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ORIGINAL ARTICLE

The Effect of Topical Insulin on Healing of Small Central Tympanic Membrane Perforations and Hearing Threshold

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ABSTRACT

Background: This study is a prospective cross-sectional study, Six months, starting from July 2020 till December 2020. The sample size was estimated to be 24 cases. As the expected number of patients attending at otorhinolaryngology surgery department and fulfilling the inclusion criteria is about 4 patients /month (24 / 6 months), and all of them were included in the as a comprehensive sample

Results: The mean age of cases was 36.42 years (range, 16 – 63 years). Females constituted 58.3% of the study group, whereas the remaining portion was occupied by males. The duration of perforations had a mean value of 2.76 months. Most cases had only one perforation, but overall, their number ranged between 1 and 4. Trauma was the commonest cause in the current study (58.3%), followed by chronic suppurative otitis media (41.7%). The right sided perforations were more prevalent as it was affected in 66.7% of cases.History of ear discharge was positive in 10 cases (41.7%). It was positive in cases with positive history of otitis media. The number of topical insulin installations ranged between 4 and 14 (mean = 8.29). Over the scheduled follow up visits, the perforation size showed a significant decrease from 1.48 mm at baseline down to 0.89, 0.67, and 0.54 at 1-week, 1-, and 2-month visits ($p < 0.001$).

Conclusions: Based on our findings, topical insulin therapy appears to be a hopeful and safe option for small central tympanic perforations, with more favorable outcomes in traumatic versus infective cases.

Key words: Air bone gap; Acute otitis media; Cerebrospinal fluid; Epidermal growth factor receptor; Round window; Tympanic membrane perforation; Vascular and epidermal growth factor.

INTRODUCTION

Tympanoplasty made the history of evolution of otology as a whole. Treating the underlying pathology and restore hearing is the aim of each surgeon (1). Among various techniques in Tympanoplasty, the best technique is that to give maximum postoperative hearing using minimal instrumentation (2).

The operative steps of myringoplasty, by using a free skin graft from the forearm were reported firstly since the 19th century (3). Causes of Tympanic membrane perforation are usually infection, trauma ,or as acomplication of tympanostmy tube insertion (4).Hearing loss, recurrent otorrhea, recurrent infections, Cholesteatoma formation, tinnitus and possible infection of the middle ear space are the manifestations of chronic tympanic membrane perforations (5).

Surgical treatment of the tympanic membrane perforations by auto grafts, including temporalis fascia or perichondrium, was mentioned in most of previous studies with a success rate between 88 and 97%. Many surgeons have studied the application of topical substances to facilitate tympanic membrane healing and alternative methods for the surgical repair (6). Human Insulin promotes healing of chronic ulcers, so it can help regeneration and healing of TM. A study was done on guinea pigs to study. This technique was found to be beneficial (7).

The use of Human Insulin may improve the results of tympanic membrane healing without local or systemic side effects by increasing

directing the vasculature from the surrounding tissues towards the margins of the perforation (8).

METHODS

The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. An informed written consent was obtained from all the patients after explanation of the benefits and drawbacks of each intervention. Also, the study gained approval from the local ethical committee.The study was a prospective cross-sectional study. It was done at the Otorhinolaryngology Department, from July 2020 till December 2020. The sample size was 24 cases. As the expected number of patients attending at otorhinolaryngology surgery department and fulfilling the inclusion criteria is about 4 patients /month (24 / 6 months), and all of them were included in the as a comprehensive sample.

Inclusion criteria

Central small perforations (< 2.5 mm). Dry tympanic membrane perforation with intact middle ear mucosa for at least 3 months before the study. Air-bone gap is of 30 dB or better on study side.

Exclusion criteria

Patients with active ear discharge. Cholesteatoma. Marginal and attic perforations. Those with suspected ossicular pathology having a more than 30dB air bone gap. Central perforations > 3 mm. Revision surgery. Immunocompromised patients.

Follow up

Follow up visits were scheduled at 1 week, 1 month, and 2 months after insulin application. Endoscopic assessment was performed for all cases in each of these visits. Pure tone audiometry was also performed, and hearing loss was classified as follows; normal hearing threshold (0-25 dB HL), mild hearing loss (26-40 dB HL), moderate hearing loss (41-70 dB HL), and severe hearing loss (71-90 dB HL).

Statistical analysis:

Statistical analyses were performed using IBM SPSS 22.0. A comparative statistical analysis of all variables was carried out using Student's t- test and Fisher's exact test. The level of significance was set at $p < 0.05$ for both tests.

