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Modern materials for the reconstruction of the cranial vault bones

A.A. Ofitserov*, N.V. Borovkova, A.E. Talypov, I.N. Ponomarev

N.V. Sklifosovsky Research Institute for Emergency Medicine,

3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia

*Correspondence to: Andrey A. Ofitserov, surgeon of the Department for Tissue Preservation and Graft Production, N.V. Sklifosovsky Research Institute for Emergency Medicine, e-mail: 3930590@mail.ru

Introduction. *The need for cranioplasty occurs after the removal of the bony structures of the cranial vault. Craniotomy can be performed both in emergency as in case of increased intracranial pressure, and as a planned operation in the treatment of neoplasms or abscesses. A long-lasting presence of an extensive bone defect is the cause of the "trephined skull" syndrome development. Currently, cranioplasty is performed with materials of synthetic or natural origin. Synthetic materials include hydroxyapatite, tricalcium phosphate, polymethyl methacrylate. The natural materials include the auto-, allo- and xenografts. The main disadvantage of bone autografts is their rapid lysis. The most promising solution to this problem may include a lyophilization method with transplant saturation with growth factors, the source of which can be autoplasma rich in platelets. Of particular relevance is the development of methods for the preparation and preservation of an autograft, its modification in order to increase osteoreparative properties, which will bring the cranioplasty method with natural transplants to a whole new level.*

The purpose of research. *Combine relevant data and the results of a comprehensive analysis of the advantages and disadvantages of existing bone-plastic materials.*

Keywords: cranioplasty, autograft, allograft, osteoinduction, osteoconduction, neurosurgery, autoplasty

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Introduction

Cranioplasty (Greek kranion, skull + plastike, sculpting, plasty) is a surgical treatment aimed at restoring the integrity of the cranial vault. The need to conduct it arises in case of the removal of bone structures in traumatic injuries, decompression surgery or the treatment of a malignancy localized in the calvaria region [1]. A long-lasting presence of an extensive bone defect is the cause of the "trephined skull" syndrome development. In addition, the patients complain of experiencing the fear of brain damage, the sense of inferiority, cosmetic problems, which all lead to depressions. All of the above clinical manifestations were combined by F.C.Grant and N.C.Norcross into the concept of "the syndrome of the trephined". The causes of its development currently include the prolapse of the brain substance due to changes in the atmospheric pressure, disturbance of liquorodynamics, the cerebral blood flow changes resulted from the loss of

a hard barrier between the brain substance and the environment. The main criteria for considering cranioplasty currently include the size and location of the bone defect.

The first scientifically grounded cranioplasty techniques were described by Gabriele Falloppio, the Italian physician and anatomist, in 1550–1560. With the clinical experience having been acquired, those techniques underwent great changes and refinements aimed at improving the surgical treatment efficacy. One of the key factors contributing to the surgery success is still the material used for cranioplasty. According to experts, it should be maximum biocompatible, retain its volume with temperature, be resistant to biomechanical stress, be easily mouldable to simulate the shape of the defect, cause neither adverse reactions from brain tissue and its membranes, nor graft rejection, and should smooth over the intracranial pressure increases [2]. Based on this, the proper materials have been introduced into practice and they can be divided into the groups of natural and synthetic ones, according to their origin. Synthetic materials include hydroxyapatite, tricalcium phosphate, polymethyl methacrylate, calcium phosphate and sulfate. Metal constructions are made of titanium in the form of perforated plates or meshes. Natural materials include autologous grafts, allo- and xenografts. The intermediate position is occupied by mixed synthetic materials with organic substances, for example, with allogeneic bone chips, collagen, living cells, or composites [2]. At the same time, technical progress provides a regular appearance of new materials in clinical practice. As a result, such a wide range of materials makes it difficult to choose one among them. And, despite the recognition of cranioplasty importance per se by experts, there is no consensus among them regarding the material for its implementation [3–6]. The purpose of this

review was to combine relevant data and the results of a comprehensive analysis of the advantages and disadvantages of existing bone-plastic materials used for cranioplasty.

