

Systemic Versus Intratympanic Corticosteroid Therapy for Idiopathic Sudden Sensorineural Hearing Loss; A Meta-analytical Study

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ABSTRACT

Background: idiopathic sudden sensorineural hearing loss (ISSHL) is one of the most controversial issues in otology. There have been countless publications and debates concerning ISSHL over the last decades. ISSHL can be defined as a sensorineural hearing loss of sudden onset or one that happens in minutes, hours or even in a few days. The hearing impairment varies as far as intensity and sound frequency are concerned, some specifically say it is a 30dB hearing loss minimum, in at least three continuous frequencies with all known causes have to be ruled out previously. **Aim of the Work:** the aim of this study was to evaluate the treatment outcomes of ITS treatment and SST based on meta-analysis, and to provide an alternative modality for clinical practice. **Materials and Methods:** the current meta-analysis assessed the therapeutic effectiveness of intratympanic (IT) steroid protocol as first and single drug method compared to a systemic steroid protocol. In the current meta-analysis study we applied 2 parameters to compare between ITS group and SST group which were : recovery rate and hearing improvement. **Results:** the results of this study showed that regarding both; recovery rate and hearing improvement, there was no significant difference between intra-tympanic steroid (ITS) and systemic steroid therapy (SST). Second both SST and ITS alone were an effective treatment in ISSNHL patients as they significantly improved PTA and also the recovery rate. Third, if patient has any systemic condition that make the use of systemic steroid risky or lead to side effect, then the option of intratympanic steroid was, not only justified but mandatory. **Conclusion:** the conclusion from our meta-analysis was shown as follows: first, according to the current study, ITS treatment produced no significant difference in both aspects PTA improvements and recovery rate than SST in ISSHL patients. Second both SST and ITS alone were an effective treatments in ISSNHL patients as they significantly improved PTA and also the recovery rate.

Keywords: Idiopathic sudden sensorineural hearing loss – Intra-tympanic – Intra-tympanic steroids

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSHL) is one of the most controversial issues in otology. There have been countless publications and debates concerning ISSHL over the last decades. Uncertainty regarding its pathophysiology and high rates of spontaneous recovery question the validity of the various recommended treatments, as well as the significance of reported results ⁽¹⁾. ISSHL may, sometimes, accompanied by tinnitus and/or vertigo, represents, not only the loss of inner ear function, but also the impairment to the patient's psychological status. It has no established cause or pathophysiology and, therefore, without established treatment. Thus, it is a problem that places the physician in a difficult clinical situation ⁽²⁾. ISSHL can be defined as a sensorineural hearing loss of sudden onset or one that happens in minutes, hours or even in a few days. The hearing impairment varies as far as intensity and sound frequency are concerned, some specifically say it is a 30dB hearing loss minimum, in at least three continuous frequencies with all known causes have to be ruled out previously ⁽³⁾.

Hearing loss may be accompanied by other symptoms such as tinnitus (in 70% of the cases) and dizziness may be sometimes present (up to 40% of the cases). There may also be ear fullness, headache and viral infection symptoms of the upper airways ⁽⁶⁾. Because ISSHL pathophysiology is still unclear, there are arguments about its true cause. According to **Nakamura et al.** ⁽⁷⁾, over 45% of ISHL cases bear unknown causes. Vascular causes also compete with autoimmune diseases and the rupture of the labyrinthine membrane, and also viral infections. There still are psychosomatic disorders ⁽⁸⁾. Many treatments for ISSHL have been tested and found ineffective. These include hyperbaric oxygen, agents that decrease blood viscosity (osmotic diuretics, pentoxifylline, procaine, and heparin), vasodilator drugs (histamine, papaverine, verapamil, and carbogen), free radical scavenging vitamins, ginkgo biloba ⁽⁹⁾. However, ever since the 1980s when two double-blind trials showed efficacy of corticosteroids in the treatment of this condition, they have become the most commonly used agents in most centers worldwide ⁽¹⁰⁾.

AIM OF THE WORK

To assess the therapeutic effectiveness of an intra-tympanic (IT) steroid protocol as first and single drug method compared to a systemic steroid protocol to treat SSSL patients.

