

## Original Research Article

# Comparison of neo-pharmatherapy and volume building therapy in USSL

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### ABSTRACT

**Background:** Objective of the study was to identify healthy individuals with idiopathic unilateral sudden hearing loss (USSL) and treating them under either of two different therapeutic protocols to judge the hearing recovery.

**Methods:** Prospective crossover series study of 72 adult patients (males and females) of Indian origin was performed. Diagnosis of USSL and treating under two different protocols as; Group "A" was treated with oral combination form of Vinpocetine, Q-enzyme, Piracetam and B. Serrata over 3 months; while Group "B" was treated with Plasma expander IV Dextran, IV Dexamethasone, I/M Cyanocobalamine and Cyclandelate for 5 days followed by oral Dexametasone for 5 days Methycobalamine over 3 months. Common audiological and communicative parameters were applied in both treated groups to assess and analyse the responses incurred at the end of treatment. The graded system was applied to evaluate the SRT. Better outcomes based on the trialed drugs and their action is assessed.

**Results:** 61 of 72 patients successfully completed the regimes. After applying Siegel's grading for judging the SRT gains; group A had 16, 10 and 5 with grade I, II, III recovery while group B had 8, 6, 16 with grades I, II, III recovery respectively. It was noticed that group A patients showed earlier recovery of higher frequencies.

**Conclusions:** Both subject groups showed improved BC gains at end treatment. There was marked hearing recovery (Gr. I, II-Siegel's classification) in group "A" was (78%) which is significant over group "B" (50%) and above natural recovery rate.

**Keywords:** DS, Neopharma, PTA, SRT, Unilateral sudden sensorineural loss

### INTRODUCTION

Definition of sudden hearing loss was thought to be based on severity, time of onset, audiometric criteria and frequency spectrum. Symptoms with sudden awareness of hearing loss over few days, at a time selective type of hearing loss with distorted speech perception, had all been classified as sudden hearing losses. It is scientifically defined as; a sensorineural hearing loss greater than 30 db over three consecutive pure tone frequencies with onset of deafness being 3 days. Majorities of cases have unilateral presentation with good

prognosis. Incidence of Bilateral presentation is infrequent (1-2%).

The consequences of USSL were thought to be negligible in 8th era of 19th century; because of presumption of speech and language development occurring with other ear being normal; in spite of educational and behavioral problems in such children. The chances of repeating the grade are 22% to 35% and need of educational assistance is from 12-41%.<sup>1</sup> In comparison, the adults who had greater incidence of USSL than children, have greater consequences resulting from miscommunication in form of reduced skill-based

performances, poorly conducting the meetings, mis-replying the queries. In many patients there is an inherent fear of losing a job or even the slippage of clientage out of misunderstandings. The international literature reports the incidence of USSL as 5-20/100,000 of population. While bilateral sudden sensorineural losses (BSSL) are reported to be less frequent and arising out of toxic, vascular and neoplastic cause with not a good prognosis; USSL of idiopathic origin has been spontaneous recovery rate of 40-60%.<sup>2</sup>

### **Etiology**

Though innumerable causes and theories have been claimed to cause USSL the most acceptable are; trauma, dominant viral infection, vascular and non-vascular compressions, toxic metabolites, deranged autoimmunity in children, drugs for penile erectile dysfunction and idiopathicity: the latter being widely agreed upon. In 1988 Schuknecht on his study conducted on cadaveric temporal bones of patients of USSL concluded that the "pattern of loss of type of hair cells, changes in stria vascularis and co-related audiograms were suggestive of viral pathology". The recovery in idiopathic USSL is better than a definite cause as tumor, haemorrhage and compression.<sup>3</sup>

### **METHODS**

A prospective crossover trial in cases of USSL was carried over from May 2018 to July 2019. 103 patients of Indian race were examined in a private institute with history of unilateral sudden deafness with variable onset of durations (Table 1). Healthy otherwise, all had complaints of single sided variable deafness with few having mild to moderate (grade I-II) tinnitus and infrequent heaviness of head and mild giddiness. All had undergone clinical and audiological assessment which confirmed normal middle ear functions with reduction of ABC on affected side and Weber test lateralised to unaffected side. There was listlessness on patient's behalf and inconsistent responses to verbal commands. Vestibular and neurological signs were absent.

