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Intratympanic injection of dexamethasone 4 mg/mL versus 10 mg/mL for management of idiopathic sudden sensorineural hearing loss

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Abstract

Background: The aim of this study was to determine whether different concentrations of intratympanic (IT) injection of dexamethasone at a dose of 4 and 10 mg/mL have an effect on hearing outcomes in patients with idiopathic sudden sensorineural hearing loss (ISSNHL).

Results: Our study was conducted on 30 adult patients with unilateral ISSNHL who failed to respond or with contraindications to systemic steroids. Patients were categorized into two groups; each one included 15 patients. IT injection of 4 mg/mL dexamethasone was done in one group (IT dexamethasone (Dex) 4 mg/mL), while 10 mg/mL dexamethasone was administered intratympanically in the other group (IT Dex 10 mg/mL). IT injection was performed twice weekly for two successive weeks. PTA thresholds were assessed at 0.5, 1, 2 and 4 kHz before and 1 month after the treatment.
In the group with IT Dex 10 mg/mL, the average PTA improved significantly from 75.50 ± 12.59 to 49 ± 24.04 dB with an average gain of 26.50 ± 14.25 ($p = 0.0007$). In the group with IT Dex 4 mg/mL, there was a significant change of PTA from a pretreatment value of 76.92 ± 11.89 dB to a post-treatment value of 59.27 ± 92.10 dB with an average gain of 17.65 ± 8.36 dB. A comparison of the post-treatment gain of PTA in both groups showed better improvement of hearing in a group treated by IT Dex 10 mg/mL compared with 4 mg/mL.

Conclusion: This study demonstrated that IT injection of dexamethasone at a dose of 10 mg/ml was associated with better hearing outcomes compared with 4 mg/mL for the treatment of ISSNHL.

Keywords: Sudden hearing loss, Intratympanic injection, Dexamethasone

Background

Sudden sensorineural hearing loss (SSNHL) is one of the most serious otologic emergencies that may have a deleterious and permanent effect of quality of life [1].

The annual incidence of SSNHL is highly variable ranging from 5 to 27 per 100,000 in the USA and up to 160 per 100,000 in Germany [2, 3].

SSNHL is usually defined as a rapid deterioration of hearing of 30 dB or more at three successive frequencies over 3 days or less [4]. The condition may be accompanied by tinnitus and vertigo. Vertigo usually resolves spontaneously, while tinnitus may persist resulting in a great influence on the patient's life [5, 6].

The cause of SSNHL is idiopathic (ISSNHL) in 70% of cases, and its pathogenesis may be elucidated by two main theories: vascular and viral theories [4].

Reviewing the literature shows that ISSNHL is spontaneously resolved in 30–64% of patients; however,

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clinical experience shows that these numbers may be optimistic [7].

The recovery of ISSNHL depends on various factors including age, degree of hearing loss, the characteristic pattern of audiometry, the time between the disease onset and initiation of the treatment, the associated symptoms like vertigo and concurrent diseases like DM and hypertension [8].

Treatment modalities of ISSNHL include steroids, antiviral medication, vasodilator and hyperbaric oxygen [9]. However, steroid therapy whether systemic or intratympanic is the most common modality used for the management of ISSNHL [9–14].

Intratympanic (IT) injection of steroids is used to achieve a very high concentration of steroids inside the inner ear fluids with negligible systemic absorption and consequently, it is indicated in conditions where systemic steroids cannot be utilized [15].

Dexamethasone and methylprednisolone are the two main steroid preparations used for IT injection in SSNHL. Methylprednisolone is less commonly used than dexamethasone. The concentration of dexamethasone varies significantly from 4 to 24 mg/mL and this may add to the heterogeneity of hearing outcomes of the studies about the effectiveness of IT injection of corticosteroids [16–21].

The study was an attempt to determine whether different concentrations of IT injection of dexamethasone (4 versus 10 mg/mL) have an effect on hearing outcomes in patients with SSNHL.

Methods

Our study was conducted on 30 adult patients who attended the outpatient clinic from July 2016 to July 2019 with unilateral ISSNHL who failed to respond or with contraindications to systemic steroids.

The procedure was clarified to all patients, and a written agreement was obtained from each patient. The ethical committee in our institution agreed on this work.

All patients were fulfilling the next criteria:

- SSNHL of at least 30 dB over three frequencies occurring within 72 h
- Free magnetic resonance imaging to exclude retrocochlear lesions
- No history of endolymphatic hydrops, autoimmune hearing loss, no otologic trauma, or other causes of SNHL
- The duration between the IT injection and onset of ISSNHL was less than 4 weeks.

