Review Article

Routine use of commercial antibiotic-loaded bone cement in primary total joint arthroplasty: a critical analysis of the current evidence

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Abstract: Antibiotic-loaded cement (ABLC) has been widely utilized as an adjuvant treatment for patients with periprosthetic joint infection (PJI) but has also evolved to play a prophylactic role against infection in primary total joint arthroplasties (TJA). Nevertheless, there is currently a paucity of studies that systematically investigated this concept. This review aimed at answering the following questions: (I) Can routine use of ABLC help reduce the current infection rates in primary TJA? (II) What are the risks associated with this approach? And (III) can routine use be justified in primary TJA from an economic standpoint? Multiple databases were queried including PubMed, EMBASE, EBSCO Host, and SCOPUS. Studies published between January 1, 1990 and March 31, 2018 were reviewed. Inclusion criteria were studies reporting: (I) clinical outcomes of routine use of ABLC in primary hip and knee arthroplasty with 2-year minimum follow-up, (II) complications related to the use of ABLC, (III) cost of using ABLC. The final analysis included 24 studies. Data from multiple studies demonstrate contradictory results for infection rates when ABLC is used in all primary procedures with a majority of studies showing similar infection rates between ABLC and plain cement. The main concerns associated with routine use of ABLC are negative effects on the mechanical stability of cement, possible systemic and local toxicity of the absorbed antibiotic, and development of resistant bacterial strains. However, current literature has not clinically validated these concerns. Lastly, with an estimated increase in 117 million dollars with the routine use of ABLC in only 50% of TJAs performed each year, it is difficult to justify the use of ABLC without clear superiority in reducing infection. The use of ABLC has undeniably changed the way orthopaedic surgeons deal with PJI today. However, the large-scale, prophylactic use of ABLC in primary TJAs requires further research and justification.

Keywords: Antibiotic-loaded bone cement; total joint arthroplasty; adjuvant; infection

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Introduction

Periprosthetic joint infection (PJI) can be a devastating complication following primary hip or knee arthroplasties leading to poor functional outcomes, quality of life, or even mortality (1). In addition, a significant cost to the healthcare system is often associated with treating these infections, with many patients requiring multiple staged revisions, hardware exchanges, and repeated readmissions (1-4). With the current growth of total joints utilization, it is estimated that more than half a million primary total hip arthroplasty (THA) and more than three millions primary total knee arthroplasty (TKA) are expected to be performed by the year 2030 (2,3). Current PJI rates have been reported at 1% to 7% of primary total joints arthroplasties. Therefore, it is projected that between 38,000 and 270,000 PJIs can be expected by the same year (2,3). Furthermore, the annual cost of infected revisions is expected to exceed $1.6 billion by year 2020 (3). It is clear that when addressing this challenge, reducing cost should also be considered as one of the primary aims undertaken by orthopaedic surgeons.

Antibiotic-loaded cement (ABLC) has been widely utilized as an adjuvant treatment for patients who have PJIs (5,6). Several studies have demonstrated its efficacy in septic revisions and correlate reduction in re-infection rates to its use (1,4,6-8). Multiple authors have also advocated its use as an essential step in the one-stage revision approach to PJIs (9-13). With wider utilization, the use of ABLC evolved to also play a prophylactic role against infection in primary total joint arthroplasties (TJA) (14). In recent studies, the adoption for routine use in primary TJA has witnessed substantial growth, and in some cases, some surgeons reportedly used it in 90% or more of their primary total knee and hip patients (15). This approach although aiming at protecting the patients against the catastrophic complication of PJIs, may not take into account factors such as efficacy, antibiotic resistance, and cost. Additionally, it has not been validated by clinical trials and clear superiority of its usage in primary TJAs is far from established (8).

PJI remains a major concern, and advocators of routine use of ABLC suggest that it can offer additional advantages protecting patients and saving the cost of revisions on the healthcare system. Nevertheless, there is currently a paucity of studies that systematically investigated this concept. Therefore, the aim of this review was to answer the following questions: (I) Can routine use of ABLC help reduce the current infection rates in primary TJA? (II) What are the risks associated with this approach? And (III) can routine use be justified in primary TJA from an economic standpoint?

