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ORIGINAL ARTICLE

Topical Insulin for Treatment of Small Central Perforations – A Pilot Study

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Abstract: Options for treatment of small central perforations (CP) of tympanic membrane (TM) such as chemical cautery of the margins arefrequently preferred totympanoplasty. The size of the perforation increases initially due to cautery or may remain the same.

Insulin may be therapeutic agent in treating such small CP of the TM by its growth enhancing effects. We used topical diluted Human R insulin in seven patients. A total of ten perforations were treated in this trial. This included a unilateral CP of the TM in five cases, bilateral CP of TM in one case, single graft perforation (GP) post myringoplasty and recurrent double graft perforation following coryza in the same patient.

A gelfoam soaked with dilute Human R Insulin was placed at the site of the perforation in the ENT outpatient. The procedure was repeated on daily basis or alternate days based on patient's convenience. Successful epithelialization of the CP was noted in as less as two instillations. A maximum of ten instillations were done before healing was noticed without local or systemic side effects. Out of ten perforations, five healed (including three GP), three did not heal, one started discharging and one cannot be commented as patient was lost for follow up.

This is the first clinical study showing application of insulin for treatment of small CP of TM or GP in patients and proves to have a beneficial effect in healing in selected patients.

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Introduction

Human Insulin has been used for treatment of chronic ulcers to promote epithelialization and healing. Based on this, TM perforations have been made in guinea pigs to study the rate and process of healing. The application of insulin for epithelializing the perforation was found to be beneficial[1]. However, the results have not been applied for treatment of TM perforations in human beings so far.

This is a pilot study of seven patients with total of seven CP (five - unilateral, one – bilateral) and three graft perforations (one patient with single graft perforation had recurrence at two sites following coryza) wherein dilute Human Insulin R was instilled at the site of perforation. The clinical appearance of the margins of the perforation and the surrounding TM or graft was noted on subsequent follow up. The study was done on an outpatient basis in ENT department of a tertiary care hospital at Manipal, Manipal University (MU) after attaining Ethical Committee clearance.

There was increase in microvasculature from the surrounding towards the margins of the perforation. Epithelialization from the periphery of the margins was vivid. There were no local or systemic side effects such as hypoglycemia or headache. Failure of epithelialization was seen in treating perforation of more than 1.5mms diameter, during focus of sinonasal infection or when aseptic precautions were inadequate.

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There are various growth factors such as epithelial or fibroblast growth factors, hyaluronic acid and such combination drugs that have been applied topically for healing of the CP of TM. However, these are not free from risk of hypertrophy of canal wall and carcinogenesis. Human Insulin acts as a self-limiting hormone rather than a drug in the treatment of small CP of TM or GP. This is the beginning of a long term study on the impact of insulin on healing of CP of TM before it may be considered as a routine, easy and cost effective outpatient procedure.

Materials and Methods

The trial of topical human insulin instillation was planned for patients with no active upper respiratory tract infections. A central perforation of 1-2.5 mm diameter and preferably non discharging ear were selected. Patients with diabetes mellitus or those who are immunocompromised were not found to be a contraindication for the procedure.

The study was approved by the Ethical Committee of the Kasturba Hospital, Manipal (India), Manipal University.

The materials needed were insulin syringe, Human Insulin R (Huminsulin R, Eli Lilly and Company Pvt ltd. 56, 1st floor, 1st Main, Raghav Nagar, NPY layout, Mysore Road. Bangalore. India), normal saline loaded in 2cc syringe with 24G needle and sterile gloves. All were funded by the research grant from Manipal University. The Insulin bottle of the respective patient was refrigerated in refrigerator.

There were seven patients of age range 22 years to 45years (from June 2010 to December 2010) who consented for the trial study. Six were male patients and one was female. Following a written and informed consent was taken, the patients were subjected to examination under microscope. 1 IU of normal saline was withdrawn from the open end of the 2cc syringe containing saline to dilute 1IU of Human Insulin R in the insulin syringe by passing the needle through the hub for withdrawal. A gelfoam of 1X1 mm size was placed at the site of the perforation with a straight pick and crocodile forceps. The gelfoam was then soaked with diluted insulin drops. Two to three gelfoams were placed in addition if the drops floated above the gelfoam placed.

