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Polymethylmethacrylate bone cements and additives: A review of the literature

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Abstract

Polymethylmethacrylate (PMMA) bone cement technology has progressed from industrial Plexiglass administration in the 1950s to the recent advent of nanoparticle additives. Additives have been trialed to address problems with modern bone cements such as the loosening of prosthesis, high post-operative infection rates, and inflammatory reduction in interface integrity. This review aims to assess current additives used in PMMA bone cements and offer an insight regarding future directions for this biomaterial. Low index (< 15%) vitamin E and low index (< 5 g) antibiotic impregnated additives significantly address infection and inflammatory problems, with only modest reductions in mechanical strength. Chitosan (15% w/w PMMA) and silver (1% w/w PMMA) nanoparticles have strong antibacterial activity with no significant reduction in mechanical strength. Future work on PMMA bone cements should focus on trialing combinations of these additives as this may enhance favourable properties.

Key words: Polymethylmethacrylate; Bone cement; Cement nanoparticle; Vitamin E additive; Arthroplasty; Artificial joint fixation; Post-operative infection; Mechanical weakness; Fat additive; Antibiotics

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INTRODUCTION

Bone cement, or polymethylmethacrylate (PMMA), has been used in surgical fixation of artificial joints for over 50 years. The primary function of bone cement is to transfer forces from bone to prosthesis. This review explores the development of bone cements, the role of bone cement additives, identifies applications and discusses future directions.

HISTORICAL BACKGROUND

The pioneering work on PMMA technology is widely credited to German chemist Dr. Otto Rohm. He patented the PMMA product Plexiglass in 1933, which was used in submarine periscopes and airplane canopies[1], leading to an exponential increase in demand and interest during the pre-war and war era. Kulzer (1936) was at the forefront of mouldable cement technology after discovering that the dough formed by mixing ground PMMA powder and a liquid monomer hardens when benzoyl peroxide is added and the mixture heated to 100 ℃ in a stone mould[2]. The first clinical use of this PMMA mix-

ture was in an attempt to close cranial defects in monkeys in 1938. Surgeons used the heat stable polymer Paladon 65 to close cranial defects in humans. The material was assembled in plates in the laboratory and later moulded in the surgical suite[2].

The era of modern PMMA bone cements stems from the patent by Degussa and Kulzer (1943), describing how MMA polymerizes at room temperature if a co-initiator, such as a tertiary aromatic amine, is added[2]. Dental surgeons were the first to use this technology for dental fixatives and fixtures.

The first bone cement use in orthopaedics is widely credited to English surgeon, Dr. John Charnley, who used "dental acrylic" in 1958 for total hip arthroplasty[3]. Initial clinical results were poor for mechanical and biological reasons, related to both cement and loading surface[2]. Dr. Charnley developed a new product called "bone cement" (Plexiglass) which had more adaptable biological characteristics[4] and which he marketed aggressively to the global orthopaedic community. American orthopaedic surgeons trained with Dr. Charnley at the Wrightington Hospital in the 1960's and 1970's to learn his pioneering technique[5]. When returning to America, these surgeons often took bags of bone cement with them, an illegal trade which was only eliminated in the mid-1970's after the Food and Drug Administration approved the use of bone cement technology in the United States[5]. This material still had many shortcomings. Over the last two decades, additives have been developed to address these shortcomings[6].

PMMA PROPERTIES AND ADDITIVES

Mechanical weakness

A common complication of cemented arthroplasty is loosening of the cemented prosthesis. Mechanical weakness in the bone cement, primarily attributed to the addition of barium sulphate and zirconium oxides (for radiological detection), increases the risk of loosening[7]. Stabilisation of the bone cement matrix improves the transfer of load across the cement-prosthesis interface, reducing the likelihood of crack formation in the cement. Various additives such as steel fibres, glass fibres, carbon fibres and titanium fibres have been developed to improve mechanical strength[8-10]. Rubber toughened cement (PMMA matrix interspersed with rubber particles; Moeseley Rubber Co. Pvt. Ltd., United States) has 167% greater fracture toughness (the structural strength to withstand further cracking in fractured materials) than non-reinforced control (PMMA), although compressive strength and elasticity are compromised (raw data not available)[11]. PMMA reinforced with embedded continuous stainless steel coil (2.5 turns of coil; distal tip of prosthesis) significantly increases compressive stress 4.5-fold (control *vs* reinforced; 0.039 ± 0.001 MPa *vs* 0.009 ± 0.001 MPa) and tensile stress 4.5-fold (control *vs* reinforced; 4.272 ± 0.015 MPa *vs* 0.95 ± 0.005 MPa) on 3-dimensional finite element computational analysis[12]. This reinforcement increases mechanical strength, thus decreasing the likelihood of fracture formation. The use of additives with rubber toughened cements and stainless steel coils may improve other properties and needs to be investigated.

