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Micro macroporous biphasic ceramics and fibrin sealant as a moldable material for bone reconstruction in chronic otitis media surgery. A 15 years experience

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Bone reconstruction is still a matter of concern in middle ear surgery despite the large number of surgical techniques proposed. Combination of biphasic calcium phosphate bioceramics with human fibrin sealant forms a moldable material easy to apply for bone reconstruction. Since 1986, we have been using this composite for reconstruction of mastoid cavities during chronic otitis media surgery. Granules of ceramic provide immediate mechanical stability and later on, promote osseoinduction when fibrin sealant forms a strong bond between granules enhancing the wound healing process. After checking feasibility, efficacy and tolerance through a controled study on dogs by filling mastoid cavities, we started a clinical series comprising yet 66 mastoid reconstructions. A retrospective data analysis on 63 patients with an average follow up of 42 months including 12 histological controls confirms the stability of bone reconstruction with a remarkable tolerance of the skin in contact. Biopsies confirmed progressive replacement of material by lamellar newly formed bone. Mastoid cavities have a randomed shape making complex bone reconstruction procedure and their filling by the composite constitutes an easy way and represents a highly satisfactory procedure. The authors considered that this should be explored in other indications of bone surgery.

Introduction

Surgical treatment for chronic otitis media requires drilling and cleaning of the inflammatory bone. Radical mastoidectomy, opening all mastoid cavities and making them in communication with the external auditory meatus, is one of the most frequently used surgical procedure for treatment of chronic otitis media mainly in presence of cholesteatoma, an abnormal skin growth into the middle ear cavities [1]. In order to avoid recurrence of infections or even cholesteatoma into these widely opened cavities, bone reconstruction appears to be necessary and should be performed immediately or with a delay. Surgical techniques for bone reconstruction using autologous materials as muscular flaps, bone or cartilage chips are time consuming with unstable results [2–4]. An immediate and easy-to-use solution to fill bone cavities with randomed shapes like mastoid cavities consists in using ceramic composites mixed with biological derivatives such as fibrin glue in order to fix or to stick together granules and to enhance the wound healing process. Wüllstein was the first in 1981 to propose the use of a mixture of ceramic granules combined with fibrin sealant to fill mastoid cavity for bone reconstruction calling the mixture Plasticine [6]. In 1986, we have designed for reconstruction of mastoid cavities a composite associating biphasic granules of calcium-phosphate ceramics thoroughly mixed with fibrin sealant. Considerable progress had been made in bone substitutes, especially calcium phosphate (CaP) ceramics, among which are the improvement of the purity, the association of various formula to benefit from the properties of each CaP derivative (high osseogenicity of Tricalcium phosphate (TCP) [7] and stability of hydroxylapatites (HA) [8–10], the control of the micropores and the macropores essential for cell adhesion, and the improvement of mechanical properties [11]. The concept of biphasic ceramics is determined by an optimum balance of the more stable phase of HA and the more soluble phase of TCP [12, 13]. This material is slowly soluble and gradually dissolves in the body, seeding new bone formation as it releases calcium and phosphate ions into the biological medium [14]. It has already been used successfully in periodontologic and orthopedic applications [15, 16]. Human implantations of this composite have been carried out by our team since 1986 after getting satisfactory results in terms of biocompatibility and osseoinduction in animals [5]. We report here a retrospective data analysis of a 15 years long experience after using this composite in 66 ears.

Materials and methods

In mastoid filling, we are using 0.5–1 mm size granules made of biphasic CaP (60% HA and 40% TCP), with 70% porosity constituted of both micropore (30% of 1–5 μm) and macroporous (50% of 400–600 μm) (Triosite®, Zimmer, or MBCP®, Biomatlante manufacturer, France).

