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REVIEW

Application and modification of bone cement in vertebroplasty: A literature review

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ABSTRACT

Vertebral compression fractures are more common in the elderly, particularly in postmenopausal women. Most of these people are accompanied by osteoporosis, which can easily lead to spinal deformities and fractures. Once a fracture occurs, the patient would have severe pain response, limited spinal movement, and need to stay in bed for a long time, resulting in a significant decrease in their quality of life. Percutaneous vertebroplasty (PVP) is a minimally invasive spinal surgery that injects bone cement into the diseased vertebrae for therapeutic purposes. It can quickly relieve pain and stabilize the spine. It is widely used in the treatment of vertebral compression fractures and is currently an ideal treatment method. There are many materials of bone cement used in clinical treatment, and each material has unique characteristics. Many scholars would modify the bone cement according to the advantages and disadvantages to make it more suitable for clinical use. In this review, we discuss the clinical application and modification of bone cement.

Keywords: Bone cement, hardness, modification, osteogenic, vertebroplasty.

In 1984, Deramond of France first applied the method of percutaneous intravertebral injection of bone cement to successfully treat a patient with vertebral hemangioma, setting a precedent for percutaneous vertebroplasty (PVP).[1] Later, PVP was widely used in the treatment of osteoporotic vertebral compression fractures (OVCFs). The PVP refers to a minimally invasive spinal surgery technique that injects bone cement into the vertebral body through the pedicle or by the pedicle to relieve back pain, increase the stability of the vertebral body, and restore the height of the vertebral body. Treatment of bone diseases such as OVCFs, vertebral fractures with osteonecrosis or nonunion after fracture.[2] Later, the PVP procedure was improved, and balloon dilation was performed before the injection of bone cement, that is, percutaneous kyphoplasty (PKP). Compared to PVP, PKP has advantages in reducing the risk of extravasation of bone cement.[3] With the development of materials, the common bone cements in PVP/PKP mainly include polymethyl methacrylate (PMMA), calcium phosphate cement (CPC), calcium sulfate cement (CSC), and composite bone cement. Bone cement has its own advantages in clinical application, but there are also some shortcomings. Some scholars have modified bone cement to improve the performance of bone cement in all aspects.

In this review, we discuss the clinical application and modification of bone cement.

POLYMETHYL METHACRYLATE

Polymethyl methacrylate bone cement, originally used in prosthetic replacement and dentistry, Charnley[4] first reported the use of PMMA bone cement in total

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hip replacement, and then widely used in various orthopedic surgery. The main component of PMMA bone cement is a self-curing acrylic compound, which is composed of powder and liquid.[5] The powder contains benzoyl peroxide, barium sulfate, etc. The liquid component is mainly methyl methacrylate monomer, N-N dimethyl methacrylate base p-toluidine and hydroquinone.

The PMMA bone cement has many advantages, such as injectability, short self-curing time, high adhesion, low price, early pain relief, and good mechanical properties. It is a commonly used bone cement in vertebroplasty. Experiments confirmed that the tensile and compressive strengths of PMMA bone cement were as high as 49 MPa and 114 MPa, respectively.[6] Due to the similar thermodynamic properties and better mechanical properties of bone, PMMA bone cement has been widely used in orthopedic surgery.[7] It is mainly used for the fixation of prosthesis and bone, dental applications, various intra-articular fixation, etc. The PMMA bone cement is a commonly used bone cement in PVP/PKP and has been used to treat vertebral compression fractures caused by various reasons such as tumors or osteoporosis. Dwivedi et al.[8] performed vertebroplasty in 52 patients with persistent pain and painful osteoporosis after vertebral compression fractures, with an average injection of 2.20 to 2.22 mL of PMMA bone cement, and the pain score at 24 h after operation decreased from 8.03 to 8.25 before operation to 2.45-2.60. Nas et al.[9] performed a retrospective analysis of 52 patients with primary malignancies who underwent vertebroplasty using PMMA bone cement, 43 of them (79 vertebrae in total) had a Visual Analog Scale (VAS) score, and the median preoperative patient VAS score was 8, decreased to 3 within one day after surgery, and decreased to 2 within one week after surgery. He et al.[10] conducted a retrospective analysis of 11 patients with symptomatic Schmorl's nodes (SNs) who were treated with vertebroplasty and injected with PMMA bone cement. The preoperative VAS score of the patients was 7.9, which decreased 4 h after surgery to 2.1. During 58 months of follow-up, the average VAS was 1.8, and no postoperative complications occurred during the follow-up period.

