CURRENT CONCEPTS REVIEW

Different Modification Methods of Poly Methyl Methacrylate (PMMA) Bone Cement for Orthopedic Surgery Applications

Fatemeh Ghasemi, PhD; Afsaneh Jahani, PhD; Ali Moradi, MD; Mohammad H. Ebrahimzadeh, MD; Nafiseh Jirofti, PhD

Research performed at Orthopedic Research Center, Bone and Joint Research Laboratory, Mashhad, Iran

Received: 18 March 2023 *Accepted: 12 June 2023*

Abstract

In clinical practice, bone defects that occur alongside tumors, infections, or other bone diseases present significant challenges in the orthopedic field. Although autologous and allogeneic grafts are introduced as common traditional remedies in this field, their applications have a series of limitations. Various approaches have been attempted to treat large and irregularly shaped bone defects; however, their success has been less than optimal due to a range of issues related to material and design. However, in recent years, additive manufacturing has emerged as a promising solution to the challenge of creating implants that can be perfectly tailored to fit individual defects during surgical procedures. By fabrication of constructs with specific designs using this technique, surgeons are able to achieve much better outcomes for patients. Polymers, ceramics, and metals have been used as biomaterials in Orthopedic Surgery fields. Polymeric scaffolds have been used successfully in total joint replacements, soft tissue reconstruction, joint fusion, and as fracture fixation devices. The use of polymeric biomaterials, either in the form of pre-made solid scaffolds or injectable pastes that can harden in situ, shows great promise as a substitute for commonly used autografts and allografts. Polymethyl methacrylate (PMMA) is one of the most widely used polymer cement in orthopedic surgery. The present paper begins with an introduction and will then provide an overview of the properties, advantages/disadvantages, applications, and modifications of PMMA bone cement.

Level of evidence: III

Keywords: Bone Cement, Infections, Modification, Orthopedic surgery, Polymethyl methacrylate (PMMA)

Introduction

Polymethyl methacrylate (PMMA), commonly referred to as bone cement, is one of the most frequently utilized polymeric structures in orthopedic surgery.[1] Bone cement is a chemical compound that consists of synthetic organic and inorganic material and is introduced as a golden standard in joint replacement surgery. In other words, it has been successfully used as implant fixation in various orthopedic, osteotomy, and trauma surgeries to strengthen and stabilize weak or damaged bones using artificial joints (prostheses).[2]

Corresponding Author: Nafiseh Jirofti, Orthopedic Research Center, Mashhad University of Medical Science, Mashhad, Iran;Bone and Joint Research Laboratory, Ghaem Hospital, Mashhad University of Medical Science, Mashhad, Iran
Email: nafise.jirofti@gmail.com

Co- Corresponding Author: Mohammad H. Ebrahimzadeh, Orthopedic Research Center, Mashhad University of Medical Science, Mashhad, Iran

Email: Ebrahimzadehmh@mums.ac.ir

Accordingly, the acquirement of the best knowledge about the structures, applications, and modification of the PMMA is of paramount importance to all orthopedic surgeons.

The PMMA was first introduced in 1901 by Otto Rohm.[3] However, this material had not been widely used in orthopedics until Sir Jan Charnley applied it to graft prostheses to the bone for total hip arthroplasty in the early 1960s.[4] The article written by Dennis Smith provides a thorough overview of the advancement of PMMA usage in orthopedics, including his partnership with Charnley.[5] Moreover, the application of bone cement for filling the medullary canal of the bone, due to the ability of bone cement to blend with the bone morphology, was discovered

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by Charnley.

Understanding the mechanical and biocompatibility properties of materials is crucial for their use in orthopedic surgery. Knowledge of the mechanical and biological properties of materials is the key point for their usage in orthopedic surgery. Furthermore, when it comes to orthopedic devices, the most critical property is biocompatibility as a biological inertness,[6] meaning the lack of reactivity with the biological surroundings. Under normal physiological conditions (depending on parameters, such as pH and temperature), a certain level of reactivity occurs, which may result in limited implant degradation. However, this is deemed acceptable as long as it does not compromise the mechanical strength of the implant or produce any harmful by-products.

In modern medicine, polymer materials have emerged as a viable substitute for various types of materials across medical fields, such as sports medicine, joint replacement, spine, and orthopedic trauma applications.[7,8] Clinical studies have indicated that bone cement can be safely used for hip and knee prosthetic fixation, as approved by the U.S. Food and Drug Administration. Orthopedic polymers can be classified in several ways, such as by their source (naturally occurring versus synthetic), absorbability (absorbable versus non-absorbable), clinical application, and availability (commercially available versus research use only).

