THE EFFECT OF HIGH DOSE INTRATYMPANIC METHYLPREDNISOLONE INJECTION IN IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS (ISSNHL) AFTER FAILURE OF SYSTEMIC CORTICOSTEROID THERAPY: A PRELIMINARY STUDY IN AMPANG PUTERI SPECIALIST HOSPITAL FROM 1ST MARCH 2015 TO 30TH JUNE 2016

HO HON LIAN

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REMARK

This is to certify that this work by Dr Ho Hon Lian has been reviewed and we undersigned are satisfied and have accepted it as dissertation for the Master of Surgery Otorhinolaryngology, Head and Neck, 2017.

Professor Dato' Dr. Lokman Saim
Dean, School of Medicine,
KPJ Healthcare University College,
Nilai, Malaysia.

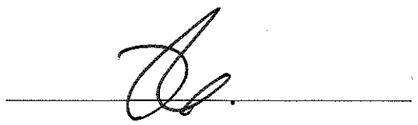
Date : 25/04/2017

Professor (C) Dr. Primuharsa Putra,
Programme Coordinator,
School of Medicine,
KPJ Healthcare University College,
Nilai, Malaysia.

Date : 25/04/2017

DECLARATION

I hereby declare that the work in this dissertation is my own original work except for references, quotations and summaries which have been duly acknowledged.



Dr. Ho Hon Lian

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Date: 25/04/2017

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ABSTRACT

In the practices of otorhinolaryngology, idiopathic sudden sensorineural hearing loss (ISSNHL) is considered to be an otological emergency. Unfortunately there is no standard protocol to treat patients with ISSNHL. Systemic glucocorticoid is the most commonly used treatment for ISSNHL. The intratympanic (IT) steroid injection technique was introduced to decrease the side effects of the usage of systemic steroid and assuming a higher concentration of corticosteroids into the affected cochlea. In this study over 15 month's periods, we evaluated the hearing outcome of the systemic corticosteroids therapy (SCT) and high dose intratympanic (IT) methylprednisolone (62.5mg/mL) as a salvage therapy among the ISSNHL. In total of 4436 patients visited our outpatient clinic, there were thirty-six (0.81%) patients diagnosed to have ISSNHL. After given two weeks of SCT, there were eighteen of 32 (56.3%) patients had hearing improvement of more than 10dB. The other fourteen (43.7%) patients had hearing improvement less than 4dB. Twelve patients were recruited into weekly intratympanic methylprednisolone for three weeks. During one month follow up after completion of IT therapy, six of 12 patients (50%) showed more than 10 dB improvement in the PTA with the median of 19.37dB ($P<0.05$). 33.3% of patients had more than 20dB hearing improvement. Almost all patients in this study had improvement from the symptoms of tinnitus and vertigo. High dose intratympanic methylprednisolone after failure of SCT had significant improvement in the patients' hearing outcome during one month follow up. The intratympanic therapy not only improves the patients' hearing but in addition reduces the symptoms of tinnitus and vertigo.

Keywords: sudden hearing loss, intratympanic, methylprednisolone, steroids

ABSTRAK

Dalam bidang otorhinolaryngology, kehilangan pendengaran sensorineural secara tiba-tiba tanpa sebab-sebab yang diketahui (ISSNHL) boleh dianggap sebagai penyakit kecemasan. Malangnya tidak terdapat protokol yang standard untuk merawat pesakit ISSNHL. Steroid sistemik adalah rawatan yang paling biasa digunakan untuk merawat ISSNHL. Teknik suntikan steroid melalui gendang telinga (IT) telah diperkenalkan untuk mengurangkan kesan-kesan sampingan dari penggunaan steroid sistemik dan juga steroid yang lebih tinggi dapat meresap ke dalam koklea yang terjejas. Dalam kajian ini yang mengambil tempoh lima belas bulan, kita menilai hasil pendengaran terapi sistemik steroid (SCT) dan methylprednisolone (62.5 mg/mL) suntikan melalui gendang telinga (IT) sebagai terapi Salvaj (menyelamat) dalam rawatan ISSNHL. Secara keseluruhan terdapat 4436 pesakit melawat pesakit luar klinik kami, di mana tiga puluh enam (0.81%) pesakit didapati mempunyai penyakit ISSNHL. Selepas diberikan dua minggu SCT, lapan belas daripada 32 (56.3%) pesakit mempunyai peningkatan pendengaran yang lebih daripada 10dB. Empat belas (43.7%) pesakit mempunyai peningkatan pendengaran kurang daripada 4dB. Dua belas pesakit telah berjaya dirawat dengan suntikan methylprednisolone IT mingguan selama tiga minggu. Semasa satu bulan selepas selesai terapi IT, enam daripada 12 pesakit (50%) menunjukkan lebih daripada 10 dB peningkatan pendengaran dengan median 19.37dB ($P < 0.05$). Sebanyak 33.3% pesakit mempunyai lebih daripada 20dB penambahbaikan pendengaran. Hampir semua pesakit dalam kajian ini mempunyai peningkatan dari gejala-gejala tinnitus dan vertigo. Suntikan methylprednisolone (62.5mg/mL) IT selepas kegagalan SCT mempunyai peningkatan signifikan secara klinikal dan

statistik dari segi pendengaran pesakit. Terapi IT ini bukan sahaja meningkatkan pendengaran pesakit tetapi dapat juga mengurangkan gejala-gejala tinnitus dan vertigo.

Kata kunci: pendengaran hilang tiba-tiba, intratympanic, methylprednisolone, steroid

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LISTS OF ABBREVATIONS

e.g.	(exampligratia); for example
et. al.	(et alia); and others
HL	Hearing Loss
IAM	Internal Auricular (Acoustic) Meatus
ISSNHL	Idiopathic Sudden Sensorineural Hearing Loss
IT	Intratympanic
IV	Intravenous
KPJUC	KPJ University College
N	Number
ORL	Otorhinolaryngology
ORL-HNS	Otorhinolaryngology Head and Neck Surgery
PTA	Pure tone audiogram
SHL	Sudden hearing loss
SSHL	Sudden sensorineural hearing loss
UAI	Upper Airway Infection

CHAPTER I

INTRODUCTION

1.1 EPIDEMIOLOGY

In the practices of otolaryngology and audiology, Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is considered to be an otological emergency. According to the American Academy of Otolaryngology – Head and Neck Surgery, ISSNHL is defined as a decline in hearing over a period of 72 hours or less, and affects 3 or more frequencies by 30 dB or greater.

Approximately 5-20 persons in 100,000 populations of patients who suffer from ISSNHL consult an otolaryngologist yearly. Nevertheless, as many patients recover their hearing within a few days and do not seek medical care, true incidences of Sudden Hearing Loss (SHL) are probably under-reported (1, 2).

ISSNHL is equal in sex distribution, common in in patients between the ages of 30 and 60 years, and can cause many negative impacts to the patient. Sudden Sensorineural Hearing Loss (SSNHL) may lead to the primary symptoms of impairment in localisation of sound, comprehension of conversations in a noisy environment, and enjoyment of stereo music. The primary symptoms may then cause secondary symptoms

such as anxiety, inadequate coping with illness, psychogenic disturbances, and an impaired quality of life (3, 4).

1.2 AETIOLOGY OF SUDDEN SENSORINEURAL HEARING LOSS

The aetiology of SSNHL falls into one of several broad categories including autoimmune, infections, metabolic, neoplastic, neurologic, traumatic, and vascular. In terms of frequency, a meta-analysis of 23 studies of SSNHL, revealed that the causes of SSNHL identified were infectious (13%), otologic (5%), traumatic (4%), vascular or hematologic (3%), neoplastic (2%), and others (2%) (4, 5).

Due to a considerable amount of circumstantial evidence, viral infection is considered to be the leading cause of SSNHL. This is because Upper Airway Infections (UAI) and intracranial infections may reach the inner ear through the blood (stria vascularis) and through the cochlear aqueduct or internal acoustic meatus (IAM). Such damages caused by acute viral infections, latent infections, and their reactivation may also explain the lesions found in most SSNHL patients. The common viruses involved are herpes simplex, herpes simplex 2, varicella-zoster (VVZ), cytomegalovirus and the Epstein-Barr (6).

Due to the fact that the cochlea is mainly supplied by a single artery – the labyrinth artery (also a terminal artery), the inner ear is very prone to circulatory alterations. Some vascular and hematologic pathology have been associated with SSNHL such as emboli, transient ischemic attacks, sickle cell anaemia, and subdural hematoma, et cetera. These pathologies decrease the blood supply to the cochlea hence decreasing intracochlear oxygen levels. This kind of obstruction can cause either a transient of permanent loss of hearing as cochlear structures are rather sensitive to even short periods of hypoxia (7).

The concept of autoimmune causes of SSNHL was introduced by McCabe (1979) as a cause of sudden of progressive deterioration in hearing due to the existence of antibodies against antigens in the inner ear, and also the presence of immune complexes in the stria vascularis, and endolymphatic sac & duct (8).

The rupture of one of the labyrinthine windows (oval and round) would cause a loss and perilymph and consequent change in pressure in the relation between with both perilymph and endolymph. This does not occur spontaneously but occurs after sudden changes in pressure in the middle ear, especially during cases of head injuries, barotrauma, stapedecomies, or intense physical exercise (8, 9).

