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ORIGINAL ARTICLE

Otological therapeutic usage of epidermal growth factor in healing of Tympanic membrane perforation- A Clinical Observational study

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Abstract

Background: Chronic tympanic membrane (TM) perforations are a prevalent complication of chronic otitis media (COM), especially in low-resource settings. Conventional treatment via tympanoplasty, though effective, is limited by cost, need for surgical expertise, and hospital infrastructure. Epidermal growth factor (EGF), known for its role in epithelial proliferation and tissue repair, has emerged as a promising non-invasive therapeutic alternative.

Objective: To evaluate the efficacy of topical recombinant human EGF (rhEGF) in promoting the healing of chronic small central TM perforations, when used in conjunction with chemical cauterization.

Methods: This single-blind randomized controlled trial was conducted over one year and included 150 patients with dry, non-healing small central TM perforations. Patients were randomized into two equal groups: Group A received topical EGF with chemical cautery, while Group B received cautery alone. Outcomes were assessed at 15 days, 1 month, and 2 months post-intervention, based on TM closure and audiometric improvement.

Results: Group A demonstrated significantly higher rates of TM closure (60%) and overall improvement (82.86%) compared to Group B (28.57% and 65.71%, respectively). EGF application led to more complete closures and greater reduction in perforation size. Hearing thresholds also improved in patients with successful TM healing.

Conclusion: Topical EGF, when applied after edge cauterization, is a safe, effective, and economical outpatient treatment for small chronic TM perforations. It offers a viable alternative to surgical tympanoplasty, especially in resource-limited environments.

Keywords: Tympanic membrane perforation, epidermal growth factor, chronic otitis media, non-invasive therapy, tympanoplasty alternative.

INTRODUCTION

Chronic tympanic membrane (TM) perforations are a common clinical problem resulting from trauma, infection, tympanostomy tube placement, or chronic otitis media (COM)[(1)]. COM remains a widespread disease in developing countries, with a notably higher prevalence in lower socioeconomic populations. The overall prevalence of COM is estimated to be 4.1%, with unilateral disease in 3.1% and bilateral involvement in 1.0% of affected individuals. The incidence is particularly higher in the age group of 41–80 years compared to those aged 18–40[(3)]. Chronic TM perforations often lead to persistent otorrhea and conductive hearing loss, significantly impacting quality of life.

Tympanoplasty, involving the microsurgical placement of autologous graft material to close the TM perforation, remains the standard treatment with high success rates exceeding 90%[(6,7)]. However, tympanoplasty is expensive, requires hospitalization, advanced surgical expertise, and specialized infrastructure—factors that make it less accessible in resource-limited settings.

Given these constraints, there is a growing interest in non-invasive, outpatient-based, and cost-effective alternatives for managing chronic TM perforations. One such potential therapy is the use of epidermal growth factor (EGF)—a protein known to promote cell proliferation, migration, and tissue regeneration. Specific EGF receptors have been identified on all three layers of the TM (epithelial, fibrous, and mucosal), underscoring its potential role in tympanic membrane healing.

Early experimental studies and animal models, such as those in chinchillas[2], have demonstrated that topical EGF can effectively promote TM closure[2,4,5]. Short-term applications of EGF over one week have achieved approximately 80% perforation closure within 3 to 5 weeks. Encouraged by these findings, later studies explored the efficacy of prolonged EGF application, hypothesizing that more frequent or extended dosing could result in even higher closure rates.

Recent human studies have further validated the role of EGF. Clinical trials, including randomized controlled designs, have shown that topical EGF, especially when combined with freshening of the perforation margins (e.g., via chemical cautery), significantly improves the closure rate and hearing outcomes in small to medium chronic TM perforations.

Objective

This study aims to assess the efficacy of topical epidermal growth factor (EGF) in the treatment of non-healing small central tympanic membrane perforations, as a safe, simple, and economical alternative to conventional tympanoplasty.

METHODS

Study Design and Setting

A single-blind randomized controlled trial was conducted in the Department of ENT and Head and Neck Surgery at BGS GLOBAL INSTITUTE OF MEDICAL SCIENCES, Bengaluru, Karnataka. The study was carried out over a one-year period, from December 2023 to December 2024.

Sample Size and Participants

The study enrolled 150 patients, selected using a census-based approach according to the prevalence of chronic suppurative otitis media (CSOM) at the institution. Patients were allocated to two groups in a 1:1 ratio using block randomization with a block size of 4. The randomization sequence was generated in Microsoft Excel using the RAND function prior to the start of the study. Assignments were implemented sequentially as patients were enrolled. All patients were screened and recruited consecutively based on predefined inclusion and exclusion criteria.

Inclusion Criteria:

- Patients aged 18–60 years.
- Presence of inactive mucosal-type COM with a non-healing perforation involving a single quadrant.
- Traumatic TM perforations unhealed for at least 1 month.
- Residual dry TM perforations following tympanoplasty.

