

# Regeneration of Traumatic Tympanic Membrane Perforations

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## Abstract

**Objectives/Hypothesis:** To analyse the therapeutic strategies for treating traumatic tympanic membrane perforations (TTMPs).

**Study Design:** Literature review

**Methods:** The relevant literature on methods for treating human TTMPs was reviewed. The advantages and disadvantages of each treatment were analysed.

**Results:** A total of 24 articles were included. Among them, eight reported the efficacy of growth factors, eight considered patches, and five only observed spontaneous healing. The remaining three studies focused on other treatment methods.

**Conclusion:** Although 80% of TTMPs tend to spontaneously heal within 3 months, large perforations usually fail to close. Topical application of growth factors or ofloxacin ear drops is simple, convenient, and inexpensive, and it can accelerate the healing of the eardrum and improve the closure rate of large TTMPs.

**Keywords:** Tympanic membrane perforation; Trauma; Patch; Growth factor; Closure

## Introduction

Traumatic tympanic membrane perforations (TTMPs) are commonly encountered by otologists. They can be caused by a physical blow to the ear (such as a collision or slap), blast, barotrauma (pneumatization of the mastoid cells) or insertion of sharp objects (such as cotton swabs, bobby pins and sticks) [1-3]. Among these, collision is more often the cause in males, while perforation induced by insertion of a cotton swab is approximately twice as common in females [2]. Moreover, some previous studies have shown that the injury occurs more often in the left ear than the right [2,4,5]. TTMP patients always suffer reversible high-frequency deafness, occasionally complicated with tinnitus and vertigo [2,6,7]. Most TTMPs (about 80%) can heal spontaneously within 3 months post injury [3,4,8-11]. However, large perforations usually fail to close, and appropriate treatment should be performed to reduce the incidence of permanent impairment [9,11-14]. In this paper, a narrative review is presented to provide an overview of the selection of current therapeutic strategies for TTMP.

## Method

A literature search was performed on PubMed up to May 2016 to identify all published studies regarding TTMP. The search

strategy is shown in Figure 1. A total of 617 articles were identified by an initial search using the following key words: "traumatic" or "trauma" and "tympanic membrane perforation" or "tympanic membrane" or "TMP" and "closure" or "regeneration" or "heal" or "healing". These articles were screened by reviewing the titles or abstracts based on inclusion and exclusion criteria.

The inclusion criteria were patients with TTMP; treatments including spontaneous healing, growth factors, patches or myringoplasty; and outcomes including closure time and/or closure rate. Studies were excluded if patients had chronic TMP, if study subjects were animal models, and/or if the reports were reviews or comments only. Ultimately, a total of 24 articles were included: 8 reported the efficacy of growth factors for treating TTMPs [15-22], 8 considered patches for TTMP repair [23-30], 5 focused only on the spontaneous healing of TTMPs [10,11,14,31,32], and the remaining 3 focused on other treatment methods [33-35].

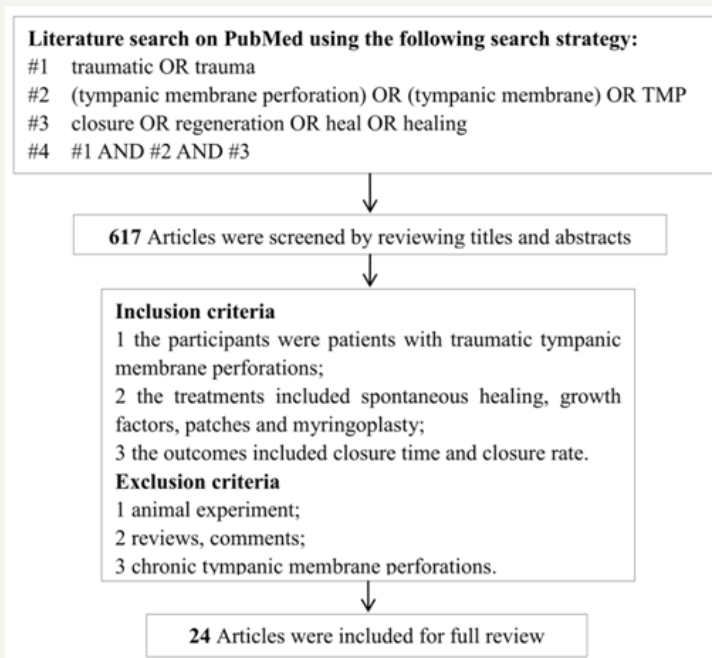
## Review

### Spontaneous healing

Although TTMPs has a high chance of healing spontaneously [9], many factors such as the size of perforations, age of

patients, aetiology (such as lightning and molten metal injuries), serosanguineous discharge and other injuries in the ear (such as malleus or umbo damage) can affect the closure rate and/or time to heal [3,12,13,32]. During spontaneous healing of TTMPs, infection is a common complication that can adversely affect the outcome

