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International consensus

International consensus (ICON) on treatment of sudden sensorineural hearing loss

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ABSTRACT

Sudden sensorineural hearing loss (SSNHL) is a common and alarming symptom that often prompts an urgent visit to an ENT specialist. Treatment of SSNHL remains one of the most problematic issues for contemporary otorhinolaryngology: although many meta-analyses and national guidelines have been issued, management is not standardized in terms of medical treatment, and duration and route of administration. We present several methodological suggestions for the study of treatments for SSNHL. These were developed from the existing level of evidence of the main treatments used in SSNHL by experts who convened at the IFOS 2017 ENT World Congress in Paris, France. All panelists agreed that one of the main limitations present in studies on SSNHL is related to the wide heterogeneity, which characterizes both the initial hearing deficit and the amount of hearing recovery. Although evidence of the efficacy of systemic steroids cannot be considered as strong enough to recommend their use, it is still the most widespread primary therapy and can be considered as the current standard of care. Therefore, systemic steroids stand as an adequate control for any innovative treatment. To reduce the number of subjects we suggest that the inclusion criteria should be restricted to moderate to profound levels of hearing loss. The efficacy of trans-tympanic steroids as a salvage therapy was suggested in several reports on small populations and needs to be confirmed with larger randomized controlled trials.

1. Introduction

Although sudden sensorineural hearing loss (SSNHL) has a relatively low incidence of 5 and 30 cases per 100,000 per year [1], it is considered one of the most common emergencies in ENT practice. SSNHL is usually defined as a unilateral hearing loss of at least 30 dB HL in three consecutive frequencies in the standard pure-tone audiogram [1,2] and can present at varying levels of severity from mild to total. SSNHL is considered idiopathic in the absence of established etiology, although several pathophysiological hypotheses have been proposed. The most common theories include viral infection [3,4], rupture of the cochlear membrane [5,6] and vascular accident [7–9]. The evolution of the condition is marked by a high rate of spontaneous recovery; estimated at 32% to 65% in case histories and placebo-controlled studies [10–12]. The audiogram characteristics have been shown to influence the evolution [11–14] with low and mid-frequency hearing losses given a better prognosis that flat and severe losses. There is general agreement that the management of SSNHL should start with diagnostic MRI scanning of the cerebello-pontine angle to discard a vestibular schwannoma [1,2,15,16] and search for a demyelinating process or a labyrinthine haemorrhage [17]. The treatment of SSNHL appears more controversial and the necessity of medication has even been questioned by several authors [18,19]. Different therapeutic approaches are based on the supposed pathophysiological

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mechanisms responsible for inner ear dysfunction: For example steroids to reduce the supposed inflammatory response to hyperbaric oxygenation to reverse the lack of oxygen in the inner ear. The heterogeneity of hearing deficits and their evolution, the diversity of possible causes and corresponding treatments are all factors that challenge evidence-based practice.

Several systematic reviews of the literature have been conducted on the effectiveness of steroids as a treatment for SSNHL in randomized controlled trials (RCT). By far most of these underlined the heterogeneity of inclusion criteria or outcome measures. Indeed, the inclusion of subjects with highly variable levels of hearing loss, accompanying symptoms (vertigo and tinnitus) or delays after onset of hearing loss can lead to a significant risk of selection bias and unmatched groups. Likewise, the wide variety of criteria used to describe the evolution of hearing function, from different definitions of pure-tone average threshold to multiple categorical classifications, reduces the relevance of comparisons made between studies. As a result, steroids are one of the most used options among the therapeutic armamentarium without any strong recommendation to refer to. Oral steroids are usually proposed as a first-line treatment based on an evaluation of the ratio risk versus benefit. The potential consequences of unilateral SSNHL may be severe in terms of quality of life, because of the impact on speech recognition in noise, on sound localization and because of the incapacitating tinnitus sometimes associated [19–21]. In contrast, the side effects expected from an acute therapy with oral steroids are mild [22,23]. Trans-tympanic steroids can also be proposed as a single primary therapy [22], but have more frequently been assessed in combination with systemic steroids [24] or as a salvage therapy [25].

This present consensus conference was held in Paris during the International Federation of Oto-rhino-laryngological Societies (IFOS) 2017 congress, with two purposes: The first objective was to provide an updated and documented overview of the level of evidence supporting the treatment of SSNHL with systemic and trans-tympanic steroids. The second goal of this international consensus conference was to identify methodological guidelines, which should be considered when designing studies on treatments for SSNHL.

