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Adjuvant Migraine Medications in the Treatment of Sudden Sensorineural Hearing Loss

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Objectives/Hypothesis: To examine the hearing outcomes of patients with sudden sensorineural hearing loss (SSNHL) treated with oral and intratympanic (IT) steroid only or a combination of steroid and migraine treatment. Our hypothesis was that adjuvant migraine medications may improve outcomes in SSNHL.

Methods: A retrospective chart review at a tertiary otology center was conducted to identify patients with SSNHL who received oral steroid and IT dexamethasone injection(s) with or without migraine medications (a combination of nortriptyline and topiramate).

Results: A total of 47 patients received oral steroid and IT dexamethasone injection(s) only, and 46 patients received oral steroid and IT dexamethasone injection(s) as well as migraine lifestyle changes plus a combination of nortriptyline and topiramate. There were no significant differences in demographics and baseline audiometric data between the two groups. Both groups demonstrated improvements in pure tone average (PTA) and hearing thresholds at 250 Hz and 8000 Hz post-treatment. However, compared to steroid-only group, the adjuvant migraine medications group had significantly greater improvements in hearing thresholds at the lower frequencies (250 Hz, 500 Hz, 1000 Hz). Patients in the latter cohort also had greater improvement in PTA (P = .01) and received fewer IT injections (P = .04) PTA improvement of ≥ 10 dB was observed in 36 patients (78%) in the adjuvant migraine medications group and 22 patients (46%) in the control group (P < .001).

Conclusion: In multimodal treatment of SSNHL, supplementing oral and IT steroid with migraine medications may result in greater improvements in lower frequency hearing thresholds and PTA. Furthermore, adjuvant migraine treatment can lead to decrease in number of IT injections, thus reducing procedure-related risks and complications.

Key Words: Hearing loss, sensorineural, SSNHL, migraine, intratympanic.

Level of Evidence: 3

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INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) can be defined as a rapid onset >30 dB reduction in sensorineural thresholds of three contiguous audiometry frequencies within 3 days. With a current estimated incidence of 27 per 100 thousand U.S. adults, SSNHL is associated with male gender and older age.[1] It most commonly presents as a unilateral hearing loss upon waking up, and concurrent or subsequent bilateral involvement is not frequent.[2,3] The pathophysiology and management of this entity has remained a subject of debate. SSNHL can arise from known etiopathologies (29%) such as infections, otologic diseases, trauma, hematologic or vascular disorders, and tumors, whereas most cases (71%) may be regarded as idiopathic.[3] It has been suggested that age and time to treatment, as well as vertigo, profound or contralateral hearing impairment, and audiogram shape, can be associated with prognosis.[4–6] Even though up to one-third to two-thirds of patients may spontaneously recover,[7,8] intratympanic (IT) and systemic steroid administration are among the widely utilized treatment options.[8–10]

Despite this, in a 2014 meta-analysis of randomized controlled trials comparing steroid and placebo treatments for SSNHL, Crane et al. demonstrated no significant difference except in the case of salvage treatment.[11] This has called for further investigation into discovering new and improved management solutions for better treating SSNHL. One of the theoretical etiologies of idiopathic SSNHL has been attributed to vascular impairment to the cochlea.[12,13] This may align with evidence suggesting a possible association between cardiovascular risk factors and SSNHL occurrence.[3,14,15] There have also been nationwide population-based and prospective cohort studies suggesting that migraine, a complex neurovascular disorder, can increase the risk for developing SSNHL.[16–18] Thus, we present an investigation to evaluate the efficacy of supplementing IT steroid injection with migraine medications in improving SSNHL treatment outcome.