Acoustic Neuroma which is the most common tumour in cerebellopontine angle may cause SSNHL. The incidences of acoustic neuroma in patients with SSNHL range from 0-25%, although most studies find at least one or two within their groups of patients (10).

1.3 TREATMENT OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

Considering that there is no standard protocol or universally accepted way to treat patients with ISSNHL, various therapies and agents such as steroids (systemic and local intratympanic), plasma- expander, antiviral agents, anticoagulants (reduction of acutely elevated plasma fibrinogen), vasodilators, anti-inflammatory agents, diuretics, vitamins, hyperbaric oxygen therapy, and topical insulin-like growth factor therapy have been proposed as therapeutic agents to treat sudden SNHL. It is not easy to assess the efficacy of detailed studies and individual agents on ISSNHL as any evaluation versus the natural history of the disease is complicated by the absence of a specific aetiology and a short therapeutic window (11, 12).

1.3.1 CLUCOCORTICOIDS

Systemic glucocorticoid is the most commonly used treatment for ISSNHL as most cases of ISSNHL are due to an infectious/inflammatory or autoimmune process. In such cases, ISSNHL is usually treated with prednisolone or dexamethasone where the recommended dosages are highly variable, ranging from 1-10 milligrams per kilogram of body weight. Improvements in hearing after systemic corticosteroid therapy occurs in 50% of the patients but approximately 20% of the patients showed no improvement at all. In cases of patients who do not benefit from systemic corticoid therapy, many studies showed that recovery of hearing is poor (13, 14).

The early and late complications of systemic corticosteroid therapy are common and are well-known to medical professionals and as such have led to a few investigations on the use of topical therapies in the inner ear for its conditions.

Alternatively, intratympanic corticosteroid treatment by direct injection into the middle ear as opposed to systemic corticosteroids is beginning to be more accepted in the treatment of ISSNHL due to the low probability of systemic adverse events and also due to the potential delivery of high concentrations of corticosteroid into the inner ear (15).

1.3.2 INTRATYMPANIC THERAPY

Chronologically, Itoh reported on the use of intratympanic steroids for inner ear disease when he treated patients for Meniere disease in 1991 while Silverstein first reported on the use of intratympanic steroids for sudden SNHL in 1996. Other authors have also described the use of intratympanic steroids in the treatment of sudden SNHL (16, 17) .

The intratympanic (IT) steroid injection technique was introduced to decrease the side effects of systemic corticosteroids. Theoretically, IT steroid injection into the middle ear cavity bolsters direct absorption of steroids through the round window hence allowing a comparatively higher concentration of the steroid to reach the perilymph in the inner ear without a systemic distribution. As opposed to systemic treatment, intratympanic therapy acts specifically on the affected ear. Therefore, apart from glucose intolerance and avascular hip necrosis, the unwanted effects of systemic corticosteroid therapy are insomnia, irritability, gastritis, and altered humor; all of which may be avoided with intratympanic therapy (18, 19).

In the treatment of ISSNHL, IT steroid injection is commonly used as salvage therapy in cases where systemic steroid therapy is not successful. The reported complications of intratympanic corticosteroid use though rare, include pain, vertigo, otitis media, perforated tympanic membrane, chronic otitis media, and subsequent hearing loss. Nevertheless, the main con of intratympanic corticosteroid use is the lack of proof regarding its superiority over systemic corticosteroid therapy (20, 21).

The commonest steroids used intratympanically are dexamethasone followed by methylprednisolone. In the literature, the concentration of the solutions used differs as is the case with dexamethasone (2-4 mg/mL to 25 mg/mL) and methylprednisolone (32 mg/mL to 62.5 mg/mL). The amount of corticosteroid injected in the middle ear in various papers range from 0.3-0.5 mL, which is approximately the volume of the middle

ear. Furthermore, various administration modes for intratympanic corticosteroids also exist such as transtympanic needle injection, myringotomy, myringotomy with a ventilation tube, myringotomy with a special perfusion needle (Micromedics, Eagan, MN), and implantable infusion pumps in the middle ear (Round Window m-Cath; Durect Corp., Cupertino, CA) for continuous steroid release. Lastly, the treatment duration, interval between injections, and the number of injections also differ among authors. These range from a single dose to weekly intratympanic injections, steroid solutions as drops applied by patients during several weeks, intratympanic injections several times a week, or implantable infusion pumps (22, 23, 24).

In Malaysia, two studies were done in ISSNHL. First study was done by Amin et al on the University Hospital Experience in ISSNHL in year 1993 (25). Second study was done by Tiong et al on the prognostic indications for ISSNHL in year 2005 (26). However, there is no study done on IT corticosteroids injections. This study will be the first in Malaysia by using high dose intratympanic methylprednisolone (62.5mg/mL) and hopefully we can provide a protocol for managing ISSNHL.

1.3.3 INTRATYMPANIC CORTICOSTEROIDS INJECTIONS FOR TINNITUS AND VERTIGO IN ISSNHL

In ISSNHL, tinnitus is the most common associated symptoms and studies reported tinnitus seen in 72-84% patients (27). This tinnitus is unexpected, may be perceived as a frightening experience and sometimes precedes the onset of hearing loss. Some studies showed that tinnitus incidence decreased from 70% to 30% after 7 to 10 days SCT. On the other extreme, some studies showed that small to moderate reductions in tinnitus incidence after 7- 10 days SCT (27, 28).

Barnard et al first descripted the IT injection for tinnitus in year 1940 followed by Trowbridge reports in year 1949 and treated tinnitus with IT ethylmorphine. Then it took several decades for the concept of IT tinnitus therapy to resurface. Firstly it was started with IT lidocaine and then subsequently shifted toward IT corticosteroid in treating tinnitus (29, 30). The most common side effect of IT lidocaine was almost all of the patients experienced vertigo during IT injections. Thus, IT lidocaine was hardly used for treating tinnitus due to its unacceptable vertigo and only transient efficacy (31).

Up to 40% of the ISSNHL patients complain of dizziness, vertigo, disequilibrium, and imbalance or Meniere's like vertigo. Meniere's disease is usually diagnosed clinically by low frequency hearing loss, episodic vertigo, tinnitus and ear fullness. There are many options of management in treating Meniere's disease like lifestyle modification, antiviral, steroids endolymphatic sac decompression and vestibular nerve section. Studies suggested that intratympanic steroid is a good modality in treating patients with Meniere disease because of the aetiology of immune mediated (31, 32).

CHAPTER II

OBJECTIVES

2.1 GENERAL OBJECTIVES

To evaluate the hearing outcome of the high dose IT methylprednisolone therapy with PTA among ISSNHL patients after failure of systemic steroid therapy presented to otorhinolaryngological outpatient clinic in KPJ Ampang Puteri Specialist Hospital from 1st March 2015 to 30th June 2016.

2.2 SPECIFIC OBJECTIVES

1. To obtain the percentage of ISSNHL patients in otorhinolaryngological outpatient clinic in Ampang Puteri Specialist Hospital from 1st of March 2015 to 30th of June 2016.
2. To obtain the treatment outcome of systemic corticosteroid in treating SSNHL patient.
3. To study the hearing thresholds based on pure tone audiogram average at 500, 1000, 2000, and 4000 Hz pre and post-therapy.
4. To assess the treatment outcome by PTA in 1 month after the completion of both systemic corticosteroids and IT therapy.
5. To generate a guideline/protocol of IT steroid therapy in treating ISSNHL patients in private hospital.

RESEARCH HYPOTHESIS

Intratympanic methylprednisolone as salvage therapy improves hearing for ISSNHL patients after failure of systemic steroid therapy.

CHAPTER III

MATERIALS AND METHODS

3.1 STUDY DESIGN AND SAMPLING

This clinical descriptive study was approved by the KPJ University College (KPJUC) Ethical Committee. The study was carried out in the otorhinolaryngology clinic, KPJ Ampang Puteri Specialist Hospital from 1st of March 2015 to 30th June 2016. Universal sampling technique was used in this study. Those patients aged between 18 to 60 years old who were presented with symptoms of sudden hearing loss proceeded with full history taking and physical examinations. It was then followed by PTA assessment and MRI brain/internal auditory meatus. Patients who fulfilled the inclusion and exclusion criteria were recruited into the study. All ISSNHL patients were offered a 2 weeks course of systemic corticosteroid therapy. After systemic steroid therapy, the patients showed a poor recovery of less than 10dB in the mean hearing level, based on pure-tone audiometry (PTA) at four tested frequencies (500Hz, 1.0 kHz, 2.0 kHz, and 4.0 kHz) were recruited into the IT methylprednisolone study. Inform consent was obtained from all participants before entering the study.

3.1.1 INCLUSION CRITERIA

1. Consented patient
2. Age of 18 to 60 years old.
3. Sensorineural hearing loss (HL) of more than 30 dB appearing on at least three consecutive frequencies within 3 days without clear reasons; normal or near normal hearing in the contralateral ear.
4. Recovery of less than 10 dB after initial systemic steroid treatment for two weeks
5. Initial corticosteroid therapy was started in less than 2 weeks after the onset of the hearing loss.