Metals and synthetic materials

The history of the widespread use of synthetic materials in cranioplasty began in the twentieth century with the start of the polymer chemical industry development; earlier the metals had been widely used, primarily owing to its high strength. The polymeric materials used in cranioplasty mainly originated from dentistry. Polymethyl methacrylate is the most common among polymers containing no calcium. It easily takes a required shape and expands during solidification, which contributes to the graft being fixed in the bone defect [7]. Its characteristics have been improved by using metal meshes that increase the strength of the material. Polymethyl methacrylate solidification is accompanied by intense heating, which can lead to thermal necrosis of the surrounding tissues and significantly worsen the patient's condition [8, 9].

Calcium-containing materials, such as hydroxyapatite or tricalcium phosphate, do not provide immediate durable recovery of the skull bones. The advantages of such materials can be attributed to their involvement in the processes of osseointegration that contributes to the formation of the bone tissue similar in architecture [10]. In many areas of surgery, biologically active materials based on calcium-containing matrices have widely been used. They carry the signal molecules or stem cells that trigger the bone regeneration processes, i.e. have a strong osteoinductive effect [11–13]. The disadvantages of such materials include their high vulnerability to fractures and the difficulty of their use in sites of cerebral sinuses. A

significant advantage of synthetic materials is a low risk of the infection development and transmission that could depend only on the conditions of surgery performance. [14].

Metals, such as gold, silver, aluminum, have relatively low strength and can pose a toxic effect [15]. Titanium remains the most common metal used in medicine currently. It has a high mechanical strength, low specific gravity, high resistance to corrosion, being “non-ferromagnetic” by nature that allows making instrumental diagnostic studies, such as computed tomography and magnetic resonance imaging. Nevertheless, it has its apt shortcomings that include labour- or time- consuming intraoperative modeling, probable development of patient's individual intolerance to the material, the appearance of artifacts in radiology imaging results, and the development of a patient psychological discomfort arising in response to a foreign body presence, which all are meaningful from the point of the quality of life. However, despite inert titanium nature, the titanium implants adhered significantly worse in patients with hypersensitivity to metals [16]. Like other metals, titanium is subject to thermal expansion. In addition, metal plates hinder an even distribution of the radiation therapy effects which is important for cranioplasty after the removal of intracerebral tumors [17].

Auto-, allo- and xenografts

A number of investigators seek to use autologous or allogeneic bone tissue in their studies [18]. This is grounded by such positive qualities as biological compatibility, the presence of osteoinductive and osteoconductive properties [19, 20].

Donor allografts are the tissue fragments taken from other humans, most often, posthumously. During World War I, cranioplasty was performed with cadaveric cartilage tissue that subsequently was not subject to ossification. Experiments with allografts of the cranial bones at that time were unsuccessful because of high complication rates, despite all the measures taken [21]. Now we know that bone tissue can be the source of many bacterial and viral infections. Moreover, the preserved cells and cell membranes contribute to the development of graft rejection reaction. In this regard, the modern methods of processing allografts imply the destruction of the cellular elements of the bone to reduce its antigenicity, but a high risk of the graft resorption limits the use of allogenic bone tissue for cranioplasty. The bone allografts widely used in trauma surgery, orthopedics, and maxillofacial surgery, have rarely been used in cranioplasty because of a labour-consuming intraoperative modeling and a high incidence of graft lysis [17].

Bone xenografts represent the cattle-derived material. Despite the fact that experiments on their use as an osteoplastic material have been carried out for many decades in various fields of medicine, the results have never been good enough to overcome the high risks of rejection and low biocompatibility [2].

The use of autologous grafts in cranioplasty has a number of indisputable advantages: they are physiological, bear no risk of incompatibility or donor-derived infection transmission, they are convenient to use, correspond to the defect shape and size, relatively inexpensive. When a craniotomy is performed, an explanted bone flap can also be used as an autograft both immediately after surgery and delayed [22]. In the latter case, there is a need for a long-term storage of the bone flap. For this purpose, the

cryopreservation or lyophilization methods can be used. Each of these graft storage methods has its advantages and disadvantages [23].

