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Progress in the Research of Skull Repair Materials

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Abstract. Skull defect is a common clinical neurosurgery disease. If not repaired in time, it will seriously threaten the safety of patients. The skull defect repair of children is more complicated because their skull is in the growth stage. To improve the treatment level of skull defect, skull repair materials used to replace skull defects have evolved in recent years. An ideal material for skull repair should meet the requirements of good osseointegration, biodegradability and conformability, and finally a perfect fusion with the surrounding bone tissue. In this article, the evolution of current materials utilized in cranioplasty are comprehensively reviewed. Firstly, the existing situation of skull repair materials used in clinical practice are first introduced, including autologous cranial materials and synthetic materials. Secondly, the research hotspots of skull repair materials are summarized, including bone-induced framework and growth factors, and points out the scientific problems that need to be solved in the current research. Finally, the future development direction and clinical application prospect of skull repair are prospected, in order to provide the thinking and reference for the treatment of skull defect.

Keywords. Skull repair, skull defect, growth factor, bone induced frame.

1. Introduction

Skull defect is a common disease in neurosurgery. Except for congenital factors such as unclosed skull, absence of bone suture and skull deformity, most of the defect is caused by acquired injuries, such as craniocerebral trauma, high-altitude blow, intracranial tumor lesions, craniotomy and infected burns [1]. If the defect is not repaired in time, skull defect syndrome and even brain injury will be caused, affecting the patient's life and health and thus resulting in psychological disease and social disorder [2]. Skull defects with a diameter of less than 3 cm can be self-healed, while skull repair surgery is needed if the defect is larger than 3 cm. The steps taken during such a surgery after craniotomy is shown in Figure 1. How to choose appropriate materials to repair the skull defects is the key to cranioplasty [4]. At present, the repair materials mainly include autogenous bone, allogeneic bone, titanium mesh and other metal materials, medical polymer materials, bone cement and tissue engineering composite materials [5]. The objective of this review is to identify the research status in the materials used for cranioplasty and to improve patient outcomes.

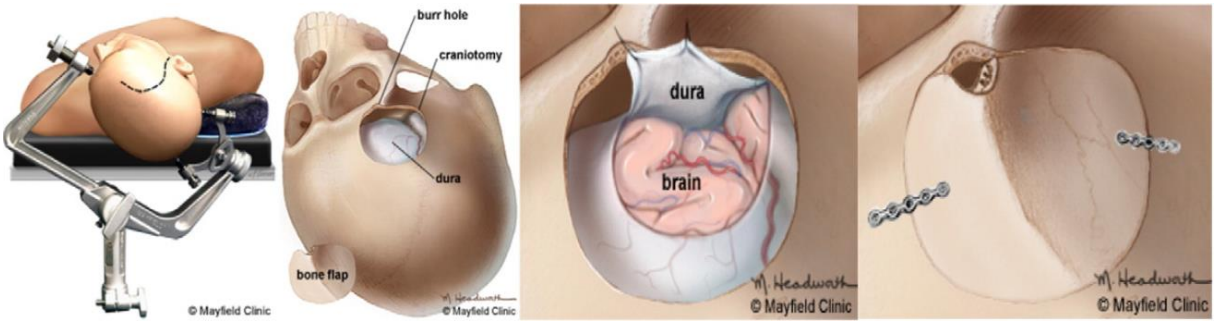

Figure 1. (Left to right) The steps taken during a cranioplasty technique after craniotomy [3].

2. Selection of restoration materials

The ideal repair material should have good biocompatibility, anti-infection, low thermal conductivity, high mechanical strength, non-magnetic, easy shaping and so on. At present, the most widely used materials include autogenous bone materials (bone flap, rib, ilium, etc., taken out during craniotomy) and synthetic materials (titanium mesh, ceramic, polymer plastic, etc.), each of which has its own advantages and disadvantages and can be selected according to different clinical needs [6]. Bone allograft is easy to cause immune rejection, therefore it is rarely used. The advantages and disadvantages of skull repair materials commonly used in clinic are listed in Table 1.

2.1. Autologous skull materials

Autologous skull most conforms to the physiological and psychological requirements. It can promote bone growth and finally achieve bone healing. Therefore, it is the first choice of cranioplasty, especially suitable for children [7, 8]. Autologous bone and skull tissue are from the same source. Both of them are relatively economic and has good biocompatibility and high enough strength, with no immune rejection and no need for plastic surgery. Autologous bone contains viable bone-generating cells, which provide ideal structure and histocompatibility for bone fusion and initiate

new bone growth. Autologous bone flap implantation can restore blood flow, induce migration and differentiation of bone progenitor cells, and accelerate the formation of new bone.