3.1.2 EXCLUSION CRITERIA

1. Recurrent or fluctuate SSNHL
2. Retro-cochlear disorder such as acoustic neuroma and space occupying lesions evidenced on magnetic resonance imaging
3. Previous surgery in the affected ear
4. Acute or chronic otitis media on otomicroscopic examination
5. Known causes of hearing impairment including Meniere's disease, autoimmune HL, trauma, radiation induced, noise-induced HL, physical trauma and barotrauma or any other identifiable aetiology for sudden hearing loss.
6. Absolute contraindications for systemic corticosteroids

3.2 DATA COLLECTION

All recruited samples that fulfilled the inclusion and exclusion criteria during the study period were selected and proceeded with complete history taking, ENT clinical examinations includes otomicroscopic examinations and pre-therapy PTA. Magnetic resonance imaging (MRI) examinations of brain/cerebellopontine angle and internal auditory meatus was performed in all the patients to rule out structural or retrocochlear pathology, such as acoustic neuroma, stroke or demyelinating disease.

3.2.1 SYSTEMIC CORTICOSTERIODS TREATMENT AND OUTCOMES

All the ISSNHL patients were given a two weeks course of systemic steroid therapy either oral prednisolone 1mg/kg/day or intravenous dexamethasone for 2 weeks. The dose for tablet prednisolone was 30mg BD for 5 days, followed by 25mg BD for 3 days, then 20mg BD for 3 days, then 15mg BD for 3 days. For IV dexamethasone, we were giving 4mg TDS for 5 days, then convert to oral prednisolone tapering dose as described above. Esomeprazole 40mg BD for two weeks was given to the patients with the risks of developing gastritis.

The primary outcome measure for systemic steroid therapy was the proportion of patients showing hearing improvement based on PTA average at four tested frequencies (500, 1000, 2000 and 4000 Hz).

PTA is repeated after completion of systemic steroid therapy and the patients with less than 10dB improved in PTA average at four tested frequencies (500, 1000, 2000 and 4000 Hz) were included in the IT methylprednisolone study.

3.3 PROCEDURES/TECHNIQUES OF INTRATYMPANIC METHYLPREDNISOLONE INJECTION

1. Prior to the procedure, explanation about the risks and expectations about the procedure were given to the patients. Then, a written informed consent was taken from the patient.

2. PTA was performed prior to the IT methylprednisolone injection and at one month follow up after completion of IT injections.

3. Examinations of ears done under microscope to confirm the intact tympanic membrane and middle ear status.

4. All the debris or ear wax in the external ear canal were cleaned.

5. The patient was in the supine position, with the head tilted 45 degree to the healthy ear side. Under a microscope guidance, local anaesthesia was administrated using EMLA 5% cream (1gram contains Lidocaine 25mg & prilocaine 25mg) on the tympanic membrane and outer ear canal.

6. Patient need to wait 45 minutes to allow sufficient time for the local anaesthesia to take effect before suction it out under microscope guidance.

7. Under microscope guidance, a 3cc syringe filled with Methylprednisolone (62.5mg/ml) attach to a 25G spinal needle, and 0.3-0.5 mls injected into middle ear cavity at the anteroinferior quadrant of the tympanic membrane.

8. Patient then lies laterally on the healthy site for 30 minutes. Patient is instructed to avoid yawning, coughing, and speaking for 30 minutes after injections to minimise drainage out of methylprednisolone from the middle ear cavity via the Eustachian tube.

9. Step 1-6 repeat in the subsequent second and third week.

3.3.1 DEFINITION OF IMPROVEMENT (ANALYSIS OF RECOVERY) FOR INTRATYMPANIC METHYLPREDNISOLONE INJECTION

The pure tone audiogram performed prior to first IT methylprednisolone injection, prior to second IT methylprednisolone injection, prior to third methylprednisolone infection, and 1 month after completion of IT methylprednisolone therapy. A 10dB hearing improvement considered a good hearing outcome improvement. A 20 dB improvement or the hearing thresholds below 20dB (normal hearing) in the PTA average at 0.5, 1.0, 2 and 4 kHz considers the intervention a successful.

3.4 STATISTICAL ANALYSIS

IBM SPSS statistics version 23 and Microsoft Excel was used for data analysis. The comparison of mean PTA average before and after SCT and IT methylprednisolone therapy were assessed with Wilcoxon Signed Rank Test. A p value ≤ 0.05 was considered significantly different

3.5 STUDY FLOW CHART:

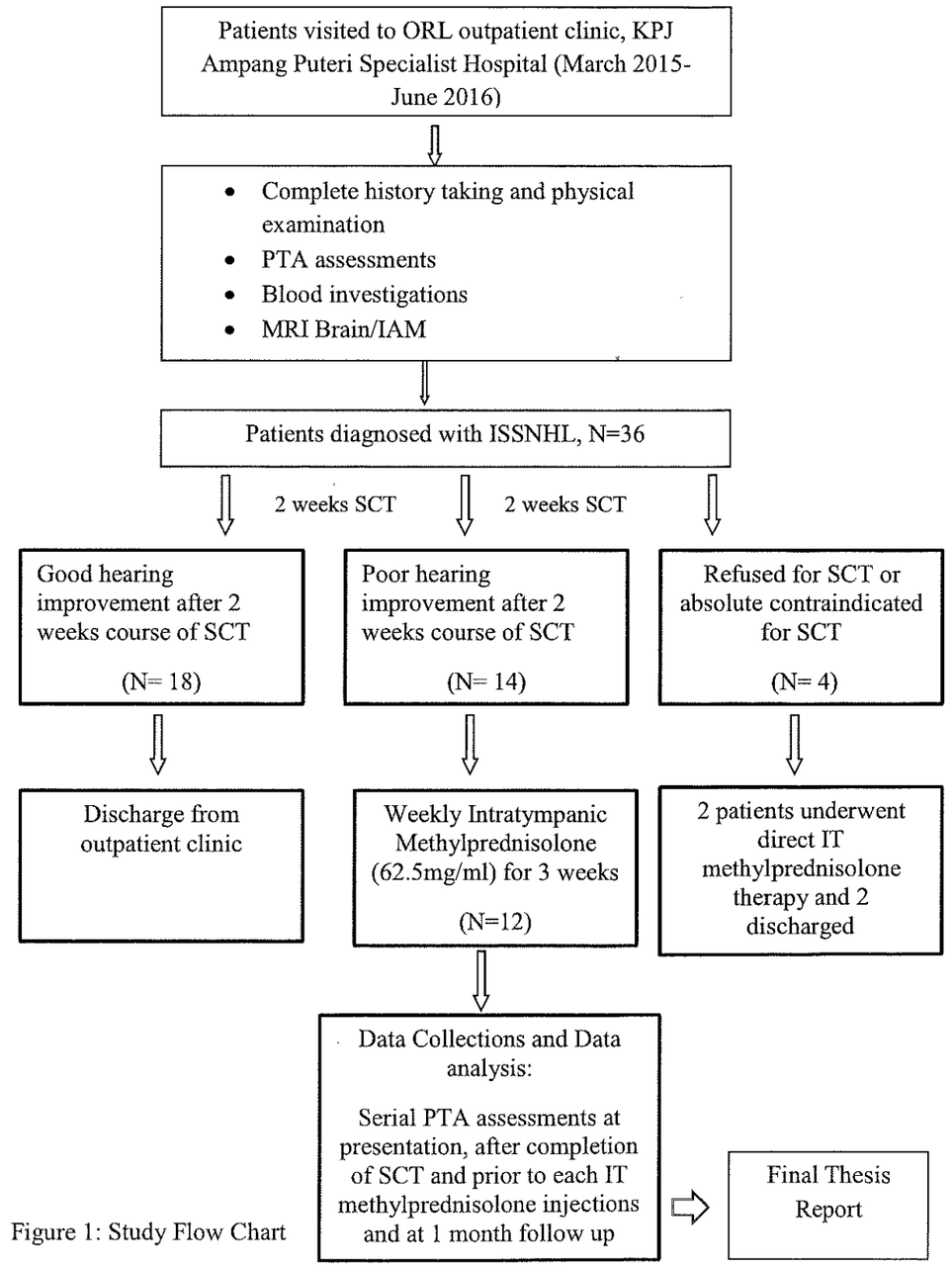

Figure 1: Study Flow Chart

CHAPTER IV

RESULTS

4.1 DEMOGRAPHICS

Among the total of 4436 patients visited to the otorhinolaryngology outpatient clinic during our study period, there were thirty six (0.81%) patients diagnosed to have idiopathic sudden sensorineural hearing loss (ISSNHL) and fulfilled the inclusion and exclusion criteria. There were twenty three (63.9%) female patients and thirteen patients (36.1%) were males. Thirty two patients completed the two weeks of systemic corticosteroids therapy. Two patients offered direct to intratympanic methylprednisolone injection due to presence of contraindications for systemic corticosteroids. Two of thirty six patients were refused for both systemic corticosteroids and intratympanic steroids injections (table 1) (Figure 2).

In our study, 77.8% of patient diagnosed to have ISSNHL without having co-morbid. The commonest co-morbid was diabetes in which seen in nine of 36 (25.0%) patients followed by hypertension seen in six patients (Table 2).

The most common associated symptoms in our patients were tinnitus seen in twenty eight of 36 patients (77.8%) and followed by vertigo seen in eight of 36 (22.2%) patients (Table 3). About 11.1% of patients had associated upper respiratory tract infection symptoms. There was only one patient (2.7%) had associated otalgia (Table 3).