Fibrin sealant (Tissucol, Tisseel®, Baxter, Glendale, USA) is an FDA approved plasma derivative obtained from pooled human plasma and containing highly concentrated fibrinogen (90 mg/ml), fibronectin and FXIII of coagulation and constituting the sealer protein concentrate. The mixing with human thrombin provides an insoluble fibrin polymer whith adhesive and hemostatic properties and there is indirect evidence that fibrin plays an important role in wound healing and normal fibrin network might be a necessary scaffold for ingrowing fibroblasts [17, 18]. Fibrin sealant is prepared from PCR tested plasmas against major blood borne virus like HIV, HBV, HCV, HAV, PVB19 and is submitted to a specific viral inactivation procedure by vapor heating. It also contains bovine aprotinin, a natural antifibrinolytic substance which allows the fibrin clot to stay at least two weeks in the bone reconstruction area [19]. Aprotinin is prepared from source material inactivated against potential prion transmission.

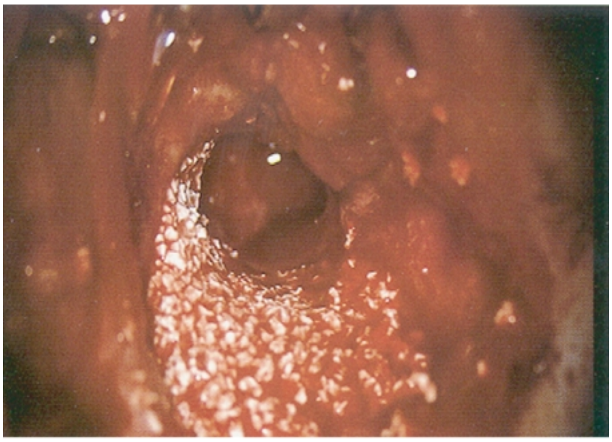

Figure 1 Mastoid cavity filling with ceramic granules mixed with fibrin glue. Immediate post-surgical aspect.

Figure 2 Mastoid cavity filling with ceramic granules mixed with fibrin glue. Immediate post-surgical aspect.

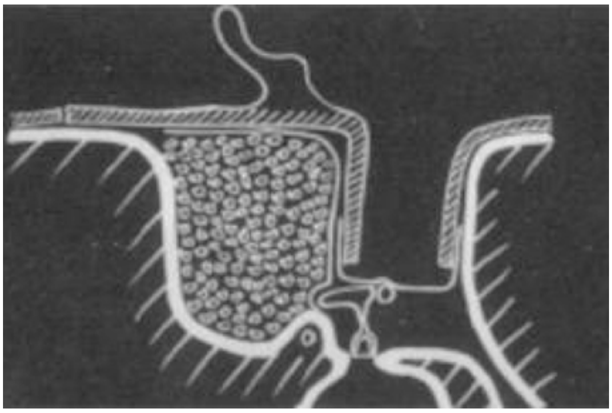

Figure 3 Total mastoid cavity filling covered by a fascia.

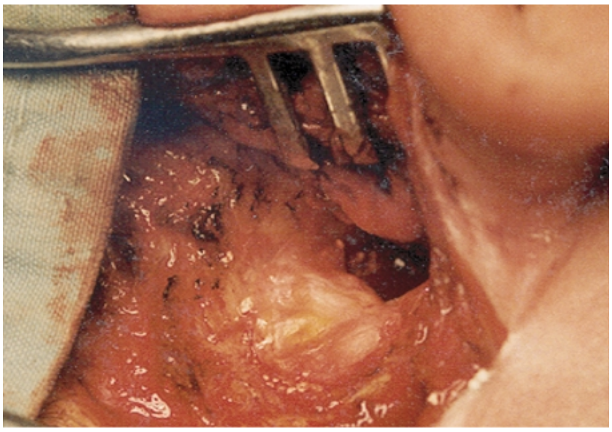

Figure 4 Total mastoid cavity filling covered by a fascia.

The composite is prepared immediately before use by the surgeon. Two ml of fibrin sealant are prepared with a 500 IU/ml thrombin solution allowing a fast setting or if preferred a 4 IU/ml solution providing a slow setting. Then granules are hydrated with a physiological salt sterile solution. According size of the cavity, 1 or 2 g of ceramic are used. Then both ceramic granules and fibrin sealant are thoroughly mixed in a cupule in a 1/1 weight ratio (around 2/1 volume ratio). Mixing the sealer protein concentrate with thrombin produces a viscous solution that quickly sets into an elastic coagulum. The composite is available for use after a few seconds and constitutes a plastic cement. Biphasic ceramic granules provide an immediate mechanical stability when the fibrin sealant forms a strong bond between granules making easy their settlement and preventing formation of hematoma between granules able to delay osseoinduction.