Patients were categorized into two groups; each one included 15 patients. IT injection of 4 mg/mL dexamethasone (Amriya Pharmaceuticals, Egypt) was done in one group (IT dexamethasone (Dex) 4 mg/mL), while 10 mg/mL dexamethasone (manufactured by West-ward pharmaceuticals, USA) was administered intratympanically in the other group (IT Dex-10 mg/mL).

Technique of IT injection

Local anaesthesia of the tympanic membrane was performed by the application of a cottonoid soaked with Emla cream 5% or xylocaine 10% spray to the tympanic membrane for 30 min. The IT injection was done with the aid of 0°, 4-mm sinuscope.

Patients were positioned in a supine position, with their head rotated to the contralateral ear. One tiny hole was done at the anterosuperior quadrant of the tympanic membrane as a ventilation hole to let air to escape from middle ear during injection, followed by IT injection just below the ventilation hole using a 25-gauge spinal needle, and dexamethasone was kept in contact with the round window for 30 min. Patients were instructed to avoid swallowing and speaking for 30 min.

The intratympanic injection was performed twice weekly for two successive weeks with an overall series of 4 injections.

Audiological evaluation

The hearing was assessed by calculation pure tone average (PTA) thresholds at 0.5, 1, 2 and 4 kHz before and 1 month after the treatment. Changes in PTA were calculated by subtracting pretreatment from post-treatment PTA values. Significant improvement of the hearing was defined as an improvement of PTA equal to or more than 20 dB.

Statistical analysis

All statistical analysis was calculated using GraphPad Prism program, version 5 for Windows (GraphPad Software, San Diego, CA, USA). Comparison between pre and post-treatment hearing results was done using the Student *t* test. Fisher exact test was used for categorical comparison between the groups.

All statistical analysis was considered statistically significant at p value < 0.05.

Results

Patients characteristics

The age of patients ranged from 45 to 70 years (56.83 ± 8.77) in the group with IT Dex 4 mg/mL, while it ranged from 40 to 65 years (53.46 ± 7.18) in the other group with IT Dex 10 mg/mL. No significant differences were present between the two groups regarding age, gender, associated symptoms and duration between onset of SSNHL and first IT injection (Table 1).

Table 1 Distribution of patients according to age, gender, associated symptoms and onset of IT injection

	IT Dex 4 mg/mL (*N* = 15)	IT Dex 10 mg/mL (*N* = 15)	*p* value
Age (Mean ± SD years)	56.83 ± 8.77	53.46 ± 7.18	0.2741 (NS)
F/M	8/7	6/9	0.7152 (NS)
Days to IT injection	18.73 ± 5.26	19.35 ± 3.87	0.6387 (NS)
Associated symptoms			
Vertigo	4 (26.67%)	3 (20%)	1.00 (NS)
Tinnitus	10 (66.67%)	11 (73.34%)	1.00 (NS)

Fisher's exact test was used for comparison of the difference in proportions. Means were compared with *t* test
p value > 0.05, statistically not significant (NS)

Hearing results

The pretreatment, post-treatment and gain of PTA were shown in Table 2. The mean preoperative PTA (0.5, 1, 2 and 4 kHz) was 76.92 ± 11.89 dB in IT Dex 4 mg/mL group, while it was 75.50 ± 12.59 dB in the group with IT Dex 10 mg /ml. Pretreatment PTA values showed no statistically significant difference between both groups (p = 0.7536, t test).

In the group with IT Dex 10 mg/mL, the average PTA improved significantly from 75.50 ± 12.59 dB to 49 ± 24.04 dB with an average gain of 26.50 ± 14.25 dB (p = 0.0007, t test).

In the group with IT Dex 4 mg/mL, there was a significant change of PTA from a pretreatment value of 76.92 ± 11.89 dB to post-treatment value 59.27 ± 19.10 dB with an average gain of 17.65 ± 8.36 dB (p = 0.005, t test).

Comparing the post-treatment gain of PTA in both groups revealed a significant improvement of the hearing in a group treated by IT Dex 10 mg/mL compared with IT Dex 4 mg/mL (p = 0.047).

A clinically significant improvement of the hearing (defined as a gain of PTA equal or more than 20 dB) was achieved in 9/15 patients (60%) in the IT Dex 10 mg/mL group compared with 6/15 patients (40%) in the IT Dex 4 mg/mL group. However, this difference was not statistically significant (p = 0.464, Fisher's exact test).

If we define a significant hearing improvement as a gain of PTA equal or more than 30 dB, there was a significant improvement in 6/15 of patients (40%) in IT Dex 10 mg/mL group versus 2/15 patients (13.33%) in IT Dex 4 mg/mL group, and this difference was also not statistically significant (p = 0.2148, Fisher's exact test)

Factor related to significant hearing improvement

Significant improvement of hearing (gain ≥ 20 dB) was not statistically associated with age, gender, or associated symptoms; however, it was linked to early IT injection and less degree of hearing loss (Table 3).