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MATERIALS AND METHODS

In this cohort study, we describe the treatment of patients with SSNHL who presented to our tertiary care neurotology practice from January 2014 to March 2019. These patients were treated with either standard care or standard care plus adjuvant multimodal migraine prophylactic regimen. Standard care for all patients was prednisone 1 mg/kg (up to 80 mg) daily for 7 days and a 6-day taper. In addition, all patients were injected with dexamethasone 10 mg/mL intratympanically at least twice, on a frequency of 2 times a week. If the patient had improvement, further injections were performed twice a week until no audiometric improvement was seen from one visit to the next. Approval was obtained from the institutional review board of the University of California, Irvine, California. Patients with sudden onset of hearing loss were evaluated using the U.S. National Institute for Deafness and Communication Disorders (NIDCD) definition for SSNHL, which is "an idiopathic loss of hearing of at least 30 dB over at least three contiguous test frequencies occurring within 3 days."[19](p2) All included patients had presented within 10 days of hearing loss onset, and time to presentation was consistent across the entire cohort. The standard workup for patients included measurement of baseline pure-tone audiometry and speech recognition threshold (SRT), word discrimination tested at a level of 40 dB above SRT, as well as magnetic resonance imaging of the internal auditory canal to rule out other causes. Pure tone average (PTA) was measured in accordance with the Committee on Hearing and Equilibrium Guidelines, utilizing thresholds at frequencies of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz.[20] Moreover, word recognition score (WRS) was obtained per American Academy of Otolaryngology–Head and Neck Surgery standardized format for reporting hearing outcome.[21]

In total, 93 patients were treated for SSNHL and included in this study. These patients were assigned retrospectively to the control group (standard care) or the adjuvant migraine medications group (standard care plus adjuvant therapy). Starting in April 2015, patients were additionally offered a regimen of adjuvant migraine prophylactic medication at the initial visit. As such, patients treated prior or following this date were assigned to the control or adjuvant migraine medications groups, respectively, with the exception of post-April 2015 patients in whom migraine medications were contraindicated (N = 3) and were analyzed as part of the control cohort. All patients were evaluated for whether they met the International Classification of Headache Disorders (ICHD) 3rd edition beta criteria for migraine with or without aura (Table I)[22] through the administration of a comprehensive questionnaire given to all patients presenting to our neurotology clinic. Patients who were already receiving migraine medications for a previous migraine diagnosis were excluded.

As part of the migraine prophylaxis, patients were counseled on implementing migraine lifestyle modifications. This included dietary modifications, which consisted of avoiding foods containing certain preservatives, fermented products, chocolate, nuts, eggs, alcohol, fresh breads/yeast products, aged/processed meats, certain beans, certain fruit (high histamine), and pickled or preserved fruits/vegetables.[23] In addition, dietary supplementation with magnesium 400 mg orally twice a day and riboflavin (vitamin B2) 200 mg orally twice a day was prescribed. We did not restrict sodium intake as long as the patient stayed well-hydrated. Patients were also instructed to eat three meals and sleep on a regular schedule to avoid fatigue, hunger, and dehydration. The patients were also prescribed pharmacologic migraine prophylaxis with nortriptyline 25 mg orally before bedtime and gradually escalated by 25 mg every 2 weeks to a maximum dose of 75 mg. In addition, topiramate 25 mg orally before bedtime with weekly escalation of 25 mg up to 150 mg was prescribed. Medication adherence was emphasized on every follow-up visit, and a lack of compliance led to exclusion from the study.

TABLE I.
Diagnostic Criteria of Migraine With or Without Aura According to ICDH 3rd Edition Beta Criteria.

Diagnostic criteria of migraine without aura:
A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hrs (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Diagnostic criteria of migraine with aura:
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
  1. Visual
  2. Sensory
  3. Speech and/or language
  4. Motor
  5. Brainstem
  6. Retinal
C. At least two of the following four characteristics:
  1. At least one aura symptom spreads gradually over ≥ 5 min, and/or two or more symptoms occur in succession
  2. Each individual aura symptom last 5–60 min
  3. At least one aura symptom is unilateral
  4. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

Hrs = hours; ICDH = International Classification of Headache Disorders, 3rd edition; min = minutes.

Patients were re-evaluated twice a week with an audiogram. After the two IT steroid injections, the decision was made whether to continue with IT dexamethasone injection: if there was improvement in hearing. In some patients, the dose escalation was performed faster initially with increase in the topiramate dose every 3 to 4 days and nortriptyline at 7 to 10 days post-onset of treatment. Thus, the treatment duration in some patients was shorter and approximately 4 weeks, whereas some patients were treated for the full 6 weeks when escalations were performed as initially planned. Patients who received migraine prophylactic medications were eventually tapered after 4 to 6 weeks when maximum dose was achieved. Posttreatment audiometry was defined as the audiometric results obtained at the final visit. Paired samples t test was performed to compare pre- and posttreatment audiometric measurements. Furthermore, chi-square and independent sample t test were used to compare categorical and numerical variables between the two groups, respectively. SPSS 17.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis with a 0.05 alpha considered significant.