Members of the discussion panel were S. Chandrasekhar (USA), J. Ito (Japan), S. Plontke (Germany) and S. O'Leary (Australia), each one being an international leading expert in the field on SSNHL. The discussion was moderated by M. Marx (France) and O. Sterkers (France).

1.1. Level of evidence for the use of steroids

1.1.1. Systemic steroids

Systemic steroids as a treatment for SSNHL have been extensively studied since the hallmark work by Wilson et al. in 1980 [26]. This paper is often cited (> 900 citations) to support the effectiveness of systemic steroids and warrants some further discussion: based on a significant difference between the proportion of patients who improved in the group who received steroids (20/33 subjects i.e. 61%) and the proportion in the placebo-controlled group (11/34, i.e. 32%), the authors concluded that steroids improved hearing better than placebo, and more specifically in a "steroid-effective" zone corresponding to moderate hearing loss. In fact, patients were included in two different centers with different steroid treatments (dexamethasone and methylprednisolone) at varying doses. The distribution of age; prevalence of accompanying symptoms such as vertigo; and audiogram profiles differed between treatment group and control group so that the randomization procedure was inadequate if at all present. Furthermore, there was a significant difference in the rate of recovery between the two centers both for oral steroids (73% versus 36%) and for placebo (50% versus 31%) so that the data should not have been pooled.

However, this article was selected for review in the Cochrane work on this topic, first published in 2006 and most recently updated in 2013 [27]. In this review, only 3 publications were included despite more than 200 studies being described as RCTs. In the same way, two [28,29] to four papers [26,28–30] were eventually selected over hundreds of studies in several reviews or meta-analyses [31–33] because of the global rarity of genuine RCTs. As for the Cochrane review and the clinical guidelines of the American Academy of Otolaryngology – Head & Neck Surgery (AAO-HNS) these papers [31–33] concluded that systemic steroids were not proven as either effective or ineffective. No recommendation can therefore be made for or against their usage, but because of the potentially severe consequences of SSNHL, the AAO-HNS guideline suggested using them as an option. The most common dose used for the prescription of oral prednisolone is 60 mg per day (i.e. approximately 1 mg/kg) but higher doses are for instance recommended in Germany (at least 250 mg per day for the first three days [34]). A recent RCT comparing high-doses (500 mg per day for three days followed by 60 mg per days for 11 days) to the common regimen (60 mg per day for 14 days) showed no significant benefit of using higher doses [35]. Nevertheless, it should be noted that the number of subjects needed to treat was not reached (67 subjects included versus 106 calculated).

1.1.2. Trans-tympanic steroids

The main theoretical advantage of trans-tympanic steroids relies on the bypass of the blood-labyrinthine barrier to reach higher concentrations in the inner ear [36,37]. Further, this mode of administration avoids the undesirable effects of systemic steroids. The global effectiveness of trans-tympanic steroids in the treatment of SSNHL is hard to determine because they may be used as a primary therapy alone [22,38–41] or in combination with systemic steroids [24,42,43], or as a salvage therapy after failure of systemic steroids [25,44–46]. Several recent meta-analyses [47,48] showed no significant difference in terms of pure-tone average (PTA) improvement and recovery rate between systemic and trans-tympanic steroids, when used as a primary therapy. However, the meta-analysis by Qiang et al. [49] found a better recovery rate in a total of 225 pooled subjects who received a first-line treatment by trans-tympanic steroids compared to 226 pooled control subjects (systemic steroids), especially in subjects with mild to moderate hearing loss. An ongoing Cochrane review led and presented by S. Plontke emphasizes that the majority of such RCTs include small samples and offer limited possibilities to assess the risk of bias.

Most studies on the use of trans-tympanic steroids as a salvage therapy showed at least a tendency to obtain better results than control for PTA improvement and/or the rate of recovery [25,44–46]. As a result, a recent meta-analysis performed on five studies [25,44–46,50] found a mean PTA improvement of 11.54 dB for trans-tympanic steroids versus 2.68 dB for placebo or no treatment controls [51]. The limited sample size of generally < 30 should also be taken into account for the interpretation of such results. The main RCTs using systemic and/or trans-tympanic steroids as a primary therapy are summarized in Table 1.

1.2. Methodological implications

RCTs are unanimously acknowledged as the gold standard in evaluating the effectiveness of a treatment, but not all RCTs are equal in value, which is particularly true in the field of SSNHL. Significant limitations, from the conception of the study design up to the reporting of the methods and outcomes, were cause for rejection of these studies in the recently updated Cochrane review [27]. The general low quality of trials on SSNHL is regularly underlined in

Table 1
Study characteristics of systemic steroids and/or trans-tympanic steroids (TTS) as a primary therapy for SSNHL.

