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Comparison of efficacy between two doses of dexamethasone as an intratympanic injection in Idiopathic Sudden Sensorineural Hearing Loss

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Abstract---Introduction: Most cases of sudden sensorineural hearing loss (SSHL) are idiopathic, so there is no specific treatment protocol for this set of patients, which is accepted worldwide. Some temporal bone studies regarding histopathological findings in SSHL cases found that most of the lesions were in the cochlea and its structures. The histological findings suggest that some inflammatory, vascular or immunological aetiology are present behind such lesions in cochlea. Inflammation being one of the major among all the aetiologies, so steroids are the mainstay of treatment for Idiopathic sudden sensorineural hearing loss (ISSHL) cases. Material and methods: A prospective comparative study was done on 56 patients aged 18 to 70 years. Patients received 4mg/ml dose (Arm A) or 8mg/ml dose (Arm B) of intratympanic dexamethasone injection. The targeted recovery on 5th day after 1st intratympanic steroid injection was compared with baseline Pure tone Audiometry (PTA) of day 1 for both the groups. Statistical analysis: More than 20db improvement in PTA average (0.5K, 1k and 2k) on assessment at 5th day after 1st injection was considered as recovery criteria. A comparison was done on improvement between two arms. Statistical analysis was calculated using MINITAB, version 17 for Windows. Comparison between pre and post-treatment hearing results was done using the Student t-test. Conclusions: Data suggested that the efficacy of 4mg/ml or 8mg/ml dexamethasone ITS injection as only treatment modality for ISSHL is similar. It is an office-based quick procedure with minimal transient adverse events and can save patients from permanent hearing loss in

ISSHL as well as from side effects of systemic steroids. The improvement depends on the time gap between onset of symptoms and first injection, severity of the hearing loss and technique of giving an injection. Still, further scope exists to study and compare the efficacy of higher doses of dexamethasone.

Keywords---dexamethasone, intratympanic injection, idiopathic, Sudden Sensorineural Hearing Loss.

Introduction

Sudden sensorineural hearing loss (SSNHL) is most often defined as a sensorineural hearing loss of 30dB or greater over at least three contiguous audiometric frequencies occurring over 72 hr¹. Estimates of incidence range from 11 to 77 per 100,000 people per year. The male to female ratio for incidence is 1.07:1². The suspected aetiologies for patients suffering sudden sensorineural hearing loss included idiopathic (71.0%), infectious disease (12.8%), otologic disease (4.7%), trauma (4.2%), vascular or hematologic (2.8%), neoplastic (2.3%), and other causes (2.2%)³. Most cases are idiopathic, so there is no specific treatment protocol for this set of patients, which is accepted worldwide. Some temporal bone studies regarding histopathological findings in SSNHL cases found that most of the lesions were in the cochlea and its structures.^{4,5} The histological findings suggest that some inflammatory, vascular or immunological aetiology are present behind such lesions in cochlea, which cause sudden sensorineural hearing loss. Inflammation being one of the major among all the aetiologies, so steroids are the mainstay of treatment for Idiopathic sudden sensorineural hearing loss (ISSHL) cases. Steroids are believed to reduce inner ear inflammation and autoimmune response and be beneficial for nerve function recovery. Steroid receptors have been found in the inner ear and may explain why steroid therapy is effective.

To treat these cases, steroids are given by various routes, oral, intravenous or intratympanic. Intratympanic steroids are preferred over systemic steroids to avoid systemic side effects.^{6,7} Intratympanic steroids (ITSs) may treat ISSHL more effectively than oral/systemic steroid⁸⁻¹⁵. ITSs usually includes dexamethasone and methylprednisolone.^{16,17} Despite the plethora of citations in various journals about intratympanic steroids in ISSHL, there is no single treatment protocol regarding dose, frequency and a total number of injections which is universally accepted and followed by most clinicians. During Covid time, we got an opportunity to avoid systemic steroids and treat patients of ISSHL with only ITSs. We share our review on the comparison of efficacy between two doses of dexamethasone, 4mg/ml and 8mg/ml, as ITSs in 56 cases.

Intratympanic steroid and inner ear fluid dynamics

When steroids are given by intratympanic injection, it provides high drug concentrations to inner ear tissues. Three prerequisites to succeed with its treatment: (1) Delivery method should be safe and reliable, and it is essential to replace the air bubbles around the round window membrane with the drug

solution. (2) Providing sequential or continuous drug administration is essential to achieve sufficient concentration of the drug in the target areas of the cochlea. (3) The method should be of short duration, simple as well as painless.