[9,11,12]. TTMPs that occur under wet conditions can easily be infected and are always associated with otorrhea and purulent discharge [5,32,36]. Thus, ears with a fresh TTMP must be kept clean to prevent infection during spontaneous healing [37].



**Figure 1:** Literature search on Pubmed using the following search strategy.

## Application of growth accelerators to promote TTMP closure

**Table 1:** Clinical studies on growth factors for treatment of human traumatic TMP.

Author, Year	Study Design	Subjects	Comparison/Groups	Outcomes
Zhang Q et al. [21] 2012	Prospective CCT	93 penetrating TMPs	Spontaneous healing vs. bFGF-treated	FGF2-treated patients showed significantly higher closure rate (100% vs. 77%) and shorter closure time (12.6±1.2 vs. 43.1±2.5 days) than patients with spontaneous healing at 3 months.
Lou ZC et al. [22] 2012	Prospective CCT	147 TMPs	Grouping base on the duration using the treatment of FGF2: within 3 days, 4-7, 8-14 days and 2-4 weeks	The healing rate was 98.6% within 3 days group, 97.6% for 4-7 days group, 96.3% for 8-14 days group, and 100% for 2-4 weeks group at one month, respectively. The closure time was 7.95±2.07 days within 3 days group, 6.75±2.67 days for 4-7 days group, 4.18±0.91 days for 8-14 days group, respectively.
Lou ZC et al. [18] 2015	Prospective RCT	86 TMPs	Spontaneous healing vs. FGF2-treated group (subgroups based on the duration of ≤3 and >3 days)	FGF2-treated group showed significantly higher total closure rate (97.8 vs 82.5%) and a shorter mean closure time (12.5±3.4 vs 34.0±5.9 days) compared with the spontaneous healing group at 6 months.
Lou ZC et al. [15] 2016	Prospective RCT	97 TMPs	Spontaneous healing vs. EGF-treatment	EGF-treated group showed significantly shorter closure time (25.1±10.5 vs. 11.7±5.2 days compared with the spontaneous healing group at 6 months)
Lou ZC et al. [16] 2016	Prospective RCT	86 large TMPs	Spontaneous healing group vs. FGF2 group vs. EGF group	The closure rates in the EGF, FGF2, and spontaneous healing groups were 86.2%, 89.3%, and 72.4%, respectively. The average closure time was 12.5±7.1 days in the EGF, 13.7±7.6 days in the FGF2, and 28.1±12.2 days in spontaneous healing at 3 months, respectively.
Lou ZC et al. [20] 2013	Prospective CCT	58 large TMPs With inverted edges	Spontaneous healing vs. edge approximation vs. FGF-2 treatment	The closure rate was 100% in FGF2 group, 60% in edge approximation group, and 56% in spontaneous healing group. The average closure time was 12.4±3.6 days in FGF2 group, 46.3±8.7 days in edge approximation group, and 48.2±5.3 days in spontaneous healing group at 6 months.



TMP: Tympanic Membrane Perforation; CCT: Clinical Control Study; RCT: Randomized Control Study; FGF2: Fibroblast Growth Factor 2.

