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Art of Replacing Craniofacial Bone Defects

Dong Kyun Rah

Abstract

In the history of medicine, many surgeons have been tried to reconstruct lost tissue and correct deformity, attempts to use implant materials have probably paralleled those involving autogenous tissue. Recently there has been an acceleration in the understanding of the requirements and potentials of implant materials caused by collaboration between material scientists, biomaterials engineers, clinicians, and clinical investigators. Alloplastic materials have become an essential part of reconstructing the function and contour of the craniofacial skeleton. Bone is a specialized form of connective tissue, which provides support, and protects vital and delicate organs. Bone is embryologically derived from mesenchymal tissue through membranous and endochondral ossification. In the clinical field, the need for bone graft has been increased due to trauma, tumor, craniosynostosis, and pure esthetic bone surgery. Various types of bone grafts have been used to repair craniofacial bone defects over many years, but the autogenous graft has many disadvantages, such as, limited donor sites, donor morbidity, pain, growth deformity and resorption. Many surgeons working in a number of centers around the world have created substitutes and simpler methods for bone replacement. As the alloplatic bone substitute has been advanced, many synthetic substitutes are replaced by bone *in vivo* over time. The ideal material should be cost effective, non-toxic, non-antigenic, non-carcinogenic, and inert in the body fluids, be easily shaped at the operating table, and maintain its desired form and consistency in situ. This article reviews several of the more commonly used materials for craniofacial reconstruction and summarizes their mechanical properties and clinical aspects.

Key Words: Biomaterial, bone, substitute

INTRODUCTION

Recently in the surgical field, the needs to bone graft have been increased due to trauma, tumor ablation, congenital absence or hypoplasia, and for pure esthetic purposes. Most surgeons have preferred to use an autogenous bone graft to reconstruct these bone defects, but autogenous bone grafts have many disadvantages, such as, a shortage of donor sites, donor morbidity, growth deformity and resorption.

Over the past 20 years, biomaterials have been developed that can function as true bone graft substitutes, rather than being inert space occupying implants. Biomaterials are sufficiently biocompatible with bone that they are bioactive to various degrees, depending on the specific preparation. The use of implantable biomaterials has become an integral part of reconstructive and esthetic craniofacial surgery. Biomaterials have demonstrated their usefulness in facial and reconstructive surgery and their ability to augment and replace portions of the craniofacial skeleton. The authors believe that if the surgeon is familiar with their exact properties, advantages and disadvantages, and how to handle these biomaterials for craniofacial reconstruction, surgeons can expand their working territories. This article focuses on materials that have been used for craniofacial reconstruction.

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Department of Plastic Surgery, Yonsei University College of Medicine, Seoul, Korea.
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Reprint address: request to Dr. D. K. Rah, Department of Plastic Surgery, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5690, Fax: 82-2-393-6947, E-mail: dkrah@yumc.yonsei.ac.kr

BONE GRAFT

Historically, the first clinical trial of a bone graft was reported in 1670 when a xenograft, canine bone, was used to repair a skull defect in a peasant in Russian. Bone graft has been used in craniofacial reconstructive surgery in a variety of ways and in a multitude of locations. Most surgeons have favorite techniques for inlay or onlay grafting. Inlay bone grafts are useful in osteotomies because they demon-

strate little resorption. Onlay bone grafts for contour and balance of craniofacial deformities show more resorption than the inlay grafts.[1] Autogenous bone grafts to fill osteotomy sites and to promote early consolidation are routinely utilized by most surgeons. Although some osteotomy sites, such as, the Le Fort I osteotomy can be left without bone graft, the space created by other types of osteotomies, such as, as required by hypotelorism correction and orbital and cranial shift, are best filled with cancellous bone graft.

The favorite donor sites for craniofacial reconstruction are the calvarium, rib, and iliac bone. It seemes that there is less resorption of cranial bone than is the case with rib or iliac bone.[2] But I believe the difference between the resorption rates of cranial and rib or iliac bone comes from the different proportions