Authors	Number of subjects (*n*)	Comparison	Outcome measures	Outcomes
Systemic steroids				
Wilson et al., 1980	*n* = 67	Steroids (*n* = 33, two different steroid treatments) vs. placebo (*n* = 34) One "control" group of 52 (or 53?) subjects added; without any treatment	Hearing recovery: complete: within 10 dB of initial PTA/SRT; partial: > 50% of initial PTA/SRT; no recovery: < 50% of initial PTA/SRT	If hearing loss > 90 dB, no effect of steroids Definition of a "steroid-effective zone", with hearing better than 90 dB Rate of recovery in the placebo-controlled study for hearing losses < 90 dB: 91% with steroids vs. 40% with placebo in one center, 57% vs. 36% in the other
Nosrati and Hultcrantz, 2012	*n* = 93	Prednisone (*n* = 47) vs. placebo (*n* = 46)	PTA and rate of PTA improvement (> 10 dB) Rate of complete recovery (within 10 dB of initial PTA)	No significant difference between prednisone and placebo at day 90: mean PTA improvement of 39 dB (± 20.1) with prednisone, 35.1 dB (± 38.3) with placebo; 18/47 complete recovery with prednisone, 18/46 complete recovery with placebo
Cinamon et al., 2001	*n* = 41	Carbogen inhalation (*n* = 11), room air (*n* = 9), prednisone (*n* = 10), placebo (*n* = 11)	Rate of PTA improvement (> 15 dB)	Overall improvement = 73.1% (30/41) No difference between 4 groups
Eftekharian et al., 2015	*n* = 67	Pulse steroid therapy (*n* = 29) with 500 mg/day for 3 days then 60 mg/day vs. standard steroid treatment (*n* = 31) with 60 mg/day	Pure-tone improvement per frequency (0.5, 1, 2, 3, 4 kHz) Word recognition score improvement Complete, partial or absence of recovery, as defined by the AAO-HNS[a]	No difference between groups for pure-tone, word recognition scores, or rate of recovery Group pulse: 7/29 complete, 10/29 partial, 12/29 no recovery Group standard: 6/31 complete, 11/31 partial, 14/31 no recovery
Trans-tympanic steroids				
Lim et al., 2012	*n* = 60	Oral steroids (20), TTS (20), oral and TTS combined (20)	PTA and SRT improvements Complete, partial or absence of recovery, as defined by the AAO-HNS[a]	No significant difference between groups. Trend for better results combined therapy (mean improvement of 22 dB vs. 12.1 dB and 12.8 dB for oral or TTS alone)
Rauch et al., 2011	*n* = 250	Oral steroids (*n* = 129) vs. TTS (*n* = 129)	PTA and rate of PTA improvement (> 10 dB) Rate of complete recovery (PTA < 30 dB) Word recognition score	No inferiority of TTS compared to oral steroids: 28.7 dB vs. 30.7 dB PTA improvement; 24% vs. 20% of complete recovery
Swachia et al., 2016	*n* = 42	Oral steroids (*n* = 21) vs. TTS (*n* = 21)	PTA improvement Furuhashi criteria[b]	No significant difference between groups: improvement of 18.24 ± 8.72 dB with oral prednisone and 14.68 ± 12.88 dB with TTS
Gundogan et al., 2013	*n* = 73	Oral steroids (*n* = 36) vs. oral and TTS combined (*n* = 37)	PTA improvement Word recognition score Siegel's criteria[c]	Significantly better results with combined therapy on: PTA: 44 dB ± 21.5 vs. 25.7 dB ± 19.8 improvement; word recognition score and rate of recovery
Filippo et al., 2013	*n* = 50	TTS (*n* = 25) vs. placebo (*n* = 25). If no improvement at day 7, supplementary oral prednisolone given for 8 days	PTA improvement Furuashi criteria[b]	At day 7, significantly better results with TTS over placebo on: PTA improvement; rate of recovery (19/25 complete recovery with TTS vs. 5/25 with placebo); 1 month after, no significant difference between groups
Hong et al., 2009	*n* = 63	Oral steroids (*n* = 31) vs. TTS (*n* = 32)	PTA and pure-tone thresholds improvement Siegel's criteria[c]	Significant difference for pure-tone improvement in high frequencies: better with oral steroids No significant difference for the rate of recovery
Dispenza et al., 2011	*n* = 46	Oral steroids (*n* = 21) vs. TTS (*n* = 25)	PTA and rate of PTA improvement (> 10 dB)	No significant difference between groups: 20/25 with TTS and 17/21 with oral steroids; numbers for PTA improvements not reported

