Basic fibroblast growth factor (b-FGF) for the treatment of tympanic membrane perforation

November 2012
**Technology, Company and Licensing**

**Register ID**  WP129

**Technology name**  Gelatin foam impregnated with basic fibroblast growth factor (b-FGF) solution

**Patient indication**  Tympanic membrane perforation due to trauma or severe otitis media

**Description of the technology**

The technology is a new method for closing tympanic membrane perforations using a gelatin sponge impregnated with basic fibroblast growth factor (b-FGF) as a patch material. The aim of the procedure is to encourage healing of the perforation by providing the conditions necessary for tissue regeneration (cells, scaffolds and chemical mediators which regulate cell growth and proliferation). The b-FGF stimulates proliferation of epidermal and connective tissue cells and the gelfoam acts as a sustained release substrate for the b-FGF. Table 1 details the components of the intervention and their relationship to the principles of tissue engineering.

**Table 1  Components of the intervention**

<table>
<thead>
<tr>
<th>Tissue engineering component</th>
<th>Intervention material</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scaffold and sustained release substrate for b-FGF</strong></td>
<td>Gelatin sponge is often used in medical procedures due to its homeostatic properties and is absorbable in vivo. The sponge may be cut to size in order to fit the perforation.¹</td>
</tr>
<tr>
<td>Gelatin sponge or 'gelfoam'</td>
<td></td>
</tr>
<tr>
<td><strong>Regulatory factors</strong></td>
<td>Derived from genetically engineered E.coli human DNA, b-FGF is a polypeptide mitogen that stimulates proliferation of epidermal and connective tissue cells. It has an inductive effect on fibroblasts and blood capillaries, current clinical applications of b-FGF include the treatment of skin ulcers or decubitis.¹</td>
</tr>
<tr>
<td>Basic fibroblast growth factor</td>
<td></td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Endogenously supplied by the perforation margin which is mechanically disrupted during the procedure. The mechanical disruption of the perforation edge is thought to stimulate the activity of stem cells of the tympanic membrane.¹</td>
</tr>
<tr>
<td>Supplied by the perforation margin</td>
<td></td>
</tr>
</tbody>
</table>

¹ b-FGF: basic fibroblast growth factor.

The intervention consists of a gelfoam sponge soaked in b-FGF which is placed at the perforation and sealed in position with fibrin glue. Local anaesthesia is administered and the perforation margin is trimmed before the sponge is placed. In paediatric patients the procedure may be performed under general anaesthesia. Patients return three weeks post-procedure for assessment and removal of any residual crust. Figure 1 is a schematic diagram of the procedure.¹
The procedure may be performed in an outpatient setting and is an alternative to myringoplasty, a surgical procedure which repairs the perforated membrane using a tissue graft. The graft is most commonly autologous tissue from the temporalis fascia, although reports in the literature of optimal graft materials to achieve complete closure and restore hearing are varied. Myringoplasty is performed under a general anaesthetic and may be conducted as a same-day procedure or involve an overnight stay.

The potential advantages of b-FGF over conventional surgical treatment include:

- reduced operative time
- avoidance of invasive incision
- reduced risk of infections, as harvesting of an autologous graft is not necessary
- the option of local anaesthesia versus general anaesthesia
- increased accessibility for remote and rural patients
- reduced costs.

The intervention is similar to wound healing applications used for burns or diabetic foot ulcers and is reportedly both simple and cost effective. The procedure is also associated with success rates of over 90 per cent. It should be noted that a recent publication indicates that a novel myringoplasty technique (hyaluronic acid fat graft myringoplasty) can be performed under local anaesthetic and is associated with reduced surgical time and cost savings as compared to traditional myringoplasty. The diffusion status of this technique could not be ascertained.
Company or developer

The intervention utilises existing medical devices and biological products for a novel application and hence there is no single manufacturer or developer of the technology. The table below details the components of the technology and several manufacturers as identified within the included studies and by a search of the Australian Register of Therapeutic Goods (ARTG).