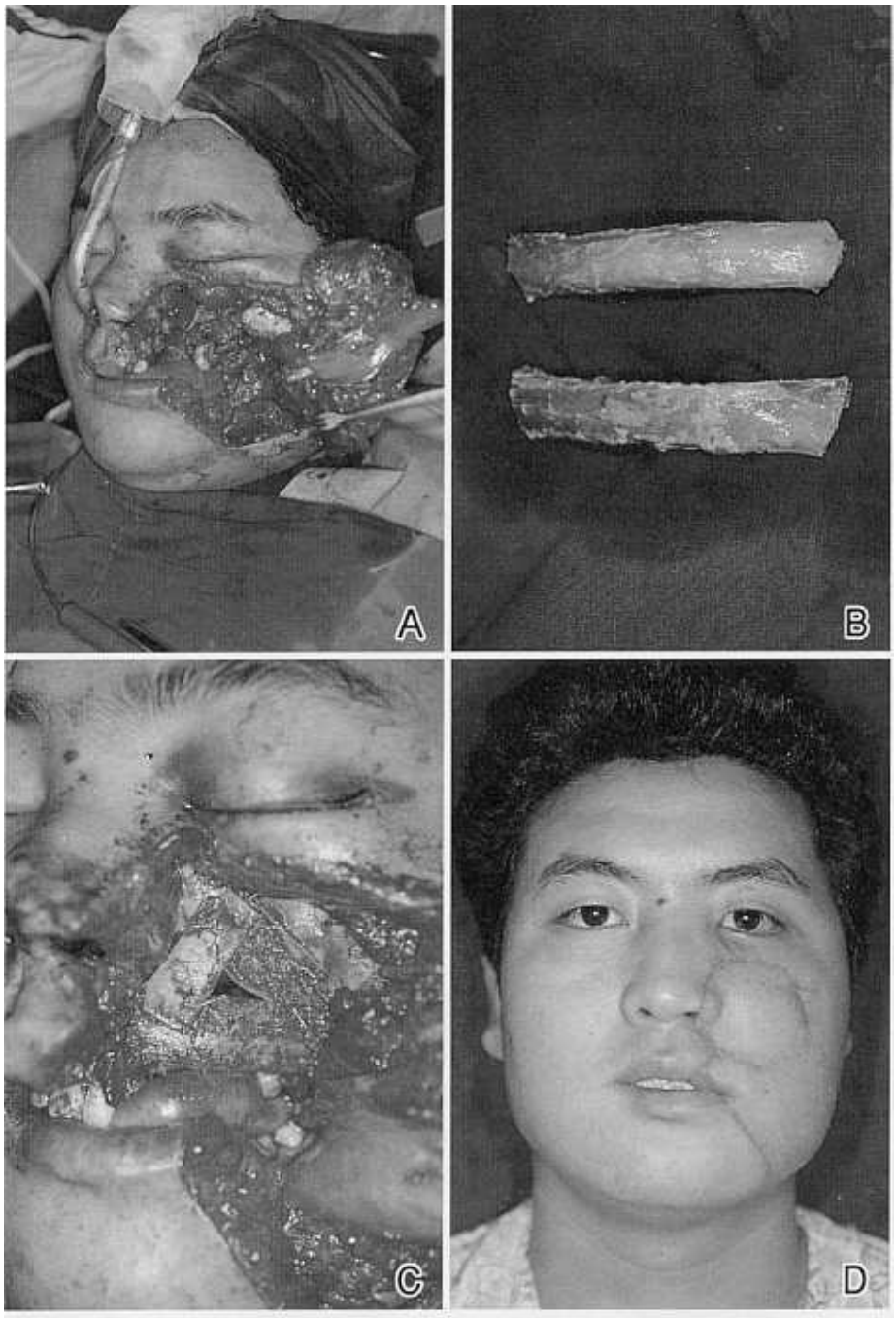

Fig. 1. Versality of split rib bone graft. (A) Extensive maxillofacial trauma with a large amount of bone loss. (B) Split rib bone. (C) Appearance of maxillary bone reconstruction using split rib bone. (D) A post-operative acceptable result.

of the cortical and canellous components. Cranial bone has some disadvantages, such as, technically difficulties in manipulation, brittleness, and limitations in the amount of cancellous bone. As for the rib graft, because of the contour of the split rib, the ease of bending, and its relatively thinness, it would seem to be one of the ideal materials for augmenting and contouring the restoration of the craniofacial region (Fig. 1), however, complications of the donor site are common, 12% involve pneumothorax. The iliac bone is adequate when a large bone segment involving cancellous bone is needed, but persistent pain is a common problem. A split thickness calvarial autogenous graft is the material of choice craniofacial reconstruction but children under the age of 6 years may need another bone source due to lack of the skull thickness.

DEMINERALIZED BONE

Demineralized bone can been used for craniofacial defects with minimal tissue reaction and remarkable little osteoclastic activity. Eight to twelve weeks after the implantation of demineralized bone, new bone growth was noticed in histologic evaluations. More bone and endothelial growth was noticed on the dural aspect of the calvaria and its continuity with the implant surface.[3] Fragmentation of the implanted demineralized bone was observed in the presence of new bone formation at 12 weeks postoperatively. It is believed that hydrolytic enzyme was the main causative factor of this degradation, as the fragmentation occurred in the absence of multinuclear cells.[4]

No marked difference was noticed between demineralized calvarial and tibial bone. In clinical trial, demineralized bone processes with micro perforation were observed, these are believed to be centers of new bone formation, and these microperforations may enhance osteoinduction within the implant.[5] Histologic evaluation 4 years after implantation, revealed that large areas of nonvital bone were lacking osteocytes in the bone lacunae and osteoblasts on the