RESULTS

Of the 93 patients included in this study, 47 were assigned to the control group (received oral and IT steroids) and 46 to the adjuvant migraine medications group (in addition to oral and IT steroids). As shown in Table II, there were no significant differences in age, sex, baseline PTA, baseline WRS, or migraine history between the two groups. There were no tympanic membrane (TM) complications on otomicroscopy plus tympanometry associated with IT injections, including permanent perforation, in either cohort. There were no reported adverse events associated with the

TABLE II.
The Cohort Demographics, Baseline Audiometry, and Total Intratympanic Steroid Injections.

	Control Group	Adjuvant Migraine Medications Group	*P* value
Age	56.8 ± 17.4	60.2 ± 14.3	.30
Sex (M:F)	27:20	27:19	1.00
Migraine history	20 (42%)	17 (37%)	.58
PTA (dB)	73 ± 26	74 ± 22	.80
SRT (dB)	62 ± 25	53 ± 26	.10
WRS (%)	29 ± 34	23 ± 34	.37
No. of IT injections	3.1 ± 2.0	2.4 ± 1.1	.04*

Asterisk denotes statistically significant *P* value.
F = female; IT = intratympanic; M = male; PTA = pure tone average; SRT = speech recognition threshold; WRS = word recognition score.

administration of migraine medications. Complaints of dry mouth and somnolence occurred when the medications were escalated to the higher dosages; however, none of the side effects led to noncompliance.

The adjuvant migraine medications group had a lower average SRT, although this difference did not reach statistical significance (62 ± 25 dB vs. 53 ± 26 dB, $P = .10$). The control group had a higher average number of IT dexamethasone injections, which met significance (3.1 ± 2.0 vs. 2.4 ± 1.1, $P = .04$). As shown in Table III, both groups demonstrated a significant improvement in hearing thresholds in both high and low frequencies at the 4 to 6 week follow-up. The control group pretreatment PTA was 73 ± 26 dB versus 61 ± 28 dB posttreatment, $P < .001$. The adjuvant migraine medication group improved from 74 ± 22 dB pretreatment to 55 ± 22 dB posttreatment, $P < .001$. Whereas both groups showed improvement in average SRT, only the control group met statistical significance ($P = .004$). Moreover, both groups experienced significant improvement in WRS outcomes: from 29 ± 34% pretreatment to 53 ± 40% posttreatment in the control group ($P < .001$), and from 23 ± 34% pretreatment to 56 ± 38% posttreatment in adjuvant migraine medications group ($P < .001$).

TABLE III.
Comparison of Pre- and Posttreatment Audiometry Between the Two Groups.

	Pretreatment Hearing Threshold/Score	Posttreatment Hearing Threshold/Score	*P* Value
Control group			
250 Hz (dB)	68 ± 25	57 ± 29	< .001*
8000 Hz (dB)	75 ± 20	68 ± 24	< .001*
PTA (dB)	73 ± 26	61 ± 28	< .001*
SRT (dB)	62 ± 25	51 ± 31	.004*
WRS (%)	29 ± 34	53 ± 40	< .001*
Adjuvant migraine medications group			
250 Hz (dB)	63 ± 27	42 ± 20	< .001*
8000 Hz (dB)	74 ± 28	64 ± 29	< .001*
PTA (dB)	74 ± 22	55 ± 22	< .001*
SRT (dB)	53 ± 26	45 ± 23	.11
WRS (%)	23 ± 34	56 ± 38	< .001*

Asterisk denotes statistically significant *P* value.
PTA = pure tone average; SRT = speech recognition threshold; WRS = word recognition score.

TABLE IV.
Comparison of Calculated Differences in Pre- and Posttreatment Hearing Thresholds at Different Frequencies, PTA, SRT, and WRS Between the Two Groups.

