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Epidural application of ionomeric cement implants. Experimental and clinical results

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Abstract

During setting and hardening, the hybrid bone substitute ionomeric cement (Ionocem®) achieves a stable and durable bond with the apatite of the adjacent bone without interpository soft tissue. Fluid contact during setting results in the release of aluminium ions which may reach critical levels as high as 3000 μg/l. On epidural application it is, therefore, essential to prevent cement constituents from gaining access to the intradural space. After the cement has hardened, the presence of aluminium is demonstrable in the adjacent bone to a maximum depth of 20 μm (EDX microanalysis). In rabbits, epidural placement of freshly mixed cement causes slight thickening of the dura. There is reason to believe that human dura, with a thickness 10 times greater, is impermeable to components of the cement.

After epidural application of the freshly mixed cement in the frontobasal and laterobasal regions and at the skull cap and petrous apex, 76 patients in all have been followed for up to 6.5 years. During this period no complications have arisen and functional (and cosmetic) results are promising. The availability of preformed implants (Ionoroc®, Ionocast®) permitted the peridural placement of minimal quantities of freshly mixed cement. These implants were fixed to localized sites on the adjacent calvarial bone by use of Ionocem®. Notwithstanding the stringent manufacturer guidelines, there have been reports in the literature that during the vulnerable stage of setting neurotoxic aluminium ions were released into the dural space with a fatal outcome in two cases. In view of potential intradural complications, such as may occur in case of dural leaks, it was considered that further application of the material adjacent to the dura was no longer warranted. The production of Ionocem® was discontinued in May 1995.

Key words: Bone cements, Skull; Duramater

Introduction

Closure of cranial bony gaps should ideally be watertight and mechanically stable, and also improve cosmetic appearance. Depending on the extent of the defect, it is possible, for instance, to transplant autogenous bone using a split-bone graft from the outer or inner table (Berghaus, 1994; Seyer and Farmand, 1994; Asgari *et al.*, 1996). The use of allogenic bony tissue has fallen into disfavour due to the fact that the risk of infection transmission cannot be excluded reliably. It is conceivable that osteoinduction may offer an answer to this dilemma in that it stimulates the generation of vital osseous tissue following implantation of morphogenetically active substances into demineralized bony tissue (Kübler *et al.*, 1994; Kübler, 1996). Alloplastic materials, such as polymethylmethacrylate (PMMA), are indispensable for achieving closure of bony skull defects. As hardening of PMMA is not associated with the development of a bond between the cement and bone, stable anchorage of the material to the adjacent bone is essential (Manson, 1986; Steimlé *et al.*, 1986; Behr and Roosen, 1996). Ceramics, e.g. Bioverit (Beleites and Rechenbach, 1992; Beleites and Gudziol, 1996) or hydroxyapatite (HA) (Holmes and Hagler, 1988) are stabilized in the implant bed by poorly resorbing sutures or by osteosynthesis employing compression plates. Hydroxyapatite reportedly becomes replaced by bone with the passage of time (Grote, 1996).

Ionomeric cement (Ionocem®, supplied by Ionos GmbH & Co. KG, Seefeld; manufacture was discontinued and facilities closed down in 5/95) is a hybrid bone substitute which while hardening bonds to the apatite of the adjacent bone. Its development has opened the way for novel, as yet impracticable cranioplasty techniques. However, in two communications to the Lancet (Hantson *et al.*, 1994; Renard *et al.*, 1994) it was argued that contact of the not fully hardened cement with body fluids such as cerebrospinal fluid (CSF) or with brain tissue may provoke life-threatening complications due to the release of aluminium ions from the material. The present report reviews our own experience obtained

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on epidural implantation of the material and outlines the experimental design and clinical application.