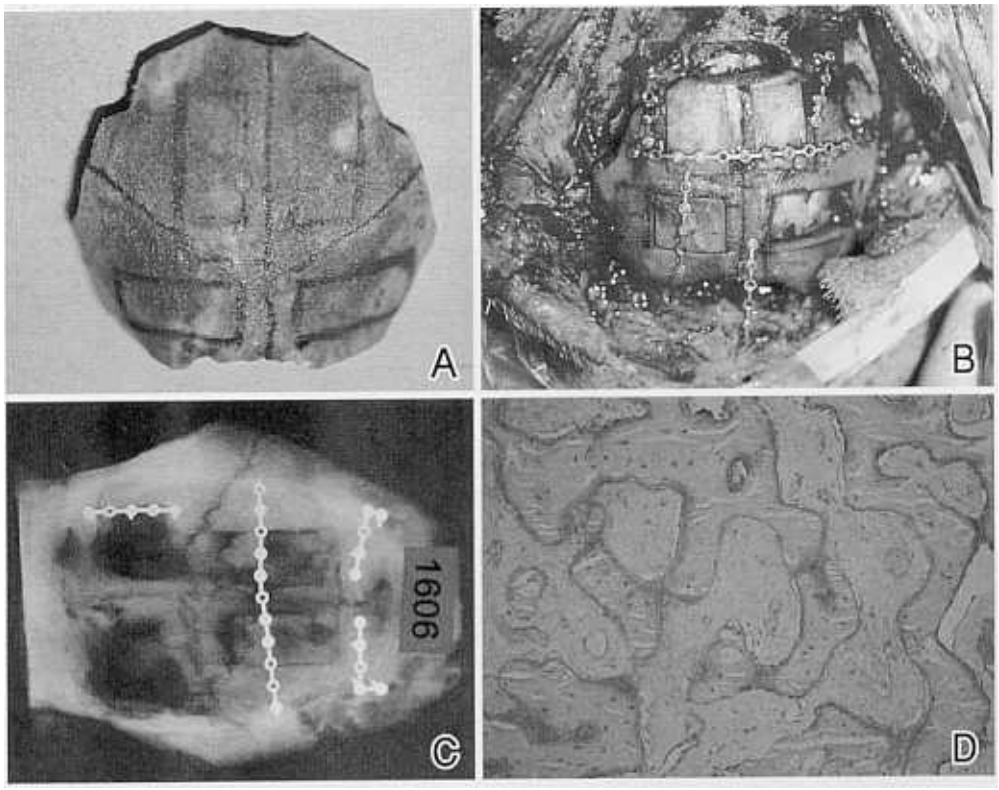

Fig. 2. Experience of the effects of demineralized pig calvarial bone on bone regeneration. (A) Cranium of young pig before craniectomy line was drawn on the skull. (B) The demineralized cranial bones were repositioned and fixed by miniplates. (C, D) Plane X-ray and histologic evaluation show evidence of bone regeneration after 12 weeks.

surface. In several areas there appeared to be fragmentation of the autogenous bone matrix. However, active resorption, osteoclasts, and inflammation or fibrous changes were not observed. Several areas contiguous with nonvital bone showed evidence of transformation into living bone and remodeling.[6] The advantages of using demineralized bone are that is pliable, easy to shape to fit the specific craniofacial defect, and in limitless supply, and that it is free from donor morbidity, which is particularly useful in pediatric patients.

The authors had experience of an animal study using young pig calvarium to evaluate whether decalcified calvarial bone has osteoconduction and osteoinduction capacity. The study revealed that decalcified cranial bone presents active osteogenesis on histologic and radiologic evaluation (Fig. 2). Properly prepared demineralized bone is a safe material for craniofacial reconstruction that eliminates the need for a second operative site to harvest a bone graft.[7]

The Boston research group has developed demineralized bone paste over many years.[8] This material is composed of living osteoblasts derived from treated homograft materials, which theoretically provide osteogenic cells capable of inducing osteogenisis. Theoretically, demineralized bone paste can be used alone or in combination with biomaterials such as hydroxyapatite. This procedure may have advantages, as when used in combination it could provide a structural supporting matrix with cells that have osteogenic ability.

HYDROXYAPATITE

Hydroxyapatite (HA) forms the principal mineral component of bone and constitutes 60% of the calcified human skeleton. It has been produced synthetically since 1970s and used clinically for the last 20 years.[9] Certain marine corals have a structure that is similar to that of human bone. All forms of HA have excellent biocompatibility and when placed in direct contact with viable bone show osteoconduction and osteointegration. There is no evidence of osteoinductive in the absence of inductive growth factors.[10] HA is available in two forms, one is ceramic and the other nonceramic. Until recently, all forms of HA in clinical use were ceramic preparations that they were very resistant to absorption *in vivo*. Non ceramic HA in not sintered after the HA crystals are formed and is, therefore, more absorbable *in vivo* than the ceramics. Significantly, non ceramic HA can also be formed into cements, whereas ceramic HA cannot.

Ceramic hydroxyapatite: Ceramic hydroxyapatite is synthesized in crystal form at low pH, and then heated (sintered) at 700 to 1,300^{0}C to form a solid mass of HA. Ceramic HA is available in two forms; dense and porous.

The dense form is entirely synthetic, it has no pores and can be fabricated into blocks or granules, which are difficult to shape and do not permit tissue ingrowth. However, granules have greater contour adaptability than the solid blocks but no intrinsic structural integrity and do not become mechanically stable until surrounded by fibro-osseous tissue. Dense HA granules are difficult to contain within the desired site of implantation, and there is a possibility of migration to unwanted areas after several month or years.[11]

Porous HA can be produced synthetically (Apacerm, Asahi Optical Co, Ltd, Tokyo, Japan), or it can be based on the skeletons of marine coral (Interpore, Interpore International, Irvine, CA, USA). The porous pattern of this implant material is based on marine coral of the genus Porites. The calcium carbonate skeleton of the coral is chemically converted to HA, and the original porous structure of the coral retained. Porous ceramic granules appear to be less prone to migration over time.[12,13] In an attempt to solve these problems of granule containment and poor structural stability, HA granules can been combined with resorbable carrier compounds. The significant advantage of porous HA is that it is ingrown by fibrous-osseous tissue and becomes fixed to the surrounding bone within several weeks. Bone growth into the implant material was demonstrated after the repair of both long bone and cranial defects. When fibrous-osseous tissue ingrowth is complete, the implant consists of approximately 17% bone, 43% soft tissue, and 40% of residual HA implant.[14] Porous HA is available in block form but this is difficult to shape because it fractures easily, and it cannot be used for stress bearing application in the head and neck, so it is most appropriate as an onlay graft or spacer material in facial osteotomies.[15] Because it is fragile and difficult to contour, its applications have been largely limited to dentistry and maxillofacial surgery. Experience with porous HA for alveolar ridge

augmentation has confirmed that the material is resistant to infection after fibro-osseous tissue ingrowth, but that it can became exposed if the overlying soft tissue is inadequate.[16,17]

