Biomaterials in otologic surgery

Stefania Goncalves¹,², Esperanza Bas PharmD², Simon Angeli², Juan A. Chiossone-Kerdel¹

¹Fundacion Venezolana de Otologia (FVO), Calle Santa Cruz, GMO Otohospital, Urb Chuao Caracas, 1061, Venezuela
²Department of Otolaryngology, University of Miami Miller School of Medicine, Miami, FL 33136, USA

Correspondence: Juan A. Chiossone-Kerdel
E-mail: jchiossonek@fvotologia.org or jchiossonek@gmail.com
Received: August 7, 2015
Published online: September 30, 2015

Scaffolds are routinely used in the middle ear to provide support after tympanic membrane and ossicular chain reconstruction, to provide hemostasis or to promote tissue regeneration. Its permanence within a body cavity will depend upon several factors, such as the scaffold composition and the surgical procedure to be performed. Autologous grafts (i.e. temporalis fascia, cartilage, perichondrium,) are considered the gold standard and are still being used; however, these are associated with high-risk donor site morbidity, multiple incisions and increased surgical time. Recently, many alternatives to autologous grafts have become available including allografts (Allo Derm™), xenografts and synthetic materials. Scaffolds can also be characterized by their reabsorption rates and host reaction, and these differences can be exploited to serve different purposes during surgery. While some of these materials have been attributed healing enhancement properties, other materials have been associated with adverse effects, mainly aberrant scarring. Therefore, there is a lack of unanimity concerning indications for its uses and/or duration for packing, which will depend upon the surgeon’s preferences and experience [⁴].

The perfect scaffold material for middle ear packing has been described as being biocompatible; causing minimal inflammation, adhesion and foreign body reaction, nonosteogenic, nonallergenic, nonototoxic, absorbable, malleable and chemically and structurally stable [², ⁶]. Additionally, these materials should also provide adequate support to the neotympanic membrane and ossicular chain, to promote wound healing, hemostasis and to prevent adhesion and fibrosis [², ⁶]. However, a surgical material with these characteristics is not yet available and adverse effects might be expected, including hearing loss due to scarring, adhesions, fibrosis, osteogenesis, or even alteration of the normal structure within the middle ear leading to surgical failure [²].

Improvements of existent tools, new technologies and
<table>
<thead>
<tr>
<th>SCAFFOLDS</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Materials</th>
<th>Otologic Applications</th>
<th>Facts</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Absorbable</td>
<td>- Less adhesion, fibrosis; good tolerance.</td>
<td>- No rejection, no foreign body reaction, no chronic inflammation.</td>
<td>- Paraffin&lt;sup&gt;7&lt;/sup&gt;</td>
<td>- Ventilation tubes&lt;sup&gt;11&lt;/sup&gt;</td>
<td>- Biocompatible&lt;sup&gt;10&lt;/sup&gt;</td>
<td>- Displacement leading to ABG &gt; 20 dB&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non Absorbable</td>
<td>- No rejection; second surgery needed for removal.</td>
<td></td>
<td></td>
<td>- ET plugs for palatosus conditions&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td>- Allows ME aeration&lt;sup&gt;21&lt;/sup&gt;</td>
<td>- Encapsulation by host tissue&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- TM grafts&lt;sup&gt;14&lt;/sup&gt;</td>
<td>- ME regeneration without rejection, chronic inflammation or foreign body reaction&lt;sup&gt;17&lt;/sup&gt;</td>
<td>- Extrusion&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Internal/external packing&lt;sup&gt;15&lt;/sup&gt;</td>
<td>- Helps preserving ME functional structure in TM and OC reconstructions&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- Infection with biofilm forming bacteria&lt;sup&gt;19,20&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Based</td>
<td>- TM graft support&lt;sup&gt;27,28&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>- Transient CHL&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>- Based</td>
<td></td>
<td>- Gelfoam®</td>
<td></td>
<td></td>
<td></td>
<td>- Severe connective tissue hyperplasia forming fibrosis and adhesions that leads to TM retraction, OC distortion and permanent CHL&lt;sup&gt;31,32&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Transient CHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Earlier reabsorption</td>
<td>- Not well know side effects</td>
</tr>
<tr>
<td>- Gelatin</td>
<td>Same</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbable</td>
<td>- Enhance TM&lt;sup&gt;10&lt;/sup&gt; and ME&lt;sup&gt;56&lt;/sup&gt; healing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbable</td>
<td>- Re-epithelization promoter&lt;sup&gt;13,34&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbable</td>
<td>- Clearance through ET&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxylate (HA)-Based</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Esterified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- MeroGel®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- EpiDisc®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- EpiDisc® T.M.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Cross-linked</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Carbylan-SX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Lyophilized Carbylan-SX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Seprafilm&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Sepragel&lt;sup&gt;TM&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Canalplasty&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Alternative sealant in the inner ear&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Carrier for drug delivery into the inner ear&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Polydioxanone (PDS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Polylactides (PLA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Collagen-Polyvi nylpyrrolidone (CPVP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Polyurethane (e.g. Nasopore)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Limited clinical use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Ventilation tubes manufacturing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Limited clinical use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Most used in orthopedics, craniomaxillofacial and urological surgery.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Drug delivery systems manufacturing.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Drug delivery systems manufacturing.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Clinical use limited due to reduced expandability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Reduced scarring and inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Does not induces foreign body reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- CPVP induces less inflammation than Gelfoam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Nasopore induces mild histological reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td>- Reported possible SNHL in guinea pigs&lt;sup&gt;47&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
surgical indications have resulted in an expanding menu of scaffolds for clinical use. This review is focused on discussing the most recent literature targeted to develop clinically applicable products with fewer side effects and with broader indications.

