Study on the Treatment and Repair of Fracture with Functional Composite Bone Adhesive

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Abstract: Compared with traditional internal fixation devices, bone adhesives have significant advantages in the treatment of bone injuries, such as improving the fixation of comminuted fractures and maintaining the spatial position of scattered bone fragments. By analyzing different kinds of bone adhesives, mechanical strength, osseointegration, bone conductivity, bone induction, application and two different research directions, this paper puts forward the concepts of "liquid stent" and "liquid plate" and discusses the research progress and future development trend of bone adhesives, in order to provide reference for clinical treatment and repair of fracture technology.

Keywords: Biomaterials, Bone Adhesives; Bone Fixation; Bone Regeneration; Bone Tissue Engineering

At present, the treatment of fractures is mainly divided into surgery and conservative treatment. However, with the exception of a few fractures that can be treated with functional reduction. During surgical treatment, strong internal fixation, such as a plate or nail, has always been regarded as the standard treatment modality. However, there are still some problems to be addressed in fracture treatment: First, most comminuted periarticular fractures require anatomical reduction to meet exercise needs and prevent osteoarthritis. But internal fixation devices are difficult to accurately hold fracture fragments together, especially comminuted fractures. Second, the osteoporotic bone cannot firmly secure the screw. Furthermore, internal fixators are prone to implant infection of bone tissue that need to be removed after bone healing. Studies have shown that metal surfaces are prone to form pseudo-membranes in vivo, thereby promoting bacterial growth. Therefore, to solve these problems, bone adhesives have been developed to treat fractures, which is more convenient, faster and safer than traditional internal fixation instrumentation.

1. Different kinds of Bone Adhesives

According to the main ingredient source, bone adhesives can be divided into natural, synthetic and bionic three categories. Since bone is composed of a mixture of organic and inorganic substances, the design of bone adhesives should consider the combination of these two materials. New bone adhesives should be designed as biomimetic, multi-component adhesives containing organic and inorganic materials. Advanced bone adhesives with good biocompatibility and porous structure can be used as Bridges to accelerate bone cell growth and promote bone regeneration, which is in great demand. From a bone tissue engineering perspective, bone adhesives are used to bond two fracture fragments together to form an intermediate scaffold that sits after curing, similar to a liquid scaffold. Bone adhesives often have the special function of promoting fracture healing and enhancing new bone remodeling after fracture healing. The main difference between liquid scaffold bone adhesives and traditional bone adhesives is that they can promote fracture healing. In addition to the liquid scaffold bone adhesive, there is an adhesive used to bind the cortical bone surface at both ends of the fracture, rather than filling the fracture space. This type of bonding usually requires pretreating the cortical bone surface with a primer and curing the bone adhesive with a photoinitiator to fix the fracture. Although this fixation is similar to plate fixation used in clinical practice, there is no hole at the fracture end to install the screw. Therefore, this bone adhesive that binds the surfaces of the two fracture fragments after curing and acts as an external fixator is called a "liquid plate." Compared to plates used in current clinical practice, liquid plates are perfectly formed before curing, adhere to the surface of cortical bone, and do not require drilling to destroy the

original bone structure. This adhesion cannot accelerate fracture healing directly by changing the composition, but it can indirectly promote fracture healing by improving adhesion strength and ensuring the fracture is firmly fixed.

2. Enhanced and Upgraded Bone Adhesives

2.1 Bone Adhesives with Enhanced Mechanical Strength

Bone cements need to be able to resist different pressures when applied to different parts of the body. Its mechanical strength usually varies in one direction due to the ratio between static and dynamic loads. Although the mechanical properties of healthy bone are not the primary criterion for determining the suitability of a bone cement, the cement should be able to withstand maximum load. At present, there is no unified standard on the mechanical strength of bone cement. However, some studies have pointed out that the elastic modulus of bone cement for fracture treatment should not be less than 50 kPa. When the bone cement alone cannot meet the mechanical strength requirements, other substances need to be added to enhance its mechanical properties.

2.1.1 Bone Adhesives Containing Organic Fillers

Biodegradable and bioabsorbed hydroxyl ester synthetic polymer scaffolds, such as poly (alpha-hydroxyl ester) and their copolymers, such as polylactic acid (PLA), polyethylene glycol acid (PGA), polylactic acid co-polyethylene glycol acid (PLGA), and polyε-caprolactone (PCL), have been widely used in various tissue engineering applications and have been shown to promote bone regeneration. PLA, PLGA and PCL are approved by the US Food and Drug Administration and are the most widely used products. Many studies on the treatment of bone defects have shown that PLGA is an unrivaled scaffold material with excellent mechanical strength. In addition, some of the absorbable fracture treatment plates in clinical use are also made of PLGA, which further demonstrates its excellent mechanical strength and biocompatibility. Inspired by the Sandcastle worm, some researchers have developed a new type of bone adhesive based on tetracalcium phosphate and serine phosphate. This new adhesive heals within minutes in a water-rich environment and provides high bone-to-bone bonding strength. Different fillers were added to the new adhesive, and the effect of polymer fillers on mechanical strength was studied by mechanical testing. The test results showed that the group containing 7% PLGA filler achieved the highest compressive strength and Young's modulus. In addition, PLGA fillers also improved fatigue resistance of bone adhesives. The researchers proposed a new concept for the development of bone adhesives, that is, before fracture healing, because the mechanical strength of bone adhesives is not enough to meet the normal load demand of bone tissue, polymer materials such as PLGA can be added to improve the mechanical strength of bone adhesives. This concept also opens up the possibility of using bone adhesives to treat load-bearing bone fractures. In addition, the effects of PLGA fiber and two different volume fractions on the compressive properties of the bonded materials were also discussed. Because PLGA sutures and fibers have the same chemical composition, the structure is more continuous, and the diameter and aspect ratio are larger. The above studies have proved that it is feasible to improve the mechanical properties of bone adhesives by using organic fillers.