Methods

Literature search

A comprehensive literature search of the following databases was performed; PubMed, EMBASE, EBSCO Host, and SCOPUS. Studies published between January 1, 1990 and March 31, 2018 were reviewed. The following key words were used in combination with Boolean operators AND or OR for the literature search; “antibiotic loaded cement”, “laden cement”, “total knee arthroplasty”, “total hip arthroplasty”, “periprosthetic”, “infection”, “advantages”, “risks”, “disadvantages”, “cost”, “complications,” “septic”, and “revisions”. Inclusion criteria for studies to be included in this review were: (I) studies reporting clinical outcomes of routine use of ABLC in primary hip and knee arthroplasty with 2-year minimum follow-up; (II) studies that reported on complications related to the use of ABLC; (III) studies that reported on the cost of using ABLC. In addition, we employed the following exclusion criteria: (I) basic science and purely biomechanical studies; (II) case reports; (III) previous reports; (IV) duplicate studies across databases, (V) studies not in English language. These inclusion criteria were applied by two independent researchers: a board-certified orthopaedic surgeon and an orthopaedic surgery clinical research fellow. If disagreement was encountered, a third independent reviewer, a senior board-certified orthopaedic surgeon was consulted.

Data acquisition

The initial search yielded 312 reports that were screened for relevant studies. This yielded 220 reports whose abstracts were thoroughly reviewed for eligibility according to the inclusion and exclusion criteria, which in turn yielded 47 studies. Next, the full text of these 47 studies were obtained and reviewed for further analysis. All available electronic copies of the reports were collected. In the event that a report was not electronically available, a digitally-scanned hard copy was requested and provided through our inter-library loan service. After thorough evaluation of the full-texts, a total of 21 studies met all our criteria. The reference lists of these studies were also reviewed for any other relevant reports, which yielded an additional four report. Therefore, our final analysis included 24 studies (5,8,16-37).

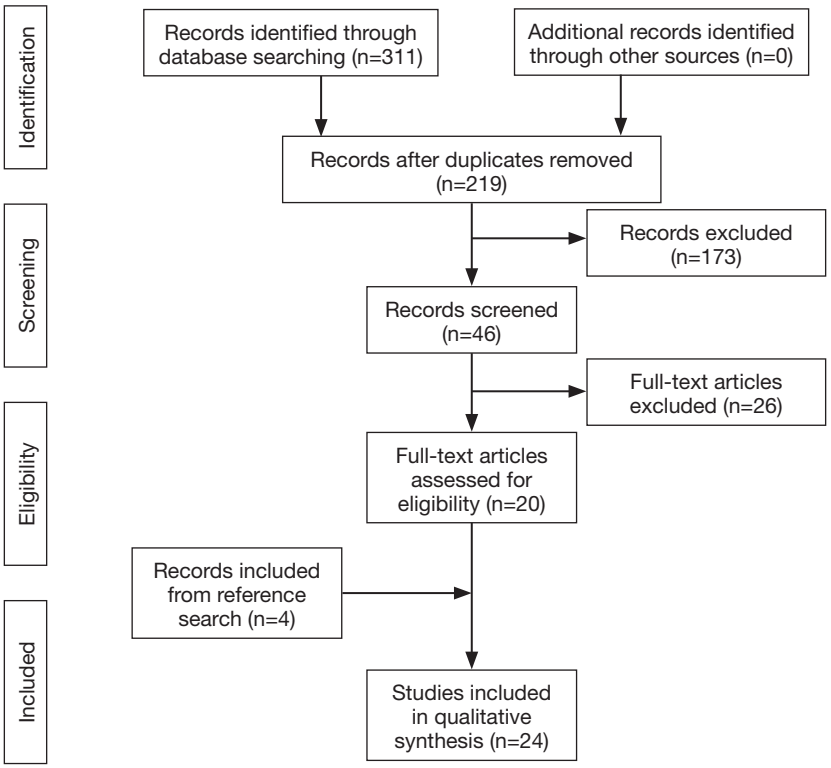

Figure 1 Flow chart of selected studies in this review.

The study selection process is summarized in *Figure 1*.

Results

Can routine use of ABLC help reduce the current infection rates in primary TJA?