The inner ear is anatomically a complex organ containing spaces (scalae) filled with fluid. Each room has multiple interfaces with other areas and different compartments, including the middle ear space and the systemic blood circulation. Perilymph fills scala tympani and scala vestibule, which has characteristics of extracellular fluid, like low potassium and high sodium concentrations. Endolymph fills scala tympani, a fluid high in potassium and a relatively high positive charge. According to recent studies, inner ear fluids do not circulate significantly and are not actively stirred. So, when the drug is applied locally to the round window membrane, it enters the ear slowly by passive diffusion. The physical properties of the diffusing molecules decide the rate at which the drug will spread, and the most crucial property is the molecular weight. Round window is semipermeable membrane as proved by animal experiments. Clearance of drugs, which expresses the rate of removal of drugs from the inner ear fluids into the circulation, determines drug concentration in the inner ear. With the intratympanic application, large drug concentration gradients can occur, resulting in higher levels of drug near the round window, with diminishing concentrations in atypical locations in the inner ear.¹⁹ The most commonly used steroid for intratympanic injection is dexamethasone^{13,14,20-25} followed by methylprednisolone.^{6,14,26-30} There are variable strengths for the solution (2-4 mg/mL^{13,22} to 25 mg/mL dexamethasone¹⁴; 32 mg/mL²⁹ to 62.5 mg/mL methylprednisolone²⁶⁻²⁸) Depending on the middle ear volume 0.5ml is the right amount of the fluid to inject.

Benefits of Intratympanic steroid

OPD procedure

Quick and painless

Less cost

It can be used in patients where systemic steroids are unsafe and contraindicated

Directly give steroids into a round window for a quick and safe supply to cochlea

Side effects/complications are uncommon

Adverse Events

Pain

Otitis media

Tympanic membrane perforation

Vertigo (usually temporary)

Tinnitus (very rare)

Material and Methods

A prospective comparative study was done on 56 patients aged 18 to 70 years from March 2020 to May 2021 who presented in our institution either walk-in or through referrals from locally informed doctors and audiologists about the research. The inclusion and exclusion criteria for selecting study group in Arm A

(Dexamethasone 4mg/dl dose for ITS injection) and ArmB (Dexamethasone 8mg/dl dose for ITS injection) are similar and given in Table 1.

Table 1 Inclusion And Exclusion criteria
<p>Patients with complaints of unilateral sudden hearing loss in last 3 days were proved as a sensorineural hearing loss with at least 30db loss over 3 frequencies.</p> <p>No evidence of retro cochlear disease as proved by MRI.</p> <p>Not associated with vertigo</p> <p>No history of using any ototoxic drug in last 3 weeks.</p> <p>No history of taking systemic steroids for any reason after the SSSL</p> <p>No history of symptoms or findings on examination suggestive of acute or chronic otitis media.</p> <p>No history of recent barotrauma or head trauma</p> <p>No record of exposure to radiation</p> <p>Pregnant females were excluded from study</p> <p>Patients with active autoimmune disease on medication were excluded</p> <p>Patients with presbycusis were excluded</p> <p>Patients with facial palsy or bell palsy were excluded.</p>

In this 14 months-long study, 6 patients were lost to follow-up, so out of the remaining 50 cases, 25 patients received 4mg/ml dose (Arm A), and the other 25 received 8mg/ml dose (Arm B) of intratympanic dexamethasone injection. All the patients were given injections within 4 weeks of the onset of symptoms. Depending on case to case total of 3 to 5 injections were given with an interval of 5 days between two doses. But for our study, we are using the first two assessments for both the study arms.

Schedule of audiometric assessment

S.no	Time for assessment
1 st	On the day of 1 st dose before the injection
2 nd	5 th day after 1 st dose