Table 1: Patients with the diagnosis of Idiopathic Sudden Sensorineural Hearing Loss

Number of patients visited ENT outpatient clinic (January 2015 –March 2016)	4436
Number of patients with ISSNHL	36
Percentage of ISSNHL seen in ENT outpatient clinic	0.81%

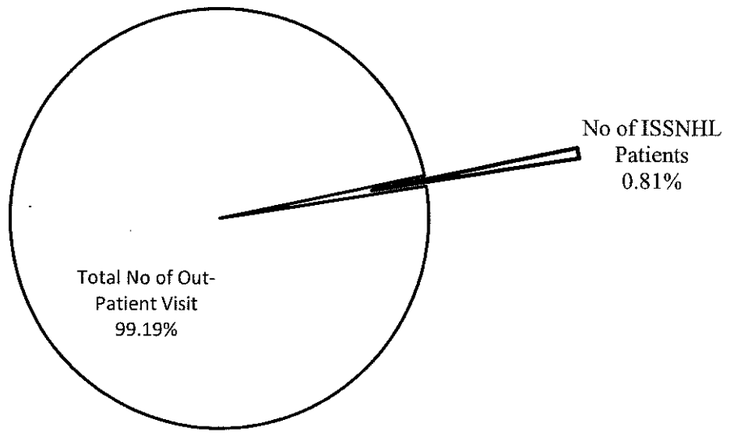

Figure 2: Percentage of ISSNHL seen in Out-Patient Clinic

Table 2: Co-morbidities

Co-morbidities	**Number (N=36)**
None	28 (77.8%)
Type II Diabetes Mellitus	9 (25.0%)
Hypertension	6 (16.7%)
Thyroid disorder	3 (8.3%)
Pregnancy	1 (2.8%)

Table 3: Associated symptoms seen in ISSNHL.

Associated symptoms	**Number (n=36)**
Tinnitus	28 (77.8%)
Vertigo	8 (22.2%)
Upper respiratory tract infections	4 (11.1%)
Otalgia	1 (2.7%)

4.2 HEARING OUTCOME AFTER SYSTEMIC STEROIDS

There were thirty two patients completed two weeks of systemic corticosteroids therapy. There were eighteen of 32 (56.3%) patients regained normal hearing or had improvement of more than 10dB in PTA average measurement. However, there were fourteen (43.7%) of patients had poor improvement in the PTA average of less than 10dB (Table 4).

4.3 INTRATYMPANIC METHYLPREDNISOLONE THERAPY AFTER FAILURE OF SYSTEMIC CORTICOSTEROIDS THERAPY

There were fourteen patients eligible for intratympanic steroids therapy. However, two patients not keen for intratympanic injections. Therefore, only twelve recruited into intratympanic methylprednisolone therapy. The mean age of this group was 43.4 years (range from 30 to 52) as shown in table 5. In our study, most of the patients came to clinic early after they presented with sudden onset of hearing loss with a mean days of 4.8. There were two patients came to clinic during the first day, two during the second days, two during the third days and there was one came at twelve day (table 6).

Table 4: Outcome of systemic corticosteroids.

Outcome	**Number (n)**
Regained normal hearing or more than 10dB improvement in PTA Average	18 (56.3%)
No improvement of less than 10 dB improvement in PTA average	14 (43.7%)
Total	32 (100.0%)

Table 5: The ages of patient underwent intratympanic methylprednisolone injections

Ages in years	Number of patient
30	1
33	1
37	1
41	1
42	1
43	1
44	1
48	1
50	2
51	1
52	1
Means: 43.4	Total: 12

Table 6 Time of initial presentation to clinic in patients with intratympanic methylprednisolone group

Time of presentation to clinic (days)	Number of patients
1	2
2	2
3	2
4	1
5	1
7	1
8	1
10	1
12	1
Means : 4.8	Total: 12

4.4 HEARING OUTCOME OF INTRATYMPANIC METHYLPREDNISOLONE THERAPY

We compare the hearing outcome of the twelve patients who underwent intratympanic methylprednisolone therapy by comparing the hearing thresholds at presentation, after systemic corticosteroids and subsequently after intratympanic methylprednisolone injections.

4.4.1 COMPARING OF HEARING OUTCOME AT PRESENTATION AND AFTER SYSTEMIC CORTICOSTEROIDS

All our twelve patients showed no improvement or improvement of less than 10dB in the four-tone average PTA after completion of the two weeks systemic corticosteroids therapy. Two of 12 patients (16.7%) showed no improvement in the PTA average measured, ten patients showed improvement of less than 10dB. However, there was no patient showed deteriorating of hearing outcome after the SCT. Mean PTA average showed an improved of 4.17dB after the SCT (Table 7).

Table 7: Comparison of PTA average at presentation and after completion of systemic corticosteroids therapy.

Patient	PTA average at presentation (dB)	PTA average after systemic corticosteroids (dB)	Outcomes: i)More than 10 dB improvement ii)No improvement or Less than 10dB improvement
1	31.25	31.25	No improvement
2	32.50	32.50	No improvement
3	33.75	31.25	Poor
4	35.00	32.50	Poor
5	42.50	38.75	Poor
6	60.00	55.00	Poor
7	66.25	62.50	Poor
8	66.25	60.00	Poor
9	70.00	61.25	Poor
10	86.25	78.75	Poor
11	86.25	81.25	Poor
12	95.00	90.00	Poor
Means	58.75	54.58	Poor: 4.1dB gained.

4.4.2 COMPARING OF HEARING OUTCOME BEFORE (COMPLETION OF TWO WEEKS OF SYSTEMIC CORTICOSTEROIDS THERAPY) AND 1 MONTH AFTER COMPLETION OF INTRATYMPANIC METHYLPREDNISOLONE THERAPY

In this study, when comparing the hearing outcome before initiation of IT therapy and at 1 month follow up after completion of IT therapy, six of 12 patients (50%) showed improvement of more than 10dB in the PTA average with a mean of 10.72dB (table 8).

In the analysis of statistics, the Wilcoxon singed-rank test showed that intratympanic (IT) methylprednisolone therapy after failed of SCT in ISSNHL did elicit a statistically significant change in the PTA average before the initiation of IT therapy and during follow up at 1 month after the completion of IT therapy (Z= -2.594, p= 0.009).

4.4.3 COMPARING OF HEARING OUTCOME DURING PRESENTATION AND ONE MONTH AFTER INTRATYMPANIC METHYLPREDNISOLONE THERAPY

In order to assess the total treatment outcome for our study group, we were comparing the hearing outcome of the patients in terms of the 4-tone PTA average during their first presentation to our clinic and during their one month follow up after completion of IT methylprednisolone injections. The results were encouraging in which seven of 12 patients (58.3%) showed improvement of more than 10dB in the PTA average (Table 9).

The improved in the hearing outcome was significant after completion of the SCT and IT therapy. Our study showed that intratympanic (IT) methylprednisolone therapy after failure of systemic corticosteroids therapy in ISSNHL did elicit a statistically significant change in the PTA average before and after completion of treatment (Z= -2.981, p= 0.003).

4.4.4 COMPARING THE STABILITY OF THE IMPROVEMENT OF THE HEARING OUTCOME AFTER COMPLETION OF INTRATYMPANIC STEROID THERAPY AND SURING ONE MONTH FOLLOW UP

In order to assess the improvement in the hearing outcome after completions of therapy were remained stable during the 1 month follow up in the clinic. The changes in the PTA averages was statistically insignificant as shown in the Wilcoxon Signed Ranks Test (Z= -1.812 and P-value at 0.07) (Table 10).

Table 8: Comparison of PTA average before initiation of intratympanic therapy (IT) and at 1 month after completion of systemic corticosteroids therapy plus IT therapy.

Patient	PTA average before initiation of intratympanic methylprednisolone therapy (dB)	PTA average at 1 month follow up (dB)	Outcomes: i)Good->10dB improvement ii)Poor:<10dB improvement
1	31.25	26.25	Poor
2	32.50	18.75	Good
3	31.25	16.50	Good
4	32.50	27.50	Poor
5	38.75	27.50	Good
6	55.00	61.25	Poor
7	62.50	60.00	Poor
8	60.00	10.00	Good
9	61.25	60.00	Poor
10	78.75	73.75	Poor
11	81.25	66.25	Good
12	90.00	78.75	Good
Means	54.58	43.86	Good with 10.72db improved.

Table 9: Comparison of PTA average at presentation and at 1 month after completion of systemic corticosteroids therapy followed by IT therapy.

Patient	PTA average at presentation (dB)	PTA average at 1 month after completion of systemic steroids followed by Intratympanic methylprednisolone therapy (dB)	Outcomes: i)Good-More than 10 dB improvement ii)Poor: Less than 10dB improvement
1	31.25	26.25	Poor
2	32.50	18.75	Good
3	33.75	16.50	Good
4	35.00	27.50	Poor
5	42.50	27.50	Good
6	60.00	61.25	Poor
7	66.25	60.00	Poor
8	66.25	10.00	Good
9	70.00	60.00	Good
10	86.25	73.75	Poor
11	86.25	66.25	Good
12	95.00	78.75	Good
Means	58.75	43.86	14.89dB Improved

Table 10: Comparison of PTA average after completion of therapy (both SCT and IT) and at 1 month follow up

Patient	PTA average after completion of therapy (both SCT and IT) (dB)	PTA average at 1 month follow up (dB)
1	23.75	26.25
2	20.00	18.75
3	16.25	16.50
4	26.25	27.50
5	25.00	27.50
6	58.75	61.25
7	58.75	60.00
8	10.00	10.00
9	53.75	60.00
10	71.25	73.75
11	66.25	66.25
12	81.25	78.75
Means	42.60	43.87

4.4.5 HEARING OUTCOME ACCORDING TO THE LEVEL OF HEARING LOSS

The hearing outcome improved for all the mild, moderate and severe-profound hearing loss groups. Mild hearing loss group had a 10.9dB improved, moderate hearing loss improved by 19.07dB and severe-profound improved by 14.69dB (Figure 2).

