Biomaterials in Craniomaxillofacial Reconstruction: Past, Present, and Future

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Abstract: Deformity and tissue loss involving the craniomaxillofacial region occurs frequently as a result of trauma, oncologic resection, or a congenital malformation. In order to maximize the patient's quality of life, reconstruction of the craniomaxillofacial skeleton must seek to restore aesthetics as well as function. Advances in diagnostic technology, surgical technique, instrumentation, and innovative biomaterials used have transformed the way reconstructive surgeons approach their patients' needs. From the advent of alloplastic reconstruction, surgeons have sought the ideal material for use in craniomaxillofacial surgery. Substances such as metals, ceramics, glasses, and more recently resorbable polymers and bioactive materials have all been utilized.

While autologous bone has remained widely-favored and the gold standard, synthetic alternatives remain a necessity when autologous reconstruction is not readily available. Today, alloplastic material, autografting via microvascular tissue transfer, hormone and growth factor-induced bone formation, and computer-aided design and manufacturing of biocompatible implants represent only a fraction of a wide range of options used in the reconstruction of the craniomaxillofacial skeleton. We present a brief review of the materials used in the repair of deformities of the craniomaxillofacial skeleton as well as a look into the potential future direction of the field.

Key Words: Alloplastic, bone, bone cement, craniofacial, cranioplasty, hard tissue replacement, internal fixation, polyetheretherketone, polyethylene, polymer, polymethyl methacrylate, reconstruction, surgery, tissue, tissue engineering, titanium, vitallium

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Deformity and tissue loss involving the craniomaxillofacial region occurs frequently as a result of trauma, oncologic resection, or a congenital malformation. To maximize the patient's quality of life, reconstruction of the craniomaxillofacial skeleton must seek to restore aesthetic form as well as function. Advances in diagnostic technology, surgical technique, instrumentation, and innovative biomaterials used have transformed the way reconstructive surgeons approach their patients' needs. From the advent of alloplastic reconstruction, surgeons have sought the ideal material for use in craniomaxillofacial surgery. Substances such as metals, ceramics, plastics, and more recently resorbable polymers and bioactive materials have all been utilized. While autologous bone has remained widely-favored and the gold standard, synthetic alternatives remain a necessity when autologous reconstruction is not readily available. Today, alloplastic material, autografting via microvascular tissue transfer, hormone and growth factor-induced bone formation, and computer-aided design and manufacturing of biocompatible implants represent only a fraction of a wide range of options used in the reconstruction of the craniomaxillofacial skeleton.

We present a brief review of the materials used in autologous as well as alloplastic craniomaxillofacial reconstruction followed by a look into the future direction of the field.

HISTORY

Earliest reported treatments of facial deformity dates to at least 2500 BC with the use of ocular prostheses in ancient Egypt. These were made from painted clay and fabric and worn outside of the orbital cavity. In 1650 BC, Egyptians documented the diagnosis and treatment of mandibular fractures with supportive head wraps; however, these injuries were largely considered incurable and prone to lethal infectious complications.[1,2] By the 3rd century BC, the Chinese are known to have constructed nasal and auricular prostheses fabricated from metals, resins, and natural waxes. In the millennia that followed, a multitude of other rudimentary prosthetic materials were used in the aesthetic management of facial deformities, including porcelain, paper-mâché, leather, and acrylic prostheses.[3,4,5]

Hippocrates would be the first to document treatment of a mandibular fracture with manual reduction and immobilization using linen or gold threads wrapped around bordering teeth.[6] Similar to circumdental wiring used today, by most accounts this proposition would prove to be ahead of its time, as little progress would be made in the following centuries. Even by the early 1800s, treatment of mandibular fractures largely would involve closed reduction with interdental wiring in combination with immobilization of the jaw with a fabric bandage.[7]

Not until the 19th century were further significant advances made in the management of the craniofacial skeleton. Most notably, the methods and materials employed in the treatment of craniofacial defects evolved from the isolated use of removable prosthetics and bridle wires and expanded to include the use of open surgical fixation of bone fragments with metals and synthetic acrylics.[8,9] In the 1840s, Baudens and Buck pioneered fracture fixation of the craniomaxillofacial skeleton using interosseous wiring of fractured mandible segments.[6,10]

One of the early pioneers of the field of orthognathic surgery was American surgeon Dr Simon Hullihen. In 1848, he performed an anterior mandibular wedge ostectomy for correction of a prognathic

