even absent drug concentration in the cochlea apex is causative assumed for the poorer outcome prognosis of ISSNHL affecting mainly the low-frequencies. The rapidity of metabolism and distribution within the entire cochlea depends primarily on the molecular properties of the applied drug. Once again, the individual molecular properties of the corticosteroids may play; therefore, an important role in the local treatment of ISSNHL (27,198,199).

ITS as therapy option for ISSNHL, can be used either as primary treatment, as combined treatment concomitantly to systemic corticosteroids or as salvage treatment after failure of primary treatment (3). The used modality shows a considerable geographic variability. According to nationwide surveys, the vast majority of otorhinolaryngologists in the United States (86%) applies ITS in combination with systemic corticosteroids, whereas salvage treatment is the most common modality in German speaking countries (74%). In the United Kingdom, ITS is utilised more or less equally as primary combined (51%) and salvage therapy (41%). The usage of ITS as primary treatment alone is clearly the least popular modality in all regions (<10%) (24–26).

There is only one RCT, that evaluated the efficacy of ITS as primary therapy alone against a placebo. Fillipo et al. compared 25 patients, who were treated with a total of 3x ITS injections at 1-day intervals, against 25 patients receiving an intratympanic placebo. Patients of both groups, who did not achieve a complete hearing recovery at the short-term follow-up visit (day 7), further received systemic corticosteroids for eight days. The ITS group showed a significant higher complete recovery rate at the short-term follow-up visit (76% vs. 20%, $p<0.001$). However, at the long-term follow up visit (day 30), the hearing recovery rate between both groups equalised (76% vs. 72%) (208).

The remaining RCTs investigating the efficacy of ITS as primary treatment of ISSNHL compared ITS to the standard therapy, namely systemic corticosteroids. The most recent systematic review upon this subject matter, published in 2020, identified ten RCTs comparing ITS vs. systemic corticosteroids. A following conducted meta-analysis of these trials revealed no significant difference in hearing recovery rate between the treatment modalities (*OR*=1.07, *CI*=0.85-1.35, *p*=0.592; I^2=0%) (19). The same conclusion was reported from previous systematic reviews and meta-analyses (14–17). The study by Rauch et al. certainly provides the highest level of evidence for this conclusion. In this high-quality non-inferiority RCT, 250 patients affected by ISSNHL were recruited from 16 academic centers. Included patients received either orally 60 mg/day prednisone for two weeks with a following 5-days taper course or 4x intratympanic injections with 40 mg/ml methylprednisolone at intervals of 3-4 days. The primary outcome parameter was the absolute hearing improvement in dB PTA at the 2-month follow up visit. As non-inferiority boundary, a difference of 10 dB was selected. The authors were able to reject inferiority of ITS to systemic corticosteroids, as the mean difference in absolute hearing improvement was solely 2 dB (ITS: 28.7 dB vs. oral steroid: 30.7 dB). The authors mentioned that both treatments were safe and effective; however, oral corticosteroids require less visits, is more cost-efficient and more comfortable for the patient. Therefore, the researchers concluded that ITS as primary treatment alone constitute an effective alternative for those patients, who exhibit contraindications to systemic corticosteroids (209).

A recent systematic review by Han and colleagues, published in 2017, identified 14 RCTs, which compared combination therapy to systemic treatment only. The authors further conducted a pooled meta-analysis on absolute hearing improvement (12 RCTs, 1192 patients), and on hearing recovery rate (13 RCTs, 1312 patients). The combined treatment resulted in a significantly higher absolute hearing improvement (M^{diff}=13 dB, *CI*:9.24–16.77, *p*<0.001, I^2=82%) and hearing recovery rate (*OR*=2.50, *CI*:1.95–3.21, *p*<0.001, I^2=0%). However, the overall risk of bias was high due to several reasons, such as methodological flaws or high study design heterogeneity. The authors concluded that these findings should be interpreted with caution and that more high-quality evidence is warranted to confirm the suggested superiority of combined treatment over systemic treatment only (21). Another, more quality-focused systematic review and meta-analysis upon this issue, included solely four RCTs and found no significant difference in hearing recovery rates between combination therapy vs. systemic therapy only (*OR*=1.11, *CI*:0.68-1.82, *p*<0.75, I^2=0%) (20). To summarise, clear evidence for the efficacy of combined therapy over systemic therapy only is lacking.

The main difficulty with primary ITS only treatment and primary combined treatment, is the same as with primary systemic corticosteroid treatment: they cannot be confirmed as actually effective neither be proven as ineffective, due to the same reasons: There is a lack of high-quality, non-treatment controlled RCTs. From an ethical point of view, it is very challenging to conduct such a study. However, considering the limited available reports of spontaneous hearing recovery and its highly variable rate ranging from approximately 30-60% (4,120,122), it is very difficult to ascertain the exact proportion of hearing improvement due to the initiated treatment. Therefore, in similarity to systemic corticosteroids, the AAO-HNSF suggests primary ITS interventions as a treatment option for ISSNHL within 2 weeks of symptom onset (3).

The situation appears different when ITS is given as salvage treatment after failure of primary treatment. The vast majority of spontaneous hearing recovery is expected to occur within the first two weeks since ISSNHL onset (4). Salvage treatment is usually initiated after two weeks since hearing loss onset; hence, the potential influence by natural hearing recovery is remarkably low in this case. Moreover, a number of high-quality RCTs comparing ITS as salvage treatment against an appropriate non-treatment control group, demonstrated the benefit of this treatment modality. All of the performed systematic reviews and meta-analyses which analysed these trials supported the usage of ITS therapy as a salvage treatment of ISSNHL, despite some methodological flaws of the trials (14–16,23). The AAO-HNSF; therefore, recommends that physicians should offer ITS therapy as salvage treatment for ISSNHL in case of insufficient hearing recovery after primary treatment (3). A Cochrane review by Plontke et al. addressing the efficacy of ITS treatment for ISSNHL is currently in progress (210).

In this context, primary treatment comprises the whole spectrum of initial interventions – including a wait-and-see strategy (3). As it is assumed that spontaneous hearing recovery is mostly completed within two weeks since symptom onset (4), the AAO-HNSF advises to offer ITS salvage treatment after two weeks of hearing loss onset (if a mere observation is chosen initially) or after failure of primary therapy. Another issue that arises is the ideal time period between completion of primary treatment and initiation of salvage treatment. To date, no study investigated the significance of the initiation time period on the treatment outcome; hence, a precise recommendation cannot be provided. The vast majority of trials started salvage treatment within two weeks after completion of primary treatment. Considering the duration of primary treatment and the available data regarding time period of salvage treatment initiation, the AAO-HNSF recommends to start ITS salvage treatment within six weeks since ISSNHL onset (3).

It is important to mention that there is no universal definition of “failure of primary treatment” (3). Agreement exists on the utilisation of the PTA as reference parameter for the failure criterion. Some clinicians may have used a fixed value, such as an absolute hearing improvement of <10 dB or <20 dB, as failure criterion. However, a patient with a normal baseline hearing function (10 dB PTA), and an initial profound hearing loss (100 dB PTA) by the episode of ISSNHL, who achieves a 30 dB hearing improvement due to primary treatment, still has a severe hearing loss (70 dB PTA). It would be unethical to deprive such a patient of a salvage therapy. A more expedient approach is to apply a relative value as failure criterion, for instance, a recovery to <10 dB or <20 dB referred to the baseline hearing function. Since complete hearing recovery according to Wilson’s (120) and AAO-HNSF’s criteria (3) is defined as a final mean hearing threshold not worse than 10 dB compared to the baseline, the absence of a complete hearing recovery would be an appropriate failure criterion. A requirement for this definition is the availability of a pre-morbid audiometric examination or a subjective pre-morbid symmetric hearing function reported by the patient. If this condition is lacking, a fixed value as failure criterion may be adopted. However, the employment of complete recovery as failure boundary (10 dB relative hearing loss) entails a shortcoming for clinical research. Patients with a persistent hearing loss just above the complete recovery cut-off, e.g., 20 dB relative hearing loss, have a considerable small range of possible absolute hearing improvement. As it is strongly recommended to apply absolute hearing improvement as primary outcome measure in clinical studies (11), the inclusion of several such patients would have a substantial impact on the primary outcome parameter. As inclusion criterion for clinical trials, it may be appropriate; therefore, to slightly increase the failure criterion, e.g., 20 dB or 30 dB relative hearing loss. However, for the welfare of the patient, the clinical routine should not change.

1.2 Aims and Hypotheses of the Dissertation Project

For the present, a universally used ITS treatment protocol does not exist. There is a variety of ITS regiments, diverging in delivery method, drug selection, concentration, application frequency and interval duration.

Concerning drug selection, the most effective corticosteroid for ITS treatment remains unknown. Commonly used corticosteroids for ITS treatment are dexamethasone and methylprednisolone. These agents are currently recommended by existing guidelines (3,39). However, recent experimental data indicated that dexamethasone and methylprednisolone do not possess ideal pharmacokinetic properties for local inner ear therapy. Contrary triamcinolone acetonide showed suitable middle and inner ear kinetics due to its molecular characteristics. Moreover, triamcinolone acetonide exhibits a high anti-inflammatory potency and otoprotective effects. These factors render triamcinolone acetonide a promising candidate for ITS treatment of ISSNHL (27). To date, there is solely one clinical trial reporting hearing outcomes of ISSNHL patients who were treated with intratympanic triamcinolone acetonide. However, this study was compromised by a few factors; hence, a conclusion regarding the efficacy of triamcinolone acetonide as agent for the ITS treatment of ISSNHL cannot be drawn (28).

At the Department of Otorhinolaryngology, Medical University of Graz, ITS injections as salvage treatment for ISSNHL were initiated in 2014. Since its initiation, triamcinolone acetonide has been used for this treatment modality due to its determined otoprotective effects. Therefore, in part one of the present dissertation project, we aimed to evaluate hearing outcomes of all primary-refractory ISSNHL patients, who received intratympanic triamcinolone acetonide injections as salvage therapy. We hypothesised that intratympanic triamcinolone acetonide injections as salvage treatment of ISSNHL results in a clinically significant hearing improvement.

The preferred ITS delivery technique is the intratympanic injection. This method has the advantages to be less invasive, safer and more cost efficient than the others (29). The AAO-HNSF; therefore, currently recommends intratympanic injection as main delivery technique. However, no consensus exists on the ideal protocol for ITS injections concerning interval length and total injection count (3). A considerable variety in these protocol parameters exists. In literature, the interval length ranges from one day to one week and the count of injections ranges from a single to several injections (29). Only a few studies investigated different interval lengths between injections and total count of injections per patient (30–34). In all of these

studies, except one, ITS injections were performed concomitantly with systemic steroids as combined therapy (30–33). The major limitation of these studies is the application of a combination therapy. It is difficult, if not even impossible, to ascertain the exact proportion of hearing improvement by ITS injections when giving as combined therapy, due to the potential confounding bias by spontaneous hearing recovery. The other study used ITS injections as primary-, salvage- and combined treatment. However, the authors failed to calculate the hearing outcomes separately for each treatment modality. Even if they had, the resulting very small and unequally distributed sample size per modality does not allow for adequate conclusions (34).

Since the initiation of ITS salvage treatment for ISSNHL at our institution in 2014, a paradigm of up to 3x ITS injections at 1-week intervals has been used, as recommended in the first clinical practice guidelines by the AAO-HNSF, published in 2012 (35). Aiming to improve the hearing outcomes of our ISSNHL patients, we recently have shortened the interval length to 2-4 days and implemented an additional 4th injection, in accordance to the current AAO-HNSF guidelines from 2019 (3). In part two of the present dissertation project, we aimed to compare the hearing outcomes of the revised ITS protocol with shortened intervals and an additional 4th injection to our previously 1-week interval ITS protocol. We hypothesised that the revised ITS protocol results in greater hearing improvements.

2 Materials and Methods

2.1 Setting

The dissertation project was conducted monocentric at the Division of General Otorhinolaryngology, Department of Otorhinolaryngology, Medical University of Graz.

2.2 Study Design

Both parts of the dissertation project were retrospective, observational studies. Part one was carried out as a non-controlled cohort study. Part two was organised as a case-control study. According to the revised 2011 evidence grading system for therapeutic studies developed by the Oxford Centre for Evidence Based Medicine, both, non-controlled cohort study as well as case-control study correspond to an evidence level of 4 (211).

In the cohort study, a retrospective chart review of all patients diagnosed with ISSNHL between January 2014 and August 2019, who failed to response sufficiently to primary systemic corticosteroid therapy and, who received up to 3x ITS injections at 1-week intervals as a salvage treatment, was performed. Patients were divided into groups according to their hearing recovery grade. The primary objective of this study was to evaluate the efficacy of triamcinolone acetonide as medication for ITS salvage treatment of ISSNHL. We hypothesised that triamcinolone acetonide represents an effective option for the ITS salvage treatment of ISSNHL. Subgroups analyses were also conducted to determine the absolute amount of hearing improvement by ITS salvage treatment based on: age (<65 years vs. ≥65 years), sex (female vs. male), presence of co-existing vertigo (yes vs. no), severity of the initial hearing loss (≥60 dB vs. <60 dB), degree of primary systemic hearing improvement (≥10 dB vs. <10 dB), and primary systemic treatment delay (≤3 days vs. >3 days). Secondary study objectives were as follows: 1.) the evaluation of the significance of each individual injection by calculating and comparing the amount of hearing improvement due to each particular ITS injection, and 2.) the identification of plausible predictors for ITS hearing improvement.

In the case-control study, all patients, who had insufficient hearing recovery from ISSNHL after primary systemic corticosteroid therapy and who received up to 4x ITS injections every 2-4 days between August 2019 and December 2020, were retrospectively enrolled. Those patients who met the eligibility criteria (= revised-protocol group), were 1:1 matched to subjects out of the cohort study (= initial-protocol group). Included patients in both protocol groups fulfilled the

same inclusion and exclusion criteria. We aimed to compare the hearing outcomes between the revised- and initial ITS salvage treatment protocols. The hypothesis of this study was that the revised protocol with shorter intervals in addition with a 4th injection results in better hearing outcomes.

2.2.1 Inclusion criteria

The following inclusion criteria applied to both studies:

- Unilateral SSNHL of at least 30 dB at three or more consecutive frequencies occurring within 72 hours and presumptively classified as idiopathic following a decent neuro-otologic investigation
- Primary treatment with systemic corticosteroids
- Start of primary treatment within 30 days since sudden hearing loss onset
- Insufficient hearing recovery after primary treatment, defined as a difference of ≥30 dB between the baseline and post-systemic PTAs of the affected ear.
- Start of ITS salvage treatment within six weeks since sudden hearing loss onset

2.2.2 Exclusion criteria

The following exclusion criteria pertain for the cohort study as well as for the case-control study:

- Bilateral ISSNHL
- Presence of acute or chronic middle ear disease
- History of recent baro-, head- or noise trauma
- Meniere`s disease
- Recent intake of ototoxic medications
- Recent ear surgery in the medical history
- Recent radio- or chemotherapy
- Known retro-cochlear pathologies

The following additional exclusion criteria refer only to the case-control study:

- Achieving a complete hearing recovery after the first ITS injection
- Refusing outstanding ITS injections for any reason

2.2.3 Patient recruitment and data collection

First, all patients treated with ITS injections in the respective time periods were retrospectively collected from the electronical hospital records through the institutional Medical Documentation and Communication System. Patient's name, birthday and identification number were transferred to encoded Microsoft-Excel© spread sheets and afterwards converted into the IBM© software Statistical Package for the Social Sciences (SPSS) for data analysis. Assessed clinical data are displayed in table 1. Patient's medical charts were reviewed for their correctness and integrity. Those patients who did not fulfill the eligibility criteria were excluded from the study.

Table 1: Assessed clinical characteristics

Parameter	**Value**
Age	years
Sex	female; male
Presence of tinnitus	yes; no
Presence of vertigo	yes; no
Vestibular function assessment	yes; no
Vestibular dysfunction	yes; no
Application method of primary systemic corticosteroid treatment	oral; intravenous
Primary systemic treatment delay	days
ITS salvage treatment delay	days
Audiometric data	see table 2
Total count of ITS injections	*n*
Adverse events	*n*

2.3 Management Protocol

A neuro-otological test battery was conducted on each patient, including a general otorhinolaryngological examination, pure-tone audiometry, tympanometry, as well as the thorough documentation of the patient's general and otologic history. All patients received a referral for a head MRI. The general otorhinolaryngological examination involved inspection/ palpation of the external ear, otoscopy, anterior rhinoscopy, direct inspection of the oral cavity and oropharynx, indirect inspection of the nasopharynx, hypopharynx and larynx. In cases of severe co-existing vertigo, an apparated assessment of the peripheral vestibular function was performed. The apparated vestibular assessment included a video-oculographic testing for spontaneous nystagmus, video-oculographic head impulse test, caloric irrigation and rotational testing.

At the Department of Otorhinolaryngology, Medical University of Graz, the primary treatment of ISSNHL is oriented on the recommendations by the GAORL-HNS (125): Patients received systemic high-dosed corticosteroids over a time period of three consecutive days as primary therapy. In general, subjects were treated as out-patients with 40 mg/day dexamethasone per-oral. In cases of insulin dependent diabetes mellitus, profound hearing loss with a high level of psycho-emotional suffering, or severe co-existing vertigo, patients obtained 250 mg/day prednisolone intravenously as in-patients. Our institution's ISSNHL protocol implies that all patients, who are treated as in-patients, will receive intravenous treatment. The rational basis for this protocol are experimental studies which reported higher corticosteroids concentrations in the perilymph after intravenous administration in comparison to oral administration (187). Individuals with contraindications to systemic corticosteroids such as severe diabetes mellitus, received ITS injections as first-line treatment. Those patients were excluded in both studies

After primary systemic therapy, patients were evaluated by pure-tone audiometry for treatment outcome. Patients with insufficient recovery from ISSNHL after primary systemic therapy were offered ITS injections as a salvage treatment. In both, revised- and initial ITS protocols, interval audiograms between injections were performed. If hearing loss resolved completely before the last injection, the outstanding injections were cancelled. Patients, who achieved a complete hearing recovery after the first ITS injection or who refused further injections due to any reason, were excluded in the case-control study. At each ITS treatment visit, patients were assessed for treatment-related adverse events such as acute middle ear infection. After completion of salvage therapy, patients were scheduled for a follow-up visit one week after the last ITS injection to evaluate treatment outcome. At the follow-up visit, patients were additionally checked for a persistent tympanic membrane perforation following ITS injection treatment.

2.4 Audiological Evaluation

Audiometric examinations were conducted by certified, well-experienced audiologists. Pure-tone hearing thresholds were obtained with appropriate masking separately for air and bone conduction from 0.125 to 8 kHz at semi-octave skips. The mean hearing function was determined by the PTA, which was calculated as the arithmetical mean of the hearing thresholds at 500, 1000, 2000 and 4000 Hz. If hearing thresholds were undetectable due to the limit of the audiometric equipment, a fixed value of 100 dB was set. Pure-tone audiometry was performed at initial consultation (= initial PTA), after the completion of primary systemic corticosteroid therapy (= post-systemic PTA), prior each ITS administration and one week after the last ITS injection (= final PTA). The mean hearing function of the affected ear before onset of ISSNHL (= baseline PTA) was determined in two ways: If a patient's pre-morbid audiogram was available in our electronic medical records, it was used to define the baseline PTA. Otherwise, the PTA of the opposite, healthy side was considered as baseline PTA.

The initial PTA displayed the mean hearing function of the affected side after sudden hearing loss onset and prior start of primary systemic therapy. The severity of initial PTA was categorized into: mild (20–40 dB), moderate (41–70 dB), severe (71-90 dB) and profound (>90 dB). The degree of initial hearing loss was calculated by the difference between the baseline and initial PTAs. Initial audiogram pattern was classified according to Mazzoli et al. into: ascending (>15 dB difference between poorest low and higher frequencies), cup-shaped (>15 dB difference between poorest mid-frequencies and low/high frequencies), descending (>15 dB difference between poorest high frequencies and lower frequencies), flat (hearing loss at all frequencies but <15 dB difference between frequencies), and deafness (hearing loss of >80 dB at all frequencies). Frequencies were classified as follows: low (≤ 0.5 kHz), mid (> 0.5 - 2 ≤ kHz) and high (> 2kHz) (119). The mean hearing function of the affected ear after primary treatment was expressed by the post-systemic PTA. The amount of hearing improvement due to primary systemic treatment was calculated by the difference between the initial and post-systemic PTAs. The respective PTA's of sequential ITS treatment visits were compared in order to determine the hearing improvement separately for each injection. The final PTA corresponded to the mean hearing function of the affected side after the completion of the ITS salvage treatment. The severities of the post-systemic and final PTAs were categorised analogous to the severity of the initial PTA. The hearing improvement by ITS salvage treatment was calculated by the difference between the post-systemic and final PTAs. The difference between the baseline and final PTAs displayed the total hearing improvement due to both,

primary systemic- and ITS salvage treatment. All assessed audiometric parameters are summarised in table 2.

Table 2: Assessed audiometric parameters

Audiometric parameter	Description, calculation
Baseline PTA	Mean hearing function of the affected ear before ISSNHL onset; through available pre-morbid audiogram or PTA of the contralateral healthy side
Initial PTA	Mean hearing function of the affected ear after ISSNHL onset, at initial consultation prior start of primary systemic treatment
Degree of initial hearing loss	Baseline PTA – initial PTA
Initial audiogram pattern	Ascending, cup-shaped, descending, flat, total deafness
Severity of PTAs	At initial consultation, after primary systemic treatment and at final follow up visit / classified in mild, moderate, severe, profound
Post-systemic PTA	After completion of primary systemic corticosteroid treatment
Systemic hearing improvement	Initial PTA – post-systemic PTA
Post-ITS1 PTA	At the first ITS treatment visit
ITS1 hearing improvement	Post-systemic PTA – post-ITS1 PTA
Post-ITS2 PTA	At the second ITS treatment visit
ITS2 hearing improvement	Post-ITS1 PTA – post-ITS2 PTA
Post-ITS3 PTA	Cohort study: corresponds to final PTA
ITS3 hearing improvement	Post-ITS2 PTA – post-ITS3 PTA
ITS4 hearing improvement	Post-ITS3 PTA – post-ITS4 PTA
Final PTA	At follow-up visit (= 1 week after completion of salvage treatment)
ITS hearing improvement	Post-systemic PTA – final PTA
Clinically significant ITS hearing improvement	ITS hearing improvement of >10 dB
Total hearing improvement	Systemic hearing improvement + ITS hearing improvement
Grade of hearing recovery	Classified in complete, partial and no recovery according to Wilson's criteria
Serviceable hearing level	At initial consultation, after primary systemic treatment and one week after ITS salvage treatment / >50 dB

2.5 Outcome Assessment of ITS Salvage Treatment

The outcome measures for ITS salvage therapy were selected according to the consensus statement on treatment of sudden sensorineural hearing loss by the International Federation of Oto-rhino-laryngological Societies in 2017 (11). All outcome measures were determined at the follow-up visit.

2.5.1 Primary outcome measure

The primary outcome measure was the *absolute hearing improvement by ITS salvage treatment*. It was calculated by the difference between the post-systemic and final PTAs of the affected ear.

2.5.2 Secondary outcome measures

The secondary outcome measures were as follows:

1.) *Clinically significant ITS hearing improvement*: Any absolute hearing improvement by ITS hearing improvement of >10 dB was considered as clinically significant (11).

2.) ITS response level: ITS hearing improvement was divided into the following categories: ≤10 dB improvement, >10–20 dB improvement, >20-30 dB improvement, >30 dB improvement, >10 dB deterioration

3.) *Grade of hearing recovery* (categorized by the Wilson criteria):

- Complete recovery was defined as a final PTA of ≤10 dB in comparison with the baseline PTA.
- A final PTA within 50% of baseline PTA or a PTA decrease of ≥10 dB was recorded as partial recovery.
- A difference of <10 dB between the final and baseline PTAs was classified as no recovery (120).