With the application of PMMA bone cement, it is found that there are many shortcomings, such as inability to degrade, low biocompatibility, easy to cause surrounding tissue damage due to polymerization exotherm, residual monomer toxicity, or bone cement leakage. The PMMA bone cement has low biocompatibility, does not form a trabecular structure with the surrounding cancellous bone, and generates a lot of heat during the polymerization process, and the local temperature can reach 44 to 113°C.[11] During the exothermic process, the toxic compound methacrylate is formed, and if the polymerization reaction of PMMA bone cement is not complete, methyl methacrylate (MMA) monomer will be released.[12] The release of monomers into the circulatory system can lead to the development of bone cement implantation syndrome.[13] Early *in vivo* release from PMMA particles and fragments also results in the release of inflammatory mediators and cellular damage.[14] Trumm et al.[15] conducted a retrospective analysis of 202 patients undergoing vertebroplasty and found that the local leakage rate of PMMA was 58.6%. The injection of PMMA bone cement into the vertebral body increases the possibility of fracture of the adjacent vertebral body. However, Hou et al.[16] confirmed in their meta-analysis that controlling the distribution of bone cement in the vertebral body could reduce the incidence of refracture of adjacent vertebral bodies after surgery.

CALCIUM PHOSPHATE CEMENT

The main components of CPC are various calcium phosphate salts, which are mixed with calcium phosphate powder and liquid components. The CPC is composed of two kinds of calcium phosphate salts such as tricalcium phosphate (TCP), tetracalcium phosphate (TTCP), calcium hydrogen phosphate dihydrate (DCPD), calcium dihydrogen phosphate (MCPM) and calcium hydrogen phosphate anhydrous (DCPA). Made in various combinations. The CPC has the advantages of excellent molding ability, slight exothermic solidification, good osteoconductivity and biocompatibility, and injectability, which has attracted the attention of scholars.[17,18] Calcium phosphate bone cement has self-curing ability and degradability under physiological conditions, and the product after hydration is hydroxyapatite. Studies have found that calcium phosphate has good biocompatibility and can be dissolved and finally replaced by bone tissue.[19] Also, CPCs have high porosity, which facilitates the resorption of bone CPCs and the formation of bone trabeculae. After continuous research and development, CPC has gradually been used in clinical practice.

Nakano et al.[20] conducted a retrospective study, 86 patients with osteoporotic fractures and pseudarthrosis used CPC for vertebroplasty, an average of 44 months, all patients experienced postoperative pain relief, six months after surgery fully healed. Ishiguro et al.[21] performed percutaneous pedicle

vertebroplasty with CPC bone cement in 36 patients with osteoporotic vertebral fractures. The back pain was relieved immediately after the operation, and the VAS score decreased significantly, which was 9.3 before operation and 9.3 after operation. The first day was 6.2, the third day after the operation was 2.8, and it was reduced to 1.5 after one month of follow-up. It can be seen that CPC bone cement can effectively relieve the pain symptoms of the patients, and all achieved bone healing without adjacent vertebral fractures. In addition, CPC has obvious advantages, good biocompatibility and degradability, but low hardness, Yoshii et al.[22] reported that cemented vertebral bodies or collapse of adjacent vertebral bodies might occur after PVP surgery with CPC. The CPC is a stable product, but its clinical application is limited due to its poor mechanical strength and long curing time.[18,23] Currently, CPC is rarely used for vertebroplasty.