When all inflammatory tissues and epidermic remnants have been removed in the middle ear and the mastoid cavity by drilling till the healthy bone and the cavity copiously rinsed, the composite is set in place into the cavity by small quantities with the aid of a spatula and compacted in order to get a close contact with the healthy bone which is appropriate to promote osseogenesis (Figs. 1 and 2). Then, a wide autologous temporal fascia is placed over the filling and glued with fibrin sealant to separate composites from the cutaneous tissues of the external auditory meatus and to prevent granules to escape through it [20, 21] (Figs. 3 and 4).

Chronic otitis media with or without cholesteatoma can be treated according severity by a radical mastoidectomy (open technique) or by tympano-mastoidectomy respecting partially the postero-superior angle of the external auditory meatus posterior wall (closed technique). In both cases, bone reconstruction is necessary to prevent formation of tympanic retraction pockets, source of recurrent infections and cholesteatoma. In case of open technique, reconstruction can be performed immediately or with delay for rehabilitation of ancient cavities [1, 3].

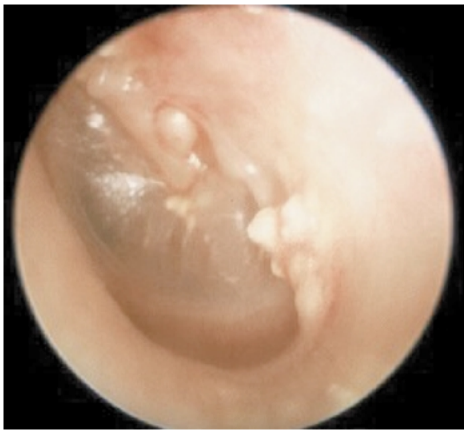

Figure 5 Normal and thin skin covering ceramic granules in external auditory meatus at month 6.

Retrospective data analysis (1986–2001)

The fibrin sealant-ceramic composite has been first tested in a controled preclinical study to fill canine mastoid cavity on one side when ceramic granules alone were used as control on the other side for 1 till 11 months ($n = 7$) [22, 23]. Then, according the interesting results obtained, we started in 1986 using this filling technique in humans for immediate or delayed reconstruction of radical mastoid cavities or partial tympano-mastoidectomy. All patients have been operated on by the same team and followed up in a standard way at 1, 3, 6, 12 months comprising clinical evaluation by otoscopic examination through microscope and once a year a CT-scan control. Patients who should have to be re-operated 6 months later or more for functional hearing reconstruction benefited at the same time of a biopsy from the bone reconstruction site. A series of 66 ears on 63 patients (3 operated bilaterally) including 35 men and 28 women with a mean age of 39.7 years (ranged from 12 to 71 years) were operated using the composite for partial [28] or total [38] mastoid obliteration during immediate [39] or delayed [27] revalidation of radical mastoidectomy cavities. Biopsy was taken for 12 patients during second surgical step 1–5 years after implantation. To assess the osseointegration and tolerance of the composite, light microscopy examinations on non-decalcified sections, X-rays-microradiographies, and microanalysis were performed on animal samples at regular intervals and on the 12 human specimens. Scanning and transmission electron microscopes were used.