Most Common Scaffolds Used in Otology

Middle ear packing agents started to be used in otologic surgery during the 1950s. There are a broad variety of materials that are traditionally classified as absorbable and non-absorbable. Our table summarizes the most commonly used materials, their indications, relevant facts and potential complications.

Theoretical Basis and Research Highlights

Initially, the primary goal of most absorbable materials was not intended for cavities or within the middle ear; they were developed as hemostatic products. However, with medical advancement the use of these hemostatic foams as absorbable packing materials in the middle ear has become a common clinical practice. While these materials are biocompatible and safe to use, they can elicit a foreign body response from the host resulting in fibrosis and osteogenesis in the middle ear, with a deleterious effect on hearing.

Packing materials, especially those that take longer time to be degraded, may trigger a foreign body reaction by the host tissue characterized at first by a matrix formation and an acute and chronic inflammation. The recruitment of inflammatory cells can be enhanced due to the scaffold nature of these foams that may act as an extracellular matrix-like environment. The acute inflammation is characterized by infiltration of neutrophils and monocytes, followed by the chronic phase in which monocytes, macrophages and foreign body giant cells (FBGC) are abundant [46]. When multiple macrophages come in contact, under the precise stimuli they undergo fusion to form FBGC. These macrophages and FBGC will persistently phagocytize particles of the biopolymers in order to remove it. In the event of a prolonged presence of the foreign body, these cells will release toxic mediators (i.e. oxygen free radicals and enzymes) to facilitate the degradation of the packing material, which can damage the surrounding tissue [46]. These events are followed by the formation of a granulation tissue that is characterized by the presence of macrophages, fibroblasts and angiogenesis. The chronic inflammatory response triggered by the presence of the biomaterial can lead to fibrosis and ossification in the middle ear. Additionally, there is also risk of immunologic reactions despite its biocompatibility, as well as risk of infections [46].

Non-absorbable scaffolds

Silastic® is the most common silicone used in otology as a middle ear spacer, for endolymphatic sac decompressions [47], cochlear implant manufacturing [48], and it has been recently studied as a frame for auricular reconstruction [49]. It has also been used in the surgical treatment of auricular hematomas by accommodating Silastic sheets on the auricular surface offering easy suture placing and wound monitoring [50]. Other non-absorbable materials used in otologic surgery are Teflon, polyethylene and titanium [8, 51-53].