CALCIUM SULFATE CEMENT

Calcium sulfate (CS) has three forms: calcium sulfate dihydrate (CSD), calcium sulfate hemihydrate (CSH), and calcium sulfate anhydrous (ACS). The chemical structure determines the characteristics of the three CSs. In CSC, the CS component exists in the form of CSH, which has high strength and self-curing properties.[24] The CSC is composed of powder and liquid components, which are mixed thoroughly to form a paste. Studies have suggested that CS is an excellent bone graft substitute, effective and safe for orthopedic and dental applications.[25] In 1892, Dreesmann[24] used CSC as a bone filling material to repair bone defects *in vivo* for the first time, and achieved good results.

The CSC has good osteoconductivity, biocompatibility, self-fixation ability, and biodegradability.[26,27] After CS hardening, many micropores would be formed, which can provide a good biological environment, promote cell adhesion, migration and proliferation, and stimulate new bone growth.[24] Yi et al.[28] found that CSC could significantly improve the pull-out strength of pedicle screw fixation, and this effect could be maintained, even if CSC was completely absorbed. Calcium sulfate cement may be a good material for fixation of pedicle screws.

Chen et al.[29] treated 28 patients with thoracolumbar burst fractures with CS vertebroplasty and intermediate screws. Vertebral height and segmental kyphosis loss improved from 55.3% and 20.2 preoperatively to 12.2% and 5.4, respectively. Preoperative pain and function levels showed a mean VAS score of 9.2 and 1.4 at the last follow-up. A retrospective study by Bu et al.[30] found that 28 patients with single-segment thoracolumbar compression fractures underwent short-segment pedicle screw fixation and CSC vertebroplasty, and the mean preoperative relative anterior height was 55.71±15.29%, the mean immediate postoperative improvement was 94.93±5.39%, the mean preoperative average local kyphosis angle was 22.23±5.65°, and the mean postoperative immediate correction was 2.67±4.43°.

Although CSC has many advantages, the currently prepared bone cement still has shortcomings. It has low injectability and biological activity, and its material properties are relatively brittle, which cannot provide sustained long-term mechanical support. Moreover, it is rapidly absorbed in the body, and the rate of degradation is faster than the rate of new bone formation, which limits its clinical application.[31,32] Currently, CSC is rarely used as a bone filling material in vertebroplasty, and it is mostly used in laboratory studies. Some scholars have added organic or inorganic salts to CSC to modify the bone cement, and have made certain research progress.

CORTOSS® BONE CEMENT

Cortoss® (Stryker®, Malvern, PA, USA) bone cement is an injectable bioactive complex, a thermosetting bis-gma (2,2-bis[4(2-hydroxymethylpropenyloxypropyl) phenyl]propane) complex system.[33] Cortoss® bone cement improves many of the shortcomings of PMMA bone cement, and has the advantages of similar mechanical properties to bone, lower exothermic reaction, better biological activity, and better pain relief.[34,35] It is in close contact with bone tissue, new bone can be formed directly on the surface of bone cement, bone cement is interlaced between trabecular bone, and the interface between bone cement and bone would be strengthened as the bone grows in.

Cortoss® bone cement has good clinical application performance, can effectively improve the symptoms of patients and improve the prognosis. Granville and Jacobson[36] performed surgery in a 65-year-old male patient with intractable back pain and failed lumbar fusion. Cortoss® bone cement was injected in the L4-5 space and around the graft. Significant relief was achieved and the spine was stabilized. Jacobson et al.[37] conducted a retrospective analysis and found that 76 patients with osteoporotic vertebral fractures underwent vertebroplasty or kyphoplasty with Cortoss® bone cement, and postoperative pain was significantly relieved. The preoperative VAS averaged 8/10, and the postoperative VAS pain level was 4/10.

