ABSTRACT

Objective: Many studies over the last decade showed favorable outcomes with intratympanic (IT) steroid treatment, alone as salvage treatment or in combination with conventional systemic therapy (ST). However, in severe to profound sensorineural hearing loss resistant to ST, the optimal infusion mode, the type and concentration of the solution, the preferable drug, its total amount, and the duration and fractionation of the treatment are still debated. Aim of the study was to investigate the feasibility and the outcomes of a direct and constant IT delivery of dexamethasone (DEX) by means of a new indwelling catheter. **Methods:** A prospective case-control study in a tertiary referral University hospital. Ninety-nine subjects treated with ST only and 28 with additional IT DEX has been included in the study. A 4 Fr catheter inserted in a sub-annular fashion with a minimal postero-inferior tympanotomy through and endocanalar approach under local anesthesia. DEX 4 mg/ml delivered daily, up to 7 days. Daily bone and air-conducted pure tone and speech audiometry were performed with a follow-up at 1, 3, 6 months after treatment. **Results.** Twenty-one out of 28 patients (75%) refractory to ST gained on average 24.0 dB ± 20.5 dB HL after IT-DEX, compared to 35.4% (average 6.7 dB ± 16.6 dB HL) of those receiving only medical ST ($p<0.001$). No significant side effects were noted. **Conclusions:** In severe to profound sudden deafness refractory to conventional ST, the daily perfusion of 4 mg/ml DEX through an intratympanic catheter is an easy, well accepted procedure that enables patients to receive a drug in the middle ear in a repeatable or sustained form, with minimal discomfort and a partial rescue (67.86 %) and a speech recognition gain of 39%.

Key-words: sudden sensorineural hearing loss, catheter, dexamethasone, sustained perfusion, salvage treatment, intratympanic

INTRODUCTION

Severe to profound sudden sensorineural hearing loss (SSHL) is commonly treated with systemic administration of steroids associated with other drugs or physical therapies such as hyperbaric oxygen, carbogen inhalation, hemodilution and plasma apheresis. [1, 2] Most series report improvement of the spontaneous recovery rate of SSHL, that ranges between 30 and 60% of untreated cases, by means of parenteral infusion of glucocorticoids. [2]

Many studies over the last decade suggest favorable outcomes also with intratympanic (IT) steroid treatment, alone as salvage treatment or in combination with standard treatment (ST). [3-5] Local administration of dexamethasone, methylprednisolone, triamcinolone and hydrocortisone seems to warrant at least the same chance of recovery, without the side effects of systemic delivery. [4] However, some administration parameters are not yet well established: the optimal infusion mode, the type and concentration of the solution, the preferable drug, its total amount, and the duration and fractionation of the treatment, are still to be identified.

Diffusion of the drug from the middle to the inner ear occurs through the membrane of the round window (RW), that can be reached by trans-tympanic injections, by instillations through ventilation tubes with or without oto-wicks, by direct application on sustained delivery vehicles positioned in the RW niche with a tympanotomy; or by intra-tympanic catheters. Experimental and clinical studies suggest an advantage of a sustained release of steroids to the perilymph, compared to repeated single shot deliveries. For this purpose, a continuous perfusion of the labyrinth, with controlled dosage, delivered through a micro-infusion pump have been proposed. [6-9]

In this prospective pilot study, we meant to investigate the feasibility and the outcomes of an intratympanic delivery of dexamethasone by means of an indwelling catheter, in order to rescue severe to profound sudden deafness not responding to conventional intravenous treatment.

MATERIALS AND METHODS

A prospective study was conducted on 28 consecutive new cases admitted at the Department of Otolaryngology of the University of Brescia for SSHL. The study spanned over a 2 years period. A retrospective analysis of selected patients from the database of the Department provided a matched control group.

The main audiological inclusion criterion was a hearing threshold that exceeded a pure tone average (PTA) of 65 dB HL at 0.5, 1, 2 and 4 KHz, and the maximum speech discrimination score (SDS) in the affected ear had to be lower than 50%. According to the generally accepted definition of SSHL, its onset and progression had occurred within a frame of 72 hours. [9] SSHL had to fit the definition of "idiopathic"; thus, exclusion criteria involved patients in whom a clear etiology could be established, such as other ear diseases (e.g. chronic otitis media, otosclerosis), previous ear surgery, ear or head trauma, previous meningitis or other neurological disorders involving the auditory pathways, use of ototoxic drugs, noise trauma, exposure to industrial solvents, inherited hearing loss, and labyrinthine fistula. Patients referred to the hospital more than 30 days from the onset of their hearing loss were excluded as well.