Currently, epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF/FGF-2) are the commonly used growth accelerators for TMPs; they can induce the proliferation and migration of epithelial cells and fibroblasts and stimulate angiogenesis, thereby facilitating wound healing [21,27,38,39]. For TTMPs, EGF and bFGF are effective agents that promote closure and seem to have equal efficacy [15,16,20,22] (Table 1). Moreover, a low dose of bFGF (0.1-0.15mL) has a better effect on reducing closure time compared to a high dose (0.25-0.3mL) [19]. Besides the dosage, history of chronic otitis media, residual tympanic membrane calcification and umbo or malleus injury are also risk factors associated with non-healing in patients treated with bFGF [17]. Healing outcomes are not affected by time-to-treatment (from injury to treatment with bFGF), the size of perforations and/or the presence of inverted edges [17,18,22]. There is insufficient evidence on the efficacy of EGF for accelerating TTMP healing, and more studies are needed. The efficacies of other growth factors have been explored for the treatment of TMPs. A previous study demonstrated the effects of repeated application of transforming growth factor- $\beta$ 1 for accelerating perforation closure in rats with acute TTMP [40]. In addition, the growth accelerator hyaluronic acid has been shown to have an equal effect as EGF for treating acute TTMP in rats and pigs [41,42]. Hyaluronic acid is a naturally occurring polysaccharide associated with various cellular processes involved in wound healing [43]. A previous study speculated that it might be a potential delivery vehicle for growth factors, thus promoting wound healing [44]. Thus, the combined application of hyaluronic acid and growth factors may have better efficacy in promoting the healing of TTMP,

which should be evaluated in future studies. There is still a lack of evidence proving the efficacy of hyaluronic acid and transforming growth factor- $\beta$ 1 in humans. On the other hand, growth factors are inexpensive, at approximately US\$3.0-4.0 per bottle. However, unfortunately, topical application of a large dose of growth factor solution may induce otorrhea and prolong closure time [15-19].

### Other agents for treating TTMP

Generally, antibiotics such as ofloxacin otic drops are used to treat infections in the ear [45,46]. These drops can shorten closure time and improve the closure rate [33], possibly by inhibiting the adverse effects of infection on TMP healing [47]. However, it remains unclear whether the antibiotics or the moist environment created by the drops accelerates healing. Some studies have shown that moisture balance is important during wound healing, and a moist environment facilitates cellular growth and collagen proliferation within a healthy noncellular matrix, thereby hastening the healing of both acute and chronic wounds and promoting the growth of new tissue [48,49]. Indeed, moist TMPs have been shown to heal more rapidly than dry perforations [49,50]. In addition, eardrum healing can be affected by the environmental pH, with an acidic environment accelerating healing and an alkaline environment inhibiting it [51]. Thus, the mechanisms underlying the closure-promoting effects of ofloxacin otic drops on TTMPs should be explored in further studies. Such eardrops are common and inexpensive at approximately US\$3.0 per bottle. An appropriate dose does not induce infection of the middle ear in TMPs [33]. In addition, other agents such as heparin, insulin and vitamins (vitamins C and E) may also help promote the healing of TTMPs [34,52-54]. However, the efficacies of these agents still need to be verified by clinical studies.

### Patches to repair TTMP

**Table 2:** The healing outcome of patching on the regeneration of traumatic TMP.

Author, Year	Study Design	Subjects	Comparison/Groups	Outcomes
Park M K et al. [28] 2011	Prospective RCT	87 large TMPs	Steri-Strips patching vs. paper patching vs. spontaneous healing	The closure rate was 93.3% in Steri-Strips patch group, 84.2% in paper patch group, and 78.9% in spontaneous healing group at 3 months, respectively. The average closure time was 46.4 $\pm$ 16.6 days in Steri-Strips patch group, 44.7 $\pm$ 19.9 days in paper patch group, and 56.42 $\pm$ 16.2 days in spontaneous healing group, respectively.
Sayin L et al. [25] 2013	Prospective RCT	155 TMPs	Epifilm® vs. spontaneous healing	The closure rate was 94.8% with 6.61 $\pm$ 4.59 weeks in Epifilm® group and 85.6% with 10.60 $\pm$ 5.23 weeks in spontaneous healing group at 6 months.
Lou ZC et al. [29]2011	Prospective RCT	91TMPs with everted edges	Gelfoam patching vs. edge-approximation vs. spontaneous healing	The closure rate was 85% in spontaneous healing group, 97% in Gelfoam patch group, and 97% in edge-approximation group at 3 months, respectively. The average closure time was 30 $\pm$ 10.1 days in spontaneous healing group, 16 $\pm$ 5.6 days in Gelfoam patch group, and 18 $\pm$ 4.7 days in edge-approximation group, respectively.
Lee JH [24] 2015	Retrospective cohort study	52 TMPs	Paper patch vs. silk patch	The closure rate was 92.3% with 13.7 $\pm$ 4.7 days in silk patch group and 84.6% with 16.7 $\pm$ 4.1 days in paper patch group at 3 months, respectively.
Lou ZC et al. [27] 2011	Retrospective cohort study	136 children TMPs	Spontaneous healing vs. FGF2-containing gelfoam patching	The healing rate was 86.8% within 27.9 $\pm$ 3.5 days in spontaneous healing group and 98.5% within 10.7 $\pm$ 6.4 days in FGF2-containing gelfoam patching group at 6 months.
Jun H et al. [55] 2013	Retrospective cohort study	78 TMPs	Edge approximation vs. egg shell membrane (ESM) patch	The closure rate was 89.7% for the edge approximation group and 92.3% for the ESM patch group. The mean closure time was 87.2 $\pm$ 41.3 days for the edge approximation group and 42.8 $\pm$ 19.8 days for the ESM patch group at 6 months.