Bae et al.[38] compared the efficacy of Cortoss® and PMMA bone cement during vertebroplasty, and the results showed that Cortoss® performed, as well as PMMA in the treatment of patients with osteoporotic vertebral fractures. Cortoss® bone cement flows more easily into smaller fractures than PMMA due to its hydrophilicity and constant viscosity, its bioactive properties allow the material to physically bond with the patient's bone, and there are fewer fractures after surgery Cortoss® bone cement-treated patients.[38] Middleton et al.[39] found that 38% of patients had asymptomatic leakage of Cortoss®, and the rate of bone cement leakage was lower than that of PMMA. However, Palussiere et al.[40] reported an asymptomatic leak rate of Cortoss® bone cement is 76%. Currently, there is a limited number of data in the literature on Cortoss® bone cement studies, and the specific efficacy and related complications need to be further evaluated.

MAGNESIUM PHOSPHATE CEMENT (MPC)

Magnesium phosphate cement was widely used in the construction industry in the early days and became a potential inorganic bone repair material through transformation. Magnesium phosphate cement has attracted attention in the biomedical field due to its rapid setting, early strength acquisition and adhesion properties.[41] It is mainly composed of magnesium oxide, phosphate, retarder and other components. Studies have found that the MPC injected into the body is completely dissolved within 10 months, and the released magnesium can enhance the activity of osteoclasts and osteoblasts, and induce the formation of autologous bone tissue.[42,43] It has high bonding strength and can directly bond small fracture fragments. Heilig et al.[44] found that MPC can effectively resist tensile loads and can significantly increase the pull-out strength of wire-based bone anchors. The evaluation results of cytotoxicity, skin sensitization, subcutaneous irritation and acute toxicity show that MPC is non-toxic, and toxicological experiments show that MPC does not cause deoxyribonucleic acid (DNA) damage and gene mutation, and it is safe.[45] The MPC can quickly solidify, has good biocompatibility, has no obvious toxic and side effects to the organism, and has good injectability and, therefore, it is a promising repair material. However, the compressive strength of MPC cannot reach the average strength of human cancellous bone (13.6 MPa) after repeated tests, suggesting that it is difficult to meet the clinical needs.[46] Mestres and Ginebra[41] developed an MPC based on MgO with sodium dihydrogen phosphate (NaH2PO4) or ammonium dihydrogen phosphate (NH4H2PO4) with early compressive strength; however, ammonium salts may impair the biocompatibility of cement and rapidly the acid-base reaction is an exothermic process. The temperature generated during the MPC mixing process is about 50°C, and the exothermic reaction may damage the surrounding tissue.[47] The MPC needs to be improved to increase strength and reduce heat release, before it can be better used in clinical practice.

PORTLAND CEMENT (PC)

The main strengthening phase of the silicate group hydrated cement is calcium silicate hydrate (CASAH).[48] Tricalcium silicate (C3S) is a typical PC and one of the main active components in mineral trioxide aggregate (MTA). Curing performance and biocompatibility can be used as a new type of bone cement.[49] Studies have shown that C3S is bioactive and biodegradable, and can induce surface bone-like apatite deposition. Silicate ions can stimulate the proliferation and osteogenic differentiation of bone-related cells, and play an important role in the expression of osteogenic genes.[50] The C3S is able to form intimate contact with surrounding bone tissue and support new bone formation, but degradation is slow, which may only be applicable in certain clinical situations that require long-term mechanical support. The PC has poor injectability and is inconvenient to operate. When the powder-to-liquid ratio (PLR) is 3 g/mL, the setting time is 3 to 4 h. Although it has natural high compressive strength, it is very brittle and has poor fracture resistance.[51]

COMPOSITE BONE CEMENT

In the process of research and application of bone cement, each type of bone cement has its own advantages and disadvantages. Experts and scholars have studied various composite bone cements based on complementary advantages, so that bone cements are more beneficial to patients' postoperative recovery and more suitable for clinical operations.

