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**MAIN ARTICLE**

# Intratympanic methylprednisolone as first-line therapy in sudden sensorineural hearing loss: preliminary results from a case–control series

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## Abstract

*Background*: Sudden sensorineural hearing loss is a true audiological emergency, and its management is much discussed. Currently, no single therapy has been proven effective according to evidence criteria. Recently, intratympanic application of steroids has been increasingly used in refractory cases; however, it has only rarely been reported as first-line therapy.

*Materials and methods*: Twenty consecutive patients with sudden sensorineural hearing loss treated between July 2008 and January 2010 were enrolled in this prospective, case–control study. Ten patients were treated with intratympanic steroids and 10 with systemic 'shotgun' therapy (including steroids, pentoxifylline, low molecular weight heparin and vitamin E). The two groups were homogeneous in all respects. Pure tone averages were assessed before and after treatment for both groups.

*Results*: There were no statistically significant differences between the two groups.

*Conclusion*: Intratympanic steroids seem to offer a valid alternative to systemic therapy, with few risks, in sudden sensorineural hearing loss patients, and we recommend their use as first-line therapy.

**Key words:** Intratympanic Steroid; Sudden Hearing Loss; Sudden Deafness Therapy; Steroids Therapy

## Introduction

Idiopathic sudden sensorineural hearing loss (SNHL) is a clinical diagnosis characterised by sudden deafness in the absence of a clear precipitating cause. Its incidence has been estimated at 8 to15 per 100 000 persons per year.[1,2]

Many different therapeutic strategies have been proposed over the years, including the use of vasodilators, diuretics, anticoagulants, plasma expanders, corticosteroids, apheresis, contrast dye and hyperbaric oxygen, individually or in combination.[3]

Assessment of the therapeutic efficacy of these treatments has been hampered by lack of understanding of the condition's pathophysiology, and by the high prevalence of spontaneous resolution (up to 65–66 per cent of cases).[4,5]

However, in recent years there has been a trend toward the use of steroids,[6] although this therapy cannot be considered the 'gold standard' treatment of sudden SNHL.[7] To be effective the steroids have to reach an adequate perilymphatic concentration that is achieved with very high systemic doses. Such a high systemic steroid concentration carries the risk of unwanted side effects,[8] especially in elderly patients and those with gastric problems, hypertension and diabetes. This is one of the reasons why the use of intratympanic steroids has gained increasing popularity.

The rationale of intratympanic steroid treatment is that it delivers a high dose of the drug to the target tissue, with minimal systemic exposure. Most previous studies of intratympanic steroid treatment have assessed salvage therapy; only a few published studies have assessed intratympanic steroids used as first-line therapy.[9,10]

The present study aimed to report our preliminary experience of intratympanic steroid application as first-line therapy for sudden SNHL, in order to add our results to the current body of knowledge on this topic.

## Materials and methods

Twenty consecutive patients with sudden SNHL treated between July 2008 and January 2010 were enrolled in this prospective, case–control study.

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Ten patients were treated with intratympanic steroids and 10 with systemic 'shotgun' therapy (including steroids, pentoxifylline, low molecular weight heparin and vitamin E). We did not plan a randomised trial because of legal problems within our hospital.

Our local ethical committee granted approval for the study, provided that the choice of treatment was made by the patient. All the patients included in the study were informed about each treatment, and selected their preferred type of therapy of their own free will.

In this way, intratympanic steroid therapy was selected by 10 patients (group A; mean age 56.4 ± 14.7 standard deviation (SD) years; age range 37–78 years; five women and five men), while shotgun therapy was selected by another 10 patients (group B; mean age 46.3 ± 21.2 SD years; age range 21–83 years; six women and four men).

All patients underwent our study protocol (i.e. general and ENT anamnesis, otoscopy, audiometry (pure tone average (PTA)), tympanometry, stapedius reflex testing, vestibular examination, blood tests, ultrasonography of neck vessels, and computed tomography and/or magnetic resonance imaging), which had been approved by the local medical ethics board.

The mean interval between the onset of sudden SNHL and the onset of therapy was 7.3 days (range 3–12 days) in group A and 6.6 days (range 1–15 days) in group B. All group A patients received one or more steroid injections.