A total of 127 patients were eligible for the study. There were 78 males and 49 females; the mean age was 56.0 years ± 13.8 (range 18 to 83 years). There were 54 right-sided and 73 left-sided affected ears. The ST group (n=99) included 64 males and 35 females, 39 right and 60 left ears. The IT group (n=28) included 14 males and 14 females, 15 right and 13 left ears. The mean age was 55 ± 15 years for the ST group and 58 ± 13 years for the IT group (p=0.5). Mean PTA before treatment was 84 ± 18 dB in the ST group and 102 ± 15 in the IT group. Clinical features of the two groups of patients are reported in Table 1.

Air (AC) and bone conduction (BC) thresholds were obtained with a 5 dB step and appropriate masking with narrow band noise of the opposite ear with the plateau method. A clinical audiometer

model AC 40 (Interacoustics, Denmark) was employed. SDS were measured with the phonetically balanced disyllabic word recognition task, delivered through TDH-49 earphones from a recorded CD. All tests were conducted in a sound isolated booth. Pure tone and speech audiometry were performed daily up to the end of treatment.

Initial systemic treatment consisted in dexamethasone aqueous solution, 4 mg/ml, 8 mg twice a day, associated with i.v. low molecular weight dextrane infusion (500 ml once a day) and subcutaneous low-molecular weight heparin (seleparin 100 units/Kg body weight twice a day). Treatment was continued over a 5-8 days period and pure-tone audiometry was checked daily. If no improvements were seen on day 4, heparin was stopped and the next day the patient underwent the surgical positioning of an intratympanic catheter under local anesthesia. (Figure 1) Care was used to clear any fibrous adherences obstructing the RW niche in all patients; a complete fibrous obliteration was found in one patient.

After the catheter insertion, all patients continued to receive dexamethasone by means of a "shotgun" intratympanic route only, with a single [daily] slow infusion of an average amount of 0.5 ml of the 4 mg/ml solution. The soluted drug was delivered through the catheter under direct control by the physician, over a 2 minutes infusion time. The patient was instructed to lie in a supine position with the head tilted 45° toward the untreated side for half an hour.

The daily infusions were repeated up to day 5 if no positive effect was noted; conversely, they were discontinued two days after a relevant improvement was observed (equal or better than 10 dB HL at PTA).

At the end of treatment, the catheter was removed under otomicroscopic control, the tympanomeatal flap repositioned. An oto-wick was left in place for 6 days and removed at the subsequent office control. Pure tone and speech audiometry were obtained at two weeks and at one, three and six months after treatment.

The results were compared with those of a control group of 99 patients extracted from the pool of 542 sudden deafness patients admitted to the clinic over the last 15 years, sex- and age-matched to

the study group, with a pretreatment PTA that exceeded 65 dB HL at 0.5, 1, 2, 4 KHz and whose characteristics were homogeneous to the study group in terms of risk factors, age, gender and who had been treated by ST only. The control group received the same systemic pharmacological treatment as the study group.

The study protocol was approved by the Institutional Review Board of our Hospital. The participation in the study was voluntary and the patients were not paid for it. The work was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2013, including, but not limited to, there being no potential harm to participants, guaranteed anonymity of participants, and written informed consent was obtained from each patient.

Data were analyzed by means of the statistical package SPSS (version 24.00, SPSS Inc., Chicago, Illinois). The chi-square test was used to compare categorical variables and the Mann-Whitney U test to compare two independent groups on one continuous variable; a $p < 0.05$ was considered statistically significant.

The F test of Friedman was selected in order to compare scores between baseline and follow-ups; the T test of Wilcoxon was chosen to compare scores at specific points along the follow-up timeline. The significance level was set at $p=0.05$ for the F test of Friedman. Multiple comparison by means of the T test of Wilcoxon were evaluated at 1/10 of the nominal significance level, i.e. at 0.005, in order to avoid a random significant result, being 10 the multiple comparison for PTA at baseline, 1, 2, 3, and 6 days and at 1/6 of the nominal significance level, i.e. at 0.008, being 6 the multiple comparison for SDS at baseline, 1, 3, and 6 months. Results are expressed as maximum, upper quartile, median, lower quartile, and minimum values.