Sulfate and phosphate composite bone cement

Common sulfate bone cements include CS, and phosphate bone cements include calcium phosphate and magnesium phosphate. Calcium sulfate and calcium phosphate composite bone cement is a new material. The dissolution rate of CS is too fast, the mechanical strength is low, and the bioresorption rate of calcium phosphate is slow. It seems feasible to combine calcium phosphate and CS to generate new bone cement to improve their shortcomings.[52]

Yang et al.[27] found that CS/MPC composites have good bioactivity and good biocompatibility, supporting cell attachment and proliferation on the surface. GeneX® (Biocomposites Ltd, Staffordshire, UK) is a clinical composite bone cement containing TCP and CS.[53] Friesenbichler et al.[53] applied GeneX® to defect filling for patients with malignant bone tumors, five of 31 patients (16%) had postoperative complications, which would cause soft tissue inflammation and pain during use. Based on their experience with delayed wound healing in three patients, including one with moderate to severe skin damage in the scarred area, they concluded that this type of bone substitute should not be used for the treatment of bone defects. Chen et al.[52] developed a composite cement derived from TTCP/dicalcium phosphate anhydrous (DCPA)/CSH. There is good biodescription and osteogenicity, and a new bone mesh can be seen in the bone tissue 12 weeks after implantation.

Calcium sulfate has low mechanical strength, cannot bind well to tissues, and CS is absorbed too quickly after *in vivo*. The MPC is a rapid repair material characterized by rapid setting and high early setting strength. Yang et al.[27] developed a new type of CS/magnesium phosphate composite bone cements (CSMPCs). By adjusting the content of CS and magnesium phosphate, the setting time, mechanical strength and degradation rate of the composite can be adjusted, and good biocompatibility can be obtained. Bioactive bone cement with excellent properties, high early setting strength and controllable rate of bone resorption. In *in vitro* tests, CSMPCs composites showed good performance and are a potential new material.

Silicate and phosphate composite bone cement

Although CPC has good biocompatibility, it still has the disadvantages of low mechanical strength after curing and inability to maintain its shape for a long time. Silicon compound is a bioactive material. Silicate can spontaneously solidify, and when mixed with other materials, it can improve the mechanical properties of the material and prolong the setting time.[54] Huan and Chang[55] found that the mechanical strength of calcium phosphate-tricalcium silicate composite bone cement was greatly improved, which was about two to four times that of simple CPC. Mariana et al.[56] compounded traditional CPC and calcium silicate, and then tested the mechanical strength of the new bone cement. When 5% calcium silicate was added, the mechanical strength reached a maximum of 50.4 MPa, and when the addition amount reached 10%, the mechanical strength was lower than before, but still higher than that of traditional CPC. A new type of bioactive composite cement was prepared by adding tricalcium silicate to the traditional CPC. The new composite cement has good biocompatibility.[54]

Some researchers have compounded tricalcium silicate (C3S) and MPC. The latter can produce cement with high mechanical strength after combining with C3S due to its fast setting and relatively dense structure after hydration. The new cement has compression resistance with high strength and short setting time.[43]

Silicate is a bioactive material, which can not only improve the strength and biological activity of composite bone cement, but also can regulate the expression of related genes and stimulate the proliferation of osteoblasts, as well as stimulate type I collagen in human osteoblast-like cells. It induces osteogenic response, and is associated with early calcification of bone tissue.[57,58] Zhao et al.[59] inoculated osteoblast-like cells on composite bone cement samples *in vitro*, which also showed active proliferation of cells and promoted cell differentiation. The most obvious feature of silicate/phosphate composite bone cement degradation *in vivo* is the increase in the formation of microporous structures. The formation of the microporous structure makes the bone tissue more easily attached to the bone cement material, and the growth along the micropore gradually replaces the bone cement material.[60]

