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Dose Effect of Intratympanic Dexamethasone for Idiopathic Sudden Sensorineural Hearing Loss: 24 mg/mL Is Superior to 10 mg/mL

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Objective: To compare outcomes in patients with idiopathic sudden sensorineural hearing loss (ISSNHL) treated with intratympanic (IT) dexamethasone (DEX) at either 10 mg/mL or 24 mg/mL.
Study Design: Retrospective case series.
Setting: Tertiary referral center.
Patients: Thirty-seven adults with ISSNHL.
Interventions: In addition to concurrent prednisone taper, patients received a series of IT DEX injections for 2 weeks with either 10 mg/mL or 24 mg/mL.
Main Outcome Measure: Greater than 30-dB improvement in pure-tone average (PTA).
Results: Baseline characteristics were similar between groups. Mean follow-up was 10 weeks. Ten (53%) of 19 patients treated with 24 mg/mL had greater than 30-dB improvement in PTA compared with 3 (17%) of 18 treated with 10 mg/mL ($p = 0.0382$, Fisher's exact test). There was a trend toward improved word recognition score outcome with 24 mg/mL. The interval between onset and initiation of IT DEX significantly affected outcome, with earlier treatment resulting in greater improvement in PTA and word recognition score. Multivariate logistic regression confirmed that IT DEX dose and interval to starting treatment were both independent predictors of PTA outcome. Change in PTA was not significantly affected by age, sex, pretreatment hearing levels, or concurrent treatment with hyperbaric oxygen.
Conclusion: To our knowledge, this is the first demonstration of superiority of IT DEX at 24 mg/mL for the treatment of ISSNHL, with significantly better recovery of PTA. Our data suggest that treatment should be initiated as soon as possible. A prospective randomized trial to confirm the optimal dose is warranted. **Key Words:** Idiopathic sudden sensorineural hearing loss—Intratympanic dexamethasone.
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Since its first description in 1944 by De Klein (1), sudden sensorineural hearing loss (SSNHL) remains a puzzling process. It is characterized by a rapid decline in sensorineural hearing occurring within less than 72 hours. A thorough workup reveals a clearly identifiable cause in less than 30% of cases (2). In the remaining majority, no definitely identifiable etiology is ever found, leading to a diagnosis of idiopathic SSNHL (ISSNHL). The disease afflicts approximately 27 out of every 100,000 people per year (3) and can have a significant negative impact on quality of life (4).

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Many different therapies have been used to treat ISSNHL, including vasodilators, antiviral agents, anticoagulants, and hyperbaric oxygen (HBO). However, corticosteroids have become the most frequently used treatment (5). Treatment with corticosteroids became prominent in large part because of a 1980 study by Wilson et al. (6) that showed significant improvement in hearing recovery with systemic corticosteroid use compared with placebo.

In the 1990s, the intratympanic (IT) route of administration of corticosteroids for ISSNHL was introduced, with the goal of minimizing systemic side effects while allowing achievement of a higher drug concentration in the inner ear (7,8). A multicenter randomized trial demonstrated equivalent hearing outcomes in patients treated with either oral prednisone or IT methylprednisolone (9). Other studies have suggested that a combination of oral and IT corticosteroids may be superior to treatment by either modality alone (10–12).

Irrespective of the delivery method, literature on the efficacy of steroids in general for the treatment of ISSNHL is conflicting. After the study by Wilson et al. (6), other placebo-controlled studies did not find a beneficial effect for systemic steroids (13,14). Recent meta-analyses have questioned the benefit of primary treatment with either systemic or IT steroids (15,16). However, these analyses combined studies using different steroid analogs (e.g., methylprednisolone, prednisone, or dexamethasone [DEX]) as well as many different doses, dosing intervals, and durations of treatment. The heterogeneity of treatment regimens could be a key reason for the lack of observed benefit in meta-analyses. Ideally, the optimal dose and regimen of a therapeutic drug of interest should first be established before larger controlled trials are performed to confirm efficacy and safety. The lack of evidence for an optimal IT corticosteroid treatment regimen was identified as an important evidence gap during the creation of clinical practice guidelines by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (17).

To date, no published study has focused on defining the optimal dose of IT corticosteroids for hearing recovery after ISSNHL. The purpose of this preliminary study is to retrospectively compare the effect of two different concentrations of IT DEX for primary treatment of ISSNHL. If a dose-dependent phenomenon exists, this would lend support to the efficacy of steroid treatment in ISSNHL and facilitate efforts to rigorously define an optimal treatment regimen.

