



A pilot study investigating basic fibroblast growth factor for the repair of chronic tympanic membrane perforations in pediatric patients



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ABSTRACT

Objective –: A pilot study to investigate the utility of basic Fibroblast Growth Factor (bFGF) in tympanic membrane perforation (TMP) closure in a small cohort of pediatric patients.

Methods –: Prospective cohort study. Suitability for inclusion in the study was confirmed by the application of defined inclusion and exclusion criteria, and informed parental consent obtained. The technique used was a modification of the bFGF-technique by Kanemaru et al. Response to treatment was monitored with serial otoscopy and audiometric outcomes were determined. Statistical analysis of the outcomes was carried out.

Results –: TMPs were successfully closed in 7/12 children at the first attempt (58%) and in 10/12 children overall (83%). Hearing improvement was observed in 8/10 successfully treated cases (80%). There were no complications or adverse outcomes.

Conclusions –: The topical bFGF regeneration technique offers a promising, minimally invasive alternative to conventional myringoplasty in pediatric patients with comparable success and reduced morbidity and cost, especially considering the option of performing repeat applications. Patients with an active infection or inflammation are not suitable for the bFGF-mediated technique.

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1. Introduction

Tympanic membrane perforations (TMP) especially in the context of chronic suppurative otitis media (CSOM) are a common problem affecting the pediatric population and are particularly prevalent in various rural and remote indigenous populations worldwide [1]. The resulting hearing loss is associated with impairment of social, emotional and academic development in children as well as an increased absence from school, lifestyle restrictions and an increased risk of antisocial behaviour [2]. A myringoplasty procedure may be performed, however significant variation in success rates between techniques and surgeons make the outcomes unpredictable and not reliably reproducible. Furthermore the procedure is relatively expensive as it requires sophisticated theatre equipment, theatre time and personnel.

Finally there is no consensus on the minimum age at which myringoplasty surgery is appropriate [3]. Delaying surgery can have a significant negative impact on a child's development thereby making earlier, less invasive and yet cost-effective intervention desirable.

Basic fibroblast growth factor (bFGF) is a polypeptide mitogen that has been shown to stimulate the proliferation of epidermal and connective tissue cells as well as promoting angiogenesis [4–6]. The application of bFGF has been shown to significantly increase the overall closure rate of TMPs and reduce the average closure time [7,8]. The bFGF regeneration technique has been reported to be safe [9,10], simple and cost-effective, with benefits over conventional surgical treatment [9,11] and high rates of success. [9,10,12].

Most studies examining the use of bFGF for tympanic membrane regeneration have investigated its use in adults. Some authors have included older children (>13 years) [8,13], there is one study that included younger children. Zhang [8] included patients as young as 3 years of age in his study however no distinction was made between children and adults in the analysis and the published results do not allow a comparison to be made.

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Furthermore, other authors used up to six repeated attempts at the treatment in quick successions where the TMP failed to completely respond to treatment [9,10] in order to investigate the efficacy of the technique. This requires significantly greater resources and is not comparable with conventional myringoplasty surgery in which the final outcome from treatment is measured 3–12 months following the surgery [3].

The aim of this study is to investigate the effectiveness of a single application of bFGF at closing TMPs in a pediatric population.

2. Methods

2.1. Patient selection

The following inclusion criteria were applied:

- Age < 16 years;
- chronic perforation (persistent for >3 months);
- central pars tensa perforation;
- size < 50% of the total tympanic membrane area;
- previous history of recurrent otorrhea;
- no otorrhea for minimum 3 months pre-operatively;
- no evidence of cholesteatoma or other complication of CSOM.

Exclusion criteria were:

- Marginal perforation;
- size > 50% of the total tympanic membrane area;
- failure to achieve a dry ear for 3 months pre-operatively;
- cholesteatoma or other complication of CSOM;
- inadequate view and access of the TMP;
- only hearing ear;
- failure to adhere to appropriate post-treatment care and follow-up.

