The Evolution of Cement Fixation in Total Knee Arthroplasty

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ABSTRACT

Sepsis loosening and infection are two of the leading causes of revision in total knee arthroplasty. While several patient-related factors can play a role in the development of these complications, there are certain modifiable surgeon factors that can help mitigate the risk. Intraoperatively, this can begin with the curing process of bone cement which is broken down into four different stages: mixing, waiting, working, and setting. Understanding each stage of the process is beneficial in obtaining successful long-term outcomes. Developing optimal bone-cement penetration is of utmost importance in establishing a strong interface. Proper penetration of cement is dependent on multiple factors including the cement’s properties along with its application to the prosthesis and bone surfaces. Combinations of different cement application techniques have yielded results with varying bone-cement interface strength. While a proper cementation technique is critical to the long-term success of a total knee replacement, other factors, such as antibiotic-loaded bone cement (ALBC), can help prevent and treat complications (such as infection). Although ALBC was not approved in North America by the Food and Drug Administration (FDA) until 2003, it was first described in 1970 and has been routinely used in revision total knee arthroplasty with reliable antibiotic elution properties and an acceptable safety profile.
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INTRODUCTION

The use of polymethyl methacrylate (PMMA), commonly known as bone cement, has been instrumental in the successful outcomes of implant fixation in total joint arthroplasty. Both the quality and longevity of implant fixation has been improved with the evolution of modern-day cement preparation and technique. While the term “cement” describes a substance that adheres to other materials that binds them together, PMMA acts as a spacer filler given its lack of intrinsic adhesive properties. This article reviews the historical perspective, curing process of cement, the effect of antibiotics on mechanical properties, and proper techniques during total knee arthroplasty (TKA).

HISTORICAL PERSPECTIVE

Primitive forms of modern-day bone cement can be dated back to the late 1800s when a German surgeon, Themistocles Gluck, experimented with copper amalgam, plaster of Paris, and a stone putty resin to anchor his hinged ivory endoprosthesis. It was not until 1943 that a patent from the companies, Kulzer and Degussa, described the method of adding a co-initiator to methyl methacrylate to allow polymerization at room temperature. This method of polymerization ultimately led to modern-day bone cement being first successfully used by Sir John Charnley in 1958 to anchor femoral stem prostheses in the femur.

Kulzer, discovered that a dough could be produced by combining ground PMMA with a liquid monomer and heating the mixture to 100°C. It was found that cementation of methyl methacrylate to allow polymerization at room temperature. This method of polymerization ultimately led to modern-day bone cement being first successfully used by Sir John Charnley in 1958 to anchor femoral stem prostheses in the femur.

CURING PROCESS

PMMA is created by the polymerization of methyl methacrylate. This process is initiated by mixing powdered methacrylate (MMA) polymer, benzoyl peroxide, and liquid methyl methacrylate. The powder also contains a radiopacifier, such as zirconium dioxide or barium sulfate. The combination of the powdered polymer and the liquid monomer begins the curing process, which consists of four stages: 1) mixing; 2) waiting; 3) working; and 4) setting.

Mixing phase

The mixing or “wetting” phase begins with the addition of the liquid monomer to the powdered polymer and ends when a homogenous dough has formed. It generally lasts one to two minutes and the cement is in a relatively low viscous state throughout this phase. Three different techniques of mixing described throughout the literature include the use of a vacuum, a centrifuge, or a closed/open bowl (Fig. 1).

Whether one technique is superior to another has been a question of debate investigated by several authors. Wixon et al. evaluated the influence of mixing technique on the porosity and compressive/tensile strength of PMMA and found a decrease in the porosity with a resultant increase in compressive and tensile strength of PMMA after vacuum mixing compared to centrifuge or bowl techniques.