Interface integrity

The long-term stability of cemented hip arthroplasty is also dependent on the integrity of the bone-cement interface. Interface integrity is related to the strength of bonding and the degree of cement penetration (extent of interdigitation into bone). Increased migration behavior and micromotions of the prosthesis and bone cement are a result of abrasion. The production of wear particles from roughened metallic surfaces and from the PMMA cement promotes local inflammatory activity, resulting in chronic complications to hip replacements[13]. Lower bone cement viscosity affects the mechanical strength of the connection, giving an immediate limitation to the benefits of certain water-based additives, like antibiotics, in comparison to those in powder form[14]. The addition of an amphiphilic bonder, such as glutaraldehyde, may lead to significant improvements in the longevity of cemented metal stems[13,15]. Strength is maximized by increasing the amount of trabecular bone in the cement[16]. Interface integrity should be the optimal outcome of any additive trial. Powder based additives should generally be preferred to their water based counterparts, with greater importance placed on ensuring increased trabecular bone in cement matrix and/or amphiphilic bonders.

Osteoconduction

Osteoconduction refers to a process in which the three-dimensional structure of a substance is conducive to the on growth and/or ingrowth of newly formed bone. Bone growth on an implant surface depends on the action of differentiated bone cells; pre-existing pre-osteoblasts/osteoblasts activated by trauma or recruited from primitive mesenchymal cells by osteoinduction[17,18]. Bone conduction is dependent on the conditions for bone repair as well as the biomaterial used and its reactions[19]. More than 60% by weight of bioactive ceramic powders should be added to PMMA powders to achieve satisfactory osteoconductive properties after setting[20].

Thermal reduction

The polymerisation of bone cement is an exothermic process that can cause tissue necrosis. The high peak curing temperatures of acrylic bone cements is a major concern that needs to be addressed. The use of oxygen plasma increases the maximum curing temperature of bone cement. For example, 100 W of oxygen plasma applied to PMMA powdered polymer (Sigma-Aldrich Chemie, Germany) increases the maximum temperature from 83.48 ± 7.35 ℃ to 96.50 ± 4.52 ℃ (no reported significance)[21]. This is explained by the catalytic activity in polymerization, which results in more rapid heat release. A number of additives have also been tested for

their potential effects on heat reduction. PMMA bone cement modification with 1-dodecyl mercaptan (DDM, Acros Organics, United States) lowers peak temperatures by 4-6 ℃ (no reported significance), possibly by acting as a chain stopping agent[21]. Endothermic reactions involving ammonium nitrate (Acros Organics United States) also help to reduce temperatures (73.64 *vs* 96.5 ℃; no reported significance). Zeolites (ZSM-5, Acros Organics, United States) further improve the exothermic profile of bone cements, reducing temperature from 90.12 to 86.9 ℃ with DDM, and from 73.64 to 72.66 ℃ with ammonium nitrate (no reported significance)[21]. In addition to limiting PMMA toxicity, the antioxidant N-Acetylcysteine (NAc) has also been shown to significantly reduce heat release in a dose dependent manner[22]. The maximum polymerization temperature was 42.6 ℃ with 1.00% (w/w) NAc, compared to 57.0 ℃ in the absence of NAc.