4.) *Recovery into a serviceable hearing range*: A serviceable hearing level was defined as a PTA of ≤50 dB, according to the Committee on Hearing and Equilibrium of the AAO-

HNSF (117). All patients with a post-systemic unserviceable hearing level (>50 dB), who returned into a final serviceable hearing range by ITS salvage treatment, were recorded.

2.6 Intratympanic Treatment Protocol

2.6.1 Medication

Since the initiation of ITS salvage therapy for ISSNHL at the Department of Otorhinolaryngology, Medical University of Graz, the corticosteroid triamcinolone acetonide has been used for this treatment modality. Table 3 shows the details of the applied ITS treatment medication (212).

Table 3: ITS treatment medication

Details	Description
Commercial Name	Volon ® A 40 mg Kristallsuspensions-Ampulle
Active ingredient	Triamcinolone acetonide
Concentration	40 mg/ml
Excipients	Benzyl alcohol 9.9 mg/ml, natriumcarboxymethyl cellulose, polysorbate 80, sodium chloride, water
Pharmaceutical form	White to cream coloured crystal suspension
Method of application	Approved for intraarticular, intramuscular, intrafocal, and sublesional application (intratympanically = “off-label”)
Marketing authorisation holder	Dermapharm GmbH, Vienna
Manufacturer	mibe GmbH Arzneimittel, Brehna
Packaging	1ml glass ampoule

2.6.2 Intervals and count of injections

ITS injections as a salvage treatment for ISSNHL were initiated at the Department of Otorhinolaryngology, Medical University of Graz in January 2014 by the leading head of the institution's neuro-otologist group at that point of time. The ITS protocol was adopted from the first AAO-HNSF clinical practice guidelines, published in 2012 (35). ITS injections were performed at 1-week intervals for a total of three sessions. A pure-tone audiometry was performed prior each subsequent ITS administration. If the patient gained a complete hearing recovery before the completion of the 3x ITS applications, he refused for any reason further injections or an adverse event, such as acute otitis media occurred, the outstanding ITS injections were cancelled. All patients were scheduled for a follow-up visit one week after the last ITS injection in order to evaluate salvage treatment outcome.

Since August 2019, a few members of the institution's neuro-otologist group already started to apply the revised ITS protocol as recommended by the updated AAO-HNSF guidelines, published in summer 2019. In January 2020, the revised ITS protocol was then officially introduced at the Department of Otorhinolaryngology, Medical University of Graz, by the current leading neuro-otologist. The revised ITS treatment protocol consisted of up to 4x ITS injections every 2-4 days. The practice of the 1-week follow-up visit after the last ITS injection, and the interval audiometric examinations to detect an earlier termination of ITS salvage treatment in case of complete hearing recovery, remained unchanged.

2.6.3 Procedure

The ITS treatment procedure was conducted according to the practice recommendations by the AAO-HNSF and was executed by well-trained otorhinolaryngologists (3). The whole procedure was performed under ear-microscopic control. The ITS application took place in the operation room of the institution's outpatient clinic. Prior the procedure, patients were evaluated by the operated physician for obstructive cerumen, middle ear disease and tympanic membrane perforation. For the ITS administration, patients were placed in the supine position with the head titled 45 degrees to the unaffected ear. All patients received local anesthesia before the injection. Prior the application of topical anesthesia, patients were asked for known allergies against the used anesthetic drugs. Among our team of clinicians, two different agents were used for local anesthesia. The first agent was oxybuprocaine (Benoxinat 1% - Lösung zur Anästhesie in der Oto-Rhino-Laryngologie, Agepha Pharma s.r.o.), that was instilled into the affected ear canal by the outpatient clinic nurse. The patient was then instructed by the

nurse to remain in the otologic position for approximately 20 minutes. The second agent, lidocaine (Xylocain 10% - Pumpspray, Aspen Pharma Trading Limited), which was applied by the operating physician, remained for a few minutes in the external ear canal. The anesthetic solution was then removed in total by suction before the ITS injection. The tympanic membrane of the affected side was punctured under ear-microscopic visualisation in the posterior-inferior quadrant via a 25-gauge spinal needle (Figure 3). An average dose of 0.4 to 0.8 ml of triamcinolone acetonide at 40mg/ml was then slowly injected into the middle ear until the tympanic cavity was nearly completely filled with the solution. Following the injection, the patient was instructed by the operating physician to stay in the otologic position for approximately 30 minutes and to avoid speaking, swallowing and any head movements in order to maintain the medication in the middle ear cavity. The patient was transported by the nurse for the post-injection time period into the anteroom of the outpatient clinic operation room. In this time period, patients were monitored and assessed for potential short-term adverse events. Following the monitoring, patients were reminded by the operating physician of the next scheduled visit.

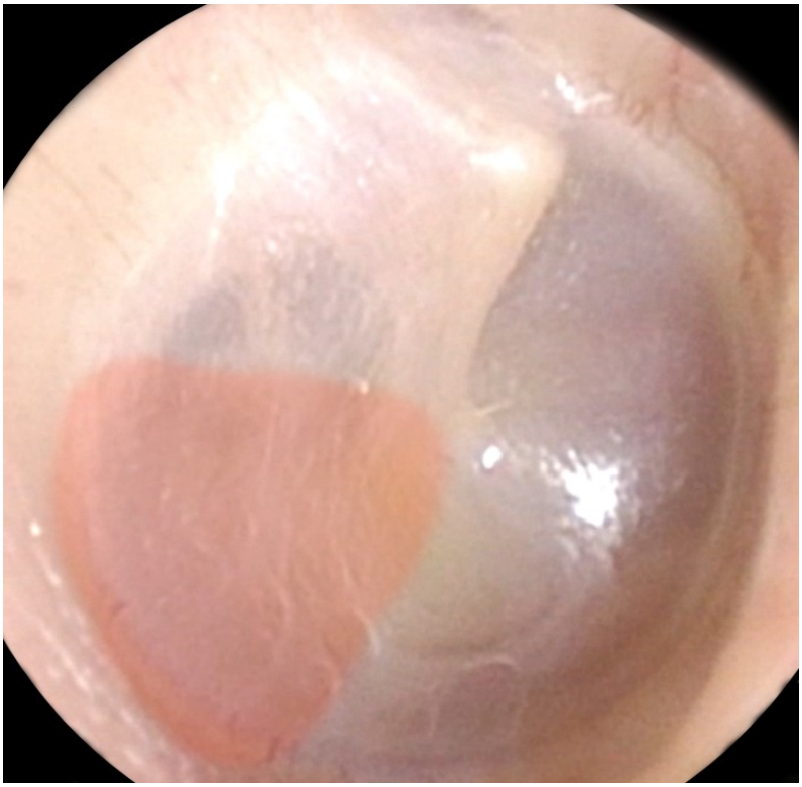

Figure 3: Posterior-inferior quadrant (red shaded) as location for needle perforation of the tympanic membrane

2.7 Ethical Considerations

The cohort study as well as the case-control study, were independently reviewed and approved by the local ethics committee of the Medical University of Graz (application numbers: 32-202 ex 19/20 and 33-088 ex 20/21, respectively). Both studies were performed in accordance with the ethical principles of the Declaration of Helsinki.

All included patients provided their written consent for the ITS procedure. Patient's informed consent for study participation was not obtained because both studies were conducted retrospectively. All patients were encoded with a consecutive number (pseudonymised). Patient's datasets were saved only with this code in an IBM© SPSS data sheet on a personal computer with restricted access at the Department of Otorhinolaryngology, Medical University of Graz. Solely authorised persons had access to the original data.

2.8 Statistical Analysis

In the cohort study, the primary analysis included the total study population. A separate analysis of the outcome measures was performed for those patients, who were treated precisely according to our institution's ITS salvage treatment protocol (Per-ITS-protocol analysis). Patients, who refused further ITS injections, or in whom outstanding ITS injections were cancelled due to an occurrence of an adverse event, were excluded in the per-ITS-protocol analysis. Subgroups were analysed for the primary outcome measure.

SPSS © statistical software, version 26.0 (IBM ©, Armonk, NY) was used for statistical analysis. Statistical significance level (Type I error rate = α-level) was set to a p-value of <0.05, two sided. Continuous variables were depicted by the means ± standard deviations. Categorical variables were presented as absolute numbers and percentages. The Levene test was utilised to check for homogeneity of variances in continuous variables. Independent t-test was performed to compare continuous parameters between two unpaired groups with equal variances. In presence of variance inhomogeneity, robust Welch's t-test was used. Differences in continuous variables between more than two unpaired groups were evaluated with one-way analysis of variances (ANOVA). One-way ANOVA with post-hoc Bonferroni test was utilised in events of variance homogeneity. For cases with unequal variances, robust Welch-ANOVA and post-hoc Games-Howell test was used. For within-comparisons of continuous variables, paired t-test and repeated measures ANOVA with Bonferroni-adjusted post-hoc analysis was used. All t-test results were presented with the mean difference (M^{diff}) and 95% confidence interval

(*CI*). The effect size of statistically significant differences in t-tests was expressed by Cohen's *d*. The effect size of statistically significant variance analyses was expressed by Cohen`s *f*. Fisher's exact test was used to compare two independent dichotomous variables. Pearson's chi-squared test was utilised to compare unpaired categorical variables. In cases of expected cell frequencies less than 5, the Fisher-Yates test was applied. Bonferroni-adjusted Z-test was performed as post-hoc test in contingency tables with more than 2x2 variables. McNemar test was conducted for intra-group comparisons of dichotomous variables. Results of categorical variables analyses were presented with the difference in empirical probability ($D^{e.p.}$). *φ*-coefficient was used to assess the effect size of statistically significant differences in Fisher's exact, and Pearson's chi-squared tests. Cramer's *V*-coefficient expressed the effect size of statistically significant differences in contingency tables with more than 2x2 variables. To identify potential predictors on the primary outcome measure, a multiple linear regression analysis with a stepwise model was performed. Effect size of the overall statistically significance in multiple linear regression analysis was presented with Cohen's squared-*f*. Effect size of identified predictors are expressed with Pearson's correlation coefficient *r*.

Post-hoc power (*P*) analysis – given *α*-level, sample size and effect size, was conducted in order to evaluate the type II error rate (*β*-level). Post-hoc power analysis was done with the statistical software G*Power, version 3.1. Table 4 displays the interpretation of the effect sizes (213).

Table 4: Effect size interpretation

Effect size measure	Small effect	Moderate effect	Large effect
Cohen's *d*	0.2	0.5	0.8
Cohen's *f*	0.1	0.25	0.4
Cohen's f^2	0.02	0.15	0.35
φ-coefficient	0.1	0.3	0.5
Cramer's *V*	0.1	0.3	0.5
Pearson's *r*	0.1	0.3	0.5

2.8.1 Hypotheses and minimum required sample size calculation

Before data collection/analysis, we performed an a-priori sample size calculation in order to determine the minimum required sample size, which would give us the ability to accept our hypotheses.

In the cohort study, the H_0 – hypothesis stated that intratympanic triamcinolone acetonide as salvage treatment for ISSNHL does not result in a clinically significant hearing improvement. The H_1 – hypothesis suggested that intratympanic triamcinolone acetonide as salvage treatment for ISSNHL improves the hearing function clinically significant. As efficacy criterion, we selected an absolute PTA decline of >10 dB. This selection relies upon that any absolute change of at least 10 dB in PTA is universally considered as a clinically significant hearing improvement (11).

In the case-control study, the H_0 – hypothesis specified that there is no clinically significant difference in ITS hearing improvement between the protocol groups. The H_1 – hypothesis implied a clinically significant difference in hearing improvement by ITS salvage treatment between the protocol groups. Similarly, we selected 10 dB PTA as the difference criterion due to the fact that the difference criterion must exceed the inherent variability expected by the test-retest reliability, which has been determined as 5 dB (176,177). The next audiometric step is usually 10 dB.

For the a-priori sample size calculations, the power was set at 80% with a type I error rate of 5%. The calculations demonstrated that a minimum sample size of 44 for the total cohort study, and 28 per group for the case-control study would give us the ability to accept our hypotheses. Sample size calculations were performed using nQuery © advisor, version 8.6 (Statistical Solutions, Cork, Ireland).

3 Results

3.1 Cohort Study

Between January 2014 and August 2019, 201 patients with SSNHL received intratympanic triamcinolone acetonide injections. 49 patients were excluded from the study. The reasons for exclusion are displayed in the study flow diagram (Figure 4). 152 patients met the study eligibility criteria and were retrospectively analysed.

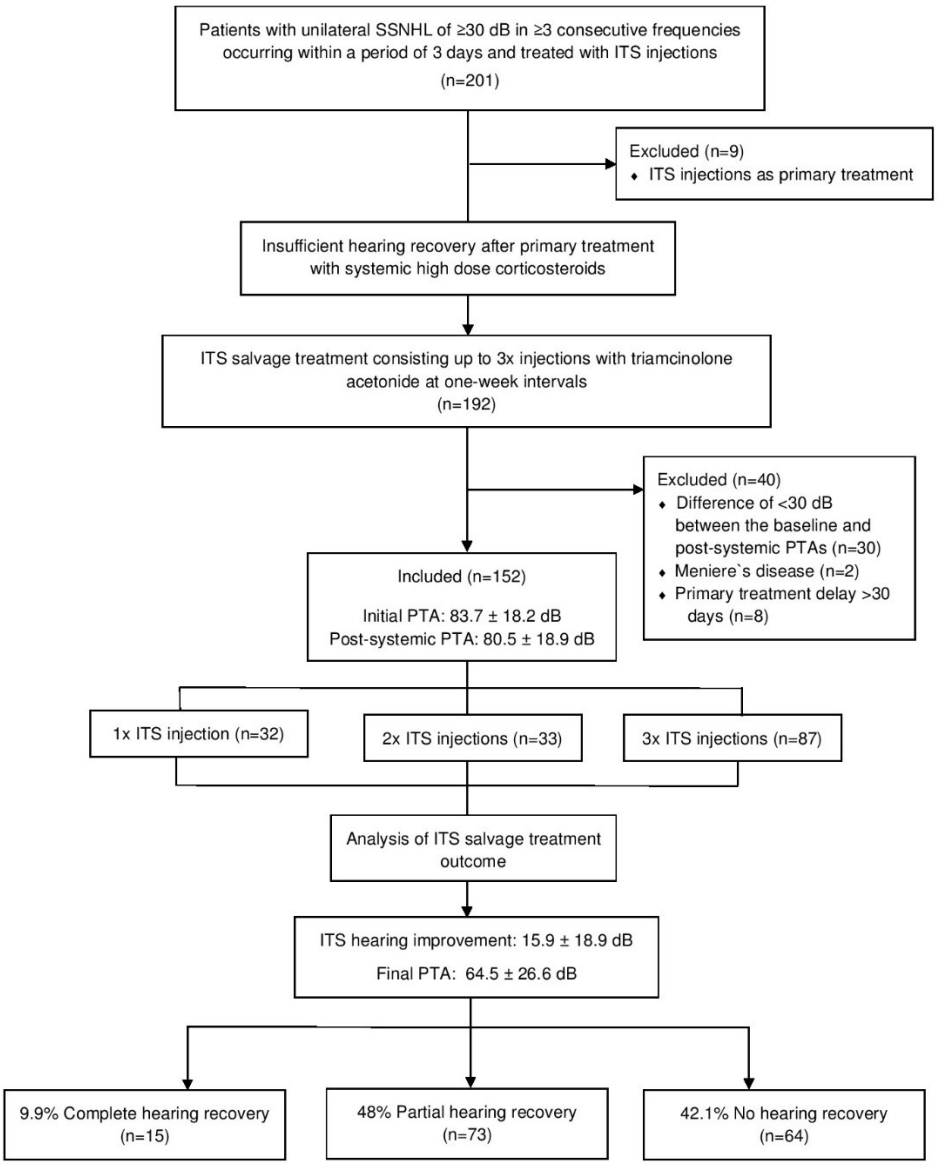

Figure 4: Cohort study flow diagram

3.1.1 Demographic data

62 females (40.7%) and 90 males (59.3%) were included in the study. The mean age of the patients at the time of initial consultation was 57.3 ± 16.5 years. 61 patients (40.1%) were elderly individuals (≥65 years). 4 patients (2.6%) were aged under 18 years. Of these, 2 patients were 14 years old and the other 2 patients had an age of 8 and 17 years. Patient's demographics according to the groups of hearing recovery are listed in table 5. There were no statistically significant differences between recovery groups regarding all demographic parameters (p>0.05).

Table 5: Demographic data according to recovery groups

Parameter	Hearing recovery			*p*-value
	Complete (*n*=15)	Partial (*n*=73)	No (*n*=64)	
Sex				0.881
Females, no. (%)	4 (26.7)	31 (42.6)	27 (42.2	
Males, no. (%)	11 (73.3)	42 (57.4)	37 (57.8)	
Age, years	54.8 ± 20.1	56.2 ± 16.2	59.1 ± 16.1	0.485
Elderly, no. (%)	5 (33.3)	24 (32.9)	32 (50)	0.106

Continuous variables are presented as means ± standard deviations and categorical variables as absolute numbers and percentages. Reproduced from (1) with permission from S. Karger AG.

3.1.2 Accompanied symptoms

Co-existing vertigo and tinnitus occurred in 69 patients (45.4%), and 89 patients (58.6%), respectively. In patients who experienced co-existing vertigo, an apparated vestibular assessment was performed in 61 cases (68.5%). Out of the 61 patients, who had undergone apparated vestibular examination, 26 patients (42.6%) had a vestibular dysfunction whereas the remaining 35 patients (57.4%) showed a normal function of the vestibular organs. Among the 26 patients with vestibular dysfunction, 17 patients (65.4%) presented a hypofunction of the vestibular organs, and a total vestibular function loss was found in 9 cases (34.6%). No statistically significant differences between recovery groups regarding accompanied symptoms were found (p>0.05). Detailed findings of accompanied symptoms according to recovery groups are denoted in table 6.

Table 6: Accompanied symptoms according to recovery groups

Parameter	Hearing recovery			*p*-value
	Complete (*n*=15)	Partial (*n*=73)	No (*n*=64)	
Presence of vertigo, no. (%)	6 (40)	34 (46.6)	29 (45.3)	0.897
Presence of tinnitus, no. (%)	10 (66.7)	46 (63)	33 (51.9)	0.318

Categorical variables are presented as absolute numbers and percentages. Reproduced from (1) with permission from S. Karger AG.

3.1.3 Baseline hearing function and initial hearing loss

Patients had a mean baseline PTA of 18.9 ± 12.1 dB. The mean initial PTA and mean degree of initial hearing loss was 83.7 ± 18.2 dB and 64.7 ± 19.2 dB, respectively. 75 patients (49.3%) showed a profound level of initial PTA. Mild, moderate and severe initial PTA levels were seen in 2 (1.3%), 38 (25%) and 37 (24.3%) patients, respectively. 143 patients (94.1%) had an initial unserviceable hearing level by the episode of ISSNHL. Regarding the shape of the initial audiogram: ascending, cup-shaped, descending, flat and deafness pattern were observed in 5 (3.3%), 4 (2.6%), 9 (5.9%), 46 (30.3%) and 88 (57.9%) patients, respectively. As the vast majority of patients (88%) presented either a flat shape or a total deafness, audiogram patterns were not further analysed.

Table 7 presents the baseline and initial audiometric findings with respect to the recovery groups. Statistically significant differences between groups were found in initial PTA [$F(2,149)=4.65$, $p=0.011$, $f=0.25$, $P=79\%$], initial hearing loss [$F(2,149)=4.94$, $p=0.008$, $f=0.26$, $P=82\%$] and initial PTA severity levels [$\chi^2(6)=12.41$, $p=0.046$, $V=0.20$, $P=42\%$]. Post-hoc analyses revealed the following statistically significant findings:

Patients with complete recovery had in comparison to partial recovery cases a lower initial PTA (M^{diff}=14.1 dB, CI=4.1-24.1, $p=0.018$), a lower initial hearing loss (M^{diff}=11.9 dB, CI=1.4–22.5, $p=0.027$), and a lower empirical probability of profound initial PTA levels ($D^{e.p.}$=38.9%, $p=0.016$).

Table 7: Baseline and initial audiometric findings according to recovery groups

Parameter	Hearing recovery			*p*-value
	Complete (*n*=15)	Partial (*n*=73)	No (*n*=64)	
Baseline PTA, dB	13.6 ± 9.5	17.8 ± 11.0	19.7 ± 11.2	0.221
Initial PTA, dB	73.5 ± 17.2 $_{a}$	87.6 ± 16.1 $_{b}$	81.6 ± 19.1 $_{a, b}$	0.011*
Initial hearing loss, dB PTA	57.7 ± 18.5 $_{a}$	69.6 ± 17.7 $_{b}$	60.8 ± 19.9 $_{a, b}$	0.008*
Severity of initial PTA, no. (%)				0.039*
Mild	1 (6.7) $_{a}$	0 (0) $_{a}$	1 (1.6) $_{a}$	
Moderate	6 (40) $_{a}$	13 (17.8) $_{a}$	19 (29.7) $_{a}$	
Severe	5 (33.3) $_{a}$	17 (23.3) $_{a}$	15 (23.4) $_{a}$	
Profound	3 (20) $_{a}$	43 (58.9) $_{b}$	29 (45.3) $_{a, b}$	
Initial unserviceable hearing level, no. (%)	14 (93.3)	70 (95.9)	59 (92.2)	0.794

*Continuous variables are presented as means ± standard deviations and categorical variables as absolute numbers and percentages. * represents statistical significance at the Bonferroni-adjusted α-level. Each subscript letter (a, b) denotes a subset of hearing recovery groups whose proportions do not differ significantly from each other at the adjusted significance level. Reproduced from (1) with permission from S. Karger AG.*

3.1.4 Primary treatment

Systemic corticosteroids as primary treatment were administered in 111 patients (73%) intravenously and in 41 patients (23%) per orally. Primary systemic treatment improved the hearing function by 3.1 ± 10.5 dB. No statistically significant difference in systemic hearing improvement between the application methods was found [intravenous: 4.1 ± 10.6 dB; oral: 0.4 ± 9.9 dB; $t(150)=1.93$, $p=0.055$]. The mean primary treatment delay was 5.9 ± 9.5 days. Patients had a mean post-systemic PTA of 80.5 ± 18.9 dB. Mild, moderate, severe and profound post-systemic PTA levels were found in 1 (0.7%), 50 (32.9%), 41 (27%) and 60 patients (39.5%), respectively. 138 patients (90.7%) presented a post-systemic unserviceable hearing level, indicating that 5 patients (3.5%) returned by primary treatment to a serviceable hearing level. This rate of return was statistically not significant [McNemar($N=152$), $p=0.180$]. The mean duration between ISSNHL onset, to start of ITS salvage treatment quantified 11.1 ± 8.7 days. Detailed post-systemic clinical findings according to recovery groups are displayed in table 8.

Table 8: Post-systemic clinical findings according to recovery groups

Parameter	Hearing recovery			*p*-value
	Complete (*n*=15)	Partial (*n*=73)	No (*n*=64)	
Primary treatment delay, days	3.6 ± 3.2 $_{a}$	3.5 ± 4.4 $_{a}$	9.1 ± 13.3 $_{b}$	0.002*
Application method of primary systemic treatment, no. (%)				0.577
oral	4 (26.7)	17 (23.3)	20 (31.2)	
intravenous	11 (73.3)	56 (76.7)	44 (68.8)	
Post-systemic PTA, dB	64 ± 16.6 $_{a}$	81.4 ± 18.4 $_{b}$	83.4 ± 18.2 $_{b}$	0.001*
Severity of post-systemic PTA, no. (%)				0.003*
Mild	1 (6.7) $_{a}$	0 (0) $_{a}$	0 (0) $_{a}$	
Moderate	8 (53.3) $_{a}$	24 (32.9) $_{a}$	18 (28.2) $_{a}$	
Severe	6 (40) $_{a}$	20 (27.4) $_{a}$	15 (23.4) $_{a}$	
Profound	0 (0) $_{a}$	29 (39.7) $_{b}$	31 (48.4) $_{b}$	
Systemic hearing improvement, dB PTA	9.5 ± 11 $_{a}$	6.1 ± 11.3 $_{a}$	-1.7 ± 6.8 $_{b}$	<0.001*
Post-systemic unserviceable hearing level, no. (%)	11 (73.3) $_{a}$	66 (90.4) $_{a, b}$	61 (95.3) $_{b}$	0.028*
ITS salvage treatment delay	8.1 ± 2.9 $_{a}$	8.8 ± 5.2 $_{a}$	14.4 ± 13.2 $_{b}$	0.004*

*Continuous variables are presented as means ± standard deviations and categorical variables as absolute numbers and percentages. * represents statistical significance at the Bonferroni-adjusted α-level. Each subscript letter (a, b) denotes a subset of hearing recovery groups whose proportions do not differ significantly from each other at the adjusted significance level. Reproduced from (1) with permission from S. Karger AG.*

Duration between symptom onset and start of primary treatment differed statistically significant between recovery groups [Welch's $F(2,48.27)=5.17$, $p=0.009$, $f=0.30$, $P=91\%$]. Games-Howell post-hoc test revealed the following statistically significant findings: Patients with no recovery started primary treatment later than patients with partial recovery (M^{diff}=5.6 days, CI=1.4–9.7, $p=0.006$), and complete recovery (M^{diff}=5.5 days, CI=1.1–10, $p=0.011$).