RESULTS

The age of the included cases ranged 16 – 63 years with a mean value 36.42 years. Females constituted 58.3% of the study population, whereas the remaining portion was occupied by males. Table (1)

The duration of perforations had a mean value of 2.76 months. Most cases had only one perforation, but overall, their number ranged between 1 and 4. Trauma was the commonest cause in the current study (58.3%), followed by chronic suppurative otitis media (41.7%). The right sided perforations were more prevalent as it was affected in 66.7% of cases. Table (2)

History of ear discharge was positive in 10 cases (41.7%). It was positive in cases with positive history of otitis media. Table (3)

The number of topical insulin installations ranged between 4 and 14 (mean= 8.29). Table (4)

Over the scheduled follow up visits, the perforation size showed a significant decrease from 1.48 mm at baseline down to 0.89, 0.67, and 0.54 at 1-week, 1-, and 2-month visits ($p < 0.001$). Table (5)

Although there was no significant improvement in the degree of hearing loss after one week, a significant improvement was detected on the subsequent follow up visits ($p = 0.002$). The cases of normal hearing threshold increased from 37.5% at baseline up to 66.7% after 2 months. At the last follow up, all of the remaining cases had mild hearing loss. Table (6)

Ear discharge was encountered in eight cases (33.3%), six of them was due to chronic otitis media. On the other hand, complete healing was achieved in 66.7% of cases, most of them were due to traumatic causes. Table (7)

Table (1): Demographic characteristics of the study cases.

All patients (n= 24)		Mean & SD	Median	Range	IQR
Age (years)		36.42 ± 15.143	35.50	16.00, 63.00	21.75, 51.50
Gender	Male	41.7% (10)			
	Female	58.3% (14)			

Table (2): Duration, cause, side, and number of perforations in the study cases.

All patients (n= 24)		Mean & SD	Median	Range	IQR
Duration (months)		2.76 ± 2.128	2.50	0.03, 6.00	1.00, 4.00
Number of perforations		1.50 ± 1.022	1.00	1.00, 4.00	1.00, 1.75
Cause	Trauma	58.3% (14)			

	Chronic suppurative otitis media	41.7% (10)
Side	**Right**	66.7% (16)
	Left	33.3% (8)

Table (3): History of ear discharge in the study cases.

Ear discharge	**All patients (n= 24)**
	41.7% (10)

Table (4): Number of insulin installations of the study cases.

All patients (n= 24)	**Mean & SD**	**Median**	**Range**	**IQR**
Installations	8.29 ± 2.645	8.00	4.00, 14.00	6.00, 10.00

Table (5): Perforation size (mm) before and after treatment of the study cases.

All patients (n= 24)	**Mean & SD**	**Median**	**Range**	**IQR**	**p**
Perforation size	1.48 ± 0.699	1.50	0.50, 2.50	1.00, 2.00	-
One week	0.89 ± 0.697	1.00	0.00, 2.00	0.35, 1.00	**< 0.001**
One month	0.67 ± 0.816	0.00	0.00, 2.00	0.00, 1.00	**< 0.001**
Two months	0.54 ± 0.833	0.00	0.00, 2.00	0.00, 1.00	**< 0.001**

Table (6): Hearing loss degree before and after treatment of the study cases.

Hearing loss degree		**All patients (n= 24)**	**p**
Basal	**Normal hearing threshold**	37.5% (9	-
	Mild hearing loss	50.0% (12	
	Moderate hearing loss	12.5% (3	
One week	**Normal hearing threshold**	45.8% (11	0.157
	Mild hearing loss	41.7% (10	
	Moderate hearing loss	12.5% (3	
One month	**Normal hearing threshold**	66.7% (16	**0.002**
	Mild hearing loss	33.3% (8	
Two months	**Normal hearing threshold**	66.7% (16	**0.002**
	Mild hearing loss	33.3% (8	

Table (7): Presence of complications in the study cases.

Healing		**All patients (n= 24)**
		66.7% (16)
Complication	**Ear discharge**	33.3% (8)

DISCUSSION

The tympanic membrane (TM), is a thin membrane acts like sound transmitter to the ossicles. This function can be affected by TM perforations (9).Within 7–10 days most TM perforations achieve spontaneous healing. If peforation lasts for 3 months. So its considered as chronic as chronic TM perforations herein (10). Chronic TM perforations can induce various symptoms or signs, such as otorrhea, cholesteatoma formation, recurrent otitis media, and conductive hearing loss (11).

Surgical procedures performed in TM perforations such as tympanoplasty and myringoplasty may have many disadvantages such as: 1) High cost of the operation, 2) defective donor sites, 3) risks of anesthesia, and 4) It needs complex microsurgical skills of surgeons (12). Structure of TM is complex and precise, this complexity affects negatively improvement in hearing recovery after these operations. On the contrary, it is possible to achieve the ideal hearing results without/with minimum air-bone gap because normal TM with three layer structures will be able to regenerate by this regenerative treatment (13,14). Insulin role in enhancing wound healing has been reported since 1960s, and its exact molecular mechanisms of healing have not been explained (15). Insulin interaction with its receptor enhances autophosphorylation of tyrosine residues distinct from the β subunits. There is an activation of the intracellular signals in the PI3K-Akt and MAPK/ERK pathways, causes glucose transport, protein synthesis, and cellular growth (16). Females constituted 58.3% of the study population in our study, whereas the remaining portion was occupied by males. Another study reported almost equal distribution between both genders regarding the incidence of TMP. The study included 641 subjects; 321 were females while the remaining cases were males (17).

