Prospective cohort comparison of bioactive glass implants and conchal cartilage in reconstruction of the posterior canal wall during tympanomastoidectomy

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Objective: To compare the effectiveness of bioactive glass implants and conchal cartilage in reconstructing the posterior canal wall during tympanomastoidectomy.
Study design: Prospective cohort clinical study.
Setting: Teaching hospital.
Patients: Patients with clinically diagnosed chronic suppurative otitis media and cholesteatoma awaiting tympanomastoidectomy were recruited.
Intervention: All patients underwent tympanomastoidectomy by the same surgeon. A first cohort of 12 patients underwent posterior canal wall reconstruction with autogenous conchal cartilage. A second cohort of 12 patients underwent such reconstruction with prefabricated bioactive glass.
Main outcome measures: *Primary* – All patients underwent out-patient review at 1, 3, 6 and 12 months postoperatively, after which a second-look procedure was performed. Reconstructions were inspected for evidence of epithelialization, granulation, infection, stenosis, depression and extrusion. *Secondary* – All patients had perioperative serial pure-tone audiometry to check for any change in hearing levels upto 1 year postoperatively.
Results: By 1 year postoperatively, both reconstructive graft materials showed good epithelialization, no granulation, no infection, no ear canal stenosis, no depression and no extrusion. At operative second-looks, bioactive glass particularly showed good tissue bonding, including both neovascularization and connective tissue integration. Overall clinical outcome was equivalent for both materials. Both graft materials showed no statistically significant difference in postoperative hearing levels.
Conclusions: Bioactive glass and conchal cartilage showed equivalent clinical outcome in reconstructing the posterior canal wall without significantly affecting hearing levels. As bioactive glass does not require second site morbidity and thus also reduces operative time, we prefer it for reconstructing the posterior canal wall following tympanomastoidectomy.

Reconstruction of the posterior canal wall, performed either primarily during or delayed after tympanomastoidectomy, restores an anatomical configuration similar to that after canal-wall-up surgery. An aerated mastoid cavity is created, which is contiguous with the tympanic cavity. Many materials have been utilized for reconstruction over the years, including a variety of autologous and synthetic options.

The most popular autologous reconstructive material is elastic cartilage from the concha, widely considered to be the standard technique in posterior canal wall reconstruction. Naturally, sourcing of this material requires second site surgery with associated prolonged operative time and potential added morbidity. There are also issues of limited availability and variable degrees of resorption over time.[1]

As alternatives to autologous cartilage, various synthetic reconstructive materials have been studied, and have found variable clinical utility. Hydroxyapatite, a biocompatible ceramic available as granular cement or prefabricated solid forms, has been popular.[2–4] Other studied materials include hybrid bone-substitute ionomeric cement,[5] porous polytetrafluroethylene-carbon filament composite[6,7] and titanium mesh.[8,9] However, biocompatibility does not relate to bioactivity, and all such synthetic grafts are unable to bond to soft tissue,[10] and so reports of early or late postoperative extrusion continue.

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Bioactive synthetic materials have been developed to overcome the problem of tissue bonding. Bioactive glasses, such as Bioglass (NovaBone Products; LLC, Alachua, FL, USA) and Ceravital (Ernst Leitz, Wetzlar, Germany and Xomed, Jacksonville, FL, USA), are likely the most suitable synthetic substitutes for conchal cartilage due to their ability to bond to both soft and hard tissues[11] and produce an antimicrobial effect.[12] Simply, the bioactive glass surface breaks down, releasing ionic species which stimulate cellular growth (Fig. 1), plus the surface of the glass changes its properties to entrap the ingrowing collagen fibres of both soft and hard tissues, so forming a biological bond (Fig. 2). In otology, bioactive glass has been tested for ossicular and canal wall reconstruction.[10,13,14] This study aims at comparing the effectiveness of bioactive glass against the standard graft material of elastic conchal cartilage in reconstructing the posterior canal wall following tympanomastoidectomy.