RESULTS

Immediate amelioration of hearing threshold was observed in 60.7% (17/28) of patients after the first IT treatment day. ($p < 0.001$) The variation of PTA thresholds measured daily after positioning of the catheter steadily improved from 102.5 dB ± 15.1 before the IT treatment to 82.3 dB ± 22.4 (day 1 and 2), 76.4 dB ± 24.8 (day 3) and 75.7 dB ± 25.3 (day 6) after treatment. (Figure 2)

The mean SDS in the IT group were 11.6 ± 13.4% before treatment (ranging between 0 and 40%) and 50.5 ± 33.3% (ranging between 0 to 100%) six months after treatment. ($p < 0.001$) The average improvement was 38.9 ± 30.0% (i.e. the initial SDS of 40% increased to about 80%). The largest improvement was observed during the first 3 months after the IT infusion. (Figure 3)

According to accepted criterion of improvement, that considers a PTA increase ≥ 10 dB HL or a SDS increase ≥ 15%, the overall recovery rate observed in our whole historical series (over a 15 years time span) with ST, was 82.5%, independently from the initial degree of hearing loss.

Mean duration of IT treatment was 4 days (range 2-7). Total dose of dexamethasone delivered in the middle ear ranged between 8 and 28 mg (mean 17 mg). No significant side effects were noted in any patient. In a few patients, mild local pain was easily controlled with paracetamol. Most patients referred a slight "burning" sensation in the ear during the infusion, and 17 of them felt some fluid flowing to the nasopharynx. Post-operative bleeding through the external auditory canal occurred in 11 patients and stopped spontaneously within an average of 2.8 days (range 1-4). Six patients complained of mild dizziness for up to 5 days. One patient out of 28 (3.5%) developed a persistent perforation and subsequently underwent an underlay repair by an endocanalar approach under local anesthesia (3 months later). No patient experienced local infections. In no instance sensorineural deterioration of the hearing threshold occurred as a consequence of the surgical approach or of the topically applied drug. Eight patients did not improve at all; another suffered a progressive worsening of his hearing threshold after a three months' improvement.

Overall, a significant benefit from IT DEX rescue treatment has been observed: 75% increased their hearing sensitivity compared to 35.4% of matched patients who received solely the ST. ($p<0.001$)

At one month of follow-up, PTA thresholds were improved of at least 10 dB in 21/28 (75%) patients by a mean value of 24.0 dB ± 20.5 (range -14 - +71 dB); they were unchanged in the other 7 patients and never improved thereafter. In the IT group, 5 of the 28 patients (17.9%) showed further improvement during the next six months. In the ST group, the PTA thresholds were improved in 35/99 (35.4%) patients by a mean value of 6.7 dB ± 16.6 (range -39 - +49 dB). The difference of PTA variation between the two groups was statistically significant. ($p<0.001$)

At six months of follow-up, the IT treated group maintained a larger mean PTA improvement after the repeated steroid infusion in the middle ear cavity: it was 23.9±19.6 dB in the IT group vs. 6.7±16.6 dB in the ST group. ($p < 0.001$) (Figure 4). The difference in hearing improvement per frequencies between ST and IT group at 6 months were respectively 7.3±22.0 dB and 30.4±27.9 dB at 0.5 kHz ($p < 0.001$), 7.4±19.1 dB and 29.1±25.6 dB at 1 kHz ($p < 0.001$), 7.8±18.3 dB and 22.9±21.6 dB at 2 kHz ($p = 0.001$), 4.4±16.3 dB and 15.0±17.3 dB at 4 kHz ($p = 0.01$) (Figure 5).

DISCUSSION

SSHL have been traditionally treated with systemic administration of glucocorticoids. [11] A variety of protocols and combinations with other drugs have been implemented. [5, 12-15]

Since spontaneous recovery has been reported in up to 65% of untreated patients [2, 16], the effectiveness of any management protocol of SSHL is hard to prove, especially when ethical reasons hinder the recruitment of a control (untreated) group However, in severe to profound SSHL, the chance of regaining a normal hearing, or even of a partial recovery is much lower. [1, 17] Thus, most clinical studies, including the present one, compare two protocols, usually differing by the administered drug or the delivery method.