Technique of Intratympanic steroid injection

The patient is positioned supine with around a 15-degree head up. A cotton ball soaked in 4% lignocaine is kept over the tympanic membrane for 2 to 3 minutes for anaesthesia. After removing the cotton, the EAC (External Auditory Canal) is suctioned to clean any drop of lignocaine. Injection Dexamethasone sodium phosphate is available in liquid formulation in a 2ml glass vial in various doses; in our study, we used 4mg/ml and 8mg/ml. The injection is loaded in an insulin syringe with a removable needle. After loading the injection, the needle is changed to a 26 gauge, 1.5-inch long needle and bent to around 30 degrees for better visualization while inserting the needle in EAC. This procedure can be done by using either an oto-endoscope or a microscope. Slowly penetrate the needle through tympanic membrane in anterosuperior or anteroinferior quadrant of tympanic membrane and slowly deliver around 0.5 ml of injection in middle ear. After injecting, turn head towards unaffected ear around 45 degrees with support

of pillow and instruct patient to close eyes and do not swallow saliva. Remain in this position for around 10 minutes. After 10 min, add two drops of Ciprofloxacin ear drops in EAC as a single stat dose to avoid infection. Use a small gauge needle (26 gauges) to prevent infection or pinpoint perforation, use long needle for better visualization. While injecting, keep your hands and patient's head still to avoid any type of injury to the middle ear and tympanic membrane. Reach TM with a slow, steady hand without touching EAC with a needle, as a small blood clot can act as a good source of bacteria to grow.

Statistical analysis

More than 20db improvement in pure-tone average (0.5K, 1k and 2k) on assessment at 5th day after 1st injection was considered as recovery criteria. A comparison was done on improvement between two arms. All statistical analysis was calculated using MINITAB, version 17 for Windows. 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 a p-value < 0.05.

Results

According to inclusion and exclusion criteria, we selected 56 patients, but 6 cases lost to follow-up visits. Out of the rest 50 cases, there were 31 (62%) men and 19 (38%) women. Targeted Improvement for our study is 20db from baseline PTA, 5 days after 1st dose. We took an average of 0.5K, 1K and 2K frequencies in Pure Tone Audiogram readings.

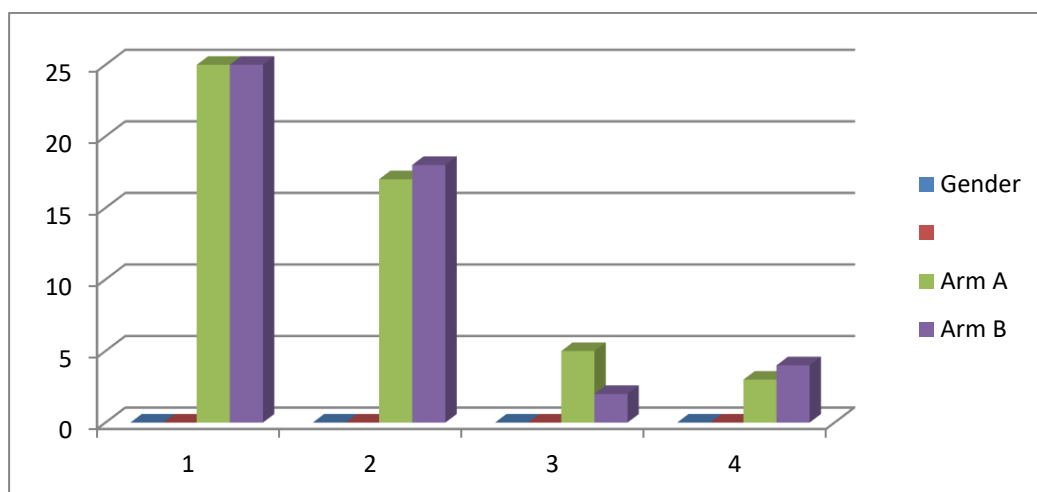
Arm A recovery

In arm A, 4mg/ml dose of dexamethasone was the drug of choice. Out of 25 patients, 17 (68%) showed more than 20 dB improvement in PTA. Among the rest 8 cases (32%) in arm A, 5 (20%) showed no improvement after the first dose, and the other 3 (12%) showed 7dB, 10dB and 12dB improvement in PTA.

Arm B recovery

In arm B, 8mg/ml dose of dexamethasone was the drug of choice. Out of 25 patients, 18 (72%) showed more than 20dB improvement in PTA. Among the rest 7 cases (28%) in arm B, 4 (16%) showed no improvement after the first dose, and the other 2 cases showed 10 and 12 dB improvement in PTA, Table 2 and Fig 1.