The answer is: unclear. Data from multiple studies demonstrate contradictory results for infection rates when ABLC is used in all primary procedures (see *Table 1*). In primary THA, Lynch *et al.* (17) reviewed 1,542 patients who received plain *vs.* ABLC and found a statistically significant difference between the cohorts in terms of PJIs (1.7% *vs.* 1.6%). Engesaeter *et al.* (18) reported on 22,170 primary THA with up to 14 years of follow-up from the Norwegian Arthroplasty Register. The combined used of systemic antibiotics and ABLC was prevalent among 71% of patients and their results demonstrated that patients who received systemic antibiotics only had 1.8 higher risk of revision due to infection (P=0.01). Results from smaller studies showed variable results.

The use of bone cement in primary THA has witnessed a sharp decline over the last few decades with a practice shift towards cementless prosthesis and therefore, the question may be more relevant to primary TKA, where the majority of patients still receive cemented implants. However, in studies that assessed the use of ABLC in primary TKAs, infection rates were not reduced. Namba *et al.* (19) reviewed a large community-based total joints registry and reported on 2030 patients who received ABLC during primary TKA. Deep infection rate was 1.4% for the ABLC cohort and 0.7% with the use of regular cement (P=0.002). Similarly, Hinarejos *et al.* (20) conducted a prospective randomized control trial and compared 1,465 primary TKAs in which plain cement was used to 1,483 TKAs in which ABLC was used. Patients were followed-up for a minimum of 12 months. Final results showed similar infection rate between the two cohorts with deep infection rates at 1.4% in the control cohort and 1.3% in the study cohort and P=0.96. Results from the Canadian Joint Replacement Registry and Canada's Hospital Morbidity Database reported by Bohm *et al.* (21) also showed that there was no difference in PJI rates. Chiu *et al.* (22) did show a reduced infection rate in their study. However, their sample size included only

Table 1 Studies that reported PJI rate following the use of antibiotic-loaded cement in primary total joint arthroplasties

Study	Number of primary PJIs	Lower rates of PJIs? (plain *vs.* antibiotic-loaded cement)
Lynch *et al.* [1987]	1,542 THAs	Yes (1.7% *vs.* 1.65%)
Josefsson and Kolmert [1993]	1,688 THAs	Yes (1.6% *vs.* 0.4%)
Espehaug [2003] Norwegian registry	22,170 THAs	No if used without systemic antibiotic; yes with adjuvant systemic prophylaxis
Chiu *et al.* [2002]	340 TKAs	Yes (3% *vs.* 0%) (5 patients in the plain cement group, all of which were diabetic)
Namba *et al.* [2009]	22,889 TKAs	No (0.7% *vs.* 1.7%, P=0.002)
Hinarejos *et al.* [2013]	2,948 TKAs (RCT)	No (1.3% *vs.* 1.4%, P=0.96)
Bohm *et al.* [2014]	36,681 TKAs	No (1.40% *vs.* 1.51%, P=0.41)

PJI, periprosthetic joint infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; RCT, randomized controlled trial.

340 TKAs. Other studies showed statistically insignificant differences without a clear superiority of using ABLC in primary TKA (23-28).

What are the risks associated with this approach?

The main concerns associated with routine use of ABLC are the negative effect on the mechanical stability of cement implicated by adding antibiotic material to the chemical structure of polymethylmethacrylate, possible systemic and local toxicity of the absorbed antibiotic, and the development of antibiotic resistant bacterial strains. Mechanical strength of acrylic cement has been shown to decrease by higher doses of antibiotics. For gentamicin for example this has been correlated with doses >4.5 g of antibiotic (29). In addition, Moran *et al.* (32) demonstrated that adding Gentamicin in concentrations of 0.5, 1.0, and 2.0 g per 40 g of Palacos cement was linked to decreasing the shear strength of cement. However, commercially available ABLC for use in primary TJA comes with much lower doses of antibiotics (<2 g of antibiotic per 40 g of cement) (38). In addition, to date there has been no study that clinically validated this effect (38). Preparation techniques can also play a role. Hand mixing the antibiotic with cement has been shown to be associated with approximately 40% reduction in the mechanical strength of cement compared to commercially available products (30,31). Therefore, better understanding of this effect is yet to be uncovered by further research.

Systemic toxicity from the local ABLC use has not been demonstrated by the current evidence. Also, the local toxic effect of antibiotics on osteoblastic and osteoclastic activity has not been clinically validated with only *in vitro* studies suggesting negative cellular effect (33-35). However, the clinical significance of such findings is unclear.