MATERIALS AND METHODS

To achieve this aim the following steps were done: Determination of the target disease. Identification and Location of articles. Screening and evaluation of the articles. Data collection. Data analysis. Reporting and interpretation of results.

Target subject: Intra-tympanic steroid vs. systemic steroid in treatment of ISSHL.

Identification and location of articles: The literature search was based on the online databases including PubMed to assess all the trials referred to compare the effect of intra-tympanic steroid (ITS) treatment to systemic steroid therapy (SST) as an initial therapy to ISSHL. The search was done by using combinations of the following key words : Sudden hearing loss. Hearing loss. Intra-tympanic steroid. Systemic steroids in hearing loss. Steroids. The study was limited to articles published in English language, conducted on human subjects in till November 2017 and yielded a total number of 412 articles and abstracts. After reading the abstracts resulting from our search, we determined the relevant studies then excluded the repeated ones and got the full texts. 26 full-texted articles were evaluated for eligibility; 8 of them were included in our meta-analysis articles and 18 articles were excluded.

Screening and evaluation of articles: The studies sought in this meta-analysis have two parameters to compare between ITS treatment groups and SST groups as an initial therapy which are hearing improvement and recovery rate.

The inclusion criteria were: Diagnosis of ISSNHL; At least 30 dB hearing loss in 3 continuous frequencies occurring within 3 days with all known causes have to be ruled out. Studies that focused on ISSNHL patients who had undergone ITS treatment or SST from the beginning; and Pure tone average (PTA) differences and recovery rate were evaluated by the studies. Patients with no somatic pathology (such as diabetes, hypertension, gastric ulcer, tuberculosis, glaucoma, and so on), for whom systemic steroids were contra-indicated; Patients

have no oncology diseases; Patients with no autoimmune diseases. Patients who have not been taking ototoxic agents; Patients without acoustic neuroma; not pregnant and nursing women; Patients without middle ear diseases, Patients were tolerant for the component of treatment; the affected ear is not the only hearing ear. Articles were in English language.

Articles were excluded with the following criteria: Patients with somatic pathology (such as diabetes, hypertension, gastric ulcer, tuberculosis, glaucoma, and so on), for whom systemic steroids were contra-indicated; Oncology patients; Patients with autoimmune diseases or those who were constantly or periodically taking steroids; Patients who were or have been taking ototoxic agents; Patients with acoustic neuroma; Pregnant and nursing women; Patients with middle ear diseases, Those who had intolerance for any component of treatment; Those who had SSNHL in the only hearing ear. Studies did not evaluate effects of ITS treatment or SST as primary or initial treatment for ISSNHL; and Insufficient data for evaluating PTA differences or recovery rate Articles not in English language.

Data analysis: The data collected from each article were statistically analyzed using Comprehensive UNISTAT® Statistical Package version 6.5.04 (UNISTAT Ltd., London, England).

RESULTS

Recovery rate between ITS treatment groups and SST group: Eight studies were available for the recovery rate evaluating between the two groups. These studies and the information of recovery rate are presented in Table 1. Pooling of the estimates using REM showed an RR 0.81 (95% CI= 0.60 – 1.10) which was not statistically significant (p value= 0.19) (figure 1). There was evidence of heterogeneity among the study (Qochrans Q p value = 0.04, I² = 53.4%). There was no evidence of publications bias (Begg-Mazumdar Rank Correlation > 0.05, Egger Regression > 0.05) as shown in (figures 2 & 3). So, from the current study results there it was concluded that there was no significant difference concerning the recovery rate between our two studied groups.

Table (1): Summary of recovery rate of eligible studies from old to recent.

Author and year	Recovery criteria	ITS group		SST group	
		Recovered	Total	Recovered	Total
Battaglia <i>et al.</i> , 2008 ⁽¹¹⁾	An improvement of PTA more than 15 dB	10	17	7	18
Hong <i>et al.</i> , 2009 ⁽¹²⁾	An improvement of PTA more than 15 dB	16	32	15	31
Dispenza <i>et al.</i> , 2011 ⁽¹³⁾	An improvement of PTA more than 10dB	20	25	17	21
Kosyakov <i>et al.</i> , 2011 ⁽¹⁴⁾	An improvement of PTA more than 15 dB	22	25	13	25
Bae <i>et al.</i> , 2013 ⁽¹⁵⁾	An improvement of PTA more than 10dB	61	94	305	444
Lim <i>et al.</i> , 2013 ⁽¹⁶⁾	An improvement of PTA more than 10dB	8	20	8	20
Filipo <i>et al.</i> , 2014 ⁽¹⁷⁾	An improvement of PTA more than 15 dB	78	106	57	111
Swachia <i>et al.</i> , 2015 ⁽¹⁸⁾	An improvement of PTA more than 10dB	16	20	19	22

