Review Article

Polymethylmethacrylate: Properties and Contemporary Uses in Orthopaedics

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Abstract

Polymethylmethacrylate (PMMA) has been used in orthopaedics since the 1940s. Despite the development and popularity of new biomaterials, PMMA remains popular. Although its basic components remain the same, small proprietary and environmental changes create variations in its properties. PMMA can serve as a spacer and as a delivery vehicle for antibiotics, and it can be placed to eliminate dead space. Endogenous and exogenous variables that affect its performance include component variables, air, temperature, and handling and mixing. PMMA is used in hip arthroplasty and vertebral augmentation, notably, vertebroplasty and kyphoplasty. Cardiopulmonary complications have been reported.

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History

Otto Röhm is credited with the development of polymethylmethacrylate (PMMA) in 1901.[1] A dough-like, workable form of PMMA was refined by the Kulzer and Degussa companies in 1943.[2] Their developments led to the introduction of cold-cured PMMA, which hardens at room temperature.

PMMA attracted interest in the field of orthopaedics in the 1940s with the development of acrylic femoral hemiarthroplasties by Jean and Robert Judet.[3] Kiaer and Haboush separately reported using PMMA to affix femoral implants in the early 1950s.[4] Modern success with and the popularity of PMMA in orthopaedics is attributable to Sir John Charnley, whose work was affected by his exposure to the field of dentistry and his inherent interest in biomaterials.[4] Charnley's early clinical accomplishments established a foundation for the continued use of PMMA in orthopaedics.

Composition

PMMA is composed of polymer powder and monomer liquid, often supplied in a 2:1 ratio. The monomer, a colorless liquid with a characteristic odor, is packaged in ampules. The liquid components remain relatively constant among commercially available cements. Methylmethacrylate comprises 97% to 99% of the liquid. N,N-dimethyl-p-toluidine acts as an accelerator, making up 0.4% to 2.8% by weight. Traces of hydroquinone (15 to 75 ppm) stabilize the monomer, preventing premature polymerization. The powder is more variable in composition among brands, which contributes to differences in properties. Microspheres of ground PMMA or copolymer contribute to 83% to 99% of the powder. The remaining components in-

clude a radiopacifier, either barium sulfate ($BaSO_4$) or zirconium dioxide (ZrO_2) (8% to 15% by weight), as well as an initiator, benzoyl peroxide (0.75% to 2.6%). Other variations include the initiator tri-n-butylborane and accelerator 2,5-dimethylhexane-2,5-hydroperoxide (in Bonemite [Mochida Pharmaceutical, Tokyo, Japan]), chlorophyll dye (in the monomer of Palacos R [Zimmer, Warsaw, IN]), and ethanol and ascorbic acid (in the monomer of CMW [DePuy, Piscataway, NJ]).[5] Other additives to the powder may include antibiotics or dyes.

Properties

Reaction

Combining powder and liquid monomer initiates an exothermic reaction. Peak temperatures in vitro reach 113°C in the anterior cortex of vertebral bodies.[6] In vivo temperatures are reported to be between 40° and 56°C.[2,7] Methylmethacrylate monomer, the basic building block of PMMA, contains carbon-carbon double bonds, which react with the free radical produced by the activator and initiator. The monomer is free to interact with other monomer molecules, creating a growing polymer chain. The powder initiates polymerization and creates a workable dough.

Curing

Curing is divided into four phases: mixing, sticky, working, and hardening. The mixing phase ends once a homogenous state has been achieved. The sticky phase is distinguished by low viscosity, in which the mixture fails to separate from a gloved finger. In the working phase, the cement can be handled without adherence. The hardening phase is the time in which cement cannot be mixed and forms a solid. Peak temperatures are reached in this last phase. There is no specific time for each phase, given the wide variation in cements and testing conditions. For most cements, hardening occurs within 10 to 20 minutes.[8,9] Commercial PMMA can be categorized as high or low viscosity based on which phase predominates during the curing process. Low-viscosity cements have longer sticky phases and shorter working phases. High-viscosity cements have long handling times and a short sticky phase.

