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Oral and Intratympanic Steroid Therapy for Idiopathic Sudden Sensorineural Hearing Loss

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Objective: To investigate the role of intratympanic (IT) therapy in the treatment of idiopathic sudden sensorineural hearing loss (ISSNHL).

Methods: This study was a retrospective review. Patients were treated for ISSNHL from January 1, 2011 to April 12, 2015 with the following: pre/posttreatment audios, treatment initiated ≤90 days and idiopathic etiology. Fifty-three ISSNHL patients were analyzed in the following subgroups: oral steroids (n = 8), combination oral+IT (n = 39), and IT (n = 6). Main outcomes measured were pre/posttreatment pure tone average (PTA) scores.

Results: The PTA changes for all treatment groups improved by 8.0 ± 19.5 dB ($P = .004$); for 31 patients treated ≤2 weeks after onset, PTA improved by 13.8 ± 16.6 dB ($P < .001$). Multivariable generalized linear model for repeated measures was conducted to investigate the association between PTA changes for treatment groups adjusted for age, gender, time-to-treatment, and vertigo. Earlier time-to-treatment and older age were statistically correlated towards improved outcomes. As time-to-treatment increased by each day, change in PTA decreased by 0.324 (95% CI [0.12, 0.52], $P = .002$). As age increased by each year, PTA changes increased by 0.802 (95% CI [0.36, 1.24], $P < .001$). For the oral+IT group, PTA changes for concurrent oral+IT (n = 20, 7.10 dB) and delayed/salvage oral+IT (n = 19, 5.43 dB) were not statistically different ($P = .79$); earlier time-to-treatment ($P = .001$), and older age ($P = .006$) remained statistically correlated towards improved outcomes.

Conclusion: Results suggest outcomes can be improved with early identification and oral steroid therapy by primary care providers. Poorer prognosis for younger patients potentially suggests a need for more aggressive diagnostic and therapeutic management for this subgroup.

Key Words: Idiopathic sudden sensorineural hearing loss, high-dose corticosteroids, intratympanic steroid injection.

Level of Evidence: 3b.

INTRODUCTION

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is an acute, usually unilateral hearing loss that develops within a 72-hour period. A double-blind study in 1980 by Wilson et al. found better recovery rates in patients with moderate hearing loss, when treated with oral steroids (61%) compared to placebo (32%).[1] This study helped to form the rationale for the widespread use of steroids in the treatment of ISSNHL.

Intratympanic (IT) steroids have also been used to treat ISSNHL, with various studies concluding that IT steroids are effective as salvage therapy for patients refractory to oral steroids.[2–4] Other protocols have seen success with simultaneous use of IT and oral steroids as initial treatment[5] and IT alone has been shown to be as efficacious as oral therapy.[6,7] The benefits of IT steroids are attributed to a higher perilymph steroid level. Dosing regimens vary from study to study, and higher concentration per dose has also been shown to be efficacious.[8]

A retrospective review was conducted in a private practice setting to evaluate our internal results in an effort to determine how to best incorporate IT therapy into a clinical practice.

METHODS

The study was approved as exempt by the University of Hawaii Institutional Review Board for this retrospective review study (CHS# 23049). All data was deidentified prior to analysis. All ISSNHL cases were reviewed in a three-physician otolaryngology group private practice in Honolulu, Hawaii, between January 1, 2011 and April 12, 2015. Eligibility criteria for inclusion in the ISSNHL group included the following: age of ≥18 years, treatment initiated ≤90 days of onset, use of steroid therapy, pre- and posttreatment audiograms, and idiopathic etiology. As most patients were referred by primary care physicians, many patients received oral steroids prior to referral. Patients were considered to start treatment at the first dose of steroids. Patients were excluded from the study if a recognized etiology

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for hearing loss was determined: eg, stroke, acoustic neuroma, Meniere's disease, demyelinating diseases.

Data collected from patient records included gender, age, time between presenting symptoms and treatment, presence or absence of initial vertigo or facial nerve palsy, type, route and timing of steroid therapy, and if a primary diagnosis for hearing loss was a cause for exclusion. Primary outcome data were pure tone average (PTA), calculated as the arithmetic mean of hearing thresholds 500, 1000, 2000 Hz in the affected ear.

