No Decreased Infection Rate When Using Antibiotic-Impregnated Cement in Primary Total Joint Arthroplasty

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As a result of reading this article, physicians should be able to:

1. Explain why periprosthetic infection is the most devastating complication of primary total joint arthroplasty.
2. Recognize the available strategies for using antibiotic-impregnated bone cement in patients undergoing primary total joint arthroplasty.
3. Discuss the potential strengths and limitations of using antibiotic-impregnated bone cement in primary total joint arthroplasty.
4. Recall the available evidence regarding the use of antibiotic-impregnated bone cement in primary total joint arthroplasty.

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ABSTRACT

There has been much debate and controversy about the routine use of antibiotic-impregnated bone cement in primary total joint arthroplasty. The purpose of this study was to undertake a meta-analysis to determine whether the use of antibiotic-impregnated bone cement would reduce the incidence of infection after primary total joint arthroplasty. Of 313 citations identified for screening, 6 trials reporting 26,791 patients were eligible for data extraction and meta-analysis. The authors found no statistically significant difference between antibiotic-impregnated bone cement and plain bone cement in terms of the incidence of infection. The results indicated that the use of antibiotic-impregnated bone cement in primary total joint arthroplasty did not lead to a decrease in the rate of infection. [Orthopedics. 2014; 37(12):839-845.]

One of the most devastating complications of total joint arthroplasty (TJA) is periprosthetic infection (PPI) resulting in substantial morbidity, often with pain, immobility, prolonged hospital stay and further surgery, and thus additional high costs.\(^1\)\(^-\)\(^3\) Compared with patients undergoing revision procedures for aseptic loosening, patients with PPI have a higher rate of postoperative complications, number of hospitalizations, reoperation rates, and outpatient charges.\(^2\)\(^-\)\(^4\) Despite the use of prophylactic antibiotics and strategies such as laminar flow, shortened operative time, and improved surgical technique, the incidence of postoperative PPI varies from 1% to 2.2% after TJA.\(^5\)\(^-\)\(^8\)

The routine use of antibiotic-impregnated bone cement (AIBC) for infection prophylaxis in primary TJA is controversial. According to the literature, some studies have shown that the prophylactic use of AIBC is associated with a lower risk of infection-based revision.\(^9\)\(^-\)\(^11\) Furthermore, some large registry databases have shown a decreased rate of revision surgery due to infection in patients who received AIBC at the time of primary TJA.\(^12\)\(^-\)\(^14\) However, other studies did not find that the use of AIBC reduced the prevalence of infection following TJA.\(^15\)\(^-\)\(^16\) Also, other concerns include the possible development of antibiotic resistance, cost, allergic reactions, toxicity, and degradation of cement material properties.\(^17\)\(^-\)\(^18\)

To the current authors’ knowledge, only 1 meta-analysis was performed on this issue in 2008.\(^13\) However, this meta-analysis included revision TJA, and all included studies were performed before 2000. Meanwhile, 2 randomized, controlled trials and 1 retrospective cohort study comparing outcomes of AIBC and plain bone cement in primary TJA were published after 2008 and indicated that the issue is still controversial. Therefore, the current authors performed an updated meta-analysis to determine whether the use of AIBC would reduce the incidence of infection after primary TJA. Because AIBC has been widely accepted for revision, the authors excluded trials referring to revision TJA in which AIBC spacers were used. Their meta-analysis included only primary TJA.

MATERIALS AND METHODS

Search Strategy

The authors searched electronic databases including PubMed (1966 to August 2013), CENTRAL (Cochrane Controlled Trials Register; issue 2, 2008), Web of Science (1994 to August 2013), Embase (1984 to August 2013), Ovid Medline (1948 to August 2013), and CBM (Chinese Biomedicine Database; 1978 to August 2013). The Medical Subject Headings arthroplasty, infection, and bone cement were used in English and Chinese to identify studies from the databases. Search strategies were adjusted based on the characteristics of each database. The authors identified all relevant studies that evaluated the efficacy of AIBC for the prevention of infection in primary TJA and searched reference lists of review articles to identify other potentially eligible studies. The authors also searched Yahoo! and Google search engines to find any additional trials. There was no limitation based on language, year of publication, or publication status.