Middle-ear disease was ruled out in all 20 patients, and the otoscopic examination was normal. Patients with a possible cause of sudden hearing loss, such as recent viral illness, autoimmune disease or acoustic trauma, were excluded from the study.

Group A patients were admitted to hospital and treated with intratympanic steroids, as previously described.[11]

Group B patients were treated with intravenous methylprednisolone (1 mg/kg once daily) and pentoxifylline (200 mg once daily). All 10 patients also received low molecular weight heparin (0.4 ml via subcutaneous injection twice daily).

Each patient's hearing loss was assessed using PTA at 0.5, 1, 2 and 3 kHz, both before ('PTA pre') and 30 days after ('PTA post') therapy. These parameters were used to calculate the change in PTA (ΔPTA), as follows: ΔPTA = PTA pre – PTA post.

Treatment response was evaluated in terms of relative gain, calculated as the relationship between ΔPTA and the pre-treatment hearing loss (ΔPTA/PTA pre).

In group A, two patients (20 per cent) presented with vertigo, and vestibular examination showed a canal paresis ipsilateral to their hearing loss. One patient (10 per cent) presented with canal paresis plus tinnitus, while three patients (30 per cent) presented with tinnitus without vertigo or canal paresis.

In group B, three patients (30 per cent) presented with vertigo, and vestibular examination showed a canal paresis ipsilateral to their hearing loss and tinnitus. Another three patients (30 per cent) presented with tinnitus without canal paresis (Table I).

On audiometry, five group A patients (50 per cent) and six group B patients (60 per cent) showed a flat curve. Three group A patients (30 per cent) and three group B patients (30 per cent) showed a downward-sloping curve. Two group A patients (20 per cent) and one group B patient (10 per cent) showed an upward-sloping curve.

Blood testing included blood count and total cholesterol, low-density lipoprotein, triglyceride, lipoprotein A, apolipoprotein A1, apolipoprotein B, homocysteine, D-dimer and antithrombin III (AT) concentrations. Three group A patients (30 per cent) and one group B patient (10 per cent) had altered lipid metabolism. Two group A patients (20 per cent) and one group B patient (10 per cent) showed a relative and absolute neutrophilia. Two group A patients (20 per cent) and three group B patients (30 per cent) had evidence of at least one type of cardiovascular disease: one group A patient (10 per cent) had arterial hypertension (well controlled by drugs) plus chronic atrial fibrillation, the other group A patient (10 per cent) had chronic cerebrovascular disease plus valvular disease, and the two group B patients (20 per cent) had arterial hypertension (well controlled by drugs).

Ultrasonography identified some alteration of cerebroafferent vessels in five group A patients and six group B patients, but none had haemodynamically significant obstruction.

Neuroradiological evaluation was negative in all patients of both groups.

### *Statistical methods*

Univariate analysis was performed using the Mann–Whitney test in cases of continuous variables (i.e. age, time to therapy, PTA pre, PTA post, ΔPTA and relative gain) and using the chi-square test in cases of 'nominal' variables (i.e. sex, neutrophilia, and the presence or absence of vertigo, tinnitus, lipid metabolism alteration and cardiovascular disease). Continuous variables were reported as mean (SD) or

TABLE I
AUDIOLOGICAL AND CLINICAL DATA BY GROUP

| Parameter | Group A | Group B |
|---|---|---|
| Vertigo (pts; *n* (%)) | 3 (30) | 3 (30) |
| Tinnitus (pts; *n* (%)) | 4 (40) | 6 (60) |
| Time to therapy (days) | 7.3 ± 2.1 | 6.6 ± 1.4 |
| PTA pre (dB) | 67.2 ± 31 | 68.1 ± 22.5 |
| PTA post (dB) | 40.9 ± 38.1 | 55.3 ± 22.9 |
| ΔPTA | 26.4 ± 22 | 12.9 ± 17.4 |
| RG | 45.4 ± 30.5 | 20.2 ± 29.1 |

Vertigo and tinnitus data are presented as means; all other data are presented as means ± standard deviations. Group A = intratympanic steroids; group B = 'shotgun' therapy; pts = patients; PTA pre = pre-treatment pure tone average; PTA post = post-treatment PTA; ΔPTA = PTA pre – PTA post; RG = relative gain

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median (interquartile range), while categorical variables were reported as number (percentage).