A simulation study performed by Geiger et al. evaluated the effect of mixing techniques on the mechanical properties of the bone-cement interface using an experimental polyvinyl chloride (PVC) tube-steel rod model. Forty-eight PMMA-implant constructs were prepared using either an open-bowl or vacuum-mixing technique with Simplex® (Stryker, Mahwah, New Jersey), Osteobond® (Zimmer Biomet, Warsaw, Indiana), Dough Type® (Zimmer Biomet, Warsaw, Indiana) or Palacos® R (Smith & Nephew plc, Memphis, Tennessee) cement. Overall, no significant differences in cement-implant interface porosity or pullout strength were observed between the vacuum and open-bowl techniques when all cement types were combined. The authors concluded that no relationship was observed between interface porosity and pushout or fatigue strength when all cement types are examined.

Waiting and working phase

The next two phases of the curing process are the waiting “sticky” and working “dough” phase. These two phases are characterized by increased viscosity, polymerization, and heat generation. In general, higher-viscosity cement has a decreased waiting time and increased working time; lower viscosity cement is characterized by an increased waiting time and decreased working time. A recent study evaluating the type of bone cement used in primary TKA in the United States from 2012–2017 showed an increase in high-viscosity cement use compared with low-viscosity cement (61.3% vs. 30.9%). Despite the trend toward increased use of high-viscosity bone cement, the outcomes of clinical and cadaveric studies investigating the role
of high- versus low-viscosity cement as the cause of early failure or implant loosening have been mixed.  

Carlsson et al. evaluated the clinical performance and radiographic stability of high-viscosity (Palacos® R) versus low-viscosity (EMD, E. Merck, Darmstadt, Germany) bone cement in a prospective, multicenter, randomized control trial of 226 primary total hip arthroplasties from 1985–1986. They found no significant difference between the cement type and prosthetic fixation at five-year follow up. In a cadaveric study by Miller et al., low-viscosity (Osteopal, Biomet-Merck, Sjöbo, Sweden) versus standard-viscosity (Simplex®) bone cements were evaluated to determine if the strength of the cement-bone interface was affected by the viscosity of the cement. A venous bleeding pressure system was used to recreate intramedullary bleeding. When evaluating the bone-cement interface, standard viscosity was 21% stronger (determined by peak failure strength) while having a 15% higher apposition (determined by contact friction) compared to low-viscosity cement.

Several cadaveric studies have evaluated cement-bone interface properties which would theoretically improve implant longevity and stability. Rey et al. performed a cadaveric study evaluating the bone penetration of three different types of cement with varying viscosities. Low-viscosity cement (LVC, Zimmer Biomet, Warsaw, Indiana) had significantly increased cement penetration at all pressures when compared with the higher-viscosity cements (Simplex® and Palacos®). The ideal depth of cement penetration was evaluated by Walker et al. The authors concluded that 3–4mm of cement penetration was optimal, and they also found an inverse relationship between cement penetration and the development of radiolucency at two years follow up, with at least 2mm of cement penetration being the threshold.

A more recent study evaluated the maximum fixation strength with the least amount of cement penetration and found that 1.1mm of cement penetration yielded the lowest threshold for bulk failure of the cancellous bone instead of the cement-bone interface.

Several studies have evaluated intraoperative techniques to improve cement penetration and mechanical properties. In a cadaveric study, Schlegel et al. compared cement penetration and tibial tray pullout strength following bone preparation with pulsatile lavage versus bulb irrigation. High-viscosity cement was used in all cases and computerized tomography (CT) scans of the cadaveric specimens were obtained just after the cementation process. There was a significant improvement in both cement penetration and pullout strength in the pulsatile lavage group. In a retrospective study by Kopeck et al., the effect of hand mixing cement and packing it onto the proximal tibia versus vacuum mixing cement and using gun pressurization was evaluated radiographically. No radiographic difference was found at three years follow up between the two groups. The application of cement to the bone and prosthesis was also evaluated in two separate studies using saw bones. vanlommel et al. compared five different cementing techniques for the proximal tibia and tibial baseplate using Simplex® on an anatomic open-pore sawbones model. While cement gun pressurization yielded the deepest bone cement penetration, the authors recommended applying cement to both the tibial baseplate and proximal tibia with either a spatula or a finger packing method to achieve the optimal cement penetration of 3–4mm as previously described by Walker et al.
Cement gun pressurization of the proximal tibia led to cement penetration >5mm, which has the potential to cause bone necrosis. A similar study was performed evaluating the femoral component during TKA. Four different techniques were evaluated using Simplex® bone cement on an anatomic sawbones model. The authors recommended applying cement to the anterior, anterior chamfer, and distal femoral cuts while applying cement to the posterior femoral component flange (Figs. 4 and 5). This technique was the only one that did not provide inferior results in any area tested. Once the components are impacted into place, all excess cement is removed to prevent any third body wear (Fig. 6).