4.4.6 HEARING OUTCOME AT PRESENTATION AND AFTER SCT AND IT INJECTIONS

We compared the hearing outcome after SCT and each IT and found out that all the hearing outcomes improved after each IT injections with significant P values range from 0.002 to 0.007. The most significant improvement happen after the third IT therapy (P=0.002) in table 11.

4.4.7 HEARING THRESHOLDS BEFORE AND AFTER IT INJECTIONS IN EACH FREQUENCY

We included the hearing thresholds before and after IT injections in the four frequencies tested (500Hz, 1000Hz, 2000Hz and 4000Hz). 500 Hz frequency had the highest gain of 14dB before and after IT therapy (P=0.05) followed by 4000Hz at 11.67dB gained (P=0.03), then 2000Hz at 7.22dB (P=0.02) and lastly 1000Hz at 6.67dB gained (P=0.01) in table 12.

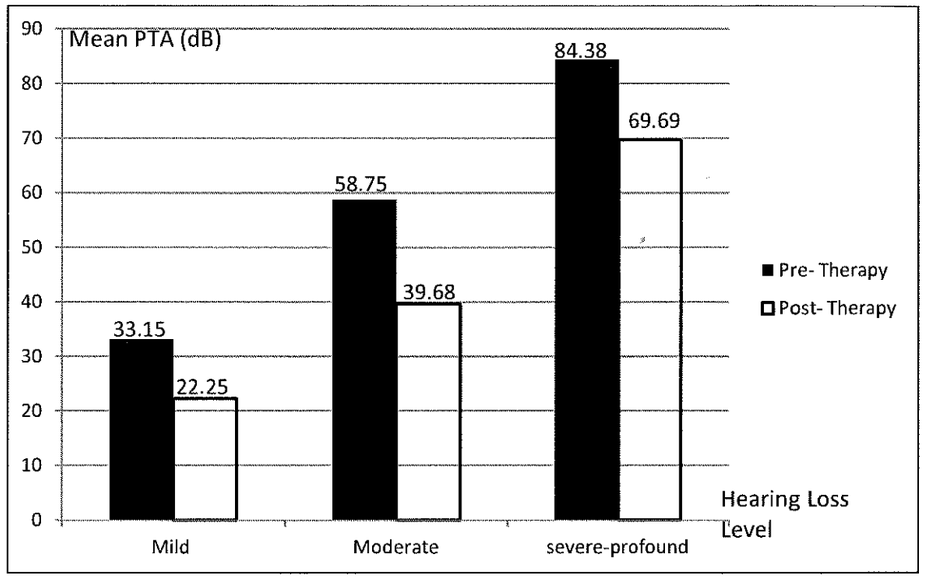

Figure 3 Mean PTA average pre and post-therapy according to the level of hearing loss.

Table 11: Hearing outcomes after SCT and each IT.

Duration	Mean of PTA (dB)	P-value
After SCT	56.37	0.005
After first IT therapy	55.87	0.007
After second IT therapy	50.95	0.005
After third IT therapy	48.50	0.002
At 1 month follow up	50.00	0.002

Table 12: Hearing Thresholds before and after IT injections in each frequency

Frequency (Hz)	Pre-therapy (Mean PTA, dB)	Post therapy (Mean PTA, dB)	PTA improved (dB)	P-value (Wilcoxon Test)
500	66.00	52.00	14.00	0.05
1000	63.89	57.22	6.67	0.01
2000	62.22	55.00	7.22	0.02
4000	60.00	48.33	11.67	0.03

4.5 TREATMENT EFFECT IN TINNITUS AND VERTIGO AFTER IT METHYLPREDNISOLONE INJECTIONS

In this study, seven of 12 patients (58.3%) had tinnitus during the presentation. After IT methylprednisolone injections, the tinnitus reduced from 58.3% to 8.3%.

Four out of 12 (25%) patients presented with vertigo. However after IT methylprednisolone injections, only one patient (8.3%) had persistent vertigo (Figure 2).

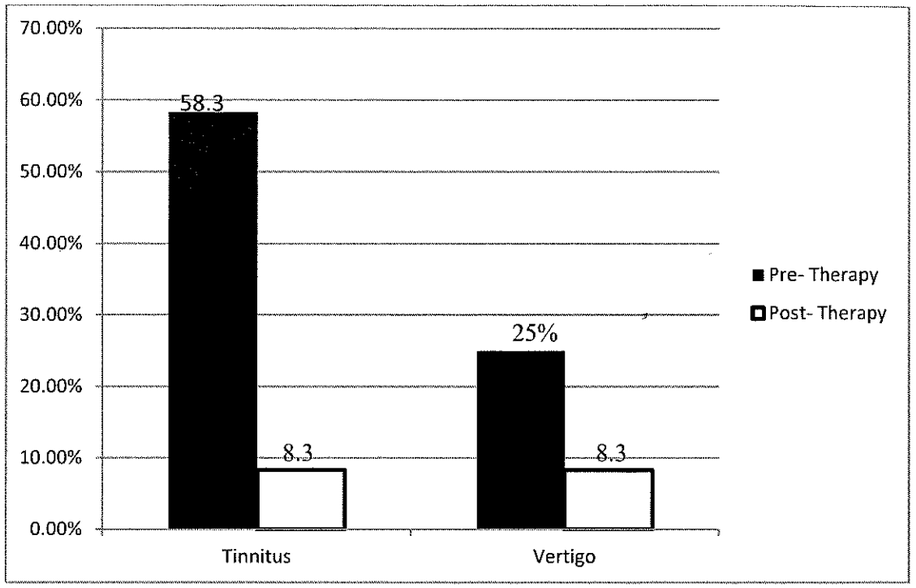

Figure 4 Treatment outcomes in tinnitus and vertigo after IT methylprednisolone

CHAPTER V

DISCUSSIONS

5.1 DEMOGRAPHICS

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is considered to be an otological emergency. Approximately 5-20 persons in 100,000 populations of patients who suffer from ISSNHL consult an otolaryngologist yearly. ISSNHL is equal in sex distribution, common in in patients between the ages of 30 and 60 years (33, 34).

In our study, there were in total of 4436 patients visited to the otorhinolaryngology outpatient clinic during study period, thirty six (0.81%) patients diagnosed to have idiopathic sudden sensorineural hearing loss (ISSNHL). There were twenty three (63.9%) female patients and thirteen patients (36.1%) were males. Thirty two patients completed the two weeks of systemic corticosteroids therapy. Two of 36 patients refused for both systemic corticosteroids and intratympanic steroids injections. The commonest co-morbid was diabetes in which seen in 9 of 36 (25.0%) patients followed by hypertension seen in 6 patients. The most common associated symptoms in

our patients were tinnitus seen in 28 of 36 patients (77.8%) and followed by vertigo seen in 8 of 36 (22.2%) patients.

5.2 COCHLEAR PHARMACOKINETICS

There is increase production of inflammatory mediators and stress hormones as a result of abnormal activation of cellular stress pathway in ISSNHL. Latest literatures showed that the increase of the inflammatory mediators and other stress related proteins occurred in ISSNL can disrupt the hemostatic balance of the çochlea and cause sudden sensorineural hearing loss. The administration of corticosteroids in the treatment of ISSNHL helps in protects the cochlea from the harmful effects of inflammatory cytokines by down-regulation of local pro-inflammatory cytokines such as IL-1, IL-6 and tumour necrosis factors. Corticosteroids help in up-regulation of aquaporins, increasing Na^{+}-K^{+} exchange mechanism in the striae vascularis and direct effect on connexion-protein expression. Thus, corticosteroids can increase cochlear blood flow, neuprotective, antioxidants and anti-apoptotic effects on the cochlear nerve in ISSNHL (35, 36).

The main advantage of the intratympanic steroids injections is the avoidance of systemic absorptions of the corticosteroids and prevents the patients from the systemic side effects of corticosteroids. The second main advantage of the corticosteroids administered intratympanically is it may attain high concentrations in the perilymph, higher than when administered intravenously or orally. This believes higher concentration of corticosteroids able diffused into cochlea and gives a better outcome in the treatment of ISSNHL (37, 38).

Some studies showed that dexamethasone diffuses well through the round window (39, 40). In our study, we chose methylprednisolone because previous study by

Parnes's et al demonstrated that it had a higher concentration and proved to remain longer in the perilymph (41). This can be explained by the molecular weight of the dexamethasone, 392.461 g/mol which is smaller than methylprednisolone, 466.525g/mol. Thus, methylprednisolone diffuse slower via the round window. Ho et al study in year 2004 showed that weekly intervals of IT corticosteroids for three injections proven to be better compared to the first two injections. Thus, weekly IT methylprednisolone (62.5mg/ml) for three weeks was used in this study.

