

TITLE: Sudden Sensorineural Hearing Loss and Intratympanic Steroids

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Sudden sensorineural hearing loss (SSNHL) is relatively uncommon but may pose a significant problem for patients and a challenge for otolaryngologists. The acute loss of hearing can be quite devastating to patients and may affect the quality of life. SSNHL was first described in 1944 by DeKleyn but its etiology is still unclear. The incidence of SSNHL has been estimated as 5 - 20 per 100,000, with 4,000 new cases reported per year in the U.S. SSNHL is defined as an idiopathic disorder with sensorineural hearing loss of at least 30 dB over three contiguous frequencies on pure tone audiometry occurring acutely under 72 hours from initial onset. Some authors may define the sensorineural hearing loss of at least 20 dB. The spontaneous partial recovery rate has been documented from 32% - 79%, usually within two weeks of onset. Spontaneous complete recovery is present in 36%. Middle ear pathology is not present in SSNHL. SSNHL presents an otologic emergency as early therapy is critical to recovery.

Although the true etiology of SSNHL is not known, there are several theories documented with some evidence for each. Vascular injury may be involved in SSNHL as its presentation is similar to that of neurologic findings following acute cerebral infarct. In 1959, Perlman demonstrated the loss of cochlear microphonic 60 seconds after occlusion of the labyrinthine artery in guinea pigs. In addition, cases of sudden hearing loss have been documented in patients with various vascular occlusive disorders including Beurger's, macroglobulinemia, sickle cell, and fat embolism. Histopathologic changes in the cochlea caused by vascular occlusion in animal models resemble the changes from SSNHL. In guinea pigs, labyrinthine vessel occlusion lead to loss of spiral ganglion cells, mild to moderate damage to organ of Corti, and cochlear duct fibrosis. An additional theory for SSNHL is intracochlear membrane rupture, resulting in loss of endocochlear potential. In 1981, Gussen discovered evidence of this phenomenon. This theory has fallen out of favor. Finally, the most popular theory is viral etiology. 25% to 63% of patients with SSNHL have a temporal association with viral upper respiratory infection prior to onset of hearing loss. In addition, serology at the time of onset may confirm the presence of herpesvirus, varicella, cytomegalovirus, influenza, parainfluenza, rubeola, rubella, mumps, as well as other. In addition, there is immunoreactivity present against various viral agents which may cross-react with native antigens of the inner ear

similar to autoimmune inner ear disease. The histopathologic findings of human temporal bones also suggest viral infection such as atrophy of the organ of Corti, spiral ganglion and tectorial membrane as well as hair cell loss and unraveling of myelin. Animal experiments have confirmed that the inner ear may be penetrated by viral agents. It is likely that there is a combination of factors involved in the development of SSNHL.

The clinical presentation of SSNHL is acute onset hearing loss and mostly unilateral. Bilateral involvement may be present in up to 2% of these patients. The left side has been documented as having a slightly higher incidence (55%). The median age of onset is from 40 to 54 years, and there is equal distribution among men and women. Patients may present with a complaint of hearing loss when awakening from sleep, and hearing a “pop” in the affected ear just prior to hearing loss. Aural fullness, tinnitus, and vertigo may also be associated with the hearing loss and may be confused with the early presentation of Meniere’s disease.

The differential diagnosis of sudden hearing loss is extensive. Infectious causes may be bacterial due to meningitis, labyrinthitis, and syphilis or viral due to mumps and CMV. Inflammatory and autoimmune disorders such as Cogan syndrome, systemic lupus, and multiple sclerosis are also possible. Traumatic injury from temporal bone fracture, acoustic trauma, and perilymph fistula possibly due to underwater diving or exposure to high pressure may also result in acute hearing loss. Neoplastic disorders such as a cerebellopontine angle tumor, internal acoustic canal tumor, and metastasis to the temporal bone are possible. Toxicity from aminoglycosides, aspirin, and chemotherapeutic agents may also lead to sudden hearing loss. Vascular/hematologic causes may include thromboembolism, cerebral infarct, transient ischemic attack, sickle cell disease, and macroglobulinemia. In younger patients, congenital malformation such as Mondini malformation and enlarged vestibular aqueduct are known to result in hearing loss.

