Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com

Research Article

CLINICAL COMPARISON BETWEEN EFFECTIVENESS OF INTRATYMPANIC *BILVADI* MEDICATED OIL AND *BILVADI* MEDICATED OIL EAR DROPS IN MANAGEMENT OF PRESBYCUSIS

Atul Bhardwaj [1]*, Riju Agarwal [2], Manoj Tanwar [3], Anoop Kumar [4]

[1]Assistant Professor of Shalakya Tantra, Chaudhary Brahm Prakash Ayurved Charak Sansthan, Guru Gobind Singh Indraprastha University, Delhi, India

[2]Associate Professor of Shalakya Tantra, Chaudhary Brahm Prakash Ayurved Charak Sansthan, Guru Gobind Singh Indraprastha University, Delhi, India

[3]Assistant Professor of Shalakya Tantra, Shri Krishna Govt. Ayurvedic College, Pt. Bhagwat Dayal University of health sciences, Kurukshetra, Haryana, India

[4]Assistant Professor of Shalakya Tantra, S.K.D. Govt. Ayurvedic College, Kanpur University, Muzaffernagar, Uttar Pradesh, India

*Corresponding Author Email: dratulbhardwaj@gmail.com

DOI: 10.7897/2277-4572.04563

Received on: 20/08/15 Revised on: 28/09/15 Accepted on: 09/10/15

ABSTRACT

Bilvadi medicated oil (BMO) is traditionally used in Ayurveda for the treatment of Hearing loss and tinnitus is enumerated in various text of Indian system of medicine. This current clinical trial as a pilot study is directed to evaluate the effectiveness of BMO when it is used as intratympanic mode through a surgically created window in the tympanic membrane to gain a higher concentration of the BMO in middle ear. 34 patients were selected for the clinical study intends to compare the effectiveness in hearing loss recovery in bilateral and symmetrical presbycusis patients by ramifying them into two trial groups. In one trial group BMO is used in a conventional Karnapoorna manner (Karnapoorna trial group – KPG) while the other trial group was reflected by an intratympanic usage of BMO (Intratympanic group – KPG). On one randomly selected ear KPG clinical trial was commenced and the other ear of the same patient was represented by ITG intervention**.** Pure tone audiometery (PTA) is used before commencing and after completion of the trial of 30 days and both the ear are compared with degree of hearing loss recovery and results was analysed comparing between Intratympanic and Karnapoorna groups. Intratympanic drug delivery approach was found to be a safe modality to foster the drug delivery to the middle ear and possibly in the internal ear. Presbycusis being primarily a cochlear pathology, higher concentration of drug of required encountering the degenerative and apoptosis related changes of the disease. The traditional Karnapoorna procedure done with the same medicated oil was found to be less effective on hearing recovery and overall recovery parameters probably because of the fact that tympanic membrane epithelial layer is an anatomical barrier in diffusion of the drug in middle ear.

Key words: Ayurveda**,** Presbycusis, Intratympanic drug therapy, *Bilvadi* medicated oil (BMO), *Karnapoorna*, Pure tone audiometery (PTA)

INTRODUCTION

The inevitable deterioration in hearing ability that occurs with age—Presbycusis—is a multifactorial process that can vary in severity from mild to substantial. Left untreated, presbycusis of a moderate or greater degree affects communication and can contribute to isolation, depression, and, possibly, dementia Hearing loss is the common endpoint of many inner ear disorders including presbycusis, sudden sensorineural hearing loss, genetic diseases, trauma, exposure to noise and ototoxic medications, and autoimmune inner ear disease. The term presbycusis signifies sensorineural hearing impairment in elderly population. Typically, presbycusis involves bilateral high-frequency hearing loss associated with difficulty in speech discrimination and central auditory processing of information. The association between advanced age and high-tone deafness was first described by Zwaardemaker in 1899. Since then, extensive research has attempted to determine the pathologic changes of presbycusis, but the exact mechanisms remain unknown. Since effects of pure aging on the physiology and morphology of the human peripheral auditory system are difficult to study given the variability inherent in genetics and the environment with which the system encounter. Presbycusis represents a combination of deteriorated function of the auditory periphery with deteriorated function of the central auditory system.