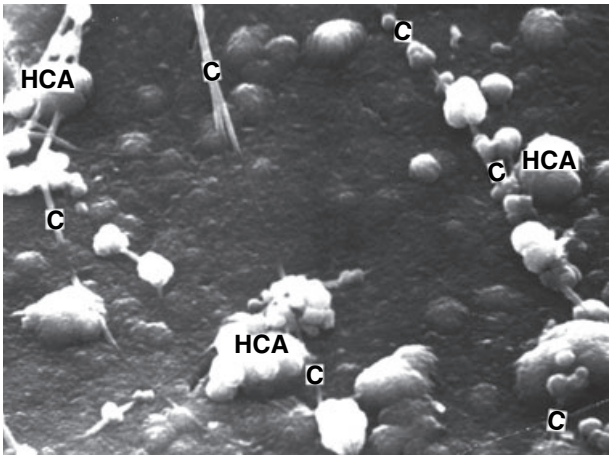

Fig. 2. Scanning electron micrograph of bioactive glass surface. Hydroxycarbonate apatite (HCA) mineral forming on the surface; collagen (C) fibres trapped into the HCA mineral, thus forming a biological bond.

Patients and methods

Ethical considerations

Ethical approval was obtained from the St Mary's Hospital Local Research Ethics Committee, and the study was registered centrally. Informed consent was obtained from all participating patients, using a customized patient information leaflet and consent form.

Patients

The study was performed in the Department of Otolaryngology – Head & Neck Surgery at St Mary's Hospital, London. Patients with clinically diagnosed chronic suppurative otitis media with cholesteatoma awaiting tympanomastoidectomy under the care of the senior author (S.A.) were recruited. Excluded patients were those

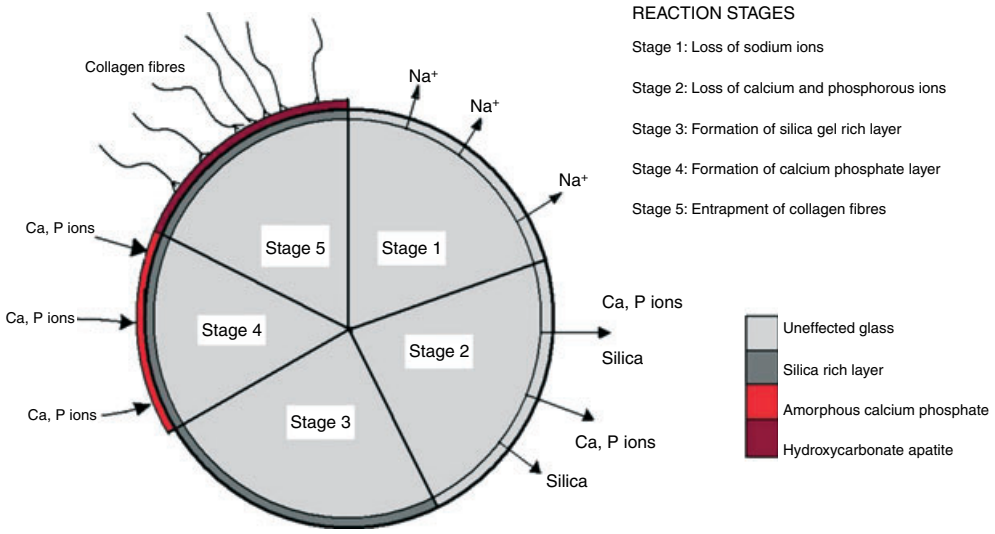

Fig. 1. Schematic diagram of bioactive glass reaction stages: (1) loss of sodium ions; (2) loss of calcium and phosphorus ions; (3) condensation to form silica gel rich layer; (4) amorphous calcium phosphate precipitates onto surface; (5) crystallization of amorphous calcium phosphate into hydroxycarbonate apatite, and thus entrapment of collagen fibres.

unable to provide informed consent and those with an only-hearing ear.

Intervention

All patients underwent tympanomastoidectomy by the same consultant surgeon (S.A.), between February 2003 and September 2005. Under general anaesthesia and via a conventional postauricular approach, the bony meatus was widened and the attic was drilled out. A cortical mastoidectomy was performed, and the excised and diseased attic and medial part of the posterior canal wall were reconstructed to prevent retraction of the tympanic flap into the mastoid and thus recurrence of disease. A first cohort of 12 patients had reconstruction with autologous conchal cartilage. Each time, cartilage was fashioned to form a tight fit within the posterior canal wall defect. A second cohort of 12 patients had reconstruction with prefabricated bioactive glass implants, which were similarly fashioned by drilling to ensure tight fits. Ossicular chain reconstruction was performed when clinically indicated. Tympanic membrane reconstruction was then performed using standard temporal fascial grafting.