The diagnosis of SSNHL requires thorough investigation to determine any known causes of sudden hearing loss. First and most importantly, a thorough and detailed history provides the information necessary to determining the diagnosis of SSNHL. A complete head and neck exam with attention to the ear exam is also critical. Tuning fork testing, otoscopy and pneumotoscopy provide additional information. Audiologic testing with pure tone audiometry (PTA), speech reception threshold (SRT), and speech discrimination score (SDS) must be obtained to assess hearing. Tympanometry may also be useful if middle ear or Eustachian tube pathology is present. Auditory brainstem response and otoacoustic emission may also be obtained. An electronystagmogram (ENG) may provide additional data for patients that have signs and symptoms of a vestibular disorder. Radiographic study is advocated for patients with unilateral sensorineural hearing loss. An MRI with gadolinium is the best form of radiographic study to investigate IAC/CPA tumors. In younger patients, a CT of temporal bones is necessary to investigate for congenital malformations of the inner ear. Laboratory evaluation may also be necessary and includes CBC, electrolyte, erythrocyte sedimentation rate, autoantibodies (ANA, 68 kD antibody), rheumatoid factor, FTA-Abs to evaluate for syphilis, coagulation studies, thyroid function testing, and lipid profile.

The treatment of choice for SSNHL is systemic steroids, and may be initiated prior to completion of certain testing such as MRI and laboratory testing for autoantibodies. Steroids may be administered orally or IV, and depends on the experience of the institution. An

important factor of therapy is to initiate systemic steroids as early as possible. The greatest rate of recovery has been found in patients who are started within 2 - 4 weeks of onset of hearing loss. Historically, steroids were believed to reduce inner ear inflammation and allow recovery of hearing. Steroid receptors have been found in the inner ear may be a reason why steroid therapy is effective for some patients. However, patients with profound SSNHL tend to have a variable to poor response. Steroid therapy may not be possible for all patients. Diabetics, patients with peptic ulcers, TB, and glaucoma, and other systemic conditions may not be amenable to systemic steroid therapy. Intratympanic (IT) steroids may be a route of therapy for this population. Additional agents used with variable to no success include antivirals, volume expanders, vasodilators, anticoagulants, and carbogen inhalation.

SSNHL is a challenging disorder for the clinician. The true incidence may be higher than estimated as patients with spontaneous recovery may not present to their primary care physician or an otolaryngologist. In addition, patients may present beyond the early therapeutic window and hearing loss may not improve with steroid therapy. The etiology is still unclear as well the appropriate therapy directed to the causative mechanism of hearing loss. In a recently updated systematic review, there were only two prospective, double-blind, randomized, controlled trials that examined the role of steroids for idiopathic sudden sensorineural hearing loss.

The classic and best study evaluating the effectiveness of steroids SSNHL therapy was by Wilson in 1980. This was conducted in a prospective, double-blind, randomized, controlled manner in patients at two separate institutions with strictly defined parameters. Inclusion criteria included 30 dB loss in pure tones over at least 3 contiguous frequencies within 3 days of onset and normal laboratory findings. 67 patients were randomly selected to receive steroids or placebo and an additional group of 52 untreated patients were also included. Patients were stratified by the type of sensorineural hearing loss present by audiogram findings, and recovery was defined as partial, complete, or not present. The results of this study indicated that patients with midfrequency loss all recovered without steroids. Of the patients with profound hearing loss, 76% had no recovery, and 24% had partial recovery. There was no improvement noted in the steroid treated group. The group of patients with hearing loss from 40-85 dB had 78% recovery in the steroid treated group as opposed to 33% in the placebo treated group. The relative odds (RO) for recovery in the steroid versus placebo groups was 4.95:1; the RO for steroids versus untreated controls was 4.06:1; the RO for untreated controls versus placebo was 1.22:1; and the RO for steroid versus all controls was 4.39:1. Another finding from this study was that there was a lower incidence of vertigo in the midfrequency hearing loss group (14%) that had complete hearing recovery as opposed to 79% in the group with profound hearing loss. This study supported the trend that younger patients tended to have favorable outcomes. In addition, it indicated that steroid therapy has a distinct role in the therapy for SSNHL.