The most commonly used method is the cryopreservation of autologous bone flap previously harvested at craniotomy. Bone tissue cryopreservation requires a local bone tissue bank in a hospital. A prerequisite is a strict compliance with the rules of aseptic technique. Common storage temperatures range from –80^{o} C to –196^{o} C. The main advantage of the method is the bone viability preservation, which contributes to the most rapid graft adherence. The disadvantages include the risk of infectious complications. R. Morton et al. studied the results of 754 cranioplasty operations performed for 10 years involving the autograft cryopreservation. The median time between craniotomy and cranioplasty was 123 days, the incidence of infectious complications was 6.6%. In 123 bone specimens obtained before cryopreservation, the microorganisms were detected, but other than those causing the infectious complications subsequently [24]. In their study D.Y.Chan et al stored 18 bone specimens for 4–55 months and recorded the growth of bacterial cultures in 5 cases (27.8%): Pasteurella multocida in 3, and methicillin-resistant S. aureus in 2 cases. Meanwhile, the specimens that appeared infected had been stored on average for a longer time and had had a larger surface area [25]. In addition, the authors demonstrated that none of the bone grafts retained viable osteoblasts after defrosting. S.Jin et al analyzed the data on 57 autotransplantations and also found that the infectious complication rate (averaging 12%) depended on the duration of bone tissue storage, as well as on the likelihood of bone tissue significant resorption [26].

The autograft lyophilization and its subsequent sterilization reduce the incidence of infectious complications. The graft prepared in this way is

sterile and does not require special storage conditions. The study by D.Anto et al included 72 patients of whom 62 (86.11%) had good clinical results; 4 patients developed osteomyelitis; 1 patient showed significant bone resorption; 5 patients had fractures and bone damage within 3 years [27].

Another method of preserving a bone autograft implies its placement into the subcutaneous fatty tissue of the anterior abdominal wall. [28-30]. B.Corliss et al analyzed the literature data and compared the results of external and internal storage of the graft after craniotomy. Among 4096 patients, the mean storage time was 69.9 days for the cryopreservation group and 69.7 days for the abdominal implantation group. There were no significant differences between the external and internal autograft storage in the incidence of infectious complications (7.3% vs. 7.1%), and the rates of marked bone resorption (9.7% vs. 7.7%). Revision surgery was required in 15.9% and 7.6% of cases, respectively [31]. Thus, when a bone graft is placed in the fatty tissue of the abdominal wall, the success of subsequent cranioplasty is directly related to the “storage” duration. A.C.Alves Junior et al indicated that the incidence of infectious complications and the implant resorption rates decreased with early plastic surgery using this method [32].

Traumatic injuries and brain tumors often destroy the skull bones, in which case bone grafts are required from other parts of the skeleton. Fragments of the tibia, ribs, scapula, sternum, and the ilium can be used as an autograft [33, 34]. In all cases, autograft harvesting may be associated with bleeding, infectious complications, functional damage of the bone from which the autograft was obtained, and a long recovery period. The autograft removal requires a separate surgical intervention. In addition, the use of autografts for the closure of large skull bone defects can be associated with a

high risk of the bone resorption that occurs, according to some data, in up to 35% of cases. [35].

Comparative characteristics of graft remodeling parameters

A large number of studies aimed at a comparative analysis of the cranioplasty results using bone autografts and synthetic allografts. A number of studies have shown the use of synthetic individual prostheses, which have several advantages over autografts [36, 37]. Gilardino et al comparatively analyzed the efficacy of restoring the skull bones by using autografting with cryopreserved bone tissue of the skull, ribs, and ilium versus using polymeric synthetic materials designed by a computer-assisted software. Having the same average cost, the use of synthetic material was characterized by a significantly lower incidence of complications and surgery duration [38]. S.Honeybul et al in their study that included 64 patients, implanted titanium plates in 31 patients, and performed autologous cranioplasty in 33. For the follow-up of 12 months, no signs of the prosthesis failure were seen in the first group; and in the second group, 7 patients required urgent secondary cranioplasty due to a significant autograft resorption [39]. In the meta-analysis that included the data of 1586 implantations from 11 studies, J.G.Malcolm et al. demonstrated that autologous implants carried a significantly greater risk of resorption than the synthetic ones (odds ratio 1.91, 95% confidence interval 1.4–2.61). In 41% of cases, the autograft resorption was complicated by the developed infectious complications. Among the patients whose implants were not subjected to resorption, the incidence of infection and other postoperative complications did not differ significantly between the groups [40].