The patient was made to lie in supine position with the ear in which the gelfoam was instilled 'up' for ten minutes. This was to avoid the insulin trickle out into the ear canal immediately after instillation. In the meantime, patient was watched for signs of hypoglycemia or headache, ear pain, tinnitus or giddiness.

This procedure was repeated similarly on subsequent days or alternate days. The patients were examined before every subsequent procedure for any ear discharge and/or granulations or tenderness. Topical insulin was stopped once epithelialization was complete. The maximum number of procedures was limited to ten and the procedure was abandoned if the ear had started discharging secondary to the procedure or due to upper respiratory tract infection.

The first patient had received silver nitrate ($AgNO_3$) 1% cauterization before. Cauterizing the margins increased the size of the perforation and did not have a synergistic role with topical insulin. Hence, cautery was stopped prior to the procedure for all the other cases.

In two patients, where the CP was 2mm to 2.5mm, a slender oval shaped silastic sheet (1 cm X 1.5cm) was fashioned. One end was placed in the middle ear through the perforation and the other end was supported against the canal wall in the external ear. The gel foam was placed on top of the silastic sheet at the site of the perforation. The silastic sheet was used to support the gelfoam preventing it falling into the middle ear and to act as a support for the new epithelial membrane

Observations

The TM or the graft being treated appeared congested with increased microvascularity at the perforation site on the second and the third day of instillation. The increased vascularity was generalized and often,a leash of vessels was clearer in one quadrant. The gelfoam liquefied and formed a thick film around the perforation. By the fourth or fifth topical instillation of insulin the size of the perforation was reduced to half the original size. White epithelium covered the perforation after two topical insulin instillation as in case No 3 (Observation Table I) or nine instillations as in case No 2. Hence thorough suction cleaning was avoided.

Table 1. Observations

No	Patient age in yrs/sex	Last ear discharge	Diagnosis	Size of CP	CP/graft perforation in trial study	Procedure with topical insulin
1.	22 M	2 yrs back	® ear CSOM (TTD), inactive	1.5mm	ONE	Cauterization of margin with AgNO3 1% and seven instillations
2.	23 M	2 mths back	(L) ear CSOM (TTD), quiescent	1.5mm	ONE	Nine instillations
3.	44 M	® ear: 1 day back and (L) ear: discharging	B/L ASOM with alcohol liver disease, ascites and Type II Diabetes mellitus	1mm ® ear and 1.5mm (L) ear	TWO (one in each ear)	Two instillations under systemic antibiotic cover (IV Ceftriaxone and Oral Augmentin)
4.	40 M	6 mths back	® ear CSOM (TTD), inactive	2.5mm	ONE	Ten instillations of insulin with silastic sheet inserted partially in middle ear cavity from EUC
5.	25 M	1 yr back	® ear CSOM (TTD), inactive	1.5mm	ONE	Four instillations
6.	32 F	4 mths back	® ear CSOM (TTD), inactive	2mm	ONE	Nine instillations with silastic sheet placed similar to Case 4. Patient refused treatment.
7.	25 M	No ear discharge 6 mthspost operative period	® ear post myringoplasty status with Hepatitis B – graft perforation in inferior quadrant. After 6 months – coryza and re-perforation of graft in anterior and inferior quadrant	1.5 mm in inferior quadrant. When recurred - 1.5 mm each in anterior and in inferior quadrant	TWO quadrant.	Eight instillations in one After graft perforation recurred in anterior and inferior quadrants -five instillations in each quadrant

®: right; (L): left; yr/yrs: year/years; mths: months; CSOM: chronic suppurative otitis media; TTD: tubotympanic disease; EUC: external auditory canal

Cauterization of the margin with $AgNO_3$ 1% as in case No 1, increased the size of the perforation and the perforation did not show signs of healing after topical insulin instillations. More than 1 mm to 1.5mm diameter perforations (two cases: No 4 and No 6), did not epithelialize despite placing silastic sheet as scaffold from the external auditory canal towards the middle ear.