Data were processed using the StatView 5 version 5.0.1 software program. Results were considered significant if $p$ was less than 0.05.

## Results

The mean pre-treatment PTA was 67.3 ± 31.0 dB in group A and 68.1 ± 22.5 dB in group B. The mean post-treatment PTA, assessed at day 30, was 40.9 ± 38.1 dB in group A and 55.3 ± 22.9 dB in group B. The value of ΔPTA was 26.4 ± 22.0 in group A and 12.9 ± 17.4 in group B. The relative gain was 45.4 ± 30.5 in group A and 20.2 ± 29.1 in group B.

After comparing the two groups using the above-described statistical analysis, we found no statistically significant differences for the following variables: age, time to therapy, pre-treatment PTA, sex, presence or absence of vertigo, presence or absence of tinnitus, presence or absence of lipid metabolism alteration, neutrophilia, and presence or absence of cardiovascular disease. These results indicated that the two groups were homogeneous.

Likewise, we found no statistically significant differences for post-treatment PTA or ΔPTA, comparing the two groups using the Mann–Whitney test, further indicating the substantial similarity of the two treatment groups. The only parameter showing any trend towards difference was relative gain: values were 45.4 ± 30.5 in group A and 20.2 ± 29.1 in group B, with $p = 0.06$ (i.e. not achieving statistical significance).

No permanent tympanic membrane damage or serious complications were observed.

One limitation of the study was the low power of our tests, given the relatively small number of patients.

## Discussion

Sudden sensorineural hearing loss is a clear audiological emergency. However, its management is currently a topic of significant debate. This is principally due to two reasons: firstly, the natural history of sudden SNHL is unknown, although some information is available;[4,5,12] and secondly, there is currently no single therapy which has been demonstrated to be effective according to accepted evidence criteria.[13]

Furthermore, it seems realistic to assume that previously published data on the natural history of sudden SNHL may perhaps not correspond completely to the clinical reality of the condition, as (1) some cases probably recover so quickly that they do not reach medical attention,[6] and (2) by definition, sudden SNHL is a diagnosis of exclusion. In other words, its diagnosis depends on the depth of the diagnostic investigation conducted. It is reasonable to assume that, with improvements in diagnostic tools, some conditions previously diagnosed as idiopathic sudden SNHL will no longer fit this diagnosis.[6] Consequently, data from studies conducted 20 to 30 years ago should be interpreted with caution, because they are probably based on investigations very different to those performed nowadays.

Moreover, to complicate matters further, there is currently no accepted definition of sudden SNHL. The National Institute of Deafness and other Communication Disorders[14] defines sudden SNHL as rapid loss of hearing occurring over a period of up 3 days, with hearing loss of at least 30 dB in three consecutive frequencies. As clearly explained by O'Malley, the above definition is limited by several difficulties, including the fact that a drop of 25 dB in two of the frequencies of social hearing will have great significance for the patient, as it will seriously affect their quality of life, despite not being defined as pathology.[15] We too believe that this definition is problematic. After all, we are treating human beings, not audiograms. For this reason, we use a different definition[16] (acknowledging that it too has its faults), which includes patients with a hearing loss of more than 20 dB in three frequencies within the sudden SNHL diagnostic category.

Despite its dramatic clinical presentation, sudden SNHL is generally the presenting symptom of an underlying pathophysiology that has yet to be identified. In as many as 88 per cent of patients, a battery of diagnostic tests fails to yield an identifiable cause.[5] In this sense, sudden SNHL should not be considered a disease per se but rather a manifestation of an underlying pathology. It has been speculated that despite the different aetiologies, the final damage-pathway might be the same and an immunologically mediated vasculitis has been demonstrated experimentally.[17]

Also regarding the interpretation of the results there is more than a little issue for concern. The use of different outcome criteria makes a serious comparison between the data really complex. We maintain that a simple improvement in PTA should not be considered the main parameter with which to evaluate therapeutic efficacy. An improvement from 95 to 70 dB represents negligible improvement to the patient, who derives very little gain in terms of social communication. We believe that evaluation of relative gain is far more important, as this parameter assesses the patient's real-life, functional improvement, and can also be used to determine how many patients regain a social hearing level.