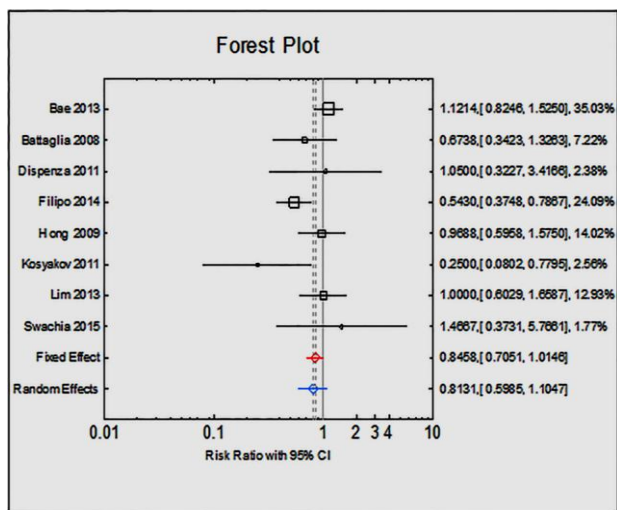


Figure (1): Forest plot for comparison of ITS and SST as regards the recovery from SSHL by the relative risk (risk ratio).

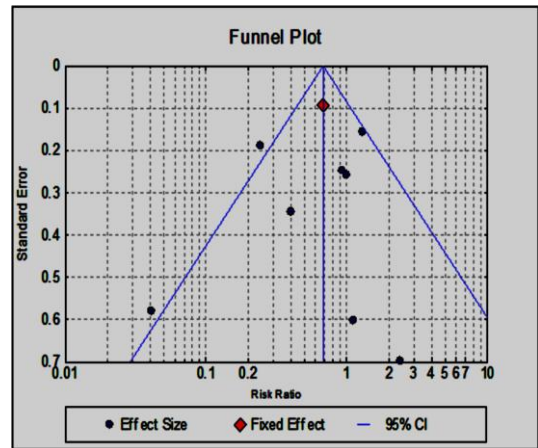


Figure (2): Funnel plot for comparison of ITS and SST as regards the recovery from SSHL by the relative risk (risk ratio).

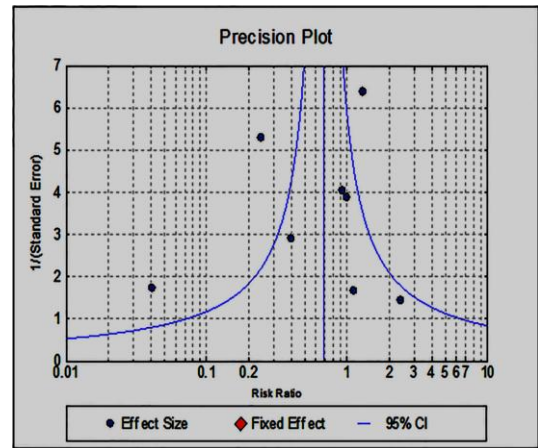


Figure (3): Precision plot for comparison of ITS and SST as regards the recovery from SSHL by the relative risk (risk ratio).

Hearing improvement in ITS treatment groups and SST Groups: Seven clinical trials were available for comparing the hearing outcomes of ITS treatment groups and SST groups as initial therapy. Hearing outcomes were assessed by PTA differences between the PTA before and after treatment, as shown in Table (2). Pooling of the estimates using FEM showed a SMD 0.15 (95% CI= -0.03_0.32) which is not statistically significant (p value =0.10) as shown in (figure 4). There was no evidence of heterogeneity among the study (Qochrans Q p value = 0.12, I2 = 40.59%). There was no evidence of publications bias (Begg-Mazumdar Rank Correlation > 0.05, Egger Regression > 0.05) as shown in (figure 5 & 6). So, It is clear that the current study shows no significant difference between the two groups of treatment regarding the hearing improvement.