J.H.Kim et al. investigated the incidence of an implant resorption after autologous cranioplasty in 91 patients who underwent surgery from 2004 to 2016. The graft aseptic resorption developed in 35.1% of patients, the mean tome to its diagnosis made 136 days. The main risk factors for resorption were the implant size and the time period elapsed between the primary surgery and cranioplasty [35]. In a study by T.K.Korhonen et al, of 41 patients who underwent autologous cranioplasty with the autograft having been cryopreserved, 37 (90.2%) were diagnosed with the signs of bone resorption of various extent within average of 3.8 years. In 13 patients, the bone size reduced to at least 80% of the original size [41, 42]. P.Krishan et al. described a clinical case of almost a complete resorption of an autologous bone graft that had been preserved in the fatty tissue of the abdominal wall [43].

In a number of studies, autologous cranioplasty and reconstruction using synthetic materials showed similar results in terms of efficacy and the complication rates. R.Leao et al made a meta-analysis of 11 studies that included data of 1256 patients where autologous material was used in 408 cases, polymethyl methacrylate in 379, and titanium meshes in 151. The follow-up period ranged from 63 days to 54.3 months, meanwhile there was no significant differences between the groups in the complication rates. In subgroups of patients with traumatic and non-traumatic causes for cranioplasty, no significant differences between the methods were observed [44]. A.W.Plum et al compared the cranioplasty efficacy between using bone autograft, bone cement, or demineralized bone matrix. Patient satisfaction with the surgery results was lower when the natural material was used. Infectious complications occurred more frequently in the group of patients who underwent cranioplasty with bone cement [19].

K.Fu et al in their study that included 41 children showed that the use of autologous and synthetic grafts in pediatric practice was equally safe. Within 3 years of follow-up, no statistically significant differences in the incidence of rejection and infectious complication rates were found [45]. In the study of S.Mohamad et al, the risk of infectious complications was not significantly different between the cases of autologous cranioplasty and mixed cranioplasty using alloplastic materials with polymethyl methacrylate. Moreover, after 172 surgical interventions, only 5 cases of infection were recorded in two groups [46].

The use of calcium-containing synthetic materials also carries the risk of complications. D.Lidner et al compared cranioplasty using titanium meshes and using hydroxyapatite materials and found that the latter have a significantly lower incidence of infectious complications, but increase the risk of developing subdural hematomas [47]. A.Moles et al showed that hydroxyapatite grafts have better cosmetic properties, but significantly lower strength, and the risk of prosthesis damage reaches 20.8% [48].

M.S.Gilardino et al compared the efficacy and the cost of using bone autografts and custom computer-generated synthetic implants. The study included 27 patients. No significant differences were found between the groups in the length of hospital stay and the need for transfusion. Among the patients who had the synthetic materials implanted, the time of surgery was significantly lower, as was the need for the Intensive Care Unit admission. The average cost of treatment was $ 25,797 for autologous transplantation and $ 28,560 for the group of synthetic implants, i.e. the difference was 10% [38]. In a study by B.Lethaus et al, the average costs for bone reconstruction with autogenous bone tissue was 10,850 euros, while the cost of

reconstruction with creating a synthetic patient-specific implant was 15,532 euros, which was 1.43 times higher [49].

Promising technologies in bone grafting are based on the use of autologous stem cells. Mesenchymal multipotent cells are able to differentiate into bone tissue cells, which in theory could be the basis for the complete bone restoration [50]. Some authors term the mixture of mesenchymal stem cells, signaling molecules, and substances necessary for bone formation a "liquid bone". The first clinical studies showed the fundamental possibility of using this technology, but its efficacy has not yet been proven in large clinical trials.