Generally, these materials have been shown to be biocompatible and to reduce adhesion formation within the middle ear [16], allowing middle ear mucosa regeneration without rejection, and minimal if any foreign body reaction [17]. Indeed, silicone materials have been shown to hinder adhesion formation between the neotympanum and the injured mucosal tissue covering the promontory [54]. Ng & Lithicum [55] found no long-term adverse effects of silicone plastic within the ME in six autopsies. However, there have been 27 reported cases of foreign body reaction in the literature where most patients presented with some degree of hearing loss (n=23), sensorineural, conductive or mixed, with or without vestibular symptoms (n=7) or perilymph fistula (n=1) [56, 57]. Furthermore, cochlear implant electrode-related fibrosis as a foreign body reaction response has been described [58-60] and associated with a negative influence on residual hearing preservation and electrical hearing performance leading to decrease sound quality perception [61]. Additionally, this inflammatory response could lead to extrusion [62] and/or device malfunction overtime [63]. Moreover, non-absorbable scaffolds have been also associated with an increased risk of biofilm forming bacterial infections and a considerable amount of research topics are related to its pathophysiology and prevention using prophylactic coatings [19-26].

Absorbable scaffolds

Gelatin-based biomaterials

Gelfoam (Pfizer, Inc., New York, NY, USA) is derived from purified porcine skin, completely made of collagen.
This material is porous, highly absorbent, no soluble in water and non-elastic. Commercially, Gelfoam comes in a sterile pack, and is around 4 mm thick with variable pore size (30-700 µm) [3, 4]. It is the most commonly used absorbable gelatin sponge. Gelfoam has been associated with severe connective tissue hyperplasia leading to fibrosis and adhesion of prostheses, grafts and ossicular chain, later resulting in tympanic membrane retractions and ossicular chain distortion that could lead to conductive hearing loss [31]. This material provides a positive environment for the housing of inflammatory cells such as macrophages and mast cells and granulocytes. New bone formation has been noted in packed middle ears packed with Gelfoam [64]. Aberrant inflammation and fibrosis in Gelfoam-packed middle ears has been noted in ears without otitis media [3, 64, 65], as well as in middle ears with injured mucosa by surgical trauma or infection [66]. The deleterious fibroinflammatory response to Gelfoam seems to be attenuated when used in combination with agents with anti-inflammatory properties such as corticosteroid ointment (1% hydrocortisone acetate) [31], 3% boric acid at pH 4.2 [3] or coating the gelatin sponge with Gelfilm (Pfizer, Inc., New York, NY, USA), a nonporous sheet-like cellophane structure made of hyaluronic acid [67]. Recently, an alternative gelatin-based biomaterial has been introduced, Geltia-Spon® Final™ (Invotec International, Inc, Jacksonville, FL, USA), structurally characterized by fewer collagen cross-linkages between the collagen fibers resulting in a decreased overall mass, earlier reabsorption and reduced risk of aberrant fibrosis when compared with Gelfoam [3].

Even though uncommon and probably of idiosyncratic nature, anaphylactic reactions have been reported with the use of gelatin sponge in patients that underwent major surgeries [68-71].

Some groups are focused on the use of these scaffolds as drug delivery carriers into the inner ear to induce [72] or prevent [73] ototoxicity. Finally, recent studies have used gelatin-based scaffolds as cellular carriers for the development of cellular therapies for wound healing enhancement of tympanic membrane perforations [74], nerve and spinal cord injury [75-77], fracture healing [78,79], among others.

Hyaluronate-based biomaterials

Hyaluronic acid is a high-molecular weight polysaccharide with anti-inflammatory and viscoelastic properties [80, 81]. It is a major component of extracellular matrix of the synovial fluid, skin and perilymph [80, 81]. This versatile molecule is involved in the control of tissue hydration, joint synovial fluid maintenance and receptor mediated roles in cell detachment (i.e. mitosis, migration and inflammation) [82]. Due to its properties, this material has been widely used in different fields, leading to multiple clinical applications in joint fluid supplementation, wound regeneration and dermal filling [83]. Hyaluronic acid is a water-soluble molecule that is rapidly reabsorbed; therefore, biochemical techniques such as esterification and cross-linking have been used to make of this molecule a more stable and clinically useful biomaterial [41, 42].