The other prospective, double-blind, randomized, controlled trial cited in the recent systematic review of steroid therapy for SSNHL was by Cinamon in 2001. Similarly, strict inclusion criteria were cited using at least 20 dB of loss on PTA over 3 contiguous frequencies. 41 patients were stratified by the type of hearing loss, and improvement was defined as an improvement in PTA of at least 15 dB. Patients were divided into four groups: prednisone (1mg/kg/day), placebo, carbogen inhalation (30 minutes/six times daily), and room air inhalation (30 minutes/six times daily). Carbogen is a mixture of 95% oxygen and 5% CO₂ shown to result in vasodilation of intracranial blood vessels using inhalation therapy. All patients received five

days of the corresponding therapy. The results of this study indicated overall improvement in PTA at follow up in 73% among all groups. 80% in the steroid group had improvement, 81% in the placebo group, 55% in the carbogen group, and 77% in the room air inhalation group. Although these results were not statistically significant, there were several trends present that supported previous findings. Those with low frequency loss had better improvement than those with high frequency loss. In addition patients without vertigo had better outcome than those with vertigo.

Intratympanic delivery of medication has become a mode of treatment for patients with various otologic disorders. In 1935, Barany has been cited to have used lidocaine for tinnitus. Schuknecht was among the first to use IT streptomycin for Meniere's disease. Recently, IT delivery of steroids has been examined in treating SSNHL. IT steroid therapy is administered to the round window niche/membrane in the middle ear to target the inner ear. There is little systemic absorption, which makes this form of steroid therapy for SSNHL ideal for patients unable to take systemic steroids. In addition, this provides a higher concentration of steroid to the end organ. The route of IT delivery may be via injection through the tympanic membrane, drops instilled through a pressure equalization tube in the tympanic membrane, continuously through a microcatheter, or perfusion through a MicroWick. In all cases aside from continuous slow perfusion, the patients head is kept in a position to allow maximal exposure of the steroid to the round window for 20 to 30 minutes. In addition to patients who are unable to tolerate systemic steroids, IT delivery may provide benefit in an attempt to salvage hearing in patients who do not respond to systemic steroids. Unfortunately, there are no prospective, double-blind, randomized, controlled trials evaluating IT steroids versus placebo against systemic steroids in the literature to date.

There are a limited number of studies examining the use of intratympanic steroids. An interesting study conducted by Shirwany in 1998 examined the effects of transtympanic steroid injection on cochlear blood flow, auditory sensitivity and histologic findings in guinea pigs. In this study, dexamethasone (4 mg/mL) was injected in through the anteroinferior portion of the TM with a 30 gauge needle. The results indicated a 29% increase in cochlear blood flow within 30 minutes of administration without a change in auditory sensitivity measured by ABR. Furthermore, the increase in cochlear blood flow was sustained for at least 1 hour. No histologic changes were present in the temporal bones of animals treated with IT dex.

In 1999, Parnes further advanced the role of steroids in therapy of SSNHL by examining the concentrations of hydrocortisone, dexamethasone, and methylprednisone in plasma, endolymph and CSF after these agents were administered orally, IV, and IT. The steroid concentrations were corrected for potency as dexamethasone is 26.7 times more potent than hydrocortisone, and methylprednisone is 5.3 times more potent than hydrocortisone. The greatest concentration of steroids in the perilymph and endolymph was found after administration via IT route. Of the steroids used, methylprednisone had the highest levels in the inner ear, and sustained higher levels for a longer period of time than the others. Parnes also documented 12 cases in which patients with SSNHL, not previously treated, had IT methylprednisone (40 mg/mL) or dexamethasone (2 mg/mL). The results indicated a 50% recovery rate overall, with 12.5% full recovery in the group treated with methylprednisone. Adverse events documented in this study included three patients who developed acute otitis media, which resolved after appropriate therapy.

In 2001, Gianoli published a prospective trial of IT steroid therapy for patients with SSNHL when oral steroids failed to improve hearing or when patients were unable to tolerate systemic steroids. Strict parameters were used in the study. IT steroids were administered through a PET after a posteroinferior tympanotomy and removal of adhesions over the round window niche endoscopically. Four applications of either methylprednisone (62.5 mg/mL) or dexamethasone (2 mg/mL) were placed over a 10 – 14 day period. The results indicated that 44% had improvement in PTA by an average of 15.2 dB at follow up. 48% had improvement of SRT with an average of 15 dB. 35% had improvement of SDS with average improvement by 21%. 4% had a worsening of SDS by 16%. When these patients were stratified by time of onset of SSNHL to therapy with 6 weeks as the cutoff period, there was no significance statistically of improvement in either group. When stratified by age, younger patients tended to have more favorable results than older patients. Finally, by separating the groups by the type of steroid administered, there was no statistical significance, but there was a trend for the methylprednisone group to have greater improvement than the dexamethasone group. There was one adverse event documented of otitis media, which resolved at follow up.