Presbycusis is an important problem in society. It occurs in an elderly population that relies on special senses to compensate for other age-associated disabilities. Elderly individuals may rely on their hearing to overcome limitations of impaired vision and slowed reaction time. In addition, age-associated decline in concentration and memory contribute to difficulty understanding speech, especially in noisy situations.

The clinical presentation of presbycusis varies from patient to patient and is a result of the various combinations of cochlear and neural changes that have occurred. Patients typically may have more difficulty understanding rapidly spoken language, vocabulary that is less familiar or more complex, and speech within a noisy, distracting environment. In addition, localizing sound is increasingly difficult as the disease progresses. Schuknecht (1974) has described four types of human presbycusis: (1) sensory, mainly affecting the cochlear hair cells and supporting cells; (2) neural, typified by the loss of afferent neurons in the cochlea; (3) metabolic, where the lateral wall and stria vascularis of the cochlea atrophy; and (4) mechanical, where there seemed to be a so-called “stiffening” of the basilar membrane and organ of Corti[1,2]. Out of these contributing factors atrophic changes in the organ of corti are attributed to a larger extent in causing as well as progression of presbycusis. Presbycusis is not curable, but the effects of the disease on patients’ lives can be mitigated.

Amplification devices are aimed at rehabilitating patients who already experience presbycusis. However, efforts are underway to develop therapies that treat the potential underlying causes of presbycusis, as well as mechanisms to actually prevent the disease

altogether but unfortunately; most of these therapies are still in the investigational stages.

Intratympanic drug therapy (ITDT) is a surgical technique of instilling medication into the middle ear to perfuse the inner ear with higher concentration of the drug[3,4,5]. Due to systemic side effects, investigators and clinicians have begun developing and utilizing techniques to deliver therapeutic agents locally. ITDT is prominently used in unilateral and bilateral Meniere's disease, progressive presbycusis, intractable tinnitus, sudden sensorineural hearing loss and various autoimmune inner ear diseases[6,7]. The delivery of medications to the inner ear through the intratympanic route dates back to 1935, when Barany used intratympanic lidocaine for treatment of tinnitus. Since then, other molecules have been used and the indications have expanded. In 1948, streptomycin was used to treat patients with unilateral Meniere's disease specifically on the basis of its vestibulotoxic effects.

In the present clinical study Bilvadi medicated oil is dispensed in the middle ear a ventilation tube/grommet/pressure equalizing tube is surgically placed in the postero-inferior quadrant or over the round window niche through a myringotomy incision after injecting the external auditory canal with 2cc of 2% xylocaine with 1:100000 adrenalin solution in four quadrants. Otoendoscope with 1.7mm diameter, 0 degree and 10 mm length is used to evaluate the middle ear health and round window niche as well. Patient is advised to instil 6 drops of BMO two times a day for 30 days. In the other ear BMO is instilled with 6 drops with an intact tympanic membrane ear/normal Karnapoorna. Patient was advised to lie in the ear position with tragal massage for 5 minutes after instillation of BMO in each ear. This positioning and massaging will help in delivering/dissemination of BMO in middle ear having grommet. If the BMO is delivered directly in the inner ear through a potentially a porous round window membrane, higher concentration of the drug is expected to be achieved by bypassing a potent drug absorption barrier viz. Tympanic membrane.

Bilvadi taila (medicated oil has been used extensively in Indian system of medicine/Ayurveda) for the management of hearing loss and tinnitus. Karnapoorna (filling/locally instillation the medicated oil in external auditory canal) is practised widely in Ayurveda and stands to be a primary modality of treatment in otological disorders. Few studies are available to evaluate Bilvadi taila Karnapoorna in management of hearing loss and tinnitus but none of the study uses this medicated oil as intratympanic mode (use of this medicated oil in surgically created window accessing the middle ear). Hence this intratympanic usage of BMO is a pilot study which is directed to evaluate the hearing outcome when BMO is allowed to be directed instilled in the middle ear through a tympanostomy tube/Grommet**.**