Materials and methods

Characteristics of the material

Glass ionomeric cements are hybrid bone substitutes which were developed in 1969 by Alan Wilson in the 'Laboratory of the Government Chemist', London, and have since found a place as a filler for dental applications (Wilson and McLean, 1988). Ionomeric cement has been specifically designed for application as a bone replacement material. The reaction between a calcium-aluminium fluorosilicate, a basic glass, and a polymaleic acid is minimally exothermic (Ionos, 1995). As the neutralization reaction proceeds, the initially low pH (1.6 as measured in the cement) rises within five minutes, attaining values above 4 (Ionos, 1995). Encapsulation of the glass particles by the polymaleinate is exceedingly stable, resulting in a composite which has fully matured after approximately 15 minutes (Lübben *et al.*, 1996) and can be shaped at will like a ceramic material, using commercial diamond burrs with constant water irrigation. During the hardening process, intimate hydrogen bonding of the cement to the adjacent hard tissue (e.g. bone) and metals is achieved. The continuous bonding zone between the cement and bone is virtually impermeable to water (Geyer *et al.*, 1994; Borrmann, 1996). When placing freshly mixed cement onto a layer of previously hardened material, the bond developing at the site of contact equals the strength of a specimen fabricated in a single process (Ionos, 1995).

Animal experiments

Cement-bone bonding.

Numerous studies have documented the intimate cement-bone bond that developed, for example, in baboon tibia (Jonck *et al.*, 1989a; 1989b) and in the middle ears of rabbits (Geyer, 1997) and baboons (Städtgen, 1994). The cement either bonded directly to the apatite of bone or new bone was found to have grown into gaps created, for example, by surgical trauma (bone drill). There was no evidence of a fibrous interpository layer, such as is seen after implantation of PMMA (Behr and Roosen, 1996). Bonding between cement and bone proved to be durable and stable (Geyer, 1997).

Calvarial implant.

Initial studies of the behaviour of freshly mixed ionomeric cement on dural contact were carried out using a rabbit model (Geyer *et al.*, 1994; Borrmann, 1996). Burr holes were placed paramedially in the skull caps of 10 rabbits. Dural incision and contact of the freshly placed cement with the cortex incited nonspecific inflammation. No reaction was seen on light microscopy when the dura had remained intact (Figure 1). Similar results have been reported by Reusche (1995) who also demonstrated minor inflammatory changes involving the peridural cortical tissue in rabbits. He speculated that these changes were attributable to the thickness of the rabbit dura – which is 0.1–0.2 mm, as compared with 1–1.5 mm in humans – and argued that the results obtained in rabbits could not be transferred to the situation in man. Using atomic absorption spectroscopy, Reusche failed to demonstrate elevated peridural aluminium levels at the cortex. In an experimental series on beagle dogs – dural thickness 0.2–0.4 mm as measured with an eyepiece graticule – no cortical lesions were demonstrable. In another animal study Brown (1995) incised the dura of beagles and effected closure using preserved dura to prevent leakage of cerebrospinal fluid (CSF). Increased aluminium concentrations were not detectable in brain tissue, blood plasma, and CSF. In experiments on nine baboons Jonck (1995) reconstructed cranial defects with freshly mixed ionomeric cement. Again, macroscopic and histological examination did not reveal any abnormalities at the cortical surface.

Clinical application

The favourable experience reported from dental practice (Wilson and McLean, 1988) and the positive evaluation of the Ethics Committee of the University of Würzburg permitted the early application of the ionomeric cement in head and neck surgery. An intimate knowledge of the physical and chemical properties of the cement, in conjunction with strict adherence to the meticulous guidelines of the manufacturer and refined surgical techniques made it possible to employ the material in the immediate vicinity of the dura.

Guidelines for application of Ionocem® (extract)

The manufacturer guidelines for Ionocem® (1991) include a specific statement to the effect that aluminium ions tend to leach from the material when entering into contact with fluids during the early stage of setting, thereby compromising the stability of the cement and dura, even in the

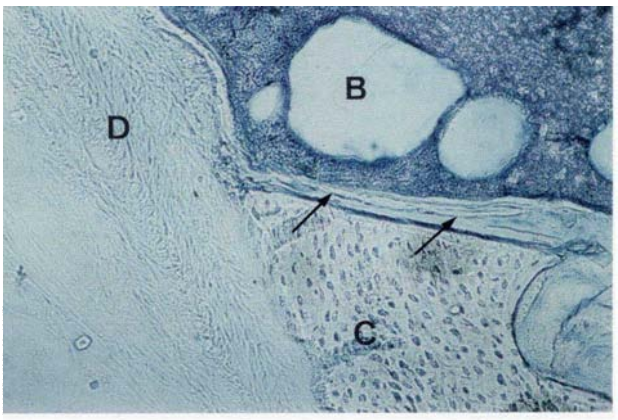

FIG. 1

Reconstruction of rabbit skull cap using ionomeric cement, the dura remaining intact (128 days post-operatively), D: slightly thickened dura underneath the cement, I: ionomeric cement with void formation (B), C: calvarial bone; note new bone formation (arrows) at the interface (50 μm, Giemsa; × 32).