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malocclusion deformity in a young female.[11] Of additional significance is the "Gunning splint," created in 1866 for the treatment of mandibular fractures. Early Gunning splints were fabricated from vulcanite and fixed in place with palatal and mandibular screws.[6]

Internal fixation of orthopedic long bone fractures was first reported in the 1860s, and the use of plates, screws, and wires was first documented by the 1880s. German surgeon Dr Carl Hansmann and Scottish surgeon Sir William Arbuthnot Lane are credited as being the first to integrate the use of plates in the internal fixation of facial fractures.[12] Dr William Halsted improved upon this method by placing fixation screws subcutaneously as opposed to percutaneously. However, early surgical fixation was frequently complicated by poor hygiene along with the use of brittle and poorly compliant plating materials. This environment led to high rates of implant exposure, fracture, and infection. Earliest examples of alloy plates used in craniofacial surgery—those constructed with chromium and nickel—had a tendency to corrode over time.

By the early 1920s, materials with enhanced resistance to corrosion came into development and were applied to the treatment of facial fractures. High-alloy steels forged with chromium and molybdenum specifically increased the resistance to corrosion/oxidation.[13] By the late 1930s, cobalt-based alloys (eg, Vitallium) were introduced to oral and craniofacial surgery. These were associated with decreased rates of corrosion, improved malleability, and increased tensile strength in comparison to traditional stainless-steel plates. Vitallium found its first use in craniofacial surgery when used for the treatment of a mandibular fracture by Bigelow in 1943.[14] Vitallium demonstrated high tensile strength and superior resistance to corrosion.

Tantalum was soon after introduced as another metallic material used in alloplastic reconstruction of cranial defects, beginning in the early 1940s during World War II. It was used successfully due to its strength, improved malleability, inertness, and lack of corrosion. Unlike autograft and Vitallium, tantalum allowed for a single-stage cosmetic repair in which the implant could be easily fabricated to patient-specific anatomy. However, tantalum as a material is expensive and of limited availability. Additionally, its thermo conductive properties resulted in >40% patients reporting new temperature sensitivity at the implant site. By the end of the 1950s, tantalum fell out of favor and was replaced by acrylic as the new standard for alloplastic cranioplasties.[15]

By 1960, titanium was introduced and later largely replaced Vitallium. Titanium had even better tensile strength, and demonstrated improved malleability. Although similar to Vitallium in its high resistance to corrosion, Vitallium was found to produce toxic byproducts which routinely induced a foreign body reaction leading to inflammation and loosening of the implant.[16] Malleability of titanium was found to be particularly useful for use on the facial skeleton as it facilitated its accommodation to fit the complex contour of the facial bones (eg, titanium mesh implant in orbital floor reinforcement of orbital floor fractures).[17] Additionally, as first described by Brånemark in 1969, the inherent osseointegrative properties of titanium implants made it the standard for use in modern day craniofacial rigid fixation and in integrated prosthetics.[18–20]

Biomedical use of titanium is well established, particularly within the realm of craniofacial surgery. This is primarily due to its biological inertness, favorable strength-to-weight ratio, and cosmetic and functional outcomes. Another key advantage of titanium is its propensity for osseointegration. This promotes active bone growth into the implant. Titanium plates used in craniofacial fixation were not without complications: the screws used in early titanium plate designs had a proclivity to "back out," leading to potential for erosion through the skin and necessitating revision surgery for removal of the implant.[21–24] Studies have shown that titanium implants for cranial and maxillofacial applications have a lower survival rate (higher complication rate) than alterative materials such as polymethyl methacrylate.[21] In addition to this risk of implant migration, surgeons developed concerns over the compatibility of titanium implants with patients' future imaging requirements, the potential for interference with radiation therapy, and temperature sensitivity. This prompted a search to find alternative materials.[25–31]

RESORBABLE BIOMATERIALS

Permanent materials such as titanium provide strong reliable fixation of facial fractures. However, the facial skeleton does not share the same load-bearing biomechanical properties of long bones, save the mandible. Since fracture fixation is necessary only until bony healing is completed, the concept of resorbable fixation material was conceived to bypass some of the inherent disadvantages of standard metallic fixation.