Autologous skull includes skull flap, skull fragment and skull powder. As early as the 1980s, there were reports on the application of autologous skull flap in skull defect repair [9]. In clinical practice, there are different degrees of absorption at the edge of the skull flap to make the skull flap smaller. It is difficult to form a complete large skull flap in comminuted skull fracture. There is a certain infection rate of the bone flap, the need for secondary surgery and long repair time, etc. What's more, the preservation of the bone flap has always been a problem. During the collection, storage and placement of bone flap, neurosurgeons try to ensure the survival status of osteogenic cells. During the implantation, they try to expand the contact area between the bone flap and the bone window to ensure a stable contact with the bone window, so as to promote the reconstruction of blood flow of the bone flap and the migration of osteogenic cells [10]. Autologous skull fragments are mainly used for clinical repair of comminuted skull fractures, requiring bone fragments to be bitten into fragments for replantation [11]. In 1998, Katsumi et al. applied autologous skull powder made from skull outer plate drilled by skull drill and human fibrin glue to repair small round and narrow gap defects formed by skull drill and wire saw in craniotomy, and ossification could be completed in the transplanted area only 2 years after surgery [12].

In general, the advantages of autologous cranial powder over cranial flaps and cranial fragments are more obvious in repairing cranial defects. However, the source of bone fragment is limited, and if the defect and trauma scope are large, too much autologous bone collection will lead to donor site dysfunction. Although autologous skull can regenerate after preservation and replantation [13-15], postoperative problems such as bone absorption and infection lead to a high failure rate, which also limits its application [16, 17].

Table 1. Advantages and disadvantages of skull repair materials commonly used in clinic

Materials	Advantages	Disadvantages
Autogenous skull	●Excellent osteogenic activity ●Safe ●No immunogenicity	●Limited source resulting in donor site injury ●Difficult to shape
Titanium alloy mesh	➢Non-inflammation ➢No corrosion ➢High strength ➢Low infection rate ➢Easy to shape	➢High price ➢Affect imaging ➢Heat conduction ➢Restriction of skull development ➢No osteogenic activity and osseointegration
PEEK	◆ Ray permeability ◆ Bioinert, good compatibility ◆ High strength, elastic ◆ Not affect the imaging ◆ Comfortable	◆ High price ◆ No osteogenic activity and bone integrity ◆ Infection
Bone cement	✧ Excellent biocompatibility and bone conductivity ✧ Non-toxic and immunogenic ✧ Without inflammation ✧ Easy to shape	✧ Rejection and higher incidence of postoperative subcutaneous effusion and rejection ✧ Lower mechanical strength ✧ Insufficient structural stability for large skull defects
PMMA	■High strength ■No heat conduction ■Bioinert ■Good compatibility ■Low price ■Easy to use	■Infection ■Brittle fracture ■Heat release during curing ■Inflammation ■No bone integration

2.2. Synthetic fills

Due to the limitation of the source and serious complications in the application of autologous bone, various synthetic biomaterials have appeared successively, including titanium alloy mesh, polyether ether ketone (PEEK) polymer material and bone cement composite material [16, 18]. Titanium alloy has excellent biocompatibility, physical and chemical properties, corrosion resistance and wear resistance, high mechanical strength (tensile strength up to 140 kg/mm^2) [19], non-aging, light density, low toxicity and other advantages, and has been widely used in the repair of skull defects. Titanium alloy is non-ferromagnetic, and postoperative imaging examinations such as CT, X-ray, MRI and electroencephalogram and other imaging tests are not affected. The mesh structure is conducive to the growth and fixation of granulation tissue through and into the tissue [20]. At present, titanium alloy has completely replaced metal forming sheet, mesh silica gel, plexiglass and other allogeneic materials in clinical application. The customized titanium mesh has excellent shaping effect after 3d reconstruction of skull defect with computer-assisted technology [21]. However, due to the high strength of titanium mesh, manual molding and fixation takes time and effort, and it is difficult to overcome the elasticity of the material itself, leading to sharp edges of forehead and skull base and easy to cut the skin. Some patients even have fine grid marks on their scalp, and postoperative scalp infection or even exposure of titanium mesh may endanger patients' lives [17]. As an emerging polymer material, PEEK is favored by patients with skull defects due to its stable physical and chemical properties, good histocompatibility and excellent shape repair effect