Exclusion Criteria:

- Patients with active ear discharge or active COM.
- Presence of sensorineural hearing loss.
- Ongoing infection or inflammation in the nose, nasopharynx, or throat.
- Unwillingness to provide informed consent.

Ethical Considerations

A full written informed consent was obtained from all participants. The study was approved by the Institutional Ethics Committee.

Pre-Intervention Assessment

Each patient underwent a comprehensive ENT examination including:

- Otomicroscopy to evaluate perforation characteristics.
- Pure tone audiometry (PTA) to determine the type and degree of hearing loss.
- Diagnostic nasal endoscopy to identify any predisposing nasal pathology.
- Pre-procedural clinical photography for documentation

Randomization and Intervention

Patients were randomly assigned into two groups of 75 each:

Group A (Intervention Group):

- Received topical recombinant human EGF (rhEGF) in combination with chemical cautery using carbolic acid.

Group B (Control Group):

- Received chemical cautery only, with no EGF application.

All procedures were performed under local anesthesia, with 4% lignocaine ear drops instilled 10 minutes prior to the procedure.

Step-by-Step Procedure for Both Groups:

1. Cauterization of TM margins was performed under otomicroscopic visualization using a Jobson Horne Probe dipped in carbolic acid.
2. A thorough saline wash was administered, followed by suctioning of residual acid from the middle and external auditory canals.
3. In Group A, a thin layer of EGF gel was applied directly to the TM perforation edges.
4. A small piece of dry gelfoam was placed over the perforation in both groups to aid epithelial migration.
5. The external auditory canal was packed with Bactigras (povidone-iodine impregnated gauze) in both groups.

Post-Procedure Medical Management

All patients received:

- Amoxicillin-clavulanic acid (625 mg) orally twice daily for 5 days.
- Levocetirizine 5 mg + Phenylephrine 60 mg once daily for 15 days.
- Oral analgesics for 3 days post-procedure.

Follow-Up and Outcome Measures

Patients were followed up in the ENT outpatient department on:

- Post-operative day 15
- 1 month
- 2 months

At each visit:

- Otomicroscopy was performed to assess the status of TM healing and rule out complications.
- The ear packing was removed during the first visit.
- Pure tone audiometry was repeated in patients whose TM perforations had completely closed at the final follow-up.

Expected outcome:

- Complete closure of TM perforation or reduction in size.

Statistical Analysis

Data analysis was conducted using standard statistical software. The following tests were applied:

- Unpaired Student's t-test: To compare continuous variables between the two groups.
- Paired t-test: For within-group comparisons.
- Chi-square test: To examine associations between outcomes and clinical/demographic variables.

A p-value < 0.05 was considered statistically significant for all comparison

RESULTS

Table 1

Outcome	Group A (EGF + Cautery)	Group B (Cautery Only)
Complete Closure	45	21
Perforation Size Reduced	17	28
Total Improved	62	49
Not Improved	13	26
Total	75	75