Regarding post-systemic audiometric findings, statistically significant differences between recovery groups were found in post-systemic PTA [$F(2,149)=7.11$, $p=0.001$, $f=0.31$, $P=93\%$], empirical probability of post-systemic PTA severity levels [$\chi^2(6)=19.95$, $p=0.003$, $V=0.26$, $P=66\%$], systemic hearing improvement [Welch's $F(2,36.96)=16.78$, $p<0.001$, $f=0.45$, $P=99\%$]

and empirical probability of post-systemic unserviceable hearing level [$\chi^2(2)=7.04$, $p=0.028$, $V=0.22$, $P=67\%$]. Post-hoc analyses showed the following statistically significant findings:

The post-systemic PTA in the complete recovery group was lower than in the partial recovery (M^{diff}=17.4 dB, CI=4.9–29.9, $p=0.003$), and in the no recovery groups (M^{diff}=19.4 dB, CI=6.8–32.1, $p=0.001$). In addition, the complete recovery group had a lower empirical probability of profound post-systemic PTA levels than the partial recovery ($D^{e.p.}$=39.7%, $p<0.001$) and no recovery groups ($D^{e.p.}$=48.4%, $p<0.001$). Moreover, patients with complete hearing recovery presented a lower relative frequency in post-systemic unserviceable hearing levels compared to patients with no hearing recovery ($D^{e.p.}$=22%, $p<0.001$). Primary treatment resulted in patients with no recovery in less hearing improvement than in patients with complete recovery (M^{diff}=11.3 dB, CI=3.6–18.9, $p=0.004$) and partial recovery (M^{diff}=7.9 dB, CI=4.1–11.6, $p<0.001$).

3.1.5 ITS salvage treatment outcome

Detailed final audiometric parameters are displayed in table 9. The mean total hearing improvement was 19.1 ± 23.5 dB. Mild, moderate, severe and profound final PTA levels were recorded in 33 (21.7%), 52 (34.2%), 36 (23.7%) and 31 patients (20.4%), respectively.

Table 9: Final audiometric findings according to recovery groups

Parameter	Hearing recovery		
	Complete (*n*=15)	**Partial (*n*=73)**	**No (*n*=64)**
Final PTA, dB	18.9 ± 13.3	57.2 ± 19.0	83.6 ± 18.1
Severity of final PTA, no. (%)			
Mild	1 (6.7)	0 (0)	0 (0)
Moderate	8 (53.3)	24 (32.9)	18 (28.2)
Severe	6 (40)	20 (27.4)	15 (23.4)
Profound	0 (0)	29 (39.7)	31 (48.4)
ITS hearing improvement, dB PTA	45.0 ± 18.0	24.1 ± 13.8	-0.1 ± 5.1
Total hearing improvement, dB PTA	54.5 ± 18.4	30.3 ± 16.5	-1.9 ± 7.0
Final unserviceable hearing level, no. (%)	0 (0)	45 (61.6)	60 (93.7)

Continuous variables are presented as means ± standard deviations and categorical variables as absolute numbers and percentages.

3.1.5.1 Primary outcome measure

As the outcome measure of primary interest, the mean hearing improvement by ITS salvage treatment was determined as 15.9 ± 18.9 dB. Due to ITS salvage treatment, the mean hearing function improved statistically significant from a post-systemic PTA of 80.5 ± 18.9 dB to a final PTA of 64.5 ± 26.6 dB [$t(151)=10.38$, $p<0.001$, $d=0.84$, $P=100\%$, figure 5].

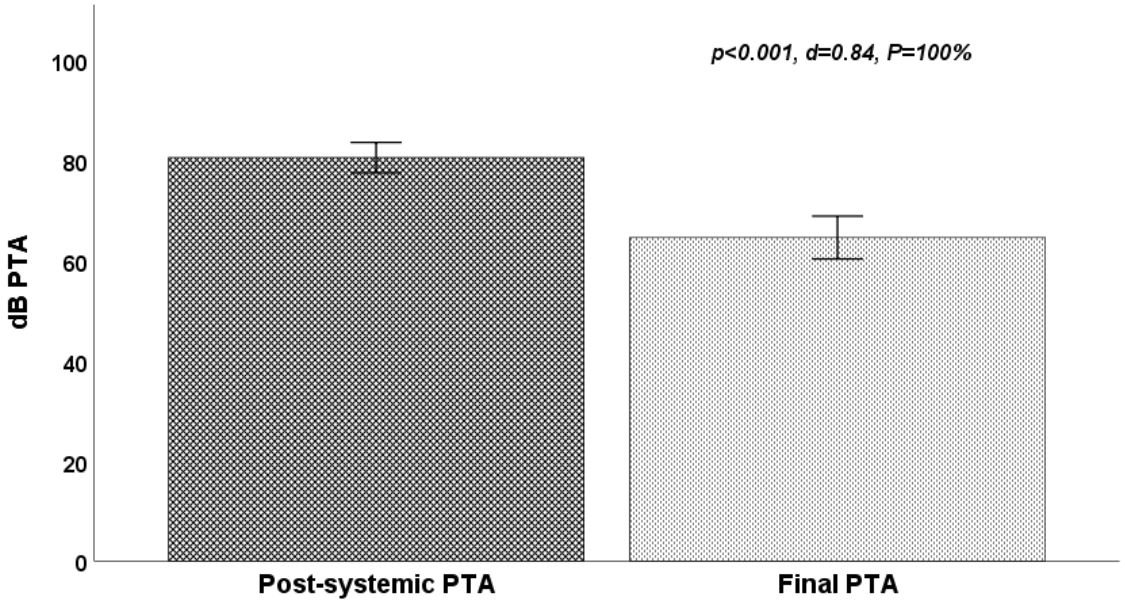

Figure 5: Hearing improvement by ITS salvage treatment

3.1.5.2 Secondary outcome measures

3.1.5.2.1 Clinically significant ITS hearing improvement

ITS salvage treatment resulted in 80 patients (52.6%) in a clinically significant hearing improvement (>10 dB). The remaining 72 patients (47.4%) did not obtain a clinically significant hearing improvement by ITS salvage treatment (≤10 dB).

3.1.5.2.2 ITS response levels

Results of ITS response levels are displayed in table 10.

Table 10: Results of ITS response levels

ITS response level	Total count	Percentage
≤10 dB improvement	69	45.4%
>10-20 dB improvement	27	17.8%
>20-30 dB improvement	19	12.5%
>30 dB improvement	34	22.4%
>10 dB deterioration	3	2%

3.1.5.2.3 Grade of hearing recovery

A complete hearing recovery was achieved from 15 patients (9.9 %). A partial recovery was seen in 73 patients (48%) and no recovery was recorded in 64 patients (42.1%).

3.1.5.2.4 Recovery into a serviceable hearing range

47 patients (30.9%) had a final serviceable hearing function. 33 out of 138 patients with a post-systemic unserviceable hearing function returned by ITS salvage treatment into a final serviceable hearing range. This rate of return was statistically significant [McNemar(*N*=152), $D^{e.p.}$=23.9%, *p*<0.001, figure 6].

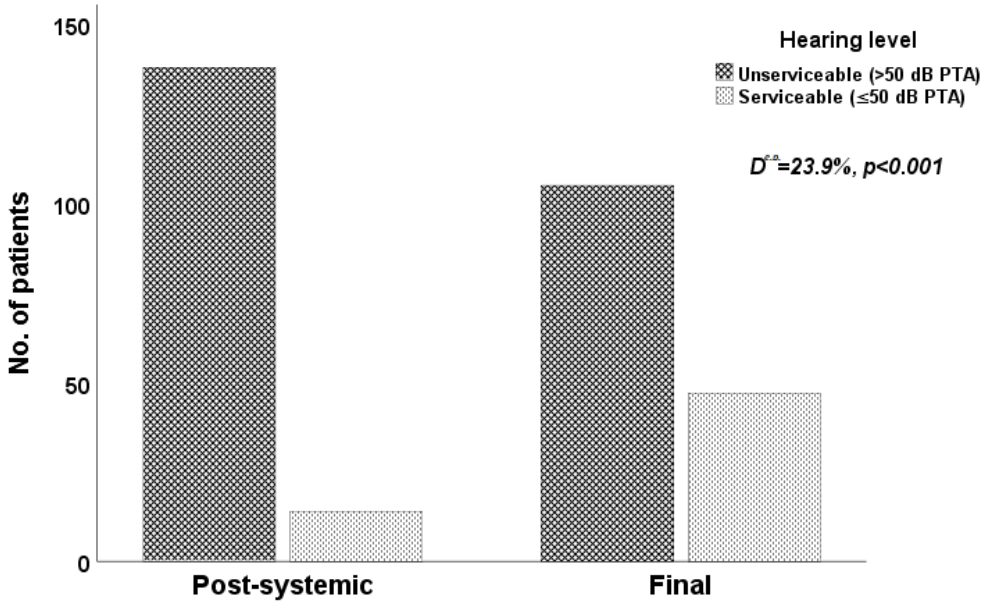

Figure 6: Recovery rate of serviceable hearing function

3.1.5.3 Per-ITS-protocol analysis

Of the 152 included patients, 48 patients (32.2%) refused outstanding ITS despite an insufficient hearing recovery. Patient's reasons for refusing were a limited treatment outcome. Of these, 31 patients got 2x ITS injections and 18 patients received solely 1x ITS injection. The mean hearing improvement by ITS salvage treatment in these patients was 9.2 ± 15.3 dB.

In one case, outstanding ITS injections were canceled due to an acute inflammation of the middle ear.

The remaining 103 patients (67.8%) were treated precisely according to the ITS salvage treatment protocol of the Department of Otorhinolaryngology, Medical University of Graz. They received up to 3x ITS injections at 1-week intervals. In cases of a complete hearing recovery already after the first or second injection, the outstanding ITS sessions were cancelled.

A separate per-ITS protocol analysis of the ITS salvage treatment outcome was performed for those patients, who followed precisely the institution's protocol. Table 10 presents the patient's clinical characteristics of the per-ITS-protocol analysis.

Table 11: Patient's clinical characteristics (Per-ITS-protocol analysis)

Characteristic	Value (*N*=103)
Sex, no. (%)	
Female	39 (37.9)
Male	64 (62.1)
Age, years	57.1 ± 16.6
Presence of vertigo, no. (%)	44 (42.7)
Presence of tinnitus, no. (%)	64 (62.1)
Baseline PTA, dB	18.3 ± 11.7
Initial PTA, dB	83.6 ± 11.7
Initial hearing loss, dB PTA	65.3 ± 18.6
Initial unserviceable hearing level, no. (%)	98 (95.1)
Severity of initial PTA, no. (%)	
Mild	2 (1.9)
Moderate	26 (25.2
Severe	25 (24.3)
Profound	50 (48.5)
Post-systemic PTA, dB	80.9 ± 18.6
Post-systemic unserviceable hearing level, no. (%)	94 (91.3)
Severity of post-systemic PTA, no. (%)	
Mild	1 (1)
Moderate	34 (33)
Severe	27 (26.2)
Profound	41 (39.8)
Systemic hearing improvement, dB PTA	2.7 ± 10
Application method of primary systemic treatment, no. (%)	
oral	32 (31.1)
intravenous	71 (68.9)
Primary treatment delay, days	6.1 ± 9.3
ITS salvage treatment delay, days	11.3 ± 9.7

Continuous variables are presented as means ± standard deviations and categorical variables as absolute numbers and percentages.

3.1.5.3.1 Primary outcome measure

In the per-ITS-protocol analysis, the mean ITS hearing improvement was 19.1 ± 19.7 dB. The mean hearing function improved by ITS salvage treatment statistically significant from a post-systemic PTA of 80.9 ± 18.6 dB to a final PTA of 61.7 ± 26.3 dB [$t(102)=9.86$, $p<0.001$, $d=0.97$, $P=100\%$, figure 7].

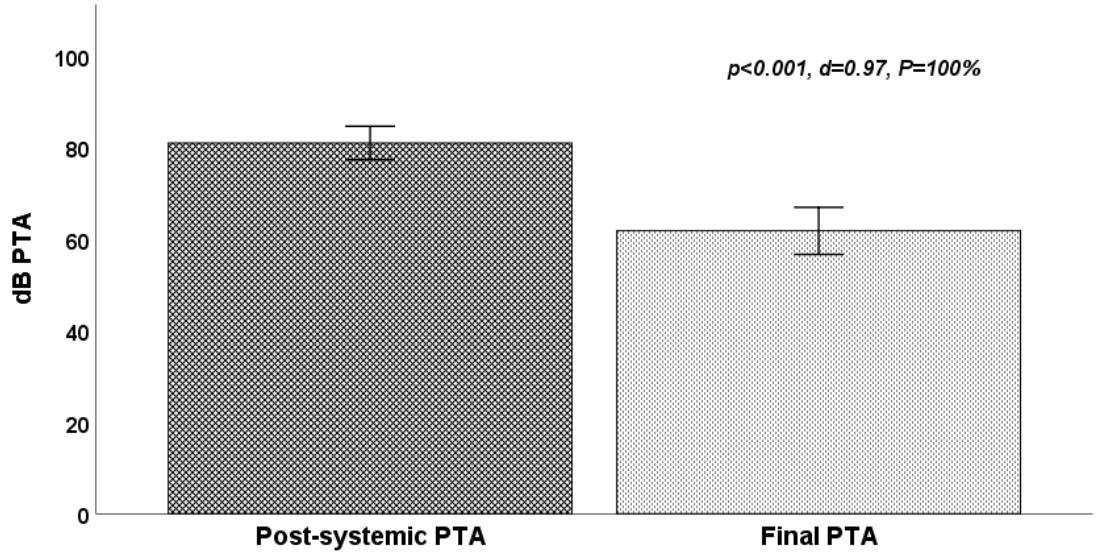

Figure 7: Hearing improvement by ITS salvage treatment (Per-ITS-protocol analysis)

3.1.5.3.2 Secondary outcome measures

3.1.5.3.2.1 Clinically significant ITS hearing improvement

In the per-ITS protocol analysis, a clinically significant hearing improvement by ITS salvage treatment was seen in 66 patients (64.1%). In the remaining 37 subjects (35.9%), ITS salvage treatment did not result in a clinically significant hearing improvement

3.1.5.3.2.2 ITS response levels

Results of the ITS response levels in the per-ITS-protocol analysis are shown in table 11.

Table 12: Results of ITS response levels (Per-ITS-protocol analysis)

ITS response level	Total count	Percentage
≤10 dB improvement	38	36.9%
>10-20 dB improvement	22	21.4%
>20-30 dB improvement	14	13.6%
>30 dB improvement	28	27.2%
>10 dB deterioration	1	1%

3.1.5.3.2.3 Grade of hearing recovery

15 patients (14.6%) gained a complete recovery, while 53 patients (51.5%) obtained a partial recovery, and 35 patients (34.1%) showed no recovery.

3.1.5.3.2.4 Recovery into a serviceable hearing range

In the per-ITS-protocol analysis, final serviceable hearing levels were found in 33 patients (32%). ITS salvage treatment returned 24 out of 94 patients with a post-systemic unserviceable hearing level into a final serviceable hearing range. This evolution was statistically significant [McNemar(N=103), $D^{e.p.}$=25.5%, p<0.001, figure 8].

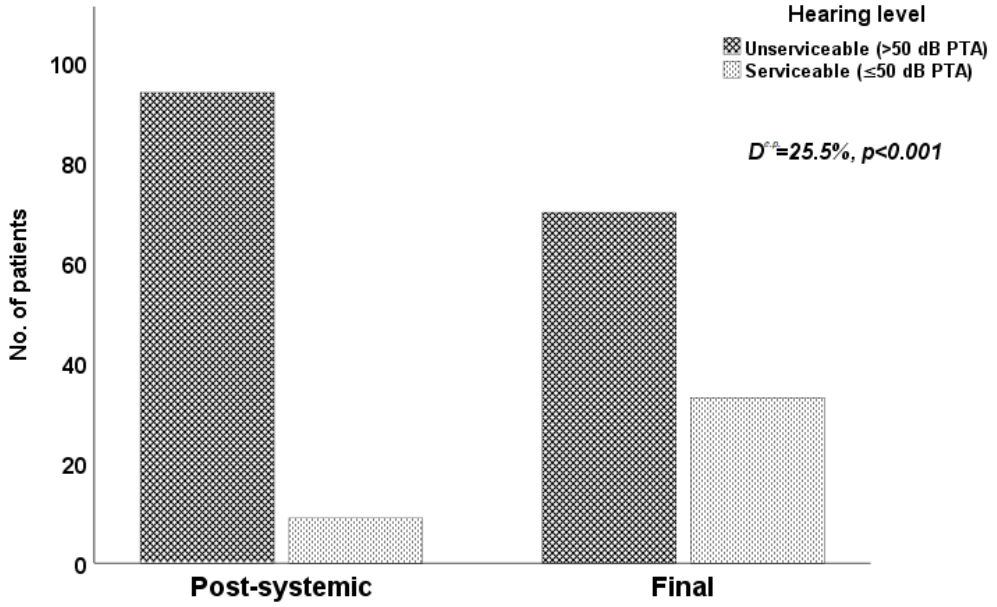

Figure 8: Rate of recovery into serviceable hearing range (Per-ITS-protocol analysis)

3.1.5.4 Age subgroups analysis

In order to evaluate the impact of age on the outcome of ITS salvage treatment, patients were divided according to their age into the following two groups: Elderly (≥65 years) and young/middle aged (<65 years). Of the 152 study patients, 61 patients (40.1%) were elderly and 91 patients (59.9%) were young/middle aged (under-aged patients were included in this group). The elderly group had a mean age of 71.8 ± 5.8 years and the young/middle aged group had a mean age of 47.5 ± 14.1 years.

Elderly patients improved in hearing function due to ITS salvage treatment by 11.8 ± 17.1 dB (*CI*=7.4-16.2). Hearing thresholds decreased statistically significant from a post-systemic PTA of 83.2 ± 16.7 dB to a final PTA of 71.3 ± 22.5 dB [$t(60)=5.42$, $p<0.001$, $d=0.69$, $P=99\%$]. The young/middle aged group showed an ITS hearing improvement of 18.7 ± 19.7 dB (*CI*=14.6-22.8), which declined the post-systemic PTA statistically significant from 78.7 ± 20.1 dB to a final PTA of 60 ± 28.3 dB [$t(90)=9.05$, $p<0.001$, $d=0.95$, $P=100\%$].

Young and middle aged patients achieved a statistically significant higher ITS hearing improvement in comparison to elderly patients [$M^{diff}=6.9$ dB, *CI*=0.7–12.9, $t(150)=2.21$, $p=0.028$, $d=0.36$, $P=69\%$], see figure 9.

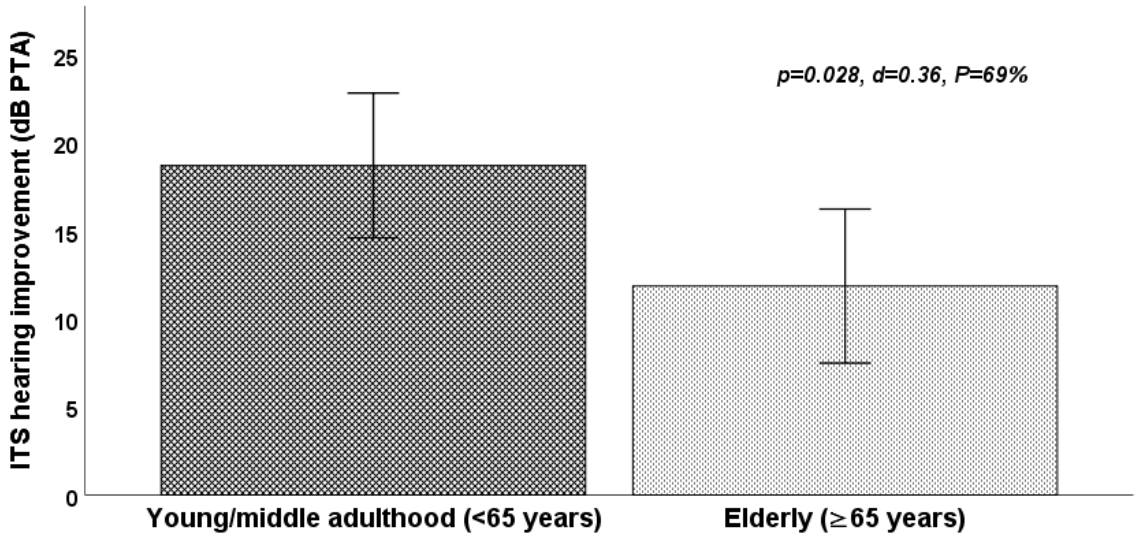

Figure 9: Hearing improvement by ITS salvage treatment according to age subgroups

3.1.5.5 Sex subgroups analysis

In order to evaluate sex-specific differences in hearing improvement by ITS salvage treatment, females and males were analysed separately. In total, 62 females (40.7%) and 90 males (59.3%) were included in the study.

Females showed a hearing threshold decline of 12.9 ± 16.2 dB (*CI*=8.86–17.11) due to ITS salvage treatment. Post-systemic PTA decreased in female patients statistically significant from 83.1 ± 18.1 dB to a final PTA of 70.2 ± 24.3 dB [$t(61)=6.29$, $p<0.001$, $d=0.79$, $P=100\%$]. ITS salvage treatment improved the hearing function in males by 18 ± 20.4 dB (*CI*=13.7–22.3), resulting in a statistically significant hearing threshold change from a post-systemic PTA of 78.8 ± 19.3 dB to a final PTA of 60.7 ± 27.6 dB [$t(89)=8.36$, $p<0.001$, $d=0.88$, $P=100\%$].

There was no statistically significant difference in ITS hearing improvement between females and males [$M^{diff}=5.1$ dB, *CI*=-1.1–11.1, $t(150)=1.16$, $p=0.108$], see figure 10.