As this was a retrospective review, steroid therapy was not controlled. Patients were given one of the following regimens: oral, oral+IT, or IT alone. Oral steroid therapy followed clinical practice guidelines: prednisone 60 mg/day in two divided doses for 7 days, followed by a 5-day taper (50 mg, 40 mg, 30 mg, 20 mg, 10 mg) or dexamethasone 10 mg/day once daily for 7 days, followed by a 5-day taper (8 mg, 6 mg, 4 mg, 3 mg, 2 mg).[9] Patients started on a lower dose by primary care were increased to one of the above regimens. Most patients were started on a proton-pump inhibitor in conjunction with steroid therapy.

Initially, IT was used for salvage but this migrated to synchronous therapy. For patients with relative contraindications to systemic steroids such as a history of gastrointestinal hemorrhage from ulcer disease, IT was used alone. In this three-physician group, one provider was referred cases for IT injections. For IT treatment, standard protocol was three treatments of 10 mg/ml dexamethasone within 7–10 days. Injection was administered using two tympanic injection sites topically treated with phenol: one site for pressure relief superiorly in the anterior superior quadrant and the second inferiorly for dexamethasone administration. Over time, this changed to using one site superiorly with a slightly larger hole than the needle size, to allow both infiltration and pressure relief. Patients were placed in the lateral decubitis position with the affected ear up for 30 minutes and instructed not to swallow by spitting saliva into a cup. They were instructed to keep the ear dry after discharge.

Statistical Analysis

Descriptive statistics are presented as frequencies and percentage for categorical variables and as mean and standard deviations for continuous variables. Differences in baseline characteristics by type of treatment were analyzed using Fisher's exact test for categorical variables and one-way ANOVA for continuous variables, and difference between pre- and post-PTA was analyzed using paired t-test. Multivariable generalized linear models for repeated measures were performed to investigate association between change in PTA adjusting for age, gender, time-to-treatment and vertigo for all treatment groups. A P-value $<.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 117 patients were identified with a diagnosis of ISSNHL. Of these, 53 ISSNHL patients were included in the analysis in the following subgroups: oral steroids (n = 8), combination oral+IT (n = 39), and IT (n = 6). The main reason for excluding cases was the lack of a posttreatment audiogram. Three patients with acoustic neuromas and one with Meniere's disease were excluded. For all patients receiving intratympanic injection, all patients received three injections with the following five exceptions: two patients with less than three IT, two patients with four IT, and one patient with six IT. From medical chart reviews, irritability, moderate hyperglycemia, and insomnia were the most frequent complaints. There were no cases of gastrointestinal bleeding or significant gastritis. There were no major events requiring hospitalization.

TABLE I.
Descriptive Statistics of ISSNHL Patients (n=53).

Age, mean in years ± SD (range)	62.8 ± 11.6 (41–89)
Gender, n (%)	
Male	29 (54.7)
Female	24 (45.3)
Vertigo, n (%)	
Yes	13 (25.0)
No	39 (75.0)
Type of Treatment, n (%)	
Oral	8 (15.1)
Combined (Oral and IT)	39 (73.6)
IT	6 (11.3)
Time between symptom and treatment in mean days ± SD (range)	21.3 ± 22.9 (1–90)
Salvage (among combined treatment only), n (%)	
Yes (delay)	19 (48.7)
No (concomitant)	20 (51.3)
Salvage treatment delay, in mean days ± SD (range)	4.8 ± 7.7 (0–28)

IT = Intratympanic; ISSNHL = Idiopathic Sudden Sensorineural Hearing Loss

Descriptive statistics are presented in Table I. The mean age of the study sample was 62.8 years, 29 (54.7%) patients were males, and 13 (25%) had vertigo. Among those with combined treatment, 19 (48.7%) had a salvage treatment delay. The average time between symptom and treatment was 21.3 days and the average salvage treatment delay was 4.8 days. Stratification of baseline characteristics by type of treatment is presented in Table II. Gender was significantly different by type of treatment ($P = .027$). Mean initial PTA in the affected ear was significantly different by type of treatment ($P = .042$), with the combined group having a greater loss at onset. Mean post-treatment PTA was significantly different by type of treatment ($P = .002$). There was no statistical difference between the groups for change in PTA from pre- to posttreatment.