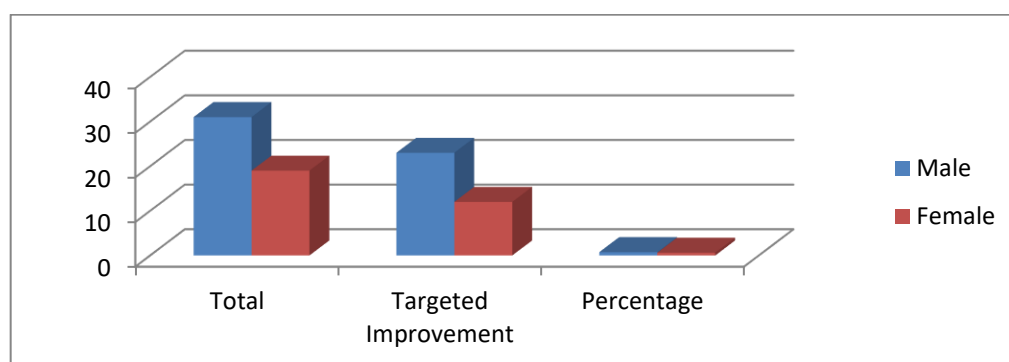
Gender	Total Cases	Cases with Targeted Improvement of 20db	Cases with Less than 20db Improvement	Cases with No Improvement
Arm A	25	17	5	3
Arm B	25	18	2	4



Gender-related recovery

Among men 23 out of 31 showed Improvement with overall recovery of 74% in men, and for women, 12 out of 19 overall recovery was 63%. Table 3 and Fig 2.

Gender	Total	Targeted Improvement	Percentage
Male	31	23	74.2%
Female	19	12	63.2%

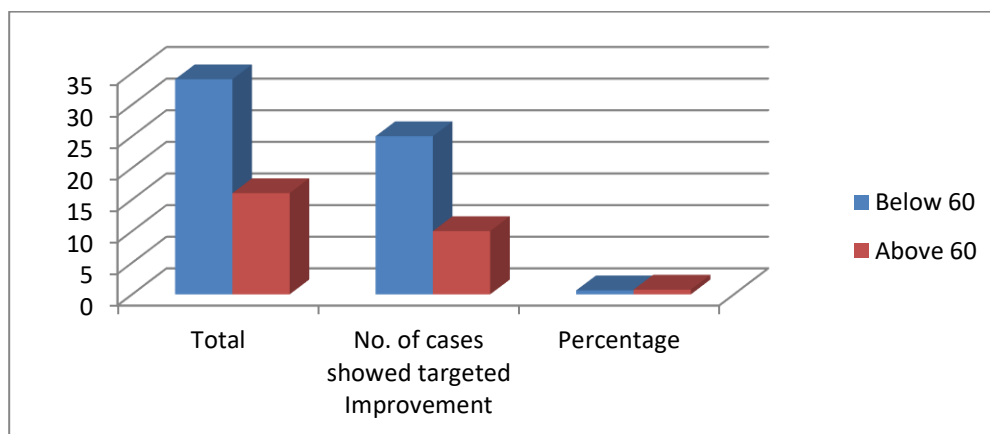


Age-related recovery

In our study 16 (32%) cases were above 60 years of age with overall recovery of 62.5% and 34 (68%) cases were below 60 years with overall recovery of 73.5%

Table 4

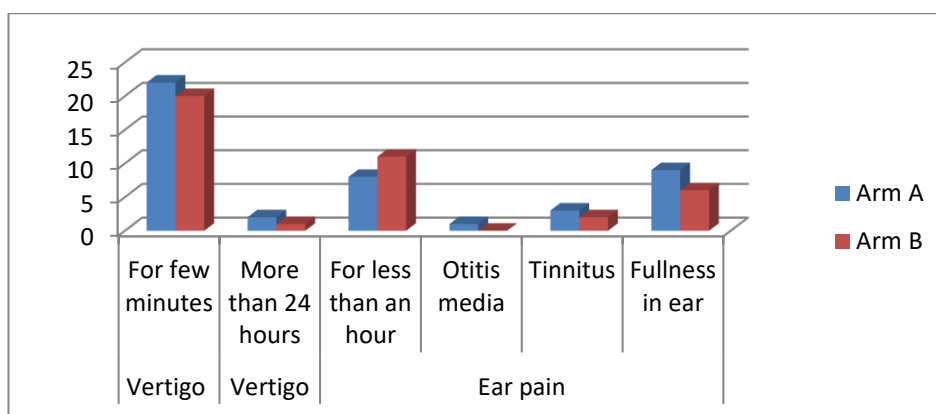
Age	Total	No. of cases showed targeted Improvement	Percentage
Below 60	34	25	73.5%
Above 60	16	10	62.5%



Adverse Events

There were mild adverse events; the most common was vertigo, which persisted for 40 seconds to a few minutes. Very rarely patients have vertigo for more than 24 hours and need medication. Fullness in-ear and ear pain were the other two adverse events that were transient for 1 to 3 days and subsided spontaneously without the need for medication. Tinnitus and Otitis media were the minor adverse events. As it is an office procedure, so chances of infection can be high. Maintaining sterility with every step of the process, adding two drops of Ciprofloxacin ear drops 10 minutes post-procedure can significantly reduce the chance of infection. Table 3 & Fig 4.