**Table 2  Company or developer of the intervention**

<table>
<thead>
<tr>
<th>Component</th>
<th>Name, manufacturer</th>
<th>ARTG number and class</th>
<th>Products reported by the included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponge</td>
<td>Sponge, haemostatic, absorbable</td>
<td>141962, Medical Device Class III</td>
<td>Sponge, Astellas Pharma, Inc., Tokyo, Japan</td>
</tr>
<tr>
<td></td>
<td>Baxter Healthcare Pty Ltd</td>
<td></td>
<td>Plenac, Gunze Co., Kyoto, Japan</td>
</tr>
<tr>
<td>Basic fibroblast growth factor</td>
<td>Search retrieved no results</td>
<td>Search retrieved no results</td>
<td>Fibrast, Kaken Pharma Co., Ltd., Tokyo, Japan</td>
</tr>
<tr>
<td>Fibrin sealant</td>
<td>Tisseel</td>
<td>147141, Medicine</td>
<td>Bolheal, Kumamoto, Japan</td>
</tr>
<tr>
<td></td>
<td>Baxter Healthcare Pty Ltd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARTG: Australian Register of Therapeutic Goods.

Reason for assessment

A novel, lost cost approach for the treatment of otitis media, a condition that is associated with high morbidity particularly in the rural and remote Aboriginal population.

Stage of development in Australia

- Yet to emerge
- Experimental
- Investigational
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Nearly established

Licensing, reimbursement and other approval

Table 2 contains information regarding the ARTG numbers associated with the intervention. Fibroblast growth factor is a recombinant product; according to the Australian regulatory guidelines for biologicals recombinant products are listed in the Therapeutic Goods (Things that are not Biologicals) Determination and regulated as therapeutic goods. The approval status of fibroblast growth factor for tympanic membrane perforation could not be ascertained. Fibrin sealants are regulated as Medicines on the ARTG and gelatin sponges are regulated as class III medical devices.8
Bone growth factor to solve chronic ear problems: November 2012

Australian Therapeutic Goods Administration approval

☑ Yes  ARTG number (s) 141962, 157704
☐ No  ☐ Not applicable

Technology type Procedure
Technology use Therapeutic

Patient indication and setting

Disease description and associated mortality and morbidity

The tympanic membrane is a thin layer of tissue which moves in response to variations in air pressure; its vibrations are transmitted to the cochlea through the ossicular chain stimulating the inner ear. Disruption of the tympanic membrane can compromise a patient’s hearing and perforation compromises the barrier between the outer and middle ear, increasing the risk of otitis media (middle ear infection). The membrane can be ruptured or perforated as a result of:

- trauma such inserting foreign objects into the ear
- differences in pressure between the middle and outer ear which may occur as a result of flying or scuba diving
- exposure to severe atmospheric pressure such as an explosion
- infection, such as acute infection of the middle ear.

Perforations vary in size and location on the drum surface and they may be temporary or persistent. Most perforations due to trauma heal spontaneously; however, larger perforations with everted or inverted eardrum flaps at the margin are less likely to heal spontaneously and may necessitate surgical intervention. When a perforation is associated with acute otitis media the perforation will usually resolve with treatment of the infection although when infections are frequent patients may develop scarring of the eardrum and middle ear (tympanosclerosis) which compromises the healing process. Recurrent ear infections which do not resolve with medical therapy may be treated with ventilation tubes (grommets); upon removal of the grommet the eardrum will usually heal spontaneously. When the perforation does not close spontaneously following trauma or resolution of otitis media the risk of hearing loss and subsequent otitis media infection is elevated. The symptoms associated with perforation include decreased hearing and an increased risk of infection during colds and when water enters the ear canal. Effusion from the middle ear (which may be sanguineous) confirms the existence of both perforation and infection.

A common cause of tympanic membrane perforation is otitis media. The condition predominantly occurs in children (0-14 years of age) and recurring or chronic infection may
lead to hearing loss, deafness and associated complications such as learning difficulties.\textsuperscript{10} Hearing loss associated with otitis media generally averages 15-30 decibels and falls in the mild to moderate category. There are three different types of otitis media associated with a perforation of the tympanic membrane: acute otitis media complicated by perforation of the tympanic membrane, presenting as otorrhea (discharge from the external ear); acute otitis media in a patient with tympanostomy tubes; and chronic suppurative otitis media, defined as tympanic membrane perforation with chronic inflammation of the middle ear and persistent otorrhea for two weeks to three months.\textsuperscript{11}

