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Regenerative treatment for tympanic membrane perforation using gelatin sponge with basic fibroblast growth factor

Kaoru Omae [a], Shin-ichi Kanemaru [a,b,c,*], Eiji Nakatani [a], Hideaki Kaneda [a], Tsutomu Nishimura [a], Risa Tona [b,d], Yasushi Naito [b,d], Atsuhiko Kawamoto [a,e], Masanori Fukushima [a]

[a] *Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, 1-5-4 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan*
[b] *Department of Otolaryngology, Head and Neck Surgery, Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation, 2-2 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan*
[c] *Department of Otolaryngology, Head and Neck Surgery, Kitano Hospital, Tazuke Kofukai Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan*
[d] *Department of Otolaryngology, Head and Neck Surgery, Kobe City Medical Center General Hospital, 2-2-1 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan*
[e] *Unit of Regenerative Medicine, Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation, 2-2 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan*

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ABSTRACT

Objective: The objective of this study was to evaluate safety and efficacy of regenerative treatment using gelatin sponge with basic fibroblast growth factor (bFGF) in patients with tympanic membrane perforation (TMP).

Methods: The current study was a prospective, multicenter, open-label, single-arm, and exploratory clinical trial to evaluate the safety and efficacy of the TM regeneration procedure (TMRP). Myringotomy was used to mechanically disrupt the edge of the TMP, and a gelatin sponge immersed in bFGF was then placed over the perforation. Fibrin glue was dripped over the sponge as a sealant. TMP closure was examined 4 weeks later and, if insufficient, TMRP was repeated a maximum of three more times. TMP closure and hearing improvement 12 weeks after the final TMRP as well as safety were evaluated.

Results: Of the 11 patients with TMP who participated in this study, one who fulfilled the exclusion criteria and did not undergo TMRP and one with cholesteatoma were excluded from the efficacy analysis. TMP closure and hearing improvement 12 weeks after the final TMRP were achieved in eight out of nine patients (88.9%). Mean bone conduction threshold significantly improved 12 weeks after the TMRP compared with baseline (35.7 ± 20.3 vs 29.4 ± 21.0 dB, $P = 0.015$). Six out of ten patients receiving TMRP experienced temporary adverse events: appendicitis (serious, severe), otorrhea (mild), otitis media (mild), and sudden hearing loss (mild). However, none were related to the protocol treatment.

Abbreviations: AE, adverse event; bFGF, basic fibroblast growth factor; CI, confidence interval; SDV, source data verification; TM, tympanic membrane; TMP, tympanic membrane perforation; TMRP, tympanic membrane regeneration procedure.

* Corresponding author at: Department of Otolaryngology—Head and Neck Surgery, Kitano Hospital, Tazuke Kofukai Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan. Fax: +81 6 6312 8867.

E-mail addresses: k-omae@tri-kobe.org (K. Omae), kanemaru@ent.kuhp.kyoto-u.ac.jp (S.-i. Kanemaru), e-nakatani@tri-kobe.org (E. Nakatani), hkaneda@tri-kobe.org (H. Kaneda), t-nishimura@tri-kobe.org (T. Nishimura), tona_risa@ent.kuhp.kyoto-u.ac.jp (R. Tona), naito@kcho.jp (Y. Naito), kawamoto@fbri.org (A. Kawamoto), mfukushi@tri-kobe.org (M. Fukushima).

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Conclusion: TMP closure and hearing improvement were frequently confirmed following the TMRPs which were safely performed. These favorable outcomes were accompanied with significant improvement of the bone conduction threshold. These promising outcomes would encourage a large-scaled, randomized and pivotal clinical trial in the future. This trial is registered at http://www.umin.ac.jp/ctr/index.htm (identifier: UMIN000006585).