TMP: Tympanic Membrane Perforation; RCT: Randomized Control Study; FGF2: Fibroblast Growth Factor 2.

Although TMPs have a high rate of spontaneous healing and they heal well with the effective application of growth factors, patching is an intermediate choice for large perforations. This strategy has good efficacy and allows surgery to be avoided when a patient complains of decreased hearing and tinnitus. Since Toynbee [23,55] successfully used a rubber disc to close a TMP in 1857, many materials have been tested for TMP repair, such as paper, silk, acellular collagen, gelfoam, Steri-Strips and water-soluble chitosan [23-28]. For TMPs, the efficacies of some patches have been evaluated in recent studies (Table 2). Gelfoam patching has a significant effect on shortening healing time without edge approximation [23,29-31]. In addition, time-to-treatment does not significantly affect its efficacy [26]. However, its results vary by the size and type of perforation [23]. Besides that, Silk [24], hyaluronic acid ester [25], Steri-Strip and paper patches [28] all significantly reduce closure time but do not significantly improve the closure rate of TMPs. However, Steri-Strips may be associated with a high incidence of otorrhea [28], which should be further investigated in future studies. In addition, some new materials have been used as patching, such as egg shell membrane and elastin, and have shown efficacy for healing TMPs [25,55]. Patching has some advantages. It facilitates centripetal epithelial migration, induces inflammation at the edges of the perforation and is associated with the proliferation of granulation tissue, which accelerates TMP closure [23]. In addition, it is associated with temporary recovery of physiological function and rapid improvement of some symptoms such as tinnitus and conductive hearing loss. Still, evidence of the effects of patching in terms of improving closure rate is still lacking [23,25,29,55]. A previous study reported that the application of gelfoam patching containing fibroblast growth factors significantly reduced closure rate and shortened closure time [27]. Thus, the combined application of growth factors and patching may be an appropriate approach for enhancing the effects of patching on closure rate. However, patches may adhere to the eardrum and be difficult to remove. In addition, although some patches such as paper and Gelfoam patches are readily available and inexpensive, other types such as acellular collagen and water soluble chitosan patches are expensive. Hence, future studies should aim to identify the most appropriate material that improves closure rate, shortens closure time and does not adhere to the eardrum.

### Myringoplasty

Tang et al. successfully used a lateral graft tympanoplasty to close a TMP and improve the air-bone gap [56]. However, early surgical intervention for TTMP is rarely performed because there is a high probability of spontaneous healing [9]. Moreover, myringoplasty requires elaborate facilities and techniques, must be performed under anaesthesia in a hospital, is associated with high medical costs and can trigger various complications. Thus, it is rarely recommended. However, it should be performed if spontaneous healing does not occur after 6 months [56]. In addition, general anaesthesia may be associated with a higher percentage of defect

closure, compared to untreated cases [57]. Thus, myringoplasty should be used prudently in the clinical treatment of TTMPs.

### Conclusion

About 80% of traumatic TMPs heal spontaneously within 3 months. However, large perforations usually fail to close and surgical intervention should be initiated when spontaneous healing does not occur within 6 months. Nonetheless, invasive surgery is not recommended because it is associated with higher costs and risk for various complications. bFGF is an effective growth factor that accelerates the healing of traumatic TMPs. Diverse materials are used in patches and many have been shown to considerably reduce healing time but not necessarily improve closure rate. More appropriate materials should be explored in further studies. The combined application of growth factors and patching is recommended to further accelerate healing and increase the closure rate.

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