Conversion of monomer molecules to fewer long-chain polymer molecules leads to shrinkage of approximately 6% to 7%.[2,9] Radiopaque material does not participate in the polymerization reaction, and residual monomer polymerizes over several weeks. A consensus of minimal standards for testing and material performance has been developed for acrylic bone cements by the American Society for Testing and Materials and the International Organization for Standardization.[10]

Like bone, cured PMMA is strongest in compression and weakest in tension and under shear stress. PMMA has viscoelastic properties, exhibiting greater stiffness at higher strain rates. Its mechanical properties lie between those of cancellous and cortical bone. The bending modulus of PMMA is between 1 and 3 GPa,[11-13] while that of cortical and cancellous bone is between 10 and 20 GPa and 10 and 2,000 MPa, respectively. PMMA has a compressive strength between 85 and 110 MPa, compared with 133 to 193 MPa for cortical bone. The tensile strength of commercial PMMA and cortical bone are 30 to 50 MPa[11] and 51 to 133 MPa, respectively.[12-14] Fatigue strength, creep, and stress relaxation may be more relevant than tensile strength to long-term clinical performance. Fatigue strength is a product of continuous cyclic loading, creep represents deformation under constant load, and stress relaxation represents the changes of stress during constant strain.

Variations

Endogenous, monomer/polymer, and exogenous variables affect in vitro and in vivo performance of PMMA. Endogenous factors include component variations, formulation ratios, molecular weights, and physical size of the specimen. Exogenous variations include entrapped air, handling and mixing times, water and body fluids, temperature, and sterilization.

Endogenous

PMMA is often the exclusive polymer, but it may be combined with other copolymers.[9] The molecular weight of the polymer and cured cement influence handling and mechanical properties. Powders with lower molecular weight facilitate diffusion of monomer during mixing but may reduce cement fatigue performance.[9,13] Antibiotics have become an important additive to PMMA. Although commercial cements are manufactured with antibiotics premixed, hand-mixed preparations are still commonplace. The amount of antibiotic in commercial PMMA is limited to ≤1 g, but additions of even >0.5 g to the standard 40 g of powder have been found to significantly affect the mechanical properties of some commercial preparations. Dunne et al[15] reported a significant drop in the mean number of cycles to failure when an additional 0.5 g gentamicin was added to Palacos R. In a comprehensive review of studies examining the properties of antibiotic-loaded cement, Lewis[16] reported compromise of fatigue performance when the mass of antibiotic to total powder expressed as a percentage is ≥1.85. He stated that lack of consensus regarding the biomechanical effects of antibiotic may be the result of variations in mixing and of the

molecular weight of antibiotics used in prior studies. Hsieh et al[17] showed that 8 g antibiotic per 40 g of powder renders cement unformable.

The addition of a radiopacifier allows identification of PMMA radiographically and constitutes 8% to 15% of powder. This fraction has been reported to have a diminishing effect by approximately 8% on overall strength compared with cement without an opacifier.[18] ZrO_2 is reported to have fewer adverse mechanical effects than do cements containing $BaSO_4$. Ginebra et al[19] showed improved tensile strength and fracture toughness in cements containing ZrO_2 compared with those without an opacifier. Kurtz et al[20] found that the addition of 36% $BaSO_4$ to Simplex P (Stryker, Kalamazoo, MI) decreased tensile strength and fatigue life. Conversely, industrially mixed PMMA and 30% $BaSO_4$ demonstrated higher tensile strength and fatigue life than did Simplex P and 10% $BaSO_4$.

Monomer/Polymer

Fewer variations in mechanical and handling properties are attributed to monomer, given its uniform composition among commercial cements, and the surgeon has little control over its elements. The recommended liquid-to-powder ratio is meant to achieve intended handling and mechanical performance and still meet relevant standards. Depending on the planned procedure, this ratio may be altered clinically to achieve the desired handling properties. Using samples of Simplex P, Haas et al[9] found little effect resulting from their variations on liquid-to-powder ratio. Conversely, Belkoff et al[21] used the same cement and reported decreased compressive properties and longer curing times as the monomer-to-powder ratio increased from 0.45 mL/g (manufacturer's recommended ratio) to 1.0 mL/g. They attributed their differences to a larger number of specimens tested.

Exogenous

Air

The effects of air and its impact on porosity are important variables to consider when using PMMA. Whether introduced by mixing and handling or from evaporation of monomer during polymerization, the inclusion of air can have detrimental mechanical effects. This realization resulted in the development of vacuum and centrifugation methods to minimize the effects of air.