The lack of absolute aseptic precautions may cause ear discharge as in case No 5. Recycled gloves were used during the procedure and is presumed to be the cause for infection. Acute coryza was the cause of ear discharge as in case No 7. The treatment was withheld and patient was treated for the acute infection by oral medication. The perforation secondary to ASOM epithelialized by two topical instillations as the ears stopped discharging under intravenous antibiotic cover. The right ear perforation healed earlier as the perforation was smaller than the left ear. Subsequently, the patient was lost for follow up with respect to treatment of the left ear.

Results

Topical insulin induced epithelialization was successful in two cases (No 2 and No 3) and three graft perforations post myringoplasty (No 7) [Figure 1].

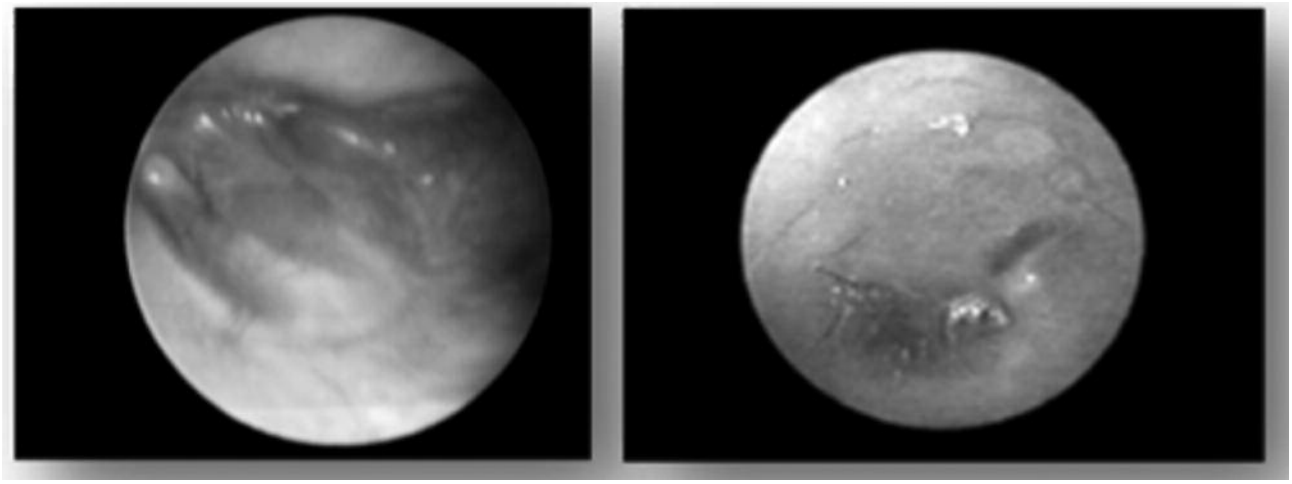

Figure 1. Anterior healed graft perforation after two months follow up following topical insulin instillation in Case 7 and two healed perforation (anterior and inferior) of graft following acute coryza after four months follow up in Case 7

The TM perforations failed to heal by epithelialization in case of previous cauterization of the margins;, lack of aseptic precautions, in TM perforations of more than 1.5mms diameter and in the presence of acute upper respiratory tract infection.

The CP following ASOM (case No 3) healed because of the ongoing initiation of the inflammatory cascade in the middle ear and intravenous antibiotic cover for infection.

There were no local or systemic side effects due to the topical use of insulin in any patients. In case of No 4 and No 6, the silastic sheet prevented the gelfoam from slipping into the middle ear soon after placement. However, the silastic sheet caused discomfort in the ear (case No 6). The patient discontinued further medical treatment. The other drawback was that silastic sheet had to be cleaned and replaced during every procedure. Sometimes it may blend with the liquefied gelfoam, concealingit during subsequent procedure.