Radio-opacifying additives

Ceramic particles, such as barium sulfate and zirconia (zirconium oxide), are incorporated into bone cement to allow visualization through X-ray imaging[23]. They have an adverse influence on the biocompatibility of PMMA, leading to mechanical weakness[23-25]. Barium sulfate ($BaSO_4$; Horii Pharmaceutical, Osaka, Japan) at 10% w/w monomer has a compressive load test strength of 85(± 5) MPa[26]. Increasing concentrations of $BaSO_4$ (20%; 30%; 40% w/w monomer) reduce this strength (86 ± 4 MPa; 87 ± 8 MPa; 69 ± 10 MPa), although only the reduction between 30% and 40% is statistically significant ($P < 0.02$)[26]. The 10% w/w monomer has a fracture load of 88 ± 10 MPa in the three point bending load test, and this strength reduces in proportion to increasing barium concentration[26]. Furthermore, impact load testing of 10% w/w monomer reveals a strength of 3.1 ± 0.9 kJ/m^2, which is the same as for the 20%, 30% and 40% w/w monomers ($P < 0.01$)[26]. Thus, increasing concentrations of barium sulfate (10%-40%) reduce mechanical strength of cement. Additionally, conventional barium sulfate (Reade Materials; Providence, RI, United States) promotes poor osteoblast (bone forming cells) function at the surface of PMMA, in human osteoblast cell culture lines (CRL-11372), as seen by scanning electron microscopy and atomic force microscopy[25]. Kobayashi *et al*[27] analysed the effect of barium concentrations in PMMA additives (10%, 30% wt and empty control; Simplex® and Spineplex®, Stryker Instruments) in animal models at 12 and 90 d. Higher concentrations of barium sulfate were associated with stronger foreign body reaction at 90 d, suggesting lower levels of biocompatibility at higher concentrations. Further work is needed weighing the benefit of higher cement visualization against the lower biocompatibility at higher $BaSO_4$ concentrations in humans.

Iodine-containing acrylic bone cement has comparable biocompatibility to the barium sulfate-containing equivalent, while maintaining its useful radiopaque properties[28]. Analysis suggested that there was no significant difference in mechanical strength (fracture toughness and four-point loading test) between iodine and barium sulfate based cements.although further work needed to assess clinical application of iodine based cement[28].

Table 1 Exothermic activity of polymethylmethacrylate mixed with nano-MgO (12.8 nm) *vs* polymethylmethacrylate control[25]

	1 s	1 min	2 min	10 min	107 min
PMMA (℃)	44.98	45.82	50.10	52.5	47.85
PMMA and nano-MgO (℃)	39.65	40.36	46.99	48.85	44.10

PMMA: Polymethylmethacrylate.

The use of ceramic nanoparticles, such as magnesium oxide (MgO; 12.8 nm; Sigma Aldrich; St. Louis, MO, United States) and $BaSO_4$ (80-500 nm; Reade Materials; Providence, RI, United States), improves osteoblast adhesion (PMMA + nanoMgO 3.25 cells/mm^2; PMMA + nano$BaSO_4$ 3.6 cells/mm^2; cell density on adhesion assay and fluorescence microscopy) compared to conventional PMMA (2.6 cells/mm^2), although this improvement is not statistically significant ($P < 0.1$)[25]. The addition of nano$BaSO_4$ (100 nm; Sachtleben, Duisburg, Germany) to PMMA (CMW1 bone cement; DePuy Orthopaedics Inc., Warsaw, IN, United States) at 10% w/w has no significant difference on uniaxial compression strength ($P = 0.08$) or uniaxial tensile strength (ultimate stress and elastic modulus; $P = 0.3$ and $P = 0.4$ respectively)[29]. The addition of nanoMgO (at 10% w/w per total PMMA cement) also reduces the exothermic nature of *in vitro* PMMA solidification (Table 1), thus minimizing tissue necrosis[25]. Overall, nanoMgO and nano$BaSO_4$ improve osteoblast adhesion, with nanoMgO minimizing tissue necrosis and nano$BaSO_4$ having no impact on mechanical strength. Further work is needed to fully assess the mechanical parameters of nanoMgO and the exothermic activity of nano$BaSO_4$.

Organobismuth compounds also have radio-opaque properties that have been tested in bone cement. One particular study found that 5%, 10%, 15% and 20% (w/w) bismuth salicylate in bone cement with a 2/1 solid/liquid ratio [MMA, 1% (v/v) dimethyl-4-toluidine, 1.25% (w/w) benzoyl peroxide, Merck] had higher radiopacity than standard admixtures containing barium sulphate (Merck)[30]. Furthermore, 10% bismuth salicylate preparations had a higher percentage of injectability than their 10% barium sulphate counterpart (85.89% *vs* 81.90%; no reported significance)[30]. The addition of contrast agents, such as gadolinium and manganese, to produce a signal-inducing bone cement formulation has also been useful for magnetic resonance imaging. Gadolinium in gadoterate meglumine-water cement (Dotarem 0.5 mmol/mL; Laboratory Guerbet, Paris, France, 12 g PMMA and 5 mL MMA) had a higher contrast-to-noise ratio (CNR) in air than the manganese-containing cement (5 mL $MnCl_2$ solution, 100 mg/L deionised water) with a maximum CNR of 157.5 in a fast T1W turbo-spin echo sequence[31].