5.3 HEARING OUTCOME OF SYSTEMIC CORTICOSTEROIDS THERAPY FOR IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

In our study, after the two weeks course of systemic corticosteroids therapy, there were 18 of 32 (56.3%) patients regained normal hearing or had good improvement of more than 10dB in PTA average measurement. However, there were 14 (43.7%) patients had poor improvement in the PTA average after completion of the systemic corticosteroid therapy. This was comparable with the previous studies done in which 45-75% of patients regained normal hearing after SCT (42, 43, and 44).

There were 14 (43.7%) of patients eligible for intratympanic steroids therapy and two of them refused for IT therapy. Therefore, we recruited 12 patients into intratympanic methylprednisolone therapy. The mean age of this group was 43.4 years (range from 30 to 52 years). All the patients in IT group presented to clinic in less than 14 days after the onset of the sudden hearing loss. These early presentations to the clinic of less than 2 weeks was important because many studies showed that initiation of the corticosteroids therapy in less than 14 days gave a better hearing outcome after completion of the corticosteroid therapy (45, 46).

5.4 HEARING OUTCOME OF INTRATYMPANIC METHYLPREDNISOLONE THERAPY

In comparing the hearing thresholds of the patients after completion of SCT and the hearing thresholds during one month follow up, six of 12 patients (50%) showed improvement in the PTA average, mean at 10.79dB ($P<0.025$). This finding was similar to other studies previously. Taghi et al study in year 2012 showed that the PTA improved range from 13.09 to 15.54 dB after IT injections. Igor et al study proved that 71.4% of patients had hearing improvement of more than 20dB after IT injections. Pinones et al study in year 2015 reported the recovery rate of 12 to 100% and PTA improvement ranged from 8 to 62 dB after IT steroids injection (47, 48).

To determine the stability of the hearing improved after completion of both SCT and IT therapy in ISSNHL, we compared the hearing outcome of the patients after completion of SCT followed by IT methylprednisolone therapy with the hearing outcome measured objectively with PTA average during one month follow up. It concluded that the PTA average improved remained stable during the one month follow up in this study. Raymundo et al study in year 2010 recruited fourteen patients treated with three intratympanic methylprednisolone injections after failed of SCT and showed that ten of 14 (71.4%) patients had hearing recovery of more than 20dB. The hearing thresholds remained stable during one month follow up. Iaonnis study et al in year 2013 concluded that the improvement in hearing outcome remained stable during 1 month and 3 month follow up.

The worsening of 1.27dB in the PTA averages was statistically not significant ($P>0.05$). Thus, in this study, the patient's PTA average may worsen minimal after completion of the corticosteroids therapy but it was clinically and statistically not significant.

5.5 Hearing Outcome in Severe-profound Sensorineural Hearing Loss Group

Studies has shown that the presences of vertigo, initial severe-profound sensorineural hearing level, down sloping pattern in the PTA and late treatment onset more than 14 days were considered as poor prognostic factors in ISSNHL. In comparison, some studies proved that the initial hearing level did not affect SSNHL except in patients with profound cases and vertigo was an insignificant prognostic factor in ISSNHL. Siegel et al showed that there was no significant relation between the initial hearing level and SSNHL (49, 50, and 51).

In our study, there were 4 of the 12 patients (33.3%) presented with severe-profound sensorineural hearing loss with the mean PTA on arrival of 85.00dB. After completion of the SCT and IT therapy, the mean PTA improved to 69.7dB. When we looked into the patient individually, none of these 4 patients regained normal hearing after the interventions. Jong et al study in year 2010 showed that IT steroid as salvage therapy in severe ISSNHL had significant improvement with a recovery rate of 37.5% compared with 5.5% in profound group ($P<0.05$) (52). Another study by Plontke et al showed the PTA threshold after intratympanic steroid salvage therapy had a statistically significant improvement of 15dB (7-24dB) (53).

In this study, one of the patients remained at severe hearing loss with a good improvement of PTA average at 12.5dB. None of the patient showed deteriorating in their hearing outcome. One of the 4 patients able to improve his hearing loss from profound to severe with a PTA average gained of 16.25dB (95dB to 78.75dB). This improvement in his hearing was clinically significant because the patient may further augmented by the conventional behind the era hearing aids.

5.6 Weekly Interval of Intratympanic Methylprednisolone Injections for Three Weeks as Salvage Therapy in ISSNHL.

The total number of injections and the intervals of IT corticosteroids injection vary among different studies ranging from a single day to weekly intratympanic injections up to multiple weeks. David et al study used a 24mg/mL intratympanic dexamethasone at a single time, Jeanette et al used a weekly IT methylprednisolone (40mg/mL) for 4 weeks and Ho et al study used IT dexamethasone once a week for 3 consecutive weeks and it proved that there was significant improvement after second IT therapy (55, 56). In year 2010, Raymundo et al study recruited fourteen patients treated with three intratympanic methylprednisolone injections after failed of SCT and showed that ten of 14 (71.4%) patients had hearing recovery of more than 20dB. Thus, in this study once a week IT methylprednisolone (62.5mg/mL) for three consecutive weeks was given to the ISSNHL patients after failure of systemic corticosteroid therapy. This weekly interval IT injection may allow sufficient time for the tympanic membrane to heal before the subsequent injection (57, 58).

In this study, IT methylprednisolone injection after failure of systemic corticosteroids therapy did help in improve the patients' hearing outcome but not all the patients need weekly IT injections for 3 weeks. This is because 2 of 12 (16.7%) patients regained normal hearing (both clinically and PTA average less than 20dB) after two weeks course of corticosteroids therapy followed by only one intratympanic methylprednisolone injection. Another 1 patient regained normal hearing after the second IT methylprednisolone therapy. This may due to the natural disease of the idiopathic sudden sensorineural hearing loss and some studies showed that about 15-20% of patients may show delayed in hearing improvement after systemic corticosteroids therapy up to 1 month. In our study, we offered IT therapy for all 12 patients after failure of systemic corticosteroids therapy in view of the low risks of intratympanic complications without further delay to avoid the patient in missing the

golden therapeutic window periods. In this study, the most significant hearing improvement occurred after third IT methylprednisolone injections with a mean PTA gained of 12dB ($P<0.025$).

5.7 TREATMENT OUTOCME FOR TINNITUS AND VERTIGO AFTER COMPELTION OF INTRATYMPANIC METHYLPREDNISOLONE INJECTIONS

Starting in the year 1990s, more research studies focus in IT corticosteroids in treating tinnitus. Sakata et al study showed a 75% improvement rate in tinnitus after IT dexamethasone injections (59). Thomas et al study in year and Guido et al study in year 2016 concluded that tinnitus associated with ISSNHL has a good prognosis for rapid improvement up to complete remission (60, 61). But some other studies showed no significant improvement in treating tinnitus with IT steroids. In this study, there was six of 7 patients had no more tinnitus after IT methylprednisolone injection which is similar with the result shown in Sakata et al study (62, 63).

Deenadayal et al study in year 2016 showed that the mean episodic of vertigo reduced from 3.8 to 0.06 after IT methylprednisolone therapy with a vertigo control rate of 98.01%. Other two studies showed excellent vertigo control rate with IT steroids. In this study, vertigo disappeared in three out of 4 patients (75%) after IT therapy. Vertigo control rate at one month remained at 75% which is inferior to the Deenadayal et al study that had more than 95% vertigo control rate (64). There was only one patient complained of persistent episodic vertigo and referred to vertigo clinic for further management.