Emergence of bacterial resistance to the low-dose antibiotics in ABLC is another concern. Studies have shown that the acrylic cement surface can be ideal for bacterial colonization and prolonged sub-therapeutic exposure to the antibiotic in the cement can allow mutational resistance to develop (15,36,39). In the event that a patient who had a primary procedure with ABLC developed a PJI, a different class of antibiotic may be necessary during a planned staged revision (36,37). This can be difficult to achieve, and an organism-specific antibiotic spacer may not be available.

Can routine use be justified in primary TJA from an economic standpoint?

Gutowski *et al.* (40) calculated the cost of using pre-mixed ALBC in TKA routinely to be $120,000 per prevented infection in their cohort of 4,826 knees. Taking this into account, it is reasonable to believe that this cost increase should be less than the cost to treat a PJI. In a study by Parvizi *et al.* (41) the cost to treat a PJI caused by a methicillin-resistant organism was calculated to be $107,000 while a PJI caused by methicillin-sensitive organisms was calculated to be $68,000. Just looking at these gross figures, one could argue that the increase cost incurred by using pre-mixed ALBC is not sustainable

Based on an estimated cost between $284 to $349 per 40-gram packet of ABLC, Jiranek *et al.* (8) estimated an increase in overall health-care costs of $117,000,000 with the routine use of ABLC for 50% of 500,000 primary TJA

performed annually, assuming the use of two packets per case. Therefore, this estimated increase in cost must be balanced by a reduction of infection rate among primary TJA to be justifiable. At an approximately $50,000 cost for the treatment of one PJI, the authors estimated that there would have to be 2,340 fewer infected patients among the additional 195,000 patients for the routine use of ABLC to maintain the current cost figures. In their analysis, they estimated that the infection rate, currently around 1.5%, must be brought down to 0.3% to balance the cost by using ABLC routinely in only 50% of patients, which can be clinically challenging especially given the current data showing no clear superiority if ABLC in reducing infection.

Discussion

The utilization of antibiotic loaded cement has notably increased, spreading to primary TJAs as a prophylactic strategy to decrease the occurrence of PJI. Currently in the United States ABLC has not received FDA approval for use in primary procedures, with most studies reporting on its usage originating mainly from European countries. However, the clear benefit of routine prophylactic use cannot be currently justified. Current evidence shows contradictory result, at best, for PJI rates with the use of ABLC. In THA, clinical practice guidelines have shifted from using cemented implants altogether, and more recently, cementless implants have also been gaining popularity in primary TKA, which further questions the benefits of routine ABLC use given the cost. Its use is not without risks, and despite the lack of evidence, large-scale adoption should be preceded by further research to truly estimate the impact of adverse effects.

This review is not without limitations. The conclusions drawn from the literature are as good as the included studies with many of them being retrospective studies. However, we have adopted a comprehensive approach to answer very specific and clinically-relevant questions. In addition, multiple studies included in this review were conducted in different countries and therefore, the results may not account for differences in patient demographics, implant and drug manufacturing and surgical techniques, which can all be potential confounders. Nevertheless, the consistent findings across these multiple studies points to a degree of internal validity of our pooled analysis.

In conclusion, the use of ABLC has certainly changed and affected the way orthopaedic surgeons deal with PJI today. However, this impact continues to be unclear for primary TJA and large-scale, prophylactic use in primary procedures requires further research and justification points. In this systematic analysis of the literature we aimed to provide an updated reference to the orthopaedic community and provide an impetus for future work. Large, prospective, and preferably multi-center studies are needed to establish a clear and substantial benefit that would justify the prophylactic use of ABLC in primary TJAs.

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Footnote

Conflicts of Interest: MA Mont: board or committee member of AAOS; paid consultant of Abbott, Cymedica, Mallinckrodt Pharmaceuticals, Pacira, Performance Dynamics Inc., Sage; paid consultant and research support of DJ Orthopaedics, Johnson & Johnson, Ongoing Care Solutions, Orthosensor, TissueGene; editorial or governing board of *Journal of Arthroplasty*, *Journal of Knee Surgery*; IP royalties of Microport; research support of National Institutes of Health (NIAMS & NICHD); editorial or governing board of Orthopedics, Surgical Techniques International; stock or stock options of Peerwell; IP royalties, paid consultant and research support of Stryker. The other authors have no conflicts of interest to declare.

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