Additionally, the inability to accommodate a growing facial skeleton resulted in limited application of titanium fixation materials among pediatric patients. Intracranial translocation of metallic plates and screws as a result of appositional growth of cranial and facial bones occurs in up to 50% of pediatric cases. There are even reports of these implants traversing the dura and coursing into neural structures.[17,32–34] Utilization of resorbable fixation material offered numerous additional advantages in comparison to titanium plates. These included: lack of restriction on skeletal growth, decreased risk of implant migration and extrusion, and diminished temperature sensitivity and palpability. In addition, resorbable polymers are radiolucent which eliminates radiographic metallic artifact.[35]

Use of absorbable plates and screws for the treatment of facial fracture was reported in 1971 in the treatment of a LeFort I fracture.[36] Initially considered ideal for pediatric craniofacial surgery; resorbable fixation materials were later applied for use in orthognathic surgery.[31] However, the technique did not initially gain widespread popularity due to lack of experience and limited knowledge regarding risks and outcomes. Materials currently employed in resorbable fixation largely consist of variable mixtures of the thermoplastic polymers polyglycolic acid and polylactic acid. Both of these compounds are broken down and eliminated through natural metabolic processes. They differ in their individual chemical and physical properties. Polyglycolic acid degrades rapidly and loses the majority of its structural integrity within 6 weeks, insufficient to allow complete bony healing. In addition, it is associated with osteolysis, local tissue inflammation, and the formation of sterile abscesses. On the other hand, pure polylactic acid undergoes much slower hydrolysis. It retains its strength for a longer period of up to 2 years. However, like other long-lasting alloplastic materials, it is prone to inflammatory foreign body reactions.[37]

When used in various proportions, copolymeric mixtures have been able to circumvent many of the downsides of permanent alloplastic materials and minimize many of the side effects of isolated aliphatic polymers. These materials retain approximately 70% to 80% of their strength by 8 weeks, appropriately facilitating structural reinforcement during osteosynthesis while degrading to avoid late inflammatory complications and foreign-body responses. Examples of present-day resorbable plating systems include Delta by Stryker, Resorb-X by KLS Martin, Lactosorb by Zimmer Biomet, and RAPIDSORB by Depuy Synthes.[37]

Although mechanically inferior to titanium, resorbable fixation systems potentially offer comparable outcomes compared to metallic fixation. Recent studies assessing the use of resorbable fixation systems in the fixation of pediatric mandibular fractures have demonstrated acceptable results with risk of postoperative

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complication comparable to standard metallic fixation.[38] Nevertheless, several important disadvantages persist, including the requirement of a heating device to activate implant malleability and the need to tap bone before screw placement.[37]

ALLOPLASTIC IMPLANTS

Beyond fracture fixation, the reconstruction of segmental tissue loss within the craniomaxillofacial skeleton provides additional challenges. These defects typically have multidimensional structural requirements. These can be challenging to restore. When the normal regenerative capacity of bone is insufficient, an autologous bone graft may be required.[39] As such, the gold standard for treatment of bony craniomaxillofacial defects is with the use of autologous tissue. Despite its widespread use and clinical success, autologous tissue transfer generally requires an extended operative time, is associated with increased donor site morbidity, and comes with an elevated risk for future fractures.[17,40] Alternative reconstructive options are required in cases with severely comminuted bony injury, infection, limited donor site options, and may be a more suitable option for pediatric patients and those affected by osteoporosis.[41]

Because of important limitations presented by autogenous bone, alloplastic materials such as PMMA (polymethyl methacrylate) were developed. Since its introduction during World War II, PMMA has been used widely as a material for reconstructive surgery. PMMA is a thermoplastic resin similar to bone in overall strength. It demonstrates better compressive resistance compared to many other synthetic materials.[42] Despite the large variety of available biomaterials used in the segmental replacement of bony defects, PMMA remains to be one of the most cost effective, widely available, and most compatible materials. In alloplastic cranioplasties performed today, PMMA is considered to be the gold standard. It is associated with the lowest rate of postoperative complications. Smooth surface characteristics of most PMMA implants prevent tissue ingrowth. Therefore, it facilitates removal. When bony integration is desired, implants have been constructed with increased porosity to allow to fibrovascular tissue ingrowth.