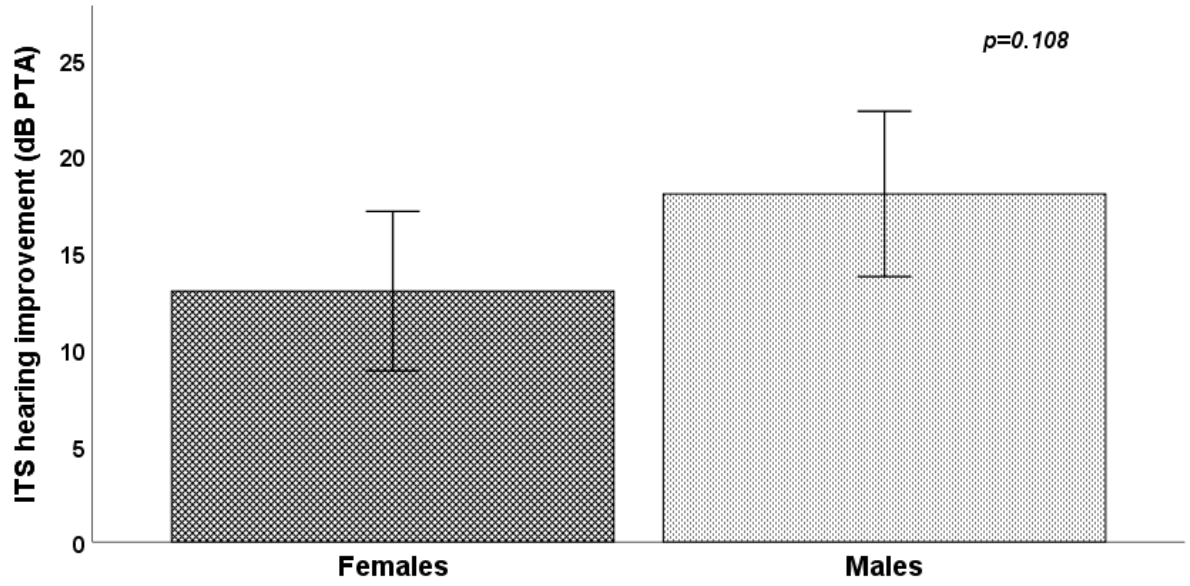

Figure 10: Hearing improvement by ITS salvage treatment according to sex

3.1.5.6 Vertigo subgroups analysis

69 patients (45.3%) had co-existing vertigo, while 83 patients (54.7%) did not experience vestibular symptoms. Of the 69 patients with accompanied vertigo, 26 patients (37.6%) presented a vestibular dysfunction. These 26 patients with a dysfunction of the peripheral vestibular organ showed a mean ITS hearing improvement of 14.7 ± 19.4 dB.

Patients with co-existing vertigo had a mean ITS hearing improvement of 14.3 ± 17.6 dB (*CI*=10.1–18.6). In these patients, post-systemic PTA decreased statistically significant from 84.5 ± 19.3 dB to a final PTA of 70.2 ± 26.6 dB [$t(68)=6.77$, $p<0.001$, $d=0.81$, $P=99\%$]. The no-vertigo group improved on average by 17.2 ± 20 dB (*CI*=12.9–21.6) in hearing function due to ITS salvage treatment. Mean hearing threshold declined in this group statistically significant from 77.2 ± 17.9 dB in post-systemic PTA to 59.9 ± 25.9 dB in final PTA [$t(82)=7.88$, $p<0.001$, $d=0.86$, $P=100\%$].

The difference in ITS hearing improvement between vertigo groups was statistically not significant [$M^{diff}=2.9$ dB, *CI*=-3.1-9, $t(150)=0.95$, $p=0.344$], see figure 11.

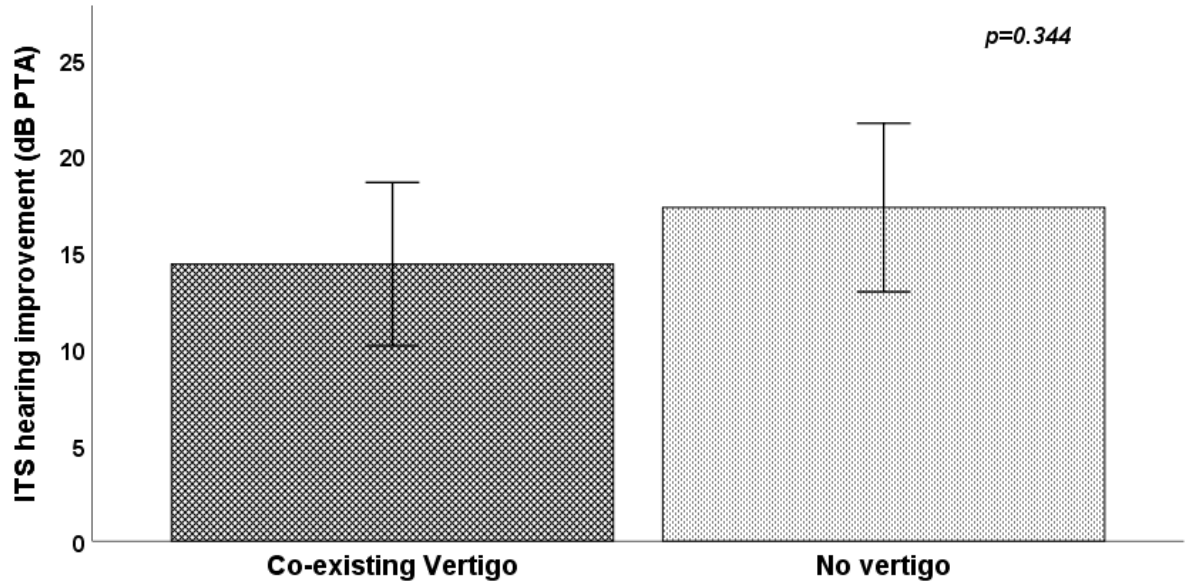

Figure 11: Hearing improvement by ITS salvage treatment according to vertigo subgroups

3.1.5.7 Hearing loss severity subgroups analysis

To investigate the impact of hearing loss severity on ITS salvage treatment outcome, patients were divided according to their degree of initial hearing loss (initial PTA - baseline PTA) into two groups: 66 patients (43.4%) presented an initial hearing loss of at least 60 dB, and 86 patients (56.6%) showed an initial hearing loss of less than 60 dB.

The ≥60 dB hearing loss group showed a mean ITS hearing improvement of 9.8 ± 15.5 dB (*CI*=6–13.7). Hearing thresholds declined in this group statistically significant from a post-systemic PTA of 68.5 ± 17.4 dB to a final PTA of 58.6 ± 24.8 dB [$t(65)=5.15$, $p<0.001$, $d=0.63$, $P=99\%$]. The <60 dB hearing loss group had a mean ITS hearing improvement of 20.6 ± 20 dB (*CI*=16.3–24.9). Post-systemic PTA decreased in this group statistically significant from 89.7 ± 14.2 dB to a final PTA of 69.1 ± 27.3 dB [$t(85)=9.54$, $p<0.001$, $d=1.02$, $P=100\%$].

The ≥60 dB hearing loss group had a statistically significant higher ITS hearing improvement than the <60 dB hearing loss group. [$M^{diff}=10.7$ dB, *CI*=5–16.4, Welch's $t(149.9)=3.7$, $p<0.001$, $d=0.6$, $P=95\%$], see figure 12.

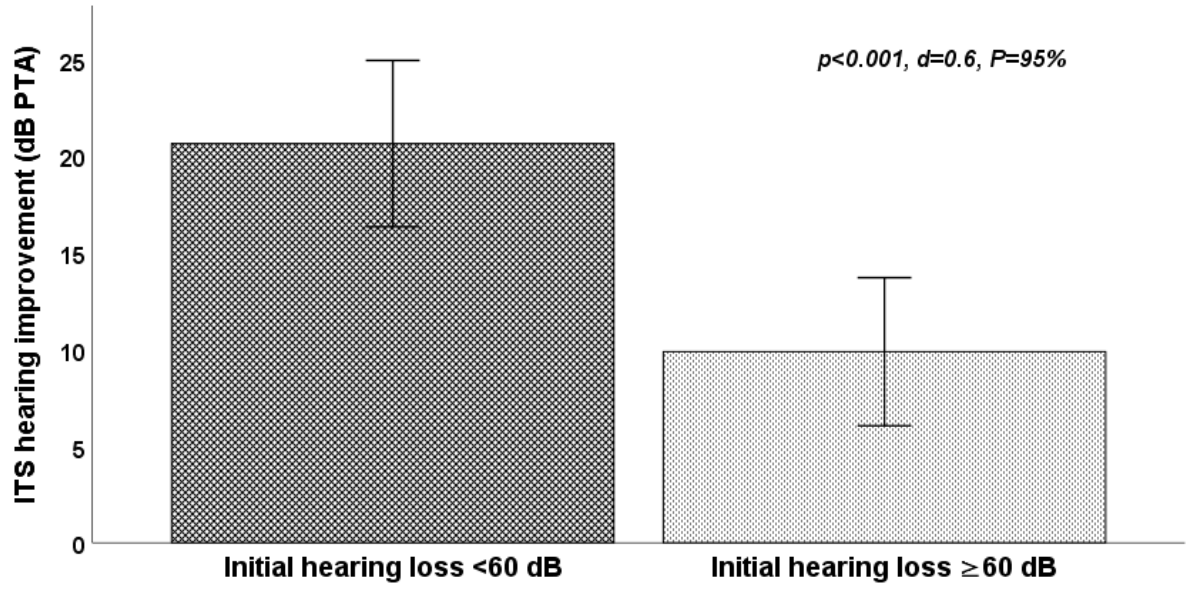

Figure 12: Hearing improvement by ITS salvage treatment according to hearing loss severity subgroups

3.1.5.8 Systemic hearing improvement subgroups analysis

Patients were divided into two groups according to their degree of primary systemic hearing improvement. Due to the fact that a hearing recovery of 10 dB is generally considered as clinically significant, a systemic hearing improvement of ≥10 dB was used as cut-off between groups. 25 patients (16.4%) gained a systemic hearing improvement of ≥10 dB (mean: 22 ± 8.7 dB). The remaining 127 patients (83.6%) improved less than 10 dB by primary systemic treatment (mean: -0.5 ± 5.8 dB).

The systemic hearing improvement ≥10 dB group had a mean ITS hearing improvement of 27.6 ± 17.5 dB (*CI*=20.4–34.9). In this group, post-systemic PTA declined statistically significant from 66.8 ± 11.9 dB to a final PTA of 39.1 ± 18.5 dB [*t*(24)=7.89, *p*<0.001, *d*=1.57, *P*=99%]. The systemic hearing improvement <10 dB group, showed a mean ITS hearing improvement of 13.6 ± 18.4 dB (*CI*=10.4–16.8). Post-systemic PTA decreased in this group from 83.2 ± 18.8 dB to a final PTA of 69.5 ± 25.2 dB [*t*(126)=8.35, *p*<0.001, *d*=0.73, *P*=100%].

The inter-group comparison revealed that patients with the higher systemic hearing improvement (≥10 dB) recovered in hearing function by ITS salvage treatment statistically significant more than patients with the lower systemic hearing improvement (<10 dB) [M^{diff}=14 dB, *CI*=6.1–21.9, *t*(150)=3.5, *p*=0.001, *d*=0.76, *P*=93%], see figure 13.

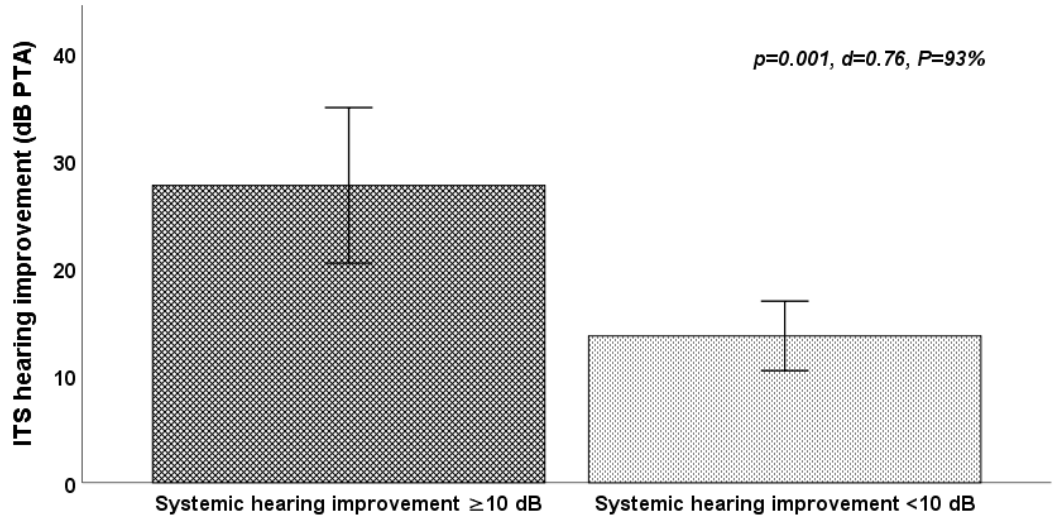

Figure 13: Hearing improvement by ITS salvage treatment according to systemic hearing improvement subgroups

3.1.5.9 Treatment delay subgroups analysis

As the differences between recovery groups in primary and ITS salvage treatment delay were very similar (see table 8), we decided to divide patients into groups based on primary treatment delay, in order to evaluate the effect of treatment delay on ITS hearing improvement: 87 patients (57%) started primary therapy within 3 days since ISSNHL onset (mean: 1.2 ± 0.9 days) while the remaining 65 patients (43%) had a primary treatment delay of >3 days (mean: 12.2 ± 12.1 days).

The ≤ 3 days delay group had an ITS hearing improvement of 19.9 ± 19.8 dB (*CI*=15.7–24.1). Post-systemic PTA declined in this group statistically significant from 84.6 ± 18.4 dB to a final PTA of 64.6 ± 27.5 dB [$t(86)=9.39$, $p<0.001$, $d=1$, $P=100\%$]. ITS salvage treatment improved hearing function in the >3 days delay group by 10.6 ± 16.3 dB (*CI*=6.5–14.6). The PTA declined in this group statistically significant from a post-systemic value of 75.1 ± 18.2 dB to a final value of 64.5 ± 26.1 dB [$t(64)=5.22$, $p<0.001$, $d=0.64$, $P=99\%$].

A comparison between the treatment delay groups showed that patients, who started primary treatment within 3 days since symptom onset, improved by ITS salvage treatment statistically significant more than patients with a primary treatment delay of more than 3 days [$M^{diff}=9.3$ dB, *CI*=3.5–15.1, Welch's $t(148.4)=3.19$, $p=0.002$, $d=0.52$, $P=88\%$], see figure 14.

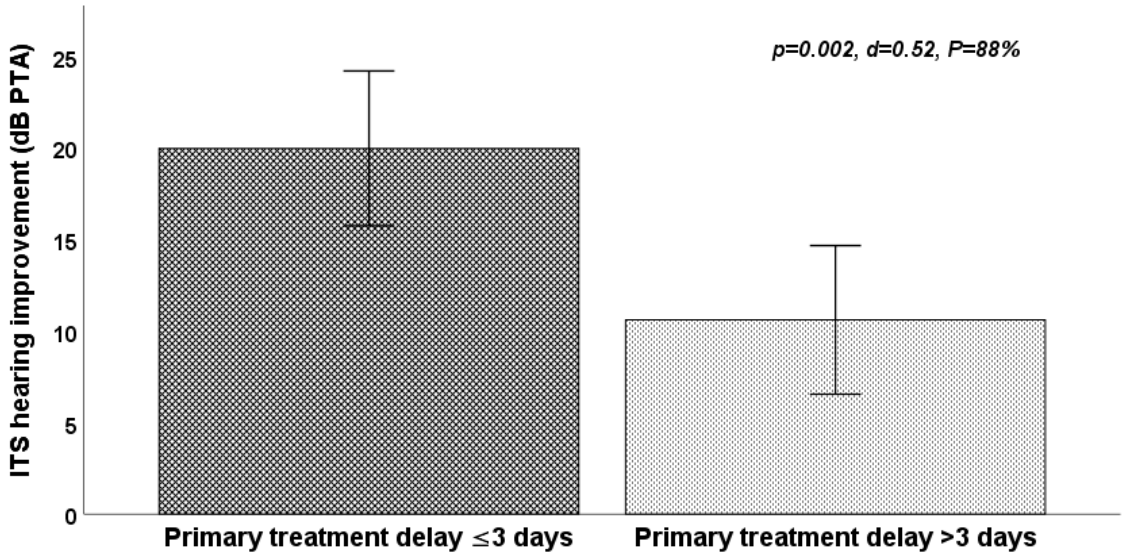

Figure 14: Hearing improvement by ITS salvage treatment according to ITS treatment delay subgroups

3.1.6 Individual ITS injection outcome

A pure-tone audiometry was performed at each ITS treatment visit in order to evaluate differences in hearing improvement between the individual ITS injections. Patients were divided into subgroups according to their total count of received injections: 89 patients (57.2%) obtained 3x ITS injections, 33 patients (21.2%) received 2x ITS injections and 30 patients (21.1%) got 1x ITS injection. Audiometric results of the ITS injection groups are displayed in table 13.

Table 13: Audiometric results according to total count of received ITS injections

Audiometric parameter	Total count of received ITS injections		
	1x injection (*n*=30)	**2x injections (*n*=33)**	**3x injections (*n*=89)**
Baseline PTA, dB	15.1 ± 10.3	22.4 ± 14.2	18.9 ± 11.5
Initial PTA, dB	78 ± 20.1	84.9 ± 17.5	85.1 ± 17.6
Initial hearing loss, dB PTA	62.9 ± 19.6	62.4 ± 21	66.2 ± 18.5
Post-systemic PTA, dB	71.6 ± 21.1	81.1 ± 17.5	83.3 ± 17.8
Systemic hearing improvement, dB	6.4 ± 13.4	3.6 ± 9.5	1.8 ± 9.6
ITS1 hearing improvement, dB	22.3 ± 22.5	7.6 ± 12.9	7.1 ± 11.2
Post-ITS1 PTA, dB	-	73.4 ± 24	76.2 ± 20.1
ITS2 hearing improvement, dB	-	2.9 ± 7.4	4 ± 7.3
Post-ITS2 PTA, dB	-	-	72.2. ± 20.7
ITS3 hearing improvement, dB	-	-	3.3 ± 6.6
Final PTA, dB	45.8 ± 34.2	70.7 ± 26.7	68.6 ± 20.6
ITS hearing improvement, dB	25.7 ± 24.7	10.3 ± 16.7	14.7 ± 16.3
Total hearing improvement, dB	32.1 ± 30.1	14.1 ± 24.3	16.5 ± 19.1

Continuous variables are presented as means ± standard deviations

3.1.6.1 First ITS injection

All included 152 patients received at least 1x ITS injection. The overall ITS1 hearing improvement was 10.2 ± 15.6 dB (*CI*=7.7–12.7). Post-systemic PTA decreased by the first ITS injection statistically significant from 80.5 ± 18.9 dB to a post-ITS1 PTA of 70.3 ± 25.7 dB [*t*(151)=8.08, *p*<0.001, *d*=0.65, *P*=100%], see figure 15A. A separate analysis was conducted for the 30 patients who received solely 1x ITS injection. In these patients, ITS hearing improvement quantified 25.7 ± 24.74 dB (*CI*=16.5–35). The PTA declined statistically significant from a post-systemic value of 71.6 ± 21.1 dB to a final value of 45.8 ± 34.2 dB [*t*(29)=5.7, *p*<0.001, *d*=1, *P*=100%], see figure 15B.

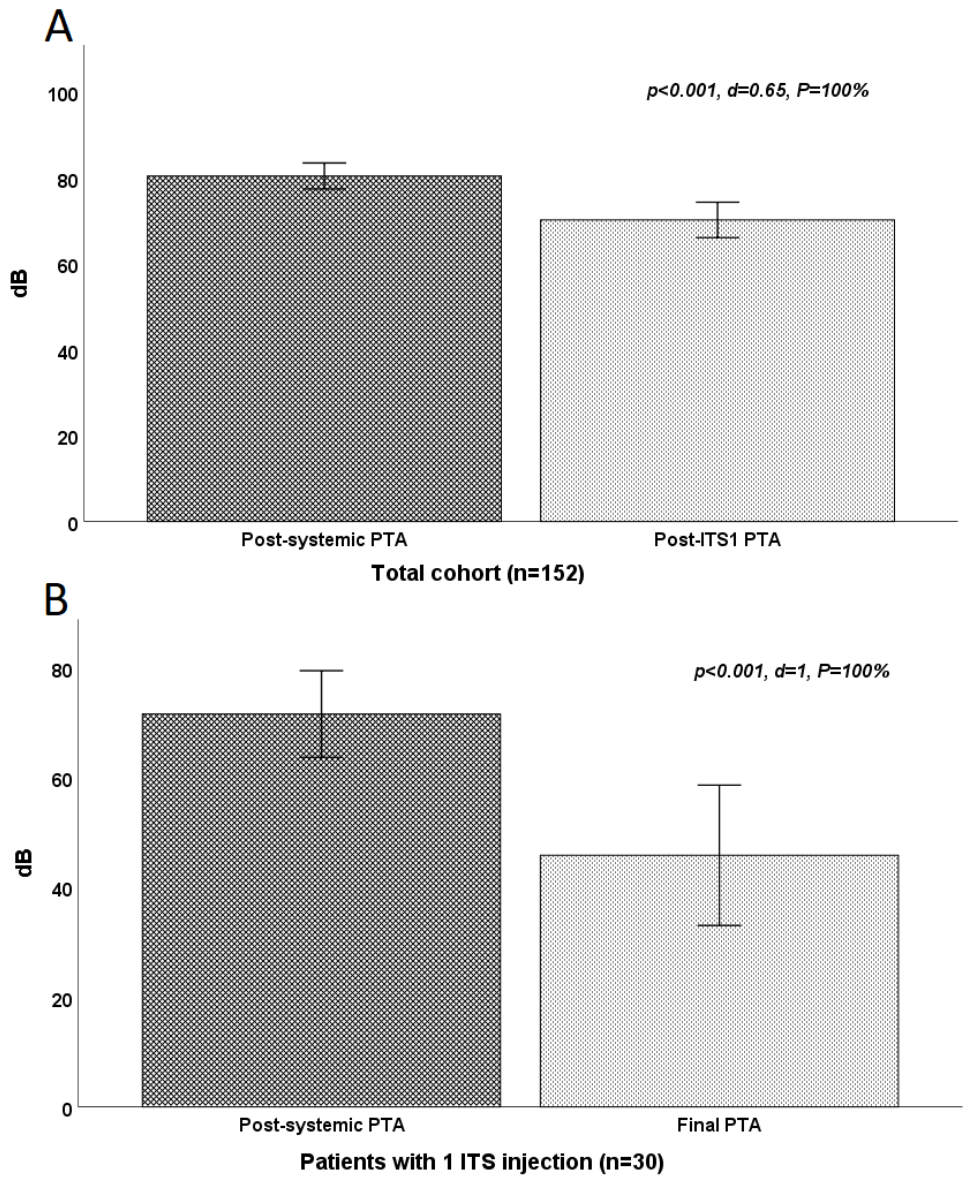

Figure 15: Hearing improvement by the first ITS injection

3.1.6.2 Second ITS injection

122 patients obtained at least 2x ITS injections. In these patients, post-ITS1 hearing improvement was 7.2 ± 11.7 dB (*CI*=5.1–9.3). Post-systemic PTA decreased statistically significant from 82.7 ± 17.7 dB to a post-ITS1 PTA of 75.4 ± 21.1 dB [*t*(121)=6.84, *p*<0.001, *d*=0.61, *P*=99%]. The second ITS injection improved hearing function statistically significant by 3.6 ± 7.3 dB (*CI*=2.3–4.9), resulting in a post-ITS2 PTA of 71.8 ± 22.43 dB [*t*(121)=5.49, *p*<0.001, *d*=0.49, *P*=99%]. A comparison between the hearing improvements by the first and second ITS injection revealed that the first injection resulted in a statistically significant higher hearing improvement [M^{diff}=*3.5, CI*=1.3-5.7, *t*(121)=3.22, *p*=0.002, *d*=0.29, *P*=88%, figure 16].