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presence of intact dura. This will serve as a transient protection until the material has fully hardened.

Before starting the first implantations, the surgeons received in-depth training and briefing by company specialists who usually were also present in the operating room during the first surgical procedures.

Patients

Epidural placement of ionomeric cement implants in patients (Würzburg/Solingen) (Table I)

1. Ionocem® (freshly mixed cement).

Calvarium, frontal bone. Freshly mixed cement was inserted in the frontal bone and calvarial regions in five patients. The implants (prepared on average from 15 1 g capsules) made direct contact with the dura. To preclude collection of cerebrospinal fluid in the space between the dura and the cement, holes were drilled over the implant surface. For added safety, protective silicon discs were temporarily placed over the intact or reconstructed dura and removed 30 minutes after hardening of the cement.

Frontal skull base/posterior wall of frontal sinus. In three patients, who had undergone tumour resection and water-tight dural closure of the intracranial cavity, large defects of the anterior cranial fossa (measuring maximally 5 × 7 cm) were covered with freshly mixed cement (using approximately 15 capsules of 1 g each). In 28 patients who had suffered extensive frontobasal injuries, ionomeric cement was implanted to stabilize the posterior wall of the frontal sinus and the anterior aspect of the ethmoid bone.

Lateral skull base. Closure of bone gaps in the lateral skull base was performed successfully in 15 cases, thus promoting stabilization of the intracranial contents after surgery for encephalocele. To obtain impermeability to fluids, the dural defect was covered extradurally with preserved dura and was further stabilized with fibrin glue. Bony deficiencies were filled with freshly mixed cement.

Petrous apex. In 19 patients, bony defects secondary to translabyrinthine resection of acoustic neuroma were sealed water-tight with muscle tissue and fibrin glue and additionally covered with preserved dura for increased safety. A disc of viscous cement placed on the adjacent bone before setting and hardening provided a mechanically stable seal over the bony gap.

2. Ionoroc® (fully matured bulk cement). In collaboration with the Neurosurgical Unit, the orbital roof was repaired in two cases using a custom-made trimmed Ionoroc® implant.

3. Ionocast® (custom-made implant). Prefabricated implants were inserted in four patients, attachment to the bone being achieved with ionomeric cement.

Results

After placement of the large calvarial and frontal bone implants prepared from freshly mixed cement (15 capsules of 1 g each), release of approximately 20 ml tissue fluid daily was required for up to five days post-operatively. Measurements (conducted by the Institut für Arbeits- und Sozialmedizin und Poliklinik für Berufskrankheiten, Erlangen) yielded maximum aluminium concentrations of 3000 µg/l. The production of tissue fluid subsided after approximately five days, and during follow-up, which in some cases ranged up to 6.5 years, the implants were found to have remained stable *in situ* without any trace of inflammation. Post-operative collection of tissue fluid after placement of the

TABLE I

EPIDURAL PLACEMENT OF IONOMERIC CEMENT IMPLANTS IN PATIENTS (N = 73)

	Number of cases	Compatibility of material	Implant rejection	Revision surgery	Revision surgery and removal	Follow-up (years)		
						Min.	Max.	Average
Freshly mixed ionomeric cement (Ionocem®)								
Calvarium/frontal bone	n = 5	+	–	–		5	6.5	5.1
Frontal skull base	n = 20	+	1 (dislocation)	–		2	6.5	3.5
Posterior wall of frontal sinus	n = 8	+	–	–		2.5	4	3.3
Lateral skull base	n = 15	+	–	1 (cholesteatoma) 1 (fluid accumulation in mastoid)	1 (infectious disease)	1	6.5	3
Petrous apex	n = 19	+	–			1	3	2
Fully matured bulk cement (Ionoroc®)								
Orbital roof	n = 2	+	–			1.8	1.8	1.8
Custom-made implant (Ionocast®)								
Calvarium/frontal bone	n = 4	+	–		1 (fracture of implant)	2	2.5	2.1

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Ionocast® implants was minimal and ceased after approximately four days.