Hyaluronic acid has been associated with enhanced wound healing of the skin [81, 84] and mucosa [80], being involved directly or indirectly with the different stages of wound healing such as cell migration, cell-cell interaction [85], interaction with inflammatory elements and scavenging of free radicals [84], reducing inflammation, fibrosis and osteogenesis [86].

Based on its properties is not irrational to find that most of research related to this compound is focused on tissue regeneration. For example, it has been associated with healing enhancement of tympanic membrane perforations [34, 87] by shortening closure times and increasing the scar quality by restoration of the fibrous connective tissue layer. Additionally, hyaluronic acid has been reported to improve wound healing in the middle ear [35], as an alternative sealant in inner ear surgery [32], as a promoter of postoperative re-epithelization of the mastoid [36, 37] and as a carrier for drug delivery into the inner ear [33], as well as cell-based therapies [88, 89].

Other biomaterials

Synthetic [i.e. Polydioxanone (PDS), polylactides (PLAs), collagen-polyvinylpyrrolidone (CPVP) and polyurethane (e.g., Nasopore)] and Plant-based biomaterials [Oxidized regenerated cellulose (ORC), carboxymethylcellulose (CMC) and sugarcane-cellulose] are other alternative scaffolds.

In a study carried out by Antonelli and collaborators [45] carbomethylcellulose (CMC) foam was compared against gelatin sponge and hyaluronic acid as middle ear packing material. Interestingly, the animals that received CMC experienced worse hearing even though the incidence in scarring was less when compared to the gelatin sponge group. Therefore, even when CMC elicits less inflammatory reaction its use whiting the middle ear should be avoided until proven otherwise. On the contrary, other study shows that the sugarcane-cellulose based biopolymer may cause a greater inflammatory response than gelatin sponge with polymorphonuclear infiltration around the sponge and lymphocytic in the underlying mucosa, at 1 week and 3 months after packing [90]. Dogru and collaborators [65] reported an early moderate to severe infiltration of macrophages and polymorphonuclear cells in the Gelfoam.
group, while absence or mild inflammation only in the cellulose based Sepragel™ and the synthetic Nasopore®. Other groups have observed similar larger inflammatory response and worsened hearing with gelfoam compared to an esterified form of hyaluronic acid [64]. No significant hearing differences were observed when Gelfoam was compared with polyurethane foam [91] or Seprafilm® and MeroGel [5]. Similarly, a stronger foreign body reaction against paper and more fibrosis and osteogenesis were found in the gelfoam-implanted middle ears than in ears treated with cellulose based scaffolds, silk fibroin [92, 93] and acellular collagen I&III [93]. Silk protein is a natural scaffolding material that can be obtained from diverse sources such as spiders, silkworms, scorpions, mites and flies and has potential as a biomaterial for the development of biomedical devices [94] or treatment for tissue regeneration such as repair of tympanic membranes [95].

Conclusions

Newer middle ear packing materials have emerged that offer comparable stability and functionality without the associated unwanted fibroinflammatory reaction observed with traditional porcine collagen sponge. The use of these new materials, particularly hyaluronic acid has the potential for offering improved hearing and healing outcomes in middle ear surgery than traditional scaffolds

Conflicting interests

The authors have declared that no competing interests exist.

References

23. Jang CH, Cho YB, Choi CH. Effect of ion-bombarded silicone


56. Suzuki N, Okamura K, Yano T, Moteki H, Kitoh R, Takumi Y, et al. Silicone impression material foreign body in the middle ear:
two case reports and literature review. Auris Nasus Larynx 2015;42:419-423.
88. Xu K, Narayan K, Lee F, Bae KH, Gao S, Kurisawa M.
Enzyme-mediated hyaluronic acid-tyramine hydrogels for the propagation of human embryonic stem cells in 3D. Acta Biomater 2015; In press