Porous granules appear to be less prone to migration than the dense granular HA. Porous ceramic HA is very versatile, in that it can be chemically combined with variable biomaterials to alter its physical properties, and it can also be used as an excellent biologically active material carrier of bioactive species, such as, bone growth protein, which increases the ingrowth of bone into the pores.[18-20]

Nonceramic hydroxyapatite: Tetracalcium phosphate cement (HA cement) is the only calcium phosphate cement that sets into a stable shape and converts *in vivo* to pure HA. It is produced by direct crystallization of HA at physiologic pH and temperature and does not require heating to form a structurally stable implant.[21] The dry cement is composed of tetracalcium phosphate and dicalcium phosphate, and it sets in approximately 15 minutes and converts to HA within 4 hours.[22] After conversion of HA, it is no longer water-soluble and it is slowly replaced by bone over time, without losing volume or changing shape in certain situations. In animal studies, 35% of the implanted HA was replaced by fibro-osseous tissue and bone accounted for approximately 75% of this fibro-osseous tissue after 12 months implantation. Four years after the experiment, no contour change was observed in the reconstructed regions. Even in human clinical trials, the cement was found to be functionally nonresorbable over 42 months on the basis of serial CT scans and by direct intraoperative inspections during secondary operations.[23,24] These biologically active forms of HA cement are more useful in situations that are not contour sensitive or in which bone replacement of the implant is necessary, such as, in the repair of cerebrospinal fluid (CSF) leaks, translabyrinthine and trans-sphenoidal defect repairs, and in orthopedic applications and pediatric craniofacial surgery. HA cement is safe for use in the growing skull and was observed to have no adverse affects on development.[25] HA has no toxic reactions, does not increase serum calcium levels, and is not associated with structural failures. Even though over 75% of the implant was in contact with the paranasal sinus or mastoid the observed infection rate was only 4%. Until conversion occurs, excess blood and serous fluid must be prevented from collecting adjacent to the implant. If an aqueous collection occurs, the cement sets in particulate form and a portion of the implant can be resorbed with a loss of volume over time.[26,27] However, HA cement has disadvantages, such as, a wide periosteal envelope, prolonged closed drainage of the surgical field, and granules settle with gravity during the process, which could produce bulging under soft tissue.[28]

Injectable Hydroxyapatite: After mixing HA granules (150−230-μm) with fibrocollagen, and autogenous blood to form a paste, it can be injected into the subperiosteal pocket. Although it does not osteointegrate it does become firmly fixed by fibrous tissue ingrowth. It can be use to augment malar bone, premaxillar, nasal dorsum, and grabella, and larger volumes of HA were used to fill craniofacial defects in children. Overall incidence of infection was about 1%, and in pediatric cases 3%.

Collagraft Bone graft matrix, which has recently become available for the treatment of long bone fractures or traumatic bone defects anywhere in the human skeleton, is produced jointly by the Collagen Corporation (Palo Alto, CA, USA) and the Zimmer Incorporation (Warsaw, IN, USA). It consists of purified type I bovine dermal fibrillar collagen (PFC) and a mixture of 65% ceramic HA and 35% of beta tricalcium phosphate (TCP) granules.[29] The HA-TCP granules and the PFC are packed separately, and mixed on the operating table to form a granular nonsetting paste. Autogenous bone marrow harvested from the fracture site or aspirated from the iliac bone can be added to the mixture. The Collagraft provides a successful environment for bone ingrowth and rapid vascularization, and the addition of autogenous bone marrow gives more osteoinductive and osteogenic properties to the mixture. The infection rate is about 5%, but by mixing with autogenous marrow, the incidence decreases to 2.5%. In long bone fractures, maintaining stability by external or internal fixation is necessary and the total amount of mixture should be no more than 30 ml. The use of this material for craniofacial osseous defects or esthetic augmentation is controversial, because there would be some contour change and volume loss due to the resorption of the collagen and tricalcium phosphate components, which amount to 35 to 40% of the total mixture. There is also the potential for implant deformation until fibro-osseous tissue ingrows, because this material

does not set like a true cement.

POLYDIMETHYLSILAXANE

Polydimethylsilaxane (Silicone) is the one of the most widely used biomaterials in the surgical field because of its soft tissue compatibility, it is easy to contour, resistant to the physiologic environment and has a wide range of mechanical properties. Silicone can be manufactured with consistencies ranging from liquid to a hard solid by changing the length of polymer chain.[30] The manufacturing process plays an important role in the purity and integrity of the silicone.