Setting phase
During the final stage of the curing process, the setting or “hardening” phase is characterized by high temperatures and decreased polymerization as the cement cures to a hard consistency. Factors affecting this stage include extremity movement and position in TKA. Motion prior to the completion of the setting phase has been associated with decreased tibial tray retention force and increased marrow lipid contamination of the bone-cement interface. A 2012 study evaluated knee position and the femoral force application point (FFAP) during the cementation process in unicompartmental arthroplasties, concluding that knee flexion >45 degrees should be avoided due to the increased posterior tibial pressures generated and potential for anterior tibial baseplate liftoff.

Antibiotic-loaded bone cement

Buchholz and Engelbrecht first described the use of antibiotic-loaded bone cement (ALBC) in 1970 by adding gentamicin to Palacos® R bone cement. It was not until 2003 that the Food and Drug Administration (FDA) approved ALBC for prophylactic use in revision arthroplasty for periprosthetic joint infections in North America. Despite this approval, ALBC has been used throughout the world in both prophylactic primary and revision settings.

Antibiotic selection
Not all antibiotics are suitable for use in bone cement. The ideal properties of antibiotics chosen include those that cover a broad spectrum of organisms, have low bacterial resistance, have low potential for toxicity, are relatively hypoallergenic, are water soluble, and are stable at high heat. The three most commonly used antibiotics in ALBC are gentamicin, tobramycin, and vancomycin. Gentamicin is an aminoglycoside that blocks protein synthesis by inhibiting the 30S ribosomal subunit. It is a broad-spectrum antibiotic that is particularly effective against gram-negative organisms. Gentamicin is useful in ALBC due to the fact that a relatively low volume of antibiotic is needed to achieve effective concentration. Commercially available, premixed gentamicin-ALBC is available in a low dose of 0.5 grams, a high dose of gentamicin is considered to be 1.0 gram. Tobramycin, another aminoglycoside, has similar coverage as gentamicin but offers greater susceptibility against pseudomonas aeruginosa. Tobramycin is dosed in 1.2 gram intervals. Finally, vancomycin is a glycopeptide that inhibits cell wall synthesis. It is effective against gram-positive organisms, particularly methicillin-resistant Staphylococcus aureus. Other agents that have been reported and studied in...
the literature but are less commonly
used in ALBC include other antibiotics,
such as cephalosporins, as well as anti-
fungals.25-28

Mechanical stability
When adding dry weight to bone
cement, the potential resulting change in
the mechanical properties of the cement
becomes a concern. The benefit of an
added antibiotic would be nullified
should it lead to catastrophic failure of
the bone/cement or cement/implant
interface. It is generally agreed that no
more than 5% of the dry weight of the
total amount of cement used should be
added in the form of antibiotics. For a
40-gram bag of cement, for example, no
more than 2 grams of antibiotics should
be added to avoid significant alterations
in the mechanical stability of the
cement.29-31 Vacuum mixing may
improve the mechanical strength of
cement by reducing porosity but will
conversely affect the elution property of
the cement.32 This is primarily a concern
for the use of ALBC in the final stage of a
two-stage revision arthroplasty. Higher
doses can and should be used for anti-
biotic spacers to help eradicate infection,
where mechanical strength is less of a
concern due to the temporality of the
construct.33 The ultimate mechanical
strength of the cement is multifactorial;
it depends on the amount of antibiotics
added, the type of antibiotic used, the
method of mixing the cement, and the
brand of cement chosen.