Outcome measures

Primary. All patients were reviewed in clinic at 1, 3 and 6 months postoperatively to note whether the operative goal of a dry ear had been achieved. More specifically, the posterior canal wall was inspected for evidence of epithelialization, granulation, infection, stenosis, depression and extrusion. At 12 months, all patients underwent second-look operative procedures, when the middle ear and mastoid cavity were inspected for disease recurrence and evidence of fibrosis in the proximity of the graft material.

Secondary. All patients had perioperative serial pure-tone audiometry. For the purposes of statistical analysis, preoperative pure-tone hearing thresholds and air-bone gaps were compared with those at 1 year postoperatively. This evaluated any clinical effect of adjacent reactive granulation and fibrosis potentially caused by graft material.

Materials

The two implant materials used were elastic conchal cartilage and bioactive glass. Bioactive glass for this study was provided by the Department of Materials at Imperial College, London. The glass was prefabricated by casting molten glass into predrilled graphite moulds, and was then annealed at 400°C to remove any residual thermal stresses created during the casting process. The glass implants were cylindrical, 2.5–3.0 mm in height and with a diameter varying from 5.5 to 7.0 mm, increasing in 0.5 mm increments. Each production run produced five implants, and each implant was inspected by eye for surface crystallization and dimensional tolerances. The two most dimensionally accurate implants were retained for autoclave sterilization. The three remaining implants were used in destructive quality assurance tests, including testing for chemical purity, dissolution profile and bioactivity. If the quality assurance test results were within limits, the two retained implants proceeded to sterilization and were released for surgical grafting.

Statistical analysis

All data were analysed by SPSS Version 13.0 (SPSS Inc., Chicago, IL, USA). Pure-tone audiometry results were normally distributed. All descriptive statistics refer to means, standard deviations and 95% confidence intervals, while all comparisons were performed using independent sample *t*-test, with or without equality of variance assumed, as appropriate.

Results

Both cohorts of 12 patients each were well matched according to age, sex and preoperative hearing. Patients undergoing conchal cartilage reconstruction had a mean age of 41 years (range 11–64), and a male to female ratio of 7 : 5. Patients undergoing bioactive glass reconstruction had a mean age of 43 years (range 12–81), and a male to female ratio of 8 : 4. Average pure-tone hearing thresholds were calculated based on 0.5, 1, 2 and 4 kHz frequencies. The average air-bone gap in the cartilage cohort was 44.2 dB HL (SD 12.8, 95% CI: 35.1–49.1) and in the bioactive glass cohort was 40.0 dB HL (SD 11.3, 95% CI: 31.1–44.7). There was no significant difference in air or bone conduction thresholds between the cohorts preoperatively ($P = 0.36$).

No patients were lost to follow-up. Reconstruction of the excised medial part of the posterior canal wall was successful in achieving dry ears in all patients, regardless of the reconstructive graft material used. Serial outpatient review occurred at one, three and six months for all 24 patients, so specific inspection of reconstructed posterior canal walls can only be reported to these intervals. By three months, otomicroscopic examination showed that both graft materials resulted in good epithelialization with no granulation, no infection, no ear canal lumen stenosis, no depression and no extrusion (Fig. 3). At the 1 year second-look procedures for all 24