METHODS

This study was approved by the University of California San Diego (UCSD) Institutional Review Board (IRB Nos. 111556 and 141168). Billing records were used to identify all adult patients (at least 18 years old) treated with IT injections in the UCSD otology clinic from September 2005 through June 2014. Charts were then examined for inclusion and exclusion criteria, and data were extracted. Patients with a unilateral SSNHL occurring within less than 72 hours were considered to have ISSNHL. Patients with known causes of fluctuating hearing loss such as Ménière's disease or autoimmune inner ear disease were excluded. All patients underwent appropriate imaging to exclude tumor as the cause of hearing loss. Patients whose treatment was initiated more than 4 weeks after onset of symptoms were excluded. In our practice, patients are routinely offered concurrent IT DEX and high-dose prednisone taper (60 mg/d for 7 d, followed by a tapering dose for 7 d). To reduce potentially confounding variables in this study, only patients receiving a course of high-dose prednisone *and* IT DEX were included.

Between March 2008 and April 2010, a commercial preparation of DEX sodium phosphate 10 mg/mL (West-Ward Pharmaceuticals [formerly Baxter US Multi Source Injectables], Eatontown, NJ, USA) was used for IT DEX injections in the clinic. Starting in April 2010, our clinic began offering IT injection of DEX sodium phosphate 24 mg/mL that was purchased through a local compounding pharmacy. The change was made based on preclinical animal data indicating that higher-concentration DEX preparations delivered to the middle ear result in increased perilymph concentrations for longer durations (18) and previous clinical studies using this dose (19–21). Beginning in August 2013, fees for newly required sterility testing imposed by the compounding pharmacy resulted in a dramatic increase in cost for the higher dose. Therefore, the clinic reverted to exclusive use of the commercially available 10-mg/mL solution. These changes in practice provided a convenient sample of patients to examine for a dose effect of DEX on ISSNHL. Only patients treated with IT DEX at 10 mg/mL or 24 mg/mL were included. Those treated with other corticosteroid analogs or doses were excluded.

Injections were performed by four faculty neurotologists at UCSD. Our typical protocol is to perform a series of four injections over a period of 2 weeks. Some patients received less than four injections, usually because of early recovery of hearing. For this analysis, patients receiving at least two injections were included. Injections were performed with or without topical anesthesia with phenol depending on physician and patient preference. The DEX solution was instilled in the middle ear using a 27-gauge needle under a microscope. The volume instilled varied based on patient anatomy but typically ranged from 0.5 to 1 mL. After the injection, patients remained in a lateral position, with the injected ear up for 30 minutes. They were instructed not to swallow during this time to minimize the chance of drainage of the medication down the eustachian tube.

Complete pretreatment and posttreatment audiometric data were available for all 37 patients included in the final analysis. Pure-tone average (PTA) thresholds were calculated as the mean of the air-conduction threshold at 0.5, 1, 2, and 4 kHz. Changes in PTA and word recognition score (WRS) were calculated by subtracting pretreatment values from final posttreatment values. To simplify graphing, improvement in PTA is reported as a positive number (i.e., the additive inverse of change in PTA). Change in PTA was analyzed as both a continuous and categoric variable. For the purposes of this study, a clinically significant improvement in PTA was defined as an improvement in threshold of 30 dB or higher. Although many studies have used 10 dB or 15 dB as the cutoff for defining significant PTA improvement (22), we felt that 30 dB, as first described by Furuhashi et al. (23), represents a more meaningful gain.

Because this was a retrospective study, only the information documented in the medical record at the time of treatment was available for analysis. The presence or absence of vertigo and tinnitus was not recorded for every patient. Therefore, these variables were not included in the final analysis. For the subset of patients with known vertigo and tinnitus status, these variables were not significant predictors of PTA or WRS outcome (data not shown).

Statistical analysis was performed using SAS Enterprise Guide 6.1 (Cary, NC, USA). Means are presented with the standard error of the mean. Means were compared with Student's t test or the Wilcoxon-Mann-Whitney test (if the distribution was not normal). Proportions were compared with Fisher's exact test. Multivariate analysis of continuous outcome variables was performed using generalized linear models. Logistic regression was used to analyze predictors of binomial PTA outcome. Two-sided tests and a level of $\alpha = 0.05$ were used to determine significance. For logistic regression, odds ratio estimates are presented with Wald 95% confidence intervals (CI).