Results

Clinical results

In this series of 66 ears operated on 63 patients between 1986 and 2001, 59 of them have been followed up for at least 6 months. During the first 2 weeks local pain could be observed. An aseptic serous otorrhea occurred in 39% of the cases (26/66) allowing some granules to escape in the meatus and 3 cases presented a post-operative infection leading to a partial and finally stable resorption of the filling which never asked for a surgical revision. In every operated ear, the otoscopic examination through microscope showed an immediate stability of the bony reconstruction and a good tolerance of the material in absence of any cutaneous reaction. In total, 43/59 (73%) of the filled cavities remained unchanged when a partial resorption of the filled volume was observed in 16 cases (27%). Fifty-seven patients were followed up in the long term with an average of 44 months and a maximum of 12.5 years (8–153 months). Tolerance of the skin covering the composite and stability of the filling appeared to be remarkable allowing for all patients (Fig. 5) except one definite disappearance of recurrent infectious episodes of the former cavities. Recurrent cholesteatomas have been observed on 2 patients in the external auditory meatus or in the thickness of the tympanic membrane and never the presence of the biomaterial prevented neither the diagnosis or the treatment. Revision surgery was performed without any difficulty and skin could easily be lifted from the ceramic as for all ears operated on a second stage for functional reconstruction. For 2 women a chronic pain in the bone filled area without any local inflammatory reaction required removal of the material which was found surrounded by granuloma tissues. Exeresis provided pain suspension.

Most of the patients experienced a CT-scan every 6 months the first 2 years and every year during 5 years where the material appeared to be highly dense in contact with the bone and remodeled during the first 12–15 months after surgery. CT-scan confirmed the stability of bone reconstruction in the external auditory meatus and the mastoids (Fig. 6). An hypodense thin layer was

Figure 6 CT scan control one year after implantation: hypodensity at the interface with the living bone.

regularly observed on the periphery of the bone filling in contact with normal bone and this aspect seems stable with time. When a columellar reconstruction was performed during the same surgical step, auditory results were most often poor due to the wound healing process occurring in the following months and destabilizing the ossicle or the prosthesis. Finally, we decided to systematically reconstruct the ossicular chain during a second step 12 months later.

Histological results

One month after implantation on animals, only part of the implanted material on both sides was enclosed in a mineralized bony formation matrix around granules and into the macropores forming a fibrous-reticulate newly formed bone when at month 3 appeared a progression of the bone neoformation and a true bone ingrowth composed of lamellar bone followed at month 6 by a complete osseointegration of the material. Month by month, microradiographies have shown the progressive increase of the osteogenetic process. In addition, tolerance was excellent in both sides without inflammatory reaction. When ceramics granules were used alone, bone ingrowth appeared delayed in time and organized more as a woven and fragile bone than as a lamellar dense bone. Polarized microscopy examinations have revealed formation of a true haversian bone with a more rapid and complete osteogenesis on the side where fibrin adhesive was added to biphasic ceramic (Fig. 7) [22–24]. On humans, after one year the newly formed bone appeared as solid, dense and milky white and all biopsies needed a gouge for removal; the scanning electron microscopy (SEM) revealed that the granules of bioceramics are closely associated with newly formed bone with fibrillar network associating the granules (Fig. 8). Again a mineralized bone matrix was found in contact of granules while microradiographies and microanalysis showed results comparable to those observed on animals. Eleven on these twelve specimen presented a complete osteointegration with true lamellar bone formation (Figs. 9 and 10).

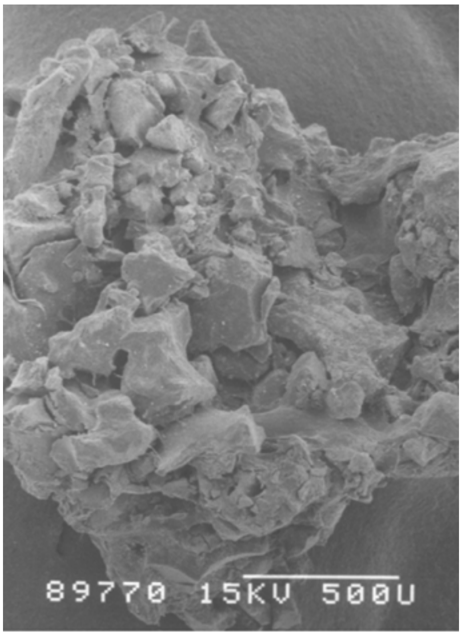

Figure 8 SEM of human biopsy of implanted granules of MBCP and Tissucol after 1 month of implantation.