BONE CEMENT MODIFICATION

Changing physical and chemical properties

When traditional bone cement is used clinically, it faces problems such as insufficient bone cement hardness, too long or too short setting time, difficult operation, and low biological activity. Zeng et al.[61] found that compared with low-viscosity bone cement, high-viscosity bone cement significantly reduced the leakage rate of bone cement during vertebroplasty for the treatment of OVCFs. The application of high-viscosity bone cement in PVP/PKP may be a potential option to improve intraoperative bone cement leakage in OVCF.[62] Many scholars have modified bone cement to facilitate clinical operations and help patients recover early after surgery. The PMMA bone cement can change the viscosity of the cement by changing the ratio of initiator and monomer.[63] Bone cement can be improved by adjusting the ratio of each component, and new components can also be added to the bone cement to change the strength, viscosity,

setting time, biocompatibility and other properties of bone cement, such as chitosan, polyethylene glycol (PEG), silicon, citric acid, silk fibroin (SF), and iron oxide nanoparticles (IONPs).

Chitosan is a natural polymer similar to protein polysaccharides with good degradability and biocompatibility.[64] Carboxymethyl chitosan is one of the most common chitosan derivatives. Liu et al.[65] added carboxymethyl chitosan to PMMA bone cement, which improved the mechanical properties of the cement, and the bone cement could well fuse with the bone. Valencia Zapata et al.[66] added 15 wt.% chitosan to PMMA, which exhibited increased porosity, roughness, setting time, bioactivity, and decreased maximum exothermic temperature. Liao et al.[67] added 0.2%-2% chitosan into MPC, and the results showed that the compressive strength of bone cement was 45 to 170 Mpa, the setting time was prolonged, the setting time was 12 to 20 min, and the setting temperature was reduced, the compressive strength and collapse resistance were greatly improved.

Polyethylene glycol is a high molecular polymer with good hydrophilicity, lipophilicity, and anticoagulation. It has excellent properties in regulating injection performance, coagulation time, and biological compatibility. The medical device industry is widely used as excipients, solvents, additives or modifying reagents.[68,69] Pina et al.[70] found that adding PEG to CPC can adjust the initial setting time to 9 to 18 min, which is suitable for clinical operations. Polyethylene glycol is often used as a pre-mixed liquid, mixed with bone cement powder to form a paste, which can be stored for a long time and begins to harden after contact with body fluids. de França Silva Azevedo et al.[71] found that PEG did not destroy the beneficial properties of bone cement and could be used as a potential alternative to control the time-temperature profile of the hardening of these materials.

Studies have found that silicon can improve the strength of bone cement. Slane et al.[72] added monodisperse silica to acrylic bone cement to improve the mechanical properties and hydration degree of the cement. While immersing CPC in simulated body fluids, silica sol can improve the physical properties of CPC and the formation rate of carbonate apatite, and silicon ions can also improve the biological function of osteoblasts.[73]

Citric acid modified bone cement can improve the biocompatibility of the material, obtain higher compressive strength than its components, and promote the proliferation of MC3T3-E1 osteoblasts.[74] Wynn-Jones et al.[51] added citrate to PC, which made the PC injection rate exceed 90%, the compressive strength could be increased to 125 MPa, and the PC coagulation time was reduced to 20 min.