As previously stated, no universally accepted therapy exists for sudden SNHL. Obviously every treatment should be considered with respect to an "unknown" spontaneous recovery. As such, if for refractory hearing loss the expected recovery is extremely low, for a first-line therapy a confounding factor is the presence of the spontaneous recovery.

Notwithstanding these concerns, there is currently a trend toward the use of steroids in the management of sudden SNHL.[3,6] It must be emphasised that their systemic administration can be associated with troublesome side effects, albeit rarely.[8] From a therapeutic

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viewpoint, it is well accepted that the earlier the treatment, the better the results.[6] Therefore, based on our experience of salvage treatments,[11] and on the assumption that refractory cases of sudden SNHL usually have a long time interval between onset and intratympanic steroid administration, we decided to treat our patients with intratympanic steroids as first-line treatment, rather than opt for other, less extensively studied, potentially risky treatments.

There have been few studies of the use of intratympanic steroids as first-line therapy.[9,10] Our preliminary experience, based on the present case–control study, appears to confirm the comparability of results for traditional shotgun therapy and for intratympanic steroids. Our two treatment groups were homogeneous in all respects. Audiologically, the mean pre-treatment PTA was $67.3 \pm 31.0$ dB in the intratympanic steroids group and $68.1 \pm 22.5$ dB in the control group. The mean post-treatment PTA improvement was $26.4 \pm 22.0$ in the intratympanic steroids group and $12.9 \pm 17.4$ in the control group. The relative gain was $45.4 \pm 30.5$ in the intratympanic steroids group and $20.2 \pm 29.1$ in the control group. No differences between the two groups reached statistical significance, although this last comparison was at the limit of significance ($p = 0.06$).

- **Sudden sensorineural hearing loss is an otological emergency**
- **Its management is controversial; no single therapy has been proven effective**
- **Steroid treatment has recently gained popularity; intratympanic adminstration minimises the risks of systemic administration**
- **This prospective, case–control study compared intratympanic steroid *vs* 'shotgun' systemic therapy**
- **No statistically significant differences were seen in outcomes**

When evaluating our results in terms of regaining social hearing, we observed that, in the intratympanic steroids group, a PTA of less than 50 dB was found in four patients before treatment but in seven patients after treatment. In the control group, a PTA of less than 50 dB was found in one patient before treatment and in three patients after treatment. Again, there were no statistically significant differences between the two treatment groups.

Although we are fully aware of the limitations of a case–control study, we maintain that our data are worthy of consideration. We are convinced that the fact that one therapy was not proven effective does not mean that that therapy does not work, but only that its efficacy has not been proved. In other words, as previously stated,[11] the limitation is probably related more to the study methodology than to the therapy itself. In this sense, the goal of our paper is not to promote a new standard of care in sudden SNHL patients but rather to add our experience to the current small body of data on this topic. Furthermore, we believe that our findings are of particular interest given the very limited morbidity associated with intratympanic steroid treatment. We emphasise that, in our overall experience with intratympanic treatments, no significant complication has been observed. As such, given our leading rule of 'primum non nocere' ('first, do no harm'), we maintain that intratympanic steroid application is worthy of serious consideration. We thus strongly recommend that multicentre case–control studies, and possibly randomised trials, be conducted in order to fully evaluate the efficacy of intratympanic steroid administration as first-line therapy for sudden SNHL.

## Conclusion

Intratympanic administration of steroids seems to offer a valid alternative to systemic administration, with virtually no risks, in the treatment of patients with sudden SNHL. On this basis, we advise its use as first-line therapy for sudden SNHL. Obviously, randomised, double-blinded, multicentre studies are mandatory to further evaluate such treatment. Further research is also needed to establish the best type of steroid and the most cost-effective treatment modality for this clinical context.

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