RESULTS

Patients

A total of 37 patients met criteria for inclusion in the study. Of these, 18 were treated with 10 mg/mL of IT DEX, and 19 were treated with 24 mg/mL of IT DEX. As shown in Table 1, the baseline characteristics were similar for the

TABLE 1. *Baseline characteristics for each treatment group*

Characteristics	10 mg/mL (n = 18)		24 mg/mL (n = 19)		*p* Value
Sex					1.0000
Men	10		10		
Women	8		9		
Age (yr)	58.9	(3.9)	61.7	(3.4)	0.5869
Pretreatment audiometry					
PTA (dB HL)	75.6	(6.4)	83.6	(5.1)	0.3259
WRS	32.0%	(8.3%)	19.2%	(7.3%)	0.2312
Days to first injection	11.2	(1.9)	9.2	(1.3)	0.3640
No. injections	3.6	(0.2)	3.4	(0.2)	0.3305
Follow-up days	69.7	(12.2)	74.9	(13.2)	0.7711
Received HBO therapy					0.6599
Yes	2		4		
No	16		15		

Means are presented with standard error in parentheses.

Proportions were compared with Fisher's exact test. Means were compared with unpaired *t* test or the Wilcoxon-Mann-Whitney test if the distribution was not normal.

PTA indicates pure-tone average; WRS, word recognition score; dB HL, decibels hearing level; HBO, hyperbaric oxygen.

two groups with regard to sex, age, and time interval between onset of hearing loss and initiation of treatment. Pretreatment hearing tended to be slightly better in the 10-mg/mL group, although the difference was not statistically significant. The mean number of injections, days of follow-up, and proportion receiving HBO therapy were similar for the two groups. A scattergram plot of baseline PTA and WRS for each group, as recommended by the AAO-HNS Hearing Committee (24), is available as supplementary digital content (see Supplemental Digital Content 1, http://links.lww.com/MAO/A322).

Hearing Results

A clinically significant improvement in PTA (defined as ≥30 dB) was attained 10 of 19 patients in the 24-mg/mL group compared with only 3 of 18 patients in the 10-mg/mL group ($p = 0.0382$, Fisher's exact test). As shown in Figure 1, there was a trend toward greater mean improvement in PTA and WRS score in the 24-mg/mL group compared with the 10-mg/mL group, although the differences were not statistically significant. The mean improvement in PTA was 28.7 ± 5.1 dB in the 24-mg/mL group and 14.9 ± 5.3 dB in the 10-mg/mL group ($p = 0.0689$, Student's *t* test). The mean improvement in WRS was 0.293 ± 0.085 in the 24-mg/mL group and 0.144 ± 0.074 in the 10-mg/mL group ($p = 0.1919$, Student's *t* test).

Using the AAO-HNS hearing classification system, Class A hearing (PTA ≤ 30 dB and WRS ≥ 70%) was attained in the affected ear in 8 of 19 patients treated with 24 mg/mL compared with 4 of 18 in the 10-mg/mL group, although this difference was not statistically significant ($p = 0.2953$, Fisher's exact test). Looking at the subset of patients who started with very poor pretreatment AAO Class D hearing (WRS < 50%), 5 of 15 patients treated with 24 mg/mL improved to Class A compared with 1 of 11 treated with 10 mg/mL ($p = 0.1973$, Fisher's exact test). If the failure to achieve statistical significance is only caused by the small sample size but the magnitude of the observed effect is real, the odds ratio for improving from Class D to Class A would be 5.000 for treatment with 24 mg/mL versus 10 mg/mL. A scattergram plot of hearing outcomes for each group, as recommended by the AAO-HNS Hearing Committee (24) with the correction recommended by Wang (25), is available online (see Supplemental Digital Content 2, http://links.lww.com/MAO/A323).

Predictors of Improvement in PTA

A multivariate logistic regression model was created to examine predictors of achieving at least 30-dB improvement in PTA (Table 2). In the full model, both IT DEX concentration and number of days between onset of hearing loss and initiation of treatment (days to first injection) were significant predictors of outcome when controlling for other factors. Age, pretreatment PTA, sex, number of injections (range, 2–4), and treatment with HBO did not significantly predict outcome. There was a trend toward improved outcome with fewer injections, which is expected given that the primary reason for receiving less than four injections was early recovery of hearing. A logistic regression model using only the two significant predictor variables revealed that the odds ratio for achieving 30-dB or higher improvement in PTA was 9.709 for those receiving 24 mg/mL compared with 10 mg/mL (95% CI, 1.289–71.43), independent of any effect of treatment delay (Table 2). Figure 2 shows the predicted probability of 30-dB or higher