All the subjects underwent PTA with masking for air as well for bone conduction threshold estimations from 250-4000Hz frequencies, SRT, Impedance test, Stapedial reflex test, Discrimination scoring for P.B. words and Spondee words. Audiometric tests were carried out in sound proof room using a 3N3 audiometer (Elkon, Mumbai, India) which was calibrated according to ISO 2011 standards. Impedance test were performed with Amplaid-EC2009 standard impedance audiometer (Ripamonti, Italy) with a probe tone frequency of 226Hz. Ipsilateral and contralateral stapedial reflexes were tested using pure tones between 80-110 dB. Speech audiometry was done using cassette recordings of CIDW-22 SD sets (AYJ Institute, Mumbai, India) and SRT was obtained with monitored live voice. BERA, ASSR tests and imaging were done only in suspected retrocochlear lesion

or central pathology. After confirmation of the diagnosis as USSL of uncertain cause; the subjects were advised to complete one of the two treatment regimens after explaining them the probable outcomes of it. A special consent was brought from an individual for his willingness to participate in the treatment protocol. Based on inclusion criteria (vide infra) only 72 patients participated in treatment programmes, which were divided into two groups (35 participants in group A and 37 in group B) to receive the treatment as under:

### **Scheduled dosages for Group A patients**

Cap Coenzyme Q 10-100 mg BID-15 days followed by 100 mg O.D-15 days.

Tab. Vinpocetin 5 mg + Tab Piracetam 400 mg + Gingo B. extract 1 BID-15 days followed by 1 O.D-30 days.

Tab B. Serrata 300 mg TID-30 days followed by 300 mg BID -60 days.

### **Scheduled dosages for Group B patients**

#### **Parenteral form**

- Dextran (40) (On days- 1,1,2,4,5- total 5 iv infusions).
- Inj Dexamethasone 24 mg IV-2 days followed by 12 mg IV 2 days and 8 mg IV 1 day.
- Inj Cyanocobalamine 750 mcg I/M -3 days

#### **Switch over to oral form**

- Tab Dexamethasone 4 mg BID- 5 days.
- Vasodilators-Cyclanate 200 mg tid- 40 days.
- Vit. B12-750 mcg O.D- 40 days.

Inclusion criteria for the treatment offered were healthy individual free from systemic disease, onset of deafness from 1-14 days, age range 16 years-80 years, normal external and middle ear function, free from retro cochlear and central lesions, normal tympanogram and present stapedial reflex.

Each individual was asked to attend audiological follow-up assessment on 15th, 30th, 60th, 90th day of treatment.

### **RESULTS**

In both subject groups males (43) were seen to be more affected than females (32). No particular side was seen to be more involved of USSL. In Group A out of 35 only 31 subjects could complete the regime; while in group B out of 37 subjects only 30 completed the regime. There were no side effects of the drugs used in group A; while 7 patients from group B complained of nausea, vomiting, presence/worsening of tinnitus with short lasting giddiness and 3 patients complained of moderate headache. The responses of A and B groups to the pre

and end-treatment for PTA, DS for PBW and SPW and SRT are shown with their p values (Table 2 and 3) along with BC gain (Table 4). A statistically significant difference was noted between group A and B pertained to following parameters in pre- and post-treatment phases as: Group A showed significant BC gain at frequencies 1/4, 1/2, 1, 2, 4 KHz ( $p < 0.008$ ,  $< 0.003$ ,  $< 0.005$ ,  $< 0.002$ ,  $< 0.002$ ) respectively. In group B too significant BC gain was observed at frequencies 1/4, 1/2, 1, 2, 4 kHz ( $p < 0.011$ ,  $< 0.018$ ,  $< 0.003$ ,  $< 0.0002$ ,  $< 0.017$ ) respectively. The mean responses for BC gains for both the groups are shown in Table 4. Recovered SRT value of subject group A was significant over subject group B ( $P < 0.0002$  vs  $< 0.109$  Table 2, 3).