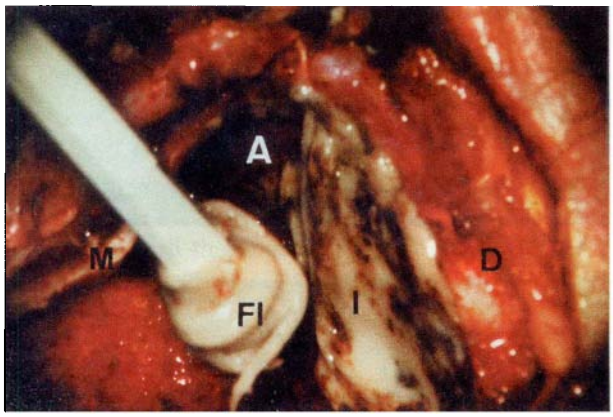
Throughout the period of follow-up of maximally more than seven years the large implants, which had been placed to stabilize the anterior cranial fossa (15 capsules of 1 g each), failed to exhibit spontaneous epithelialization on the surface facing the nose. CT scans obtained in the immediate post-operative period did not reveal accumulation of tissue fluid in the anterior cranial fossa as an indicator of possible tissue irritation. Nor did periodic screening endoscopies show any evidence of crazing of the implant surface on the nasal side as a clue to desiccation with a subsequent loss of material stability. In one patient the cement placed for repair of a small defect of the ethmoid bone (1 × 1 cm) was extruded. It was seen that formation of a dense scar had effected watertight closure of the dura.

In no case was there any evidence pointing to a dislocation of the cement implanted into the lateral skull base to promote stabilization. In one patient the development of cholesteatoma necessitated revision surgery four years post-operatively. The cement showed complete overgrowth of middle-ear mucosa and the implant could be left in place (Figure 2a–c).

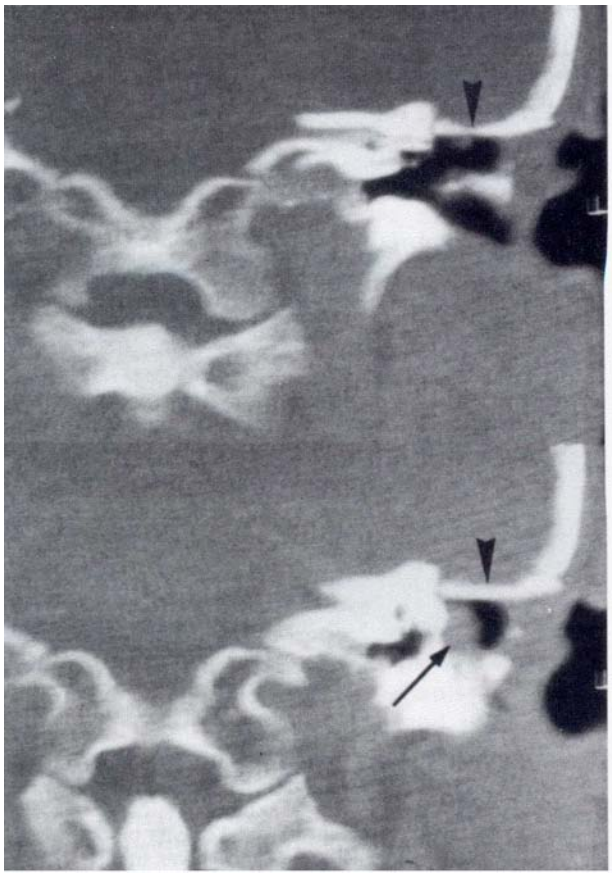
Nineteen patients who had undergone closure of the petrous apex after resection of acoustic neuroma were followed for up to five years. In none of them were there any clinical signs of CSF leaks or implant dislocation, nor did radiographic screening carried out in five cases suggest any such failure.

Ionoroc® implants (unpublished) inserted for repair of the orbital roof (Figure 3) reliably and durably precluded a transmission of cerebral pulsation to the orbital contents.

The follow-up period for the four Ionocast® implants was for a maximum of five years. Except for a minimal accumulation of tissue fluid between the implant and the skin, the post-operative course in these patients was uneventful (Figure 4a–c). In one patient a shattered implant was stabilized transiently using freshly mixed cement. After three days, however, loosening of the implant necessitated its removal. Three months later, insertion of an iliac crest transplant resulted in both functional and cosmetic rehabilitation.