MATERIALS AND METHODS

The present work is randomised, single blind, prospective, crossover and single centre study comprising patients of either sex in the age group 50-80 years. The patients for the research were selected from Department of Shalakya Tantra OPD, M.S.M. Institute of Ayurveda, B.P.S. Mahila Vishwavidyalaya, Khanpur Kalan, Haryana, India. Pure tone audiometery (PTA) established patients of bilateral and symmetrical sensorineural hearing loss were selected for the trial and diagnosed patients satisfying inclusion/exclusion and criteria of assessment were divided into two trial groups after having written and informed consent from the patient to participate in the study on a recorded and standardized Performa. The patient was also briefed about the research protocol, surgical intervention, duration of trial, route of administration of drug prior to the consent. An official permission from institution's research ethical committee and hospital core committee was also taken before the commencement of the trial vide communication letter no. MSM/EC/SKT/2012/19.

Statistical analysis

The data was analysed for statistical significance by using statistical package for social sciences (SPSS Inc. Chicago, USA, 17.0). The student's 't' test (paired) was used to analyze the data for the level of significance. The related't' test was used to analyze intra differences in pre/post protocol. For all analysis the 'p' value used for statistical significance was 0.05.

Selection of the patients

39 patients were selected for the clinical study intends to compare the effectiveness in hearing loss recovery in bilateral and symmetrical presbycusis patients by ramifying them into two trial groups. 5 patients are drop out/lost because of tinnitus, vertigo and pain and the trial is completed by 34 patients. The framework and treatment initiated in two different groups is as under:

Trial Group 1 or ITG (Intratympanic group): BMO as an Intratympanic usage **(**BMO is allowed to be directed instilled in the middle ear through a tympanostomy tube/Grommet).

Trial Group 2 or KPG (Karnapoorna group): BMO as Karnapoorna (filling/locally instillation the medicated oil in external auditory canal)**.**

Right and left ear selection was made randomly to avoid selection bias. On one side of the patient Karnapoorna with BMO was done and on the other side of the same patient surgical intervention and intratympanic BMO administration was done. Pure tone audiometery (PTA) is used before commencing and after completion of the trial of 30 days and both the ear are compared with degree of hearing loss recovery and results was analysed comparing between Intratympanic BMO and Karnapoorna with BMO instillation groups. Adequate masking was done during PTA to prevent transcranial sound distribution to the better hearing ear as hence only patients having strictly bilateral and symmetrical sensorineural heaving loss were selected for the trial.

Inclusion criterion

- Tunic fork and Pure tone audiometric approved presbycusis patients.
- hearing loss is >40 dB (Arithmetic mean of 500, 1,000, 2,000, and 4,000 Hz in PTA)
- Patients having bilateral and symmetrical sensorineural hearing loss.
- Age between 50-80 years.

Exclusion criterion

- Patients having pre-existing perforations of the tympanic membrane.
- Patients having features of conductive hearing loss suggested in otomicroscopy, Tunic fork and Pure tone audiometery.
- Patients having history of ototoxic drugs, congenital sensorineural hearing loss and post meningitis sensorineural loss.
- History of previously done otological surgical intervention.
- History of substance abuse and noise induced hearing loss.
- Suggestion of other middle disorders existing, if any.
- Patients hypersensitive to local anaesthetic agent i.e. lignocaine.

Criteria of assessment for the present study

Grading and scoring system of hearing loss was procured from American Speech-Language-Hearing Association (ASHA), in order to statistically establish the treatment outcome by subjecting paired t-test (Table 1). Modified criteria for Hearing Recovery in Idiopathic

Sudden Sensorineural Hearing Loss as proposed by the ad hoc committee of the Japanese Ministry of Health was adopted in order to establish criteria for Hearing Recovery (Table 2)

OBSERVATIONS AND RESULTS

Though the degree of hearing loss recovery was found to be statistically insignificant in both the groups viz. ITG and KPG (Table - 3), ITG group was found to be having better hearing loss recovery in Overall outcome of the treatment (Table 4). In overall hearing parameter outcome as well ITG group shows average hearing gain of 14.2 db as compared to KPG which reflected an average hearing gain of only 6.3 db (Table – 5). In overall recovery outcome only 20.58% of KPG patient shows fair recovery in comparison of 41.17% recovery observed in ITG. On the same parameter only 8.8% of the ITG patients showed deterioration/disease progression, whereas 17.64% on the KPG patients turns up with deterioration/disease progression.