Discussion

Cauterizing the TM margins in small central perforations induces microvascularity at the margins of the perforation to promote healing. This has been the easy method adopted so far but not always effective[2].

In vivo experiments have shown that insulin acts as a growth hormone by increasing the rate of growth of fibroblast and proliferation, migration and differentiation of keratinocytes from the wound margins. This is dependent on the activation of the PI3K-Akt pathway, followed by activation of Rac1. Insulin activates both its own receptor and the IGF-1 (insulin growth factor -1) receptor and stimulates keratin migration in an insulin receptordependent manner. It also stimulates EGF (epithelial growth factor) expression in wound marginal keratinocytes of deep partial thickness scald wounds in rats[3].

Since insulin accelerates re-epithelization and maturation of healing tissue, it is used for diabetic ulcers as insulin spray. Regular dressing of chronic wounds with 20ml normal saline containing 2 IU of human soluble insulin (actrapid) for seven days have been found to heal wounds without systemic hypoglycaemia[4]. Topical Huminsulin -R 1IU applied on TM perforations of 2 mms diameter daily in guinea pigs showed finger - like projections, edema, neovascularization, fibroblastic activity and inflammatory cell in the lamina propria confirming sensitivity of the tympanic membrane to insulin as applied to chronic ulcers[1].

In our pilot study of seven cases, we treated ten perforations with topical human insulin. In three patients with total of five perforations of 1 mm to 1.5mm diameter, topical insulin was beneficial in epithelializing the perforation. There was increased micro-vascularity from the surrounding TM or graft towards the site of perforation. This induced inflammation and epithelialization from the margins of the perforation. However, the same effect failed after cauterizing the margins of the perforation. Also when topical insulin was applied to small TM perforation secondary to acute otitis media, the healing was rapid than in the patient following acute coryza. This is probably because in acute otitis media, the inflammatory cascade was induced towards phase of resolution while in acute coryza, the nasosinusal source of infection was persisting. Once the infection subsided, the effect of insulin induced fibroblast differentiation and keratin migration persisted to effect closure of the perforated sites. The side effects after topical insulin such as giddiness or increased sweating were absent.

Basic fibroblast growth factor, epidermal growth factor, transforming growth factor (TGF) alpha and other growth factors have been instilled topically on the perforation to promote healing in animal trial studies[5-9]. However, the results are inconsistent.There may be no healing of chronic TM perforation in adults showing the limitation of use of topical growth factor[10]. Hyaluronic acid is another drug used topically for medical management of central perforations[11]. A combination of growth factors and hyaluronic acid have yielded better results in healing than use of a single growth factor topically[11,12].

When insulin was added to a growth factor such as TGF beta and used topically in animal studies, the healing was more rapid than the use of epithelial growth factor or insulin alone[5]. However, the use of growth factors may not only induce moderate to severe canal wall hypertrophy[13] but the increased expression of growth factor receptors may lead to carcinogenesis[3].

Topical Huminsulin of CP or GP of not more than 1 mm to 1.5 mms diameter reveals clinical gradual closure of perforation on frequent reviews. In selected patients under aseptic precautions, it is a cost effective outpatient procedure. This is the first trial study in literature so far to highlight that topical insulin may be used in patients with CP or post tympanoplasty GP without local or systemic side effects. In the long run, this procedure may be a rapid microscope guided outpatient procedure lasting for a week. This medical management may bring immediate results or a positive outcome on the subsequent monthly follow up visit.

A long term study is required to know the time to effect closure of perforation after the last instillation of topical insulin in delayed cases or any systemic outcome thereof. The molecular genesis of healing using topical insulin on CP of TM in animals is applied to patients. In future, a comparison at the molecular level of healing may be required to highlight any differences in the cascade of events between human and animal model.

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