Table 1
(*Continued*)

Authors	Number of subjects (*n*)	Comparison	Outcome measures	Outcomes
Battaglia et al., 2008	*n* = 51	TTS + oral placebo taper (*n* = 17) vs. high-dose prednisone taper (HDPT) and trans-tympanic placebo injections (*n* = 18) vs. combined TTS and HDPT (*n* = 16)	PTA and rate of PTA improvement (> 15 dB) Word recognition score and rate of improvement > 25% points	Greater improvement for PTA and word recognition with combined therapy Better rate of complete recovery for combined therapy compared to treatment by HDPT

SSNHL: sudden sensorineural hearing loss; PTA: pure-tone average; SRT: speech recognition threshold.

[a] AAO-HNS criteria. Complete recovery with return to within 10 dB HL of the unaffected ear and recovery to word recognition score to within 5% to 10% of the unaffected ear. Partial recovery defined in 2 ways (clinically meaningful/not meaningful recovery based on whether or not the degree of initial hearing loss after SSNHL rendered the ear nonserviceable). No recovery: anything less than 10 dB HL.

[b] Furuashi criteria. Complete recovery: PTA ≤ 25 dB HL or identical to the contralateral non-affected ear. Marked recovery: PTA improvement > 30 dB HL. Slight recovery: PTA improvement between 10 and 30 dB HL. No recovery: anything less than 10 dB HL.

[c] Siegel's criteria. Complete recovery: PTA ≤ 25 dB HL or identical to the unaffected ear. Partial improvement if improvement > 15 dB HL and final PTA between 25 and 45 dB HL. Slight improvement if improvement > 15 dB HL and final PTA poorer 45 dB HL. No recovery if improvement ≤ 15 dB HL and final PTA poorer than 75 dB HL.

the conclusion of other literature reviews or meta-analyses [31,33]. It must be recognized that the relative rarity of SSNHL, combined with the heterogeneous level of hearing deficits and the high rate of spontaneous recovery, usually complicates the conception of studies and the analyses of the outcomes. But several suggestions were made during the international consensus conference to improve the global quality of RCTs in that field.

1.2.1. Inclusion criteria

Although it has an impact on the ease of recruitment, the restriction of inclusion criteria is a good solution to reduce the initial heterogeneity, and the level of hearing loss is probably the most variable characteristic in subjects with SSNHL. Several valuable studies thus selected only patients with moderate hearing loss [52] or with at least moderate hearing loss [22,25,35] to study the effect of steroids in a relatively homogeneous populations. It might be all the more relevant to focus on these patients as the probability of spontaneous recovery (and its influence on outcomes) is reduced in case of severe to profound hearing loss [10,11,53].

1.2.2. Outcome measures

The question of the outcome measures, which should be chosen is prominently controversial. This can be illustrated by the multiplicity of categorical criteria existing in the literature. The landmark study by Wilson et al. [26] defined recovery as complete if the follow-up PTA (dB HL) or speech recognition threshold (SRT) improved to within 10 dB of pre-sudden hearing loss hearing levels. Complete recovery was differently defined using Furuashi or Siegel's criteria as a final PTA better than 25 dB HL [43,52,54,55], or by the ministry of health, Labor and Welfare in Japan as final PTA better than 20 dB HL [56]. If the definition of complete recovery is so problematic, it is not hard to imagine the variety of definitions for "marked" or "slight" recovery. Likewise, the restoration of useful hearing is a notion, which may generate multiple interpretations. In certain patients, it can refer to PTA allowing speech recognition with a hearing aid. In others, the restoration of hearing thresholds compatible with the perception of some environmental sounds. It is obvious that "ideal" hearing measurements should include pre- and post-treatment pure-tone thresholds and word recognition scores but the reporting of the evolution of these parameters remains problematic. To compensate for the lack of standardization for reporting combinations of hearing performance Gurgel et al. [57] proposed a classification system basing on a scattergram; they plotted pure-tone thresholds against recognition scores for words. However, this is still mainly used only for the English language. Furthermore, there is unfortunately no validated tool to assess the equivalence of speech recognition tests across the different languages and pure-tone audiogram remains the only true international common standard.