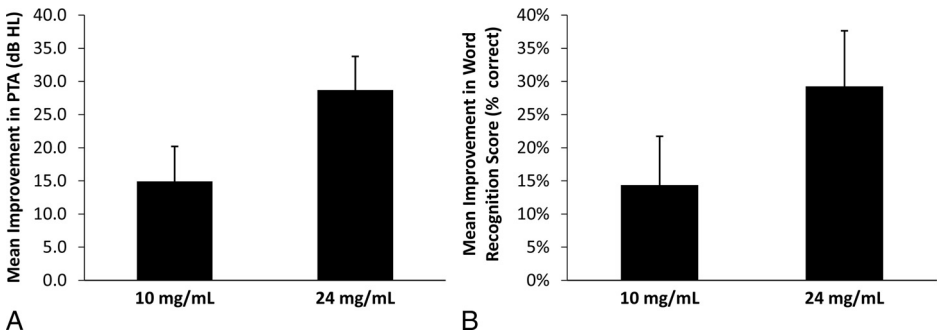

FIG. 1. Mean improvement in PTA hearing thresholds (*A*) and word recognition score (*B*) after treatment. Error bars represent the standard error of the mean.

TABLE 2. *Results of multivariate analyses of predictors of hearing improvement*

	Predictors of Achieving ≥30-dB Improvement in PTA			Predictors of Improvement in PTA as a Continuous Variable			Predictors of Improvement in WRS as a Continuous Variable		
Full Models	Odds Ratio Estimate	95% CI for Estimate	*p* Value	Parameter Estimate	95% CI for Estimate	*p* Value	Parameter Estimate	95% CI for Estimate	*p* Value
Days to first injection	0.705	(0.524–0.947)	0.0204	−1.742	(−2.844 to −0.639)	0.0031	−0.023	(−0.040 to −0.006)	0.0091
IT concentration (24 mg/mL versus 10 mg/mL)	31.355	(1.569–626.6)	0.0242	14.953	(0.494 to 29.412)	0.0432	0.132	(−0.088 to 0.352)	0.2289
Age	0.973	(0.908–1.042)	0.4331	−0.288	(−0.769 to 0.193)	0.2301	−0.005	(−0.012 to 0.002)	0.1607
Pretreatment PTA	1.005	(0.962–1.048)	0.8361	−0.110	(−0.407 to 0.187)	0.4547	−0.003	(−0.008 to 0.001)	0.1807
Sex (female versus male)	1.503	(0.149–15.13)	0.7292	−3.633	(−17.812 to 10.546)	0.6038	−0.063	(−0.279 to 0.153)	0.5545
HBO therapy (yes versus no)	0.592	(0.035–9.953)	0.7158	−7.040	(−26.932 to 12.853)	0.4745	0.072	(−0.231 to 0.374)	0.6319
No. injections									
2 versus 4	2.688	(0.121–59.51)	0.2497	6.660	(−12.874 to 26.194)	0.4907	0.073	(−0.224 to 0.370)	0.6188
3 versus 4	0.180	(0.009–3.728)	0.1617	−10.862	(−29.840 to 8.114)	0.2509	0.020	(−0.268 to 0.309)	0.8870
Elimination models with significant predictors only	Odds Ratio Estimate	95% CI for Estimate	*p* Value	Parameter Estimate	95% CI for Estimate	*p* Value	Parameter Estimate	95% CI for Estimate	*p* Value
Days to first injection	0.755	(0.607–0.938)	0.0113	−1.690	(−2.664 to −0.717)	0.0012	−0.026	(−0.041 to −0.011)	0.0010
IT concentration (24 mg/mL versus 10 mg/mL)	9.709	(1.289–71.43)	0.0274	10.264	(−2.816 to 23.345)	0.1200			

Odds ratio estimates for achieving at least 30-dB improvement in PTA hearing thresholds derived from logistic regression are shown in the leftmost column. For the full logistic regression model, the likelihood ratio test, $p = 0.0097$; for the abbreviated logistic regression model, $p = 0.0002$. For the multivariate generalized linear models of improvement in PTA and WRS as continuous variables, parameter estimates represent the predicted improvement (positive numbers) or worsening (negative numbers) in the outcome variable per unit change in continuous predictor variables or for the presence of the indicated state for ordinal predictor variables. Units of measurement for the outcome variables are dB HL for PTA and proportion of words correct for WRS. For the full PTA model, $R^2 = 0.437$, $p < 0.0001$; for the abbreviated PTA model, $R^2 = 0.335$, $p < 0.0001$. For the full WRS model, $R^2 = 0.417$, $p = 0.0011$; for the abbreviated WRS model, $R^2 = 0.268$, $p < 0.0001$.