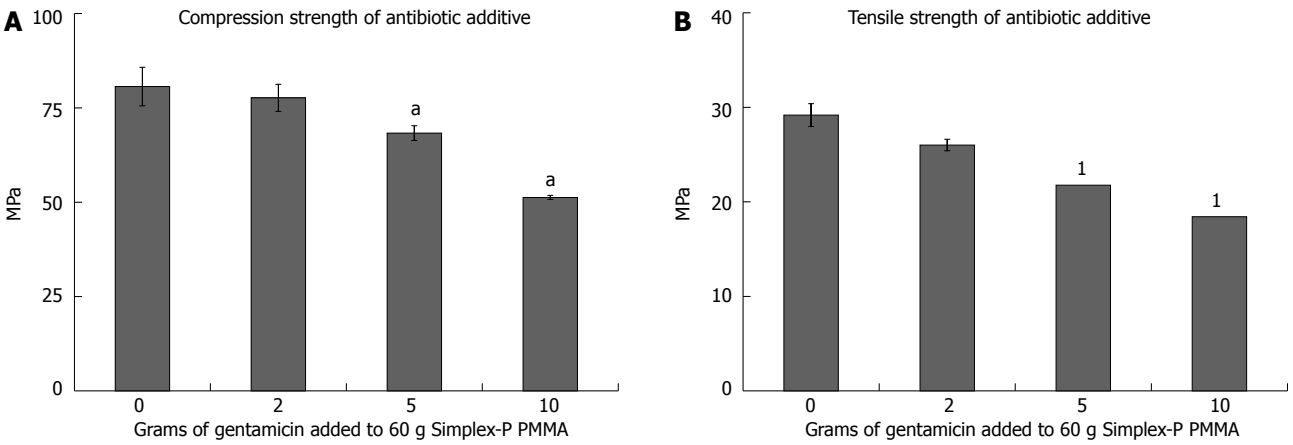

Figure 1 Mechanical strength of antibiotic (gentamicin) additives[38]. A: Compression strength, [a]$P < 0.05$ *vs* 0 g addition of Gentamicin; B: Tensile Strength, [1]invalid result as cements failed to fracture in a non-brittle manner.

Antibiotic additives

There is a high incidence of post-operative infections (0.25%-2.0%) in individuals receiving total joint replacements[32]. In cases where PMMA is used this rate increases to 13%[33]. Use of antibiotic-loaded bone cement for prophylaxis and prosthesis related infections has been documented since the 1970s, with erythromycin one of the earliest additives used[34,35]. Despite achieving clinical efficacy, erythromycin was found to diffuse poorly from the cement matrix into surrounding bone[34,35]. Aminoglycosides, such as gentamicin and tobramycin have since become popular additives for bone cements, due to their broad spectrum activity and low allergy profiles[36,37].

One study found that addition of gentamicin (2/60 g cement) did not significantly alter compressive or diametral tensile strength compared to control PMMA (Simplex-P; Figure 1). However, higher gentamicin levels of 5/60 g or 10/60 g, significantly reduced compressive strength ($P < 0.05$), although results for tensile strength could not be interpreted[38]. Although higher doses of gentamicin mean greater antibiotic availability, the mechanical properties of the additive are adversely affected.

Another study compared four antibiotics (sodium oxacillin, sodium cefazolin powder, gentamicin powder and gentamicin sulphate aqueous solution; 40 mg/mL of PMMA mixture), evaluating them for compressive (80, 70 and 65 MPa; 2g gentamicin powder, 250 mg aqueous gentamicin and 800 mg aqueous gentamicin solution respectively) and diametral tensile strength (27, 23 and 15 MPa; 2 g gentamicin powder, 250 mg aqueous gentamicin and 800mg aqueous gentamicin solution respectively) in comparison to control PMMA (Simplex-P)[39]. Powered gentamicin (2/40 g) made no statistically significant difference to compressive or diametral tensile strengths whereas aqueous forms produced weakened bone cements, as result attributed to the water in the mixture[39]. We recommend use of 2/60 g, or less, of antibiotic in powdered form. This lowers post-operative infection rates while only causing modest reductions in compressive (< 5% reduction) and tensile (< 5% reduction) strength.