Hearing improvement and relation to the time between of onset of SSNHL and IT injection

The average duration between onset of disease and IT injection was 16.20 ± 3.32 days in patients with improvement of PTA equal or more than 20 dB compared with 22.07 ± 3.67 days in patients with improvement of PAT less than 20 dB (p < 0.0001, t test), and therefore, early IT Injection of dexamethasone was significantly associated with better hearing outcome.

Hearing improvement and relation to the severity of hearing loss

The average pretreatment of PTA was 67.83 ± 8.49 dB in patients with improvement of PTA equal or more than 20 dB versus 84.58 ± 8.847 dB in patients with improvement of PAT of less than 20 dB (p < 0.0001, t test).The previous result showed a strong association between severe degree of pretreatment hearing loss and poorer hearing result following IT injection of dexamethasone.

Table 2 Pretreatment, post-treatment and gain of PTA in dB in both groups

PTA in dB	IT Dex 4 mg/mL (*N* = 15)	IT Dex 10 mg/mL (*N* = 15)	*p* value
Pretreatment	76.92 ± 11.89	75.5 ± 12.59	0.7536 (NS)
Post-treatment	59.27 ± 19.10	49 ± 24.04	
Improvement	17.65 ± 8.36	26.50 ± 14.25	0.047[#]
Gain of PTA ≥20	6/15 (40%)	9/15 (60%)	0.215 (NS)

Proportions were compared with Fisher's exact test. Means were compared with *t* test
p value > 0.05, statistically not significant (NS)
[#]*p* value < 0.05 statistically significant

Table 3 Factors related to significant improvement of hearing (PTA gain ≥ 20 dB)

	PTA gain ≥ 20 dB	PTA gain < 20 dB	*p* value
Age (years)	55.13 ± 8.40	54.93 ± 7.93	0.9470 (NS)
F/M	6/9	8/7	0.7152 (NS)
Duration till IT injection (days)	16.20 ± 3.32	22.0 ± 3.67	< 0.0001[#]
Pretreatment PTA (dB)	67.83 ± 8.49	84.58 ± 8.847	< 0.0001[#]
Vertigo	2 (13.33%)	5 (33.33%)	0.6722 (NS)
Tinnitus	12 (80%)	9 (60%)	0.4270 (NS)

Proportions were compared with Fisher's exact test. Means were compared with *t* test
p value > 0.05, statistically not significant (NS)
[#]*p* value < 0.05 statistically significant

Discussion

Itoh introduced Intratympanic injection of steroids for the treatment of Meniere's disease in 1991 [22]. Silverstein et al. was the first one who performed Intratympanic steroids for SSNHL in 1996 [23].

The precise basis of improvement of hearing in SSNHL after administration of steroids is still unknown; however, steroids may mediate their actions through anti-inflammatory effect, modulation of the immune system inside the inner ear, improved microcirculation of inner ear, antioxidant effect and their role in ions and water homeostasis [24].

Parnes et al. in a study about the pharmacokinetics of corticosteroids in the inner ear showed that steroids delivered intratympanically achieved a very high concentration in perilymph as compared with intravenous or oral administration [15].

IT injection of steroids is generally used according to the following protocols: as initial therapy without systemic administration of steroids, simultaneous systemic and intratympanic injection, or salvage therapy after the failure of systemic steroids [25, 26].

Crane et al. in a recent meta-analysis concluded that IT and systemic steroids as initial therapy had no substantial effect on the recovery of SSNHL, while steroids as salvage treatment had a positive effect [27]. This conclusion was based on 6 studies: Two of these studies used IT methylprednisolone, and IT injection of dexamethasone was used in the remaining four studies. Three out of 4 studies showed no beneficial effect of IT dexamethasone at a dose of 5 mg/mL [28–30]. IT dexamethasone at 12 mg/mL was used in the fourth study and had a significant improvement in the hearing [31].

Clinical practice guideline developed by the American Academy of Otolaryngology encourages the use of IT injection of steroids, either alone or with concomitant hyperbaric oxygen as rescue therapy for patients with partial recovery of hearing following any initial management for SSNHL [7].

Multiple meta-analyses of RCTs have reported a significant effect of IT injection of steroid as salvage treatment in the SSNHL [20, 27, 32].

Spear and Schwartz in the systematic review reported that IT injection of steroids for salvage treatment of SSNHL demonstrated a positive effect in most studies [33].

Many RCTs reported that salvage IT steroid therapy is associated with better hearing outcomes [19, 34–36]. However, Plontke et al. [37] showed that IT injection of steroids as a rescue treatment for SSNHL had non-significant value on hearing recovery. The critical point of the previous study is that the number of patients was limited to identify a statistical difference.