PTA indicates pure-tone average; WRS, word recognition score; dB HL, decibels hearing level; HBO, hyperbaric oxygen.

FIG. 2. Predicted probability of achieving at least a 30-dB improvement in PTA hearing thresholds as a function of IT DEX dose and treatment delay.

improvement in PTA for each dose of IT DEX as a function of days to first injection.

The results of multivariate regression analysis of predictors of PTA outcome as a continuous variable are also shown in Table 2. In the full model, both IT DEX concentration and days to first injection reached the threshold of significance. In a model containing only these two variables, only days to first injection reached statistical significance. For each day of delay in treatment, the expected improvement in PTA decreases by 1.690 dB (95% CI, 0.717–2.664).

Predictors of Improvement in Speech Discrimination

Although there was a trend toward greater WRS improvement in the 24-mg/mL group, IT DEX concentration was not a significant predictor of WRS outcome in multivariate analysis (Table 2). Only the number of days to first injection was predictive of WRS. For each additional day of delay between onset of symptoms and initiation of IT DEX treatment, the expected recovery in proportion of words correct on the WRS test decreased by 0.023 (95% CI, 0.006–0.040).

Adverse Effects

IT DEX injections were well tolerated at each dose. A total of four patients were noted to have small pinpoint tympanic membrane perforations at follow-up after their last injection (three in the 10-mg/mL group, one in the 24-mg/mL group, $p = 0.3398$, Fisher's exact test). Two of the patients in the 10-mg/mL group were observed to have spontaneous resolution of the perforations (at 47 and 93 days after the last injection). One patient from each group failed to return for recommended follow-up, and the current status of their perforations is unknown. All of the four patients who had at least temporary perforations after their last injection received topical phenol (out of 29 total patients treated with phenol). None of the eight patients injected without topical phenol developed perforations. The rate of perforation was not

significantly different with or without phenol ($p = 0.5574$, Fisher's exact test). No infections were reported.

DISCUSSION

Despite gaining widespread acceptance since first being introduced in 1996 (7), the optimal dose for IT injection of corticosteroids to treat ISSNHL has not been defined. To our knowledge, this is the first published study to describe a dose effect in humans for IT corticosteroid injection to treat ISSNHL. The proportion of patients achieving a clinically significant improvement in PTA was greater with 24 mg/mL of DEX compared with that with 10 mg/mL. There was a trend toward improved WRS with the higher dose.

Both animal (26–29) and human (30) studies have demonstrated increased perilymph and endolymph concentrations of corticosteroids for longer durations with IT injection as compared with systemic administration. The study by Parnes et al. (26) found increased cochlear penetration for a longer duration with methylprednisolone compared with DEX and hydrocortisone. Based on these findings, some authors have advocated the use of methylprednisolone as the corticosteroid analog of choice. Others recommend DEX primarily because of its tendency to cause less patient discomfort during instillation in the middle ear and an expectation that anti-inflammatory properties should be equivalent with equivalent dosing (9). No trials have directly compared the efficacy of methylprednisolone and DEX for IT treatment of ISSNHL.

The concentrations of IT DEX used in published studies for the treatment of ISSNHL range from 4 mg/mL to 40 mg/mL (22). In general, the rationale for choosing a particular dose is not described within each individual study. Presumably, the convenient availability of a commercial preparation was the key factor in the selection of a concentration to administer, at least early on in the evolution of this treatment. Animal data have shown that higher concentrations of IT DEX result in greater accumulation within the cochlea as well as a longer duration of presence of the drug within the inner ear (18,31). This has led some centers to recommend clinical use of higher doses based on the presumption that high cochlear concentrations should improve efficacy.

Historically, a preparation of DEX at 24 mg/mL was the highest concentration commercially available in the United States, and some centers adopted this dose for IT injections. By 2004, the 24-mg/mL commercial preparation had been withdrawn from the market (32). In 2007, Haynes et al. (21) published a compounding pharmacy recipe for creation of a 24-mg/mL DEX solution to be used for the treatment of ISSNHL.