Table (2): Summary of PTA differences of eligible studies from old to recent.

Author and year	Frequency for PTA (kHz)	PTA before treatment (dB)		PTA after treatment (dB)		PTA differences (dB)	
		ITS group	SST group	ITS group	SST group	ITS group	SST group
Battaglia <i>et al.</i> , 2008 ⁽¹¹⁾	0.5, 1, and 2	82 (28)	80(27)	51 (25)	59 (33)	31 (25)	21 (33)
Hong <i>et al.</i> , 2009 ⁽¹²⁾	0.5, 1, 2, and 3	77.5 (27.6)	79.9 (32.5)	NR	NR	26 (19)	25 (18)
Dispenza <i>et al.</i> , 2011 ⁽¹³⁾	0.5, 1, 2, and 4	65	51	NR	NR	28 (19)	20 (16)
Kosyakov <i>et al.</i> , 2011 ⁽¹⁴⁾	0.5, 1, 2, and 4	41 (12.87)	39.1 (16.97)	16.1 (8.5)	25.1 (15.3)	24.9 (15.4)	14 (16.2)
Bae <i>et al.</i> , 2013 ⁽¹⁵⁾	0.5, 1, 2, and 3	61.0 ± 19.9	68.0 ± 27.0	41.5	44.8	19.3	22
Lim <i>et al.</i> , 2013 ⁽¹⁶⁾	0.5, 1, 2, and 3	58.9 (31.2)	57.8 (28.5)	46.8 (28.2)	39.1 (26.1)	12.1 (14.6)	18.7 (19.1)
Filipo <i>et al.</i> , 2014 ⁽¹⁷⁾	0.5, 1, 2, 4, and 8	61.74 (26.66)	66.94 (26.26)	36.22 (23.94)	43.92 (28.08)	25.6 (15.8)	23.02 (18.4)
Swachia <i>et al.</i> , 2015 ⁽¹⁸⁾	0.5, 1, 2, and 4	66.12(24)	60.95 (21.98)	51.44 (25.01)	42.11 (19.53)	14.68 (12.88)	18.24 (8.72)

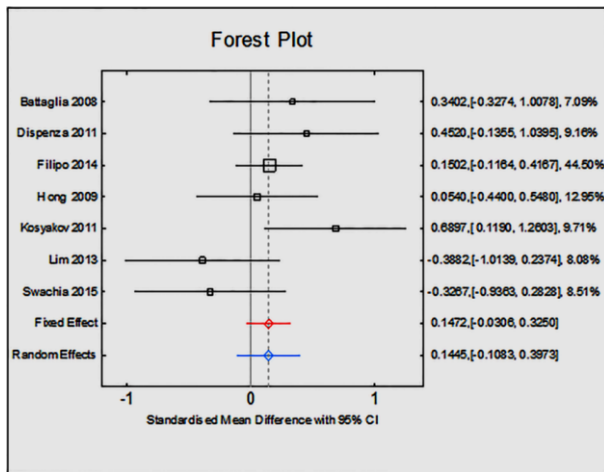


Figure (4): Forest plot for comparison of ITS and SST as regards the hearing improvement (reduction in PTA).

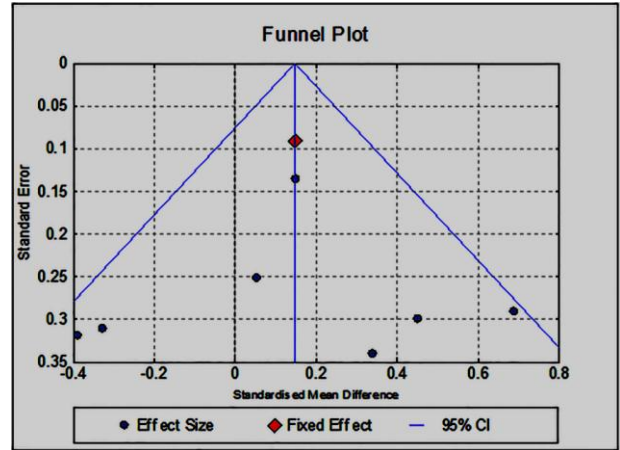


Figure (5): Funnel plot for comparison of ITS and SST as regards the hearing improvement (reduction in PTA).