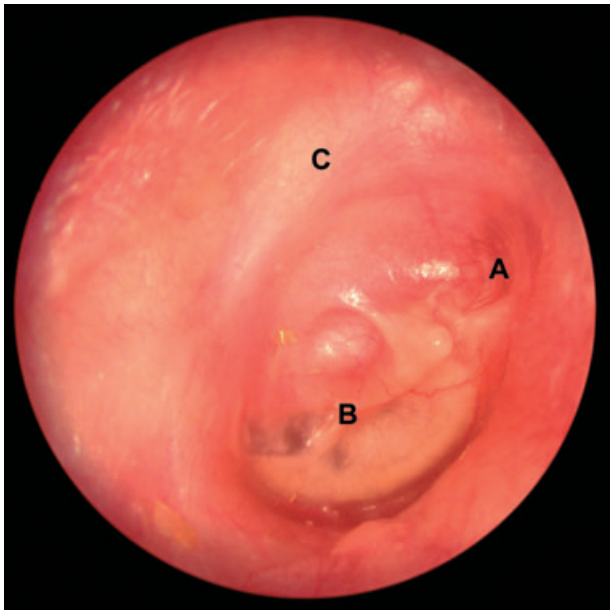

Fig. 3. Right ear canal (otoendoscopic) at 3 months follow-up: (A) attic excised; (B) handle of malleus; (C) posterior canal wall (reconstructed with bioactive glass).

patients, both graft materials were found to have remained *in situ*. In particular, bioactive glass showed good tissue bonding, including both neovascularization (Fig. 4) and connective tissue integration (Fig. 5). Incidentally, there were five cases of recurrent and/or residual cholesteatoma (two in the cartilage cohort, and three in the bioactive glass cohort), all of which were easily managed during second-look procedures without recourse to further drilling. Also, eight cases required ossicular chain reconstruction (six in the cartilage cohort, and two in the bioactive glass cohort; see Tables S1 and S2). Overall, however, clinical outcome was equivalent in both cohorts, and no patients suffered any surgical complications.

Analysis of perioperative pure-tone audiometry revealed no statistically significant differences in audiometric outcomes between the two groups (summarized in Table 1; individual case data in Tables S1 and S2 on-line). Specifically, using as reference the preoperative bone conduction thresholds, the average postoperative air-bone gap in the bioactive glass cohort was 28.8 dB HL (SD: 15.5, 95% CI: 20.4–44.5), and 22.9 dB HL (SD: 15.6, 95% CI: 15.2–33.9) in the cartilage cohort (difference not statistically significant, $P = 0.26$). Using as reference the postoperative bone conduction thresholds, the postoperative air-bone gap was 27.5 dB HL (SD: 15.6, 95% CI: 12.8–38.1) in the bioactive glass cohort, compared to 25.4 dB HL (SD: 12.7, 95% CI: 14.6–31.2) in the cartilage cohort (difference not statistically significant, $P = 0.72$). Similarly, all other comparisons between the two groups (change of air conduction thresholds, change of bone conduction thresholds, change in individual frequencies) did not show any significant differences between the two groups.

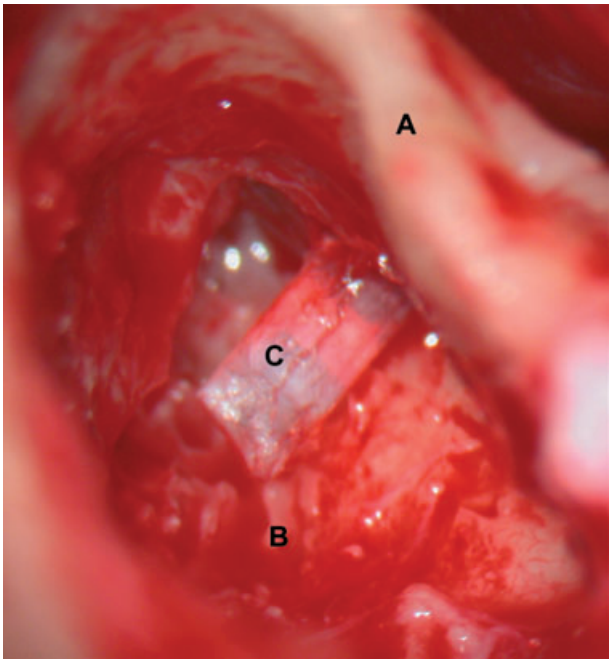

Fig. 4. Right mastoid cavity – second look procedure at 1 year's follow-up: (A) posterior canal wall; (B) mastoid cavity; (C) bioactive glass graft with supporting strut (with neovascularization).