IT route avoids the systemic effects and overcomes the problem of the blood-perilymph barrier; [4, 8, 17] furthermore, the organ of Corti and the stria vascularis harvest glucocorticoid receptors [18] and steroids have a stabilizing effect on the cellular membranes and increase the cochlear blood flow when delivered trans-tympanically. [19]

The concentrations reached in the perilymph when the tympanic cavity is filled with the drug are comparable or greater [20] than by systemic administration and, more recently, the combination of both route has been also proposed as salvage therapy [3, 21] or primary approach. [4, 5, 22] When applied as a salvage treatment, the IT steroids are likely to improve hearing, but the variability in the literature is rather large (range: 25-83% of the treated patients). This wide range is partially explained by the different criteria adopted to assess the outcome: when stricter rules are applied, the favourable results range decrease. [23]

Earlier systematic review of literature and metanalyses of the literature by different researchers [2, 3, 11, 13, 24-27] concluded that reliable evidence on the efficiency, optimum dosage and administration schedule of IT steroid therapy was still lacking.

A recent guideline published by a panel of experts of the AAO-HNS after a systematic review of the literature [12] recommends clinician to "….*offer intratympanic steroid perfusion when patients*

have incomplete recovery from idiopathic sudden sensorineural hearing loss after failure of initial management…", with the latter being based on oral corticosteroids.

The preferred access point is the membrane of the RW, that can be reached by trans-tympanic injections [21, 21] and by instillations through ventilation tubes [28] or oto-wicks. [29-31] Direct application of a solution can be accomplished through a tympanotomy, especially if sustained delivery vehicles are added in order to enhance the duration of contact with the RW: collagen sponges [32], fibrin glue/gelfoam [33], thermosensitive gels [34, 35], hyaluronic acid [24, 33, 36], microspheres [37] or by intra-tympanic catheters [8, 9, 38, 39], while a direct intracochlear injections through the RW is not a recommended procedure due to the risk of leakage. [40]

Among the different delivery methods, the easiest and more widespread is the trans-tympanic injection. [3] It can be performed as an office procedure under local (contact) anesthesia of the eardrum. Unfortunately, there is no control of the amount of drug effectively reaching the RW membrane and inner ear, and there is a certain discomfort for the patients when the procedure has to be repeated on a daily basis.

The pharmacokinetics of steroid diffusions in the inner ear, especially for dexamethasone, have been extensively studied [20, 41]; on these bases, in our study, we selected this drug for middle ear perfusion. Corticosteroids applied to the RW membrane readily reach all the inner ear cells at concentrations inversely proportional to the distance, i.e. higher at the base and lower at the apex. [41] A sustained administration seems to achieve higher progressive concentrations in the inner ear fluids. [20]

An appealing system is based on the use of a shaped catheter that can be inserted into the RW niche through a minimal access tympanotomy, allowing a continuous perfusion of the labyrinth, with controllable micro-doses when connected with a micro-infusion pump. [37, 40] Although it could be argued that single trans-tympanic injections are easily administered and they avoid the need for surgery, our procedure can be performed in the office under local anesthesia and is usually well tolerated.

On the other hand, in a couple of studies, the use of micro-catheters does not seem to attain greater recovery rates vs. the single (or repeated) trans-tympanic injections, [8, 38] and few catheters commercially available have been implemented in clinical practice, with variable outcomes. [3, 7, 9, 39] Our results confirm at least the non-inferiority of the catheters compared to the single injection.

However, the accurate positioning of an IT catheter can be a rather time-consuming procedure, if performed through a posterior tympanotomy or through tunnels drilled in the outer ear canal such as described by Plontke et al. [9] For this reason, in this study, a minimal postero-inferior tympanotomy through an endocanalar approach has been proposed and resulted sufficient to provide access to the RW niche.