PMMA is also used as a bone cement. It has been used in craniofacial bone applications since the 1990s. It is easy to use and provides a relatively high mechanical strength compared to alternative bone cements. However, during implantation PMMA bone cement undergoes an exothermic reaction that can lead to damaging thermal tissue necrosis, which has been shown to impair bone healing.[40,43,44] Since these properties are directly related directly to the shaping and curing process, the use of prefabricated and customized craniofacial implants minimizes this drawback.[21]

Polyethylene (HDPE, Medpor, Porex Surgical) is another material frequently used in craniofacial hard tissue replacement. It is a highly biocompatible, has long-lasting structural stability, and is frequently highly porous to allow to for enhanced bony integration. It has a wide variety of uses in craniomaxillofacial surgery, including nasal and auricular reconstruction, midface and mandibular bony contour augmentation, and cranioplasty. The porous structure of these materials increases fibrovascular ingrowth, which can be seen in as little as 3 weeks.[45,46] Its major disadvantage is its relatively elevated incidence of implant exposure and resultant infection. Titanium mesh embedded within porous polyethylene is of particular interest. This implant provides additional strength, malleability, and radiopaque properties to the tissue integration and smooth contour of the polyethylene implant.

Polyetheretherketone is another biocompatible material used in craniofacial reconstruction. It provides structural properties similar to that of human bone. However, it is hydrophobic and biologically inert, which prevents integration with adjacent tissues following implantation. A number of coated polyetheretherketone implants have been developed and have been shown to help mitigate these issues.[21]

Computed tomography data can be used to create patient-specific implants, which are constructed to replace larger bony defects.[47] Customized implants can be constructed from a variety of materials including polyethylene, polyetheretherketone, and PMMA to avoid injury to anatomic structures, for example tooth roots. Implants are then fixated with titanium or resorbable plating systems. Although successful in mirroring the complex contour of the facial skeleton, these implants are costly and take weeks of preparation.

CERAMIC MATERIALS

While the aforementioned synthetic materials do provide long-lasting structural stability and are able to reliably reconstruct the craniomaxillofacial skeleton, they are permanent. Therefore, they are at elevated risk of infection, extrusion, and implant failure. Alternatively, a more ideal material is one that mirrors the natural physiologic mechanisms involved in bony regeneration and autologous graft healing. These processes include providing viable bone-forming cells to the recipient site (osteogenesis), a three-dimensional scaffold upon which bone is laid down (osteoconduction), and inducing the differentiation of mesenchyme into new bone-forming cells (osteoinduction). For an extended interval, a wide variety of ceramic materials have been used in craniofacial surgery. The majority of these materials are successful in providing osteoconductive properties of bone regeneration. However, they frequently lack in osteoinductive and osteogenic mechanisms.

Calcium sulfate, or ''Plaster of Paris'' is the oldest ceramic materials applied to craniofacial reconstruction. It was first used in the late 1800s. It provides a reliable osteoconductive template for bone formation. It is resorbed rapidly at a rate that exceeds bony healing and provides limited structural support. Calcium phosphate is another ceramic material that has been used in craniofacial surgery since the 1990s. Cranial applications include obliteration of the frontal sinus, blockage of cerebrospinal fluid leaks, and correction of contour deformities of the cranium. It is osteoconductive and easily molded under physiologic conditions but provides limited mechanical strength and can be brittle.[47]

Hydroxyapatite (HA) is another calcium phosphate-based ceramic material, similar in structure to the natural carbon-bound compound found in bony tissue. As such, it is highly biocompatible and does not promote any significant inflammatory response. Frequently it is applied as a bony filler and as a coating for implants to promote bony ingrowth and improve tactile contour. Hydroxyapatite has been used as a moldable bone cement since the 1990s. It can be manipulated under physiologic conditions and quickly stabilizes to bone. PMMA bone cement, on the other hand, produces an exothermic reaction during implantation potentially damaging surrounding bony tissue and must be fixed to prevent infection and exposure.[21,24] Hydroxyapatite cement has been used in combination with titanium mesh in cranioplasties. It has been shown to minimize corrosion, improve structural support, and provide an osteoconductive scaffold for bony regrowth.[48]

Similar to previously described hard tissue replacement polymers, prefabricated and 3D-printed ceramic scaffolds have been developed. They provide several important benefits including osteoconductivity and physiologic resorbability. Additionally, a macroporous structure within these prefabricated calcium phosphate implants allows for tissue and capillary ingrowth which is critical for reconstruction of larger bony defects. However, the benefits of porosity must be carefully balanced with its associated loss of mechanical strength to the implant.[49]

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ALLOGRAFT

Allograft-based bone grafts have also been used for the reconstruction of craniofacial defects in the form of cadaveric demineralized bone matrix. Although devoid of immunogenic potential, it has been widely demonstrated that demineralized bone provides osteoinductive properties due to the presence of growth factors such as bone morphogenic proteins (BMPs). However, the acid demineralization process comes at a predictable cost to its mechanical strength and osteogenic potential due to loss of viable osteoblasts.[50,51] Demineralized bone matrix has also been developed for use as a bone paste/putty. This is easily molded and can serve as a scaffold and stimulus for new bone formation.

