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Review article

Repair of tympanic membrane perforation using novel adjuvant therapies: A contemporary review of experimental and tissue engineering studies

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ABSTRACT

Objective: To perform a contemporary review of experimental studies to describe the effects of various novel adjuvant therapies in enhancing tympanic membrane (TM) perforation healing.
Methods: A PubMed search for articles from January 2000 to June 2012 related to TM perforation, along with the references of those articles, was performed. Inclusion and exclusion criteria were applied to all experimental studies assessing adjuvant therapies to TM healing.
Results: Many studies have assessed the efficacy of biomolecules or growth factors, such as epidermal growth factors and basic fibroblast growth factors, in TM regeneration with significant success. More recent strategies in TM tissue engineering have involved utilizing bioengineered scaffold materials, such as silk fibroin, chitosan, calcium alginate, and decellularized extracellular matrices. Most scaffold materials demonstrated biocompatibility and faster TM perforation healing rates.
Conclusion: Although several studies have demonstrated promising results, many questions still remain, such as the adequacy of animal models and long-term biocompatibility of adjuvant materials. As well, further studies comparing various adjuvant substances and bioscaffolds are required prior to clinical application.

Contents

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1. Introduction

Tympanic membrane (TM) is a thin semi-transparent structure composed of three layers, which includes a keratinizing squamous epithelial outer layer, fibrous middle layer, and mucosal inner layer [1]. Perforations of the TM are a common problem encountered by otolaryngologists and the most common etiologies include trauma, otitis media, and tympanostomy tubes [2].

Although most acute TM perforations heal spontaneously, large or chronic perforations may require surgical intervention for closure [3]. If left untreated, perforations may lead to increased susceptibility to infection and otorrhea, conductive hearing loss (CHL) and associated speech problems, and cholesteatoma formation [2].

Closure of a TM perforation is typically driven by epithelial migration [4]. Yet, the spontaneously healed neomembrane usually lacks the fibrous middle layer, which can result in a TM that may be acoustically suboptimal and be more susceptible to the formation of retraction pockets. As well, there may be added vulnerability to re-perforation, which can result from an even minor barotrauma [4,5]. Thus, reconstructive options that permit the formation of a trilaminar structure that resembles the native TM are still required.

Current surgical management of TM perforations includes myringoplasties and tympanoplasties. Myringoplasty is usually performed on small central TM perforations with absorbable scaffolding materials. Traditionally, materials such as rice paper, fat, or Gelfoam have been utilized but the efficacy of this technique is questionable, since the results have been inconsistent [6,7]. The paper patch is likely the most widespread material used historically, given that it is inexpensive, easily obtained and simply applied [2]. The paper patch, like other graft materials, serves as a scaffold in guiding the epithelial cells to migrate from the borders of the perforation. In addition to poor closure rates, the paper patch is thought to have other limitations, such as easy detachment, non-resistance to infection, inflexibility, and non-transparency [8,9]. The same disadvantages can be applied to other myringoplasty scaffold materials [2].

For failed myringoplasties or for large chronic TM perforations, tympanoplasties are usually performed in an operating room [10]. Most commonly, autologous grafts from muscle fascia or perichondrium in the periauricular region have been utilized, with good success rates [2,11]. However, a residual or re-perforations can still occur [12,13]. As well, there are other limitations to tympanoplasties, which include: (1) the high cost of the surgery, (2) the need for general anesthesia, and (3) the challenging microsurgical skills required of the surgeon [8]. Furthermore, failures or re-perforations can require multiple operations, which in turn, may cause donor site morbidity [14], and lead to poor availability of autologous graft materials. In addition, in developing countries where rates of TM perforation are relatively high, access to surgical facilities may be limited, and outpatient approaches would be particularly useful.

In an effort to overcome these drawbacks, the use of novel adjuvant substances and tissue engineering techniques have been applied in both the laboratory and clinical settings to enhance the healing of TM perforations and to potentially replace autologous grafts in human patients [3,7,15]. The basic approaches in tissue engineering involve the use of cells, scaffolds and/or signaling biomolecules or growth factors. Typically, tissue-specific or alternatively sourced cells are seeded onto a scaffold material along with appropriate signaling factors or biomolecules. Ideally, the scaffold material provides a structure and an environment for cells to attach, expand and perform their normal functions. The signaling biomolecules or growth factors serve to enhance the cellular function and overall tissue growth or maintenance [16].

In this paper, a contemporary narrative review of the literature, to describe the current state of TM tissue engineering and the effect of novel adjuvant therapies, is performed.

2. Methods

A search of the online database of the National Library of Medicine (PubMed) was performed from January 2000 to June 2012 to identify all publications regarding tympanic membrane perforation. The key terms "tympanic membrane" and "perforation" were searched and combined, which identified 782 titles and abstracts. These were reviewed and the inclusion and exclusion criteria were applied to narrow the list of studies to 24. Hand search of the reference lists of these articles was performed, which yielded 2 more studies. The total articles included for full review was 26 (Fig. 1).

The inclusion criteria were as follows: (1) testing of novel adjuvant therapies to enhance TM perforation healing and (2) the presence of control and/or comparison group(s).

Exclusion criteria included: (1) assessment of different surgical techniques; (2) testing of well-established graft materials (or variations of traditional graft materials); (3) assessment of different graft preparation techniques; (4) use of modified or diseased animal models; (5) poor quality uncontrolled case series (University of Oxford CEBM Level of Evidence 3 or above [17]); (6) use of novel ear canal packing or additional ototopical substances; (7) no comparison and/or control groups; and (8) retrospective chart reviews. As well, review articles, case reports, and non-English language publications were also excluded.

To be inclusive, the meaningfulness of statistical analyses was not considered to be part of the inclusion criteria due to the paucity of statistically robust studies.

3. Review

Many adjuvant substances with regenerative capabilities have been tested in experimental models of TM perforation. As well, several studies using tissue engineering approaches have been conducted during the last decade. Current strategies in TM tissue engineering include the application of: (1) source cells, (2) scaffold materials, and (3) biomolecules or growth factors. They can be applied alone or in any combination. Generally, TM perforation studies involve the analysis of scaffold materials alone or in combination with source cells (fibroblasts) and growth factors [18–20].