**Table 1: Clinical data of USSL cases based on inclusion criteria in the present series.**

Group	A (35)	B (37)
Sex M:F	22/13	21/16
Side Right/Left	20/15	17/20
Age- Mean±SD (years)	40±22	42±20.5
Onset-Mean±SD (days)	9±5	8±6
Rx- protocol completed	31 (M:F=21:10)	30 (M:F=18:12)
Follow-up- Mean±SD (weeks)	13±2	14±3

**Table 2: The detailed statistical data of hearing thresholds, DS and SRT in pre- and post-treatment stages of subject group "A" (n=31).**

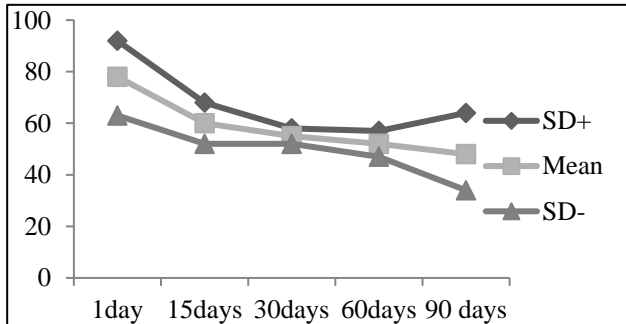
Frequency	Treatment	AC (Mean±SD)	P value	BC (Mean±SD)	P value
1/4	Pre	57.80±17.91	P<0.0001	43.80±13.79	P=0.008
	Post	36.0±14.14		27.80±12.16	
1-2	Pre	68.60±14.033	P=0.0004	60.00±13.61	P=0.0003
	Post	43.60±16.04		36.20±14.81	
1	Pre	72.20±14.44	P=0.0003	62.80±11.64	P=0.0005
	Post	45.40±17.40		38.20±12.81	
2	Pre	68.0±16.70	P=0.0006	60.6±14.74	P =0.0002
	Post	46.4±18.23		40.6±15.5	
4	Pre	79.40±20.83	P=0.0006	69.80±16.29	P=0.0002
	Post	56.60±23.39		49.20±20.29	
pbw	Pre	77.40±21.80	P=0.18		
	Post	85.80±22.34			
Spw	Pre	71.80±22.12	P=0.14		
	Post	81.60±24.14			
Srt	Pre	77.6±14.51	P=0.0002		
	Post	49±15.87			

**Table 3: Detailed statistical data of hearing thresholds, DS and SRT at pre and post-treatment stages in subject group "B" (n=30).**

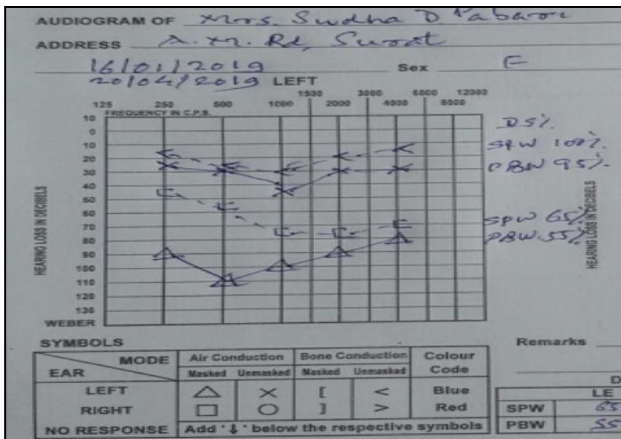
Frequency	Treatment	AC (Mean±SD)	P value	BC (Mean±SD)	P value
1/4	Pre	68.40±12.66	P=0.00017	51.59±12.28	P=0.011
	Post	51.59±14.34		40.90 ±14.60	
1/2	Pre	69.77±13.49	P=0.0005	59.77±15.07	P=0.018
	Post	53.63±15.13		48.86±14.55	
1	pre	74.77±12.95	P=0.0003	64.09±13.76	P=0.003
	post	58.86±14.30		51.13±14.05	
2	pre	68.0±16.70	P=0.0006	60.6±14.74	P =0.0002
	post	46.4±18.23		40.6±15.5	
4	pre	79.77±21.68	P=0.061	66.13±16.75	P=0.017
	post	66.13±25.30		51.59±21.89	
Pbw	pre	60.90±31.57	P=0.48		
	post	67.95±34.62			
Spw	Pre	65.68±32.04	P=0.66		
	post	70.00±34.15			
Srt	pre	77.60±14.51	P=0.109		
	post	454.00±15.87			