Antibiotic elution
Several factors come in to play when
considering the effectiveness and rate of
antibiotic elution. The hydrophilicity,
concentration, and combination of
antibiotics chosen, in addition to the
porosity, viscosity, and brand of the
cement used have the potential to affect
the elution properties of ALBC.34-36
Elution occurs in three phases. The
first phase is the burst phase, which
occurs in the first 24 hours after
implantation. The highest concentration
of antibiotic is released in this phase.
The second phase is between 24–72
hours, in which there is a rapid decline
in elution as the amount of antibiotic
remaining in the cement is significantly
decreased. The final phase occurs over
the following six weeks (or longer),
where the remaining antibiotic concen-
tration has been shown to remain above
the minimal inhibitory concentra-
tion.34,36 An in vitro study by Squire et
al. investigated the antibacterial proper-
ties of five FDA-approved premixed
antibiotic cements using a seven-day
Kirby-Bauer assay with PMMA discs
and S. aureus-inoculated growth
media.34,35 The authors observed a rapid
decline in the zone of bacterial growth
inhibition over the first three days, fol-
lowed by a plateau in antimicrobial effi-
cacy, supporting the notion that the
majority of antibiotics are released in
the first 72 hours. The authors addi-
tionally noted that low-viscosity cement
had higher elution at day one when com-
pared to high viscosity, but that high-vis-
cosity cement demonstrated a higher
inhibitory effect on day two and there-
after.36
Cement is hydrophobic, yet the
antibiotic must be hydrophilic to be
effectively leached from the cement by
the surrounding joint fluid. On average,
only 10% of added antibiotic is released
from the bone cement when placed in a
hydrophilic environment.37 While vacu-
um mixing increases the mechanical
strength of the cement, hand mixing
allows for increased porosity, which
may have situational benefit with use of
ALBC. The exothermic reaction of
polymerization leads to the creation of
bubbles. As cement hardens, some bub-
bles escape while those that remain
become pores. Increased porosity pro-
vides a reservoir for antibiotics that can
elute over time as joint fluid penetrates
the cracks and pores in the cement.38
Combining two or more antibiotics
to bone cement has been shown to be
synergistic. Penner et al. demonstrated
the additive effect of combining
tobramycin and vancomycin, which
increased the elution of each antibiotic
by 68% and 103%, respectively.38 The
majority of research on ALBC elution
has, however, been performed in vitro.
Thus, the true generalizability of these
studies to in vivo clinical application
remains uncertain. Masri et al. reported
on intra-articular antibiotic levels in 49
patients after undergoing stage one of a
two-staged revision in 34 hips and 15
knees; antibiotic concentration was
measured at the time of spacer removal
and reimplantation (mean=118 days).39
The intraarticular concentration of
tobramycin remained above the break-
point sensitivity limit for sensitive
organisms when at least 3.6 grams were
added to 40 grams of cement.39 Their
study further supported Penner’s find-
ings of the synergistic effect between
vancomycin and tobramycin. At 3.6
grams of tobramycin, vancomycin had
higher elution properties and was noted
to have effective intra-articular concen-
trations at four months, irrespective of
the amount of vancomycin used (1 gram
versus 2 grams).39 In conclusion, it is
recommended that at least 3.6 grams of
tobramycin and 1 gram of vancomycin
per 40 gram package of cement be used
for antibiotic-loaded cement spacers in
two-stage exchange arthroplasty.39