By the age of 12 months, 73 per cent of Australian children have experienced one episode of otitis media and in 2008 temporary hearing loss was estimated to have affected more than 354,475 children with 87,655 children likely to have been affected by tympanic membrane perforation.\textsuperscript{12} Aboriginal Australian children are disproportionately affected by otitis media as compared to non-Aboriginal children; a national survey of general practice consultations found that Indigenous children were significantly more likely to have severe otitis media (chronic and/or suppurative and/or perforation; 8% versus 2%, $p<0.001$) than non-Indigenous children.\textsuperscript{13} Data from the Australian Institute of Health and Welfare (AIHW) indicated that almost 12% of Indigenous children who received a Child Health Check on or before 30 June 2009 had chronic suppurative otitis media, three times higher than the rate (4%) classified by the World Health Organization as a massive health problem.\textsuperscript{14} The hearing loss associated with infection represents a significant burden to the individual and community as it is most prevalent during early years while children are developing their speech and language capacity as well as having their first encounters with the education system.\textsuperscript{14}

Data from a retrospective general practice based study of otitis media in New Zealand showed that the incidence of otitis media was 2.7 per 1,000 person years in children less than two years of age, and was lower in older age groups (2.02–2.04/1,000 person years in 2 to 5-year-olds, 0.74–0.81/1,000 person years in 6 to 15-year-olds, and 0.09–0.10/1,000 person years in >15-year-olds). Mahadevan et al\textsuperscript{12} also reports that a retrospective search of hospital admission and mortality data due to otitis media was conducted (covering years 2000 to 2007); the otitis media hospital admission rate for children less than five years of age was 11 per 1,000 and the annual myringoplasty rate in children less than two years of age was 0.8 per 1,000. A recent cohort study to examine the incidence of acute otitis media in children less than five years of age in New Zealand found that the raw incidence was 273 per 1,000 children.\textsuperscript{16} A publication from the Centre for Public Health Research (Massey University, New Zealand)\textsuperscript{17} analysed data from the New Zealand Ministry of Health to report the incidence of otitis media among children aged 0-14 from 1994 to 2010 in New Zealand. Overall the age-standardised rate of hospitalisations for otitis media decreased by 41 per cent between 1994 and 2010 and 5,428 children were hospitalised with otitis media in 2010. The highest rates of hospitalisation during 2006 were found in Maori children.
(78.6 per 10,000) and Pacific children (64.1 per 10,000); these rates were noted to be substantially higher than for European (46.3 per 10,000) or Asian (22.4 per 10,000) children.\textsuperscript{17}

**Number of patients**

The AIHW data cubes indicate that in 2009–10 there were 4,167 hospital separations for perforation of the tympanic membrane; of those, 48 per cent were separations for children aged between one and 14 years of age.\textsuperscript{18}

**Speciality** Surgical, ear, nose and throat (ENT)

**Technology setting** General hospital, specialist hospital and ambulatory care

**Impact**

**Alternative and/or complementary technology**

The intervention is likely to substitute for current treatments of tympanic membrane perforation. It is unlikely that failure of b-FGF for tympanic membrane perforation would exclude subsequent myringoplasty.

**Current technology**

Conventional treatment for tympanic membrane perforation includes myringoplasty, a surgical procedure which uses a tissue graft to reconstruct the tympanic membrane. Reports in the literature indicate variation in the surgical techniques and graft materials used in myringoplasty procedures; it is unclear whether this variation occurs in practice.

Patients with otitis media are generally managed in the first instance with observation and analgesia; patients may be treated with amoxicillin if their infection is persistent or associated with effusion. A patient may be referred for further intervention if the infection resolves but the perforation does not, or if the infection is recurrent or persistent.\textsuperscript{9} Closure of the tympanic membrane is contraindicated in patients with purulent effusion from the middle ear; patients with frequent episodes of otitis media, which does not resolve with medical therapy, may receive ventilation tubes. Upon removal of the ventilation tubes a perforation closure procedure may be indicated.

**Diffusion of technology in Australia**

The technology appears to be in the investigational phase within Australia; there is currently one clinical trial underway at Freemantle Hospital in Perth although it does not appeared to be registered with the Australian and New Zealand Clinical Trials Registry.
International utilisation

A search of Clinicaltrials.gov and the Australian and New Zealand Clinical Trials Registry retrieved no relevant results (search: tympanic membrane perforation, tympanic, fibroblast, fibro*, membrane AND repair).