Kopke conducted a study in 2001 to evaluate IT steroid therapy via microcatheter continuous infusion for a small sample of patients with SSNHL refractory to oral prednisone therapy. The microcatheter was placed under general anesthesia after elevating a tympanomeatal flap to identify the round window niche and clear any obstructing adhesions. A 1.5 – 2.0 mm microcatheter was then placed into the niche and connected to a continuous infusion pump with methylprednisolone (62.5 mg/mL) delivered for 14 days at a rate of 10 microliters per hour. The results indicated that all patients treated within six weeks of onset had improvement in PTA scores, and 83% of these had improved SDS with 66% returning to normal hearing. There was no improvement the group treated after 6 weeks from onset. Lefebvre conducted a similar study in six patients in 2002 with similar promising results. Since this time, the FDA has removed this microcatheter from the market.

Silverstein developed another device used to deliver medication to the round window niche, which he called the MicroWick. This device is placed through a posteroinferior myringotomy with topical anesthetic. After the round window niche is identified, any obstructing adhesions removed with a pick, the MicroWick, measuring, 1mm diameter by 9mm length, is placed into the RW niche. A PET is then placed through the myringotomy while keeping the MicroWick within its lumen. Medication drops may then be instilled into the ear, allowing absorption and perfusion of the round window. Silverstein used the MicroWick for patients with SSNHL refractory to systemic steroids by perfusing dexamethasone (4 – 24 mg/mL). His results indicated an improvement at least 10 dB PTA in 23%, and 35% improvement in SDS by at least 15%.

Guan-Min in 2004 conducted a prospective, controlled trial studying the effectiveness of IT dexamethasone in patients with severe to profound SSNHL. Patients who were diagnosed with SSNHL were treated according to the protocol and those refractory to this regimen were selected for the study. The protocol included methylprednisone, nicametate, vitamin B complex, benzodiazepine, and carbogen inhalation. One group underwent therapy according to the protocol except for carbogen inhalation and steroid therapy. The other group received IT dexamethasone (4 mg/mL) delivered through a myringotomy at the posterior TM with a 22 gauge needle (0.4 – 0.7 mL), placed once weekly for three applications. The results indicated that 53% in the IT

dexamethasone group had improvement in hearing, and half of these had return to normal hearing. Only 7% had improvement in the control group. Additionally, the recovery for severe SSNHL was 44% and profound SSNHL was 9.5%. There was no statistical significance to age difference, sex, and treatment delay time. The side effects noted were vertigo and acne to IT dexamethasone.

Another study by Battista in 2005 also addressed the role of IT dexamethasone used concurrently with oral steroids for treating profound SSNHL in a sample of 25 patients. Systemic methylprednisolone (64 mg/day, tapered over 11 days) was administered along with IT dexamethasone (0.3 cc of 24 mg/mL) via 27 gauge needle. Four injections were given over a 14 day period. The results indicated that 8% returned to normal hearing and 12% partial hearing recovery. These patients were treated with 14 days. There was one patient with a perforated TM in the study, which was repaired with a paper patch. This study had indicated greater overall improvement in profound SSNHL when steroids were administered early both systemically and IT.

Recently, Xenellis published the results of another study examining the effects of IT steroids for SSNHL when initial systemic steroids failed. All patients were admitted within 20 days of onset of SSNHL. Patients were initially treated with prednisolone IV (1 mg/kg/day, tapered), acyclovir (4 g/day, 5 days), buflomedil (300 mg/day, 10days), and ranitidine. Patients in the treatment group were given IT methylprednisolone (40 mg/mL) with a 21 gauge needle, four times over 15 days. The results indicated that 47% treated with IT steroids had improvement in PTA of at least 10 dB. No controls improved.