The advantage of this new approach with an indwelling catheter stands in the applicability of repeated or sustained infusions in the middle ear without the discomfort of multiple injections. It is best suited for short-term delivery of drugs (up to 2 weeks), although there are reports of longer in-stays. One collateral advantage of the insertion of a sub-tympanic catheter is the need to raise a minimal tympano-meatal flap that warrants the exploration of the round window niche and the removal of partial or total fibrous adhesions that could obstruct it

A few adverse effects of the use of IT catheters have been reported in the literature: eardrum perforations (1.7%) [42], persistent dizziness, vertigo and worsening of the hearing loss. [8] In the present series, only one persistent perforation of the eardrum has been observed and about one third of the patients complained of mild dizziness lasting up to 5 days.

In accordance with a recent study of Nakagawa et al., [21] also in our study, a certain advantage might be attributed to the time effect since IT salvage therapy was started earlier (5 to 7 days after admission) than in all other studies, which reported a delay of over 2 weeks and, in some instances, even months. [24] Conversely, the concentration of DEX used by our team is lower than in other studies (4 mg/ml vs. 8-24 mg/ml), due to ethical committee limitations. Nevertheless, a significant benefit from IT DEX treatment has been observed in 3/4 of our IT patients compared to 1/3 of controls. Within the IT responders, the amount of hearing gain was only marginally superior when

compared to the controls who responded to ST. However, one possible limitation of this study is the retrospective selection of the control group, nevertheless matched by age and level of initial hearing loss with the study sample.

Interestingly, more than half of the patients improved the very first day of treatment, and 4 others gained hearing over the next month. The mean PTA improvement 6 months after treatment was still significant (23.9±19.6 dB in the IT group vs. 6.7±16.6 dB in the ST group). A minority of patients did not show any improvement (19.6 %); this data is much lower than those reported in other studies on profound SSHL [3, 7-9, 37, 39]; an in-depth analysis failed to identify any particular risk factor in this subgroup.

The most impressive change observed within the 3/4 of the sample population responding to IT salvage treatment involved the speech discrimination, which raised almost 40% on average, similarly to other studies. [3, 4, 9]

CONCLUSION

The delivery of DEX through an IT catheter has been evidenced to be an easy, well accepted procedure that enables patients to receive a drug in the middle ear in a repeatable and comfortable modality. In severe to profound sudden deafness refractory to conventional i.v. therapy, the daily perfusion with 4 mg/ml DEX allowed to rescue 21/28 further patients, with a significant average threshold improvement and an important speech recognition gain.

On the other hand, everyone might agree with the criticism about the design of most clinical studies on SSHL expressed by some Authors [2] and also our preliminary results, although promising, are biased by the limited number of patients. For this reason, we believe that large pool of patients must be collected, to be included in strictly randomized, prospective, controlled studies.

Conflicts of Interest and Source of Funding. This paper has not been published elsewhere and has not been submitted simultaneously for publication elsewhere. Authors have no relationship with commercial companies. No funding sources supported research. There is no conflict of interest, such as a paid consultancy, stock ownership or other equity interest, or patent-licensing agreements, for all the authors. Patients have given written consent for publication.

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FIGURE LEGENDS

Figure 1. Schematic drawing of the procedure in a left ear. A: posterior-inferior trancanal incision; B: raising of posterior-inferior tympano-meatal flap; C: drilling of a groove (optional); D: clearance of fibrous adhesions in the round window niche; E: positioning of the catheter; F: repositioning of the tympano-meatal flap; G: catheter sutured to the concha and helix root.

Figure 2. Outcome of IT dexamethasone treatment: pre-operative vs. post-operative PTA at 1, 2, 3 and 6 days (maximum, upper quartile, median, lower quartile, and minimum). T test of Wilcoxon with significance level at 0.005.

Figure 3. Outcome of IT dexamethasone treatment: pre-operative vs post-operative speech discrimination scores (SDS) at 1, 3 and 6 months (maximum, upper quartile, median, lower quartile, and minimum). T test of Wilcoxon with significance level at 0.008.

Figure 4. Improvement of PTA at 6 months after treatment in the 2 groups of patients (maximum, upper quartile, median, lower quartile, and minimum). Mann-Whitney U test with significance level at 0.05.

Figure 5. Improvement of hearing thresholds at 6 months in the 2 groups of patients (maximum, upper quartile, median, lower quartile, and minimum). Mann-Whitney U test with significance level at 0.05.