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cost infrastructure and economic consequences

The new technique represents a simple intervention for tympanic membrane perforation which affects a large number of patients worldwide and can be associated with lifelong disability. No literature on the cost-effectiveness of the intervention was identified. However, it appears that the immediate costs associated with the regenerative procedure are reduced as compared to traditional surgery. Additionally the intervention may be more accessible to remote and rural patients.³

Although the initial success rates of the procedure appear to be high, the available evidence contains limited safety data; thus, it is difficult to identify the potential benefits and harms associated with the technology. No evidence comparing b-FGF to myringoplasty (conventional or novel) for tympanic membrane perforation was identified; hence the reported advantages of the technology over conventional treatment cannot be quantified. The table below summarises several aspects of the technology relevant to a consideration of the economic impact of its introduction.
Ethical, cultural or religious considerations

None identified

Evidence and Policy

Safety and effectiveness

Three studies have been included, one which assessed both the safety and effectiveness of b-FGF for repair of tympanic membrane perforations and two which considered effectiveness only. Table 4 outlines the characteristics of the included studies.
Table 4 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Level of evidence</th>
<th>n, Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety and effectiveness</strong></td>
<td>Kanemaru et al. 2011¹</td>
<td>Level II</td>
</tr>
</tbody>
</table>
| Japan | | | Chronic tympanic membrane perforation that was perfectly dry and showed no active inflammation/infection. Inclusion was also limited to patients who could fully understand the procedure and gave ‘informed consent’.
| **Effectiveness only (infection reported)** | Lou et al. 2011⁵ | Level III – 3 Historical control study | n=136 |
| China | | | Traumatic tympanic membrane perforation patients who:
| | | • were aged under 18 years
| | | • were without a previous history of middle ear disease
| | | • had acute dry tympanic membrane perforations
| | | • had membrane perforations with everted edge flaps at least 1/8 of the area of the tense part in size
| | | • had a perforation that was managed within 72 hours of injury.
| **Effectiveness only** | Lou et al. 2012⁷ | Level IV Prospective case series | n=147 |
| China | | | Traumatic tympanic membrane perforation patients who:
| | | • had no previous disease of middle ear and
| | | • were consulted within 3 months since they experienced the perforation.

n; number of patients

Kanemaru¹

In this study 56 patients (63 membrane perforations) were randomly selected from a group of outpatients (n unspecified); the selected patients were then randomised to receive either gelfoam with b-FGF (n=48; 53 perforations) or gelfoam without b-FGF (placebo; n=8; 10 perforations). The included patients had a mean age of 55 years (range 10 to 85) and of the included ears (63), perforation was associated with otitis media (n=37), postoperative reperforation (n=6), old traumatic perforation (n=6), residual perforation after surgery (n=5) and perforation after insertion of ventilation tubes (n=9).

Patients were classified into three grades based on the size of their perforation:

- Grade I: perforations spanning less than 1/3 of the total membrane surface area (b-FGF [n = 9]; control [n = 2]).
- Grade II: perforations spanning from 1/3 to 2/3 of the total membrane surface area (b-FGF [n = 25]; control [n = 6]).
- Grade III: perforations spanning more than 2/3 of the total membrane surface area (b-FGF [n = 19]; control [n = 2]).
Safety

A total of eight patients experienced complications within the three-month follow-up period; all eight experienced serious otorrhea (temporary effusion), six showed slight retraction of the tympanic membrane and two patients with aural fullness (pressure or fullness in the ear) had to be treated by puncture of the tympanic membrane. There were no reports of infection within the study period. Overall the time required to complete each procedure ranged from seven to 15 minutes and there were seven cases in which technical difficulties arose. Of those seven difficult cases, five were Grade II and two were Grade III. The total follow-up period was three months.