In this study, comparison of the pretreatment and post-treatment hearing results showed statistically substantial improvement of PTA following IT injection of dexamethasone in both groups. And these results were in agreement with most of the previous meta-analysis and RCT studies. The hearing improved from 76.92 to 59.27 dB in IT Dex 4 mg/mL group, while it was improved from 75.50 to 49 dB in IT Dex 10 mg/mL group.

Despite the popularity of IT injection of steroids since first being used in 1996 [7], there is no consensus regarding the most effective dose of steroids used for IT injection. On reviewing the published studies, the dose of dexamethasone used for IT injection ranged from 4 mg to 40 mg/mL [33]. Commercial availability of dexamethasone is the factor which determines the dose selection of dexamethasone rather than the scientific background [38].

Fu et al. reported in his animal study that dexamethasone doses of 10 mg/mL and 20 mg/mL led to a higher concentration inside inner ear tissues that persisted for a longer duration in comparison with 5 mg/mL dexamethasone. However, there was no significant difference between 10 mg/mL and 20 mg/mL groups [25].

As the concentration of dexamethasone inside the fluid of the inner ear is dose-dependent, many researchers used higher doses of dexamethasone for IT injection. Battaglia et al. demonstrated that ISSNHL patients treated with IT dexamethasone combined with high-dose systemic steroids had better hearing than those treated with systemic prednisolone alone. In these

studies, a higher concentration of dexamethasone at10–12 mg/mL was administered. In 2007, Haynes et al. showed that intratympanic injection of 24 mg/mL dexamethasone before 6 weeks from the onset of disease had a significant value on the improvement of hearing in patients with ISSNH [18]

Alexander et al. studied retrospectively the effect of different concentrations of IT dexamethasone (10 mg/ml versus 24 mg/mL) in addition to concomitant systemic steroids on hearing results in patients with ISSNHL. He achieved a better improvement of hearing (greater than 30 dB) in patients treated with 24 mg/mL dexamethasone compared with those treated with 10 mg/mL dexamethasone [38].

However, by 2004, 24 mg/mL dexamethasone was not commercially available in the market [24].

The objective of this work was to compare the hearing results after IT injection of dexamethasone at a dose of 4 mg/mL versus 10 mg/mL. This work revealed a statistically significant improvement of average PTA over (0.5, 1, 2 and 4 kHz) in patients treated with IT injection of 10 mg/ml dexamethasone compared with 4 mg/mL. The gain of PTA was 26.5 dB in IT Dex 10 mg/mL group versus 17.65 dB in IT Dex 4 mg/mL group.

In this work, a significant hearing improvement (≥ 20 dB) was found in 9/15 of patients (60%) in IT Dex 10 mg/mL group versus 6/15 (40%) patients in IT Dex 4 mg/mL group. In spite of the clear difference between both concentrations in achieving significant improvement of hearing, this result was not statistically significant and this result may be due to the small number of patients included in this study.

The time between the onset of SSNHL and IT injection is a critical issue. The importance of early IT injection of steroids and its significant influence of hearing recovery had been reported by many researchers [39, 40].

Battaglia et al. 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 1 week of onset of SSNHL had significantly better hearing recovery compared with those initiating treatment after the first week [39]. This was consistent with our results that showed that early IT injection was associated with a better prognosis,

It was found that the degree of pretreatment hearing loss had a statistically significant effect on hearing recovery following IT injection of dexamethasone as a significant improvement of hearing (gain ≥ 20 dB) was associated with less degree of hearing loss 67.83 dB versus 84.58 dB in patients with improvement of hearing of less than 20 dB. Severe loss of hearing has been shown in several studies to have poorer recovery rates [18, 40, 41].

Conclusion

This study showed that IT injection of dexamethasone at a dose of 10 mg/ml was associated with better hearing outcomes compared with 4 mg/mL for the treatment of ISSNHL.

Good hearing outcomes following IT injection of dexamethasone for the management of ISSNHL was statistically associated with early intervention and less degree of pretreatment hearing loss.

Abbreviations

IT: Intratympanic; Dex: Dexamethasone; ISSNHL: Idiopathic sudden sensorineural hearing loss

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Authors' contributions

YS: Contributions to the conception and design of the work; the acquisition, analysis and interpretation of data; drafted the work, revised it and approved the submitted version; and agreed both to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved and the resolution documented in the literature. SA: Contributions to the conception, substantively revised it and approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved and the resolution documented in the literature.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ethical committee of Faculty of Medicine, Alexandria University, Egypt, approved this work (ethical number 00007652) and written consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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