The PMMA is an illustration of a biocompatible and non-absorbable synthetic polymer that consists of a powder polymer and a liquid monomer.[9] The monomer is mainly (approximately 97%) methyl methacrylate, which also contains an accelerator and stabilizer.[10] The color or composition of the powder varies by brand; however, it generally contains microspheres of finely ground PMMA or copolymer with small amounts of radiolucent material and primers.

Antibiotic loading on bone cement is the first strategy to prevent or treat infections that are associated with some problems. It is confirmed that the addition of antibiotics to cement is a factor that significantly impairs the strength of cement.[11-13] Moreover, other factors, such as molecular weight, mixing, and sterilization methods also affect the mechanical properties of PMMA.[14-16] In addition, despite the wide and successful use of PMMA in orthopedic surgery, relatively rare complications, such as tissue necrosis occur due to the high heat of the polymerization process during implantation.[17,18]

Bone cement implantation syndrome (BCIS) is a serious complication that can occur during or after total hip arthroplasty, and in rare cases, it may even be fatal. Common clinical symptoms of BCIS can include hypoxia, hypotension, cardiac arrhythmia, and in severe cases, cardiovascular collapse.[19] Removal of the cement from the potentially fatal site of the implant can lead to "cement embolism", which is a complication.[20,21]

Several studies have been conducted to modify and enhance the structural, mechanical, and biological properties of PMMA bone cement. The focus of these studies was to control the essential parameters in bone cement synthesis, such as polymerization temperature,[22-28] setting time,[23] compressive strength,[22,27,29,30] flexural modulus, bone reconstruction efficacy,[22] promotion of porosity,[23,26] and enhancement of biological activity. In addition, improvement of cell viability,[31] promotion of the proliferation and differentiation of bone marrow stromal cells,[31] promotion of crosslinking and reduction of the quantity of monomer required for polymerization process,[24] higher osteoblasts activity,[24,26] and enhancement of the binding ability of bone cement and bone are essential parameters for the improvement of bone cement quality.[28]

Every year, many studies are performed on PMMA. One of the most important topics of these articles is the modification of this polymer with different methods. Despite the potential applications of bone cement in orthopedic surgery, the mentioned problems are a drawback of bone cement in most biomedical and biological applications. In this regard, the present review article focuses on different modification methods of PMMA bone cement for orthopedic surgery applications and will have a general look at this issue

Materials and Methods

Different modification methods of polymethyl methacrylate bone cement

The PMMA is a commonly used material for implant fixation in orthopedic and trauma surgery. However, its high exothermic reaction temperatures, low bioactivity, and toxicity of the monomer can be considered drawbacks for orthopedic applications [Figure 1]. In order to overcome the mentioned disadvantages, a combination of PMMA with different inorganic bioactive fillers is suggested. The most important inorganic bioactive materials include tricalcium silicate (TCS),[32] β-TCP,[33-35] hydroxyapatite (HA), titanium dioxide (TiO2),[36] bioactive glass,[37] as well as polymer materials and nanomaterials,[38,39] and mixed materials, all of which have been described in the following with details.

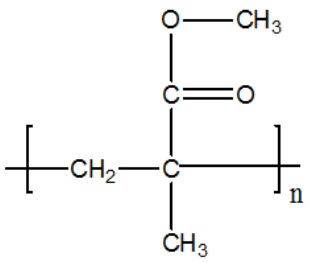

Figure 1. Chemical Structure of PMMA

Polymethyl methacrylate modifications with inorganic bioactive compounds (bioceramics or bioglass): Tricalcium silicate

Researchers have found that the incorporation of 30% of TCS into cement setting and hydration processes can lead to a decrease in exothermic temperature and pH variation. Moreover, the reduction of the process temperature and addition of TCS did not negatively affect the mechanical and handling properties of the bioactive PMMA/TCS composite. In fact, an *in vitro* study revealed that the PMMA/TCS composite had higher cell viability, compared to pure forms of PMMA and TCS. Animal models used in an *in vivo* study

also indicated that the composite materials reinforced the biocompatibility of the proposed PMMA/TCS bone cement, making it more effective at bone formation. By the combination of the advantages of each component, a more effective composite bone cement material can be created.[32]