2.1.2 Bone Adhesives Containing Inorganic Fillers

Inorganic bone adhesives are widely used medical materials, which mainly include alkaline compounds, phosphates, calcium-phosphate cement and retarders for artificial joint fixation, screw fixation and fracture fragment bonding. This adhesive is characterized by a fast hydration rate and high early strength, which allows it to close quickly during surgery, thus reducing the risk and complexity of surgery.The final hydration reactants of inorganic bone adhesives are composed of magnesium ammonium phosphate biocore and hydroxyapatite, which have good biocompatibility. This means that after implantation, this material not only does not cause rejection by the body, but also can be gradually metabolized and absorbed by the body, creating good conditions for the growth of new bone.

In general, inorganic bone adhesive is a safe, effective and easy to be accepted by the body of medical materials, it has a very broad application prospect in the medical field.

2.1.3 Binding of Bone Adhesive to Organic or Inorganic Fibers

A common way to increase the strength of a material is to add fillers, however, for polymer materials such as PLGA, it can have an impact on the viscosity of the adhesive. In order to improve the mechanical strength, we can use other substances to assist. This material and the bone adhesive are packaged separately, and a specially designed application process ensures that the viscosity is not reduced. When the bone adhesive is laid like a steel plate at both ends of the fracture, the fibers at both ends protect the adhesive from being destroyed, thus providing a stable fixation effect. The purpose of adding the fiber layer is to form a hard shell over the bone adhesive. Similar to the liquid plate mentioned above, the liquid plate may require a light-triggered reaction and sufficient contact area to fix the crack, so that it is possible to add a reinforcement layer.

However, uncontrollable shaking often occurs when a fracture is fixed with an internal fixation device. Therefore, a bone adhesive that can immediately adhere to the fracture may be better than an internal fixation device.

2.2 Bone Adhesives with Bone Fusion Effect

In the treatment of fractures, osseointegration is regarded as an important means to achieve clinical asymptomatic fracture healing. Bone adhesives, due to their binding properties, provide primary stability to bone and prevent early fixation failure, which is also a novel explanation for osseous integration. However, in order to repair soft tissue, it is usually necessary to improve the fatigue resistance of hydrogels, and bone adhesives need to increase the hardness of the material to ensure the stability of the bone tissue. In fracture surgery, whether it is internal fixation or bone adhesive fixation, it is necessary to provide stable alignment to promote fracture healing.

Notably, the minimum distance the implant interface moves is 150μm, which results in the formation of soft tissue rather than bone. Internal fixation devices can be securely attached to both sides of the fracture. However, orthopedic surgeons cannot ensure that there are no complications such as local deformities after fracture treatment, although they can ensure that the fracture is properly fixed. In fact, uncontrollable shaking often occurs after a fracture is fixed with an internal fixation device. Therefore, a bone adhesive that can immediately adhere to and immobilize the fracture may be more ideal than an internal fixation device.

2.3 Bone Adhesive with Bone Conduction Upgrade

Bone conduction is a phenomenon in which bone forming cells grow on the surface of bone. This conductive bone surface has special properties that allow bone cells to grow on it or pass through pores, channels, or conduits on the surface. Bone conduction is a process by which bone cells adapt to the surface of a material, and through this process, bone cells can better integrate with the surface of the material.

In the treatment of fractures and bone defects, scaffolds with good bone conductivity are more effective than scaffolds with poor bone conductivity. However, the bone conduction effect of traditional bone adhesives is not ideal. Therefore, we began to try to combine bone adhesives with bone conductive materials such as bioactive glass (BGs) and CaPs in the hope of better promoting bone tissue regeneration during fracture treatment.

2.3.1 Bone Adhesive Containing Bioactive Glasses

After analysis, this paper mainly discusses the important role of BG synthesized from calcium and silicon in bone binder. Experiments show that bioactive porous forming binder containing BG can effectively promote new bone formation and fracture healing. The mechanical strength of this bone binder is high, and BG has superior biological activity in promoting fracture healing. However, the toxicity of formaldehyde from OCA to cells limits the further improvement of its biological activity. At the same time, PPF/HEMA/NBG can enhance the adhesion of the binder to the wet bone surface and improve the biommineralization ability of the composite binder in simulated body fluids. It was also found that NBG had good bone conductivity to bone binder.