SSNHL is a life-altering disorder for patients and can be a challenging disorder for otolaryngologists. It is an otologic emergency and required early therapy to save hearing. The best form of therapy continues to be systemic steroids. However, IT steroids may provide another means of treating this disorder. IT steroids may be most beneficial as primary therapy in patients unable to take to systemic steroid therapy. In addition, IT steroids may be attempted to salvage hearing in those who do not respond to systemic steroids. The complications of using IT steroids include TM perforation, vertigo, infection, and acne in the studies reviewed. IT steroids may be delivered in the outpatient setting in a variety of manners as examined in the studies. An important factor to be noted for a patient is that a 10 – 15 dB improvement in PTA may not subjectively provide enough improvement for that patient. Hearing graded initially as profound may only improve to severe to profound, yet speech discrimination scores may remain poor. These results must be tempered to the patient's sense of improvement. Appropriate counseling for the patient with an audiologist is important to optimize hearing, especially if the ear may be aided.

Bibliography

Rauch ST. Intratympanic steroids for sensorineural hearing loss. *Otolaryngol Clin N Am* 2004; 37:1061-74.

De Kleyn A. Sudden complete or partial loss of function of the octavus system in apparently normal persons. *Acta Otolayngol (Stockh)* 1944; 32:407-29.

Fetterman BL et al. Prognosis and treatment of sudden sensorineural hearing loss. *Am J Otology* 1996; 17:529-36.

Doyle KJ et al. Intratympanic steroid treatment: a review. *Otology and Neurotology* 2004; 25:1034-39.

Wilson WR et al. The efficacy of steroids in the treatment of idiopathic sudden sensorineural hearing loss. *Arch Otolayngol* 1980; 106:772-6.

Cinamon U et al. Steroids, carbogen or placebo for sudden hearing loss: a prospective double-blind study. *Eur Arch Otorhinolaryngol* 2001; 258:477-80.

Shirwany NA et al. Effect of transtympanic injection of steroids on cochlear blood flow, auditory sensitivity, and histology in the guinea pig. *Am J Otology*; 19:230-5.

Parnes LS et al. Corticosteroid pharmacokinetics in the inner ear: an animal study followed by clinical application. *Laryngoscope* 1999; 109:1-17.

Chandrasekhar SS et al. Dexamethasone pharmacokinetics in the inner ear: comparison of route of administration and use of facilitating agents. *Otolaryngol Head and Neck Surg* 2000; 122:521-8.

Kopke RD et al. Targeted topical steroid therapy in sudden sensorineural hearing loss. *Otology and Neurotology* 2001; 22:475-9.

Gianoli GJ et al. Transtympanic steroids for the treatment of sudden hearing loss. *Otolaryngol Head and Neck Surg* 2001; 125:142-6.

Banerjee A et al. The biology of intratympanic drug administration and pharmacodynamics of round window drug absorption. *Otolaryngol Clin N Am* 2004; 37:1035-51.

Lustig LR. The history of intratympanic drug therapy in otology. *Otolaryngol Clin N Am* 2004; 37:1001-17.

Seidman MD et al. Intratympanic treatment of hearing loss with novel and traditional agents. *Otolaryngol Clin N Am* 2004; 37:973-90.

Guan-Min H et al. Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. *Laryngoscope* 2004; 114:1184-9.

Light JP et al. Transtympanic perfusion: indications and limitations. *Curr Opin Otolaryngol Head and Neck Surg* 2004; 12:378-83.

Battista RA. Intratympanic dexamethasone for profound idiopathic sudden sensorineural hearing loss. *Otolaryngol Head and Neck Surg* 2005; 132:902-5.

Herr BD et al. Intratympanic steroid perfusion for refractory sudden sensorineural hearing loss. *Otolaryngol Head and Neck Surg* 2005; 132:527-531.

Slattery WH et al. Intratympanic steroid injection for treatment of idiopathic sudden hearing loss. *Otolaryngol Head and Neck Surg* 2005; 133:251-9.

Banerjee A et al. Intratympanic corticosteroids for sudden idiopathic sensorineural hearing loss. *Otology and Neurotology* 2005; 26:878-81.

Xenellis, J et al. Intratympanic steroid treatment in idiopathic sudden sensorineural hearing loss: a control study. *Otolaryngol Head and Neck Surg* 2006; 134:940-5.