(a)



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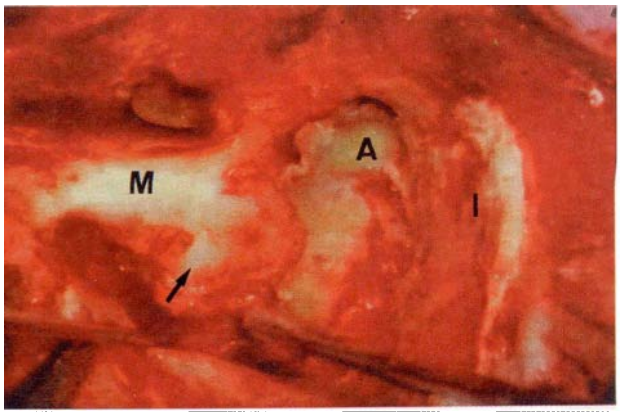

(c)

FIG. 2

Stabilization of the left lateral skull base by use of ionomeric cement (Ionocem®).

a. FI: freshly mixed, viscous ionomeric cement, I: fully-hardened cement supporting dura (D) of middle cranial fossa, M: posterior meatal wall, A: mastoid antrum
b. Coronal CT scan of petrous temporal bone (at four years post-operatively), arrow: cholesteatoma, arrowhead: intact cement plate
c. Revision procedure done four years post-operatively. A: mastoid antrum with cholesteatoma matrix. Newly formed bone apposition (arrow), I: intact cement plate sealing middle cranial fossa, M: posterior meatal wall.

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Discussion

The vulnerability of the glass ionomeric cements during the setting stage has been known for years from dental practice. A proportion of the cement-forming aluminium, calcium, fluoride and polyacrylate ions are dissolved out of the cement by aqueous solutions (Wilson and McLean, 1988). It was recognized that the longer the cement is allowed to set before being exposed to an aqueous solution – for example an electrolyte solution – the smaller the release of ions, specifically aluminium ions. Taking into account that aluminium ion concentrations of more than 2 mg/l were detectable in body fluids during the setting and hardening phase of the cement, it is appreciated that such highly elevated ionic strengths may indeed induce toxic effects involving, for example, the central nervous system (Forth, 1995). The implantation of freshly mixed cement into the tibia of primates produced a temporary increase of the serum aluminium levels to 70 ng/ml. With values returning to normal within 30 minutes post-implantation, systemic effects could be excluded (Forth, 1995). EDX analysis performed on rabbit bone and human meatal explants revealed that aluminium ions from the hardening cement had penetrated the bony implant site to a maximum depth of 20 μm. The likelihood of systemic effects could thus be ruled out (Geyer, 1992). A slightly looser structural arrangement of the calvarial dura in rabbits was the only clue to a potentially adverse effect of the cement constituents (Figure 1). As the thickness of the human dura is 10 times that of rabbits, it is safe to conclude that human dura serves a superior protective and sealing function when making contact with the glass ionomeric cement (Brown, 1995; Reusche, 1995).