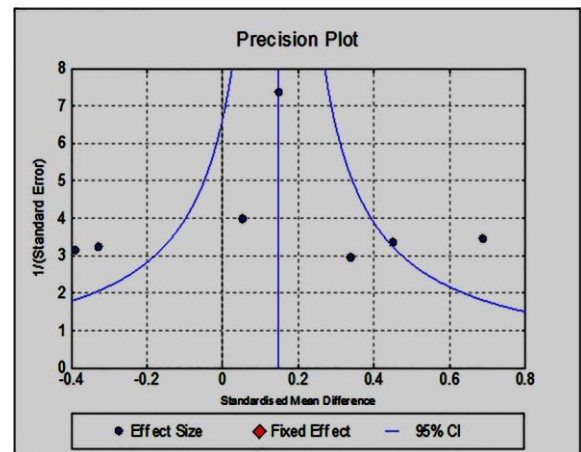


Figure (6): Precision plot for comparison of ITS and SST as regards the hearing improvement (reduction in PTA).

DISCUSSION

There is controversy held in ISSHL treatment, and no standard protocol is accepted worldwide. Many studies indicated that spontaneous recovery occurs in 30-65% of cases. Generally, the recovery happens within the first two weeks after the disease onset. *Zhao et al.* ⁽¹⁹⁾ claimed that the treatment which was started within 2 weeks after the onset is more effective than the treatment started 2 weeks after the onset and later ⁽²⁰⁾. Systemic steroid therapy (SST) regarded as the most effective and fundamental therapy for ISSHL but the side effect limits its application in clinical practice ⁽²¹⁾. In contrast, ITS treatment could directly deliver a high concentration of steroid to the inner ear and reduce the systemic steroid

toxicity, especially in long-term use ⁽²¹⁾. ITS treatment is usually applied as salvage therapy for non-responding patients or primary therapy for patients with systemic steroid contraindication ⁽²²⁾. The aim of this study was to evaluate the treatment outcomes of ITS treatment and SST based on meta-analysis, and to provide an alternative modality for clinical practice. This study was a meta-analysis of 8 studies. We assessed the efficacy of ITS treatment compared to SST for ISSHL as initial therapy. The comparison between the two regimens of treatment was held upon two parameters; the recovery rate and hearing improvement. Regarding the recovery rate between ITS treatment groups and SST groups, In the current study we defined the recovery rate as an improvement of PTA more than either 10 dB or 15 dB (some trials consider 10 dB improvement as a recovery, others consider 15 dB in the accepted limit). So, if the patient in these trials gain 10 dB or 15 dB in PTA after the treatment, then he is considered a recovered one. The result of the current study showed no significant difference between ITS group and SST regarding the recovery rate. The results of the current study is concordant with handful of trials such as **Bea et al.** who find no significant difference in recovery rate between the tested groups ⁽¹⁵⁾. Also, **Lim et al.** ⁽¹⁶⁾ in his study showed that there were no significant differences statistically among the groups regarding the recovery rate. **Hong et al.** ⁽¹²⁾ results were consistent with ours and they mentioned that no significant differences were noted among the hearing recovery rates between the IT group and the oral group. On the other hand, there are some studies that have different results from our study. In the meta-analysis done by **Qiang et al.** they found that ITS treatment provided a better recovery rate than SST. This meta-analysis included only 6 RCTs but in our current study we added 2 more studies and it may cause the difference of the results ⁽²³⁾. **Filipo et al.** concluded that IT protocol was significantly more efficacious regarding the recovery rate. But we can argue that patients were distributed into 4 audiometric curve groups: up-sloping (low frequencies affected), down-sloping (high frequencies affected), flat moderate-to-severe (all frequencies involved) and profound (flat audiogram with PTA >90 dB), and the significant efficacy of ITS protocol over SST has been only proven regarding the up- and down-sloping curves