Table. Comparative characteristics of materials for the reconstruction of the cranial vault bones

Material	Positive properties	Disadvantages
Allograft	Osteoconductive, biocompatible, relatively cheap	High risk of infection and resorption
Autograft	Osteoconductive, completely compatible	High risk of resorption
Titanium plates	Inert, non-toxic, resistant to corrosion, flexible high mechanical strength, low specific weight, non-ferromagnetic	Risk of rejection, interact with radiation, relatively expensive, have electrical conductivity
Hydroxyapatite and tricalcium phosphate	Similar to bone tissue in mineral composition, osteoinductive, easily obtainable	Low strength, the risk of rejection, relatively expensive
Polymethyl methacrylate	Easy to use, cheap, easily obtainable	Thermal damage to soft tissue, the risk of rejection, the additional use of burs and cutters

Discussion

Today, despite many years of experience in cranioplasty surgery, there is no generally accepted and dominating material. The synthetic materials preferably used for cranioplasty include the titanium plates and meshes. Depending on the composition, different types of metal prostheses may cause their material-related specific complications. The rate of successful operations is comparable to the use of autografts, but synthetic constructs increase the cost of surgery and their use may entail the risk of additional complications.

The modern technologies of generating patient-specific implants are worthwhile special mentioning. The development of three-dimensional prototyping and its implementation into clinical practice provides a high accuracy while producing a required graft either of synthetic or natural materials. The efficacy of metallic and solid polymeric materials has significantly increased with implementing the production of individual patient-specific prostheses based on a three-dimensional model [51]. Computed tomography yields the data that enable obtaining the exact dimensions of the defect, and the modern equipment for manufacturing prostheses is compact enough for the prosthesis placement. A significant role in the work of modern surgeons is played by stereolithography techniques, i.e. the manufacture of prostheses according to an exact three-dimensional model of an existing defect. The practice of accurate modeling of titanium prostheses has existed for a relatively long time, and a wide spread of 3D printers has simplified the stereolithography of plates made of polymers [52].

Bone tissue allografting has recently been relatively common in reconstructive trauma surgery and orthopedics, however, it has not been so

widely used in cranioplasty and still is associated with many side effects. Cranioplasty with an autologous graft is a cost-effective and most physiological method for closure of trephination defects. The autograft is physiologically adaptable and biocompatible, non-toxic, characterized by a low heat and electrical conductivity, and also has an osteoconductive effect.

The stimulation of bone regeneration processes still remains a pressing issue. A promising solution might be the autograft saturation with cytokines and factors promoting cell migration, cell proliferation and differentiation. Human Type 1 collagen is one of the most well-known available materials used for this purpose. It is known to attract the connective tissue cells to the bone defect area and to contribute to their proliferation, to stimulate the vascular growth, to promote the adhesion of immobilizing structures and implants. In this case, the collagen performs mainly an osteoconductive function, being a conductor for cells, contributing to their migration and the growth of future bone tissue. At the same time, collagen per se possesses no osteoinductive properties. The regeneration processes can be stimulated directly in the bone defect area using various growth factors: platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor beta 1 (TGF-β1), insulin-like growth factor-1 (IGF-1), vascular and endothelial growth factors (VEGF, VGF). All of these factors are contained in the granules (secretory vesicles) of biologically full-value platelets [53]. To date, it has been shown that human platelets have very high reparative and regenerative potential, which can be used to repair damage to the bone tissue, including the skull bones.

Conclusion

Thus, the development of methods for the preparation and preservation of autograft, its modification aimed at enhancing osteoreparative properties is of particular relevance, which would bring the cranioplasty technique to a qualitatively new level. At the same time, there is the reason to believe that the saturation of the autograft with collagen and platelets will significantly speed up the regeneration of the bone defect.

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Information about authors

Andrey A. Ofitserov, Surgeon of the Department for Tissue Preservation and Graft Production, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0003-2170-0009

Natalya V. Borovkova, Dr. Med. Sci., Head of the Scientific Department of Biotechnologies and Tranfusiology, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-8897-7523

Aleksandr E. Talypov, Dr. Med. Sci., Leading Researcher of the Urgent Neurosurgery Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-6789-8164

Ivan N. Ponomarev, Cand. Med. Sci., Researcher of the Department of Biotechnologies and Tranfusiology, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-2523-6939

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