β-tricalcium phosphate

Combination of PMMA and β-TCP is the most common bone graft mixture used in orthopedic applications. Although biocompatibility, bioactivity, mechanical stability, and the ability to combine with the bone tissue of the host are the important features of bone cement, enough *in vivo* studies (animal models) that have evaluated and confirmed the mentioned properties are not available.[33]

By the addition of β-TCP to PMMA, bone cement with a porous structure is formed, which improves many of the previously mentioned disadvantages, including lower polymerization temperature (44 °C), faster setting time (approximately 9 min), as well as lower flexural modulus (900 MPa), and lower compressive strength (50 MPa).[21] Additionally, bone cement with a microporous structure provides blood vessels and osteocytes the opportunity to colonize the surface of the remaining bone space after cement reabsorption. This also allows osteoblasts to uniformly regenerate bone tissue at the bone-cement interface.[21]

Bioglass

The bioactive glass family (glass and glass-ceramic) is constituted of a combination of silicon dioxide, sodium oxide, calcium oxide, and phosphorous pentoxide. This biomaterial and HA are biocompatible and bioactive ceramic materials with excellent properties, such as good bioactivity and high mechanical strength that make it useful for a wide range of medical applications for bone and joint replacement.[40-42] Addition of glass-ceramics, such as bioglass ($Na_2O–CaO–SiO_2–P_2O_5$) and Ceravital ($Na_2O–K_2O–MgO–CaO–SiO_2–P_2O_5$), to the PMMA bone cement structure can significantly reduce peak temperatures (39.1–47.2°C) during polymerization process.[23]

These compounds are known to form a chemical bond with bone tissues. Researchers have shown that besides glass-ceramic with a composition of $MgO–CaO–SiO_2–P_2O_5–CaF_2$, containing apatite and wollastonite (AW glass synthesized by Kokubo et al.),[43] bone cement that includes micron-sized titania particles (titanium oxide) can help stabilize prostheses and vertebroplasty.[36]

Polymethyl methacrylate modifications with polymers: Chitosan

Chitosan, the second most abundant among all known natural polymers, is a biodegradable, nontoxic, and biocompatible polymer with many applications in the field of medicine.[44-47] Chitosan is a component of bone extracellular matrix (i.e., glycosaminoglycans) and possesses excellent biological and biocompatible properties. As a result, it can promote more stable binding between bone and cement.[48]

Studies have shown that the addition of 5-10% of chitosan into cement composite enhances the mechanical properties and reduces the polymerization temperature.[24] If acrylic bone cement is used without chitosan, it may affect the activity of osteoblasts, the cells responsible for bone formation. The absence of chitosan in the bone cement could lead to a decrease in the attachment and proliferation of osteoblasts, which could ultimately result in reduced bone growth and healing. Therefore, the addition of chitosan to acrylic bone cement can be beneficial for the improvement of the interaction between the biomaterial and osteoblasts, as well as for the enhancement of bone regeneration.[25]

As the percentage of chitosan added to the modified acrylic bone cement increases, the mechanical properties demonstrate a reduction to varying degrees.[49] Accordingly, researchers have speculated that the higher stiffness of fillers, compared to the surrounding bone is the main cause of osteoporotic fractures around PMMA bone cement.[50-52] In this regard, an *in vitro* study examined the low-modulus PMMA cement, and the results indicated that the fracture resistance of reinforced functional spine units can be better maintained through the use of low-modulus PMMA as opposed to conventional PMMA cement. The fracture resistance of reinforced functional spine units can be better maintained using low-modulus PMMA, compared to conventional PMMA cement.[53]

Linoleic acid

In another study, conventional PMMA was modified by the addition of linoleic acid (LA) to create a low-modulus bone cement.[54] Modification by the addition of linoleic acid in the formulation shows the potential to prevent such fractures, thanks to its bone-friendly mechanical properties, and also provides comfortable handling properties.[55] Additionally, tests using animal models suggest that the addition of LA into PMMA bone cement does not result in increased cytotoxicity to the surrounding tissue at the implantation site. Furthermore, it has been observed that modified bone cement exhibits no significant differences, compared to conventional PMMA cement in terms of tissue response at the bone-implant interface, biocompatibility, and bone repair.[29]

Polymethyl methacrylate modifications with nanomaterial

Prosthetic joint infection (PJI), as a tremendous burden for individual patients, is the most serious complication following total joint arthroplasty. Although only a small percentage of joint arthroplasties will develop an infection, it can be challenging to manage due to its association with other health issues. The high morbidity and low quality of life that result from such infections make them even more difficult to manage. Antibiotic-loaded PMMA bone cement is commonly used in orthopedic surgery for both prophylaxis and management of PJI, with the aim of minimizing infection rates.