1. Introduction

Tympanic membrane perforations (TMP) can result from disease (e.g. otitis media), trauma, or medical treatments (e.g. eardrum tube placement surgery). TMP may impede hearing because the sound that directly reaches the tympanic cavity is cancelled by the sound simultaneously conducted through the round window of the cochlea and the oval window via the auditory ossicles [1]. In addition, since the middle ear is directly exposed to the external auditory canal, TMP increases the risk for infection and the susceptibility to otitis media. If vulnerability to infection continues for a long time, TMP may predispose the inner ear to hearing disorders (e.g. otorrhea and sensorineural hearing loss). The TMP should therefore be sealed as soon as possible [2–4]. If the inner and middle ear are undamaged, hearing improvement can be achieved after TM closure, which greatly contributes to the quality of life.

TMP is categorized as either temporary or persistent. Although most perforations close spontaneously (77–94%) [5,6], surgery is indicated for a perforation persisting for over 2 months [7]. Various therapies are available for TMP closure depending on the size of the perforation, and the most common treatments are surgeries such as myringoplasty and tympanoplasty. Both surgeries require skin incisions in the opisthotic region, peeling in the external auditory canal, and sampling and transplantation of autologous tissues [8,9]. As the TMP becomes larger, surgical procedures to repair the TM with autologous tissue (temporal fascia) become more difficult. In addition, these operations do not always improve hearing; patients may also develop sequelae such as postoperative re-perforation of the TM, ear discomfort, and tinnitus. Moreover, the TM after surgery is markedly different from its original state as a result of lateralization and thickening, leading to decreased hearing in some patients [10]. Another disadvantage of these operations is that they normally require tissue transplant treatment, and so the physical and economic burden for patients is far from negligible [11].

Kanemaru et al. [11] developed a novel therapy using gelatin sponge with basic fibroblast growth factor (bFGF) and fibrin glue. Hearing improved immediately after the treatment, which took approximately 10–30 min in the outpatient department. Furthermore, in a randomized clinical trial for 63 patients with chronic TMP, complete closure of the TMP was achieved in 98% (52/53) of the patients in the bFGF group while the closure rate was only 10% (1/10) in the control patients. Hearing levels were improved in all patients with successful TM repair and serious sequelae were not observed in any patients. However, this clinical trial was a single center study, in which bone conduction threshold was not evaluated [11].

Vijayendra and Parikh [12] and Saliba et al. [13] recently reported that TMP closure by surgery (e.g. myringoplasty and ossiculoplasty with closed or open cavity mastoidectomy for chronic otitis media, stapes mobilization for tympanosclerosis, and stapedotomy for otosclerosis) improved the bone conduction threshold. We therefore conducted a multicenter clinical trial to evaluate the safety and efficacy of the TM regeneration procedure (TMRP), including assessment of the bone conduction threshold.

2. Methods

2.1. Enrollment and assignment

The study was carried out in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research issued by the Ministry of Health, Labour and Welfare in 2003. The study protocol and other relevant documents were reviewed and approved by the Ethics Committee of the Foundation for Biomedical Research and Innovation, Kitano Hospital and Kobe City Medical Center General Hospital (22 September, 2011 No.11-03, 25 July, 2011 No.P11-07-007, and 8 August, 2011 No.1101-7, respectively). Written informed consent was obtained from all participants before enrollment. Eligible patients were centrally registered using a web enrollment system.

The main inclusion criteria were as follows: (1) chronic otitis media with TMP, an old traumatic TMP, or a perforation remaining after myringotomy for otitis media with effusion and placement of a tympanic membrane tube; (2) no active inflammation of the tympanic membrane and no epithelial invagination or cholesteatoma mass; (3) sufficient air in the mastoid antrum and tympanic cavity by temporal bone computed tomography and no abnormal soft tissue shadow or abnormalities in the auditory ossicles or their linkages by computed tomography; (4) hearing improved to bone-conduction hearing on a hearing acuity test using the patch test. Details are shown in Table 1.

2.2. Protocol treatment schedule

The initial treatment was performed within 3 months of registration, and the TM photographs were examined 4 weeks after treatment. TM photographs were taken for evaluation of TMP closure. If the perforation had not closed, the protocol treatment and examination were repeated every 4 weeks a maximum of three times (up to four times in total including the initial treatment). When closure was confirmed, the patients returned to the hospital for evaluation after a further

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