Discussion

The objective of filling the mastoid cavity is to definitely cure recurrent otitis and cholesteatoma formation, to perform plastic repair of the outer ear and to authorize patients for swimming or wearing hearing aids. Composite of biphasic ceramic and fibrin sealant has for main advantage its ability to be easily manipulated as a plastic cement and mold in place. In a few minutes, randomed shape mastoid cavities are filled with an anatomical reconstruction of the posterior wall of the external auditory meatus. Surrounding walls of the bone cavity need to be meticulously drilled to stimulate bone formation and composite has to be compacted for stabilization but not too strong since this could be related with initial post-operative pain. Bioactive ceramic provide the immediate and long-term stability thanks to a long process of bone remodeling when fibrin sealant is immediately sticking granules together and with the cavity walls and enhancing later on the osseoinduction

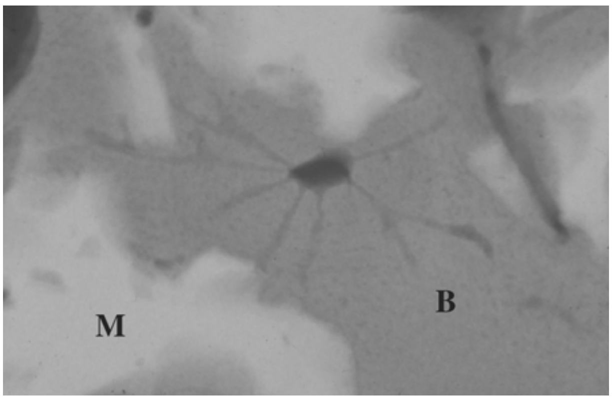

Figure 7 Haversian lamellar bone (B) formed into Triosite® macropores (M) showing bone remodeling of the first formed bone, canine mastoidal cavity, X-rays microradiography.

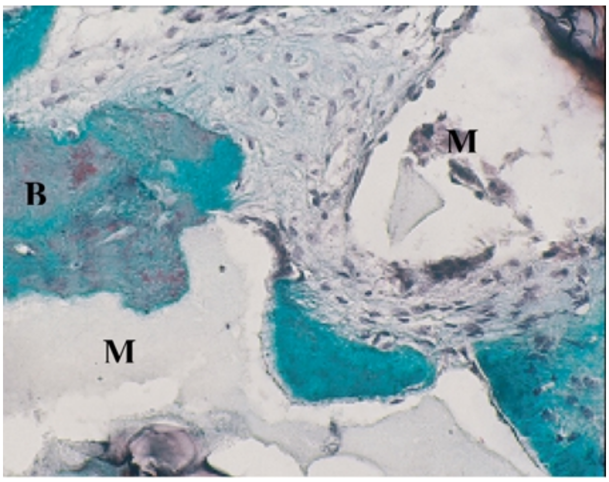

Figure 9 One year after implantation: Bone ingrowth (B) occurs around the granules and inside the macropores (M). Decalcified section stained with Masson's Trichromic staining.

process. Serous otorrhea observed in the first 2 weeks in 39% of the cases may be provoked by hyperosmolarity of fibrin sealant and require regular suctions through microscopic examination. Local resistance to infection of the material limited consequences to a small resorption of the bone filling. CT-scan provides an easy monitoring and reveals the osteoinduction potential of the composite starting at month 2 and ending at month 12 as confirmed by histological findings. Clinical results were considered as highly satisfactory by all patients who appreciated disappearance of recurrent otitis when swimming and wearing hearing aid became possible. Stability of the bone reconstruction after the sixth month is confirmed by long-term follow-up making this technique valuable for clinical situations requiring bone reconstruction in other surgical fields but keeping in mind that quite no local constraints of pressure exist in the mastoid area.

Conclusion

Mastoid cavities have a randomed shape complicating the bone reconstruction procedure. Filling of such cavities by biphasic ceramics mixed with fibrin sealant forming a moldable material constitutes an easy way to get an immediate stability and to promote osteogenesis. According to our 15 years experience, this composite has been proved to procure a reliable, efficient, safe and economical way for bone reconstruction of mastoid cavities with long-term stability. Biopsies performed either on animals or humans have demonstrated progressive and partial replacement of the biomaterial by lamellar newly formed bone. Further extension of indications for filling bone cavities in different surgical fields should be envisaged.