Table 1: Grading and scoring of hearing loss

Possible grading of hearing loss	Degree of hearing loss	Hearing loss range (dB HL)
Grade 0	Normal	–10 to 15
Grade 1	Slight	16 to 25
Grade 2	Mild	26 to 40
Grade 3	Moderate	41 to 55
Grade 4	Moderately severe	56 to 70
Grade 5	Severe	71 to 90
Grade 6	Profound	91+

Table 2: Criteria for Hearing Recovery in presbycusis

Grade 4	Complete recovery	Hearing level returns to within 20 dB at 500, 1,000, 2,000, and 4,000 Hz.
Grade 3	Good recovery	Improvement in the hearing level is >30 dB (Arithmetic mean of 500, 1,000, 2,000, and 4,000 Hz in PTA)
Grade 2	Fair recovery	Improvement in the hearing level is >10 dB but <30 dB
Grade 1	No change	Improvement in the hearing level is <10 dB
Grade 0	Deterioration	Hearing loss progresses in PTA

Table 3: Effect of therapy in ITG and KPG

Hearing loss in decibel (audiometric average)	n	Mean		X(d) B.T.-A.T.	S.D.+/-	S.E.+/-	't' value	'p' value	Remark
		B.T.	A.T.						
ITG	34	4.7	3.8	0.9	0.64	0.08	0.33	P>0.05	NS
KPG	34	4.8	4.1	0.7	0.66	0.08	0.25	P>0.05	NS

Table 4: Overall recovery outcome of the treatment

Profile parameter	ITG		KPG	
	No. of patients	Percentage	No. of patients	Percentage
Complete recovery	0	0	0	0
Good recovery	8	23.52	1	2.9
Fair recovery	14	41.17	7	20.58
No change	9	26.47	20	58.82
Deterioration/disease progresses	3	8.8	6	17.64

Table 5: Overall hearing parameters outcome

Parameter	ITG	KPG
Average hearing gain in decibel	14.2 db	6.3 db
Average hearing level after treatment in decibel	47.7 db	56.3 db

DISCUSSION

It is a settled opinion that when the drugs are made available to the middle ear and round window niche the drug concentration is conspicuously enhanced in the internal inner fluids with a better clinical outcome as well[8]. This probably can be explained because of 1) bypassing the blood labyrinthine barrier, 2) resulting in higher concentrations in the inner ear fluids 3) avoiding major unwanted effects of systemically administered medications.

Concerns exist regarding the clinical efficacy of many systemic medications currently in use for the treatment of inner ear disorders. Despite this fact, the primary concern regarding their usage has been the potential side effects associated with delivery via the systemic route. These side effects can range from minor nuisances to potentially life threatening effects[9].

Various drugs have been tested for higher concentration and better clinical outcome when used with Intratympanic route including dexamethasone, gentamycin and methylprednisolone[10,11]. This fascinating idea of self medication by the patient is not only safer option but also delivers a better concentration of drug in the internal ear in order to revert and impede the ever degenerative changes associated with disease like presbycusis. The proper instruction of lying down in specific ear up position for sometime also probably enhances the drug delivery time too. It has been shown in animals and humans that systemically applied drugs reach only low drug concentrations in the perilymph. Exchanges between endolymph and plasma are through the stria vascularis and between perilymph and

plasma through the capillaries perilymphatic[12]. So enhanced concentration of drug in perilymph and surrounding blood capillaries is expected to having an augmented clinical and biochemical effect on the end organ of hearing i.e. Organ of corti. The outer epithelial layer of round window contains some microvilli and abundant mitochondria, suggesting that it may be able to absorb substances and carry out metabolic activities. The inner epithelial layer has areas of discontinuous basement membrane that may provide space for substances to traverse the membrane. Silverstein concluded that intratympanic dexamethasone is an effective therapy for low frequency hearing loss[13].