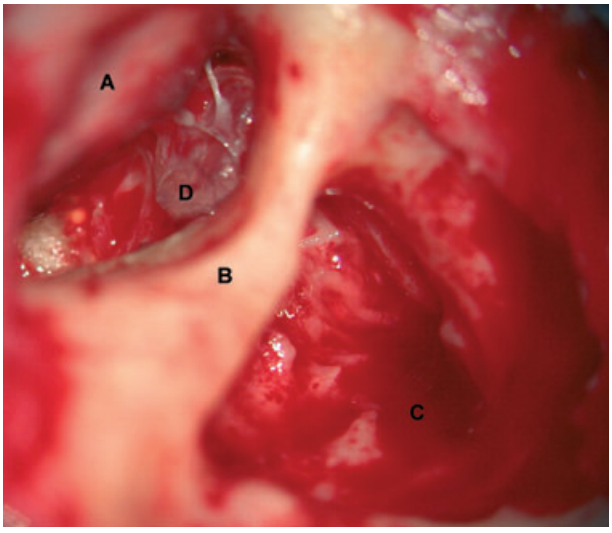

Fig. 5. Left ear canal and mastoid cavity – second look procedure at 1 year's follow-up: (A) tympanomeatal flap; (B) posterior canal wall; (C) mastoid cavity; (D) bioactive glass implant in canal wall defect (with connective tissue bonding to elevated tympanomeatal flap).

Table 1. Summary analysis of audiometric outcomes

Cartilage cohort			Percentage						
AB gap (dB HL at 0.5, 1, 2, 4 kHz)	Mean	SD	≤0	1–10	11–20	21–30	31–40	41–50	50+
Preoperative	44.2	12.8	0	0	8	8	8	50	25
Postoperative (using postop BC)	25.4	12.7	0	17	33	17	25	8	0
Postoperative (using preop BC)	22.9	15.6	8	17	25	17	25	8	0
Cartilage cohort			**Percentage change**						
AB gap (dB HL at 0.5, 1, 2, 4 kHz)	Mean	SD	<−20	−19–−10	−9–0	1–10	11–20	21–30	30+
BC (average dB HL at 0.5, 1, 2 kHz)	2.5	6.17	0	17	58	25	0	0	0
AC (dB HL at 4 kHz)	6.25	17.7	17	42	8	25	0	0	8
Bioactive glass cohort			**Percentage**						
AB gap (dB HL at 0.5, 1, 2, 4 kHz)	Mean	SD	≤0	1–10	11–20	21–30	31–40	41–50	50+
Preoperative	40	11.3	0	0	0	25	33	25	17
Postoperative (using postop BC)	27.5	15.6	0	8	33	33	8	8	8
Postoperative (using preop BC)	28.8	15.5	0	8	33	33	0	17	8
Cartilage cohort			**Percentage change**						
AB gap (dB HL at 0.5, 1, 2, 4 kHz)	Mean	SD	<−20	−19–−10	−9–0	1–10	11–20	21–30	30+
BC (average dB HL at 0.5, 1, 2 kHz)	2.5	7.9	0	17	50	33	0	0	0
AC (dB HL at 4 kHz)	1.3	19.3	8	17	33	17	25	0	0

AC, air conduction; BC, bone conduction; AB, air-bone gap. Negative values indicate better hearing postoperatively.

Discussion

Bioactive glasses were developed in the early 1970s by Larry Hench at the University of Florida,[15] their principal application being a bone graft substitute material. A series of powdered products were released, and found a number of clinical applications in dentistry, maxillofacial and orthopaedic surgery.[16] The clinical application of bioactive glass in otology, however, has relatively been hampered by the lack of solid preformed material.

The purpose of a biomaterial is to replace diseased or damaged tissue. Biologically inert materials do not interact with host tissue, and essentially become surrounded by non-adherent fibrous layers, thus minimizing scar formation at the interface. Biologically active (bioactive) materials essentially interact with host tissue, eliciting specific biological responses at the interface, resulting in the formation of biological bonds.

The bioactive glass system works by series of reaction stages over the first 48 h of implantation (Fig. 1). First, within minutes, there is a release of sodium ions, which increase the local pH above 7.4. Such alkalinity induces an antimicrobial effect within the local tissues.[12] Within 12 h, the glass surface further reacts with the local aqueous environment to create an amorphous calcium phosphate layer. Then, over a further 12 h, the calcium phosphate layer crystallizes into a hydroxycarbonate apatite layer, which is chemically and structurally similar to bone matrix. It is this final layer, which entraps ingrowing collagen fibres to create an adherent fibrous capsule and thus a biological bond (Fig. 2). So, within 48 h, the implant is coated with a surface of synthetic bone-like material that promotes both hard and soft tissue bonding, whilst simultaneously mitigating the otherwise expected foreign body reaction.