The PTA difference pre- and post-treatment is reviewed for all groups in Table III. For all groups together, the mean PTA improvement was statistically significant, 8.0 ± 19.5 dB ($P = .004$). For 31 patients treated ≤2 weeks after onset, PTA improved by13.8 ± 16.6 dB ($P < .001$). Multivariable analysis results are presented in Table IV. Earlier time-to-treatment and older age were significantly associated with improved PTA outcomes. As time-to-treatment increased by each day, change in PTA decreased by 0.324 (95% CI [0.12, 0.52], $P = .002$]. As age increased by each year, change in PTA increased by 0.802 (95% CI [0.36, 1.24], $P < .001$]. For the combined oral+IT group alone, earlier time-to-treatment ($P = .001$) and older age ($P = .006$) remained

TABLE II.
Baseline Characteristics by Type of Treatment.

Variable	Oral (n = 8)	Combined oral+IT (n = 39)	IT (n = 6)	*P*-value
Age	64.0 ± 14.2	61.9 ± 10.9	66.7 ± 13.5	.626
Gender, n (%)				.027*
Male	3 (37.5)	21 (53.9)	5 (83.3)	
Female	5 (62.5)	18 (46.1)	1 (16.7)	
Time to Treatment (days)	23.8 ± 21.1	21.5 ± 24.4	17.0 ± 16.9	.871
Vertigo, n (%)				.089
Yes	1 (12.5)	10 (26.3)	2 (33.3)	
No	7 (87.5)	28 (73.7)	4 (66.7)	
Pretreatment PTA in affected ear	37.7 ± 26.8	65.4 ± 28.6	48.6 ± 19.9	.042*
Posttreatment PTA in affected ear	24.6 ± 18.1	57.9 ± 27.8	36.4 ± 20.9	.002*
Difference in PTA	13.1 ± 17.9	7.6 ± 21.0	12.2 ± 24.2	.575

*$P < .05$; Column percentage used for categorical variables. IT = Intratympanic; PTA = Pure Tone Average

significantly associated with improved outcomes. PTA changes for concurrent oral+IT (n = 20, 7.10 ± 24.0 dB) and delayed/salvage oral+IT (n = 19, 5.43 ± 13.1 dB) were not statistically different ($P = .768$).

DISCUSSION

This study represents the experience in a small private practice where all providers saw patients with ISSNHL, with referral to one provider to perform the majority of IT injections. The goal was to better understand the use of oral+IT combined therapy, as well as IT therapy alone for patients where systemic steroid therapy may be contraindicated. Although the literature supports both synchronous or salvage oral+IT therapy in the literature, we have evolved into recommending synchronous therapy considering the low risk profile of IT injections in the literature and in our practice.

As this is a retrospective review, the results must be viewed cautiously due to lack of control of multiple factors that could impact outcomes. These factors include the following: oral steroid type and dose, IT frequency, IT timing with oral therapy (synchronous vs. salvage), IT steroid concentration, timing of pre-and posttreatment audiometry, and inclusion of patients within a fixed time period from ISSNHL onset. For oral steroid therapy, we utilized high dose prednisone or dexamethasone therapy as recommended by clinical practice guidelines.[9] Patients who were started on lower dose therapy by their primary care provider such as methylprednisolone dose packs were increased to high-dose therapy.

Multiple variables exist surrounding IT therapy. The frequency utilized was three synchronous injections or salvage/delayed therapy for patients presenting after completion of oral steroids as recommended by the literature and practice guidelines.[9] Nearly all patients received three injections. Steroid concentration is an important factor in improving outcomes, with recent retrospective data showing statistically improved PTA for dexamethasone 24 mg/ml (compounded) versus 10 mg/ml (stock).[8] This higher dose is also recognized in clinical practice guidelines.[9] We utilized dexamethasone 10 mg/ml since it is commercially available and the latter requires compounding with a short shelf life and is not readily available.

Timing of pre-and posttreatment audiograms should be carefully controlled in any study to best determine the impact of therapy on PTA. If the pretreatment audiogram is obtained further from the date of onset, some return may have already occurred when the audiogram is obtained. Posttreatment audiograms may also be done too early, potentially missing hearing gains over time. Anecdotally, we have seen several patients where long-term audiometric results were much better than short-term results, and this has been substantiated in the literature.[10] In this study, there was no control in the timing of pre- and posttreatment audiograms. It is

TABLE III.
Difference Between Pre- and Posttreatment Pure Tone Average.

Variable	Pretreatment (Mean ± SD)	Posttreatment (Mean ± SD)	Mean Difference (Mean ± SD)	*P*-value
PTA initiated within 90 days of onset (n = 53)	58.5 ± 29.3	50.5 ± 27.9	8.0 ± 19.5	.004*
PTA initiated within 2 weeks of onset (n = 31)	60.9 ± 32.4	47.2 ± 26.5	13.8 ± 16.6	<.001*

*$P < .05$; PTA = Pure Tone Average; SD = Standard Deviation.