	Improvement in Threshold (Δ dB) or Score (Δ %)		
	Control Group	Adjuvant Migraine Medications Group	*P* Value
250 Hz (dB)	11 ± 16	21 ± 22	.02*
500 Hz (dB)	14 ± 15	24 ± 20	.01*
1000 Hz (dB)	13 ± 17	25 ± 16	.001*
2000 Hz (dB)	11 ± 14	16 ± 13	.09
4000 Hz (dB)	9 ± 13	10 ± 12	.78
8000 Hz (dB)	7 ± 12	10 ± 13	.14
PTA (dB)	12 ± 13	19 ± 13	.01*
SRT (dB)	11 ± 20	7 ± 30	.54
WRS (%)	23 ± 30	33 ± 33	.14

Asterisk denotes statistically significant *P* value.
PTA = pure tone average; SRT = speech recognition threshold; WRS = word recognition score.

The comparison of calculated differences in pre- and posttreatment hearing thresholds at different frequencies, PTA, SRT, and WRS between the two groups are shown in Table IV. The adjuvant migraine medications group showed a significantly greater improvement in hearing compared to the control group, as measured by change in PTA ($P = .01$). Specifically, the greater improvements on hearing thresholds were statistically significant in the contiguous lower frequencies of 250 Hz, 500 Hz, and 1000 Hz ($P = .02$, $P = .01$, and $P = .001$; respectively). PTA improvement of ≥ 10 dB was observed in 36 patients (78%) in the adjuvant migraine medications group and 22 patients (46%) in the control group ($P < .001$), whereas PTA improvement of ≥ 20 dB was observed in 28 patients (61%) in the adjuvant migraine medications group and 12 patients (25%) in the control group ($P < .001$).

DISCUSSION

This retrospective study of SSNHL patients demonstrated that supplementing oral steroid and IT dexamethasone injections with migraine medications led to greater hearing improvement in lower frequency thresholds and PTA as well as a need for fewer IT injections. Although both "oral and IT steroid with migraine treatment" and "oral and IT steroid only" groups experienced symptomatic improvements, the statistically significant greater improvement of the adjuvant migraine medications cohort (Fig. 1), despite a similar prevalence of migraine history, may shed light on a similar underlying vascular etiology among both migraine and idiopathic SSNHL. If

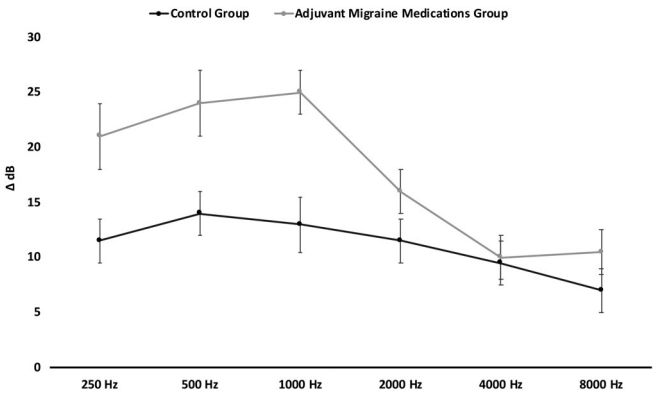

Fig. 1. Posttreatment improvement in hearing thresholds among the two cohorts, demonstrating a significant improvement in the experimental group (oral and intratympanic steroid with migraine treatment; N = 46) compared to controls (oral and intratympanic steroid only; N = 47) in the low frequencies. Error bars represent ±1 standard error of means.

true, this can result in further investigative pursuit of potentially novel treatment strategies for SSNHL.

Among various causes of hearing loss, idiopathic SSNHL has attracted disproportionate research interest. This is likely due to its potentially reversible natural course as well as its emergent treatment window, rendering all otolaryngologists as key clinicians for care of these patients.[24] With no current consensus on a treatment regimen, otolaryngologists may use one or a combination of options, such as systemic steroid, IT steroid, antiviral or anticoagulating agents, hyperbaric oxygen, antioxidants, and vasodilators. It is suggested that older age and delayed time to treatment, as well as associated vertigo, hypertension, and diabetes, can be associated with lower recovery rates.[4,5] There is abundant evidence supporting the efficacy of IT steroid therapy for SSNHL hearing improvement, especially if refractory to systemic medication or for salvage treatment.[24–30] In accordance with the literature, our control group experienced symptomatic improvements with oral and IT steroid injections. However, this manuscript is the first to report additional SSNHL outcome improvements with supplementing migraine medications such as nortriptyline and topiramate.