Therefore, the panelists suggested using the change in pure-tone thresholds as the primary outcome measure for studies on treatments for SSNHL. It was added that any PTA change exceeding 10 dB HL could be considered as significant if the audiometry was performed under adequately controlled conditions [58]. Besides the absolute evolution of pure-tone thresholds a 10 dB change in PTA could thus serve as a categorical criterion to determine the presence or absence of hearing improvement. Likewise, the use of final pure-tone threshold allows the definition of complete recovery as a secondary outcome measure. The evolution of speech recognition scores after treatment remains highly informative, as well as the proportion of subjects improving in each treatment group for PTA and word recognition. The duration between the onset of the hearing loss and the final PTA measurement is also variable in the literature, from 30 days [52] to 3 months [30], although longer intervals allow including delayed recoveries.

1.2.3. Calculation of the sample size

The calculation of the sample size is an element regularly lacking in studies on SSNHL although it should appear as stated in the general guidelines for the reporting of randomized controlled trial published by the Consolidated Standards of Reporting Trials (CONSORT) group [59]. It is not uncommon to calculate numbers of subjects needed to treat greater than 150–200 to show an advantage of a treatment over natural evolution with the significant rate of spontaneous recovery [60]. However, such sample sizes are built upon the assumption that all patients can improve, while the inter-individual variability for hearing recovery is an intrinsic characteristic of SSNHL. Actually, both spontaneous evolution and uneven distribution of recovery should be taken into account to model the sample size. During his presentation, S. O'Leary demonstrated that this number could decrease significantly if only subjects with moderate and more severe levels of hearing loss were included. He also emphasized the need to apply non-parametric statistics to the analyses of the outcomes because of the non-normal distribution of hearing recovery.

1.2.4. The control group

The nature of the control group is also a matter of debate and influences the choice of hypothesis. The question of effectiveness of a new treatment for SSNHL theoretically requires a placebo control. Numerous RCTs were for instance excluded from the Cochrane review because the true effect of steroids could not be determined in the absence of such a group [22,37,38,41,61–67]. However, some of these studies addressed a more relevant question from a clinical point of view, which is the superiority of a new treatment over the

standard of care. Systemic steroids can be considered as the current clinical practice and are for sure the most widely used treatment, as demonstrated in several surveys [68,69] with rates of prescription by otolaryngologists as high as 100% [69]. These clinical considerations question the ethical value of placebo in the assessment of treatments for SSNHL. All panelists agreed that a new treatment should provide better hearing results than steroids to deserve further attention from the medical community but also from the regulatory authorities.

Insulin-like growth factor-1 (IGF1) in topical application to treat SSNHL is a good example of an innovative therapy: IGF-1 plays a role in the protection of cochlear hair cells [69,70] which may be damaged to various degrees in cases of SSNHL. Initial animal experiments showed the safety of IGF-1 and suggested its efficacy by protecting hair cells from noise exposure, ischemic injury [69,71,72] and ototoxic drugs [70]. Pilot clinical trials in a limited number of subjects with refractory SSNHL followed these results to demonstrate safety and efficacy of trans-tympanic topical IGF-1 delivered using gelatin hydrogels [73,74]. A larger multicenter RCT was finally performed to compare topical IGF-1 to the standard trans- tympanic dexamethasone treatment as a salvage therapy [75]. In this RCT the primary outcome measure was the rate of improvement (change in PTA > 10 dB). The sample size ($n = 120$) was calculated basing on the expected proportions of subjects improving after each treatment determined by the previous clinical trials for IGF-1 and the main recent findings in the literature for dexamethasone. Randomization was stratified by the mean hearing thresholds to distribute equally the number of profound hearing losses. The primary objective of the trial was not achieved because the proportion of subjects improved did not differ significantly between the two groups with a rate of 66.7% in IGF-1 group and 53.6% in dexamethasone group, but the change in PTA was more favorable in IGF-1.

2. Conclusion

SSNHL is a difficult condition to study because of the wide heterogeneity, which characterizes both the initial hearing deficits and the amount of hearing recovery. Although the evidence supporting their efficacy is still debated, systemic steroids are the most widespread primary therapy and stand as an adequate control for any innovative treatment for SSNHL. Likewise, the true effect of trans-tympanic steroids used as a salvage therapy is debatable but several RCTs showed significant hearing improvements in comparison to control groups.

The statistical power of studies may be increased by restricting inclusion to moderate and more severe levels of hearing loss and/or by the use of a stratified randomization. When modelled, this restriction has also an influence on the calculation of the sample size, requiring a lower number of study subjects. Changes in pure-tone thresholds are currently the only common, international outcome measure and should therefore be employed in primary end-points.

Disclosure of interest

The authors declare that they have no competing interest.

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