Surgeons can use silicone as a custom mold by mixing with the hardening agent at room temperature the vulcanized (RTV) form of the material can be produced, either before implantation or in situ. The natural host response to the smooth surface of silicone is fibrous encapsulation, so if the soft tissue coverage is thin, unstable, or under tension the implant may be extruded. Injections of large amounts of liquid silicone for purposes, such as breast augmentation may induce systemic toxicity. When a silicone block is used for craniofacial augmentation, surgeons should be careful of silicone migration and bone erosion. Two cases of granulomatous hepatitis, confirmed by liver biopsy, and one case of lethal pulmonary edema, after the inadvertent intravascular injection of liquid silicone are documented.[31] It is controversial that silicone breast implants may cause connective tissue disease. Gabriel (1994) reported that breast implants may induce connective tissue disease, but the Sanchez-Guerrero (1995) study found no such increased risk after silicone breast augmentation.[32,33]

POLYETHYLENE

Polyethylene, is available in a porous form is called Medpor (Porex Surgical, Inc College Park, GA), it has a simple linear carbon chain structure and is one of the most commonly used biomaterials over the past 25 years. It is the base polymer for other materials such as polypropylene and polytetrafluoroethylene, and it elicits a minimal tissue reaction when manufactured in its high-density, high molecular weight form. It serves as the reference standard as an inert substance in terms of tissue reaction to biomaterials.

The porous structure of polyethylene provides ingrowth of soft tissue after 1 week and bone after 3 weeks. Its porosity makes it easy to carve, but difficult to remove.[34] When a skull base defect due to tumor ablation or craniofacial trauma is reconstructed using porous polyethylene with titanium, excellent craniofacial symmetry and stability are achievable.[35] There are many commercially available implant forms, such as, malar, chin, mandible, nasal reconstruction, and orbital implant. Flexblock, porous polyethylene is ideal suited for the repair of small to medium sized cranial defects.[36] Augmentation of the lower maxilla with polyethylene provides a similar cosmetic effect to that obtained with autogenous materials. This simplifies the correction of midface deformities, such as, those due to Binder's syndrome and dish face deformity, which are frequently associated with surgically corrected cleft and severe midfacial fracture. During operation, polyethylene implants should not be placed on fabric or come into contact with the patients skin because the implants tend to pick up deris. Host response to polyethylene is very variable but complications are rare. Porous polyethylene has advantages over autogenous bone, because it is not susceptible to subsequent change in contour secondary to bone resorption. We conclude that porous polyethylene has been a safe and effective bone substitute for contouring the facial skeleton.

METHYL METHACRYLATE

Methyl methacrylate has been used as a bone cement, and has been proven to be an acceptable space filler with no resorption, and it is also stronger than the adjacent skull bone by compression and torsion testing. Methyl methacrylate has two different components, mixing powder polymer and a liquid monomer. The chemical reaction is exothermic and the associated toxicity is related to the free monomer.[37] The free monomer has direct vascular effects in experimental animals. During total hip replacement with freshly mixed methyl methacrylate, patients have suffered acute hypotension that may progress to cardiovascular collapse and death.[38,39] However, there is no case report of cardiovascular depression in craniofacial surgery. Methyl methacrylate has been used to reconstruct traumatic skull defect for many years. The free methyl methacrylate

monomer may also cause asthmatic reactions.[40] Even the cost of methyl methacrylate is low and the resultant shape is predictable, in craniofacial surgery methyl methacrylate is not readily resistant to infection and trauma and may become exposed as a late complication. Manson and colleagues reviewed routine cranioplasty and found that the incidence of infection was in the range of 5%. They found that rarely patients with isolated cranioplasty experienced infection, but the infection rate was increased in those patients that had undergone simultaneous reconstruction involving the orbital wall or nose. In these patients the infection rate was about 23%. All of these patients had a previous infection and the subsequent reconstruction was done within 1 year.[41] As methyl methacrylate is not filled by host tissue, it would not seem to be adequate material for reconstructing the craniofacial bone in the growing child. When the esthetic requirement is high, methyl methacrylate delivers a predictable shape on a permanent basis without subsequent resorption. Methyl methacrylate can be used in the adult with good soft tissue covering and no previous infection.

PROPLAST

Proplast (Vitek, Houston, Texas, USA) is a composite material consisting of polytetrafluorethylene combined with either carbon fibers (Proplast I) or aluminum oxide (Proplast II). As Proplast has porosity and offers the relatively inert reaction with the carbon particle, particularly when mixed with Teflon, it seems to have theoretic advantages. Although the clinical results with Proplast are not superior to hydroxyapatite, it is better than silastic, methyl methacrylate, and other solid materials. It is currently available as Porplast II, which is white, and thus offers certain esthetic advantages in facial contour reconstruction over the old Proplast I, which is black in color. When Proplast is used for malar or maxillary augmentation, the complication rate is relatively low, but the complication rate is increased if Proplast is used for mandibular augmentation.[42]

The Proplast implant contains some growing bone, but in this situation the material was disrupted because it was not strong enough to withstand the force of the invading fibrous and osseous tissues. When Proplast is used for malar augmentation, the complication rate was; infection (4.1%), displacement (3.5%), and implant removal (7.6%). It is a porous implant material that is no longer manufactured in the United States.