**Table 4: Mean BC gains for speech frequency after the treatment in subject groups "A" and "B".**

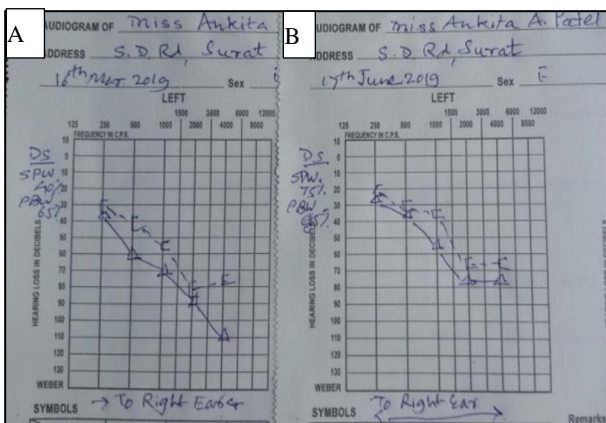
Frequency (KHz)	1/4	1/2	1	2	Mean
Gr A (dB) (n=31)	27	26	27	23	26
Gr B (dB) (n=30)	10	16	18	11	14



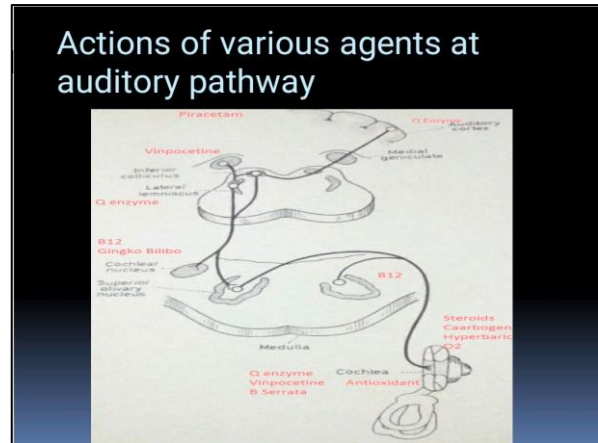
**Figure 1: Post treatment SRT estimations over the periods in subject group "A".**



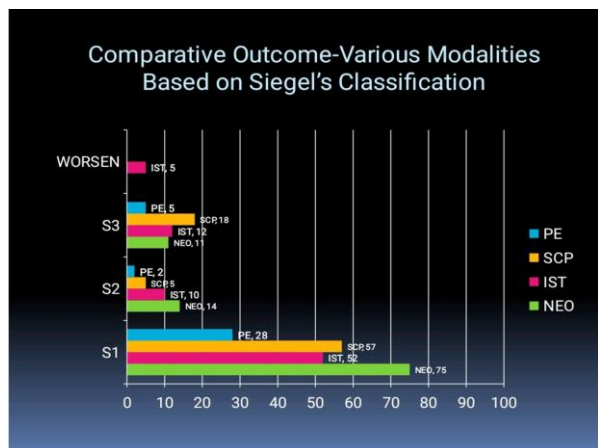
**Figure 2: On left- audiogram of a case (group A) with marked improved hearing thresholds with DS>95% at the end of the treatment.**