	Vertigo For few minutes	Vertigo More than 24 hours	Ear pain For less than an hour	Otitis media	Tinnitus	Fullness in ear
Arm A	22	2	8	1	3	9
Arm B	20	1	11	0	2	6



Discussion

The association between hearing impairment and dementia has emerged as a major public health challenge, with significant opportunities for earlier diagnosis, treatment and prevention. One of the extensive cohort studies with a sample size of 1000,000 individuals in Taiwan concluded that patients with SSHL were 1.39 times more likely to develop dementia than those without SSHL (95% confidence interval = 1.13-1.71). Women who were < 65 years of age with SSHL had the highest risk of developing dementia³² Cognitive decline is relatively faster, increasing the risk for cognitive impairment in patients with hearing loss(HL)³³. Midlife HL may be responsible for an average of 9.1% of dementia diagnoses worldwide.³⁴

Sudden hearing loss is considered a medical emergency that needs immediate attention and evaluation, including examination, audiological assessment and imaging. Among sensorineural hearing loss cases, in many cases HL can be reversed by comprehensive assessment and commencing treatment on time. As around 70 % cases of SSHL are Idiopathic and the maximum spontaneous complete recovery percentage is only 35% to 39%, as found by Mattox and Simmons and Nosrati-Zarenoewhich, which would make it straightforward for patients and physicians that treatment is warranted^{35,36} Systemic steroids have a positive effect on cochlear function. Some studies have proved to decrease inflammation in labyrinthitis with steroids,³⁷ increase cochlear blood flow,³⁸ helps protecting cochlear ischemia,³⁹ also protect against noise-induced HL,⁴⁰ and promote inner ear de novo protein synthesis.⁴¹ Studies have shown that the potential pathology in sudden HL is in stria vascularis, which maintains Na⁺/K⁺ secretion vital for maintenance of the endo cochlear potential⁴²

In many studies, it has been proved that there is no evidence of histologic changes suggestive of retro cochlear dysfunction after intratympanic steroid injection⁴³⁻⁴⁶ It increase cochlear blood flow,⁴³ prevents drill-induced noise trauma⁴⁴ helps in improving ion homeostasis necessary for cochlear function⁴⁶ and prevent aminoglycoside toxicity⁴⁷ Many studies showed the impact of various treatment modalities with steroids like using only systemic steroids (oral or parenteral), intratympanic steroids after failure of systemic steroids and combined treatment with systemic and intratympanic steroids, but very few studies are done on only intratympanic steroids as initial treatment.

Due to massive public awareness about impact of systemic steroids in Covid era and well-known medical facts about side effects of systemic steroids and the limitation of their use in many comorbidities, we should use intratympanic steroids as first line of treatment for Idiopathic Sudden Sensorineural hearing loss. Our study is one of the few studies with more than 40 patients with only Intratympanic steroids as initial treatment, comparing two doses of dexamethasone. Measures to avoid infection:

- Maintaining sterility with every step of the procedure,
- Adding two drops of Ciprofloxacin ear drops 10 minutes post-procedure
- Giving nasal spray, antibiotics, and anti-histaminic to selective patients with a history of allergic rhinitis or rhinosinusitis

- Keep hands steady while injecting to avoid touching the needle to External Auditory Canal (EAC). Touching EAC with a needle carry some microorganism from EAC skin to middle ear, secondly blood from EAC skin can act as a good culture for bacterial growth.
- In case of unhealthy EAC skin like dermatitis, dried fungal debris, Otitis externa with itching as only symptom, first clean the skin and apply steroid and antibiotic combination ointment and call patient next day to assess EAC if it is safe to give an injection.

Conclusions

Data suggested that the efficacy of 4mg/ml or 8mg/ml dexamethasone ITS injection as only treatment modality for ISSHL is almost same. It is an office-based quick procedure with minimal transient adverse events and can save patients from permanent hearing loss in ISSHL. The improvement depends on the time gap between onset of symptoms and first injection, severity of the hearing loss and technique of giving an injection.. Still, further scope exists to study and compare the efficacy of higher doses of dexamethasone.

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