In clinical practice today, a variety of allograft materials are available for commercial use. Many have been combined as hybrid materials to take advantage of the individual benefits. For example, internal fixation plates composed of osteoconductive hydroxyapatite and bioresorbable polyglycolic acid /polylactic acid polymers have shown success in the management of midface fractures with improved bioactivity and mechanical properties.[52–54] Nevertheless, even the most recent developments have failed to overcome several inherent problems with alloplastic material. Further research will be required to develop materials that can safely and effectively reconstruct the craniomaxillofacial skeleton in a cost-effective manner.

FUTURE

Although the roots of the field of craniomaxillofacial surgery originated many centuries ago, much of the transformation and innovation occurred within the last 50 years. Even by the second half of the 20th century, craniofacial deformities were still largely managed with antiquated techniques and materials. Often these resulted in unsuccessful clinical outcomes. To date, the improvements made in the field are derived from an enhanced comprehensive appreciation of the mechanisms involved in osteosynthesis along with advances in biomedical engineering that reflect the complex functional anatomy of the craniomaxillofacial skeleton.

In the treatment of facial fractures, internal fixation will continue to rely upon the utility of both titanium and bioresorbable plates for specific indications. In the future these technologies will likely be applied with other alloplastic materials to synergistically maximize the benefits of stability, biocompatibility, and functionality. Nevertheless, while each method and material discussed has unique characteristics, no presently utilized system exists that can effectively replicate the biologic functions of autologous tissue. Advances in technology and improvements in tissue engineering and regeneration will continue to occur and will ultimately lead to improvements patient care and cost-effective outcomes.

With regards to the challenges of segmental bony loss within the craniomaxillofacial skeleton, the future will likely bring a paradigm shift from the use of prosthetics and bone and tissue grafts toward the standardized use of synthetic biodegradable tissue scaffolds. Latter will be combined with biologic molecules, cells, and drug delivery systems capable of reconstructing anatomy that parallels the pre-existing or optimal functional, structural, and aesthetic standards.[9] A substantial amount of preclinical research has been applied to biomedical tissue engineering over the past 20 years. A number of case series and reports have shown its applicability to the field of craniofacial surgery. Biocompatible osteoconductive implants with intrinsic controlled release of a variety of growth factors, hormones, antibiotics, stem cells, and other osteoinductive and anti-resorptive sources have demonstrated very positive effects on bone regeneration in the preclinical setting. Mesenchymal stem cells capable of differentiating into mature osteoblasts have been reliably isolated from adipose tissue and bone marrow[55–66]

Bone morphogenic proteins (BMP) show great potential as an osteoinductive adjunct in craniofacial surgery. BMPs are multifunctional growth factors that guide differentiation of mesenchymal stem cells into functional bone-forming cells. Recombinant BMP-2 has been approved for use in spinal surgery since 2002. Additionally, it is widely-employed off label as an adjunct for the treatment of long bone fractures and nonunions. It has notably demonstrated experimental success as an alternative to autologous bone grafting for secondary alveolar cleft repair. The potential of BMPs to assist in the recapitulation of physiologic bone healing has been applied to the preclinical setting. Researchers successfully transduced the BMP-2 gene (osteoinductive) into mesenchymal stem cells (osteogenesis), which were applied to a porous hydrogel scaffold (osteoconductive).[67,68] Although this may be impractical for clinical use, it does serve as a manifestation of the significant progress made in biomaterial engineering. Perhaps it will demonstrate a window into the future.

While advances like these in tissue engineering and biomaterials technology will continue to provide more tools for these procedures, their widespread utilization will continue to be limited by high costs, lack of randomized control studies, and uncertainty regarding long term outcomes. Future work should endeavor to provide the manifold benefits of biomaterials in craniomaxillofacial reconstruction in an evidence-based, cost-effective manner.

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Dr Salyer with the great Chinese plastic surgeon Dr Chang's bronze statue.

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