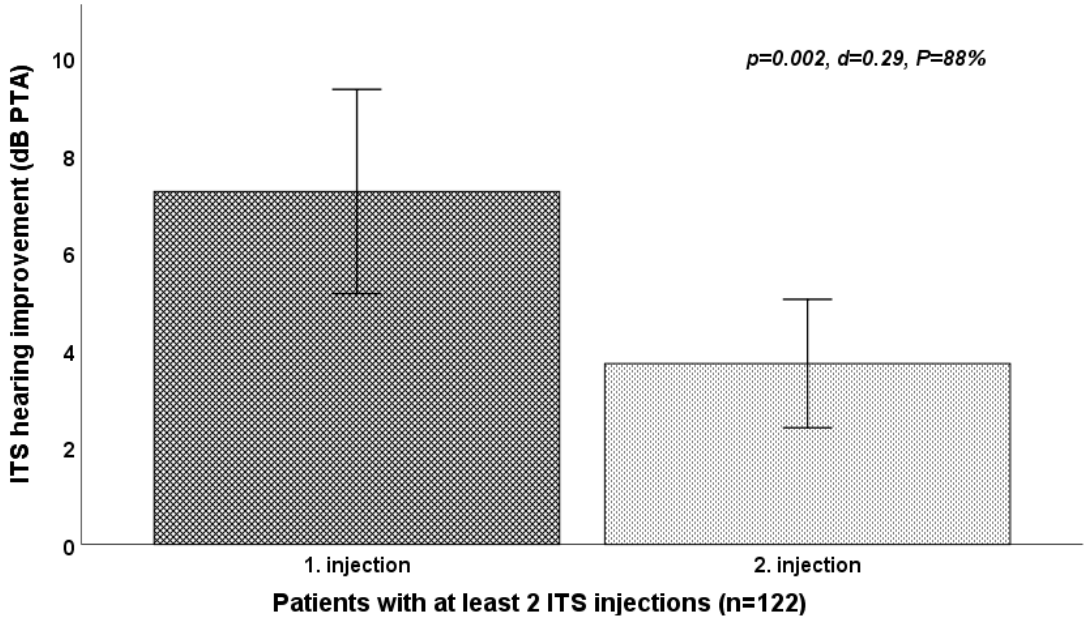

Figure 16: Hearing improvement of individual ITS injections in patients who received at least 2x injections

A separate analysis was performed for the 33 patients, who received exactly 2x ITS injections. They had a total ITS hearing improvement of 10.3 ± 16.7 dB (*CI*=4.3–16.2). Post-systemic PTA decreased in these patients statistically significant from 81.1 ± 17.5 dB to a final PTA of 70.7 ± 26.7 dB [*t*(32)=3.53, *p*=0.001, *d*=0.61, *P*=92%]. The first injection resulted in a hearing improvement of 7.6 ± 12.94.7 dB (*CI*=3–12.2) and the second injection improved the hearing function by 2.9 ± 7.4 dB (*CI*=0.2–5.5). A comparison between the hearing improvements by the first and second ITS injections showed that the first injection led to a statistically significant greater hearing improvement [M^{diff}=4.7 dB, *CI*=0.1-9.2, *t*(32)=2.08, *p*=0.045, *d*=0.36, *P*=51%], see figure 17.

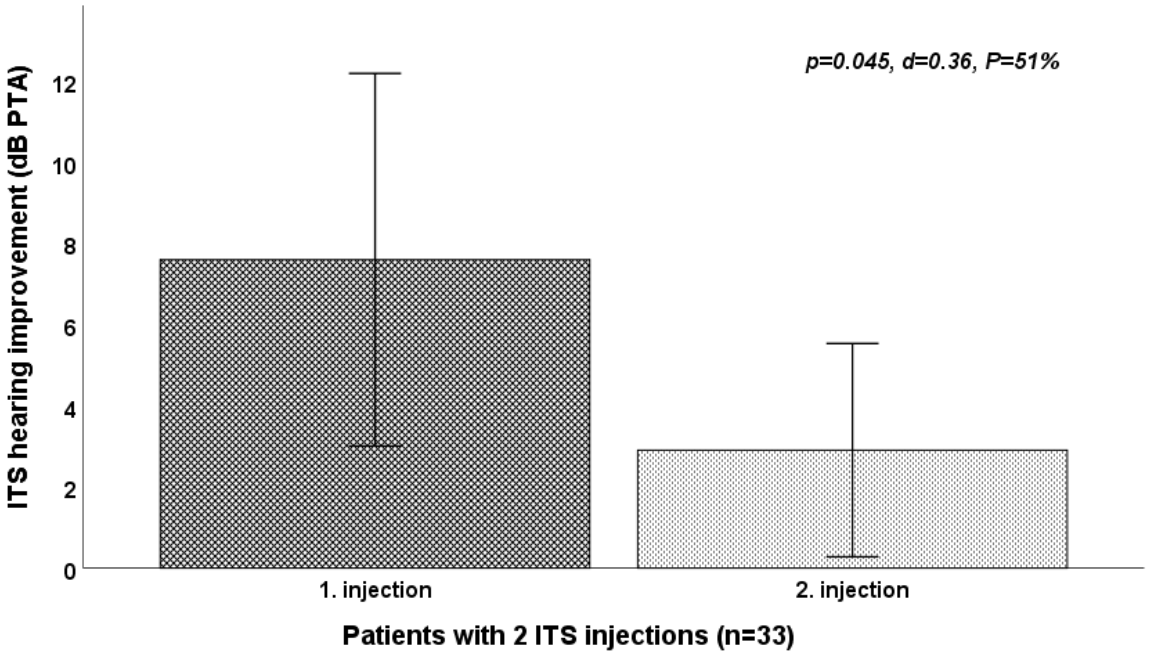

Figure 17:Hearing improvement of individual ITS injections in patients who received 2x injections.
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3.1.6.3 Third ITS injection

The 89 patients, who received 3x ITS injections, gained an ITS hearing improvement of 14.7 ± 16.3 dB (*CI*=1.3–18.1). Hearing function improved in these patients statistically significant from a post-systemic PTA of 83.3 ± 17.8 dB to a final PTA of 68.6 ± 20.6 dB [$t(88)=8.53$, $p<0.001$, $d=0.9$, $P=100\%$]. A repeated measures-ANOVA was performed to evaluate differences in hearing improvement between the particular ITS injections. As the Mauchly test was significant [$W(2)=0.82$, $p<0.001$] with a Greenhouse-Geisser's ε-coefficient of 0.853, an Huynh-Feldt correction was applied to rectify sphericity. Hearing improvement between the particular ITS injections differed statistically significant [$F(1.74, 152.7)=5.27$, $p=0.009$, $f=0.25$, $P=100\%$], see figure 18. Bonferroni-adjusted post-hoc analyses revealed that the first injection resulted in a statistically significant higher hearing improvement compared to the second injection (M^{diff}=3.1 dB, *CI*=0.1–6.1, $p=0.046$) and third injection (M^{diff}=3.7 dB, *CI*=0.2–7.2, $p=0.031$). No statistically significant difference was found between the second and third injection (M^{diff}=0.6, *CI*=-1.73–3.02, $p=0.998$).

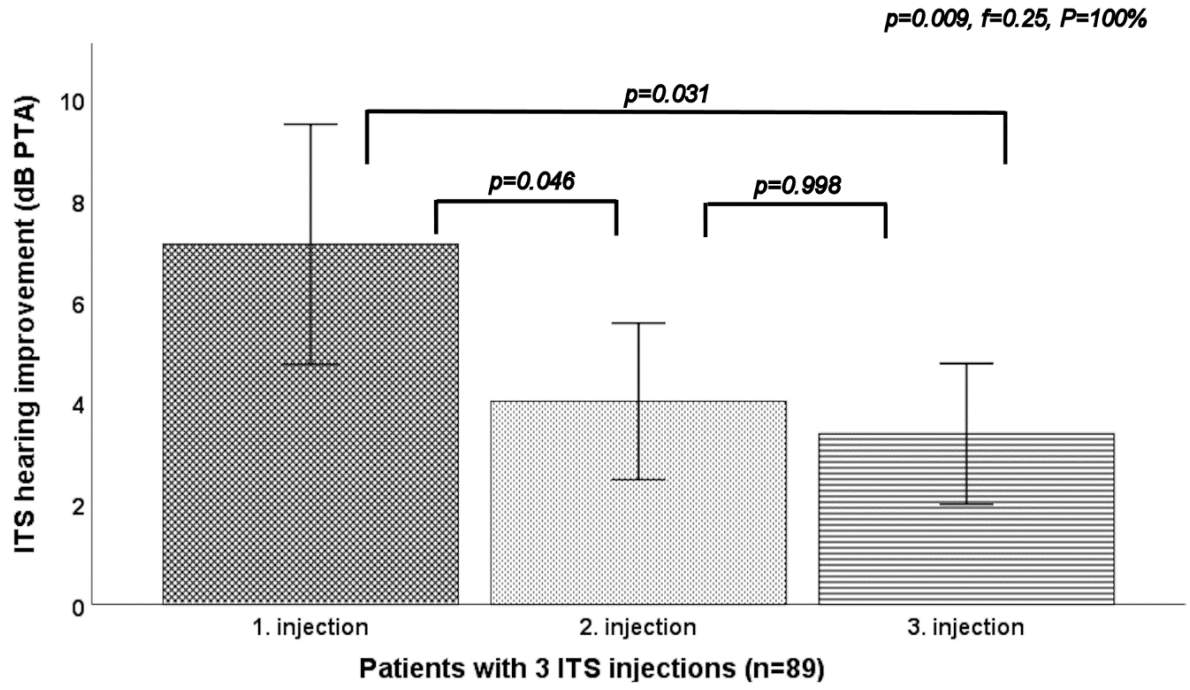

Figure 18: Hearing improvement of individual ITS injections in patients who received 3x injections.
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3.1.7 Predictors for ITS salvage treatment outcome

In order to determine independent prognostic factors for hearing improvement by ITS salvage treatment, a multiple linear regression analysis with a stepwise model was performed. Potential predictors included in the analysis were: age, sex, presence of co-existing vertigo and tinnitus, initial hearing loss, systemic hearing improvement primary treatment delay and application method of primary treatment.

All required assumptions for a multiple linear regression analysis were observed: The dependent variable showed linearity to all independent metric variables. The case-wise diagnostics revealed no outliners outside 3x standard deviations. All studentised deleted residuals were found in a range of -3 to 3. The highest leverage value quantified 0.19. Co-linearity between included predictors was ruled out as the highest correlation-coefficient was 0.265, the highest value of the variance influence factor was 1.181 and the lowest tolerance value was 0.756. Auto-correlation was excluded as the Durbin-Watson value quantified 2.24. The White test revealed heteroscedasticity of the residuals [White's $\chi^2(32)=34.38$, $p=0.354$].

The performed model turned out statistically significant in the prediction of the hearing improvement by ITS salvage treatment [$F(3)=7.58$, $p<0.001$, $f^2=0.15$, $P=99\%$].

Multiple linear regression analysis identified primary treatment delay (p=0.004), initial hearing loss (p=0.047) and degree of systemic hearing improvement (p=0.049) as independent predictors for ITS hearing improvement. The highest independent effect on ITS hearing improvement had primary treatment delay (r=0.28), followed by initial hearing loss severity (r=0.21) and systemic hearing improvement (r=0.2), respectively. Detailed results of the identified predictors are displayed in table 14. Age, sex, presence of co-existing vertigo/tinnitus and application method of primary treatment had no significant independent impact on hearing improvement by ITS salvage treatment (p>0.05).

Table 14: Identified independent predictors for ITS hearing improvement

Independent variables	ITS hearing improvement (p<0.001, f^2=0.15, P=99%)				
	Coefficient B	Standard error	Standardized B	Pearson's r	p-value
Primary treatment delay	-0.45	0.15	-0.23	0.28	0.004*
Severity of initial hearing loss	0.16	0.07	0.16	0.21	0.049*
Systemic hearing improvement	0.29	0.14	0.15	0.2	0.047*

** represents statistical significance at the 0.05 α-level. Reproduced from (1) with permission from S. Karger AG.*

3.1.8 Adverse events

Within the included 152 patients, 2 adverse events (1.3%) occurred. One patient developed an acute inflammation of the middle ear, induced by the second ITS injection. The outstanding injections were cancelled and the acute otitis media was successfully treated with oral antibiotics. The other patient developed a persistent ear drum perforation after the third ITS injection, which was surgically closed by a myringoplasty six months after the ITS treatments.

A moderate proportion of patients experienced short-term and self-resolving dizziness and mild otalgia after the ITS injections. These minor adverse events were not documented systematically in the medical records, and therefore not statistically evaluated.

3.2 Case-control study

From September 2019 to December 2020, 43 newly diagnosed SSNHL patients with failure of primary systemic treatment were treated with up to 4x ITS injections every 2-4 days as salvage treatment at the Department of Otorhinolaryngology, Medical University of Graz. 11 patients were excluded from the study. Reasons for exclusion are displayed in the study flow diagram (Figure 19). At the end, 32 patients were included in the revised-protocol group. 32 matched ISSNHL patients out of the cohort study, who received up to 3x ITS injections at 1-week intervals as salvage treatment (between January 2014 to August 2019), were enrolled in the initial-protocol group.

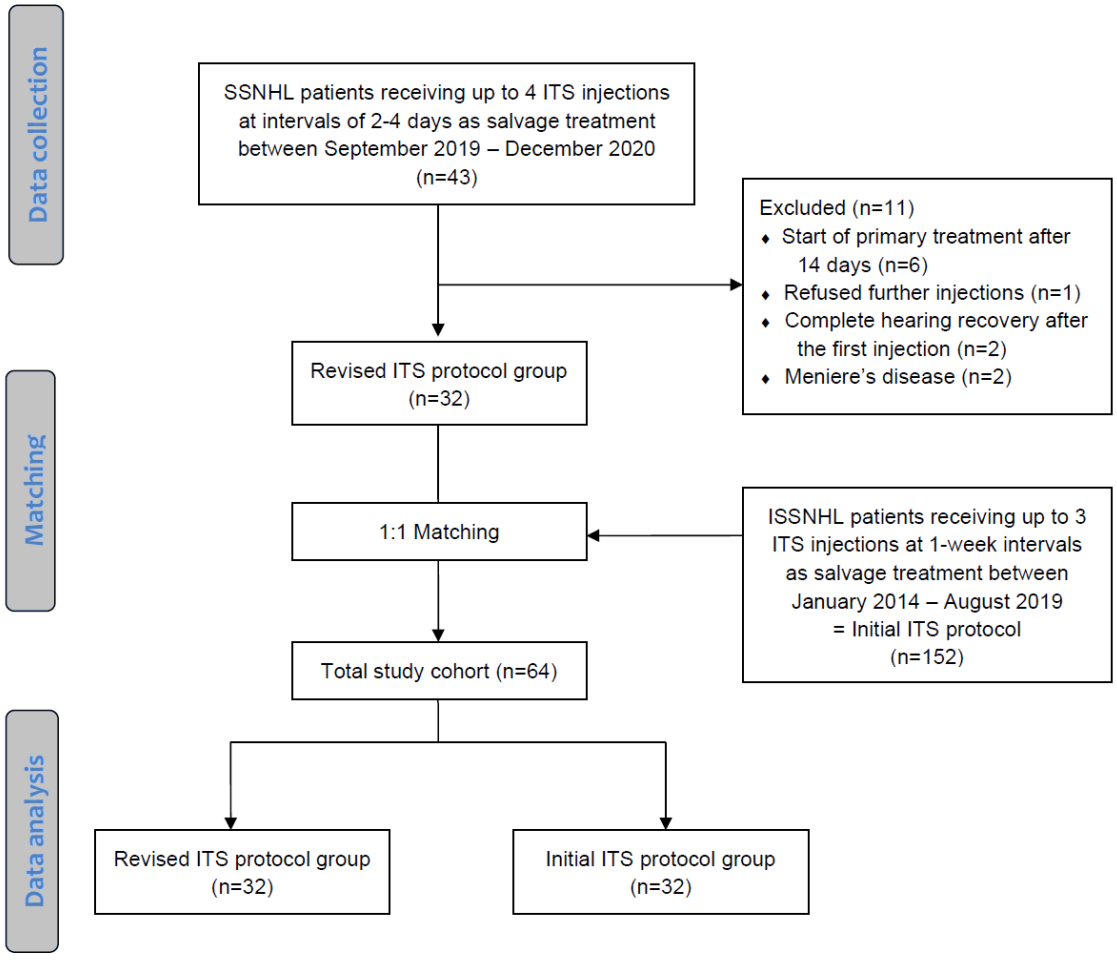

Figure 19: Case-control study flow diagram.
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3.2.1 Baseline characteristics

41 females (35.9%) and 23 males (64.1%) were included in the study. The mean age of the total study cohort was 57 ± 16.1 years. 24 patients (37.5%) were elderly individuals (≥65 years), and 40 patients (62.5%) were young/middle aged (<65 years).

Co-existing vertigo occurred in 32 patients (50%). An apparated vestibular assessment was performed in 21 out of the 32 cases (65.6%) with co-accompanying vertigo. Of these: 10 patients (57.4%) showed a normal function of the peripheral vestibular organs, and 11 patients (52.3%) had a vestibular dysfunction. 6 patients (54.5%) presented a hypofunction of the vestibular organs, and a total vestibular function loss was found in 5 cases (45.5%). Co-existing tinnitus was noted in 45 patients (70.3%).

Baseline and initial PTAs were 17.9 ± 11 dB and 80.1 ± 19.1 dB, respectively. The amount of initial hearing loss quantified 62.2 ± 19 dB. Moderate, severe and profound initial PTA levels were seen in 24 (37.5%), 13 (20.3%) and 27 (42.2%) patients, respectively. No case of mild initial PTA level was included in the study. 59 patients (92.2%), had an initial unserviceable hearing level by the episode of ISSNHL.

Systemic corticosteroids as primary treatment were administered in 33 patients (51.6%) intravenously, and in 31 patients (48.4%) per orally. Primary systemic treatment improved the hearing function by 5 ± 8.3 dB on average. No statistically significant difference in systemic hearing improvement between the application methods was found [intravenous: 3.7 ± 7.7 dB; oral: 6.3 ± 8.7 dB; M^{diff}=2.6, *CI*=-1.5–6.7, $t(62)$=1.27, p=0.208]. The mean primary treatment delay was 4.3 ± 4.5 days.

Patients had a mean post-systemic PTA of 75.1 ± 21.1 dB. Mild, moderate, severe and profound post-systemic PTA levels were found in 2 (3.1%), 28 (43.8%), 13 (20.3%) and 21 patients (32.8%), respectively. 53 patients (82.8%) presented a post-systemic unserviceable hearing level. The mean duration between sudden hearing loss onset to start of ITS salvage treatment quantified 9 ± 4.6 days.

Table 15 displays the patient's baseline characteristics according to ITS protocol groups. There were no statistically significant differences between protocol groups regarding: sex, age, accompanied symptoms vertigo and tinnitus, baseline-, initial- and post-systemic audiometric data, and treatment delay (p>0.05). A statistically significant difference between protocol groups was solely found for the application method of primary treatment [Fisher's exact test(1)=7.57, $D^{e,p}$=34.3%, p=0.012, φ=0.34, P=77%].

Table 15: Patient's baseline characteristics (Case-control study)

Characteristic	Initial-protocol (*n*=32)	Revised-protocol (*n*=32)	*p*-value
Sex, no. female/male	13/19	10/22	0.603
Age, years	57.7 ± 16.4	58.1 ± 16.1	0.933
Presence of vertigo, no. (%)	14 (43.8)	18 (56.3)	0.454
Presence of tinnitus, no. (%)	19 (59.4)	26 (81.3)	0.099
Baseline PTA, dB	18 ± 10.2	17.9 ± 12.0	0.984
Initial PTA, dB	80.6 ± 19.9	79.7 ± 18.5	0.849
Initial hearing loss, dB PTA	62.6 ± 19.1	61.7 ± 19.2	0.858
Initial unserviceable hearing level, no. (%)	30 (93.8)	29 (90.6)	0.998
Severity of initial PTA, no. (%)			0.246
Moderate	12 (37.5)	12 (37.5)	
Severe	4 (12.5)	9 (28.1)	
Profound	16 (50)	11 (34.4)	
Post-systemic PTA, dB	76.8 ± 20.8	73.4 ± 21.4	0.524
Post-systemic unserviceable hearing level, no. (%)	27 (84.4)	26 (81.3)	1
Severity of post-systemic PTA, no. (%)			0.391
Mild	0	2 (6.3)	
Moderate	15 (46.9)	13 (40.6)	
Severe	5 (15.6)	8 (25)	
Profound	12 (37.5)	9 (28.1)	
Systemic hearing improvement, dB PTA	3.8 ± 7.3	6.2 ± 9.0	0.237
Application method of primary systemic treatment, no. (%)			0.012*
oral	10 (31.3)	21 (65.6)	
intravenous	22 (68.2	11 (34.4)	
Primary treatment delay, days	4.4 ± 4.5	4.1 ± 4.5	0.806
ITS salvage treatment delay, days	9.4 ± 4.7	8.6 ± 4.6	0.505

*Continuous variables are presented as means ± standard deviations and categorical variables as absolute numbers and percentages. * represents statistically significance at the 0.05 α-level. Reproduced from (2) with permission from Springer Nature.*

3.2.2 ITS salvage treatment outcome

3.2.2.1 Primary outcome measure

Both protocols improved the mean hearing function statistically significant by ITS injections as salvage treatment (p<0.05, see Figure 20).

In the initial-protocol group, patients received up to 3x ITS injections at 1-week intervals. One patient in this group gained a complete hearing recovery after the second ITS injection. Patients with injections at 1-week intervals had a mean ITS hearing improvement of 12 ± 11.7 dB. The hearing thresholds in this group declined statistically significant from a post-systemic PTA of 76.8 ± 20.8 dB to a final PTA of 64.8 ± 21.5 dB [t(31)=5.82, p<0.001, d=1, P=99%].

In the revised-protocol group, patients obtained up to 4x ITS injections every 2-4 days (average 3.1 days). A complete hearing recovery was achieved in one patient after the third injection and in 2 patients after the second injection. Patients, who received injections every 2-4 days, showed a mean ITS hearing improvement of 13.4 ± 19.1 dB. ITS salvage treatment decreased hearing thresholds in these patients statistically significant from a post-systemic PTA of 73.4 ± 21.4 dB to a final PTA of 60 ± 27.7 dB [t(31)=3.97, p<0.001, d=0.7, P=98%].

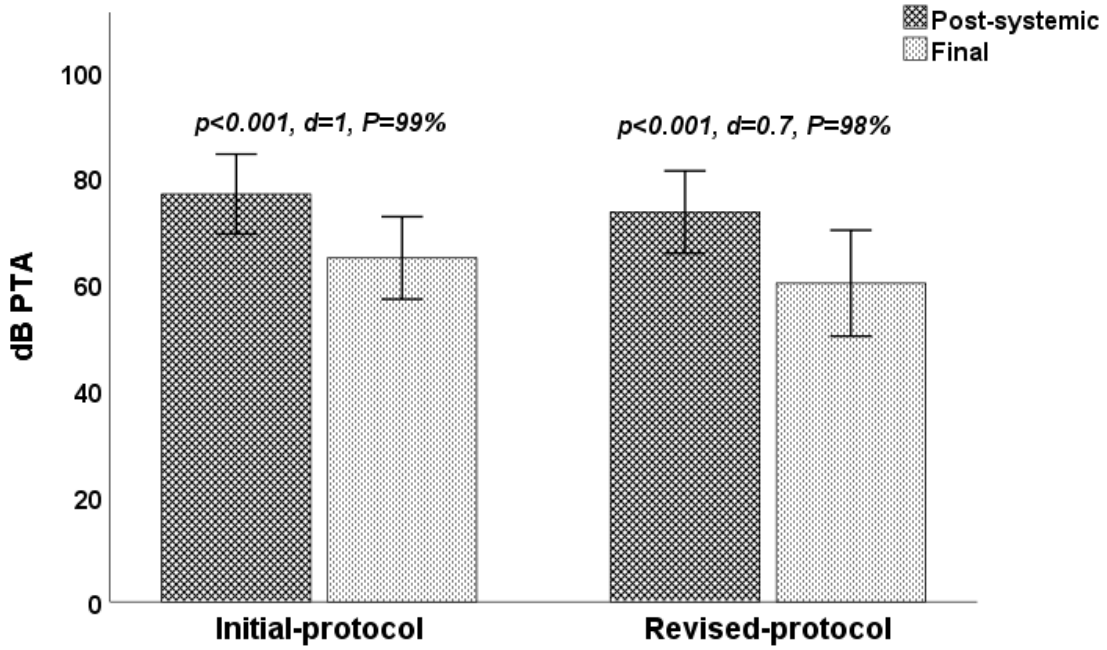

Figure 20: Hearing threshold changes by ITS salvage treatment.
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A comparison of the hearing improvements by ITS salvage treatment between protocol groups revealed no statistically significant difference [M^{diff}=1.4 dB, p=0.730, P=10%], see figure 21.