Vancomycin has also been used as a bone cement additive, with concentrations less than 5% having no effect on the mechanical properties of the bone cement[40,41]. However, this has been found to be less efficacious than similar concentrations of tobramycin and gentamicin[37,42]. Interestingly, when used in combination with tobramycin, a synergistic effect appeared[43,44], with a 68% greater elution of tobramycin ($P = 0.024$), and 103% greater elution of vancomycin from the bone cement ($P = 0.007$), compared to controls containing only one antibiotic[43].

Vitamin E additives

The polymerisation process utilises a redox system, comprising benzoyl peroxide (BPO) as an initiator and *N,N*-dimethyl-4-toluidine (DMT) as an activator. This produces benzoate and amine free radicals which are thought to induce local inflammation and alter macrophage activity[45]. Vitamin E is a free radical "scavenger" in the oxidative process[46]. Mixed Vitamin E (MVE) additive (1 part liquid MVE: 1.8 part solid cement) shows increased cytocompatibility (as measured by total cellular DNA, cellular proliferation and differentiation *vs* control PMMA group) and decreased exothermic activity (peak temperature: 15% wt MVE-MMA 53 ℃ *vs* PMMA 76 ℃), reducing the likelihood of bone necrosis. However, setting time is increased (20.7 min 15% wt MVE-MMA mixture *vs* 12.2 min PMMA control), which exposes the operative site to the environment for longer[46]. Compositions of > 25% wt MVE-MMA have no effect on compressive strength, but significantly reduce tensile strength (Figure 2), although this still remains within the range for clinical usage[46]. The use of 15% vitamin E yields a lower compressive strength compared to additive concentrations of 10% and 20% (Figure 2), though this could be attributed to experimental error. Greatest clinical scope exists for 10% vitamin E additives as they have a positive effect on free radical oxidation and exothermic activity, with only modest reduction (< 5%) in tensile strength.

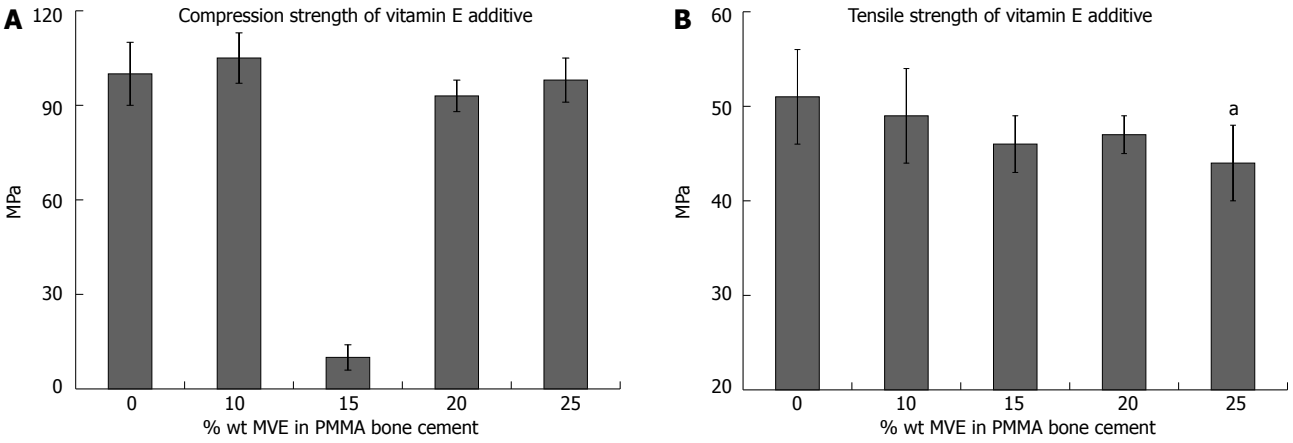

Figure 2 Mechanical strength of vitamin E additives[46]. A: Compression strength, great reduction at 15% appears to be an anomaly, but requires further review; B: Tensile strength, $^{a}P < 0.05$ *vs* 0%.

Table 2 Diametral tensile strength of polymethylmethacrylate and MMA:AA: MA co-polymer mixtures[47]

PMMA quantity (g)	MMA:AA:AMA quantity (g)	MMA:AA:AMA ratio	Tensile strength (Mpa)
20	0	-	31.3 ± 9.0
19	1	80:20:10	39.3 ± 3.0
17	3	80:20:10	36.2 ± 4.7
19	1	70:30:10	33.1 ± 4.2
17	3	70:30:10	26.6 ± 6.1

PMMA: Polymethylmethacrylate.