**Figure 3: A) audiogram of a case (Group B) at pre-treatment. B) Post treatment audiogram after 90 days with lowered thresholds at mid frequency and DS >70%.**



**Figure 4: An artist's impression of topographic actions of various drugs used in USSL.**



**Figure 5: Displays bar diagram of various modalities of treatment producing the positive outcomes based on 10-30 dB BC gains. #SCP= Steroids, Carbogen, PgE1\*PE= PgE2 ^^IST = Intratympanic steroid \$Neo= Neopharma combination.**

After applying Siegel's grading for judging the SRT gains; group A (Figure 1) had 16, 10 and 5 with grade I, II, III recovery while group B had 8, 6, 16 with grades I, II, III recovery respectively. It was noticed that group A patients showed earlier recovery of higher frequencies (e.g., Figure 2, 3A) and steeply recovering PBW score unlike to SPW score. No such trend of recovery was observed in group B.

**DISCUSSION**

Pharmaco-agents used in this study having mechanism of actions in vivo can be briefed as;

**Ginkgo Biloba**

It is the extract of *Ginkgo* leaves contains flavonoid glycosides and terpenoids (ginkgolides, bilobalides). It is a MAOI (monoamine oxidase inhibitor). It has anti-platelet and vascular modulatory actions that improves

blood flow and appropriately regulates vascular tone with anti-oxidant and protective effects on nerve cells in the brain, auditory cortex and sub-cortical areas. Mild side-effects like nausea, headache, stomach upset and palpitations may be observed in few persons.<sup>4</sup>

#### **Piracetam**

It is acyclic derivative of the neurotransmitter GABA. It Improves the function of acetylcholine via muscarinic ACh receptors. It increases neuronal oxidation (NMDA glutamate Receptors) and facilitates residual auditory signals and learning process. Further, it acts at cortical level and its projections to parieto-motor complex and memory centres by way of acting on vascular system by reduction of RBC adhesion to vascular endothelium, hinder vasospasm and facilitate microcirculation. No side effects reported except diarrhoea and abdominal pain reported in case of acute intoxication (75 grams).<sup>5</sup>

#### **Vinpocetin**

It is a synthetic derivative of vinca alkaloid vincamine extracted from the seeds of *Voacanga africana* or the leaves of *Vinca minor*. Mechanism of action is; blockage of sodium channels, reduction of cellular calcium influx. Anti-oxidation, inhibition of PDE (Phospho-di-esterase). It also increases selective brain circulation and Oxygen utilization. Thus, brain becomes more resistant to hypoxia and ischemia. Side effects are flushing, nausea, dry mouth, heartburn, dizziness, headache, transient hypo/ hypertension, agranulocytosis.<sup>6</sup>

#### **Boswellia serrata**

It is a gum resin product brought from genus *Boswellia* tree grown in dry mountainous regions of India, Northern Africa and Middle East. It's acetyl -keto-B-boswellic acid is known as a strong anti-inflammatory agent by virtue of inhibiting pro-inflammatory enzymes like 5-lipoxygenase and for its antioxidant property.<sup>7</sup> It is a strong JNK inhibitor. It prevents apoptosis (programmable cell death) by enhancing phosphorylation (Figure 3).

#### **Co-enzyme Q-10**

Also known as Co-Q-10 and Vitamin Q-10. Co-enzyme Q-10 is the active ingredient. It is an organic no-protein molecule and Q refers to the Quinone chemical group and 10 refers to Isoprenyl subunits. Mechanism of action can be explained by its electron accepting ability at the level of mitochondrial transport. It is also a co-factor used in process of aerobic respiration. Thus, its function can be described as anti-oxidant, membrane stabilizer and production of Adenosine-triphosphate (ATP) in the oxidative respiratory process. For most adults Co-enzyme Q-10 is well tolerated and safe. However, it is cautioned to use it carefully in the patients who are on anti-coagulants.<sup>8</sup>