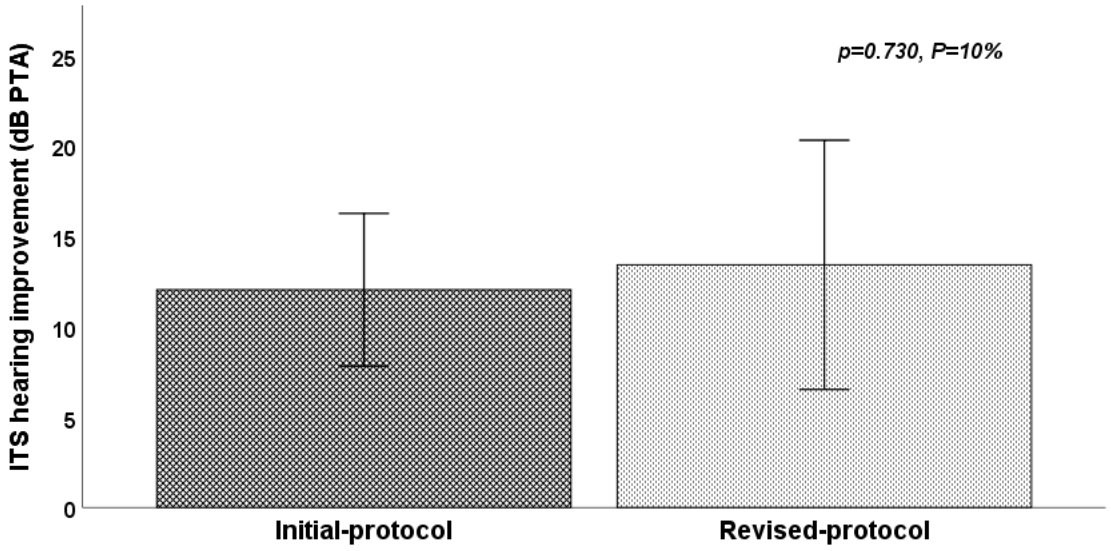

Figure 21: Comparison of ITS hearing improvement between protocol groups.
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3.2.2.2 Secondary outcome measures

3.2.2.2.1 Clinically significant ITS hearing improvement

A clinically significant hearing improvement by ITS salvage treatment (>10 dB) was achieved from 18 patients (58.1%) in the initial-protocol group and from 13 patients (41.9%) in the revised-protocol group. No statistically significant difference in the empirical probability of clinically significant ITS hearing improvement between the protocol groups was found (Fisher's exact test(1), p=0.317, P=23%).

3.2.2.2.2 ITS response levels

Results of the ITS response levels for each ITS protocol are shown in table 16. There were no statistically significant differences in the empirical probabilities of ITS response levels between protocol groups [$\chi^2(3)$=3.54, p=332, P=31%].

Table 16: Comparison of ITS response levels between protocol groups

ITS response level	Initial-protocol (*n*=32)	Revised-protocol (*n*=32)	*p*-value
≤10 dB improvement	14 (43.8)	19 (59.4)	0.211
>10 – 20 dB improvement	10 (31.2)	6 (18.8)	0.248
>20 – 30 dB improvement	5 (15.6)	2 (6.3)	0.229
>30 dB improvement	3 (9.4)	5 (15.5)	0.449
>10 dB deterioration	0	0	1

Categorical variables are presented as absolute numbers and percentages (%). Reproduced from (2) *with permission from Springer Nature.*

3.2.2.2.3 Grade of hearing recovery

In the initial-protocol group: complete, partial and no recovery were noted in 12 (37.5%), 17 (53.1%), and 3 (9.4%) patients, respectively. In the revised-protocol group: complete, partial and no recovery were recorded in 15 (46.9%), 12 (37.5%), and 5 (15.6%) patients, respectively. A comparison between protocol groups revealed no statistically significant differences in the empirical probabilities of hearing recovery grades [$\chi^2(2)=1.69$, $p=0.530$, $P=19\%$].

3.2.2.2.4 Recovery into a serviceable hearing range

9 patients (28.1%) in the initial-protocol group presented a final serviceable hearing level. 4 of the 27 patients with a post-systemic unserviceable hearing level returned by ITS salvage treatment into a serviceable hearing range. This rate of return was statistically significant [McNemar(n=32), $D^{e.p.}$=14.8%, p=0.046].

In the revised-protocol group, a final serviceable hearing level was seen in 13 patients (40.6%). ITS salvage treatment returned 7 of the 26 patients with a post-systemic unserviceable hearing level into a final serviceable hearing range. This evolution was statistically significant [McNemar(n=32), $D^{e.p.}$=26.9%, p=0.020].

There was no statistically significant difference in the rate of recovery into a serviceable hearing range between protocol groups [Fisher's exact test(1), $D^{e.p.}$=12.1%, p=0.430, P=18%].

3.2.2.3 Adverse events

In both protocol groups, no severe adverse events induced by ITS injections such as persistent tympanic membrane perforation or acute otitis media were detected.

Similar to the cohort study, minor adverse events, including short-term and self-resolving dizziness and otalgia, were not documented systematically in the medical records, and therefore not statistically evaluated.

4 Discussion

4.1 Cohort Study

In the first part of the present dissertation project, a retrospective chart-review of all patients affected by ISSNHL between January 2014 and August 2019, at the Department of Otorhinolaryngology, Medical University of Graz, who had insufficient hearing recovery after primary systemic treatment and who were treated with ITS injections as salvage therapy, was conducted. Patients received up to 3x ITS injections at 1-week intervals with triamcinolone acetonide at 40mg/ml. As primary study objective, we aimed to evaluate the efficacy of triamcinolone acetonide as medication for the ITS salvage treatment of ISSNHL. The total cohort improved in hearing function by 15.9 ± 18.9 dB. 52.6% of the patients had a clinically significant hearing improvement. A complete and partial hearing recovery was achieved from 9.9% and 48% of the patients, respectively. 23.9% of the patients with an unserviceable hearing level, returned by ITS salvage treatment into a serviceable hearing range. Secondary study objectives were to evaluate the significance of each individual injection, and to identify plausible predictors for ITS hearing improvement. The first of the three ITS injections yielded the greatest hearing improvement. Significant factors influencing the outcome of ITS hearing improvement turned out to be: treatment delay, degree of primary systemic hearing improvement and severity of initial hearing loss.

No consensus exists on the most suitable corticosteroid for ITS treatment of ISSNHL. The most commonly used corticosteroids are dexamethasone and methylprednisolone. According to nationwide surveys, dexamethasone is the most frequently applied medication, with 51% in the United Kingdom (24), 61% in German-speaking countries (25) and “similar values” (not specified) in the United States (26). Methylprednisolone is the second most commonly administered corticosteroid: 39% - United Kingdom (24), 12% - German-speaking countries (25), “similar values” (not specified) - United States (26). Triamcinolone acetonide is used by solely 3% of the otorhinolaryngologists in the United Kingdom (24). In Germany and Austria, triamcinolone acetonide is applied more frequently, with 10% (25). There are no available data of the usage rate of triamcinolone acetonide in the United States. The remaining applied corticosteroids are hydrocortisone and betamethasone, both with negligible proportions (0-3%) (24,25). The reasons for the choice of the particular agent were unfortunately not obtained in these nationwide surveys. Presumptively, the majority of the physicians have been guided by clinical data or national guidelines. For instance, a meta-analysis by Ng et al. reported a superior hearing outcome for dexamethasone (23). The by far most comprehensive guidelines

on ISSNHL, provided by the AAO-HNSF, recommends to use dexamethasone or methylprednisolone, without favoring one of the two drugs (3). The same recommendation is given by the SAORL (39). The German guidelines do not state a specific recommendation regarding drug selection (125). None of the existing systematic reviews and meta-analyses have included a study which used triamcinolone acetonide for the ITS treatment of ISSNHL. Similarly, none of the pre-stated national guidelines even mention triamcinolone acetonide within their drug selection paragraph (3,39,125). Clearly, the reason for these facts is that there is no RCT which has used triamcinolone acetonide as drug for the ITS treatment of ISSNHL. Besides clinical data and guideline recommendations, few physicians may have oriented their drug choices to experimental evidence, as we did. Over the past years, the inner-ear specific molecular properties of the various corticosteroids have been increasingly studied:

Unfortunately, limited data exist on the inner-ear specific pharmacokinetic profile of methylprednisolone. Methylprednisolone is practically insoluble in aqueous solutions (aqueous-solubility: 120 µg/ml). Its' ester methylprednisolone succinate, as approved formulation for the intravenous application, is generally used for the ITS treatment (aqueous-solubility: >125 mg/ml). The addition of the succinate group raises the polarity by elevating the TPSA and decreases the lipophilicity by decreasing the WLOGP. These molecular alterations of methylprednisolone increase its aqueous solubility but on the other side reduce its capability to diffuse through semi-permeable membranes (27). Due to these modifications, it is assumed that methylprednisolone accesses the inner ear at a slower rate than methylprednisolone succinate. Nevertheless, this assumption remains theoretical as no researcher has yet been able to confirm it in an experimental approach. The widely administered methylprednisolone succinate is an inactive pro-drug until converted to its active base form methylprednisolone. This conversion is carried out primarily by carboxylesterases, which can be found in the liver and potentially in the blood plasma (214,215). To consider, carboxylesterases have currently not been identified in the inner ear. Moreover, no research group has yet been able to establish that methylprednisolone succinate is converted to its active form within the cochlea and if, at which frequency. Similarly, the exact elimination rate of methylprednisolone and its inactive pro-drugs within the inner ear remains unknown (27). Parnes et al. measured in guinea-pigs the perilymph concentrations of methylprednisolone, hydrocortisone and dexamethasone after intratympanic application. The authors observed the highest corticosteroid concentration in the perilymph for methylprednisolone and subsequently suggested a superiority of methylprednisolone for the local treatment of inner ear diseases. However, the concentration of the intratympanically administered methylprednisolone was 10x times higher than that of dexamethasone. This conclusion can therefore not be endorsed (187). Plontke and colleagues

(216), re-analysed the findings of the study by Bird et al., in which the authors measured the concentration of methylprednisolone at various time points after pre-operative intratympanic administration in perilymph samples of patients undergoing cochlea implant surgery (196). By applying a computer simulation, the Plontke et al. estimated the combined (middle ear and cochlea) elimination half time for methylprednisolone succinate as 27 minutes (216). When comparing the TPSA and WLOGP values between the active base forms of the respective corticosteroids, methylprednisolone diffuses through membranous boundaries more readily than triamcinolone, and approximately equally as dexamethasone. With respect to local inner ear treatment, this suggests that methylprednisolone and dexamethasone, compared to triamcinolone, pass more rapid through the round window membrane and stapes into the cochlea, but are also eliminated faster in the perilymph. However, as there are still no experimental data of the inner-ear specific kinetics of methylprednisolone, these comparisons are just theoretical (27,215).

Similar to methylprednisolone, dexamethasone is hardly soluble in aqueous solutions (aqueous-solubility: 89 µg/ml). Hence, the most commonly used form is dexamethasone phosphate (aqueous-solubility: 50mg/ml), available as solution. The attachment of the phosphate group to dexamethasone leads to the same effects as the addition of the succinate group to methylprednisolone, regarding polarity and lipophilicity. Dexamethasone phosphate is more polar and less lipophilic; therefore, it has a less permeability through membranous boundaries than its active form, dexamethasone. The inner-ear specific kinetic properties of dexamethasone and its inactive pro drug dexamethasone phosphate have been increasingly explored in experimental animal-based studies (27): After the application into the tympanic cavity, dexamethasone phosphate is rapidly lost. It has been reported that the concentration of dexamethasone phosphate at the round window niche decreased down to approximately 10% at 93 minutes after administration. The calculated middle-ear clearance half time of 28 minutes, is similarly as fast to that of methylprednisolone succinate (27 minutes). Whereas, the active base form dexamethasone, showed a constant middle ear concentration over time. 1 hour after the intratympanic application, 2.3% of dexamethasone and solely 0.13% of dexamethasone phosphate have passed through the round window membrane and entered the perilymph. Even after correction of the varying middle ear elimination rates, dexamethasone entered the cochlea at an 8x higher rate than dexamethasone phosphate. There is experimental proof, that the inactive pro drug dexamethasone phosphate is converted in the cochlea to its active form dexamethasone, as both forms were identified in the perilymph after the intratympanic application of dexamethasone phosphate (27,217). Moreover, the enzyme CYP17A, which is inter alia responsible for the dexamethasone phosphate

metabolism in the liver, has been identified in the cochlea (218). Within the inner ear, dexamethasone phosphate is eliminated at a slower rate than dexamethasone. The clearance halftime of dexamethasone phosphate quantified 291 minutes at the scala vestibuli, and 18 minutes at the scala tympani, whereas dexamethasone had an elimination half time of 91 minutes at the scala vestibuli, and 46 minutes at the scala tympani (217,219). Due to the gradient along the cochlea, the concentration of dexamethasone in the low-frequency area (0.5 kHz) was 500x times lower than in the vestibule and high-frequency area (8 kHz). This drug exposure difference within the cochlea was even larger for dexamethasone phosphate, which showed a 2000x lower concentration in the 500 Hz area than in the vestibule, and 8 kHz area. To summarise: these unfavorable pharmacokinetic properties (rapid middle ear elimination; limited entry into the inner ear; rapid metabolism within the perilymph into dexamethasone, which is lost quickly from the inner ear; low distribution along the cochlea), render dexamethasone phosphate, the most commonly utilised form of dexamethasone, an absolutely inappropriate candidate for the local inner ear treatment. The base form dexamethasone possesses a more favorable pharmacokinetic profile for the therapy of cochlea disorders (27). However, a liquid dexamethasone formulation is commercially not available in Austria (212).

Triamcinolone has a similar low aqueous-solubility (80 µg/ml) as methylprednisolone and dexamethasone. As an approved preparation for the intravenous application, triamcinolone is commercially only available as triamcinolone acetonide, due to the fact that triamcinolone acetonide has a much higher anti-inflammatory activity than its base form. In contrast to methylprednisolone succinate and dexamethasone phosphate, the addition of the acetonide group to triamcinolone decreases its polarity. The pro-drug triamcinolone acetonide is even less polar and more lipophilic than its already polar active base form (aqueous-solubility: 26 µg/ml). Therefore, triamcinolone acetonide and its base form have the ability to pass readily through membranous boundaries. When comparing the TPSA and WLOGP values of all three corticosteroids and their base forms, triamcinolone acetonide shows the highest permeability, followed by dexamethasone and triamcinolone, respectively (27,215). A recently published study reported the first inner-ear-specific pharmacokinetics of triamcinolone: Triamcinolone and its pro-drug are available as crystalline suspensions due to their lipophilicity. This property provides both forms with ideal middle ear kinetics. The resulting “depot effect” by suspensions, prevents a rapid drug elimination from the tympanic cavity. Triamcinolone particles were found in the middle ear cavity even a few days after the intratympanic administration. Due to their lipophilicity, both forms diffused rapidly through the round window membrane and stapes into the inner ear. Owing to its actually higher lipophilic property, triamcinolone acetonide entered

the perilymph faster than its base form (exact values not specified). There was evidence to conclude that triamcinolone acetonide is metabolised within the perilymph to its active base form: after the intratympanic application of triamcinolone acetonide, both forms were identified within the inner ear. Indeed, it must be noted that the detected portion of the base form triamcinolone represented solely 1.4% of the entire drug amount. Within the perilymph, both forms showed similar high drug concentrations. However, a considerable difference in perilymph elimination rate between both forms was found. The concentration of triamcinolone acetonide in the perilymph decreased within 2 hours to 5-10% of the baseline concentration. The elimination half time was calculated as 34 minutes at the scala vestibuli, and 12 minutes at the scala tympani. By comparison, triamcinolone acetonide was eliminated in the perilymph more rapid than dexamethasone, and much faster than dexamethasone phosphate. In contrast, triamcinolone was eliminated extremely slow in the perilymph, with an estimated clearance half time of 700 minutes at the scala tympani and 278 minutes at the scala vestibuli. Due to this slow elimination rate, triamcinolone was able to disseminate along the entire cochlea. By comparison, triamcinolone acetonide and dexamethasone did not distribute in detectable measurements to the apical area of the cochlea. To summarise, both triamcinolone forms had ideal middle ear kinetics and a readily cochlea entry - suitable properties for the local inner ear therapy. However, triamcinolone acetonide was lost rapidly after entering the perilymph. Contrary, triamcinolone remained much longer in the inner ear. These molecular properties indicate that triamcinolone may be the most suitable corticosteroid for ITS treatment of inner ear disorders. However, the authors also noted a potentially bias regarding this conclusion: The more rapid elimination of triamcinolone acetonide within the perilymph may have been the result of its more rapid entry into the inner ear, since both forms exhibited the same perilymph concentration (220).

These data and conclusions derive from experimental animal-based trials focusing on the pharmacokinetic drug properties. The clinical efficacy of the various corticosteroids in the ITS treatment of ISSNHL certainly depends on several other additional variables. One of these factors may be the anti-inflammatory potency of the corticosteroids (220). The relative glucocorticoid potencies of methylprednisolone, dexamethasone and triamcinolone are generally specified as 5, 5-6 and 25-30, respectively. In other words, dexamethasone has a 5-6x fold higher anti-inflammatory potency than methylprednisolone and triamcinolone (221,222). It has been reported that triamcinolone acetonide exhibit a binding affinity to the glucocorticoid receptor which is 4x times higher (relative potency: 20) than its base form triamcinolone, and approximately equivalent to dexamethasone (27,221,223). This is also the reason why triamcinolone is no longer commercially available as intravenous formulation

(215). To the best of our knowledge, the potency at the glucocorticoid receptor for the steroid esters methylprednisolone succinate and dexamethasone phosphate have yet not been evaluated. Taking the anti-inflammatory potencies and the pharmacokinetic profiles of the corticosteroids into account, triamcinolone acetonide may constitute the optimal candidate for the ITS treatment of ISSNHL. However, the anti-inflammatory activity of a particular corticosteroid depends on numerous variables; for instance, species and the type of the targeted tissue (220,223–225). To note, the anti-inflammatory activity of corticosteroids has yet not been examined in the cochlear tissue. Therefore, it is not entirely excluded that corticosteroids exhibit a completely different anti-inflammatory potency in the inner ear than in other parts of the human body (220).

A factor that has been poorly investigated so far, is the influence of the varying corticosteroid concentrations on its efficacy in the ITS treatment. Methylprednisolone solutions are commercially available at concentrations ranging from 20 mg/ml to 125 mg/ml (27). The most commonly (49%-66%) used concentration of methylprednisolone in ITS treatment is 40 mg/ml, followed by 62.5 mg/ml (25%-27%) (24,25). The AAO-HNSF recommends to use methylprednisolone at 30 mg/ml or 40 mg/ml for the ITS treatment of ISSNHL (3). However, no trial has directly compared the clinical efficacy of different methylprednisolone concentrations for the ITS treatment of ISSNHL. Moreover, experimental data are absent. In literature, the concentration of intratympanic applied dexamethasone for ISSNHL treatment ranges between 3.3 mg/ml to 40 mg/ml (15). According to nationwide surveys from the United Kingdom, middle Europe, and United States, concentrations at 3.3 mg/ml and 4 mg/ml represent the by far most frequently used formulations (>90%) (24–26). Perilymph analyses after intratympanic applied dexamethasone at different concentrations, are lacking in literature. However, recent experimental as well as clinical data indicated that higher concentrations of dexamethasone may result in better hearing outcomes (226,227). In an experimental study, dexamethasone at 5 mg/ml, 10 mg/ml and 20 mg/ml was instilled into the tympanic cavity of rats. Afterwards, the concentration within the cochlea tissue was measured at various time points by using fluorescent signals. The authors observed stronger fluorescent signals with a longer duration for the 10 mg/ml and 20 mg/ml groups compared to the 5 mg/ml group (226). These results have led Alexander et al. to change their intratympanic dexamethasone formulation for ISSNHL treatment from 10 mg/ml to 24 mg/ml. Subsequently, the authors compared both formulations retrospectively on hearing outcomes. They found for the 24 mg/ml group a significant larger rate of hearing recovery (>30 dB) and a higher absolute hearing improvement with a trend towards significance (28.7 dB vs. 14.9 dB, p=0.068). Therefore, the authors suggested a superiority for the higher concentration (227). However, the study was

retrospective in nature with a very small sample size per group (n= 18, 19), and the hearing outcomes of the 24 mg/ml group were similar to other existing studies using lower concentrations. Thus, the clinical superiority of higher concentrations remains debatable. Moreover, a recent meta-analysis calculated in 1257 ISSNHL patients, who received primary ITS treatment, the intra-cochlear corticosteroid concentration by using computer simulation methods. The authors found no significant correlation between the calculated drug concentrations and hearing improvements (193). Nevertheless, the study by Alexander et al. is the only trial which has clinically compared different corticosteroid concentrations in the intratympanic therapeutic management of ISSNHL (227). The AAO-HNSF therefore implemented these results into their clinical practice guidelines and currently recommends to use dexamethasone at 10 mg/ml or 24 mg/ml for the ITS treatment of ISSNHL (3). It must be noted that dexamethasone at concentrations higher than 10 mg/ml is widely commercially no longer available, and has to be separately compounded (227). Triamcinolone acetonide suspensions are commercially available at concentrations ranging from 10 mg/ml to 80 mg/ml. The most frequently utilised formulation for the ITS treatment of ISSNHL is 40 mg/ml (62-75%), according to nationwide surveys (24,25). Interestingly, in the material and methods section of the pre-mentioned pharmacokinetic perilymph study was noted that triamcinolone acetonide has been used at 40 mg/ml in two animals, and at 60 mg/ml in six animals. Unfortunately, a separate analysis for each concentration was not conducted. A reason for the choice of two different formulations was not specified by the authors (220).

Another factor to be considered is the composition of the applied drug formulation. Pharmaceutical corticosteroid formulations include several excipients; for instance, different emulsifiers (e.g., Polysorbate 80) and binding agents (e.g., cellulose derivatives). In few of the commercially available preparations of all three corticosteroids (methylprednisolone, dexamethasone, triamcinolone), benzyl alcohol is added as a bacteriostatic preservative. An experimental study with a guinea-pig model observed that benzyl alcohol at a concentration of 10mg/ml enhances the permeability of the round window membrane by a factor of 3 to 5 (203). Benzyl alcohol has the potency to harm sensory cells (228). However, researchers were able to preclude the ototoxicity of benzyl alcohol in an animal-based trial (229). The triamcinolone acetonide formulation Volon® A 40 mg-Kristallsuspension-Ampulle, Dermapharm GmbH that was used in the present study, contains benzyl alcohol at 9.9 mg/ml. In Austria, there is currently no approved intravenous formulation of methylprednisolone and dexamethasone containing benzyl alcohol (212). In the United States for example, intravenous corticosteroids preparations with benzyl alcohol are available for dexamethasone at 10.4 mg/ml and for methylprednisolone at 8.8 mg/ml (203). Nevertheless, whether these small differences or

whether even the presence of benzyl alcohol have a significant influence on the clinical efficacy of ITS treatment for ISSNHL, remains unknown.

Triamcinolone acetonide has been attributed otoprotective effects: In an animal-based in-vitro study, researchers exposed cultured organs of Corti with triamcinolone acetonide and 4-hydroxy-2-nonenal (HNE) over four days, in order to evaluate the otoprotective ability of triamcinolone acetonide (229). HNE is a toxic molecule that is naturally released during oxidative stress reactions within a cell. It has been demonstrated that HNE initiates apoptosis of sensory neurons within the cochlea (230). Cellular oxidative stress has also been proposed as the underlying cause of ISSNHL (50). The researchers observed a significant higher count of auditory hair cells in samples exposed with triamcinolone acetonide and HNE, in comparison to solely HNE exposed samples (229). In their study, triamcinolone acetonide was chosen as corticosteroid because it has been applied by some other authors during cochlea implant surgery to decrease the electrode impedance by suppressing fibrous tissue reactions (231). The same author group reported in a further experimental study that extra cochlear administration of triamcinolone acetonide prevents hearing loss after the procedure of a cochleostomy (232). The results of these studies were causative for the selection of triamcinolone acetonide as medication of the ITS treatment for ISSNHL at our Department.