BMO formulation is elucidated in classical texts of Ayurveda at more than one place and is very commonly used Ayurvedic formulation in the management of hearing loss and tinnitus. Traditionally BMO is a neural regulator (Vatahara property) and a nervine tonic. The distinct statistically efficient outcome of ITG may be attributed to better drug delivery concentration of the medicated oil through a relatively semi permeable round window whereas in KPG medicated oil drug distribution in middle ear and internal ear is negligible[14]. This non admittance of KPG medicated oil is because of outer epithelial layer of the tympanic membrane which is reflected and extrapolated canal skin only. The factors which restrict the drug delivery of ITG medicated oil in the internal ear are loss of BMO from Eustachian tube, only little appreciable fluid mobility in the internal ear and semi permeable behaviours of the anatomical partition between middle and internal ear viz. Round window[15]. Possible complications of the ITG are persistent perforations, conductive hearing loss associated with the tympanostomy window and otorrhoea.

There is now substantial evidence that age-related hearing loss uncomplicated by environmental and genetic variables is largely the result of pathologies in the cochlear lateral wall rather than just a general loss of hair cells. Hence a multifarious pharmacological action is required by an agent who can perform a Cytoprotective and a antioxidant action on cochlear cell. *Aegle marmelos* which is a principal component of the BMO is reported for the availability of steroids, terpenoids, flavonoids, phenolic compounds, lignin, fat and oil, inulin, proteins, carbohydrates, alkaloids, cardiac glycosides and flavonoids[16].

Antioxidants are the compounds with free radicals scavenging activity and capable of protecting the cells from free radical mediate oxidative stress. Antioxidant activity of this plant is due to the presence of flavones, isoflavones, flavonoids, anthocyanin, coumarin lignans, catechins and isocatechins. *A. marmelos* is extensively reported to possess antioxidant activity against a variety of free radicals[17]. Cytoprotective effect of the leaves of *Aegle marmelos* was reported by stabilization of plasma membrane and modulation of antioxidant enzyme system. Anti-inflammatory activity unripe fruit pulp of *A. marmelos* was reported to possess anti-inflammatory activity. Inflammation was induced by injecting 0.1 ml of 1% λ carrageenan into the subplaner side of left hind paw of Sprague Dawley rats. Extract treatment of the inflammated rats significantly reduced the λ carrageenan induced inflammation[18].

Hence the cumulative pharmacological functions including steroidal properties, antioxidant action, cytoprotective action and inflammation arrest property may be attributed to the BMO therapeutic positive outcome in the management of degenerative cascade like presbycusis.

CONCLUSION

Intratympanic drug delivery approach was found to be a safe modality to enhance the possible drug penetration in the internal ear complex. Presbycusis being primarily a cochlear pathology, higher concentration of drug of required encountering the degenerative and apoptosis related changes of the disease. Medicated oils are frequently used in Indian system of medicine to manage ontological disorders. Bilvadi taila is popular medicated oil which was found to be effective in management of presbycusis when used with intratympanic route in the current clinical study. The traditional Karnapoorna procedure done with the same medicated oil was found to be less effective on hearing recovery and overall recovery parameters probably because of the fact that tympanic membrane epithelial layer is an anatomical barrier in diffusion of the drug in middle ear. Active alkaloids of the principal ingredient i.e. *Aegle marmelos* in Bilvadi medicated oil with its cumulative pharmacological action including steroidal properties, antioxidant action, Cytoprotective action and inflammation arrest property may be attributed to the BMO therapeutic positive outcome in the management of presbycusis.