Effectiveness

The authors defined primary effectiveness as the following outcomes: closure rates, hearing level, surgical sequelae, improvement of tinnitus and aural fullness three weeks after treatment. The final evaluation was performed three months after the initial treatment with hearing levels measured before treatment and at three months. The definition of success was the rate of complete closure of the perforation within four courses of treatment. In statistical analysis the Mann-Whitney U test was used. All outcomes are reported as number of ears rather than number of patients. Table 5 shows effectiveness outcomes for patients in the b-FGF group, overall the closure rate of the b-FGF group was 98 per cent as compared to 10 per cent (1/10; 10%) in the control group. Average improvement in hearing loss (measured in decibels) tended to be slightly greater in the lower frequency range as compared to the higher frequency range (Table 5, LA versus NA).

Table 5  Effectiveness outcomes according to perforation grade in the b-FGF treatment group

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closure rate</strong></td>
<td>52/53 (98.1)</td>
<td>9/9 (100)</td>
<td>25/25 (100)</td>
<td>18/19 (94.7)</td>
</tr>
<tr>
<td>1 treatment</td>
<td>41/52 (77.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required 2 treatments</td>
<td>7/52 (13.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required 3 treatments</td>
<td>3/52 (5.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required 4 treatments</td>
<td>1/52 (1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatments, range (mean)</strong></td>
<td>1-4(1.4)</td>
<td>1-3(1.3)</td>
<td>1-4(1.4)</td>
<td>1-4(1.6)</td>
</tr>
<tr>
<td><strong>Improvement in hearing loss, average (dB)</strong></td>
<td>NA</td>
<td>21.7</td>
<td>18.3</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>LA</td>
<td>31.7</td>
<td>28.5</td>
<td>31.7</td>
</tr>
</tbody>
</table>

LA indicates average hearing level of 0.125, 0.25, and 0.5 kHz; NA, average hearing level of 0.5, 1, and 2 kHz.
Table 6 summarises the improvement in subjectively measured effectiveness outcomes between the b-FGF group and the control group; the outcomes were superior in the b-FGF group for both improvement of tinnitus and aural fullness ($p<0.0001$ for both measures).

### Table 6 Subjective effective outcomes in the b-FGF group versus the control group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>b-FGF group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of tinnitus</td>
<td>50/51 (98.0%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Improvement of aural fullness</td>
<td>44/46 (95.6%)</td>
<td>1/9 (11.1%)</td>
</tr>
</tbody>
</table>

All data is reported as a proportion with percentage in brackets.

Lou et al 2011

This study is a retrospective review of patients with traumatic tympanic membrane perforation ($n=67$); these patients were compared to those who underwent no treatment and who spontaneously healed ($n=69$) at the same institution. The inclusion criteria are detailed in Table 4; the study included a total of 136 patients with a mean age of 15.3 years (range of 6 to 18 years). A total of three patients failed to complete treatment and were excluded from the analysis ($n=1$ in the control group and $n=2$ in the b-FGF group). The relative size of perforation was categorised as medium ($1/8$–$1/4$ of the surface area of the tympanic membrane) or large (greater than $1/4$ of the surface area of the tympanic membrane). Of the group who chose to undergo spontaneous healing, 45 had a medium-sized perforation and 22 patients had a large-sized perforation. In the b-FGF group, 46 had a medium-sized perforation and 23 patients had a large-sized perforation.

Perforation healing was confirmed by otoscope and acoustic immittance tests. Total follow-up time was not reported; however, the authors state that endoscopic examinations with image capturing were conducted at least two times a week and outcomes appear to be reported for up to three months. Patients appear to have undergone only a single treatment session.

**Safety**

No safety outcomes were discussed. However, the results table included in the study indicates that in the spontaneous healing group nine patients experienced infection of the ear and in the b-FGF group one patient experienced infection. The exact nature of infection and the time to occurrence was not reported.

**Effectiveness**

A comparison of the infection rate, the healing rate and the average perforation closure time between the b-FGF group and the control group found that in all measures the b-FGF group performed significantly better ($p <0.05$). Within each group, no statistically significant difference was found between patients with an eardrum flap area to perforation area ratio of less than $1/2$ versus more than $1/2$ across any measure. Table 7 summarises the
effectiveness outcomes reported; results are assumed to be per patient as the number of
ears equates to the number of patients included.