2.3.2 Bone Adhesive and Caps

Many kinds of calcium apatite (CaPs), such as hydroxyapatite (HA) and tricalcium phosphate (TCP), are widely used in the construction of biomimetic inorganic bone. In particular, HA scaffolds with appropriate porosity showed good mechanical strength and bone conduction

properties. In addition, the introduction of HA into bone adhesives ensures that the adhesive has a higher filling volume, increased hardness and elastic modulus, and thus improved bone conduction properties. Similarly, the introduction of HA into chitosan-based adhesives can improve the tensile strength of the adhesives under physiological conditions. In addition, the hydrogels formed by calcium carbonate and hyaluronic acid covalently crosslinking showed excellent biocompatibility in vitro.

2.4 Bone Adhesives with Osteoinductive Upgrading

Osteogenic induction means that primitive, undifferentiated and pluripotent cells are stimulated to develop into osteoblast lineage. Bone induction is the process of inducing osteogenesis. In recent fracture nonunion surgery, the use of bone induction materials is an effective treatment. Traditional bone adhesives do not always have good osteoinductivity. It includes bone-inducing materials such as bone morphogenetic protein (BMP) and citrate to improve the osteoinductivity of bone adhesives.

2.4.1 Bone Adhesive Containing Bone Morphogenetic Protein

BMP-2 has been widely used in the treatment of bone nonunion and bone defects. Studies have shown that BMP-2 is an effective inducer of bone remodeling that can directly affect osteoblast differentiation and osteoclast activity. Incorporating BMP-2 into bone adhesives has shown a broad prospect as a means of fracture treatment.

2.4.2 Bone Adhesives Containing Citrate

Citric acid is an intermediate product of the Krebs cycle and is highly conserved in natural bone. More than 90 % of the body 's total citric acid content is located in the skeletal system and is closely related to bone formation metabolism. 'Osteoblast citrate ' plays a key role in the osteogenic differentiation and subsequent mineralization of bone marrow mesenchymal stem cells. As a metabolic factor, citric acid improves the cell energy state during bone differentiation through the metabolic gene regulation process, thereby promoting bone differentiation. Therefore, citrate has been used as a cornerstone for the development of hydrogels or adhesives.

2.4.3 Other Bone Adhesives With Osteoinductive Upgrading

In addition, many substances have bone-inducing effects, such as magnesium ions (Mg^{2+}) and zinc ions (Zn^{2+}). Many studies have confirmed the induction effect of Mg^{2+} in bone tissue engineering. For example, magnesium oxide (MgO), which can be injected into IC-EPE (iCMBA, iC) via a simple hybrid crosslinked PEG-PPG-PEG (EPE) diol, is considered to have great potential as a bone binder. Magnesium plays an active role in inducing osteoblast differentiation and promoting fracture healing. However, although magnesium calcium phosphate cement is used as bone cement to treat fractures, its clinical application may be challenging due to its poor degradability. In addition, some clinical drugs with bone-inducing effects, such as simvastatin, have also been used to study the actual efficacy of pseudo-ketothermal gel in the treatment of fractures in vitro and have shown good therapeutic effects.

3. Conclusion and Discussion

In recent years, significant research progress has been made in bioactive stent implantation and other bone tissue engineering techniques for the treatment of bone defects and non-healing. These approaches are intended to improve the effectiveness of liquid stents or plates in fracture treatment. However, some current examples usually improve only one or at most two aspects of fracture adhesives. The identification or discovery of bone cement with four simultaneous properties of mechanical strength, bone integration, bone conduction and bone induction will be regarded as a milestone of bone cement in fracture treatment.

In order to ensure the mechanical strength of the fixed bone, bone fusion, bone conduction and bone induction of the bone adhesive should be improved to allow the fracture bone to heal as soon as possible after bonding. By adding or changing the composition of bone adhesives, fracture healing can be faster and better, and bone function can be restored earlier than before. This is the most significant advantage of bone adhesives over plates. By adding a crosslinking agent, the sensitivity of this adhesive to water can be reduced and can be used to adhere to tissues and even bone fractures.

Future directions for bone adhesives can be studied at the microscopic level to determine how to improve their ability to withstand large-scale non-linear degradation. At present,

orthopedic surgeons often consider the occasional use of bone adhesives when dealing with bone fragments of fracture fragments around the joint. However, orthopedic surgeons generally do not expect to use bone adhesives to treat long bone fractures. This restriction violates the AO principle for the treatment of fracture fragments. However, in recent years, the principle of fracture treatment has also changed from the AO principle to the biological osteogenesis (BO) principle. Although current research on bone adhesives has focused on improving their bond strength, future bone adhesives should improve their fracture healing properties. The development of standard animal models for in vivo testing of bone adhesives also requires attention. We believe that the improved strategy will help overcome existing challenges and open up new avenues for fracture adhesive treatment."

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