Saha and Pal[22] found an increase in ultimate compressive strength and energy absorption capacity of 10% to 15% after reducing porosity. Lewis[23] and Kuehn et al[13] separately reported that the introduction of air and increased porosity shortens the fatigue life of PMMA. Cements with high viscosity may have increased handling times, leading to an increase in air and porosity. Hand mixing introduces air into the cement mixture. Vacuum mixing and centrifugation reduce the introduction of air and, subsequently, porosity,[24] but there is no agreement on the virtues of one method versus another. Both methods have been shown to increase fatigue life. Increases in mixing speed have been implicated in porosity development, but this outcome must be weighed against the disadvantages of slower mixing, which results in a less homogenous mixture. The introduction of air and pores affects cement volume, producing voids that reduce shrinkage.[9,13]

Fluid/Moisture

The influence of water and body fluids on PMMA is significant given its intended physiologic environment, yet these substances are not always incorporated during laboratory testing. De Santis et al[25] reported water absorption of 1% to 2% in plain cement, which was attributed to the polymer network and voids. In vitro experiments have shown that absorption is ongoing over a 4- to 8-week period at body temperature.[13] Increased water content leads to a decreased modulus of cement and an associated decrease in fatigue life and tensile strength.[24,26] Lee et al[18] reported an increase in compressive strength of 3% when equilibrium in moisture content is reached; however, the incorporation of blood into cement has been shown to decrease ultimate compressive strength by 8% to 16%. One advantage of circulating blood during implantation is its effect on reducing peak temperatures of polymerization. This may be partly responsible for lower in vivo temperatures. Relative humidity affects cement handling, and decreased working times have been reported with relative humidity >40%.[27]

Temperature

One commonly manipulated and controversial variable that affects PMMA handling during polymerization is ambient temperature. Higher temperature during mixing increases the rate of polymerization, leading to decreased working and setting times, but with no effect on peak temperature.[28] These effects have led to the popularity of prechilling high-viscosity cements to slow polymerization. Concerns regarding this practice include increasing porosity because of a lengthened working time and, ultimately, a compromise in strength.

Sterilization

Commercial sterilization of PMMA powder currently takes two forms: radiation, which is the most prevalent, and ethylene oxide, a more time-consuming and expensive alternative. The two forms of radiation include gamma and beta irradiation. Both have been implicated in reducing the molecular weight of PMMA,

Table 1

Dosing for Hand-mixed Antibiotic Spacers and Beads Per 40 g Polymethylmethacrylate Powder[59-63]

Antibiotic	Dose (g)
Tobramycin	1.2–4.8
Vancomycin	1–6
Gentamicin	40 mg–4.8 g
Cefazolin	4.5–6

resulting in decreased fatigue life and fracture toughness. Ethylene oxide sterilization has no effect on molecular weight.[29] At no time should PMMA powder be exposed to resterilization temperatures; this process deactivates benzoyl peroxide, leading to failure of polymerization.[13,18]

Contemporary Uses

Arthroplasty

PMMA is used to fill voids left by mismatches between host bone and implant, thus creating immediate stability. The transfer and distribution of forces from implant to bone is thereby subject to a more physiologic transition as a result of mechanical properties of PMMA, which approximate bone. PMMA also dampens excessive forces that would otherwise be directly applied to host bone. PMMA has no adhesive properties to implants on a molecular level. It is dependent on surface properties and shape to enhance stability.[30] The quality of apposition between the implant-cement and bone-cement interfaces is of paramount importance in determining the longevity of a cemented prosthesis. These interfaces are directly or indirectly affected by surgical technique and loading characteristics as well as by the properties of cement, bone, and implant.

Gravius et al[31] reported fewer cement mantle cracks and gap defects with the use of femoral stems that are anatomically formed, collared, and well rounded. An anatomic stem results in a uniform cement mantle, while the collar decreases tensile stresses on the mantle. More cement defects were reported with titanium alloy stems. The defects were attributed to increased stress imparted on the mantle secondary to a lower implant modulus. Clinical studies of the surface characteristics of implanted cemented femoral components have not established a difference in outcomes between polished and precoated or matte finishes.[32-34] Fewer studies have addressed the effect of implant characteristics on the cement mantle in areas other than the hip. Pittman et al[35] found no difference between titanium alloy and cobalt-chromium cemented tibial components but did note that bond strength increased with surface roughness. Maximizing cement-bone contact is important in creating a mechanically sound interface. Enhanced fixation strength of femoral and tibial components is linked to increases in bone porosity and cement penetration into bone.[36-39]