#### **Dextran**

Dextran the plasma expander is a polysaccharide in which the glucose units are joined together 1:6 glucoside links. Low molecular weight dextran increases capillary blood flow in general by hypervolaemic haemodilution and by decreasing factor VIII, decreasing blood viscosity and resulting in an increased tissue blood flow. Low molecular weight dextran increases plasma viscosity, and should be used with caution in patients with heart disorders or renal impairment.<sup>9</sup>

#### **Dexamethasone**

It is a glucocorticoid and acts by Inhibition of phospholipase A2, IL-2, histamine release. It has anti-inflammatory properties with upregulation of both cytokine and ion hemostasis genes. It has an impact on SSNHL carriers of macrophage migration inhibitory factor 173-C alleles. Side effects like headache, eye pain, blurring of vision, irregular heartbeats, muscle cramps, hyperglycemia are known.<sup>10</sup>

#### **Cyclandelate**

Cyclandelate is in a class of drugs called vasodilators. Cyclandelate relaxes veins and arteries, which makes them wider and allows blood to pass through them more easily. Pharmacological action is due to calcium-channel antagonism. It targets Voltage-dependent calcium channel subunit alpha-2/delta-1 and Liver carboxyl-esterase. It may cause gastrointestinal distress and tachycardia.<sup>11</sup>

#### **Cynacobalamine**

Cyanocobalamin (commonly known as Vitamin B12) is a highly complex, essential vitamin, owing its name to the fact that it contains the mineral, cobalt. Vitamin B12 serves as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase enzymes. Methionine synthase is essential for the synthesis of purines and pyrimidines that form DNA. Cyanocobalamin normalizes the processes of cell division, myelination of nerve fibers, lipid and protein metabolism, and has a haemopoietic, erythropoietic, antianemic, metabolic effect.<sup>12</sup>

The hearing process in human is a complex process and can be better understood stepwise. 1) Sound conduction by Air and or bone media. 2) Transduction at inner hair cell membranes to auditory nerve endings (dendrites). 3) Signal transporting upto auditory cortex. 4) Inner cortical processing. 5) Further transmission of modified signals (coded) through complex projectile network to memory, intelligence, speech and motor areas. While diagnosing a case of USSL is not difficult, at the same time it is treacherous to be agreed upon an universal accord to treat it. In very few cases the etiology is definite as; e.g. in barotraumas where hyperbaric oxygen promises good outcome and in post-usage of Vardenafil (blamed to

cause prolonged spasm of labyrinthine vessels) where significant numbers recover spontaneously. The majority of the patients are idiopathic; hence various methods to treat those are practised.<sup>13</sup> When the literature is reviewed upon, we realise that followed-up cases of SSL with MRI imaging makes one to sense, the better hearing recovery rate than a definite cause as tumor, hemorrhage and compression.<sup>14</sup>

Medline research from 20 RCT studies conclude that there is no role of oral steroids and or antiviral drugs on positive outcomes in USSL. Further to say different methods of studying vasoactivity and hemodilution leads to inconclusions. The claims of graphical recovery after magnesium and carbogen therapies are not supported with actual numbers of report of recovered patients.<sup>15,16</sup> However the combination of oral steroid, carbogen inhalation and lipoprostaglandinE1 has been reported by Kim et al., a hearing gain of more than 20dB in 63% cases.<sup>17</sup>

Traditional treatment of vasodilators and IV or oral steroids along with plasma expanders along with intravenous steroids used were targeted at cochlear hair cells, stria vascularis and intravascular compartments of organ of corti. This was thought to improve diffusion of vital elements across the inner hair cell membrane to set in anti-inflammatory process with questionable homeostasis and non-assistance to neurotransmission. Though cyanocobalamin has been used by some workers to improve neuro-transmission with some benefit in selected cases; it has no proven action on cortex and subcortex. Vasodilators were presumed to improve peripheral capillary blood circulation is not much supported by analysers.<sup>18</sup>