Regarding bonding to hard tissue, namely bone, bioactive materials are described as having osteoconductive and/or osteoproductive qualities. Osteoconduction refers to the establishment of extracellular scaffold to allow for the ingrowth of capillaries and perivascular tissue of the host into the three-dimensional structure of an implant. This is a passive process that guides bone formation. Osteoproduction refers to the colonization of this scaffold by osteogenic stem cells, which provides an intracellular acceleration of bone matrix deposition. This is an active process that actually forms bone. Hydroxyapatite is osteoconductive, whereas bioactive glass is both osteoconductive and osteoproductive. Moreover, bioactive glass engenders a

high degree of local neovascularization, as evidenced during our second-look procedures (Fig. 4), which may be important in supporting new bone formation, as well as for protection against graft infection. Neither material, however, is osteoinductive, a process that requires the presence of bone growth factors and morphogenic proteins, which are only present in natural bone. Incorporating or coating bioactive glass with such osteoinductive agents remains an avenue for further research.

Regarding bonding to soft tissue, bioactive glass includes this ability in addition to its osteoconductive and osteoproductive qualities. However, hydroxyapatite and other synthetic bone graft systems do not bond to soft tissue, and are thus vulnerable to extrusion. Hence, cases continue to be reported where hydroxyapatite grafts are extruded from the body effectively via a typical foreign body reaction.[17,18]

As bioactive glass is granular and brittle in nature, such graft material can be difficult to mould during an operation. Unlike conchal cartilage, bioactive glass would rather break than bend. However, the senior author found that minimal adjustment to an appropriately sized prefabricated bioactive glass implant was easily achieved intraoperatively, using a diamond drill burr, to ensure a snug fit into any particular posterior canal wall defect. Nonetheless, manufacture of appropriately shaped, as well as appropriately sized, bioactive glass stock would certainly facilitate an operation by minimizing any time required for intraoperative moulding.

Of course, the use of any synthetic material in the middle ear cleft gives rise to questions about potential ototoxicity. Our study reveals no evidence of such a side effect from statistical analysis of perioperative audiometry, and indeed there are no such reports in the literature. Nonetheless, our follow-up period is short, and we appreciate that long-term results are essential, and we hope to publish these at five and 10 years.

Finally, any synthetic material has a financial cost limitation. For the purposes of our study, the actual cost of processing each bioactive glass implant from raw material amounted to no more than £5.00. An estimate of commercial cost, taking into account quality control, marketing and other business requirements, amounts to £100.00.

Strengths of the study

Despite the short-term follow-up reported so far, ours is the first prospective study of bioactive glass as an implant for posterior canal wall reconstruction. Ours is also the first study to directly compare bioactive glass, measure for measure, against the essentially standard technique of using autologous conchal cartilage for such reconstruction during tympanomastoidectomy. This comparison is strengthened by having cohorts well-matched with respect to patient demographics and disease, as well as having a single operator undertaking all cases.

Comparison with other studies

Studies of bioactive glass in otology have largely focussed on its application as an ossicular reconstructive material.[10,13] To date, only one study reports long-term (>10 years) results of posterior canal wall reconstruction using bioactive glass (Ceravital) after canal wall down mastoidectomy.[14] This was a retrospective review from private otologic practice of a case series of 19 consecutive patients with a mean follow-up of 13.1 years. Prosthetic posterior canal walls remained intact in 16 patients at the long-term follow-up. Infection, displacement and cholesteatoma were independent causes of ultimate implant removal in three cases. The review concluded that Ceravital has been and is a useful option for posterior canal wall reconstruction after canal wall down mastoidectomy.