In our study, trauma was the commonest cause in the current study (58.3%), followed by chronic suppurative otitis media (41.7%). In another study, TMP were caused by chronic otitis media in 67 cases (77.0%), barotrauma in 11 cases, treatment of otitis media in 7cases, and foreign-body insertion in 2 cases (18). Definitely, both trauma and infection remain the two most common causes of TMP, and the prevalence of each etiology could differ between different geographical regions.

In the current study, the number of topical insulin installations ranged between 4 and 14 (mean = 8.29). Pujary reported that a maximum of ten installations were needed before healing with no reported side effects (8). This lies within the range reported by our study.When it comes to the perforation size changes in the current study, it showed a significant decrease from 1.48 mm at baseline down to 0.89, 0.67, and 0.67 at 1-week, 1-, and 2-month visits ($p < 0.001$). Complete healing was achieved in 66.7% of cases, most of them were due to traumatic causes. Insulin enhances cellular regeneration and growth (19,21). Insulin enhances proliferation and migration of keratinocytes in vitro (20,22), stimulates the re-epithelialization of skin wounds in mice(18,22), and enhances the maturation of epidermal scar in mice with and without diabetes(23).

Insulin enhances myofibroblast synthesis which is included remodeling of tissue collagen and extracellular matrix during tissue repair (24). Insulin stimulates DNA synthesis in skin fibroblast cultures in vitro, having a mitogenic role (25).

Liu et al. reported that insulin helps in the migration of keratinocytes in wounds away from the epidermal growth factor receptors (22). Additionally, insulin activates peroxisome-proliferator activated receptor-gamma which has also been considered as one of the factors causing angiogenesis (25). Insulin like growth factor-1 inhibits the apoptotic pathway, interferes with the production of anti-inflammatory cytokines and enhances production of extracellular matrix component (26). Ghahary et al. reported that insulin like growth factor 1 produces transforming growth factor- beta in dermal fibroblasts contributing to wound healing (27). Not only cutaneous cells were promoted to heal faster with topical insulin, even corneal ulcer in rodents healed rapidly through production of insulin-like factor (28).Topical insulin has the ability to increase bacterial clearance in the wounds as compared to normal saline thus reducing the wound infection (29).

All of the previous factors could explain the beneficial role of topical insulin and the promising results we achieved in the current study. In a previous pilot study of seven cases, the first authors who used topical insulin for TM perforations used topical human insulin in ten patients. Topical insulin was beneficial in enhancing perforation epithelialization. There was increased micro-vascularity from the surrounding tissues towards the site of perforation (8).In a previous study conducted in 2016 handling the same perspective of ours, in insulin-treated TMs, the perforations became smaller after 3 to 5 days ($P < 0.01$) of insulin application than the control

group. TM perforations healing occurred in most of cases after 5 days, and 100% of the perforations were healed after 7 days in insulin treated group; however, 20% the control group had not healed (30). The results of the previous study showed that insulin increased the outer epithelial layer cells proliferation, accelerating the TM healing. Insulin induced epithelialization, that was proved by the early increase in epithelial thickness and the greater immune-labeling of the TM by cytokeratin (30).

In the same context, and in support with our findings regarding the healing power of topical insulin, insulin is used for diabetic ulcers as insulin spray as stimulates healing tissue growth and maturation. Regular dressing of chronic wounds with 2 IU of human soluble insulin and 20ml normal saline for seven days have been found to increase wounds healing without systemic hypoglycemia(31). In our study, although there was no significant improvement in the degree of hearing loss after one week, a significant improvement was detected on the subsequent follow up visits ($p = 0.002$). The cases of normal hearing threshold increased from 37.5% at baseline up to 66.7% after 2 months. At the last follow up, all of the remaining cases had mild hearing loss.

As regard complications encountered in the current study, no systemic complications of insulin administration were encountered. However, ear discharge was reported in 8 cases (33.33%). Perhaps installation of drops enhanced entry of organisms to the middle ear. That is why, patient education about ear hygiene must be encouraged. Discharge was managed by medical treatment (antibiotics).

The limitations of this study, it is a single center study. Also, the included sample size was relatively small. Moreover, we should have compared traumatic and infective cases but the resulting subgroups would be too small for reliable statistical analysis. The intermediate and long-term follow up of these cases should be documented. So, more studies including more patients from different ENT centers should be conducted soon.

CONCLUSIONS

Topical insulin therapy appears to be a hopeful and safe option for small central tympanic perforations, with more favorable outcomes in traumatic versus infective cases.Topical insulin therapy should be commended for selected patients with small traumatic TMP with good outcome. More studies handling the role of topical insulin in TMP should be conducted. The outcome of that method should be compared in traumatic versus infective cases to clearly choose the best treatment option for each etiology.

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