Selection Criteria

Trials were included if they were clinical trials evaluating the efficacy of AIBC for the prevention of infection in primary TJA, with adequately reported data on the incidence of infection. Prospective and retrospective trials were included, and the authors did not confine the meta-analysis to randomized, controlled trials. After excluding duplicates, one reviewer (Z.Y.) performed an initial title and abstract screening of articles to discard those that were clearly ineligible. Studies on drug trials, letters and review articles, and studies without available data were excluded. Then 2 reviewers (S.B., Y.J.) independently examined the full articles to assess the trials for eligibility for inclusion, with disagreement resolved by discussion. Citations that were clearly not relevant or were not clinical trials were not reviewed in full. If necessary, the reviewers attempted to contact the authors of the original articles to obtain further details.

Validity Assessment

Two reviewers (Z.Z., K.P.) rated the quality of the eligible studies independently. Study quality was judged using the Jadad 5-point scale\(^19\) for randomized, controlled trials and the Newcastle-Ottawa quality assessment scale\(^20\) for other studies. The Jadad 5-point scale contains 2 questions each on randomization and masking and 1 question on the reporting of dropouts and withdrawals. The total possible score is 5.\(^19\) For the Newcastle-Ottawa quality assessment scale, the authors assessed studies based on 3 aspects: the selection of the study groups (0-4 points), the comparability of...
the groups (0-2 points), and the ascertainment of either the exposure or outcome of interest (0-3 points). The total possible score was 9.

Data Extraction
The authors extracted the following data from each included study: (1) patient demographics, including age, sex, indication for TJA, study location, follow-up duration, and type of study; (2) type and manufacturer of prosthesis, type of cement, and AIBC strategy; and (3) incidence of infection after TJA.

The authors focused on the incidence of infection after TJA between patients receiving AIBC and those receiving plain bone cement. The primary outcome was the incidence of infection after TJA from all included trials, with subsequent subgroup analyses based on the type of study (randomized, controlled or retrospective cohort), operative site (knee, hip, or shoulder), and follow-up duration (short-term follow-up at less than 24 months or midterm follow-up at more than 24 months) as the secondary outcomes.

Statistical Analysis
All outcomes in this study were dichotomous variables and expressed as risk ratios (RR) with 95% confidence intervals (CI). Statistical heterogeneity was tested using the chi-square test and $I^2$ statistic. A chi-square statistic less than 0.1 or an $I^2$ statistic greater than 50% was indicative of statistical heterogeneity. Depending on the heterogeneity, meta-analysis was performed using a fixed-effects or random-effects model. When there was no statistical evidence of heterogeneity, a fixed-effects model was adopted; otherwise, a random-effects model was used. Publication bias was tested by funnel plots. Statistical analysis was performed using RevMan version 5.0 software (The Cochrane Collaboration, Oxford, United Kingdom), and a $P$ value less than .05 was considered statistically significant for outcome measures.

RESULTS
Included Trials
Figure 1 shows details of study identification, inclusion, and exclusion. The authors’ search strategy initially yielded 313 citations. Of these, 6 clinical trials with 26,796 knees were included in the meta-analysis.$^9,11,21-24$ Four of these trials were randomized, controlled trials$^9,11,22,24$ and 2 were retrospective cohort studies$^{21,23}$; 2 of the articles were from 1 trial.$^9,11$

Table 1 shows study characteristics. Two trials were performed in Taiwan, 1 in Germany, 1 in Canada, 1 in the United States, and 1 in Spain. All trials were published after 2000, and 3 trials were published after 2010. All patients in the 6 trials were adults. Mean patient age ranged from 67.5 to 76.06 years, and mean follow-up duration ranged from 12 to 50 months. All patients underwent primary TJA: 26,254 patients in 4 trials underwent total knee arthroplasty (TKA),$^9,11,21,24$ 28 patients in 1 trial underwent total hip arthroplasty (THA),$^{22}$ and 501 patients in 1 trial underwent total shoulder arthroplasty (TSA)$^{23}$.

According to the quality assessment, 4 randomized, controlled trials that clearly reported the details of randomization and blinding were of high quality (Jadad score $\geq$3). According to Newcastle-Ottawa quality assessment scale, 1 retrospective cohort trial scored 8 points$^{23}$ and 1 scored 7 points,$^{21}$ indicating they were both of high quality.