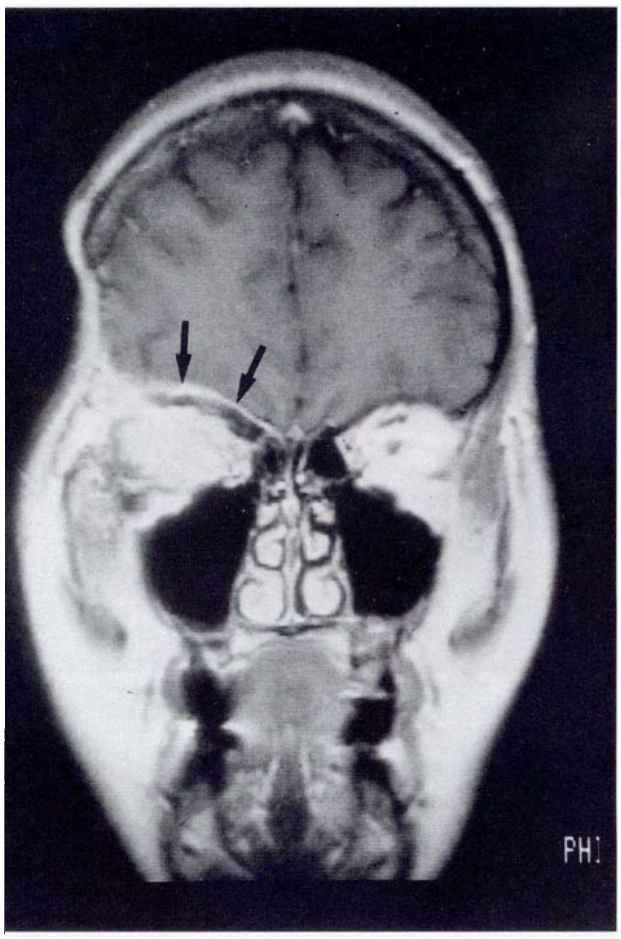
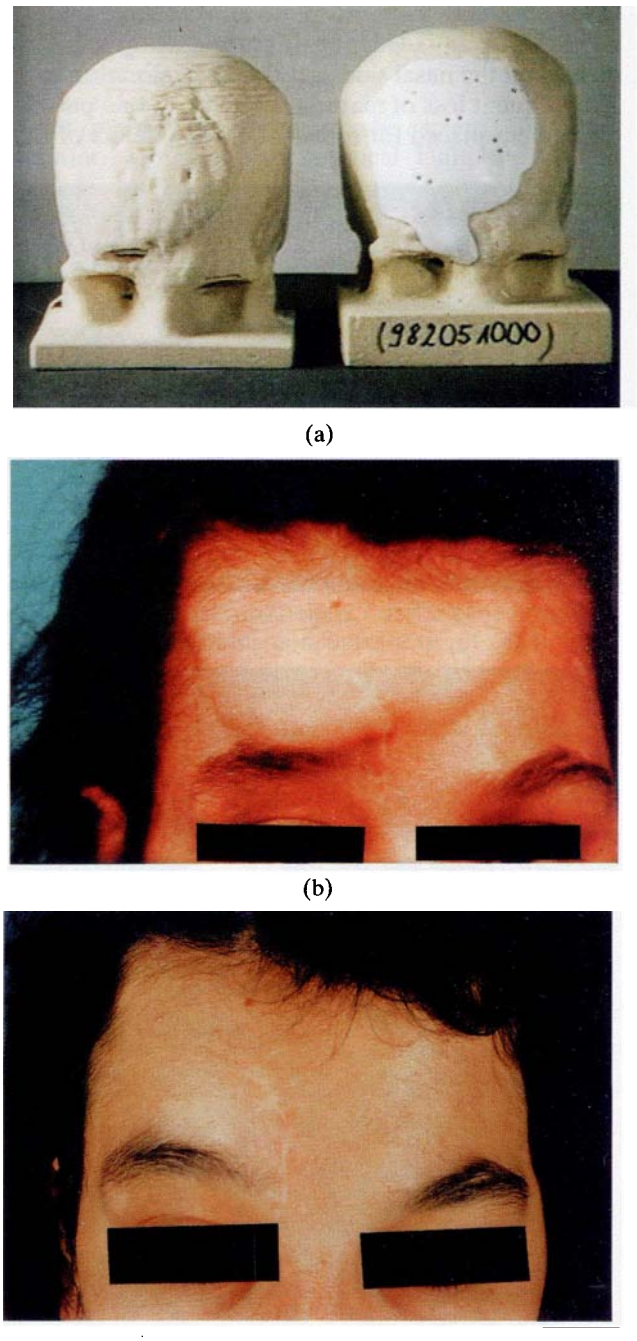


FIG. 3

Reconstruction of right orbital roof following surgery for recurrent meningioma. Magnetic resonance (MR) image in coronal projection at six months post-operatively. Arrows: Ionoroc® implant.



(a)

(b)

(c)

FIG. 4

Reconstruction of frontal bone using a custom-made implant (Ionocast®)

a. Polyurethane model of skull
left: PMMA implant placed 12 years before
right: implant fashioned from a wax model
b. pre-operative view
c. view two years post-operatively.