and not for the all four audiometric curve groups ⁽¹⁷⁾. **Kosyacov et al.** ⁽¹⁴⁾ mentioned in his trial that 6 months after the beginning of the therapy the highest efficacy was observed in the group of patients treated with IT steroids (the maximal rate of complete and partial recoveries and of hearing improvements) compared to the group of patients who had received systemic steroid therapy. We can argue that 6 months follow up is longer than the average of follow up periods adapted by most studies and this may raise doubts about the results. Regarding hearing improvement in ITS treatment groups and SST groups, eight trials were available for comparing the hearing outcomes (improvement) of ITS treatment groups and SST groups. Hearing outcomes were assessed by PTA differences between the PTA before and after treatment. The current study indicated that there was no significant difference between the two groups of treatment regarding the hearing improvement. There are trials results concordant with our conclusions like **Bea et al.**, who mentioned that there was no significant difference in hearing improvement among the groups ($p = 0.147$). Furthermore, no significant difference in the ratio of improvement in hearing was observed among the groups ⁽¹⁵⁾. The same result was found by **Filipo et al.** ⁽¹⁷⁾, who mentioned that regarding the efficacy of the two treatment protocols there was no significant difference in the improvement of the PTA value for IT steroid treatment compared to oral steroid treatment. Also, **Lim et al.** ⁽¹⁶⁾ find that the difference in hearing gain among the tested groups was not statistically significant. In the study done by **Hong et al.** it was found that the average hearing threshold improvement at 500, 1000, 2000, and 3000 Hz was also similar between the two groups. Also, when the hearing threshold improvement of each frequency was examined after the treatments, the thresholds at low frequencies (250, 500, and 1000 Hz) were higher in the IT group than in the oral group, but this difference was not statistically significant ⁽¹²⁾. **Dispenza et al.** ⁽¹³⁾ mentioned that PTA improvements after IT treatment were higher than after systemic treatment, but these differences were not statistically significant. On the other hand there are some findings that disagree with ours such as the meta-analysis done by **Qiang et al.** who mentioned that the results of the study indicated that ITS treatment yielded better PTA improvement

than SST. But their study included only 6 RCTs and our study consisted 2 more studies⁽²³⁾. **Kosyakov *et al.*** who concluded that 6 months after the treatment's beginning the PTA changes in the IT- Dexamithazone group were significantly different from systemic group within the high-frequency range and on all frequencies overall⁽¹⁴⁾. For Intra-tympanic steroid, there is another modality of treatment to use it as a salvage therapy after failure of systemic steroids. Several authors reported hearing improvement in patients with SSHL who failed to recover with primary systemic therapy. These results are consistent with the last recommendation of the American Academy in the field of SSHL that considers the salvage intra-tympanic steroids as a recommended therapy⁽¹³⁾. In the study done by **Dispenza *et al.*** they revealed that the mean improvement of PTA was 12.8 dB (SD±15.2 dB) in the group of patient who was treated with ITS after failure of systemic steroids. They recommended that salvage treatment with intra-tympanic dexamethasone should be suggested to all patients who failed the first systemic treatment⁽¹³⁾. In another study done by **Erdur *et al.***⁽²⁴⁾ on 51 patients who did not respond to initial systemic steroid therapy were analyzed. 21 patients received intra-tympanic steroids as a salvage therapy (intra-tympanic group) and the other 30 patients has no further treatment (control group). Improvement was detected in 10 (47.6 %) of 21 patients in the intra-tympanic group with mean PTA gain, 19.9 dB (SD ± 16.5 dB) and in 3 (10 %) of 30 patients in the control group with mean PTA gain, 4.76 dB (SD±9.6 dB). The degree and rate of improvement were significantly better in the intra-tympanic steroid group. The overall, the results of our meta-analysis revealed that ITS treatment showed no significant difference from SST in the treatment of ISSHL patients as initial therapy. Therefore, this conclusion indicated that both ITS and SST can be offered alone as a primary treatment for ISSHL patients.

CONCLUSION

The conclusion from our meta-analysis is shown as follows: first, according to the current study, ITS treatment produce no significant difference in both aspects PTA improvements and recovery rate than SST in ISSHL patients. Second both SST and ITS alone are an effective treatment in ISSNHL patients as they significantly improves

PTA and also the recovery rate. Third, if patient have any systemic condition that make the use of systemic steroid risky or lead to side effect, then the option of intra-tympanic steroid is, not only justified but mandatory.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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