5.8 KPJ AMPANG PUTERI SPECIALIST HOPSITAL PROTOCOL IN TREATING ISSNHL PATIENTS

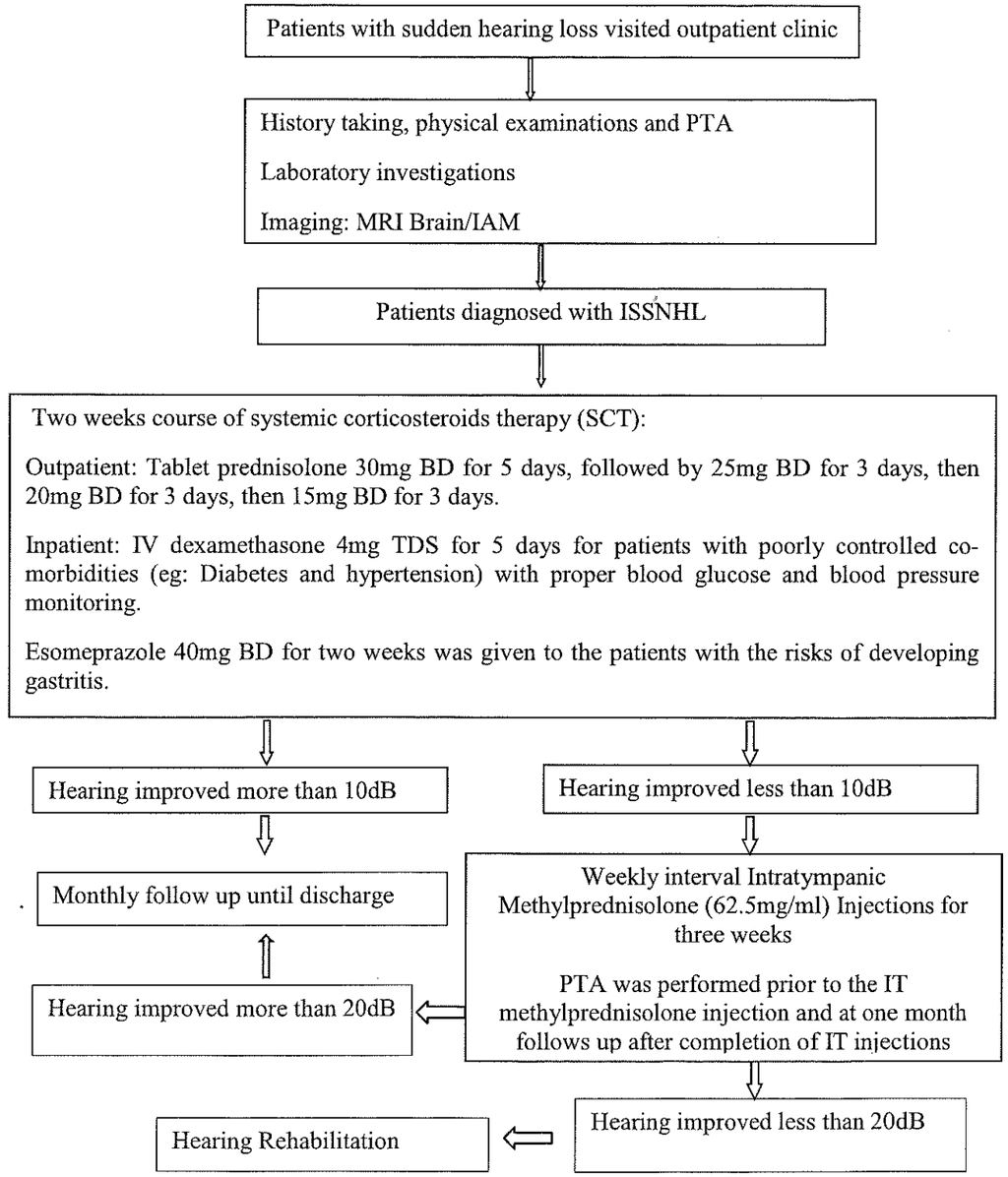

Figure 5 Protocol in treating ISSNHL in KPJ Ampang Puteri Specialist Hospital

CHAPTER VI

CONCLUSIONS

In this study, there was 0.81% of patient visited outpatient clinic diagnosed to have ISSNHL. Most of the patients presented to ENT clinic early with a mean of 4.8 days and all of them received treatment in less than two weeks' time.

There were 56.3% of patients with ISSNHL clinically improved after 2 weeks course of systemic corticosteroids therapy (SCT). However, there were 43.7% of patients showed improvement less than 10dB after SCT. In the intratympanic methylprednisolone salvage therapy, 50% showed more than 10 dB improvement in the PTA with the median of 19.37dB ($P<0.025$). 33.3% of patients had more than 20dB hearing improved. We concluded that intratympanic methylprednisolone salvage therapy after failure of systemic corticosteroids therapy had significant improvement in the patients' hearing outcome. IT methylprednisolone improved tinnitus associated with ISSNHL up to 85%. IT steroids injection improved vertigo symptoms in ISSNHL patient. For those patients with failed SCT, the intratympanic therapy can further improve the patients' hearing outcome and reduced the symptoms of tinnitus and

vertigo. Thus, high dose intratympanic methylprednisolone (62.5mg/mL) is highly recommended as a salvage therapy after failed SCT in treating ISSNHL.

LIMITATIONS OF THE STUDY

The limitations of our study were the sample size was not large enough; single center prospective clinical study; it did not contain a control group to compare the results of treated and untreated patients.

This was because most of the patient (12 of 14) available patients for therapy , after unsuccessful systemic therapy , chose to enter the study; we found it unethical to block access to Intratympanic therapy and also the two patients that refused for intratympanic study were too small in sample for us to make them as the control group.

RECOMMENDATIONS

1. We suggest a longer period of duration for sample collection and analysis.
2. We suggest multiple centres for data collection so that the sample could be bigger.

CHAPTER VII

REFERENCES

1. Chau, J. K., Lin, J. R., Atashband, S., Irvine, R. A., & Westerberg, B. D. Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. *Laryngoscope, 2010; 120*:1011-1021.
2. Maggie, K., Selena E. H., Jamil, A. S., & Pamela, C. R. *Sudden Sensorineural Hearing Loss: A Review of Diagnosis, Treatment, and Prognosis. Trends in Amplification, 2011; 15 (3): 91-105.*
3. *Neil, F., Nishchay M., & Theo, J. Sudden Onset Hearing Loss Causes, Investigations and Management. Australian Family Physician, 2013; 42(9): 641-644.*
4. *David, S. H., Matthew, O., Seth. C., Kenneth, W., & Robert, F. L. Intratympanic Dexamethsone For Sudden Sensorineural Hearing Loss After Failure of Systemic Therapy. Laryngoscope, 2007; 117: 3-15.*
5. Takayuki N., Kozo K., Shin-ichi U., Naohito H., Keiji T., Mariko T., Keizo F. Akira S., Shizuo T., Harue T., Michio T., Atsushi Y., Toshiko I., Takafumi I., Akira S., Yasuhiko T., & Juichi I. A Randomised Controlled Clinical Trial of

Topical Insulin-like Growth Factor-1 Therapy for Sudden Deafness Refractory to Systemic Corticosteroid Treatment. BMC Medicine 2014, 12:219.

6. Wilson WR, Byl FM, Laird N: The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. Arch Otolaryngol 1980, 106:772–776.
7. Rauch SD: Clinical practice. Idiopathic sudden sensorineural hearing loss. N Engl J Med 2008, 359:833–840.
8. Schreiber BE, Agrup C, Haskard DO, Luxon LM: Sudden sensorineural hearing loss. Lancet 2010, 375:1203–1211.
9. Markus S. Perspectives on the Pathophysiology and Treatment of Sudden Idiopathic Sensorineural Hearing Loss. Dtsch Arztebl Int 2009; 106(41): 669-676.
10. Paulo R. L., Ana C. K. C. Idiopathic Sudden Sensorineural Hearing Loss: Etiopathogenic Aspects. Brazilian Journal of Otorhinolatyngology, 2006; 72(4): 554-561.
11. Emanuele F., Antonio F., Anna C. F., Enrico A., Giacomo S., & Maurizio A. Intratympnaic Steroid Treatment for Idiopathic Sudden Sensorineural Hearing Loss after Failure of Intravenous Therapy. ISRN Otolaryngology 2012, 1-6.
12. Rauch SD, Halpin CF, Antonelli PJ, Babu S, Carey JP, Gantz BJ, Goebel JA, Hammerschlag PE, Harris JP, Isaacson B, Lee D, Linstrom CJ, Parnes LS, Shi H, Slattery WH, Telian SA, Vrabec JT, Reda DJ: Oral vs intratympanic corticosteroid therapy for idiopathic sudden sensorineural hearing loss: a randomized trial. JAMA 2011, 305:2071–2079.
13. Mingming W., Yuechen H., Zhaomin F., Daogong Z., & Haibo W. Therapeutic Effect on Idiopathic Sudden Sensorineural Hearing Loss with Duration of Onset More Than 3 Months. Indian J Otolaryngology Head Neck Surgery. Jan-March 2016, 65(1): 61-65.

14. Alex B., Raoul B., and Roberto C. Combination Therapy (Intratympanic Dexamethasone + High-Dose Prednisolone Taper) for the Treatment of Idiopathic Sudden Sensorineural Hearing Loss. Otology & Neurotology 2008, 28:453-460.
15. Shima A., Ardavan T., Pedram B. Combined Intratympanic and Systemic Steroid Therapy for Poor-Prognosis Sudden Sensorineural Hearing Loss. Iranian Journal of Otorhinolaryngology, 2013; 1(25): 23-28.
16. Mohamad T. K. A., Pedram B., Nasrin Y., & SHirin M. The Effect of Intratymapnic Dexamethasone with Oral Prednisolone as a Primary Treatment in Idiopathic Sudden Sensorineural Hearing Loss. Iranian Journal of Otorhinolaryngology, 2012; 1(24): 19-22.
17. Igor T. R., Fayez B. J., Jairo B. F., Thais G. P., Nilda A. M., & Carlos A. O. Intratympanic Methylprednisolone as Rescue Therapy in Sudden Sensorineural Hearing Loss. Brazillian Journal of Otorhinolaryngology, 2010; 76(4):499-509.
18. Pinones J., Villarreal I., Chilleron R, Trinidad C., Camacho R. et al. Intratympanic Methylprednisolone for Sudden Sensorineural Hearing Loss: Comprehensive Re Examination of the model. J Otolarngol ENT Res, 2015; 3(2): 60.
19. Thomas H. A., Jeffrey P. H., Quyen T. N., and Nopawan V. Dose Effect of Intratympanic Dexamethasone for Idiopathic Sudden Sensorineural Hearing Loss: 24mg/ml Is Superior to 10mg/mL. Otology & Neurotology 2015; 36: 1321-1327.
20. Iordanis S., Dimitrios P., Antonios F. and Dionysios E. K. Succesful Salvage Therapy with Intratympanic Dexamethasone in a Diabetic Patient with Severe Idiopathic Sudden Sensorineural Hearing Loss. International Journal of Case Reports in Medicine 2013; 10: 5171-77.