Cement mantle thickness has been shown to affect fatigue resistance, stress transfer, and heat production. Thin cement mantles are associated with lower fatigue resistance. Significant differences have been found by varying thickness by as little as 0.5 mm at the glenoid[40] and 1.0 mm at the femoral stem.[41] Using a computer-generated model, Terrier et al[40] calculated an optimal cement mantle thickness of 1.0 to 1.5 mm for the glenoid. In the same study, thicker mantles were found to transfer excessive stress to the cement-bone interface. Increased cement thickness is also accompanied by increased heat production and risk of thermal necrosis. The effect of heat is a function of temperature and time of exposure. Several in vitro studies using standard surgical techniques have reported temperatures >50°C for 1 minute, the temperature and exposure time considered necessary for bone necrosis, which may lead to prosthetic loosening.[42-45]

Cement viscosity has been shown to have effects on each interface, which could affect prosthetic longevity. High-viscosity cement may be more capable of resisting hemodynamic backflow and has demonstrated increased bone penetration and femoral stem apposition.[46,47] The consequences of porosity in arthroplasty are subject to conflicting data. Janssen et al[48] and Topoleski et al[49] reported the unpredictable nature of pores to initiate cracks and to deviate or decelerate cracking. Other authors have demonstrated only adverse effects of porosity, including instability and decreased fracture toughness.[50,51] Zhang et al[52] have shown that the brand of cement used, in combination with a polished femoral stem, is the most important factor in determining static shear strength, and that viscosity and porosity play a limited role.

Infection

Two studies separately established the effectiveness of antibiotic delivery via PMMA.[53,54] PMMA can serve as a delivery vehicle for antibiotic, act as a spacer, and be a filler of dead space, thus eliminating it. Antibiotic-loaded PMMA has been used successfully to manage infected joint arthroplasties, osteomyelitis, and open fractures with bone defects[55-63] (Table 1).

Antibiotics are eluted from the surface and pores of cement as well as from the microcracks within it. Elution characteristics vary by brand. Palacos has demonstrated favorable elution characteristics, and several studies have shown that it is capable of delivering high local concentrations of antibiotics with long elution times.[61,64,65] The amount of antibiotic

Figure 1

A B

A, Photograph of an open IIIB tibia fracture. **B,** Photograph demonstrating insertion of an antibiotic bead chain following débridement in preparation for a bead pouch.

delivered also depends on the overall surface area of the implant and the characteristics of the antibiotic used. General qualifications for a successful pairing of an antibiotic with PMMA include heat stability during the exothermic reaction, ability to diffuse in water, low potential for allergic reaction, and an appropriate spectrum against potential or confirmed organisms.