Monomer and nanoparticle additives

The co-polymer [poly (methylmethacrylate-acrylic acid-allylmethacrylate) or poly (MMA-AA-AMA); MMA, Kanton Chemical Co. Japan; AA, Alfa Aesar, Ward Hill, MA, United States; AMA, Acros Organics, Morris Planes, NJ, United States] reduces bone cement shrinkage (a problem in traditional compositions) as it absorbs body fluids and swells to compensate for shrinkage. An MMA:AA:AMA ratio of 80:20:10 resulted in improved mechanical strength (Table 2). In contrast, 70:30:10 did not yield any significant improvements, possibly due to increased acrylic acid concentration[47]. Co-polymerisation with MMA:AA:AMA also resulted in improved fracture toughness, due to a roughened surface, as identified with scanning electron microscopy. Further, cross-linked poly (MMA-AA-AMA) copolymer is able to induce bone ingrowths at the interface of bone and copolymer[48].

Bone cement composites have been trialed with nanoparticle additives, such as multi-walled carbon nanotubes and nano-sized titanium fibers. While there were measurable improvements in the flexural strength and bending capacity by 12.8% and 3.7% respectively, adverse effects on surrounding cell *in vitro* biocompatibility were observed[9] At the optimal concentration of 1% by wt, nano-titania fibers-give a significant increase in fracture toughness (67%), flexural strength (20%) and flexural modulus (22%), compared with control PMMA cement, while retaining handling properties and *in vitro* biocompatibility[9].

Recently, nanoparticles have been trialed *in vitro* as bactericidal agents. PMMA (DePuy International Ltd., UK and Biomet, Merck, Germany) with and without gentamicin was loaded with chitosan (CSNP, CarboMec Inc) and quaternary ammonium CS derived nanoparticles (QCSNP) at weight ratios of 15% and 30%, and then examined for their antibacterial (*Staphylococcus aureus* and *Staphylococcus epidermidis*, analysed by sphectrophotometry), mechanical (tensile and three point bending test, Young's and bending modulus) and cytotoxic properties (3T3 mouse fibroblast assay)[49]. Bone cement mixed with CSNP and QCSNP significantly ($P < 0.05$) decreased cell count for both strains (500 to 200 CFU/cm^2 for CSNP; 500 to 40 CFU/cm^2 for QCSNP)[49]. Cytoxicity assay and mechanical testing showed no significant difference between CSNP, QCSNP and control PMMA[49]. Further *in vivo* assessment of CSNP and QCSNP as potential bone cement additives is suggested for future studies.

Silver ions (AgNP) inactivate enzymes vital to bacteria and disable the mechanism for bacterial DNA replication[50]. Clinical application is limited by the difficulty of incorporating and dispersing AgNP into acrylics. *In situ* generation of AgNP (University of Texas Health Science Center, Texas) has been trialed[51]. Silver benzoate (AgBz; 1.0% w/w of total monomer; Sigma Aldrich) was blended with PMMA and extra benzoyl peroxide (B; 0.5%, 1.0%, 1.5% and 2.0% w/w; Sigma Aldrich) and diamethyl-p-toludine (D; 0.5, 1.0, 1.5 and 2.0% w/w; Sigma Aldrich) added. AgNP released silver ions *in vitro* for over 28 d (analysed by Atomic Absorption Spectrometry), inhibited 99.9% of bacterial growth at 48 h (*Acinetobacter baumannii, Pseudomonas aeruginosa, Proteus mirabilis and Staphylococcus aureus*; *in vitro* antimicrobial assay) and showed a continued antibacterial effect against *P. aeruginosa* for over 28 d (1.5B: 0.5D 1% AgBz, 1B: 1D 1% AgBz and 0% AgBz; 4.8, 6.3 and 0 mm inhibition; long term antimicrobial assay)[51]. However, AgNP (1%) mixtures have reduced mechanical strength (three point bending flexural test) compared to controls. Further work is needed to assess optimum loading, other mechanical properties and long term antimicrobial activity against other bacterial strains.