Nevertheless, its usage is still debated due to dissatisfaction with the continuous increase in bacterial resistance to antibiotics. This has led to numerous research efforts aimed at developing different types of cement that do not contain antibiotics, yet exhibit excellent antimicrobial effectiveness. There is an emerging new generation of antimicrobial PMMA bone cement known as antibiotic-free antimicrobial PMMA bone cement (AFAMBCs).[13] Regarding the problem of bacterial resistance to antibiotics loaded on PMMA, nanoparticles may increase their effectiveness.[56,57] One of

the advantages of AFAMBCs is their ability to eliminate the problem of bacterial resistance while exhibiting bactericidal activity.[39] It appears that nanoparticle carriers have a longer delivery period in comparison to the release of antibiotics.[57]

Effectiveness of antibiotic-loaded bone cement in reducing the risk of PJI after implantation surgery ranges from 20 to 84%.[58] Regarding the obtained results,[59] antibiotic-loaded bone cement was combined with TiO2 nanotubes (TNTs) to facilitate an enhanced release of antibiotics. It is reported that over 50% of the antibiotics loaded into the carriers (such as gentamicin or vancomycin) were released within two months.[60]

The ideal physical-chemical properties of compounds in the nanoscale range consist of a high surface area-to-mass ratio, high activity, and minimal diffusion restrictions. These properties differ significantly from those exhibited by the same materials on a micro or macro scale.[61] In this regard, the addition of nanomaterials in structure can increase the mechanical properties and fracture toughness.[62] Moreover, nanoparticles have made significant contributions to the fields of drug therapy, gene therapy, modern drug development and delivery methods, diagnostic imaging techniques, and other related fields.[63]

Among nano-metals, nano-silver is the most widely used.[64] Based on a study performed by Bhattacharya et al., it has been found that PMMA cement loaded with 1 wt. % of nano-silver exhibits complete resistance to various bacterial growth, surpassing gentamycin efficacy, without causing any cytotoxicity. Nano-silver and antibiotics[65] were added in other investigations to bone cement. Reports have indicated the beneficial effects of nano-silver and nano-copper on antibacterial efficiency; however, it should be noted that nano-copper has also been associated with cytotoxicity.[66,67]

Moreover, graphene oxide (GO) is a nanomaterial that consists of oxidized graphene[68] and exhibits biocompatibility. When incorporated into the PMMA matrix at a concentration of 0.1 wt% GO or G powder, it enhances the mechanical properties of the material in both static and fatigue conditions.[69] Furthermore, the presence of functional groups on the surface of GO powder contributes to improved dispersion of GO within the PMMA matrix. This enhanced dispersibility enhances the interface bonding between GO and PMMA, resulting in a stronger bond without any noticeable cytotoxic effects.[69]

In previous studies, it has been demonstrated that the incorporation of GO leads to approximately a 19% reduction in the maximum temperature reached during the polymerization process. Additionally, the setting time of the material was prolonged, indicating the inhibitory and delaying effects of GO on the polymerization process.[26] Upon investigation, it was discovered that the introduction of 0.3 wt% GO to acrylic bone cement resulted in favorable antibacterial activity.

Polymethyl methacrylate modifications with mixed materials

Despite the fact that PMMA bone cement commonly serves as prosthetic fixation in orthopedic applications, the interface between bone and cement is known to be a point of weakness; therefore, this is a disadvantage. Nevertheless, the addition of just a single material tends to focus on one aspect of modification, the effect being one-dimensional. Conversely, the addition of multiple materials simultaneously allows for a more comprehensive improvement in the overall performance of the material. In this regard, Tsukeoka et al.[28] addressed this issue by developing bioactive PMMA cement through modification with a specific amount of γ methacryloxypropyltrimethoxysilane and calcium acetate. They compared the handling, mechanical, and histological properties of the modified bone cement with those of conventional cement. Their obtained results demonstrated that the modified specimens displayed significantly enhanced bonding strength between the bone and implant. Furthermore, histological observations and micro-focus X-ray computed tomogram (micro-CT) images revealed the presence of osteoconduction in the modified cement. This characteristic was absent in the conventional PMMA bone cement. These results indicated that modification can effectively enhance osteoconduction with PMMA bone cement, providing stable fixation for an extended period following implantation.[28]