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Being aware of the vulnerable nature of the hardening cement, it was mandatory to provide for water-tight intracranial protection and a largely dry implant site. Therefore, when implanting the freshly mixed cement into large cranial defects involving, for example, the frontobasal and calvarial regions, the temporary placement of protective silicon discs over the intact or reconstructed human dura for added safety was standard procedure (Geyer and Behr, 1994). Collections of tissue fluid above the implant, which required puncture for approximately one week, were found to contain aluminium concentrations as high as 3000 μg/l. These levels thus were comparable to the *in vitro* results of Hantson *et al.* (1994). During surgery for defects of the petrous apex (Ramsden *et al.*, 1992; Helms and Geyer, 1994) and the anterior (Geyer and Helms, 1992) and middle cranial fossa (Fig. 2a–c) (Geyer and Helms, 1992; Helms and Geyer, 1993) it was our practice to seal the site of repair with autogenous and/or allogenic tissue before the cement placed for transplant stabilization had hardened on the adjacent bone. After implanting freshly mixed ionomeric cement into the rabbit skull cap, with the dura left intact, and subsequent irradiation with therapeutic doses at one week post-operatively, Schwab (1996) had observed diffuse brain lesions, for which a conclusive explanation is still outstanding. In the light of these experimental results, we decided not to use ionomeric cement as a bone substitute in patients in whom post-operative irradiation was contemplated.

With the availability of fully hardened cement blanks (Ionoroc®) (Thallemer and Draf, 1994) it was possible to reduce the quantity of freshly mixed cement, thus also lowering the release of aluminium ions. Using only small quantities of ionomeric cement, the bulk implants were trimmed with diamond burrs and then 'glued' on to the adjacent bone to replace, for example, an orbital roof (Figure 3).

As the ionic release in fully hardened ionomeric cements is negligibly small (Forth, 1995), it was possible to fit large, prefabricated implants (Ionocast®) into anatomically critical regions of the skull (Schmitz *et al.*, 1990), such as the frontal bone (Figure 4a–c). Only small quantities of liquid cement were needed to achieve fixation in the bony implant site, and their contact with the adjacent dura was restricted to a few localized sites (Geyer, 1994; Geyer and Behr, 1994). As with other materials (Elkins and Cameron, 1946; Swenson and Koopmann, 1984), slight fluid accumulation indicative of a foreign body-type inflammatory reaction was observed. Schmitz (1992) reported favourable functional and cosmetic results following reconstruction of cranial deficiencies in 40 patients by use of Ionocast®. Contact with the infected sinus system necessitated the removal of two implants. Overall, the surgeons using the ionomeric cement showed a distinct preference for insertion of fully hardened implants together with small amounts of freshly prepared cement, particularly for repair of larger cranial bone defects.

Our own results obtained over an uncomplicated post-operative period of up to 7.5 years (Table I) were functionally and cosmetically gratifying (Figure 4c) and agreed with the data reported by other authors (Schmitz, 1992; Weber and May, 1996). It thus appeared that ionomeric cement was well suited for application as a potential bone substitute in head and neck surgery. The experimental work of Borrmann has demonstrated that, in rabbits, direct contact of freshly mixed cement with the underlying brain has adverse effects. Further findings from animal studies (Borrmann, 1996; Schwab, 1996) and toxicological data have raised suspicion that aluminium ions eluted during setting might lead to aluminium encephalopathy (Forth, 1995). The possible sequelae of cerebral damage due to aluminium toxicity were evidenced by two deaths traceable to release of aluminium ions from the cement, during the vulnerable stage of setting, into the dura mater and attendant settling in brain tissue (Hantson *et al.*, 1994; Renard *et al.*, 1994).

The explicit recommendation of the manufacturer (1991) that a silicon disc be inserted between the cement and the intact dura during setting implied that any brain/implant contact should be strictly avoided. Given the apparently critical handling of the material and the potential risks arising in case of inadvertent or subsequent defects it was deemed advisable to abandon further epidural application. As an alternative material that might have replaced aluminium as an important constituent element was not available (Wilson and McLean, 1988), the manufacturer decided to stop further sales of ionomeric cement and closed down production in 5/95.

Conclusion

The bone substitute ionomeric cement is well suited to obtain consistently positive functional and cosmetic results in reconstructive head and neck surgery. During the critical setting stage, fluid contact may cause leaching of aluminium ions which when entering the intradural space may induce aluminium encephalopathy. For increased safety the material should, therefore, not be used in the epidural region. However, its unique qualities make it desirable to develop a comparable material suitable for use in cranial surgery. The experiences obtained with the ionomeric cement have clearly illustrated the need for a more comprehensive design of both *in vitro* and *in vivo* tests supplemented by toxicological investigations of the material. Such newly acquired knowledge would entail a substantial improvement in unequivocally defining potential uses, while at the same time pinpointing applicational limitations.

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