Silk fibroin is a collagen-like structural protein with hydroxyl and carboxyl termini, which forms a chemical bond with sulfate, which can improve the cohesion between CSC molecules and improve the durability and compressive strength of CSC prolong the clotting time of CSC.[75,76]

Some scholars added IONPs to CPC, and the alkaline phosphatase (ALP) activity and osteogenic gene expression increased significantly. Stem cells have the strongest promoting effect on osteogenic differentiation. The morphological and chemical niche provided by IONP promotes human dental pulp stem cells (hDPSC) viability, promotes cell spreading, and promotes cell osteogenic differentiation and bone matrix formation.[77,78]

Increased antibacterial properties

In clinical treatment, it was found that some patients had secondary infection after injection of bone cement. Bacterial osteomyelitis remains one of the most significant clinical problems in orthopedic surgery. Biomaterials have a high risk of deep infection in orthopedic surgery, one of the main reasons is the phenomenon of bacterial adhesion to biomaterials and the formation of biofilms by strains. Conventional treatment with systemic antibiotics is expensive and difficult to reach local bone tissue. Scholars hope to solve this problem by increasing the antibacterial properties of bone cement.

Chitosan is known for its hemostatic and antibacterial properties, and some scholars have found that adding chitosan to PMMA can significantly reduce the viability of Candida albicans on PMMA biofilms.[79] Adding antibiotics to bone cement to make antibiotic-loaded bone cement (ALBC) is also an effective way to treat local infection.[80] Placing ALBCs at the surgical site helps to maintain high local drug concentrations that cannot be achieved with intravenous administration and reduces complications and toxicity associated with systemic administration.[81] Grubhofer et al.[82] conducted a retrospective study of periprosthetic infections treated with antibiotic-containing bone cement spacers, and the infection was successfully controlled in 36 of 38 patients (95%). Opalko et al.[83] included 50 patients with vertebral fractures due to osteoporosis or trauma, who underwent vertebroplasty with antibiotic-containing PMMA

bone cement, and were followed up for one year after surgery. The results showed that none of the patients developed infection. The PMMA bone cement containing antibiotics has been widely used in the treatment of osteomyelitis.[84] To better prevent infection, antibiotics in bone cement must have a long-term stable release. Some studies have found that PMMA bone cement is unstable in combination with antibiotics, and PMMA bone cement is non-absorbable, a potential foreign body for bacterial colonization, and needs to be removed by a second surgery.[85] The CPC has better absorbability and higher porosity. Good porosity is not only conducive to osteogenesis, but also enhances its ability to load growth factors or drugs, so CPC is also used as a carrier for controlled drug release.[86,87] The CPCs have received increasing attention for their controlled release of water-soluble drugs.[88]

Studies have shown that ALBC is more effective in reducing the incidence of deep infection than standard bone cement plus systemic antibiotics.[89] The advantage of ALBC is that high concentrations of antibiotics can be delivered to the surgical site and maintained at a high concentration, which is the most effective way to eradicate local microorganisms while reducing systemic side effects. However, there is also evidence that antibiotic-containing cement is not immune to the development of resistant bacteria. Walker et al.[90] found that no studies were found to investigate the potential for bacteria to develop resistance to CS-impregnated antibiotic beads. Therefore, the application of antibiotic bone cement needs to be further evaluated.

Enhanced osteogenicity

In vertebroplasty, different bone cements have different properties, and some bone cements have relatively poor osteogenic properties, which affects the prognosis. Therefore, some scholars increase the osteogenicity by improving the composition. Metal ions with low human content are increasingly used in the modification of bone graft materials and bone cements. Low doses of bioactive metal ions have the potential to accelerate bone defect healing and promote osteogenesis and neovascularization.

In the human body, the content of strontium (Sr) is very small, but 99% of Sr is accumulated in the bones. The Sr can simultaneously stimulate bone formation and prevent bone loss and has been used in the treatment of systemic osteoporosis.[91] Lode et al.[92] introduced Sr ions into CPC. Studies have found that Sr-containing bone cement can stimulate bone precursor cell proliferation and *in vitro* osteogenic differentiation compared to other Sr-free bone cements. Schumacher et al.[93] found that Sr-modified calcium phosphate bone cements (SrCPCs) affected the expression of osteoclast characteristic markers (TRAP, CAII, Cx43), confirming the effect of SrCPCs on osteoclast absorption is inhibited. The new Sr-containing hydroxyapatite (Sr-HA) bone cement is superior to PMMA in terms of mechanical properties, biocompatibility and osseointegration. Korovessis et al.[94] performed vertebroplasty in 38 patients, with an average follow-up of 28 months. The results showed that Sr- Sr-HA had the same effect as PMMA. The vertebral body is replaced by bone resorption and is a good bioactive cement.