Clinical applicability of the study

Patients who wish to be free from lifelong aural toilet may be offered the choice of posterior canal wall reconstruction during their tympanomastoidectomy. Our study shows that such reconstruction with bioactive glass appears to have equivalent clinical outcome to using the traditional standard of conchal cartilage. Over the short-term of this study, results were equivalent for both bioactive glass and cartilage graft cohorts, with no statistically significant differences in hearing thresholds between cohorts. Of course, we intend to continue our follow-up of all these cases to determine long-term results. Nonetheless, for now, as use of bioactive glass avoids problems of limited availability and second site morbidity, not to mention thus saving operative time, whilst promoting good healing, hard and soft tissue formation and bonding, all without ototoxicity, we are beginning to prefer it for posterior canal wall reconstruction during tympanomastoidectomy.

Conflict of interest

None to declare.

References

1 Dornhoffer J.L. (2004) Retrograde mastoidectomy with canal wall reconstruction: a follow-up report. *Otol. Neurotol.* **25,** 653–660

2 van Blitterswijk C.A., Hesseling S.C., Grote J.J. *et al.* (1990) The biocompatibility of hydroxyapatite ceramic: a study of retrieved human middle ear implants. *J. Biomed. Mater. Res.* **24,** 433–453
3 Grote J.J. (1998) Results of cavity reconstruction with hydroxyapatite implants after 15 years. *Am. J. Otol.* **19,** 565–568
4 Estrem S.A. & Highfill G. (1999) Hydroxyapatite canal wall reconstruction/mastoid obliteration. *Otolaryngol. Head Neck Surg.* **120,** 345–349
5 Geyer G., Dazert S. & Helms J. (1997) Performance of ionomeric cement (Ionocem) in the reconstruction of the posterior meatal wall after curative middle-ear surgery. *J. Laryngol. Otol.* **111,** 1130–1136
6 Johns A.N. (1981) The use of Proplast in reconstruction of the posterior meatal wall. *J. Laryngol. Otol.* **95,** 899–904
7 Shea J.J., Makenbaum B.T. & Moretz W. (1984) Reconstruction of posterior canal wall with Proplast. *Otolaryngol. Head Neck Surg.* **92,** 329–333
8 Zini C., Quaranta N. & Piazza F. (2002) Posterior canal wall reconstruction with titanium micro-mesh and bone pâté. *Laryngoscope* **112,** 753–756
9 Jung T.T. & Park S.K. (2004) Reconstruction of mastoidectomy defect with titanium mesh. *Acta Otolaryngol.* **124,** 440–442
10 Wilson J., Douek E. & Rust K. (1995) Bioglass middle ear devices: ten year clinical results. In *Bioceramics*, Hench L.L., Wilson J. & Greenspan D.C. (eds), Vol. 8, pp. 239–245. Pergamon, Oxford
11 Hench L.L. & Wilson J. (1984) Surface-active biomaterials. *Science* **226,** 630–636
12 Allan I., Wilson M. & Newman H. (2002) Particulate Bioglass reduces the viability of bacterial biofilms formed on its surface in an in vitro model. *Clin. Oral Implants Res.* **13,** 53–58
13 Rust K.R., Singleton G.T., Wilson J. *et al.* (1996) Bioglass middle ear prosthesis: long-term results. *Am. J. Otol.* **17,** 371–374
14 Della Santina C.C. & Lee S.C. (2006) Ceravital reconstruction of canal wall down mastoidectomy: long-term results . *Arch. Otolaryngol. Head Neck Surg.* **132,** 617–623
15 Hench L.L., Splinter R.J., Allen W.C. *et al.* (1971) Bonding mechanisms at the interface of ceramic prosthetic materials. *J. Biomed. Mat. Res.* **5,** 117–141
16 Hench L.L. & West J.K. (1996) Biological applications of bioactive glasses. *Life Chemistry Reports* **13,** 187–241
17 Vrabec J.T., Stierman K. & Grady J.J. (2002) Hydroxyapatite prosthesis extrusion. *Otol. Neurotol.* **23,** 653–656
18 Shinohara T., Gyo K., Saiki T. *et al.* (2000) Ossiculoplasty using hydroxyapatite prostheses: long-term results. *Clin. Otolaryngol. Allied Sci.* **25,** 287–292

Supporting Information

Additional supporting information may be found in the online version of this article.

Table S1. Audiometry results (in dB HL) for cartilage grafted patients

Table S2. Audiometry results (in dB HL) for bioactive glass grafted patients

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