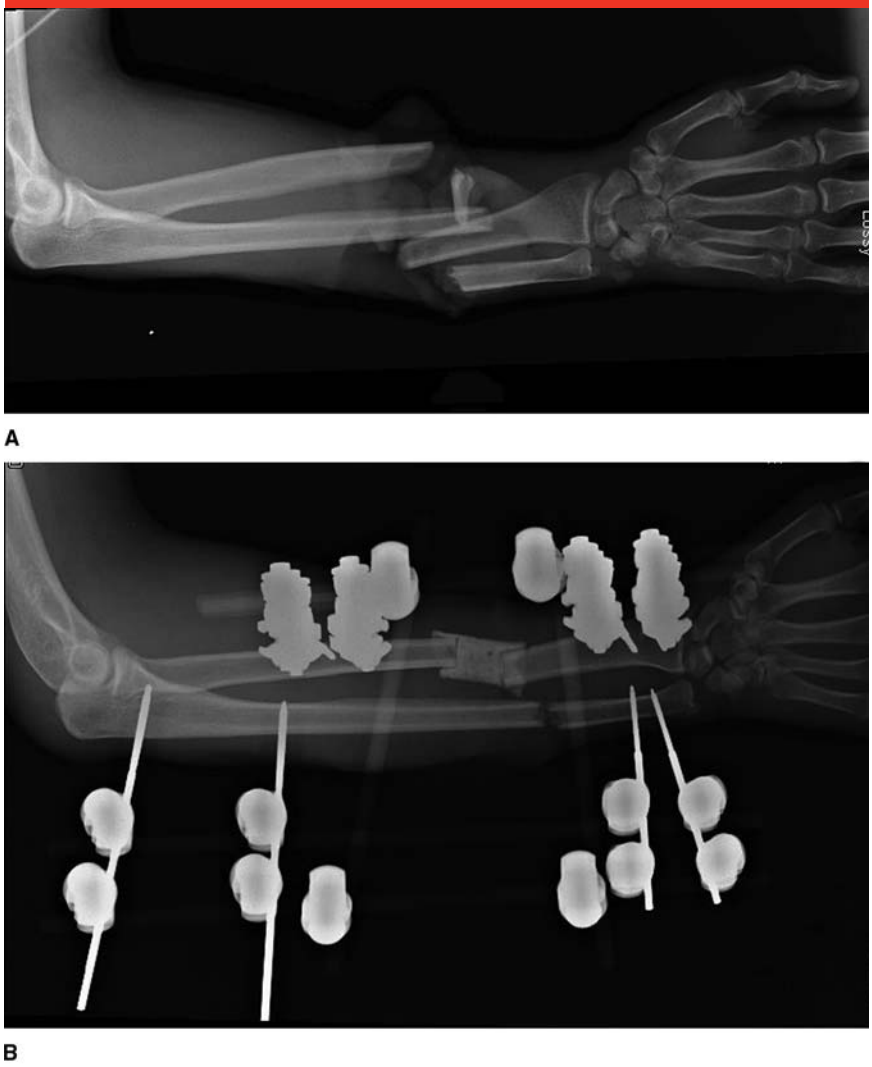
Tobramycin and gentamicin are the most frequently used and most studied antibiotics. Vancomycin and cephalosporins continue to be used as well. Tobramycin is popular because it comes in powder form, which is easy to mix, and because of its broad spectrum, which includes antipseudomonal coverage. It has been shown to potentiate the elution of other antibiotics, such as vancomycin.[66] Gentamicin is often supplied in liquid form, which may have more adverse mechanical effects on cement.[67] Vancomycin is used for its effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA) and its low allergenic potential. Some authors have discouraged its routine use except for patients with a demonstrated specific need for MRSA coverage because of concerns regarding the development of resistant organisms during the time of waning concentrations.[64] Cephalosporins can be used with PMMA and have better gram-positive coverage than do tobramycin and gentamicin. McLaren et al[68] found no difference in average cumulative release of antibiotic, whether first added to a monomer or to PMMA powder. Elution rates of antibiotics, such as gentamicin, have been shown to be adversely affected by hand mixing, possibly because of reduced uniformity of distribution.[69]

Treatment of active infections with antibiotic-loaded PMMA requires eventual removal of the delivery device. Commercially preloaded cements used for prophylaxis are intended to be permanent, and the antibiotic concentration is selected so as not to substantially degrade the mechanical properties of the cement. These cements are US FDA-approved for use in reimplantation arthroplasty after infection and for patients at high risk of infection during primary arthroplasty. None carries a large enough dose of antibiotic to treat active infections. Most are loaded with gentamicin or tobramycin. Spacers also serve to maintain a more physiologic environment with regard to soft-tissue tension and limb alignment until a more definitive procedure can be performed. They facilitate mobility and better exposure during joint reimplantation.[58,70] Commercial systems, such as the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC, DePuy), allow greater precision in the creation of an articulating antibiotic spacer.

Antibiotic bead chains have been traditionally used in the management of bone defects associated with osteomyelitis or open fracture. Initially favored because of the large amount of available surface area, difficulty in removal of the beads and soft-tissue intrusion have led some clinicians to use spacers for defects instead (Figures 1 and 2). This method may preserve a more natural avenue for bone reconstruction; it can also be used as a structural strut within the defect. Internal fixation may be anchored into the spacer until bone grafting can be safely performed.

The duration of antibiotic elution in vivo is difficult to characterize. Bertazzoni Minelli et al[71] reported that gentamicin- and vancomycin-loaded cement explants elute at sufficient levels after several months. Most antibiotic implants elute most of their antibiotic by 9 weeks, but they continue to diffuse at sufficient levels for months. Masri et al[62] reported bactericidal levels of elution at 4 months when tobramycin was combined with vancomycin. Despite often high doses of local antibiotic delivered im-

Figure 2



A, Preoperative AP radiograph of an open IIIB forearm fracture. **B,** AP radiograph demonstrating insertion antibiotic spacer radius defect following the third débridement, 96 hours after injury.

mediately after implantation, rare cases of toxicity have been reported. Springer et al[63] reported using up to 10.5 g vancomycin and 12.5 g gentamicin without adverse effects. One should be diligent about recognizing the clinical symptoms of toxicity with each individual antibiotic. Appropriate serum levels should be obtained, if necessary.