The current AAO-HNS Clinical Practice Guideline for the treatment of ISSNHL advises that clinicians *may* choose to treat primarily with systemic or IT corticosteroids (17). The authors of the guideline concluded that the available evidence for efficacy was equivocal but felt that the chance of benefit outweighed the risks in this condition that can severely impact quality of life. However, recent meta-analyses and systematic reviews have questioned the use of IT steroids for primary treatment of ISSNHL (15,16,22). As the authors of these studies acknowledged, pooling of data from studies with completely different treatment regimens is problematic. If there is a dose-dependent response to treatment, inclusion of studies with subtherapeutic doses will bias the meta-analysis toward finding no effect for treatment. In the most recent meta-analysis by Crane et al. (16), the conclusion of no benefit for primary IT steroids was based on pooled data from six studies that compared primary treatment with IT steroids to treatment with systemic steroids. Two of the studies used methylprednisolone and four used DEX for IT injection. Of the four DEX studies, the three that showed no beneficial effect used a concentration of 5 mg/mL (33–35). The one positive study used IT DEX at a concentration of 12 mg/mL (36). Based on our data and the trends seen in the meta-analysis, we think that 5 mg/mL is likely a subtherapeutic dose for IT treatment of ISSNHL and that primary treatment with a higher concentration of IT DEX is likely to improve outcomes.

Our data support the notion that ISSNHL should be treated as an otologic emergency, with early initiation of therapy maximizing the chances of recovery. In our series, the probability of significant improvement in pure-tone thresholds declined from a maximum of 0.93 on the day of onset of symptoms to less than 0.05 by Day 21 for those treated with 24 mg/mL. The natural history of the disease must be considered when interpreting the effect of treatment delay on outcomes. Reported rates of spontaneous recovery for ISSNHL have ranged from 32% to 65%, with the majority occurring within the first 14 days (6,37,38). Because of this, patients who present early for treatment may be more likely to recover than those who present late, regardless of treatment. However, our finding that a higher dose of IT DEX significantly improves outcomes *independent* of treatment delay helps support the notion that there is a true therapeutic effect of treatment. Based on our data, it seems that the window of opportunity for significant benefit from primary IT DEX is less than 3 weeks.

Previous studies have also reported a significant effect of treatment delay on response to IT DEX (10,19,39). Battaglia et al. (10) looked at patients treated with a combination of IT DEX at 12 mg/mL and concurrent prednisone versus prednisone alone. For both treatment groups, those treated within 7 days of onset had significantly better hearing outcomes than those initiating treatment after 7 days. The effect was more pronounced in the group that received combination therapy.

Reported rates of adverse events for IT steroid injections have been very low. Three retrospective studies specifically examining IT DEX at a concentration of 24 mg/mL found no significant long-term adverse events (19–21). For the combined 251 patients in the three studies, only three adverse events were reported. Two patients (0.8%) developed tympanic membrane perforation that resolved with simple office treatment. Another patient developed tongue paresthesia that resolved spontaneously within 2 weeks.

The most rigorous prospective evaluation of side effects of IT steroid injection was performed as part of the multicenter trial by Rauch et al. (9) in 2011. Methylprednisolone at a concentration of 40 mg/mL was used in this study. The most common significant adverse events were otitis media in 4.7% of patients and persistent tympanic membrane perforation in 3.9%. The rate of adverse events in our study was also low, and there was no dose-dependent relationship observed. The use of phenol may increase the risk of developing a perforation after IT DEX injection, although this study was underpowered to identify a significant effect. As others have suggested (40), we feel that careful application of a minimal amount of phenol results in excellent anesthesia of the tympanic membrane with a low risk of perforation.

The relatively small sample size and retrospective nature of the study are limitations that should be recognized. The retrospective nature of this study could be problematic if outcome was influenced by an environmental factor that fluctuated during the period of the study. For example, the prevalence of a causative virus in the community could vary with time and influence outcomes if an ''outbreak'' occurred during the time one particular treatment was being offered. The failure to find significant effects of predictor variables may be caused by insufficient statistical power, especially in the multivariate analyses. Also, the incomplete data regarding other variables that can influence outcome such as vertigo are limitations. However, we feel that this preliminary retrospective study provides important data that can be used to help guide the design of a larger prospective trial.

CONCLUSION

This study provides the first demonstration of superiority of IT DEX at 24 mg/mL for the treatment of ISSNHL, with significantly better recovery of PTA compared with 10 mg/mL. Our data suggest that treatment should be initiated as soon as possible to attain the best outcome. A prospective randomized trial to confirm the optimal dose is warranted.

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