TABLE IV.
Results of Multivariable Analysis for Delta Pure Tone Average.

Variable	Estimate	Standard Error	95% Confidence Limits		*P*-value
All Treatment Groups (n = 53)					
Intercept	−39.472	15.01	−69.71	−9.23	.012
Age	0.802	0.22	0.36	1.24	<.001*
Gender (Female vs. Male)	7.806	4.632	−1.53	17.14	.099
Time to treatment	−0.324	0.10	−0.52	−0.12	.002*
Vertigo (Yes vs. No)	2.201	5.19	−8.25	12.65	.673
Combined Treatment only (n = 39)					
Intercept	−35.279	18.98	−73.96	3.401	.072
Age	0.788	0.26	0.25	1.33	.006*
Gender (Female vs. Male)	5.776	5.31	−5.04	16.59	.285
Time to treatment	−0.373	0.11	−0.59	−0.16	.001*
Vertigo (Yes vs. No)	−1.963	6.15	−14.48	10.56	.752
Salvage/Delay (Concurrent, n = 20 vs. Salvage/Delay, n = 19)	−1.609	5.40	−12.61	9.39	.768

*$P < .05$; Salvage/Delay = Time between completing oral and starting intratympanic (IT). Concurrent = oral+IT given at the same time.

possible that with earlier pre-and later posttreatment audiograms, PTA results could have been better.

We chose to review cases within 90 days of onset, whereas prospective series may evaluate patients within two to three weeks of onset to show better cause-and-effect of treatment. Current clinical practice guidelines recommend therapy for patients within three months of diagnosis.[9] We still consider treatment for patients up to three months, but counsel patients closely that chances for improvement are less with increased time-to-treatment.

Our data show that earlier treatment leads to improved PTA outcomes for the overall group and for the combined oral+IT subgroup. One study reported similar results for combined oral+IT therapy, with earlier time-to-injection statistically correlated with improved outcomes in patients with ≥30 dB improvement in PTA.[4] We have established relationships with primary care physicians in our immediate referral network to assist with rapid diagnosis, initial treatment with steroids, and timely referral of these cases. Tuning fork identification or the Rauch test[11] (patient hums with sound only heard in good ear for sensorineural, bad ear for conductive) can assist in diagnosing ISSNHL leading to immediate steroid therapy.

Our regression analysis indicates that younger patients have a poorer prognosis with ISSNHL. These results contradict the literature. In a similar regression analysis for patients receiving combined oral+IT having greater than 30 dB improvement in PTA, age was not statistically correlated with outcomes.[8] In earlier literature, older age in treated ISSNHL patients tends to be associated with a worse prognosis[12–15] or no change in hearing improvement.[16–18] One prospective, longitudinal cohort study of 127 ISSNHL patients found no significant difference in PTA recovery rates in the various age groups studied (≤30, 31–50, 51–70, ≥71 years old), but did note a trend in poorer results in the more extreme age groups (≤30, ≥71 years old)[19] Attanasio et al.[20] found increased age was associated with worse hearing outcomes in their study of 496 patients; on subgroup analysis divided by age >65 years old, patients in the older subgroup had a statistically significant higher PTA both pre- and posttreatment.

Our study results contradict the literature with regards to age, with improved outcomes seen in older patients versus younger patients. This is a small series and it is always possible that the results of one or two older or younger patients could skew the results. However, more aggressive combined oral+IT therapy may potentially lead to improved results in the older patient. This also implies that younger patients may have more aggressive disease, which may warrant more aggressive therapy for this subgroup, or for any patient that fails initial therapy.

CONCLUSION

In the diagnosis and treatment of ISSNHL, results suggest that earlier treatment with steroids is better than later treatment, which follows accepted practice guidelines for ISSNHL. Timely diagnosis, early treatment with steroids, and referral by primary care providers to otolaryngologists will facilitate combined high dose oral and IT steroid therapy as supported by the literature and results of this study. Age at onset may potentially impact outcomes, but this would not influence whether combined oral plus IT therapy should be offered.