The introduction of Cu^{2+} into CPC is a suitable way to prepare multifunctional bone graft materials, which enables CPC to have dual functions of osteogenesis and angiogenesis.[95] Bernhardt et al.[96] incorporated Co^{2+}, Cu^{2+}, and Cr^{3+} into bone cement. The study found that these bone cements released very low metal ions, reducing the risk of cytotoxic reactions. The Co^{2+}-doped calcium phosphate can promote angiogenesis. Low-dose Cu^{2+} cement may be beneficial for bone regeneration. Compared to unmodified calcite cement, Cr^{3+}-doped cement can improve the viability of bone grandmother cells. Therefore, Cr^{3+}-doped CPC is a promising new material for bone regeneration.[96]

Bisphosphonates (BPs) are anti-resorptive drugs commonly used to inhibit bone resorption. They are divided into two groups based on whether or not they contain nitrogen. etidronate, clodronate and tiludronate are non-nitrogenic BPs, while pamidronate, neridronate, olpadronate, alendronate, ibandronate, risedronate, incadronate, and zoledronate belong to the nitrogen-containing category.[97] Some studies have found that adding phosphate-rich bone cement can play an important role in improving bone microstructure, increasing bone volume fraction and trabecular thickness, and reducing trabecular spacing.[98] Verron et al.[99] added alendronate to CPC, the bone volume/total volume percentage (BV/TV), trabecular thickness (TbTh), and trabecular number (TbN) values were significantly increased. Wu et al.[100] added zoledronic sodium to CPC, and zoledronic sodium implants improved bone-implant contact, bone regeneration, and bone density in cancellous rats.

Bone morphogenetic protein (BMP) is a multifunctional growth factor belonging to the transforming growth factor superfamily, released by platelets and osteoprogenitor cells, and has a positive effect on bone grafting, stimulating

cell proliferation, osteoblast differentiation and direct bone matrix formation, of which BMP-2 is the most extensively studied.[101,102] Porous HA scaffolds with macroporous structure are suitable for blood vessel formation, nutrient delivery and bone ingrowth, and can provide an optimal three-dimensional microenvironment for carrying bone-related growth factors or nutrients.[103] Jun et al.[104] added BMP-2 to the hybrid coating on porous HA scaffolds and found that BMP-2 could be released continuously for up to six weeks and could significantly increase new bone formation. Geibel et al.[105] performed posterior lumbar interbody fusions (PLIFs) in 48 patients, using recombinant human bone morphogenic protein type 2 (rhBMP-2) during the operation. Compared to autologous bone transplantation, the fusion rate is higher, and studies have shown that the use of rhBMP-2 in PLIFs is safe and effective. The BMP can increase the osteogenicity of bone fillers and is a very potential bioactive molecule in filler modification.

In conclusion, the development of bone cement has attracted the attention of clinicians. Common bone cements include PMMA bone cement, CPC, CSC, MPC, etc. Each bone cement has its own characteristics. In clinical practice, appropriate bone cement should be selected according to the characteristics of bone cement. In vertebroplasty, CSC can significantly improve the pull-out strength of pedicle screw fixation, and is often used to fix pedicle screws. The ALBC is used to prevent surgical site infections. In recent years, there has been some progress in bone cement research in vertebroplasty. The researchers modified the bone cement to change the strength, setting time, viscosity, biocompatibility, antibacterial properties, and osteogenicity of the bone cement to meet the clinical needs. Undoubtedly, long-term efficacy and safety assessments are required, before the results can be translated into clinical practice.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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