REFERENCES

1. Schuknecht HF, Gacek MR. Cochlear pathology in presbycusis. Ann Otol Rhinol Laryngol.1993; 102: 1–16.
2. Pierre Bonfils, Yues Bertrand, Alain Uziel. Evoked otoacoustic emissions: Normative and presbycusis, Audiology.2005; 27: 27-35.
3. Plontke S, Lowenheim Hm Preyer S, et al. Outcomes research analysis of continuous intratympanic glucocorticoid delivery in patients with acute severe to profound hearing loss: basis for planning randomized controlled trials. Acta Otolaryngol. 2005; 125(8): 830-9.
4. Hendricks JL, Chikar JA, Crumling MA, et al. Localized cell and drug delivery for auditory prostheses. Hear Res. 2008; 242(1-2): 117-31.
5. Batts SA, Raphael Y. Transdifferentiation and its applicability for inner ear therapy. Hear Res.2007; 227: 41–47.
6. Boleas-Aguirre MS, Lin FR, Della Santina CC, et al. Longitudinal results with intratympanic dexamethasone in the treatment of Meniere's disease. Otol Neurotol. 2008; 29: 33–38.
7. Battista RA. Intratympanic dexamethasone for profound idiopathic sudden sensorineural hearing loss. Otolaryngol Head Neck Surg. 2005; 132: 902–905.
8. Nakagawa T, Ito J. Drug delivery systems for the treatment of sensorineural hearing loss. Acta Otolaryngol Suppl.2007; (557): 30-35.
9. Andrew A. McCall, Erin E. Leary Swan, Jeffrey T. Borenstein, William F. Sewell, Sharon G. Kujawa, and Michael J. McKenna. Drug Delivery for Treatment of Inner Ear Disease: Current State of Knowledge. Ear Hear. 2010; 31(2): 156–165.
10. Salt AN, Plontke SK. Local inner-ear drug delivery and pharmacokinetics. Drug Discovery Today. 2005; 10(19): 1299-306.
11. Silverstein H, Jackson LE, Rosenberg SI. Silverstein Microwick for treatment of inner ear disease. Operative Techniques in Otolarynoglogy- Head and Neck Surgery. 2001; 12(3): 144-147.
12. Alzamil KS, Linthicum FH., Jr. Extraneous round window membranes and plugs: possible effect on intratympanic therapy. Ann Otol Rhinol Laryngol. 2000; 109: 30–32.
13. Silverstein H, Choo D, Rosenberg SI, Kuhn J, Seidman M, Stein I. Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report). Ear Nose Throat J. 1996; 75(8): 468-71.
14. Becarovski Z, Bojrab DI, Michealides EM, et al. Round window gentamicin absorption: an in vivo human model. Laryngoscope. 2002; 112(9): 1610-13.
15. McCall AA, Swan EE, Borenstein JT, et al. Drug delivery for treatment of inner ear disease: current state of knowledge Ear Hear. 2010; 31(2): 156-65.
16. S. Rajan, M. Gokila, P. Jency, P. Brindha, R. K. Sujatha, Int. J. Curr. Pharm. Res.2011; 3: 65-70.

17. R. Sivaraj, A. Balakrishnan, M. Thenmozhi, R. Venckatesh, International Journal of Pharmaceutical Sciences and Research.2011; 2: 132-136.

18. Dinesh Kumar Sekar, Gaurav Kumar, L. Karthik and K. V. Bhaskara Rao. A review on pharmacological and phytochemical properties of *Aegle marmelos* (L.) Corr. Serr. (Rutaceae). Asian Journal of Plant Science and Research.2011; 1(2): 8-17.

Source of support: Nil, Conflict of interest: None Declared

QUICK RESPONSE CODE	ISSN (Online) : 2277 –4572
	Website http://www.jpsionline.com

How to cite this article:
Atul Bhardwaj, Riju Agarwal, Manoj Tanwar, Anoop Kumar. Clinical comparison between effectiveness of intratympanic bilvadi medicated oil and bilvadi medicated oil ear drops in management of presbycusis. J Pharm Sci Innov. 2015;4(5):284-288 http://dx.doi.org/10.7897/2277-4572.04563

Disclaimer: JPSI is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publish quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. JPSI cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of JPSI editor or editorial board members.