Table 2 summarizes prosthetic type and manufacturer, cement type, and AIBC strategy. Simplex P bone cement (Howmedica Inc, Rutherford, New Jersey) was used in 5 trials.$^9,11,22-24$ Cefuroxime was mixed with bone cement in 2 trials,$^9,11$ tobramycin was used in 1 trial,$^{22}$ erythromycin and colistin were used in 1 trial,$^{23}$ tobramycin or gentamycin or vancomycin was used in 1 trial,$^{23}$ and the antibiotic was unclear in 1 trial.$^{21}$
Results of Meta-analysis

Table 3 shows the results of the meta-analysis and subgroup analysis. All 6 studies reported the incidence of infection after primary TJA. In the AIBC group, PPI was found in 51 (1.28%) of 3982 TJAs. In the plain bone cement group, PPI was found in 194 (0.85%) of 22,809 TJAs. There was statistical heterogeneity between studies (P < .1; I² = 77%) using a random-effects model. The overall RR was 0.6 (95% CI, 0.23-1.56), suggesting that there was no statistical significance between the 2 groups (P = .30) (Figure 2).

Results of Subgroup Analysis

To eliminate heterogeneity, 6 studies were under subgroup analysis based on the type of study, operative site, and follow-up duration. In subgroup analysis of different study types, 4 were randomized, controlled trials and 2 were retrospective cohort studies. In subgroup analysis of operative site, 4 trials reported the results of TKA, 1 reported THA, and 1 reported TSA. In subgroup analysis of follow-up duration, 2 trials reported short-term results and were assigned to the short-term subgroup, and 4 trials reported mid-term results and were assigned to the mid-term subgroup. Table 3 shows the results of subgroup analysis of the cumulative data from these 6 trials. There was no significant difference in any analysis confirming that the incidence of infection was decreased in the AIBC group.

Discussion

Periprosthetic infection is a debilitating complication of TJA and has been cited as the most common cause of implant failure. Since its introduction in 1970, AIBC has been widely accepted in revision TJA with AIBC or with plain bone cement. Since then, several retrospective studies have been published to evaluate the efficacy of AIBC in control of PPI. However, there is no consensus regarding the availability of AIBC for primary TJA. To elucidate the effectiveness of AIBC when comparing patients who underwent TJA with AIBC or with plain bone cement, this literature review and meta-analysis was conducted. In the overall comparison and subgroup analysis, there were no statistically significant differences in the incidence of infection when comparing patients who underwent TJA with AIBC or with plain bone cement.

Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Mean Age, y</th>
<th>No. of M:F</th>
<th>Diagnosis</th>
<th>Outcomes</th>
<th>Surgery</th>
<th>FU, mo</th>
<th>Study Type</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al11</td>
<td>51 (41 knees)/32 (37 knees)</td>
<td>72±6.6/69±5.9</td>
<td>28:13/25:12</td>
<td>OA</td>
<td>Positive</td>
<td>TKA</td>
<td>50</td>
<td>RCT</td>
<td>4</td>
</tr>
<tr>
<td>Chiu et al1</td>
<td>178 (178 knees)/162 (162 knees)</td>
<td>70±7.4/68±6.9</td>
<td>86:37/112:50</td>
<td>OA=300; RA=16; PA=16; GA=3; ON=5</td>
<td>Positive</td>
<td>TKA</td>
<td>49</td>
<td>RCT</td>
<td>3</td>
</tr>
<tr>
<td>Namba et al11</td>
<td>2030 knees/20,869 knees</td>
<td>67.5/68.1</td>
<td>759:1245 (26 UK)/736:1132 (256 UK)</td>
<td>OA=21,139; other=1750</td>
<td>Negative</td>
<td>TKA</td>
<td>&gt;24</td>
<td>RCS</td>
<td>7</td>
</tr>
<tr>
<td>Rohm et al12</td>
<td>16 (18 hips)/12 (12 hips)</td>
<td>73/72</td>
<td>10/18</td>
<td>–</td>
<td>Negative</td>
<td>THA</td>
<td>24</td>
<td>RCS</td>
<td>5</td>
</tr>
<tr>
<td>Nowinski et al13</td>
<td>236 (236 shoulders)/265 (265 shoulders)</td>
<td>68±6.9/70±7.4</td>
<td>73:16/380:185</td>
<td>CTA=417; PA=53; fracture=28; RA=6; IA=3; ON=2; OA=2</td>
<td>Positive</td>
<td>TSA</td>
<td>37</td>
<td>RCS</td>
<td>8</td>
</tr>
<tr>
<td>Hinarejos et al14</td>
<td>1483 (1483 knees)/1465 (1465 knees)</td>
<td>75.84±7.36/76.06±6.66</td>
<td>346:1137/353:1112</td>
<td>Any diagnosis leading to TKA</td>
<td>Negative</td>
<td>TKA</td>
<td>12</td>
<td>RCT</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: AIBC, antibiotic-impregnated bone cement; CTA, cuff tear arthroplasty; F, females; FU, follow-up; GA, gouty arthritis; IA, inflammatory arthritis; M, males; OA, osteoarthritis; ON, osteonecrosis; PA, posttraumatic arthritis; RA, rheumatoid arthritis; RCS, retrospective cohort study; RCT, randomized, controlled trial; RV, revision; TKA, total knee arthroplasty; TSA, total shoulder arthroplasty; UK, unknown.