21. Garcia B. J, Ramirez C. R, Trinidad A, Gonzalez G. J. Verdaguer J., et al. Cetral role of supporting cells in cochlear homeostatis and pathology. Med Hypothesis, 2004; 67 (3): 550-555.
22. Ho H.G., Lin H. C., Shu M.T. and Yang C. C. et Al. Effectiveness of Intratympanic Dexamethasone Injection in Sudden-deafness Patients as Salvage Treatment. Laryngocope 2004; 114: 1184-9.
23. Parnes L.S., Sun A. H., and Freeman D. J and McElveen J. T. Coticosteroid Pharmacokinetics in the Inner Ear Fluids: An Animal Study Followed by Clinical Application. Laryngoscope 1999; 109: 1-17.
24. Wen Y. H., Chen P. R. and Wu H. P. Prognostic Factors of Profound Idiopathic Sudden Sensorineural Hearing Loss. Eur Arch Otorhinolaryngology 2014; 271 (6): 1423-1429.
25. Amin J., M. Idiopathic Sudden Sensorineural Hearing Loss. University Hospital Experience. Med J Malaysia, 1993; 48(4), 407-409.
26. Tiong T. S. Prognostic indicators of management of sudden sensorineural hearing loss in an Asian hospital. Singapore Medical Journal 2007; 48(1):45-49.
27. Bennet M., Kertesz T., at al. Hyperbaric oxygen therapy for idiopathic sudden sensorineural hearing loss and tinnitus: a systematic review of randomized controlled trials. J Laryngol Otology 2005; 119 (10): 791-798.
28. Hikita W. N., Kitahara T., Horii A., et al. Tinnitus as a prognostic factor of sudden deafness. Acta Otolaryngology 2010; 130 (1): 79-83.
29. Yu C. L., Fan H. C., Ting H. Y., and Tien C. L. Assessment of complicatons due to intratympanic injections. World Journal of Otorhinolaryngology- Head and Neck Surgery 2016; 2: 13-16.
30. Pradeep P., Kanwar S., and Priti L. Effect of Intratympanic Dexamethasone in intractable unilateral Meniere's disease. Annals of Otolaryngology and Rhinilogy 2015; 2(5): 1041.

31. Deenadayal D. S., Vidyasagar D., et al. Role of intratympanic steroids in the management of Meniere's disease- A review of 151 cases. International Journal of Otolaryngology and Head & Neck Surgery. 2016; 5: 108-113.
32. Noell C. and Meyerhoff W. Tinnitus. Diagnosis and treatment of this elusive symptom. Geriatrics. 2003; 58(2): 28-34.
33. Lazarini P. and Bahmad F. Idiopathic sudden sensorineural hearing loss: etiopathogenic aspects. Braz J Otorhinolaryngology 2006; 72(4) : 554-561.
34. Penido S., Halpin C., and et al. Clinical, etiological and progression factors of hearing in sudden deafness. Braz J Otorhinolaryngology 2005; 71 (5): 633-638.
35. Gouveris H., Schuler S., Mewes W. and Mann W. Intratympanic dexamethasone/hyaluronic acid mix as and adjunct to intravenous stroid and vasoactive treatment in patients with severe idiopathic sudden sensorineural hearing loss. Otology & Neurotology 2011; 32: 756-760.
36. Bird P. A., Begg E. J., Zhang M. at al. Intratympanic versus intravenous delivery of methylprednisolone to cochlear perilymph. Otology & Neurotology 2007; 28: 1124-1130.
37. Salt A. N. and Plontke S. K. Principles of local drug delivery to the inner ear. Audiology Neurotology 2009; 14: 350-360.
38. Conlin A. e. and Parnes L. S. Treatment of sudden sensorineural hearing loss: A systematic review. Archives of Otolaryngology-Head & Neck Surgery 2007; 133: 582-586.
39. Bird P. A., Myrray D. P., Zhang M. and Begg E. J. Intratympanic versus intravenous delivery of dexamethasone and dexamethasone sodium phosphate to cochlear perilymph. Otology and Neurotology 2011; 32: 933-936.
40. Goycoolea M. V. and Lundman L. Round window membrane. Structure function and permeability: A review. Microscopy research and technique 1997; 36: 201-211.

41. Banerjee A. and Parnes L. S. The biology of intratympanic drug administration and pharmacodynamics of round window drug absorption. Otolaryngologic Clinics of North America 2004; 37: 1035-1051.
42. Cinamon U, Bendet E, Kronenberg J. Steroids, carbogen or placebo for sudden hearing loss: a prospective double-blind study. Eur Arch Otorhinolaryngol 2001; 258: 477-80.
43. Chandrasekhar SS. Updates on methods to treat sudden hearing loss. Oper Tech Otolaryngol Head Neck Surg 2003; 14: 288-92.
44. Tucci DL, Farmer JC, Kitch RD, Witsell DL. Treatment of sudden sensorineural hearing loss with systemic steroids and valacyclovir. Otol Neurotol 2002; 23: 301-8.
45. Hu A, Parnes LS. Intratympanic steroids for inner ear disorders: a review Audiol Neurootol 2009; 14: 373-82.
46. Foden N, Mehta N, Joseph T. Sudden onset hearing loss-causes, investigations and management. Aust Fam Physician 2013; 42: 641-4.
47. Spear SA, Schwartz SR. Intratympanic steroids for sudden sensorineural hearing loss: A systematic review. Otolaryngol Head Neck Surg 2011; 145: 534-43.
48. Moon IS, Lee JD, Kim J, Hong SJ, Lee WS. Intratympanic dexamethasone is an effective method as a salvage treatment in refractory sudden hearing loss. Otol Neurotol 2011; 32: 1432-6.
49. Arslan N, Oğuz H, Demirci M, Şafak MA, İslam A, Kaytez SK, et al. Combined intratympanic and systemic use of steroids for idiopathic sudden sensorineural hearing loss. Otol Neurotol 2011; 32: 393-7.
50. Gundogan O, Pinar E, Imre A, Ozturkcan S, Cokmez O, Yigiter AC. Therapeutic efficacy of the combination of intratympanic methylprednisolone and oral steroid for idiopathic sudden deafness. Otolaryngol Head Neck Surg 2013; 149: 753-8.

51. Battaglia A, Burchette R, Cueva R. Combination therapy (intratympanic dexamethasone + high dose prednisone taper) for the treatment of idiopathic sudden Sensorineural hearing loss. Otol Neurotol 2008; 29: 453-60.
52. Jong D. L., Moo K. P., Chi K. L., Kye H. P., and Byung D. L. Intratympanic Steroids in Severe to Profound Sudden Sensorineural Hearing Loss as Salvage Treatment. Clin Exp Otorhinolaryngol. 2010 Sep; 3(3): 122–125.
53. Plontke S. K., Hubert L. , Jürgen M., Corinna E., Christoph M., Andy W., Rainer Z., Serena P., Assen K., Hans P. Z. Randomized, Double Blind, Placebo Controlled Trial on the Safety and Efficacy of Continuous Intratympanic Dexamethasone Delivered via a Round Window Catheter for Severe to Profound Sudden Idiopathic Sensorineural Hearing Loss After Failure of Systemic Therapy. Laryngoscope 2009; 119 (2), 359-369.
54. Choung YH, Park K, Shin YR, et al. Intratympanic dexamethasone injection for refractory sudden sensorineural hearing loss. Laryngoscope 2006;116:747-52.
55. Plaza G, Herraiz C. Intratympanic steroids for treatment of sudden hearing loss after failure of intravenous therapy. Otolaryngol Head Neck Surg 2007;137:747-8.
56. Dallan I, Bruschini L, Nacci A, et al. Transtympanic steroids as a salvage therapy in sudden hearing loss: preliminary results. ORL J Otorhinolaryngol Relat Spe 2006; 68:247-52.
57. Roebuck J, Chang CY. Efficacy of steroid injection on idiopathic sudden sensorineural hearing loss. Otolaryngol Head Neck Surg 2006;135:276-279.
58. Raymando I., Bahmad F. J., Piaheiro T. and Oliveira C. Intratympanic methylprednisolone as rescue therapy in sudden sensorineural hearing loss. Braz J Otorhinolaryngol. 2010 Jul-Aug;76 (4):499-59.
59. Sakata E., Ito Y., and Itob A. Clinical Experiences of Steroid Targeting Therapy to Inner Ear for Control of Tinnitus. International Tinnitus Journal, 1997; 3 (2):117-121.

60. Hyun J. S. Intratympanic Steroid Injection in Tinnitus Management. Hanyang Med Rev 2016;36:125-130.
61. Guido M., David B., Tony C., Tony., Markus S., Meyer T. Characteristics and Spontaneous Recovery of Tinnitus Related to Idiopathic Sudden Sensorineural Hearing Loss. Otology & Neurotology 2016; 37(6): 634–641.
62. Choi SJ, Lee JB, Lim HJ, In SM, Kim JY, Bae KH, et al. Intratympanic dexamethasone injection for refractory tinnitus: Prospective placebo-controlled study. Laryngoscope 2013; 123:2817-22.
63. She W., Dai Y., Du X., Chen F., Ding X., Cui X. Treatment of subjective tinnitus: a comparative clinical study of intratympanic steroid injection vs. oral carbamazepine. Med Sci Monit 2009; 15: 135-139.
64. D. S. Deenadayal*, D. Vidyasagar, Vyshanavi Bommakanti, Madisetty Naveen Kumar, Nakirikanti Ravi Kumar, Ramesh Chintha. Role of Intratympanic Steroids in the Management of Idiopathic Sudden Sensori Neural Hearing Loss— Our Experience of 67 Cases. International Journal of Otolaryngology and Head & Neck Surgery, 5, 174-180.