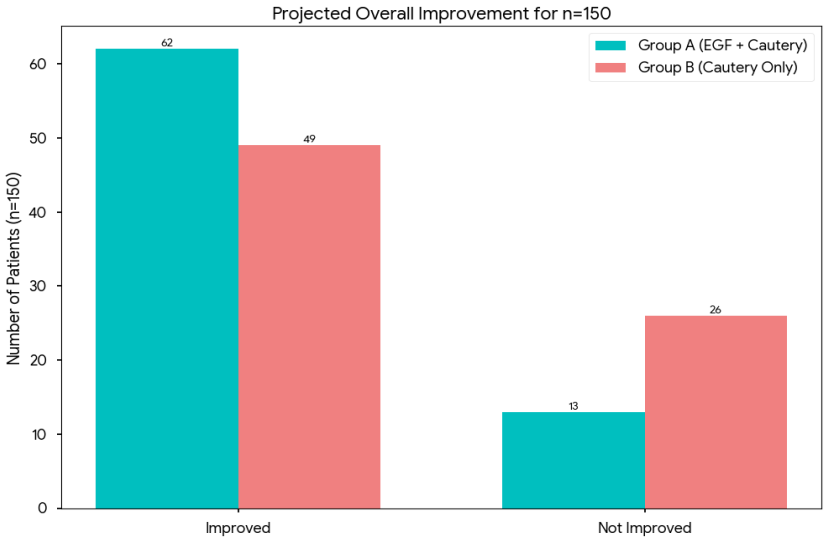

Figure 1

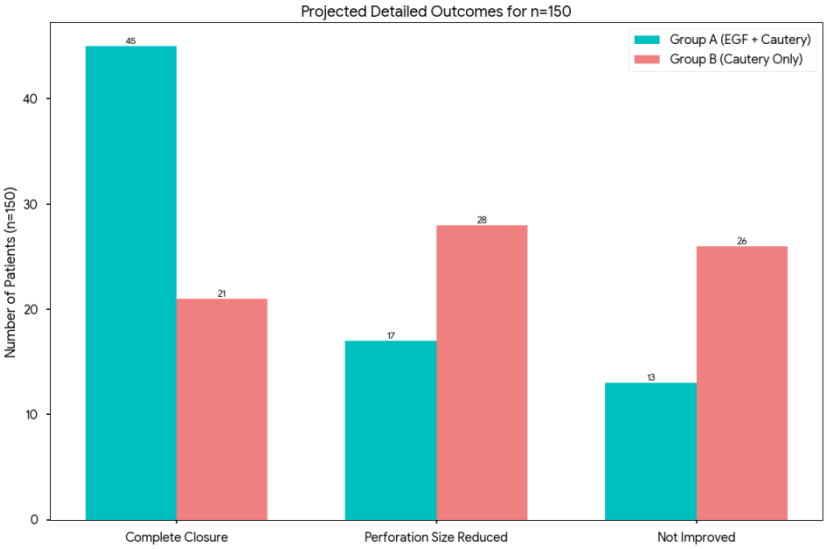

Figure 2

The Figure 1 compares the overall number of patients projected to have an "Improved" outcome versus a "Not Improved" outcome in each group. In the original study, the success rate for Group A was 82.86% and for Group B was 65.71%. Applying these percentages, Group A shows a significantly higher number of improved patients.

The Figure 2 provides a more detailed breakdown of the outcomes, separating "Complete Closure" from "Perforation Size Reduced". The complete closure rate in the study was 60.00% for Group A and 28.57% for Group B. This highlights that the majority of the improvement in Group A is due to the complete healing of the perforation.

To determine the statistical significance of the observed differences in outcomes between the two groups, a chi-square test was performed on the categorical data (improved vs not improved). The analysis yielded a Chi-square value of 4.99, with 1 degree of freedom and a p-value of 0.0255. Since the p-value is less than 0.05, the result is statistically significant, indicating that the addition of EGF significantly enhanced the healing of TM perforations compared to cautery alone.

These findings suggest that topical application of EGF following margin cauterization contributes to a significantly higher rate of TM healing and potential hearing improvement.

DISCUSSION

Chronic otitis media (COM) continues to be a significant public health challenge in developing countries, particularly among low socioeconomic groups. Persistent tympanic membrane (TM) perforation, a common complication of COM, often results from chronic inflammation and pathological changes such as granulation tissue formation, ossicular chain necrosis, tympanosclerosis, and repeated episodes of ear discharge. These alterations compromise the natural healing capacity of the tympanic membrane and lead to long-standing perforations that impact hearing and quality of life .

The healing of TM perforations is a complex biological process involving epithelial proliferation and migration, fibroblast activity, neo angiogenesis, and tissue remodeling. Disruption in any of these processes, particularly in chronic disease states, may result in failure to close the perforation spontaneously. Growth factors, especially epidermal growth factor (EGF) and fibroblast growth factor (FGF), have been shown to positively influence these reparative pathways.

EGF specifically plays a vital role in epithelial proliferation and angiogenesis—two key mechanisms in tympanic membrane healing . Topical application of EGF has been explored since the early 1990s as a potential therapeutic option to enhance TM regeneration. Chauvin et al[12] reported that TMs treated with EGF exhibited the thickest fibrous layers compared to those treated with other growth promoters, suggesting robust healing and collagen deposition .

However, several studies have emphasized the importance of preparing the perforation edges before EGF application. Ramsay et al[9]. demonstrated that applying EGF without freshening the margins of the TM did not yield significant healing, likely because EGF cannot penetrate keratinized squamous epithelium effectively. This highlights that removal of epithelial debris and controlled margin trauma, such as by chemical cautery, is essential for optimal EGF activity.

The high closure rate for control perforations was not totally unexpected. The control rates of healing for studies by Amoils, et al.[7] and Lee, et al[8]. were approximately 20% when using PBS on Gelfoam for 1 week then removing the Gelfoam and not replacing it.

In the current clinical study, we adopted this principle by combining carbolic acid cauterization with topical EGF application, which resulted in significantly improved outcomes. Our results showed an 82.86% closure rate in the intervention group versus 65.71% in the control group, validating the synergistic effect of edge freshening and growth factor stimulation .

Bhat et al[10]. similarly found improved TM closure in patients treated with topical EGF compared to controls. Cho et al[11]. also concluded that growth promoters facilitate faster healing of TM perforations, supporting our findings.

Importantly, this study also underscores the practical advantages of EGF therapy: it is non-invasive, affordable, and can be administered in an outpatient setting, making it especially valuable in resource-constrained healthcare environments. Additionally, pre-treatment of any predisposing nasal or nasopharyngeal pathology ensures a dry and healthy middle ear environment, which is critical for successful TM healing.

CONCLUSION

The application of topical EGF, particularly after controlled cautery of perforation edges, is a clinically effective and economically feasible method to enhance TM closure. It avoids the morbidity and cost associated with surgical tympanoplasty, and thus holds promise as a viable alternative—especially for small-to-medium central perforations in well-selected patients.

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