POLYTETRAFLUOROETHYLENE

Polytetrafluoroethylene (Gore-tex: W.L. Gore, Flagstaff, Ariz) has a microstructure composed of solid nodes and fibrils. Host cell migration and collagen deposition can occur between the fibrils. The current Gore-Tex product sold for facial implant is known as subcutaneous augmentation material (SAM). The advantages of Gore-Tex are that it is very pliable and evokes a minimal foreign body response with the absence of nodular scarring. Its disadvantages are that

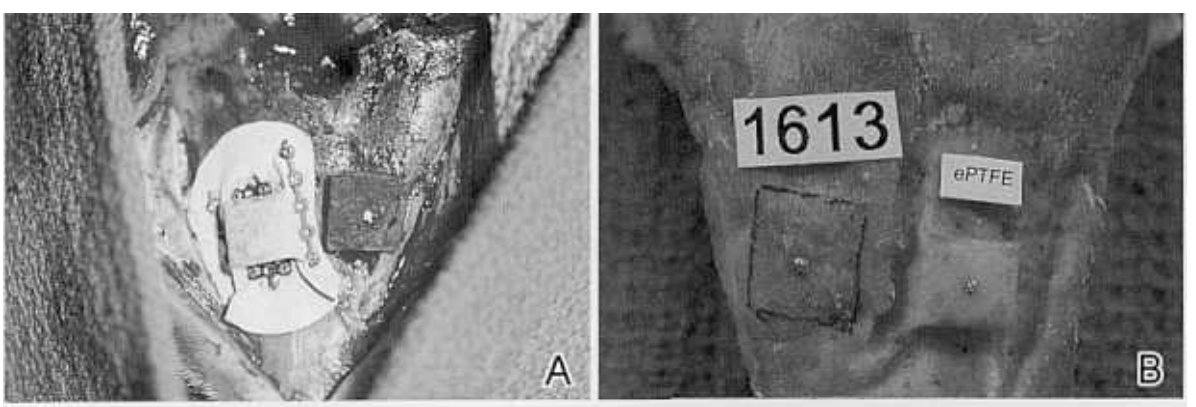

Fig. 3. Experience of the prevention of bone absorption in the pig skull using Gore-tex. (A) Experimental onlay cranial bone was covered by Gore-tex. (B) Gore-tex covered cranial onlay bone graft to keep the contour, but the control side was absorbed almost completely after 8 weeks.

is not rigid enough to be carved. To solve this problems, the SAM implant was reinforced with layers of fluorinated ethylene propylene (FEP) which has the advantages of; active collagen ingrowth, it is rigid enough to be carved, remains soft, and it easy to remove. However, when placed in subcutaneous tissue in contact with the dermis it will extrude. Gore-Tex can be used for 'guided tissue regeneration', which is frequently used for dentolveolar bone augmentation. The author has experience that polytetrafluoroethylene prevents bone absorption in pig cranium, when the cranial bone onlay graft was covered by polytetrafluoroethylene (Fig. 3). When the efficacy of expanded polytetrafluorethylene (ePTFE) sheets to increase bone regeneration and remodeling in cranial defects in a rabbit model was evaluated by mechanical testing, e-PTFE was found to improve the cranial defects. The porosity of the e-PTFE provides a stable scaffold for the migration of tissue regenerating cells, which may be preferentially localized near the cranial suture lines.[43] The overall complication rate is about 1%, with 95% patient satisfaction.

DEGRADABLE BONE SUBSTITUTE

An ideal bone substitute is a biomaterial, that has osteoconductive and inductive properties and be replaced by regenerating host bone.[44] To achieve this purpose, growth factor such as bone morphogenic protein (BMP), platelet derived growth factor (PDGF), or transforming growth factor (TGF) should be combined with other bioactive materials. The author developed a bone substitute, which was composed of poly lactic acid, hydroxyapatite and atelocollagen. After making two critical bone defects (diameter: 1 cm) on the rabbit cranium, the defects were replaced by a developed bone substitute. The replacement of bone defect by host regenerating bone was confirmed by plane X-ray, magnetic resonance imaging (MRI)