Clinical data of intratympanic triamcinolone acetonide in the therapeutic management of ISSNHL are extremely limited in literature (28). We therefore aimed in the present study to evaluate the hearing outcomes of all patients diagnosed with ISSNHL at our Department, who were treated with intratympanic triamcinolone acetonide injections as salvage treatment since its initiation in 2014. We hypothesised that intratympanic triamcinolone acetonide injections as second-line treatment of ISSNHL, result in a clinically significant hearing improvement. According to our a-priori sample size calculation, we gathered a sample size far higher (N=152) than the minimum required (N=44). The absolute hearing improvement by intratympanic triamcinolone acetonide injections as salvage therapy quantified 15.9 ± 18.9 dB in the total cohort. ITS salvage treatment decreased the patient's hearing thresholds statistically significant from a post-systemic PTA of 80.5 ± 18.9 dB to a final PTA of 64.5 ± 26.6 dB. The effect size of this significant result was remarkably high with an effect coefficient d=0.84. Statistically significance should not automatically be equated with clinically significance. We selected therefore a >10 dB difference in PTA as the clinically significance criterion, due to the fact that the difference criterion must exceed the inherent variability expected by the test-retest reliability, which has been determined as 5 dB (176,177). Moreover, a hearing threshold decline of at least 10 dB is widely considered as clinically significant (11). Since the mean

hearing improvement by ITS salvage treatment, = 15.9 dB, clearly exceeds the 10 dB criterion, we were able to reject the H_0 – hypothesis and accept the H_1 – hypothesis. A post-hoc power analysis revealed that the probability to false-positive agree with the H_1 – hypothesis is practically zero (β<0.001). Regarding secondary outcome parameters, an ITS hearing improvement of more than 10 dB was achieved from 52.6% of the patients. A complete and partial hearing recovery was gained by 9.9% and 48% of the patients, respectively. 23.4% of patients with a post-systemic unserviceable hearing function returned by ITS salvage treatment into a final serviceable hearing range. We further performed a per-ITS-protocol analysis, which included solely patients who were treated precisely according to our institutions ITS treatment protocol. In the per-ITS-protocol analysis, the absolute ITS hearing improvement increased up to 19.1 ± 19.7 dB, nearly twice as high as the clinically significance criterion. Patient's hearing thresholds declined statistically significantly from a post-systemic PTA of 80.9 ± 18.6 dB to a final PTA of 61.7 ± 26.3 dB. The effect size d=0.97 of this significant result is even higher than the already considerable effect in the total cohort analysis. Similar to the total cohort analysis, we were able in the per-ITS-protocol analysis to reject the H_0 – hypothesis and accept the H_1 – hypothesis with a power of >99% (β<0.001). Concerning secondary outcome variables in the per-ITS-protocol analysis, all values increased in comparison to the total cohort analysis: 64.1% of the patients had an ITS hearing improvement of more than 10 dB. 14.6% of patients achieved a complete recovery, and 51.5% of the patients obtained a partial recovery. 32% of patients with a post-systemic unserviceable hearing level returned into a final serviceable hearing range.

Dahm et al. recently published the first clinical data of ISSNHL patients who were treated with triamcinolone acetonide as medication for ITS treatment. The authors included 89 patients who received intratympanic injections with triamcinolone acetonide at 40mg/ml, the same formulation as we have used (Volon® A 40 mg-Kristallsuspension-Ampulle, Dermapharm GmbH). As a major benefit of the present study, our sample size consisted of 152 subjects, which is approximately twice as many. The primary systemic treatment in the study of Dahm et al. was either intravenous 500 mg prednisolone for two days as outpatients, or, in case of severe comorbidities such as diabetes mellitus, intravenous prednisolone, for six days as inpatients. All patients received after the intravenous treatment, an oral taper of eight days. The proportions of out- and inpatients as well as the medication and concentration of the oral taper were not specified. After two days of intravenous therapy, patients were audiometrically evaluated for treatment success. Patients with an insufficient hearing recovery were offered up to 4x ITS injections within one week. A definition of insufficient recovery was not stated by the authors. Patients who improved by >10 dB due to ITS injections, and who have not

completely recovered in hearing function, were offered a fifth injection at the 1-week follow up visit. The majority of their patients received 3x injections (47%) or 4x injections (35.9%). Their total cohort was analysed, including those who refused further injections due to limited improvement, and who gained a complete recovery before the last injection. A separate per-protocol analysis, as performed in the current study, was not conducted. Dahm et al. reported a complete, partial and no recovery rate of 32%, 17%, and 51%, respectively. In comparison, we observed in our population a lower proportion of complete recovery and a higher percentage of partial recovery. However, their patients suffered from an initial hearing loss of 49 dB, whereas the patients in our study presented a mean initial hearing loss of 65 dB. The higher severity of hearing loss in our patients could explain the lower rate of complete hearing recovery. Their primary outcome parameter, absolute hearing gain, quantified 20 dB on average, and included hearing improvements due to both primary systemic and ITS salvage treatments. Our total hearing improvement was similarly high (19.1 ± 23.5 dB). However, in contrast to the present study, Dahm et al. failed to calculate the hearing improvements separately for each treatment modality. Moreover, even if they had calculated the individual hearing improvements, there would have been an considerable confounding variable: patients received ITS injections concomitantly to the 8-days oral taper course. It would be very difficult, if not impossible, to ascertain the exact proportion of hearing improvement due to each treatment modality. An adequate conclusion regarding clinical efficacy of triamcinolone acetonide as medication for the ITS treatment of ISSNHL, can therefore not be drawn from this study. Consequently, we provide the first efficacy results of intratympanic triamcinolone acetonide as treatment modality for ISSNHL (28).

Several high-quality studies have investigated and demonstrated the clinical efficacy of ITS treatment as salvage therapy for ISSNHL. To our knowledge, there are currently eight RCT upon this subject matter (233–240). It must be emphasised that the study by Zhou et al. (235) was pseudo-randomised and Park et al. (236) compared ITS salvage treatment to primary ITS combination treatment. Consequently, six high-quality RCTs evaluated the efficacy of ITS salvage treatment with an appropriate control group (233,234,237–240). Table 17 displays a summary of the RCTs. Three of the eight RCTs used methylprednisolone, all at 40 mg/ml. (234,235,239). Unfortunately, only one of these studies precisely stated whether methylprednisolone or its succinate ester form has been applied (239). The remaining five RCTs utilised dexamethasone, either at 4mg/ml [*n*=3, (237,238,240)] or at 5mg/ml [*n*=2, (233,236)]. It is again unfortunate, that solely two of the five studies reported whether dexamethasone or dexamethasone phosphate has been administered (233,238). The potential influence on hearing outcomes by the completely different inner ear specific

pharmacokinetics between base forms and pro drugs of the corticosteroids, may constitute a bias when interpreting the results of these studies. Moreover, the vast majority of the trials did not specify the brand of the applied corticosteroid; hence, it remains unknown if the formulation contained benzyl alcohol. Anyway, meta-analyses of the published RCTs supported the beneficial effect of ITS salvage treatment for ISSNHL on hearing outcome (14,16,18,23). One of the meta-analyses evaluated hearing outcomes additionally according to the used medication. In this analysis, Ng et al. (23) included three dexamethasone RCTs (233,237,238) and two methylprednisolone RCTs (234,239). The authors reported that dexamethasone resulted significantly more likely than methylprednisolone in a clinically meaningful hearing improvement. They did not include the RCT by Ho et. al (240). When the weighted hearing outcome values of the six high-quality RCTs (including the study by Ho et al.) are pooled, an absolute ITS hearing improvement and clinically significant hearing improvement of 13.9 dB and 52.2% for dexamethasone and 10.9 dB and 41.9% for methylprednisolone can be found, respectively (233,234,237–240). Dexamethasone shows a 10.3% higher rate of clinically significant hearing improvement. Whether this difference demonstrate an unequivocal superiority, remains debatable. Triamcinolone acetonide resulted in the present study in similar values as dexamethasone: 15.9 dB - ITS hearing improvement and 52.6% - clinically significant hearing improvement. However, ISSNHL is known as a very heterogenous disease, making unbiased comparison of clinical research data difficult. Several factors, such as presence of vertigo, hearing loss severity, audiogram type or cardiovascular risk factors may have influenced the hearing outcome. Moreover, the still poorly studied natural course of hearing recovery must be considered. Furthermore, the underlying etiology of ISSNHL and its impact on the outcome remain unknown. Despite their high level of evidence, RCTs have a high risk in this case to prone selection bias, due to their small sample sizes. Because of that, Liebau et al. included 30 ITS salvage treatment studies with sufficient available data into their meta-analysis, regardless their study design (randomised and controlled, non-randomised, non-controlled, retrospective-controlled) in order to gain a high number of samples. A performed linear regression analysis revealed that the absolute hearing improvement was independent of the applied medication (methylprednisolone or dexamethasone). When the results of the present study are implemented into their initial PTA x ITS hearing gain - linear regression plot, triamcinolone acetonide has an absolute ITS hearing improvement negligible below the mean of all included studies using methylprednisolone or dexamethasone (241). In light of the current available clinical data, it appears that the corticosteroid choice for the ITS treatment of ISSNHL does not have a huge impact on the hearing outcomes, despite experimental evidence.

Table 17: Summary of RCTs investigating the efficacy of ITS salvage treatment for ISSNHL

Study	Age	Female/Male	Vertigo	Tinnitus	Primary treatment delay	ITS salvage treatment delay
Present study, 2020 N=152	57.3 ± 16.5	62/90	45.4%	58.6%	5.9 ± 9.5	11.1 ± 8.7
Lee et al., 2011 n=21 (233)	44 ± 16.2	12/9	28.6%	66.7%	5.1 ± 5.6	17.1 ± 5.6
Li et al., 2011 n=24 (234)	53.5	15/9	n/a	n/a	n/a	n/a
Park et al., 2011 n=44 (236)	48 ± 10.8	23/21	18%	61.3%	3 ± 2.5	20 ± 2.5
Wu et al., 2011 n=27(237)	49.1 ± 14.2	18/9	25.9%	74.1%	4.4 ± 1.6	21.4 ± 1.6
Zhou et al., 2011 n=37(235)	53.8 ± 14.9	n/a	n/a	n/a	11.2 ± 6.2	28.2 ± 6.2
Plontke et al., 2009 n=11 (238)	53 ± 21	3/8	63%	63%	n/a	14.7
Xenellis et al., 2006 n=19 (239)	50.9	10/9	21.1%	n/a	11.8	n/a
Ho et al., 2004 n=15 (240)	46.1 ± 19.9	8/7	35.9%	87.2%	9.7 ± 12	19.7

Study	Drug/concentration	Initial PTA	Post-syst PTA	Final PTA	ITS hearing improvement	ITS recovery
Present study, 2020 N=152	40 mg/ml triamcinolone acetonide	83.7 ± 18.2	80.5 ± 18.9	64.5 ± 26.6	15.9 ± 18.9	52.6% [a]
Lee et al., 2011 n=21 (233)	5 mg/ml dexamethasone phosphate	80.7 ± 26.6	74.6 ± 25.2	63.2 ± 25.6	11.4	47.6% [a]
Li et al., 2011 n=24 (234)	40 mg/ml methylprednisolone*	64.8 ± 10.7	60.7 ± 12	52.9 ± 13.7	7.8 ± 9.7	37.5% [a]
Park et al., 2011 n=44 (236)	5 mg/ml dexamethasone*	73.1 ± 17	n/a	39.7 ± 25.4	n/a	87.1% [b]
Wu et al. 2011 n=27 (237)	4mg/ml dexamethasone*	77 ± 19.1	64.6 ± 17.7	54.9	9.7 ± 8.5	44.4% [a]
Zhou et al. 2011 n=37 (235)	40 mg/ml methylprednisolone*	71.7 ± 17.6	68.4 ± 21.8	n/a	n/a	45.9% b
Plontke et al., 2009 n=11 (238)	4 mg/ml dexamethasone phosphate	104 ± 16.9	98.5 ± 18.2	84.6 ± 25.2	13.9 ± 21.3	54% [a]
Xenellis et al. 2006 n=19 (239)	40 mg/ml methylprednisolone acetate	75.6 ± 4.6	70.1 ± 4.8	55.1 ± 4.2	14.9 ± 3.9	47.4% [a]
Ho et al. 2004 n=14 (240)	4 mg/ml dexamethasone*	n/a	81 ± 13.2	56.7 ± 22.9	24.3	73% [a]

*Continuous variables are presented as means ± standard deviations and categorical variables either as absolute numbers or percentages. * no precise details of used drug formulation. n/a = not available. a = PTA improvement of ≥10 dB. b =PTA improvement ≥15 dB.*

Many factors, such as greater age, the presence of vertigo, a higher hearing loss severity, and longer treatment delays, have been reported as predictors of poorer hearing recovery from ISSNHL (6,7,10,48,49,109,112). In order to identify prognostic factors for ITS salvage treatment outcome in our cohort, we performed a multiple linear regression analysis with a stepwise model. All relevant parameters were included in our analysis. Sex, the presence of coexisting vertigo or tinnitus, and the application method of primary systemic treatment had no significant impact on the outcome of ITS salvage treatment. Age showed a tendency towards significance. These findings are in consistency with the results of the clinical characteristic comparisons between recovery groups, as no significant differences in these variables were found. Moreover, subgroups analyses revealed no statistically significant differences in ITS hearing improvement between females and males, and between patients with and without co-existing vertigo. We identified treatment delay, the degree of primary systemic hearing improvement, and the initial hearing loss severity as significant prognostic factors for hearing recovery. When both, primary- and salvage treatment delay were inserted into the analysis, a co-linearity was found between these variables – a violation of the requirements for a multiple linear regression. Since both variables showed the same significance when included individually into the analysis, a unified conclusion concerning treatment delay can be made. Patients with longer treatment delays, lower systemic hearing improvement, and higher initial hearing loss were less likely to recover. Treatment delay had the highest negative effect on hearing improvement by ITS salvage treatment (r=0.28), followed by initial hearing loss severity (r=0.21) and systemic hearing improvement (r=0.2). These findings are supported by the results of the clinical characteristics comparisons between recovery groups: Patients with complete recovery had a significantly lower initial hearing loss than patients with partial recovery. Interestingly, patients with partial recovery had a higher initial hearing loss than patients with no recovery. After primary treatment, partial and no recovery groups had similar post-systemic PTA values. So, patients with partial recovery improved by primary treatment significantly more than patients with no recovery. The reason for this was presumably the significant earlier start of primary treatment. The complete recovery group showed a significant lower post-systemic PTA than the partial and no recovery groups. This stems from the fact that patients with complete recovery had the lowest initial hearing loss and the highest degree of primary systemic hearing improvement. Regarding start of ITS salvage treatment, patients with no recovery had a significant longer delay than patients with complete and partial recovery. The significance of the identified prognostic factors is further verified by subgroups analyses: Those patients who started treatment within 3 days after ISSNHL onset achieved a significantly higher ITS hearing improvement, as compared to individuals with treatment delays more than

3 days. Patients with mild and moderate hearing loss had significantly greater improvements from ITS salvage treatment than did patients with severe and profound hearing loss. Individuals who had a systemic hearing improvement of >10 dB also achieved greater hearing improvements due to ITS salvage treatment. Elderly patients gained a significant lower ITS hearing improvement than young- and middle-aged patients. The small effect size of this finding (d=0.36) is in agreement with the tendency of age towards significance in the multiple linear regression analysis. Hearing loss severity and treatment delay are often-reported prognostic factors. The pre-mentioned meta-analysis by Liebau et al. also evaluated the 30 included ITS salvage treatment trials for factors influencing the hearing outcome. The authors observed that solely the initial hearing loss severity is significantly correlated to the absolute hearing improvement by ITS salvage treatment. In a further performed meta-regression analysis, age was additionally determined as a significant predictor for hearing outcome. However, the meta-regression analysis included only 54% of the studies due to limited reports of standard deviations. Treatment delay showed no correlation to hearing improvement by ITS salvage treatment (241). The authors have conducted before, a similar meta-analysis upon studies in which ITS treatment was used as first-line therapy. Interestingly, in this analysis, there was a tendency towards significance with respect to the correlation between treatment delay and hearing outcome. The authors ascribed this tendency to spontaneous hearing recovery (193). This conclusion was supported by their ITS salvage treatment meta-analysis by the lack of significance of the correlation between treatment delay and ITS hearing improvement (241). It is assumed that the vast majority of spontaneous recovery occurs within two weeks after sudden hearing loss onset (4). In all of the 30 included studies, ITS salvage treatment was initiated long after two weeks since ISSNHL onset (241). In the present study, the mean time between symptoms onset and start of ITS salvage treatment was 11.1 days. This difference can be explained by our short, highly-dosed 3 days-course of primary systemic corticosteroids as primary therapy, in accordance to the German guidelines (125). Patients with complete and partial hearing recovery had an ITS salvage treatment delay of approximately 8 days while patients with no recovery started ITS salvage treatment after approximately 14 days since hearing loss onset. Therefore, it cannot be entirely excluded that the significance of treatment delay as a prognostic factor in our cohort, is attributed to spontaneous recovery. Accordingly, hearing loss severity and treatment delay have often been reported in literature as a prognostic factor for hearing recovery from ISSHNL (6,7,49,109). To the best of our knowledge, no other study has determined the degree of primary systemic hearing improvement as a predictor for ITS salvage treatment. It seems that those patients, who respond to some degree to primary systemic corticosteroid therapy, also achieves a

greater hearing recovery by ITS salvage treatment. Those patients may have had the same etiology of ISSNHL. This assumption supports the theory that the therapeutic response to corticosteroids, regardless of their application method, depends on the pathophysiological process causing ISSNHL. As no underlying cause can be found in up to 90% of the ISSNHL cases (9), future research should be focused more on the identification of the etiology of ISSNHL.

We evaluated hearing threshold declines due to each instance of an ITS injection. Regardless of the total count of ITS injections, the first injection resulted in the highest hearing improvement. In patients who received 2x injections, the first injection (7.6 ± 12.94.7 dB) led to a statistically significant higher hearing improvement than the second injection (2.9 ± 7.4 dB). Due to their large standard deviations and the small sample size (n=33), the effect size of this significant result was small to moderate (d=0.36), and the probability for a type II error was 49%. Our comparisons in patients who received 3x injections, revealed that the hearing improvements from the first injection (7.1 ± 11.2 dB) were significantly higher than those from the second (4 ± 7.3 dB) and third injections (3.3 ± 6.6 dB). The second and third injections resulted in similarly low hearing improvements. The effect size of these significant differences was moderate to high (f=0.25). Thanks to the larger sample size (n=89), the probability for a type II error was practically zero in this case (β<0.001). It appears that the first injection is the most important one. However, the potential influence of natural recovery on the hearing improvement by the first injection must be considered. The first injection was performed 11.1 days on average after hearing loss onset. The second injection was administered one week later, so approximately on day 18. As the vast majority of spontaneous recovery is expected to occur within 14 days after ISSNHL onset (4), the hearing improvement by the first injection has a much higher likelihood of being influenced by spontaneous recovery. Contrary, similar findings concerning the significance of the first injection were reported by Ho et al. who started ITS salvage treatment 19 days after ISSNHL onset on average – far outside the two weeks period (240). If the first injection does not result in an adequate hearing improvement, it can therefore be assumed that further injections will lead to similar, unsatisfied hearing threshold declines. Our current institution's ISSNHL protocol implies that patients, who present a PTA of 40 dB or more at the final follow-up visit after completion of ITS salvage treatment, will be offered HBOT as third-line treatment. The AAO-HNSF stated in their ISSNHL guidelines that physicians may offer HBOT as salvage treatment within one month after hearing loss onset (3). This statement was based on a recent high-quality RCT that reported significant better hearing outcomes when the HBOT was initiated within four weeks after hearing loss onset (242). Our cohort started the ITS salvage treatment 11.1 days on average after the occurrence

of ISSNHL. Considering the time course of ITS salvage treatment and the time that passes during the arrangement of HBOT, patients in need of a third-line therapy will potentially exceed the four weeks delay period. The European Committee for Hyperbaric Medicine stated in their current guidelines, that it is appropriate to offer patients hyperbaric oxygen therapy as additional treatment if they present between two and four weeks since hearing loss onset, especially to those with severe and profound degree of hearing loss (165). Taking these facts into consideration, I suggest the following implementation into our institution's ISSNHL protocol: Patients with a post-systemic severe or profound hearing loss (post-systemic PTA of ≥70 dB), who fail to respond sufficiently to the first ITS injection (<10 dB PTA improvement) will be scheduled instantly for additional HBOT, concomitantly to the outstanding ITS injections.

El Sabbagh et al. evaluated the adverse events of six RCTs using ITS treatment for ISSNHL. The authors reported that adverse events occurred in 65 of the 416 included patients (15.6%). They further proposed an ITS adverse event scale by categorising the events into four types according to relationship, duration and severity: The first type (13%) involved intervention related, short living and self-healing adverse events, including otalgia, short-term vertigo, aural fullness and headache. This kind of side effects emerged in 54 cases. The second type (1.2%) were intervention related, short-living adverse events, which required some form of iatrogenic interference (severe dizziness needing antiverginous medication or otalgia needing analgetics). The third type (0.7%) were intervention related, long living adverse events, which needed some form of medical or surgical action: one patient developed a chronic middle ear infection. A tympanic membrane perforation needing surgical closing occurred in one patient and another subject experienced an external ear canal skin defect. The fourth type (0.7%) were medication related adverse events. The authors identified cases of acne vulgaris and infectious diarrhea as this type. Whether or not these side effects were clearly induced by the intratympanically applied corticosteroid, remain debatable. 87% of the occurred adverse events were classified as mild. No serious adverse event was observed (15). We also evaluated patients of the present study for occurred adverse events. Within the included 152 patients, two adverse events (1.3%) were documented: one patient developed an acute inflammation of the middle ear, induced by the second ITS injection. The outstanding injection was cancelled and the acute otitis media was successfully treated with oral antibiotics. The other patient developed a persistent ear drum perforation after the third injection, which was surgically closed by a myringoplasty, six months after the ITS treatments. Both events can be classified as intervention related, long living side effects, which needed some form of medical or surgical action (type 3). The proportion of 1.3% is comparable to the 0.7% determined in the

meta-analysis by El Sabbagh et al. (15). Unfortunately, short living and self-healing adverse events, such as otalgia or short-living dizziness were not documented systematically in our cohort, and therefore not statistically evaluated. However, it can be concluded that intratympanic triamcinolone acetonide injections are a relatively safe treatment modality for ISSNHL.

4.2 Case-control Study

In part two of the present dissertation project, we compared the hearing outcomes of two different ITS injection protocols, regarding interval length and total count of injections, as salvage treatments for ISSNHL. We could demonstrate that both protocols improved the patient's' hearing function significantly. We failed to find a significant difference in hearing outcomes between the two protocols. Our revised ITS salvage treatment protocol with shortened intervals in combination with an additional injection, did not result in better hearing recovery compared to our previous protocol with longer injection intervals.