[22, 23]. Among all the synthetic skull repair materials, PEEK is the closest to autologous skull at present. Personalized three-dimensional PEEK can accurately repair skull defects, especially for patients with skull defects that affect the skull base and are difficult to shape with titanium mesh. According to clinical results, PEEK is safer and more effective than titanium mesh, and has a high degree of molding satisfaction. Postoperative complications are greatly reduced, and the application of PEEK is relatively less but increases rapidly [24, 25]. The disadvantages are listed as follows. On one hand, the cost of PEEK material is very high, and it is not covered by medical insurance at present. On the other hand, PEEK also faces problems such as tissue nonfusion, prone to rejection and subcutaneous effusion and infection. The safety of PEEK needs to be verified by time and case control. Other prostheses for embedded repair include cement preforms and polymethacrylate resin (PMMA). Bone cement has been rarely used in neurosurgery centers due to rejection reaction, high incidence of postoperative subcutaneous effusion and rejection, and inferior to metal materials in mechanical strength and initial stability before bonding or fusion with surrounding bone tissues [26]. PMMA material is durable, has good ductility and low cost. It is similar to PEEK material in terms of treatment success rate and complication rate, and can avoid the occurrence of bone absorption. However, it is not compatible with surrounding tissues and has high brittleness, and is also prone to repair failure [27, 28].

After implantation, synthetic materials will inevitably face a certain degree of tissue diffusion and have the risk of immune rejection. With the wide application of prefabricated three-dimensional plastic titanium mesh in hospitals of all sizes, titanium mesh has rapidly become the mainstream of skull repair materials, replacing autologous skull. PEEK skull material also begins to be used in neurosurgery centers. Bone cement material has gradually been neglected and abandoned.

3. Current research hotspots

Although skull defect repair materials are constantly being improved, there is no material that can achieve perfect fusion with bone tissue. For large skull defects, bone flap replantation involves a series of steps, such as bone revascularization, bone conduction, bone induction and new bone formation. Meanwhile, the microenvironment of the defect area will not be enough to promote the formation of new bone. In recent years, the research and use of new adjuvants such as bone-induced frames and growth factors are becoming more and more popular.

3.1. Bone induced frame

Bone induction framework at present, the laboratory research progress of bone repair has moved from bone conduction to bone induction framework. That is, the patient's mesenchymal cells were harvested and cultured in vitro, combined with synthetic scaffolds with biocompatibility, and transplanted into the skull defect area, so as to induce the undifferentiated mesenchymal cells differentiation into bone formation between the cells to repair defects [29]. Commonly used mesenchymal cells include pluripotent stem cells, bone marrow stem cells and adipose stem cells, etc. Compared with pluripotent stem cells and bone marrow stem cells, adipose stem cells have the advantages of abundant sources, easy availability and multidirectional differentiation potential, etc., and occupy a very important position in bone tissue engineering [30-31]. The microstructure and biological properties of mineralized collagen, such as bone conduction, are almost the same as those of autologous bone. Implants made of mineralized collagen can fuse with newly formed bone by crawling replacement process. Wang's team in Tsinghua University compounded biomimetic mineralized collagen with degradable polymer material to construct a child skull regeneration and repair scaffold with excellent bone integration and certain osteogenic induction, which can effectively promote bone fusion without restricting bone growth [5, 32-33].

3.2. Growth factors

Many growth factors have been proved to play a significant role in stimulating osteocytes, inducing osteocyte differentiation to ensure bone regeneration, and promoting skull defect repair, some of which have been applied in clinic. Such as transforming growth factor-1 can be directly involved in regulating bone flap healing of chondrocytes and osteoblasts, bone form protein-2 can significantly shorten the healing time of skull defect and insulin-like growth factor 1 can stimulate bone cell replication and bone matrix synthesis, vascular endothelial growth factor can promote the proliferation and differentiation of osteoblast [34, 35]. Hu et al. prepared a biomaterial by combining concentrated growth factor and adipose stem cell sheet, which can promote the repair of skull defect in rats [36]. Novais et al. showed the importance of fibroblast growth factor-2 in tissue engineering for craniofacial bone repair [37].

It is believed that with the deepening of research on multifunctional stem cells and adipose stem cells, the development of bone tissue engineering in the future will provide a more effective treatment for clinical patients with skull defect repair.

4. Overlook

With the development of computer-aided design and the study of growth factors and stem cell colonization, the future focus of skull defect repair materials will be on the development of a class of biocompatible materials that are easy to customize and shape, have excellent anti-infection ability, strength and durability to resist trauma and absorption. The cranial defect repair is more complicated because the cranial brain is in the growth stage. We hope that through

multi-factor evaluation, multi-disciplinary cooperation and individualized treatment, neurosurgeons can provide a variety of repair materials for patients to choose, so as to improve the success rate of skull defect repair surgery and reduce the incidence of complications. We also urgently look forward to the emergence of a material that can achieve perfect healing.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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