AUTHOR CONTRIBUTIONS

Conception and design: J.H.H., J.A.Z., A.F., W.B., and L.P.B.; provision of study materials and patients: W.B. and L.P.B.; collection and assembly of data: J.H.H., J.A.Z., M.A.L., L.P.B., and W.B.; data analysis and interpretation: K.R.G., J.H.H., J.A.Z., W.B., and L.P.B.; manuscript writing: J.A.Z, J.H.H., and L.P.B.; critical revision and final approval of manuscript: all.

MEETING INFORMATION

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

BIBLIOGRAPHY

1. Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. *Arch Otolaryngol* 1980;106:772–776.
2. Ho HG, Lin HC, Shu MT, Yang CC, Tsai HT. Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. *Laryngoscope* 2004;114:1184–1189.
3. Kilic R, Safak MA, Oguz H, et al. Intratympanic methylprednisolone for sudden sensorineural hearing loss. *Otol Neurotol* 2007;28:312–316.
4. Wu HP, Chou YF, Yu SH, Wang CP, Hsu CJ, Chen PR. Intratympanic steroid injections as a salvage treatment for sudden sensorineural hearing loss: a randomized, double-blind, placebo-controlled study. *Otol Neurotol* 2011;32:774–779.
5. Battaglia A, Burchette R, Cueva R. Combination therapy (intratympanic dexamethasone + high-dose prednisone taper) for the treatment of idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 2008;29:453–460.
6. Filipo R, Attanasio G, Russo FY, et al. Oral versus short-term intratympanic prednisolone therapy for idiopathic sudden hearing loss. *Audiol Neurotol* 2014;19:225–233.
7. Rauch SD, Halpin CF, Antonelli PJ, et al. Oral vs. intratympanic corticosteroid therapy for idiopathic sudden sensorineural hearing loss: a randomized trial. *JAMA* 2011;305:2071–2079.
8. Alexander TH, Harris JP, Nguyen QT, Vorasubin N. Dose effect of intratympanic dexamethasone for idiopathic sudden sensorineural hearing loss: 24 mg/ml is superior to 10 mg/mL. *Otol Neurotol* 2015;36:1321–1327.
9. Stachler RJ, Chandrasekhar SS, Archer SM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;146(3 Suppl):S1–S35.
10. Yeo SW, Lee DH, Jun BC, Park SY, Park YS. Hearing outcome of sudden sensorineural hearing loss: long-term follow-up. *Otolaryngol Head Neck Surg* 2007;136:221–224.
11. Rauch SD. Clinical practice. Idiopathic sudden sensorineural hearing loss. *N Engl J Med* 2008;359:833–840.
12. Nakagawa T, Yamamoto M, Kumakawa K, et al. Prognostic impact of salvage treatment on hearing recovery in patients with sudden sensorineural hearing loss refractory to systemic corticosteroids: A retrospective observational study. *Auris Nasus Larynx* 2016;43:489–494.
13. Chen C, Wang M, Fan Z, Zhang D, Lyu Y, Wang H, Wang H. [Correlations between the pathogenesis and prognosis of sudden sensorineural hearing loss and blood lipid]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2015;50:793–798.
14. Edizer DT, Celebi O, Hamit B, Baki A, Yigit O. Recovery of idiopathic sudden sensorineural hearing loss. *J Int Adv Otol* 2015;11:122–126.
15. Lee HS, Lee YJ, Kang BS, Lee BD, Lee JS. A clinical analysis of sudden sensorineural hearing loss cases. *Korean J Audiol* 2014;18:69–75.
16. Na SY, Kim MG, Hong SM, Chung JH, Kang HM, Yeo SG. Comparison of sudden deafness in adults and children. *Clin Exp Otorhinolaryngol* 2014;7:165–169.
17. Suzuki H, Tabata T, Koizumi H, et al. Prediction of hearing outcomes by multiple regression analysis in patients with idiopathic sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 2014;123:821–825.
18. Xenellis J, Karapatsas I, Papadimitriou N, et al. Idiopathic sudden sensorineural hearing loss: prognostic factors. *J Laryngol Otol* 2006;120:718–724.
19. Bogaz EA, Maranhao AS, Inoue DP, Suzuki FA, Penido Nde O. Variables with prognostic value in the onset of idiopathic sudden sensorineural hearing loss. *Braz J Otorhinolaryngol* 2015;81:520–526.
20. Attanasio G, Covelli E, Cagnoni L, et al. Does age influence the success of intra-tympanic steroid treatment in idiopathic sudden deafness? *Acta Otolaryngol* 2015;135:969–973.