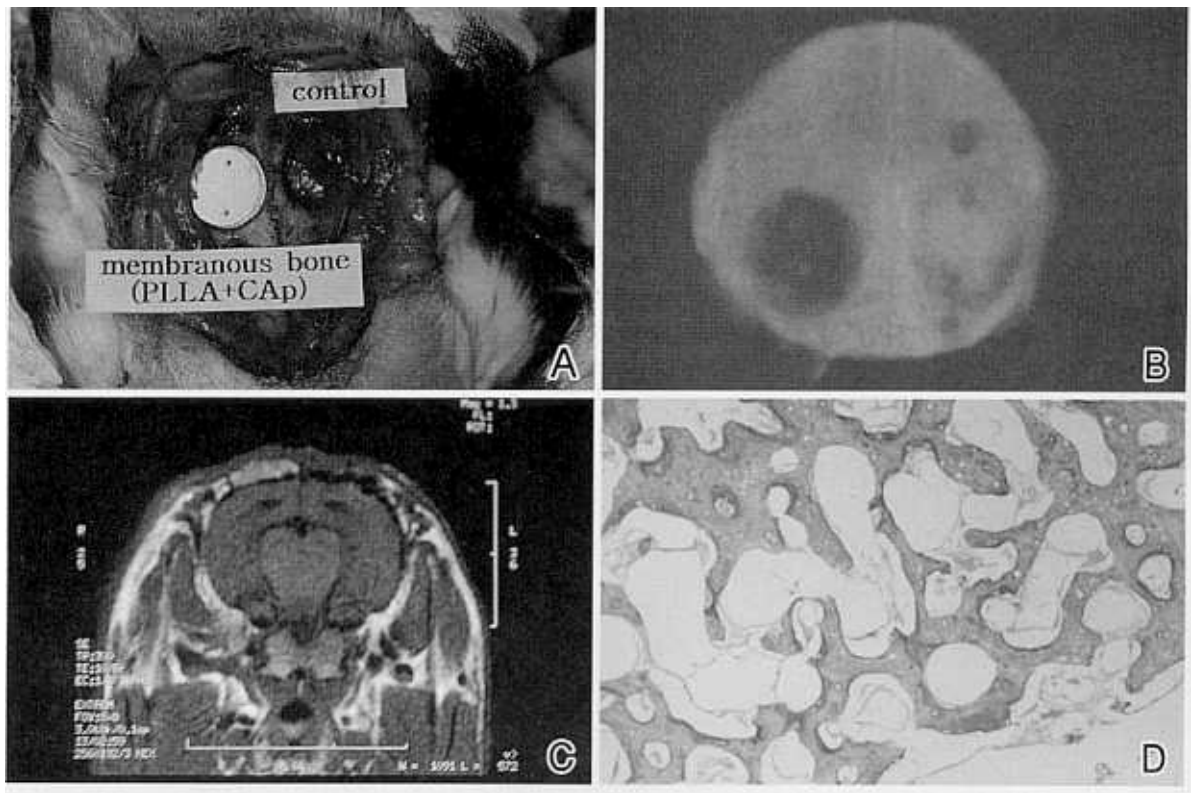

Fig 4. Experimental results of the developed degradable bone substitute. (A) After making critical bone defects on both sides of the rabbit cranium, the defects were replaced with the new degradable bone substitute. (B) The plane X-ray suggests more bone formation on the experimental site than the control site after 6 weeks. (C) The MRI suggests more bone formation on the experimental site than the control site after 6 weeks. (D) The histologic evaluation shows regenerated matured bone after 12 weeks.

and histologic evaluation (Fig. 4).

CONCLUSION

The craniofacial region presents a unique challenge for implantable biomaterials because the pull of the craniofacial muscles produces variable loading in different regions. In addition, craniofacial skin loses elasticity with age and develops subcutaneous tissue sags.

Even though surgeons are familiar with the use autogenous bone grafts for craniofacial reconstruction, the usage of alloplastic bone substitutes has increased continuously, because autogenous bone is difficult to harvest, time consuming, causes significant donor morbidity, and bone resorption, but the most important thing is that the biocompatibility of current alloplastic materials are improving.

Many articles report that some biomaterials present higher complication rate than autogenous tissue. But it is difficult to attribute many of the complication rates solely to the implant material itself. Many factors, such as, surgical technique, host response and potential toxicity of the implant itself may influence such complication rates. For example, the variation of antibiotic regimen, varying attention to aseptic techniques, differences in the normal flora, susceptibility to antibiotics, and variations in the method of mechanical fixation can influence infection rates for a given material and site

In the craniofacial bone reconstruction field, the author believes that an universal biomaterial, which has osteoinduction and osteoconduction properties and which satisfies the ideal implant characteristics will be developed in near the future.

REFERENCES

1. Salyer KE, Taylor DP. Bone graft in craniofacial surgery. Clin Plast Surg 1987;14:27-35.
2. Zins JE, Whitaker LA. Membranous versus enchondral bone: Implications for craniofacial reconstruction. Plast Reconstr Surg 1983;72:778-85.
3. Chow KM, Rabie AB. Vascular endothelial growth pattern of enchondral bone graft in the presence of deminerlized intramembranous bone matrix-quantitative analysis. Cleft Palate Craniofac J 2000;37:385-94.
4. Salyer KE, Bardach J, Menendes JL. Cranioplasty in the growing canine skull using demineralized perforated bone. Plast Reconstr Surg 1995;96:770-9.
5. Salyer KE, Gendler E, Menendez JL, Simon TR, Kelly KM, Bardach J. Demineralized perferated bone implants in craniofacial Surgry. J Craniofac Surg 1992;3:55-62.
6. Hubli EH, Salyer KE, Gendler E. Demineralized bone bandeau in patient with kleeblattschadel skull deformity. Ann Plast Surg 1998;41:81-5.
7. Neigel JM, Ruzicka PO. Use of demineralized bone implant in orbital and craniofacial reconstruction and a review of the literature. Ophthal Plast Reconstr Surg 1996;12:108-20.
8. Glowacki J, Kaban CB, Murray JE. Application of the biological principle of induced osteogenesis for craniofacial defect. Lancet 1981;1:959-62.
9. Jarcho M. Calcium phosphate ceramics as hard tissue prosthesis. Clin Orthop 1981;157:259-78.
10. Ono I, Takheiko O, Murata M. A study on bone induction in hydroxyapatite combined with bone morphogenic protein. Plast Reconstr Surg 1992;90:870-9.
11. Harvey WK, Pincock JL, Matukas VJ, Lemons JE. Evaluation of a subcutaneous implanted hydroxyapatite-Avitene mixture in rabbits. J Oral Maxillofac Surg 1985;43:277-80.
12. Byrd HS, Hobar PC, Shewmake K. Augmentation of the craniofacial skeleton with porous hydroxyapatite granules. Plast Reconstr Surg 1993;91:15-21.
13. Rawlings CE, Wilkins RH, Hanker JS. Evaluation in cats of a new material for cranioplasty: A composite of plaster of Paris and hydroxyapatite. J Neurosurg 1988;69:269-77.
14. Holmes RE, Hagler HK. Porous hydroxyapatite as a bone graft substitute in cranial reconstruction: A histometric study. Plast Reconstr Surg 1988;81:662-71.
15. Salyer KE, Hall CD. Porous hydroxyapatite as an onlay graft substitute for maxillofacial surgery. Plast Reconstr Surg 1989;84:236-44.
16. Piecuch JF, Fedorka NJ. Result of soft tissue surgery over implant replamineform hydroxyapatite. J Oral Maxillofac Surg 1983;41:801-6.
17. Block MS, Kent JN, Ardoin RC, Davenport W. Mandibular augmentation in dogs with hydroxyapatite combine with demineralized bone. J Oral Maxillofac Surg 1987; 45:414-20.
18. Ono I, Takheiko O, Murata M. A study on bone induction in hydroxyapatite combined with bone morphogenic protein. Plast Reconstr Surg 1992;90:870-9.
19. Ripamonti U, Shu-Shan M, Reddi AH. Induction of bone in composite of osteogenin and porous hydroxyapatite in baboons. Plast Reconstr Surg 1992;89:731-9.
20. Grenga TE, Zins JE, Bauer TW. The rate of vascularization of coralline hydroxyapatite. Plast Reconstr Surg 1989;84:245-9.
21. Chow LC, Takagi S, Costantino PD, Friedman CD. Self setting calcium phosphate cements. Mater Res Soc Symp Proc 1991;179:3-24.
22. Jackson IT, Yavuzer R. Hydroxyapatite cement: an alternative for craniofacial skeletal contour refinements. Br J Plast Surg 2000;53:24-9.