Spine

Although PMMA is used frequently in the spine, its use has been limited mostly to vertebral augmentation (VA). Galibert et al[72] first reported successful results after injecting PMMA in the management of painful hemangiomas of the vertebral body. Pain elimination was accompanied by prevention of further collapse. This application was later used in patients with metastatic disease and myeloma to help prevent collapse of the vertebral body and canal compromise.

Current VA techniques include vertebroplasty and kyphoplasty. Both procedures focus on stabilization and pain relief through percutaneous transpedicular introduction of PMMA into the vertebral body. Despite recent reports refuting the benefits of vertebroplasty, this technique remains an alternative method of managing osteoporotic compression fractures of the thoracic and lumbar spine.[73,74] In vertebroplasty, PMMA is injected into the affected vertebral body. In kyphoplasty, a more concerted effort is made to restore vertebral height and, more important, to create a void before the injection to enhance the safe application of PMMA. Although other bioactive materials are available, PMMA is currently favored for the management of VA because of its documented clinical success as well as its structural integrity, handling properties, and radiopacity.

The ability of PMMA to cure rapidly to a mechanically sound state is particularly advantageous in the compromised patient who requires immediate mobilization. Essential PMMA characteristics required for successful execution of VA include radiopacity and optimal viscosity. Radiopacifiers are necessary to allow monitoring for extravasation. Adequate viscosity is essential to enable unimpeded travel during injection yet prevent extravasation from a compromised vertebral body. Lieberman et al[75] recommended ideal cement states for vertebroplasty and kyphoplasty. Cement with a longer sticky or liquid phase should be considered for vertebroplasty, whereas cement with a short sticky phase and longer working phase is preferred for kyphoplasty.

Commercial preparations of PMMA have emerged with formulations to facilitate use in VA. These cements contain between 15% and 33% by weight of $BaSO_4$ or ZrO_2. Some contain additional amounts of tungsten or tantalum, neither of which is an approved radiopacifier in the United

States. Mechanical changes as a result of increasing amounts of radiopaque material are varied.[5,75] Using American Society for Testing and Materials standards, Kurtz et al[20] tested commercial preparations of Simplex P with 10% $BaSO_4$, Simplex P with 36% $BaSO_4$, and KyphX HV-R (Kyphon, Sunnyvale, CA) with 30% $BaSO_4$. The authors concluded that the static and fatigue properties of PMMA with elevated $BaSO_4$ content were enough to withstand loading conditions in the vertebral body.

Restoration of compressive strength and stiffness of the involved vertebra is dependent on the brand of cement, the vertebral level, and possibly, the volume of cement. These factors and variations in testing methods have led to disparate results.[76-78] Belkoff et al[76] reported restoration of compressive strength in PMMA-augmented fracture models using 2 mL cement in the two brands tested. Several authors have shown similar or superior restitution of compressive strength in vertebral fracture models. Others have revealed a decrease in overall stiffness from prefracture levels.[77,78]

Cardiopulmonary Complications

Cardiopulmonary complications associated with PMMA have been reported in conjunction with hip arthroplasty and VA. Prior studies have postulated that PMMA-associated hypoxia, hypotension, and death may occur as a result of the toxic effects of monomer[79] or anaphylaxis.[80] Other literature indicates that the application of PMMA may lead to embolization of marrow debris and neurogenic reflex, thus adversely affecting cardiopulmonary function.[81-84] Pulmonary infarction and death have been reported as a result of embolization of PMMA that was injected in liquid state following VA.[85]

Summary

Despite widespread utilization, the composition and properties of PMMA are not completely appreciated. Advances in implant interfaces and biomechanics and the development of bioactive materials may alter the role of PMMA in orthopaedics, but it continues to play a vital role, albeit a changing one. PMMA has gained favor as a vehicle for the delivery of antibiotics and for use in VA. Its propensity to act as a structural pharmaceutical repository and slow-release vehicle has made PMMA a powerful tool in the management of complex musculoskeletal infections.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 31, 72, and 73 are level I studies. References 35 and 82 are level II studies. Reference 33 is a level III study. References 2, 16, 32, 53-58, 62, 69, 71, and 84 are level IV studies. References 3 and 59 are level V expert opinion.

Citation numbers printed in **bold type** indicate references published within the past 5 years.

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