a Positive = Antibiotic-impregnated bone cement was effective in the prevention of postoperative infection after arthroplasty.

b Negative = Antibiotic-impregnated bone cement did not decrease the rate of postoperative infection after arthroplasty.
TJA because it helps in the treatment of infection. However, there has been much debate about the use of AIBC in primary TJA or uninfected TJA. The use of AIBC in primary TJA varies in different countries. In Europe, AIBC is routinely used in 90% of primary TJAs, compared with approximately 10% of primary TJAs in the United States.

The proponents of AIBC believe that it has several advantages. Antibiotics are stable during the exothermic polymerization reaction, with only minor adverse effects on the cement’s strength. Antibiotic-infused bone cement is effective against gram-positive, gram-negative, and anaerobic bacteria, which inhibit 96% to 98% of anaerobic and aerobic organisms tested in vitro. The antibiotic delivery brings about a high concentration in the first 3 postoperative days, and there is no decrease in the mechanical properties of cement. However, other authors have a negative opinion about AIBC. They think the routine use of AIBC in primary TJA may contribute to antimicrobial-resistant organisms, making the management of infected implants more difficult. They also report a risk of hypersensitivity or toxicity and suggest that

Table 2

<table>
<thead>
<tr>
<th>Trial</th>
<th>Prosthesis</th>
<th>Cement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Duracon implants (Howmedica, Inc, Limerick, Ireland)</td>
<td>Cement: Simplex P (Howmedica Inc, Rutherford, NJ); AIBC: 2 g cefuroxime in 40 g Simplex P</td>
</tr>
<tr>
<td>Chiu et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Duracon implants fixed in a hybrid form, with femoral components uncemented and tibial and patellar components cemented</td>
<td>Cement: Simplex P; AIBC: 2 g cefuroxime in 40 g Simplex P</td>
</tr>
<tr>
<td>Namba et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bohm et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Exeter femoral stems coupled with Trident acetabular cups (Stryker Orthopaedics, Mahwah, New Jersey)</td>
<td>Cement: Simplex P; AIBC: tobramycin-laden cement</td>
</tr>
<tr>
<td>Nowinski et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Aequalis system (Tornier, Edina, Minnesota) used in 415 shoulders and Delta III system (DePuy, Warsaw, Indiana) used in 86 shoulders</td>
<td>Cement: Simplex P or DePuy 1 bone cement; AIBC: 1 g tobramycin per 40 g bone cement, 1 g gentamycin per 40 g bone cement, or Simplex Speed-Set hand mixed with 1 g vancomycin and 1.2 g tobramycin powder</td>
</tr>
<tr>
<td>Hinarejos et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Cement: Simplex P; AIBC: 0.5 g erythromycin and 3 million units colistin in 40 g cement</td>
</tr>
</tbody>
</table>

Abbreviation: AIBC, antibiotic-impregnated bone cement.