23. Friedman CF, Costantino PD, Jones K. Hydroxyapatite cement, part II: Obliteration and reconstruction of the cat frontal sinus. Arch Otolaryngol Head Neck Surg 1991; 117:385-9.
24. Shindo ML, Costantino PD, Friedman CD, Chow LC. Facial skeleton augmentation using hydroxyapatite cement. Arch Otolaryngol Head Neck Surg 1993;119:185-90.
25. Lykins CL, Friedman CD, Costanino PD, Horioglu R. Hydroxyapatite cement in craniofacial skeletal reconstruction and its effects on the developing craniofacial skeleton. Arch Otolaryngol Head Neck Surg 1998;124:153-9.
26. Costantino PD, Chaplin JM, Wolpoe ME, Catalano PJ, Sen C. Application of fast setting hydroxyapatite cement: cranioplasty. Otolayngol Head Neck Surg 2000;123:409-512.
27. Maniker A, Cantrell S, Vaicys C. Failure of hydroxyapatite cement of set in repair of a cranial defect: case report. Neurosurgery 1998;43:953-4.
28. Burstein FD, Cohen SR, Hudgins R, Boydston W, Simms C. The use of hydroxyapatite cement in secondary craniofacial reconstruction. Plast Reconstr Surg 1999;104:1270-5.
29. Cornell CN. Initial clinical experience with use of Collagraft as a bone graft substitute. Tech Orthoped 1992;7: 55-63.
30. Holmes RE. Alloplastic implants in MacCarthy JG: Plastic Surgery, 1st ed. New York: W.B. Saunders; 1990. p.698.
31. Ellenbogen R, Rubin L. Injectable fluid sil icone theraphy: Human morbidity and mortality. JAMA 1975;234:308-9.
32. Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LT. Risk of connective tissue disease and other disease after breast Implantation. N Engl J Med 1997; 336:719-25.
33. Sanchez-Guerrero J, Colditz GA, Karlson E, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective tissue disease and symptom. N Engl J Med 1995;332:1666-70.
34. Wellisz T. Clinical experience with the medpor porous polyethylene implant. Aesthetic Plast Surg 1993;17:339-44.
35. Janecka IP. New Reconstructive technology in skull base surgery: role of titanium and porous polyethylene. Arch Otolaryngol Head Neck Surg 2000;126:396-401.
36. Welliz T, Dougherty W, Gross J. Craniofacial application for the Medpor porous polyethylene flexblock implant. J Craniofac Surg 1992;3:101-7.
37. Stelnicki EJ, Ousterhout DK. Prevention of thermal injury induced by the application of polymethylmethacrylate to the calvarium. J Craniofac Surg 1996;7:192-5.
38. Kepes ER, Underwood PS, Becsey L. Intraoperative death associated with acrylic bone cement: report of two cased. JAMA 1972;222:576-7.
39. Milne IS. Hazards of acrylic bone cement: A report of 2 cases. Anesthesia 1973;28:538-43.
40. Picking CA, Bainbridge D, Birtwistle IH, Griffiths DL. Occupational asthma due to methyl metharylate in an orthopaedic theatre sister. Br Med J 1986;292:1362-3.
41. Manson PN, Crawley WA, Hoopes JE. Frontal cranioplasty: risk factors and choice of cranial vault reconstructive materials. Plast Reconstr Surg 1986;7:888-900.
42. Freeman BS, Weimer DR. Clinical uses of proplast: Expectations and result. In: Rubin LR, editor. Biomaterals in Reconstructive Surgery. St Louis: CV Mosby; 1983. p.494-515.
43. Valdevit A, Turegun M, Kambic H, Siemionow M, Zins J. Crainal defect repair using e-PTFE: part I. Evaluation of bone stiffness. J Biomed Mater Res 2000;53:62-6.
44. Suh H, Lee C. Biodegradable ceramic-collagen composite implanted in rabbit tibia. ASAIO J 1995;41:652-6.