A pre-operative audiogram and video-otoscopic photograph was taken for each case and the size of the perforation was measured using Image J software (NIH Bethesda MD USA).

2.2. Surgical technique

The surgical technique is a modification of the technique described by Kanemaru [9]. Under general anaesthesia and by a transcanal (permeatal) approach the TMP edges were freshened by excision of a

rim of tissue, the size of the TMP measured and an appropriately sized piece of gelatin sponge placed in the defect. The bFGF solution (at a concentration of 21,000 IU/5 ml) was dropped onto the gelatin sponge and once this was saturated the excess solution removed. One or two drops of blood were then applied to the sponge to seal the gelfoam-bFGF-plug. Initially patients had the technique as originally described by Kanemaru et al. utilizing fibrin glue but this was subsequently modified to use of one drop of cyanoacrylate in lieu of fibrin glue. Patients were followed up regularly for a minimum of 12 months following the intervention: the minimum follow-up was at 1, 2, 3 and 4 weeks post-procedure and then at 2, 3, 6 and 12 months post-procedure. At each post-operative visit an otoscopic photograph was acquired and where there was evidence of a residual perforation the size of this was measured. A post-operative audiogram was acquired from 2 months post-treatment

2.3. Patients consent/ethics

Ethical approval for the study was granted by the Institutional Review Board and written information leaflets were provided to the parents of all study participants when informed consent was obtained.

2.4. Statistical analyses

Students *t*-test and the Wilcoxon signed rank test were utilized to analyse the audiometric outcome in the successful group. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Patient profiles

The parents of all patients satisfying the inclusion and exclusion criteria for the trial were invited to participate in the trial. This minimized selection bias on the part of the investigators.

Thirteen children (male:female ratio of 9:4) were enrolled in the study, one of which was subsequently excluded due to failure to adhere to post-operative care instructions and failure to attend follow-up. The 12 children included for analysis (Table 1) had an age range of 6–16 years (mean 10.9 years, median 11 years). There were seven right and five left TMPs. The perforation size ranged from 6% to 40% of the tympanic membrane. Where known, the aetiology for the TMP was secondary to insertion of ventilation tube or previous recurrent acute otitis media. One patient had

Table 1
Patient profiles.

Patient	Side	Gender	Aetiology of TMP	Subjective hearing loss?	History of otorrhea?	Previous attempt at closure?	Age at Surgery (years)	Pre-treatment FFA (dBHL)	Post-treatment FFA (dBHL)	Successful?
1	L	M	VT	Yes	Yes	No	15	30	30	No
1(r)	L	M	VT	Yes	Yes	Yes	16	30	17.5	Yes
2	R	M	AOM	Yes	Yes	Yes	6	31.25	3.75	Yes
3	L	M	VT	No	Yes	No	13	27.5	22.5	Yes
4	L	F	AOM	No	Yes	No	7	17.5	7.5	Yes
5	R	M	U	No	Yes	No	13	20	16.25	Yes
6	R	M	U	No	Yes	No	14	12.5	12.5	Yes
7	R	F	AOM	Yes	Yes	No	6	27.5	10	Yes
8	L	M	VT	No	Yes	No	8	10	16.25	No
8(r)	L	M	VT	No	Yes	Yes	8	16.25	15	No
9	R	M	VT	Yes	Yes	No	12	12.5	18.75	No
10	L	M	U	Yes	Yes	No	12	27.5	27.5	No
10(r)	L	M	U	Yes	Yes	Yes	13	27.5	16.25	Yes
11	R	M	VT	No	Yes	No	10	18.75	20	No
11(r)	R	M	VT	No	Yes	Yes	11	20	5	Yes
12	R	F	VT	No	Yes	No	10	7.5	5	Yes

(r) = revision procedure, R = right, L = left, M = male, F = female, VT = ventilation tube, AOM = acute otitis media, U = unknown, TMP = tympanic membrane perforation, FFA = four frequency average air-conduction audiometry (air conduction thresholds at 500 Hz, 1 KHz, 2 KHz, 4 KHz).

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