The similar prevalence of migraine history between the two cohorts further suggests that the prophylactic regimen may independently provide therapeutic benefit regardless of a history of classical migraine. Similar benefits from migraine prophylactic regimen have also been demonstrated in other complex otologic disorders such as hyperacusis, vertigo, and Meniere disease.[31–33] This may be due to similar underlying vascular pathophysiology between SSNHL and migraine, which is in line with Dogan et al.'s finding that prophylactic migraine treatment such as topiramate may reduce endothelial pulse wave velocity and also lead to decreased long-term cardiovascular risks.[34] Topiramate's positive role in regulating cerebrovascular autonomic control has also been speculated.[35] The potential neuroprotective effects of nortriptyline against cerebral ischemia further support these prophylactic medications' vascular effects,[36] which could explain its observed benefits to patients with migraine as well as SSNHL. Verapamil, which is another drug commonly used for treating migraine, is also associated with significantly decreased cerebrovascular resistance.[37–39] The aforementioned studies, among others, suggest that migraine prophylactic medications may provide therapeutic benefit to both migraine and SSNHL by altering vascular flow and addressing a potentially similar underlying pathophysiology.

In this investigation, we demonstrated that supplementing oral and IT steroids with migraine medications led to significantly improved recovery of low frequency (250, 500, and 1000 Hz) hearing loss. Furthermore, there was both a greater improved PTA as well as a lesser frequency of required IT injections in the combination-treated cohort. The decreased number of required injections were likely due to patients' earlier hearing recovery back to normal compared to those who did not receive adjuvant migraine treatment. Because migraine is a complex neurovascular disorder, this can imply that SSNHL may have an underlying vascular or neurogenic inflammatory pathophysiology similar to migraine, which can explain the improved outcomes observed in this experiment. Oh et al.'s recent report of a unique gene associated with progressive SNHL associated with migraine may be one route to examine this close relationship.[40] It is already well established that migraine and vestibular symptoms can have a close relationship and association in the diagnosis of vestibular migraine.[41–43] Similarly, there has been continuous speculation of whether migraine can damage the inner ear in association with pathologies such as sudden hearing loss and delayed endolymphatic hydrops.[44] Investigation of large nation-wide databases have further revealed that migraine is a risk factor associated with developing SSNHL.[17,18] It is thus plausible to consider a theoretical vascular relationship between migraine and idiopathic SSNHL as an explanation for our observed significantly improved hearing recovery with the supplementation of migraine treatment.

A prospective study by Arslan et al. reported that although SSNHL patients had a higher prevalence of migraine, the rates of SSNHL recovery between patients with or without migraine were statistically similar.[16] The previously mentioned study by Chu et al. also observed that migraine medications such as acetaminophen, NSAIDs, and triptans were not risk factors for developing SSNHL among migraine patients.[17] It is reasonable to argue that these findings support our interpretation that the improved SSNHL recovery stemming from supplementing migraine medication may be applicable to all SSNHL patients as opposed to only those with symptomatic migraine comorbidities.

Our lack of TM complications or permanent injury with IT injection was consistent with reports in the literature describing its relative safety.[45] However, because multiple IT injections do add theoretical risk to TM injury and may subsequently impact low-frequency PTA,[46–48] the investigation of novel treatments that may decrease the number of necessary IT injections, such as the described migraine prophylactic medications, is important. The lack of TM complications following IT injections in our studied cohort can be attributed to: 1) application of a very small amount of phenol (approximately the size of a 25 Ga needle) on the TM to minimize the chance of

perforation persistence, 2) performing subsequent injections in a different area of the TM to minimize trauma to the same spot, and 3) patients were instructed on dry ear precautions and no nose blowing to minimize the chance of perforation persistence.