### Table 7  A comparison of the healing rate and average healing time at three months

<table>
<thead>
<tr>
<th></th>
<th>Total ears</th>
<th>Healed ears (%)</th>
<th>Average healing time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous healing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with eardrum flap area &lt; 1/2</td>
<td>36</td>
<td>31/36 (86.1)</td>
<td>27.3 ± 2.4</td>
</tr>
<tr>
<td>with eardrum flap area ≥ 1/2</td>
<td>32</td>
<td>27/32 (84.4)</td>
<td>28.6 ± 3.1</td>
</tr>
<tr>
<td>Total spontaneous healing:</td>
<td>68</td>
<td>58/68 (85.3)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>b-FGF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with eardrum flap area &lt; 1/2</td>
<td>35</td>
<td>34/35 (97.1)</td>
<td>10.4 ± 2.5</td>
</tr>
<tr>
<td>with eardrum flap area ≥ 1/2</td>
<td>30</td>
<td>30/30 (100)</td>
<td>11.1 ± 1.9</td>
</tr>
<tr>
<td>Total b-FGF group</td>
<td>65</td>
<td>64/65 (98.5)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: not applicable

Lou et al 2012

In this study patients were prospectively enrolled to receive a treatment of b-FGF at
different time intervals (3 days, 4 to 7 days, 8 to 15 days and more than 4 weeks after
the injury). A total of 147 patients with a mean age of 32.1 years (range 5 to 56, standard
deviation 1.9 years) were included. The relative size of perforation was determined to be either:

- small (n=121), less than one fourth of the area of membrana tensa, or
- large (n=26), at least one fourth of the area of membrana tensa.

Of the 147 patients, 136 were diagnosed as having dry perforation and 11 were diagnosed
as having secondary water or bloody otorrhea. Patients who were diagnosed as having
secondary purulent otorrhea were prescribed concurrent oral antibiotics for a period of one
to two weeks and the perforation was examined by otoscope twice a week until healing
occurred.

**Safety**

No safety outcomes were reported.

**Effectiveness**

Following treatment, 120 of the 121 small perforations (99%), and 24 of the 26 large
perforations (92%) were healed. Amongst the small perforations, the healing rates at three
days, four to seven days, 8 to 14 days and two to four weeks after injury were 98.2 per cent,
100 per cent, 100 per cent and 100 per cent respectively. Statistical significance between
the overall healing rate at different time intervals was not found (significance level $p<0.05$).
A comparison of the first three time intervals found that the average healing time was shortest in patients admitted within eight to 14 days since injury \((p<0.01)\). In the case of admissions within three days after perforation, the average healing time from injury to healing was the shortest. Using pairwise comparisons with the Student-Newman-Keuls method, the results of the first three groups with small perforations in time from treatment to healing and from injury to healing were all significant \((p<0.01)\).

In healed ears the pure tone hearing test showed that the airborne gap (conductive hearing loss) was \(25 \pm 9\) decibels at perforation, whereas it was \(8 \pm 8\) decibels when it was healed \((p<0.01)\).

**Table 8  Healing time and rate in small perforations**

<table>
<thead>
<tr>
<th>Consultation period (post injury), size of perforation</th>
<th>Healing rate*</th>
<th>Time from treatment to perforation healing (days)</th>
<th>Time from injury to perforation healing (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 days, small</td>
<td>56</td>
<td>7.95 ± 2.07</td>
<td>9.75 ± 2.04</td>
</tr>
<tr>
<td>≤ 3 days, large</td>
<td>14</td>
<td>13.14 ± 1.16</td>
<td>14.57 ± 1.02</td>
</tr>
<tr>
<td>4–7 days, small</td>
<td>36</td>
<td>6.75 ± 2.67</td>
<td>12.14 ± 2.28</td>
</tr>
<tr>
<td>4–7 days, large</td>
<td>6</td>
<td>11.4 ± 3.13</td>
<td>17.6 ± 3.05</td>
</tr>
<tr>
<td>8–14 days, small</td>
<td>22</td>
<td>4.18 ± 0.91</td>
<td>15.95 ± 2.21</td>
</tr>
<tr>
<td>8–14 days, large</td>
<td>5</td>
<td>10.5 ± 3.11</td>
<td>21 ± 2.16</td>
</tr>
<tr>
<td>2–4 weeks, small</td>
<td>3</td>
<td>6.33 ± 0.91</td>
<td>25 ± 2.64</td>
</tr>
<tr>
<td>More than 4 weeks, large</td>
<td>1</td>
<td>11</td>
<td>72</td>
</tr>
</tbody>
</table>

* Healing rate is reported as the number of patients who experience closure of the perforation. Time from treatment to perforation healing and time from injury to perforation healing were both reported as mean days with standard deviation.