Systemic toxicity
"Sola dosis facit venenum" (“The dose
makes the poison”). Gentamicin,
tobramycin, and vancomycin all have
nephrototoxic potential at large systemic doses. These antibiotics have been shown to be detectable in the serum when used in bone cement, with reports of associated acute kidney injury.\textsuperscript{40-42} This leads us to consider the morbidity of our intervention. Springer et al. looked at the systemic safety of high-dose antibiotics added to cement spacers at their institution, which contained an average of 10.5 grams of vancomycin and 12.5 grams of gentamicin.\textsuperscript{43} Of 34 patients, all of whom were also treated with six weeks of organism-specific intravenous antibiotics, only one had a transient bump in creatinine and no other systemic side effects/complications were reported.\textsuperscript{44} It is important to note that different brands of cement have different elution profiles. One must be familiar with the elution kinematics of the cement they use and always proceed with caution when using high doses of antibiotics in ALBC.

**Prophylaxis**

Antibiotic-loaded bone cement was first approved by the Food and Drug Administration (FDA) in 2003 for prophylactic use in revision arthroplasty for periprosthetic joint infections. Although it is commonly used in Europe for prophylaxis in primary total joint arthroplasties, it was not FDA approved in North America.\textsuperscript{45} Data from the American Joint Replacement registry shows the use of antibiotic-loaded bone cement in primary TKA decreased from 44.2% in 2012 to 34.5% in 2017.\textsuperscript{10} Criticisms of routine ALBC use include the questionable antibiotic efficacy at prophylactic doses, the potential to introduce bacterial resistance, the effect on mechanical strength, and additional cost.\textsuperscript{23,46} Despite this, most agree that high-risk patients should receive low-dose (≤1g/40g) ALBC in primary arthroplasty. Any patient who is relatively immunocompromised may be considered high risk, including those with malignancy, hemophilia, diabetes mellitus, inflammatory arthropathies, malnourishment, as well as those with a history of prior knee or hip surgery, or native joint infection.\textsuperscript{23,34,60}

When eliminating high-risk patients, random controlled prospective studies have not shown a decrease in periprosthetic joint infection (PJI) with the use of prophylactic ALBC.\textsuperscript{47,49} There is compelling evidence for the use of prophylactic low-dose ALBC in total hip arthroplasty (THA) from European joint registries. Retrospective studies from the Norwegian and Swedish registries demonstrate a significant decrease in PJI within the THA cohort with the use of ALBC.\textsuperscript{46,50,51} These large population-based studies demonstrated a 1.8 times higher rate of infection among patients that only received systemic antibiotics compared to those who received both systemic antibiotics and ALBC. However, during the same time span between 1978 and 1990, overall infection rates decreased among all patients, regardless of ALBC use. This is presumed to be due to improved surgical techniques, perioperative management, and new methods of infection control employed during this period.\textsuperscript{22,46,50} Parvizi et al.\textsuperscript{51} performed a meta-analysis demonstrating a reduction in THA infection from 2.3 to 1.2% with the use of prophylactic ALBC. To our knowledge, there are no prospective nor retrospective studies that support the use of prophylactic ALBC in TKA for low-risk patients.\textsuperscript{22,46,51}

In the current climate of value-based care medicine, efficiency, quality, and cost must be mutually considered when choosing treatment modalities. We must critically examine the interventions chosen and whether or not there is evidence to support their use. Commercially available ALBC carries a higher cost than plain bone cement (PBC), and there is little evidence to date that supports its use in low-risk patients, particularly in TKA. A recent meta-analysis looked at the cost associated with ALBC and potential savings when replacing ALBC with PBC.\textsuperscript{52} Three hypothetical cement regimens were considered: 1) two bags of ALBC, 2) one bag ALBC and one bag of PBC, and 3) two bags of PBC. In a model that assumed 1000 total joint arthroplasties performed per year using institutional costs for each cement type ($215/bag for ALBC and $65/bag for PBC) estimated a cost savings ranged from $155,000 to $310,000 annually with the exclusive use of PBC.\textsuperscript{45} The cost of treating a PJI ranges from $50,000 to $100,000 depending on the infecting organism. The cost of using premixed ALBC for TKA has recently been calculated at $112,000 per prevented infection if used routinely.\textsuperscript{52} Antibiotic stewardship is becoming an increasing concern as the number of total joint replacements is projected to increase exponentially over the next 30 years. There currently is no direct evidence that ALBC leads to antibacterial-resistant organisms. However, in vitro studies show that most of the antibiotic elutes in the first day. There is concern that the remaining low dose of prophylactic antibiotic in the cement is not sufficient enough to prevent infection and that prolonged exposure to antibiotics at a concentration below the inhibitory dose will allow for the development of mutational resistance in bacteria.\textsuperscript{15,17,53}