Mineralized collagen (MC) is a composite material consisting of organic type I collagen and nano-hydroxyapatite. This unique composition closely resembles the chemical composition and microstructure of the natural bone matrix. Consequently, MC holds great potential for the modification of PMMA bone cement.[70]

Recent studies have shown that MC-PMMA bone cement can have a beneficial impact on both the proliferation and differentiation of bone marrow stromal cells (BMSCs).[70] In a study conducted on a rabbit vertebral animal model, it was found that implanting MC-PMMA resulted in significant bone repair after just 4 weeks. Furthermore, after 8 weeks, the MC material had undergone degradation, leading to noticeable remodeling lacunae and infiltration of osteoblasts. After 12 weeks, the borders and a significant portion of the interior areas of the MC had been nearly entirely replaced by the newly formed bone. The research team conducted a small-scale clinical study and conclusively confirmed the favorable long-term efficacy of MCPMMA bone cement.[31]

Another study revealed that the addition of HA nanofibers and two-dimensional magnesium phosphate (MGP) nano-sheets to PMMA bone cement effectively enhances its compressive strength. Furthermore, the addition of MGP nano-sheets to PMMA can induce the formation of apatite on the surface of the material, thereby enhancing its biological activity.[30] Similarly, it has been established that the addition of HA nanofibers and MGP nano-sheets to PMMA can improve cell viability in a similar manner.[30]

Conclusion

Humans have always sought to find a way to heal damaged organs or replace disabled parts of their bodies with suitable materials; however, it is not an easy task to reach a material

that is suitable and compatible with the human body. Throughout history, humans have used wood, natural organs of animals, plants, stones, and primary metals as the first bio-implants. Orthopedic implants must be able to withstand significant and repeating mechanical loads. Therefore, when choosing a biological material for orthopedic applications, special attention should be paid to the mechanical properties of the material (for example, ultimate strength and resistance to fatigue and wear). Although metals were the first biomaterials to be used in orthopedic surgery and are still widely used today, bone cement as implant fixation in orthopedic surgery has attracted a lot of attention. Accordingly, the present review article aimed to investigate one of the most common polymer bone cements in orthopedics (i.e. PMMA). The PMMA has long been a standard material used for bone defect repair, while its use has exposed several deficiencies; nevertheless, PMMA is still widely used in the field. Scholars have employed various modification methods to enhance the performance of PMMA, aligning it more closely with the purpose and clinical treatment requirements. Although the research and development of novel materials are currently being explored, the rapid production and refinement of these materials pose significant challenges. Additionally, the long-term efficacy of diverse materials necessitates further observation and improvement in the future.

Acknowledgement

The authors would like to thank the Bone and Joint Research Laboratory, Ghaem Hospital, Mashhad, Iran, Orthopedic Research Center, Department of Orthopedic Surgery, Mashhad University of Medical Science, Mashhad, Iran, for the provision of the facilities for this research.

Conflict of interest: None

Funding: None

Fatemeh Ghasemi PhD [1,2**]
Afsaneh Jahani PhD [1, 2, 3**]
Ali Moradi MD [1, 2]
Mohammad H. Ebrahimzadeh MD [1, 2]
Nafiseh Jirofti PhD [1,2]

1 Orthopedic Research Center, Mashhad University of Medical Science, Mashhad, Iran

2 Bone and Joint Research Laboratory, Ghaem Hospital, Mashhad University of Medical Science, Mashhad, Iran

3 Department of Biomedical Engineering, Faculty of New Sciences and Technologies, Semnan University, Semnan, Iran

** Fatemeh Ghasemi and Afsaneh Jahani equally contributed as co-first author.

Table. List of abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
AFAMBCs	Antibiotic-free "antimicrobial" bone cements	MMA	Methyl methacrylate
BMSCs	Bone marrow stromal cells	PJI	Prosthetic joint infection
HA	Hydroxyapatite	PMMA	Poly (methyl methacrylate)
LA	Linoleic acid	TCS	Tricalcium Silicate
MBFs	Mineralized bone fibers	B-TCP	β-tricalcium phosphate
MC	Mineralized collagen	Titania	Titanium oxide
MGP	Magnesium phosphate	TNTs	Titanium dioxide (TiO_2) nanotubes

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