**Economic evaluation**

No literature on the cost-effectiveness of the intervention was identified. However, there may be significant costs associated with the procedure including, but not limited to the:

- cost of the growth factor
- cost of general anaesthesia and associated hospital charges for paediatric patients.

**Ongoing research**

A current trial at Freemantle Hospital is underway and will involve both adults and children; the trial will reportedly replicate that conducted by Kanemaru et al\(^1\) and has thus far treated 11 patients. A second trial will also begin at Princess Margaret Hospital for Children in Perth, Western Australia.\(^3\)

Phage pharmaceuticals Inc. is currently preparing to initiate a U.S. Department of Defence funded Phase I study for the treatment of chronic tympanic membrane perforation.\(^19\)
Other issues

In one of the included studies (Lou et al 2012) no safety data was included. It could not be determined whether complications did not occur or whether complications were not reported. In Lou et al (2011) infection was reported; however, it was unclear whether other safety data was omitted.

All studies compared treatment with b-FGF and gelfoam to spontaneous healing or a control group (who received a saline soaked gelfoam\(^1\)); therefore, no direct comparison between the effectiveness of this intervention versus myringoplasty, conventional or novel, can be made.

The study by Kanemaru et al\(^1\) reported rates of closure in the control group of 10 per cent as compared to 98 per cent. In contrast, Lou et al 2011\(^5\) reports a closure rate in the control group of 85 per cent. It is possible that the source of this disparity is the small sample size of Kanemaru; however, this disparity may also illustrate a difference in the rate of spontaneous closure in patients with perforation due to trauma versus infection. The size and location of the perforation on the tympanic membrane was also a confounding factor and the patient population most likely to benefit from this intervention is an area for further research.

Lou et al (2012) examined the effect of delayed intervention in patients with traumatic membrane perforation and found no statistically significant differences in the rate of healing between the groups (3 days, 4 to 7 days, 8 to 15 days, and more than 4 weeks after the injury). The measurement of conductive hearing loss in patients with a healed membrane was significantly less after healing than prior to \((p<0.01)\).

Summary of findings

Limited safety data related to the procedure were identified; in the single study reporting safety data there were eight patients who experienced 16 complications within a three-month follow-up period. The complications included serious otorrhea \((n=8)\), slight retraction of the tympanic membrane \((n=6)\) and aural fullness \((n=2)\). In a second study which reported only infection, one patient in the treatment group experienced infection as compared to nine patients in the control. No evidence to indicate that the procedure is associated with severe safety concerns was identified.

The evaluation of efficacy is limited by the lack of comparative data, as no studies reported the relative effectiveness of b-FGF treatment compared to myringoplasty. The included studies found perforation closure rates associated with the procedure are over 90 per cent; however, only two studies included a control group and in one the control sample size was 10 patients. In one study the average perforation closure time in patients treated with b-FGF was significantly lower \((p<0.05)\) as compared to patients whose perforations healed spontaneously. Overall the procedure is reportedly simple to perform, does not appear to
be associated with major adverse events and results in higher rates of perforation closure than untreated perforations (total treated patients = 262; total untreated = 79).

**HealthPACT assessment**

Based on the level and availability of evidence, and the potential for widespread uptake of this technology, it is recommended that the technology be monitored for 24 months with a view to obtaining evidence from the Australian trial currently underway.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

- Total number of studies 3
- Total number of Level II studies 1
- Total number of level III-3 studies 1
- Total number of level IV studies 1

**References**

10. Australian Institute of Health and Welfare (2011). *The health and welfare of Australia’s Aboriginal and Torres Strait Islander people, an overview 2011*, Cat. no. IHW 42. Canberra: AIHW.


**Search criteria to be used (MeSH terms)**

- Tympanic Membrane Perforation/therapy*
- Fibroblast Growth Factor 2/therapeutic use*
- Hearing Loss/therapy*