Transtympanic (TT) steroids are widely used over a last decade in many major centres across the world with its published results. However, in spite of labeled etiology in these studies as idiopathic, the sampled subject population appeared as heterogeneous with existence of co morbidities as hypertension, diabetes and coronary disorders within them. Further the statistical data lacks confidence limits as well upgrading the project to level 1b.<sup>16</sup> One of the earliest report on small series of using TT steroids performed by Silverstein et al concluded that steroids were no better than placebo in treating HL.<sup>19</sup> Since then there is rising interest and reporting on use of steroids. Chou et al in a controlled prospective trial reported 53% success rate.<sup>20</sup> However, the technique used in different papers vary in selection of cases, doses of Dexamethasone/Methylprednisolone, dosing frequency and analysis of audiological parameters too.<sup>21</sup>

The proposed neopharma therapy in the present study is unique and the authors, till this date are not aware of this kind of study undertaken by any other institute. Hence, its exact comparison with other published series of different modalities based on varied subjective criteria won't make it rational one. Next, NICDC-Cochrane analysis of 611

studies (1965-2010) concluded that only two articles met the criteria for metanalysis; yet few inferences from recent studies are noteworthy as; 1) no different outcome between carbogen and placebo therapy, 2) No recovery with vasodilators, 3) Carbogen, PGE2 and steroids combination yields 68% recovered cases which is higher than a use of single drug.<sup>17,18,22</sup>

Based on different pharma agents used in combination (Vide supra-methods) used in this study; the gratifying results can be looked upon due to their action having larger coverage of auditory pathway compared to other agents used (Figure 5). When the results of groups A and B of present study are compared, we notice a significant statistical difference in pre and post treatment values of AC and BC thresholds of 1/4-4 Khzs in both groups; hence one would expect similar favorable response in values of SRT and DS after treatment; which is observed to be absent (Table 2 and 3). This may be attributed to incomplete recovery of cognition in the subject group. When similar data from group "A" is reviewed upon; one may appreciate a significant gain in SRT values and marginally statistically different evaluation or DS after the treatment over the subject group "B" (Tables 2 and 3), which may be attributed to improved cognition.<sup>23</sup> Thus, physiological restorative process from transduction to cognition had been taken care of with use of combination of drugs used in group "A". At the same time, drugs used in group "B" yielded inferior results in terms of improved quality of audition. Applying the criteria of BC gain of more than 20 dB in the group A 26/31 responded as against 14/30 responded in group B (vide supra-results). This therapeutic approach differs from all other studies by non-systemic outdoor and non-invasive method, drugs used have multicentric mechanism of action, application of selection criteria's suggested by NCBI, well tolerated drug regime with high compliance.<sup>24</sup>

While choosing the method to treat USSL one needs to advocate the patient the modality of proven value with safety features, so that he can be a compliant to complete the treatment with its assessment. Recording all vital features as BC thresholds, SRT, DS are mandatory at every follow-up visit for analysis along with weighing the final recovery against Siegel's criteria. Longitudinal follow-up for 3-12 months is desirable.

## CONCLUSION

USSL an otological emergency needs to be quickly assessed for all vital audiological and communicative parameters. These necessarily include AC, BC thresholds for speech frequencies SRT and DS for Phonetically balanced words and Spondee words recorded at all follow-up testings. The treatment modality proposed by a clinician shall be based on the outcome of therapy which can be at par or better than the spontaneous natural recovery rate. Single modality alone used as; carbogen therapy, PGE1 and PGE2, oral and IV use of steroids,

stellate ganglion block; fail to produce recovery beyond the natural recovery rate. Plasma expanders and vasodilators too fail to achieve acceptable outcomes. The proposed neopharma combination usage in a small series yields encouraging and more appreciable audiometric results in USSL (78%) over plasma expanders, steroid and vasodilator therapy in a properly selected subject group. Neopharma therapy in out-patient set-up is well tolerated without noticeable side effects with cost effectiveness and may be considered in place of TT steroid. In the same regards, a multicentric study of proposed medicinal therapy is desirable.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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