Table 3 Summary of polymethylmethacrylate bone cement additives

Additive	Summary
Gentamicin	Reduces post-operative infection rates. Powdered format (2/60 g or 2/40 g) shows no significant impact on mechanical strength, however increased gentamicin concentration decreases mechanical strength
Vitamin E	Improves cement cytocompatibility and reduces peak temperature. 10% vitamin E concentration does not significantly affect mechanical strength. Increasing concentrations associated with increased setting time and decreased mechanical strength
Polymer MMA:AA:AMA	Reduces bone cement shrinkage and improves fracture toughness. 80:20:10 significantly improves mechanical strength *vs* control
NanoMgO and NanoBaSO$_4$	Improves osteoblast adhesion, nanoMgO (12.8 nm) minimizes tissue necrosis and nanoBaSO$_4$ (100 nm) improves mechanical strength
Barium sulfate	Allows radiological identification of cement. 10% concentration is not associated with significant decrease in mechanical strength *vs* control. As concentration increases, mechanical strength decreases
Chitosan nanoparticles	*In vitro* studies show significant antibacterial activity against *S. aureus* and *S. epidermidis* with no significant difference in cytoxicity and mechanical strength *vs* control PMMA
Silver nanoparticles	AgNP (1%) has strong and continued antibacterial activity (against *A. baumannii*, *P. aeruginosa*, *P. mirabilis* and *S. aureus*) but with reduction in mechanical strength. Nanosilver (5-50 nm) has antibacterial activity against *S. epidermidis*, MRSE and MRSA with no significant difference in cytotoxicity *vs* control

PMMA: Polymethylmethacrylate; MRSE: Methicillin-resistant *S. epidermidis*; MRSA: Methicillin-resistant *S. aureus*.

Nanosilver (5-50 nm; 0.1%, 0.5% and 1.0% w/w monomer) mixed with PMMA (Coripharm, Dieberg, Germany), PMMA mixed with 2% w/w gentamicin sulphate (Schering-Plough, Brussels, Belgium) and PMMA control were compared for antimicrobial activity (on microplate proliferation assays) against *S. epidermidis*, methicillin-resistant *S. epidermidis* (MRSE) and methicillin-resistant *S. aureus* (MRSA)[52]. PMMA control had no antimicrobial effect, whereas 1% Nanosilver and 2% gentamicin loaded cements completely inhibited *S. epidermidis*. Furthermore, 1% Nanosilver completely inhibited MRSA and MRSE growth whereas gentamicin had no effect. This may be due to gentamicin resistance in tested strains[52]. The antimicrobial effect of Nanosilver was dose dependent, with higher concentrations of Nanosilver having higher antimicrobial effect. *In vitro* cytotoxicity was not significantly different (human osteoblast quantitative elusion testing and qualitative growth) between Nanosilver and PMMA controls[35]. Further, biocompatibility (measured by human osteoblast on growth) was similar between Nanosilver and the control group.

FUTURE APPROACHES

The focus of bone cement research is better mechanical quality, curing time and biocompatibility. Biomaterials, such as calcium phosphates and hydroxyapatite, more efficiently induce bone growth. Advances in the biocompatibility of PMMA bone cements might be achieved by introducing osteogenic agents, such as bone morphogenic proteins or transforming growth factors, to cement surfaces that contact the surrounding bone[53].

PMMA for vertebroplasty has greater stiffness than vertebral cancellous bone, causing higher incidences of fracture of neighboring vertebral bodies[54]. More porous bone cement has been developed by introducing an aqueous phase in PMMA cements, which is released *in vivo* with powder particles and thus increases risk of embolism. Beck and Boger (2009) showed that delaying the addition of the aqueous phase to acrylate mixture minimizes the amount of particles released[54].

CONCLUSION

As demonstrated in this review, there are many bone cement additives, none of which is perfect as strength often being adversely affected with minor additions of an additive (Table 3). There is scant data focusing on the effect of combining various additives. We suggest that this approach may yield bone cements that display the beneficial properties of each additive, while still maintaining structural integrity. Low index (< 15%) vitamin E and low index (< 5 g) antibiotic impregnated additives should be investigated further. These target inflammatory and infective pathologies, respectively, related to long term failure in bone cements, with only modest reductions in mechanical strength of the cement matrix. Mechanical strength and interface integrity should be improved through the use of rubber-toughened cements, amphiphilic bonders and/or increasing trabecular bone concentration in the cement matrix. Chitosan (15% w/w PMMA) and silver (1% w/w PMMA) nanoparticles have strong antibacterial activity with no significant reduction in mechanical strength. The field of nanoparticle technology holds promise.

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