No consensus exists on the ideal interval length and total count of intratympanic corticosteroid administrations as treatment of ISSNHL (3). Corticosteroids can be delivered into the tympanic cavity by intratympanic injection, transtympanic instillation through a ventilation tube or by sustained-released drug carrier devices. The most preferred delivery technique is the intratympanic injection. This method has the advantages to be less invasive, safer and more cost efficient than the others (29). Therefore, the AAO-HNSF currently recommends intratympanic injection as main delivery technique. The used ITS protocol with respect to interval length and total count of injections shows a considerable variability in literature (3). Of the eight existing RCTs evaluating the efficacy of ITS as salvage treatment for ISSNHL (233–240), seven have used intratympanic injections as delivery technique (233–237,239,240). The other study performed a daily corticosteroid administration via a round window catheter for two weeks (238). Details of the seven RCTs with ITS injections are denoted in table 18. In these studies, the interval length ranged from one day to one week, and the total count of injections ranged from three to six (233–237,239,240). An unbiased direct efficacy comparison of these trials appears very challenging due to several reasons, including the protocol variability, disease's heterogeneity and the small sample sizes. Liebau et al. correlated the interval length and total count of injections to the absolute hearing improvement and final hearing thresholds in two separate meta-analyses, including 25 primary ITS treatment studies and 30 ITS salvage treatment studies with sufficient available data, regardless their study design (randomised and

controlled, non-randomszed, non-controlled, retrospective-controlled) (193,241). Given as primary treatment, neither the total count of injections nor the interval length between the injections showed a significant correlation to the absolute hearing improvement or final hearing thresholds in the linear regression analyses (193). Similar linear regression findings were observed in the other meta-analysis, including ITS salvage treatment studies. The authors further conducted a meta-regression analysis to adjust for the varying sample sizes and intra-study variances. Interestingly, a positive correlation between interval length and ITS hearing improvement was found in the meta-regression analysis. This means that hearing improvement by ITS salvage treatment enhanced with increased interval length between injections. The authors concluded that this result could be false-positive as no correlation was found in the linear regression analysis and the meta-regression analysis included only 54% of the studies due to limited reports of standard deviations (241). Nevertheless, when simply comparing the hearing outcomes of the RCTs in table 18, the study with the longest injection interval (7 days) also had the highest absolute hearing improvement by ITS salvage treatment (240).

Table 18: Interval length and total injection count in RCTs investigating the efficacy of ITS salvage treatment for ISSNHL

Study	Drug/Concentration	ITS injections		ITS hearing improvement	ITS recovery
		Count	Interval		
Lee at al. 2011 *n*=21 (233)	5 mg/ml dexamethasone	4	Within 2 weeks	11.4	47.6% [a]
Li et al. 2011 *n*=24 (234)	40 mg/ml methylprednisolon	4	3 days apart	7.8 ± 9.7	37.5% [a]
Park et al. 2011 *n*=44 (236)	5 mg/ml dexamethasone	6	Within 2 weeks	n/a	87.1% [b]
Wu et al. 2011 *n*=27 (237)	4 mg/ml dexamethasone	4	4 days apart	9.7 ± 8.5	44.4 % [a]
Zhou et al. 2011 *n*=37 (235)	40 mg/ml methylprednisolone	4	1 day apart	n/a	45.9% [b]
Xenellis et al. 2006 *n*=19 (239)	40 mg/ml methylprednisolone	4	Within 2 weeks	14.9 ± 3.9	47.4% [a]
Ho et al. 2004 *n*=15 (240)	4 mg/ml dexamethasone	3	7 days apart	24.3	73% [a]

Continuous variables are presented as means ± standard deviations and categorical variables either as absolute numbers or percentages. n/a = not available. a = PTA improvement of ≥10 dB. b =PTA improvement ≥15 dB.

The first clinical practice guidelines by the AAO-HNSF published in 2012, recommended to perform ITS injections every 3-7 days for a total of 3 to 4 sessions (35). This recommendation was presumably based on the three existing RCTs at that point of time: Ho et al. performed 3x ITS injections at 1-week intervals (240). Xenellis et al. used a paradigm consisting of 4x injections at intervals of 3-4 days (239). Both studies demonstrated significant higher hearing outcomes of their intervention group against their non-treatment control group. When comparing both trials, the protocol by Ho et al. clearly resulted in greater hearing recovery (14.9 dB vs. 24.3 dB in ITS hearing improvement and 47.4% vs. 73% in clinically significant hearing improvement) (239,240). The third RCT used a continuous drug delivery technique, namely a round window catheter. The authors compared a daily transtympanic instillation for two weeks of 4mg/ml dexamethasone phosphate as intervention and 0.9% sodium chloride as placebo. The trial was preliminary terminated after the first study step including 21 patients, due to the lack of a statistically significant difference in the primary outcome measure (= absolute ITS hearing improvement, treatment group: 13.9 ± 21.3 dB, placebo group: 5.4 ± 10.4 dB, $p = 0.07$). The used protocol in this study was therefore presumably not incorporated into the AAO-HNSF recommendations. However, it must be emphasised that this study is currently the only RCT upon ITS salvage treatment that was conducted in a double-blind fashion, and administered an intratympanic placebo; hence, making it the study with the highest level of evidence (238). Nevertheless, we have adopted the recommendations provided by the 2012 AAO-HNSF guidelines and have used since the initiation of ITS salvage treatment at our institution in 2014, a paradigm of up to 3x ITS injections at 1-week intervals (35). This protocol is the most commonly applied (46%-60.3%) in the United Kingdom, United States and continental Europe according to national surveys (24–26). Since the release of the 2012 guidelines (35), all further RCTs on ITS injections as salvage treatment for ISSNHL administered at least 4x injections within a 2-weeks period (233–237). In 2019, the AAO-HNSF published their revised guidelines on ISSNHL in which they implemented these protocols into their recommendations. Aiming to improve the hearing outcomes of our patients, we have changed in August 2019, our institution's ITS salvage treatment protocol according to the revised guidelines (3): we performed ITS injections every 2-4 days for a total of 4 sessions. We presumed that a shortened interval together with an additional 4th injection, will improve the hearing outcomes of patients affected by ISSNHL, as we have identified treatment delay to have the greatest negative effect on hearing outcome.

To confirm our assumption, we retrospectively reviewed all ISSNHL patients who were treated according to our revised ITS salvage treatment protocol since its initiation, and aimed to compare their hearing outcomes to those of patients, who received our initial protocol. The

retrospective review started in December 2020, approximately one year after the official initiation in January 2020. Based on the findings from the first cohort, we expected a sample size of 30 to 40. In order to compensate for the unequal sample sizes, we have chosen a case-control study design. This also gave us the opportunity to reduce the broad heterogeneity of the disease: we selected the significant prognostic factors identified in the multiple linear regression analysis (treatment delay, hearing loss severity and systemic hearing improvement) as matching factors. A comparison of the patient's clinical characteristics revealed no statistically significant differences between the protocol groups. Therefore, we were able to arrange similar groups with respect to our previously identified outcome predictors as well as the other often-reported influencing factors, such as presence of co-existing vertigo and age. Thus, the protocol-groups were adequately comparable for statistical analysis of treatment outcome.

Concerning our findings, salvage treatment with ITS injections resulted in both protocol groups in a statistically significant hearing improvement. Patients with injections at 1-week intervals had a mean ITS hearing improvement of 12 ± 11.7 dB. The hearing thresholds in this group declined statistically significant from a post-systemic PTA of 76.8 ± 20.8 dB to a final PTA of 64.8 ± 21.5 dB. The effect size of this significant result was remarkably high (d=1) and the probability for a type II error was less than 1% (β< 0.001). Patients, who received every 2-4 days injections, showed a mean ITS hearing improvement of 13.4 ± 19.1 dB. ITS salvage treatment decreased hearing thresholds in these patients statistically significant from a post-systemic PTA of 73.4 ± 21.4 dB to a final PTA of 60 ± 27.7 dB. This amount of hearing improvement was highly effective with an effect size of d=0.7 and was highly powered at 99% (β<0.001). A clinically significant hearing improvement was observed in 58.1% in the initial-protocol group and in 41.9% in the revised-protocol group. In both groups, no case of clinically significant PTA deterioration by ITS salvage treatment was noted. Regarding grades of hearing recovery, a complete and partial recovery was achieved from 37.5% and 53.1% of the patients receiving the initial-protocol, and from 46.9% and 37.5% of patients receiving the revised-protocol, respectively. Both protocols resulted in a statistically significant rate of recovery from an unserviceable hearing level into a serviceable hearing range. (Initial-protocol: 14.8%, revised-protocol: 26.9%).

The revised-protocol group showed a slightly higher absolute ITS hearing improvement, whereas the initial-protocol group had the higher proportion of clinically significant hearing improvements. This can be explained by the fact that the revised-protocol led more often to an ITS response of >30 dB and less frequent to an ITS response of <10 dB. Due to this higher

variability within the ITS response levels, the revised-protocol group had a greater standard deviation of the absolute ITS hearing improvement (11.7 vs. 19.1). This is also the reason why the effect size of the absolute ITS hearing improvement of the initial-protocol group was greater (1 vs. 0.7), despite its lower mean value (12 dB vs. 13.4 dB). Due to the disease's intrinsic heterogeneity, a potential variability was to be expected with the sample size provided in the present study. The small difference between both large effect sizes should therefore not be interpreted too strictly. To allow such variability to be ruled out totally, much larger sample sizes are necessary in this particular case. However, our aim was to identify a difference in treatment outcome between the two different ITS protocols that is meaningful for the clinical routine. We selected; therefore, a 10 dB difference in PTA as the clinically significance criterion because the difference criterion must exceed the inherent variability expected by the test-retest reliability, which has been determined as 5 dB (176,177). Moreover, a hearing threshold decline of at least 10 dB is widely considered as clinically significant (11). According to our a-priori sample size calculation, we had an adequate sample size per group to detect a clinically significant difference in ITS hearing improvement between the protocol groups. When comparing statistically the hearing improvements by ITS salvage treatment between the protocol groups, we failed to find a clinically significant difference (M^{diff}=1.4 dB, p = 0.730). Therefore, we could not reject our H_0 – hypothesis and accept our study hypothesis, which suggested a clinically meaningful difference in ITS hearing improvement between the protocol groups. This finding does not automatically confirm equal efficacy. A post-hoc power analysis revealed a 10% power for this test result. This means that the probability to false-negative agree with the H_0 – hypothesis, which stated that there is no clinically significant difference between the protocols, is noteworthy high (90%). Such "negative results" require an incredible high sample size to statistically validate with a high power. In this particular case, we would need a sample size of approximately 1600 per group to achieve a power of 80%. However, conducting such a study would not make any sense. Same findings were observed in all secondary outcome measures, in which no significant differences were found between protocol groups.

To our knowledge, there are solely five other studies comparing different protocols of ITS injections as treatment for ISSNHL, regarding interval length and total count of injections (30–34). Four of them have used ITS injections concomitantly with systemic steroids as primary treatment (30–33): Sung et al. compared the hearing outcomes of 51 ISSNHL patients who were treated with 4x intratympanic 4mg/ml dexamethasone phosphate injections at two different intervals: daily administration or at intervals of 2-3 days. Patients received concomitantly either orally or intravenously systemic corticosteroids for five days and a

following oral taper for further five days. At the 2-week follow-up visit, they found no significant differences in absolute hearing improvement (25 ± 20.3 dB vs. 25.5 ± 26 dB) and recovery rate (66.7% vs. 66.7%) between the protocol groups. As shortcomings of the study, the proportions of the application methods differed between groups and included patients did not receive the same systemic corticosteroid (prednisolone or dexamethasone) (32). In the study by Suzuki et al., the interval lengths differed considerably more between injection protocols. The authors applied a total of 4x ITS injections of dexamethasone phosphate at 4mg/ml either daily or at 1-week intervals. The 197 included patients received concomitantly intravenous prednisolone for nine days and a following oral taper for further five days. Even at this injection interval length difference of six days, similar hearing outcomes between interval groups were observed at the long-term follow-up visit: recovery rates in the daily and weekly administration groups were 79.3% and 75.2%, respectively (30). In contrast, Kwak et al. reported a significant effect of the interval length on hearing outcome. The authors performed ITS injections of dexamethasone phosphate at 5mg/ml every 1, 2, 3 or 4 days for a total of 4x sessions and compared these four groups. The 75 included patients were treated concomitantly with oral prednisolone for 14 days. The authors reported that the 1-day interval group had a statistically significant higher rate of complete recovery in comparison to the 4-day interval group (34.8% vs. 4.2%, p=0.008). However, no significant difference was found in the absolute hearing improvement (28 dB vs. 17 dB). The 1-day interval group had an approximately 10 dB lower initial PTA and 10% higher WRS than the 4-day interval group. Even if these differences were not statistically significant, it must be emphasised as those values are fundamental for the calculation of the hearing recovery grade. Moreover, the adjusted Bonferroni p-value for the post-hoc testing in the chi-squared analyses was miscalculated. The correct α level would have been 0.003, which would make the difference in complete recovery rates not significant (33). Our findings are in consistency with the results of Sung et al. (32) and Suzuki et al. (30). The reduction of the injection interval length from one week to an average of 3.1 days did not result in significant better values with respect to all outcome measures. A further study by Suzuki et al. evaluated the effect of the total count of ITS injections on hearing outcome. As the authors have previously determined the independency of injection interval length on hearing outcome, they further assumed that the total count of injections does not influence the hearing recovery. For that reason, they changed their ITS protocol by reducing the total injection count from 4 to 2. To confirm their assumption, the authors subsequently compared 92 patients who were treated with 2x injections on the first two days versus 100 patients, who received the previous protocol, namely 4x injections within 1 week. Both protocols improved the hearing function significantly and no difference in recovery rate between the protocols was found at the long-term follow up

(79.3% vs. 79.0%) at. The authors indicated that the 3rd and 4th injection may be unnecessary for the final hearing outcome (31). We could observe similar findings in the present study. The implementation of an additional 4th injection did not affect the hearing outcome. Hence, the further performance of fewer injections may reduce costs and physical/mental stress of patients with similar hearing outcomes. Moreover, it may lower the risk of remaining tympanic membrane perforation (31). Although no persistent ear drum perforation occurred in both protocol groups, our sample sizes were too small to validate this conclusion as the rate of persistent tympanic membrane perforations after ITS injections is approximately 1% (243). Nevertheless, the occurrence of a remaining perforation may increase with the total number of injections. Topf et al. evaluated the rate of persistent tympanic membrane perforations in 192 patients affected by Meniere's disease and ISSNHL, who received either a single ITS injection (n = 112, 58.3%), 2x ITS injections (n = 47, 24.5%) or ≥ 3x ITS injections (n = 33, 17.2%). Patients with an injection count of 2x, 3x or more, presented a persistent tympanic membrane perforation rate of 4% and 3%, respectively, whereas no remaining ear drum perforation occurred in patients with a single injection despite the vastly larger sample size (243). Suzuki et al.; therefore, stated that the efficacy of a single injection against multiple injections should be evaluated in future studies (31).

The major limitation of the pre-mentioned studies is the usage of ITS injections concomitantly to systemic steroids (30–33). It is difficult, if not even impossible, to ascertain the exact proportion of hearing improvement due to ITS injections when giving as combined therapy. Furthermore, the by far largest proportion of primary therapy usually takes place within the first 14 days since hearing loss, especially in case of short injection intervals. So, there is a high risk that hearing improvement may be confounded by spontaneous hearing recovery (4). ITS salvage treatment is usually initiated after two weeks since hearing loss onset; hence, the potential influence by natural hearing recovery is remarkably low in this case. There is only one other study which reported hearing outcomes of patients receiving ITS injections as salvage therapy at different intervals. In this study, patients were treated with intratympanic 10 mg/ml dexamethasone injections at intervals of 1-4 days (n=21), 5-10 days (n=29) and 11-30 days (n=20), either as primary-, salvage- or combined therapy. No significant differences in hearing outcome (absolute hearing improvement and hearing recovery rate) between the frequency schedules were found (1-4 days: 23.6 ± 22.0 dB, 61.9%; 5-10 days: 19.7 ± 18.4 dB, 58.6%; 11-30 days: 24.9 ± 24.7 dB, 75%). However, the groups included all patients, regardless of their treatment modality (primary, salvage and combined). The authors missed to analyse the hearing outcomes separately for each treatment modality. Even if they had, the resulting low and unequally distributed sample size per interval group in the salvage treatment

sub-cohort (n= 8, 17, 12) would not have allowed for an adequate conclusion for this modality. Thus, we present the first hearing outcome data of ISSNHL patients who received ITS injections at different intervals as salvage treatments.

There is one other study comparing various frequency schedules of ITS salvage treatment, though with a different application technique. Chou et al. prospectively enrolled 30 primary-refractory ISSNHL patients, who received ITS salvage treatment by using a sustained-released drug carrier system (Silverstein MicroWick). Subjects were briefed to applicate 3x drops of dexamethasone at 4 mg/ml twice a day for a consecutive 14-days period. These patients were compared to retrospectively collected, primary-refractory ISSNHL patients, who were treated with intratympanic dexamethasone injections at 4 mg/ml every 4 days for a total of 4x sessions. The authors used a case-control study design, like we did. In contrast to our study, patients were matched by age and sex. We selected treatment delay, systemic hearing improvement and hearing loss severity as matching factors, due to the fact that they have been identified as prognostic factors in the multiple linear regression analysis from our previously conducted cohort study. Nevertheless, Chou and colleagues were able to arrange similar groups with respect to all clinical baseline characteristics. To note, no initiation time interval of ITS salvage treatment was specified. Both protocols resulted in a significant decline of mean hearing thresholds. The authors reported that the continuous application group had a statistically significant greater hearing improvement (15 ± 9.7 dB vs. 10.7 ± 9.8 dB). However, statistically significance should not automatically be equated with clinically significance (244). The evaluated mean difference of 4.3 dB does not exceed the test-rest reliability of pure-tone audiometry, which has been determined as 5 dB (176,177). So, if this small difference is clinically meaningful, remains a matter of debate. Moreover, we found in the patients of our cohort study, who received 3x ITS injections at 1-week intervals, a similar hearing improvement (15.9 ± 18.9 dB). The Silverstein MicroWick and other sustained-released drug carrier systems require a temporary insertion of a ventilation tube. Compared to injections, tympanostomy tubes have a higher risk for a remaining ear drum perforation. Robey et al. analysed 166 patients, who received a transtympanic Silverstein tube for ITS treatment, and found a persistent tympanic membrane perforation rate of 29% (245) - far higher than the reported 1% rate for ITS injections (15). With similar efficacy, lower complication rate and lower costs, intratympanic injection by tympanic membrane needle perforation is therefore currently recommended as main delivery technique for the ITS treatment of ISSNHL (3).

To summarise, it appears that the interval length and total count of ITS injections, regardless of the modality, does not significantly affect the hearing outcome in patients affected by ISSNHL. A further revision of our institution's ITS protocol by reducing the total injection count would not yet be acceptable at this point of time, because our data has too littler power due to the small sample size. A further analysis in this context may be carried out in the future, when a sufficiently large cohort has been assembled.

4.3 Strengths and Limitations

The present dissertation project has several strengths but also some limitations that must be addressed. The key strength of our cohort study was the high sample size. We included almost four times as many patients as the a-priori calculated minimum required sample size. By comparison, we had a study sample size approximately twice as many as Dahm et al (28). The benefit of the large study population can be seen in the results: we were able to accept our study hypothesis with a practically 100% power in both, total cohort- and per-ITS-protocol analyses. A further major strength of our cohort study was the exclusive usage of ITS injections as salvage treatment. In the study by Dahm et al., patients received intratympanic triamcinolone acetonide injections concomitantly to an oral steroid taper (28). It is very difficult, if not impossible, to ascertain the exact proportion of hearing improvement due to each treatment modality. An adequate conclusion regarding clinical efficacy of triamcinolone acetonide as medication for the ITS treatment of ISSNHL cannot; therefore, be drawn from this study. In the present cohort study, all included patients received no additional treatments concomitantly to ITS injections. Consequently, we provide the first efficacy results of intratympanic triamcinolone acetonide as treatment modality for ISSNHL. As a further note, no other study has determined, to our knowledge, systemic hearing improvement as a prognostic factor for hearing improvement by ITS salvage treatment. This correlation indicates the potential dependence of hearing outcome on the unknown etiology of ISSNHL. With respect to the case-control study, this was the first trial comparing different ITS injection protocols as salvage treatments for ISSNHL. The strength of the case-control study was the similarity of the two groups regarding the often-reported predictors of poor hearing recovery from ISSNHL. This allowed us to significantly reduce the broad heterogeneity of this disease. The recruitment of homogenous groups clearly strengthened the validity of the study.

There are also a few limitations that should be acknowledged. First, both studies were retrospective in nature. Retrospective studies provide a lower level of evidence (211). Second,

the case-control study design is prone to cause selection bias. However, if comparing the ITS hearing improvement of the matched controls and the total cohort of origin, similar values can be found (12 dB vs. 15 dB). Third, both studies were conducted in a non-treatment controlled approach. As a result, the natural evolution of hearing improvement could not be assessed. The nature of the control group in ISSNHL research is still a matter of debate. It would be unethical to not offer a salvage treatment in case of insufficient hearing recovery from ISSNHL, owing to the fact that ITS as salvage therapy is currently recommended by national guidelines due to its demonstrated significant benefit (3,39,125). Therefore, the International Federation of Oto-rhino-laryngological Societies concluded during its consensus conference on treatment of sudden sensorineural hearing loss, that any kind of new treatment should be compared against the current recommended treatment (11). Fourth, the administration method for primary systemic treatment was in both studies not consistent in the included patients. They were either treated orally with dexamethasone as outpatients or intravenously with prednisolone as inpatients. However, all patients received systemic corticosteroids in equivalent dosages over the exact same amount of time. In the cohort study, there was no significant difference in systemic hearing improvement between the application methods. In the case-control study, both protocol-groups had similar systemic hearing improvements. Fifth, as a consequence of the exclusive usage of triamcinolone acetonide as medication for ITS salvage treatment in our department, a direct comparison to other corticosteroids was not possible in the cohort study; therefore, we compared our results to historic cohorts. Sixth, although we had an adequate sample size for statistical analyses in the case-control study, negative results require a much higher sample size to statistically validate with a high power. Seventh, because speech-audiometry is not routinely included in our institutional management of ISSNHL, we were not able to evaluate treatment-related evolutions in WRS. These would additionally provide important information regarding the patients' functional auditory ability. Moreover, the WRS is necessary to determine the grade of hearing recovery according to the current recommended definition by the AAO-HNSF (3). Eighth, the 4-frequency variant of the PTA used in this study covers the frequencies of the human speech. Hearing loss in the very low and high frequencies is not covered by this parameter. However, the vast majority of the included patients presented either a flat or a total deafness hearing loss pattern. On the other hand, we were not able; thereby, to evaluate the influence of the affected frequencies on hearing outcome. Finally, cases of delayed hearing recovery may have been missed due to the lack of long-term follow-up data.

5 Conclusion

Intratympanic triamcinolone acetonide injections as salvage treatment of ISSNHL resulted in a clinically significant hearing improvement. Therefore, triamcinolone acetonide constitutes an effective candidate for the ITS treatment of ISSNHL. In comparison to previous studies using commonly applied corticosteroids, namely dexamethasone and methylprednisolone, similar results were found. From a clinical point of view, a clear superiority of a particular corticosteroid over the others cannot be supported. In light of the current available clinical data, it appears that the choice of the corticosteroid agent has no significant impact on the outcome of ITS treatment, despite experimental evidence. The first ITS injection in a salvage treatment setting achieved significantly the greatest hearing improvement. If the first injection does not result in an adequate hearing improvement, it can be assumed that further injections will lead to similar unsatisfied hearing threshold declines. Therefore, patients with a severe or profound hearing loss after primary treatment, who fail to respond sufficiently to the first ITS injection, may be scheduled instantly for additional HBOT, concomitantly to the outstanding injections, as early HBOT has been associated with a better outcome prognosis. Longer treatment delays, lower hearing improvement by primary systemic treatment, and higher severity of hearing loss have been associated with poorer prognosis of hearing recovery. The significance of the association between treatment delay and treatment outcome is a subject of controversy, due to the potential confounding bias by spontaneous hearing recovery. As the likelihood of this influence is very low in the salvage treatment scenario, our results support the prognostic relevance of treatment delay. To the best of our knowledge, no other study has determined the degree of primary systemic hearing improvement as a predictor for ITS salvage treatment. This factor can be taken additionally into account when informing the patient about prognosis of treatment outcome. Patients, who responded to a certain degree to primary systemic corticosteroid therapy, also achieved a greater hearing recovery by ITS salvage treatment. This association affirms the theory that the therapeutic response to corticosteroids depends on the unknown pathophysiological process causing ISSNHL. Both ITS protocols resulted in a similar significant hearing recovery. These results indicate that a shorter injection interval does not lead to better hearing outcomes. Moreover, the implementation of an additional injection also had no impact on the hearing outcome. The usage of fewer ITS injections may reduce costs, physical/mental stress of the patients and lower the risk of persistent tympanic perforations, while maintaining similar treatment efficacy. Further high-quality research is warranted to confirm the results of the present dissertation project.

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