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Studies</th>
<th>No. of Surgeries</th>
<th>P</th>
<th>RR (95% CI)</th>
<th>Heterogeneity P (I&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>26,791</td>
<td>.30</td>
<td>0.60 (0.23-1.56)</td>
<td>&lt;.1 (77%)</td>
<td>Random</td>
</tr>
<tr>
<td>RCT</td>
<td>4</td>
<td>3391</td>
<td>.22</td>
<td>0.43 (0.11-1.67)</td>
<td>.08 (60%)</td>
<td>Random</td>
</tr>
<tr>
<td>RCS</td>
<td>2</td>
<td>23,400</td>
<td>.72</td>
<td>0.62 (0.05-8.36)</td>
<td>.01 (84%)</td>
<td>Random</td>
</tr>
<tr>
<td>Operative site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>4</td>
<td>26,265</td>
<td>.64</td>
<td>0.80 (0.32-2.00)</td>
<td>&lt;.1 (75%)</td>
<td>Random</td>
</tr>
<tr>
<td>Hip</td>
<td>1</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Shoulder</td>
<td>1</td>
<td>501</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td>2</td>
<td>2973</td>
<td>.97</td>
<td>0.99 (0.53-1.83)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mid-term</td>
<td>4</td>
<td>23,818</td>
<td>.25</td>
<td>0.35 (0.06-2.08)</td>
<td>&lt;.1 (82%)</td>
<td>Random</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RCS, retrospective cohort study; RCT, randomized, controlled trial; RR, risk ratio.
there is an increase in the cost of the cement.17,18,29

Authors who propose the routine use of AIBC have stated that the use of AIBC led to a decrease in the incidence of infection after primary TJA. Chiu et al11 performed 2 randomized, controlled trials that included 240 primary TKAs in healthy patients and 78 primary TKAs in patients with diabetes mellitus. The results showed that cefuroxime-impregnated cement was effective in the prevention of early to intermediate deep infection after primary TKA with the use of perioperative systemic antibiotic prophylaxis. Joseffson et al30 conducted a randomized, controlled trial in which the prophylactic effect of systemic antibiotic was compared with AIBC in 1688 consecutive THAs; the results showed the prophylactic value of AIBC against PPI after THA. In a large retrospective study, data on 22,170 primary THAs from the Norwegian Arthroplasty Register during the period from 1987 to 2001 showed that patients who received only systemic antibiotic prophylaxis (5960 hips) had a 1.8 times higher rate of infection than patients who received systemic antibiotic prophylaxis combined with gentamicin-impregnated bone cement (15,676 hips).12

Furthermore, other national arthroplasty registry studies from the United Kingdom13 and Sweden14,15 also showed statistically significant reduced PPI with a combination of AIBC and systemic antibiotics. Hence, 48% of surgeons in Norway, 85% of surgeons in Sweden, and 69% of surgeons in United Kingdom reported using AIBC routinely for TJA.12,31,33

However, authors of other studies do not advocate the routine use of AIBC as an infection prophylaxis in primary TJA.34 It has been reported that the use of AIBC was associated with a paradoxical increase in the risk of infection.15 A large clinical study performed by Namba et al15 found that the use of AIBC did not prevent infection after TKA. In another study of 22,889 primary TKAs, Namba et al21 found no reduction of primary TKA deep PPI with the routine use of low-dose, commercially available AIBC in a community setting. In a cohort of 1625 patients in which 50% had received AIBC, Gandhi et al16 found that the use of AIBC did not reduce the rate of infection following TKA. Hinarejos et al24 performed a prospective study with 2948 patients who underwent TKA and reported that AIBC with colistin and erythromycin did not reduce the rate of deep PPI. Furthermore, Engesaeter et al35 provided an update on the Norwegian registry and examined revision rates for THA due to infection after uncemented THA, cemented THA, and AIBC THA; results showed no statistically significant differences between groups. In the current meta-analysis, the authors also found no statistically significant differences in the incidence of infection between AIBC and plain bone cement in primary TJA.

This meta-analysis has some limitations. First, the implants, cements, and antibiotic impregnation strategies were not consistent through the trials. Although subgroup analysis was performed, the efficacy of different implants, cements, and antibiotics was variable due to the different design principles, which may influence the accuracy of the conclusion. Second, the populations among included studies differed widely, and heterogeneity was high. The random-effects model was used when heterogeneity appeared. Third, because there were some nonrandomized, controlled trials included in this study, this may have produced bias with an adverse effect on the reliability of the authors’ conclusions. Finally, the length of follow-up in most of the included studies was short, with 2 trials reporting outcomes at less than 24 months. However, PPI is an early postoperative complication that seldom occurs beyond 60 months after TJA.

CONCLUSION

This meta-analysis of currently available evidence indicated that the use of AIBC in primary TJA did not lead to a decrease in the rate of infection. More high-quality studies with a larger number of participants and longer follow-up are needed to confirm the use of AIBC as infection prophylaxis.

REFERENCES


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