References

1. M. PORTMANN, ''Traité de technique chirurgicale ORL et cervico-faciale'' (Masson, Paris, 1986) p. 223.
2. T. PALVA, *Arch. Otolaryngol. Head Neck Surg.* **77** (1963) 570.
3. M. TOS, *Clin. Otolaryngol.* **3** (1978) 255.
4. R. PERKINS, *Laryngoscope* **86** (1976) 416.
5. M. GERSDORFF, D. FRANCESCHI, M. BAGOT D'ARC, A. DHEM and G. DACULSI, in ''Transplants and Implants in Otology'', edited by G. Babighian and H. Feldmann (Kugler Pub., Amsterdam, 1988) p. 69.
6. H. L. WULLSTEIN, S. R. WULLSTEIN, K. KÖSTER and H. HEIDE, in ''Plastic and Reconstructive Surgery of the Head and Neck'', The International Symposium, Rehabilitative Surgery 2 (Verlag Grune & Stratton, New York, 1981) p. 354.
7. D. S. METSEGER, T. D. DRISKELL and J. R. PAULSTRUD, *J. Am. Dent.* **105** (1982) 1035.
8. M. JARCHO, *Clin. Orthop.* **157** (1981) 259.
9. J. F. OSBORN, *J. Bioeng.* **1** (1980) 108.
10. C. P. KLEIN, A. A. DRIESSEN, K. DE GROOT and A. VAN DER HOOF, *J. Biomed. Mater.* **17** (1983) 769.
11. O. GAUTHIER, J.-M. BOULER, E. AGUADO, P. PILET and G. DACULSI, *Biomaterials* **19**(1–3) (1998) 133.
12. G. DACULSI, N. PASSUTI, S. MARTIN, C. DEUDON, R. Z. LEGEROS and S. RAHER, *J. Biomed. Mater. Res.* **24** (1990) 379.
13. E. NERY, R. Z. LEGEROS and K. L. LYNCH, *J. Periodontol.* **63** (1992) 729.
14. R. Z. LEGEROS and G. DACULSI, in ''Handbook of Bioactive Ceramics'', edited by T. Yamamuro *et al.* (CRC Press, 1991).
15. R. Z. LEGEROS, *Adv. Dent. Res.* **2** (1988) 164.
16. N. PASSUTI, G. DACULSI, J. M. ROGEZ, S. MARTIN and J. V. BAINVEL, *Clin. Orthop. Relat. Res.* **67** (1990) 234.
17. B. ZEDERFELDT, in ''Fibrin Sealing in Surgical and Nonsurgical Fields: Wound Healing – Vol. 1'', edited by G. Schlag and H. Redl (Springer-Verlag Berlin-Heidelberg, 1994) p. 18.
18. M. -F. HARMAND, D. MICHEL and M. BAGOT D'ARC, in ''Fibrin Sealing in Surgical and non-Surgical Fields'', edited by G. Schlag (Springer Pub., Heidelberg, 1994) p. 52.
19. G. SCHLAG, H. REDL, M. TURNHER and H. P. DINGES, in ''Fibrin sealant in operative medicine'', Vol 1. edited by G. Schlag and H. Redl (Springer, Berlin Heidelberg New York, 1986) p. 3.
20. M. BAGOT D'ARC, P. CORLIEU and G. DACULSI, in ''Transplants and Implants in Otology'', edited by N. Yanagihara and J. Suzuki (Kugler, Amsterdam, 1992) p. 145.
21. M. BAGOT D'ARC and G. DACULSI, in ''Proceedings of the XXth European Congress of ENT'', edited by Monduzzi (Berlin, 2000).
22. G. DACULSI, M. BAGOT D'ARC, P. CORLIEU and M. GERSDORFF, *Ann. Otol. Rhinol. Laryngol.* **101**(8) (1992) 669.
23. P. J. CORLIEU and M. BAGOT D'ARC, *Transpl. Impl. Otol. II* **1**(5) (1992) 147.
24. A. W. BLAYNEY, J. P. ERRE, A. DHEM and Y. CAZALS, *Interfaces Med. Mech.* **13** (1987) 34.

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