### Complications

**Bone cement implantation syndrome**

Bone cement implantation syndrome (BCIS) is a rare but potentially fatal complication of cemented arthroplasty. It is most commonly seen during THA, and it is typically believed to occur at one of three time points during surgery: 1) cementation/pressurization, 2) prosthesis insertion, or 3) joint reduction. The true incidence of BCIS is difficult to discern because the spectrum of attributable adverse clinical events varies so widely in the literature.\textsuperscript{54} Although there is no universally accepted definition, BCIS is generally characterized by the clinical features of hypotension, hypoxia, cardiac arrhythmias, increased pulmonary vascular resistance, and/or cardiac arrest.\textsuperscript{56}

In a retrospective institutional review of 21,895 cases, Ereh et al. reported 19 intraoperative deaths among 15,211 cemented THA compared to zero intraoperative deaths among 6,684 uncemented THA.\textsuperscript{57} All 19 deaths occurred at the time of implantation. The authors also prospectively evaluated for embolism with transesophageal echocardiogram in 35 patients undergoing elective THA. Embolization was noted to be significantly greater at the time of prosthesis insertion in cemented THA compared to uncemented THA.\textsuperscript{57} Parvizi et al. retrospectively evaluated 38,488 patients undergoing THA and hemiarthroplasty.\textsuperscript{58} The authors noted 23 intraoperative deaths among 23,277 patients who received a cemented prosthesis compared to zero deaths among the 15,211 patients who received...
particles, air, bone particles, and aggregates of debris of fat, marrow, cement and bone cement. The utility of bone cement in total knee arthroplasty is expanding with more studies revealing the impact of antibiotics-laden bone cement during revision arthroplasty as well as prophylaxis in primary joint arthroplasty.

Preventing bone cement implantation syndrome

There are two proposed theories regarding the etiology of BCIS. The first is the monomer-related model, which suggests that BCIS is caused by methyl- methacrylate (MMA) circulating in the blood stream. In vitro studies have shown that MMA molecules cause vasodilation, which can theoretically lead to ultimate cardiopulmonary failure. In vivo animal studies performed by McLaughlin et al. and Rothberg et al., however, have shown that the plasma MMA concentration reached is not high enough to cause these systemic effects. The second theory is the embolic model. Systemic micro-emboli have been detected by bronchoscopy following cement pressurization/implantation in multiple studies. The physiologic consequences of the micro-emboli are thought to be the result of both a mechanical effect and mediator release leading to increased pulmonary vascular tone and consist of debris of fat, marrow, cement particles, air, bone particles, and aggregates of platelets and fibrin. These theories have been postulated as an explanation for BCIS during total hip arthroplasty. Regardless of the true etiology, it is important to consider ways to reduce the incidence of BCIS intraoperatively. Overall, preventing and treating BCIS is largely based on anticipating changes in cardiopulmonary systems; anesthesia colleagues should be notified prior to cementation so that appropriate adjustments in monitoring and symptomatic treatment can be made.

CONCLUSION

In conclusion, modern-day bone cement and its properties continue to evolve to provide improved bone-cement and cement-implant interfaces with the end goal of preventing aseptic loosening. The utility of bone cement in total knee arthroplasty is expanding with more studies revealing the impact of antibiotics-laden bone cement during revision arthroplasty as well as prophylaxis in primary joint arthroplasty.

AUTHORS’ DISCLOSURES

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