The selected dosages of nortriptyline and topiramate have previously been shown to be both safe and effective for treatment of other otologic conditions.[31–33,49,50] However, it is worth noting that these migraine medications have potential side effects that should be considered and monitored. Nortriptyline can cause lightheadedness, whereas topiramate can lead to mild disturbance in taste, appetite, and paresthesia of distal extremities. Nortriptyline can also cause sedation and disturbance in cardiac rhythm, the latter of which can be monitored with electrocardiograms. The studied cohort did not experience any major adverse events, which can be attributed to careful dose escalation or de-escalation depending on symptomatic improvement and tolerance. We have noticed that the patients with sudden hearing loss tend to be more compliant with the migraine medication regimen compared to our vestibular migraine patients. The nature of the deficit with sudden hearing loss and the perceived long-term consequences may play a role in improved compliance even in the presence of side effects. Though we remain cautious regarding potential risks associated with IT injection and migraine prophylactic medications, it is important to balance these risks with potential reward of SSNHL treatment.

It was observed that although there were no significant differences between the two cohorts' pretreatment PTA and SRT, the adjuvant migraine group had a nonsignificant larger difference between PTA and SRT compared to the control group. In our clinical experience, we have observed that the SRT in general tends to be sensitive to a single threshold in a non-PTA frequency. For instance, if a patient has a 25-dB threshold at 250 Hz or 3000 Hz, the SRT tends to be significantly better than the PTA (if the thresholds at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz are lower than that single good frequency). Whereas the PTA-SRT difference seemed different between the two cohorts, it did not reach statistical significance, and thus the two cohorts' different levels of improvement from statistically similar baselines can be attributed to their treatments. In addition to observing greater improvements in low-frequency hearing thresholds, it was demonstrated that a significantly higher proportion of migraine-adjuvant patients experienced improved PTA (which was derived from 500, 1000, 2000, and 4000 Hz frequencies) compared to controls. Namely, 78% and 46% of the adjuvant migraine group experienced 10 dB and 20 dB improvements compared to 46% and 25% in the control group, respectively, demonstrating hearing improvement affecting a significantly larger proportion of patients. Additionally, the mere 25% of control patients experiencing ≥ 10 dB improvement is low, which leads us to consider further treatment that can result in improved hearing and possibly translate to better quality of life. Lastly, although WRS improvement was not significantly different between the two groups, its relatively larger change in the treatment cohort (33% vs. 23%) may be nonsignificant due to the retrospective nature of the current study and its limitations, which will be discussed further. Despite this, the aforementioned findings suggesting favorable outcomes following adjuvant migraine medication treatment warrant further investigations into its utility for SSNHL. Future research is especially important because many SSNHL patients may not receive any treatment besides steroid therapy, even if it proves not efficacious.

Although great effort was taken to ensure the validity of this study from methodology and patient inclusion to analysis, there exist some limitations. First, the retrospective chart-review nature of this study precludes concluding that migraine medication is efficacious for all SSNHL patients as opposed to a subset of patients with certain characteristics or presentations. Future placebo-controlled prospective cohort studies are warranted to better characterize treatment outcomes of SSNHL following standard care (oral and IT steroid) versus standard care plus adjuvant migraine medications. As part of the migraine prophylactic regimen, patients were thoroughly counseled on the dietary and lifestyle modifications on every clinic visit and were offered handouts with written information. However, due to the multifactorial and patient-specific nature of the dietary and lifestyle modifications, there may exist a sizable variety in patient compliance that was not measured. Medication compliance was also subjectively reported by patients on follow-up visits, which can be improved upon via routine medication adherence self-reported questionnaires or medication monitoring devices in future research.[51,52] Lastly, SSNHL is a relatively rare entity, further limiting the cohort sizes for experimentation and statistical comparison. Despite these limitations, this study may serve as an initiative to further investigate the possible efficacy of migraine medications for an enhanced treatment of SSNHL in a randomized clinical trial.

CONCLUSION

SSNHL patients who received adjuvant migraine medications experienced greater improvement in lower frequency hearing thresholds and PTA compared to patients who only received standard oral and IT steroid injections. Furthermore, the utilization of migraine medications in SSNHL treatment was also associated with fewer IT injections, which can reduce risks of procedure-related complications.

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