Evidence Review

Topic: Outcomes of primary and revision aseptic total hip and total knee arthroplasty with antibiotic-loaded bone cement

Background

Deep infection following total hip or total knee arthroplasty is a troublesome and debilitating complication that results in extremely high costs for all parties involved. According to recent data published by the Canadian Institute for Health Information (CIHI)[1], of the 58,351 primary THAs and TKAs performed during 2005-2006 across Canada (not including Quebec) 780 (1.3%) were diagnosed with an infection that required re-hospitalization within one year of their joint implantation. The costs associated with deep infection following arthroplasty often include additional pain and suffering for the patient, tarnished reputations for the surgeon and facility, and an expensive revision process. Hence, there is a constant interest to incorporate techniques that can reduce or eliminate the risk of post-operative infection following total hip arthroplasty (THA) or total knee arthroplasty (TKA).

Antibiotic-loaded bone cement, first introduced in the 1960s, is increasingly looked upon as a technique to further reduce deep infection rates following THA and TKA. The main effect of antibiotic-loaded bone cement is to establish strong local resistance to potential infection following total joint implantation by the local release of antibiotic to the surrounding tissues. Mixing cement with antibiotics is a simple procedure, and several large case series reports suggest that the prophylactic use of antibiotic-loaded bone cement significantly reduces the rate of deep infection following primary THA and TKA[2].

Large-scale national joint replacement registries constitute informative case-series data, the analysis of which lends support to the prophylactic use of antibiotic-loaded bone cement. For example, a study of 10,905 THA patients (1987-1995) of the Norwegian Arthroplasty Register found that patients who received antibiotic bone cement and systemic antibiotics had significantly less deep infections than using systemic antibiotics alone[3]. Consequently, in Norway the use of antibiotic-loaded bone cement with THA has climbed to over 90%.

A follow-up report on the Norwegian Arthroplasty Register assessed the results of 22,170 THAs performed between1987 and 2001 and also concluded that antibiotic-loaded bone cement is an important prophylactic agent in the prevention of deep infection following THA[4]. The authors of that case series concluded that antibiotics should be delivered via bone cement in addition to systemic administration.

Analysis of 92,675 primary THAs done from 1979 to 1991recorded in the Swedish Hip Registry also found that the use of antibiotic-loaded bone cement was associated with significantly less deep infections following arthroplasty[5]. Furthermore, study of that registry also found that antibiotic-loaded bone cement is associated with the lowest revision rates following primary THA. Taken together, these case series studies suggest that the use of antibiotic-loaded bone cement an effective prophylactic method to prevent deep infection following total joint replacement and this method is cost-effective in eliminating infection and reducing revision costs.

The benefits of using antibiotic-loaded bone cement in the revision of infected joints are widely known and include the localized delivery of antibiotic without the risk of systemic toxicity and an antibiotic elution profile that provides antimicrobial levels for an extended period (i.e., up to 4 months)[6]. However, the use of antibiotic-loaded bone cement for prophylaxis in aseptic primary and revision joint arthroplasty remains a contentious issue. The benefit of reduced deep infections observed in large follow-up reports must be weighed against the potential hazards of its routine use, which include the potential development of antibiotic resistance, toxicity, allergic reactions and reduced mechanical strength of the cement [7].

The aim of this evidence review is to summarize the best available literature from Cochrane reviews, experimental clinical studies and official guidelines on the efficacy of antibiotic-loaded bone cement in primary and revision aseptic THA and TKA.

Review Design

- This review is structured on a format similar to a Cochrane systematic review;
- The relevant Cochrane systematic review, if available, will be included and summarized in this evidence review;
- Next, the search strategy and inclusion/exclusion criteria of the Cochrane review will be used or developed if a Cochrane review does not exist, prospective comparative studies (RCT, Controlled Clinical Trail, Cohort Study) and systematic reviews published after the Cochrane review will be selected for this evidence review;
- If prospective comparative studies are not available then retrospective comparative studies and case series reports will be included in this review;
- Finally, applicable clinical practice guidelines will also be included in this review;
- Selected literature and clinical practice guidelines must pass quality control (discussed below) for inclusion into this evidence review.

Search Strategy

The objective of this evidence review is to assess the efficacy of using antibiotic-loaded bone cement in primary and revision aseptic total hip and total knee arthroplasty. To ensure that high-quality primary studies would be selected for this evidence review, preference was given for the selection of prospective comparative trials although retrospective comparative studies could be included here as well. Non-comparative studies, such as case series, case studies, and expert opinions, are regarded as having the lowest level of evidence [8] and were not included in this review.

A search of the Cochrane Database of Systematic Reviews was performed with the following search strategy:

> ((antibiotic or antimicrobial).mp OR (prophylactic).mp) AND (cement OR fixation).mp AND (arthroplasty OR replacement).mp

No applicable Cochrane Systematic Reviews were identified.

Next, a search for prospective comparative clinical trials published in the major medical databases (MEDLINE/PubMed, EMBASE, CINAHL) was performed with the following search strategy:

> Search Term: (antibiotic OR antimicrobial OR prophylactic) AND (cement OR fixation) AND (arthroplasty OR replacement) AND English[la] AND (Clinical Trial[pt])

Clinical Study Inclusion and Exclusion Criteria

Inclusion criteria for published studies were as follows:

- Patient population limited to elective primary and revision aseptic total hip and total knee arthroplasty; and
- Comparative prospective studies wherein the intervention is antibiotic-loaded bone cement while the control group is standard bone cement; and
- Outcome measures reported as patient-level results (e.g. adverse events, revision rate); and
- Studies published in English.

Exclusion criteria included:

- Studies that include infected primary and revision total hip or total knee replacements; and
- Joint replacements other than the hip and knee; and
- Studies based on hip replacement prostheses that are not conventional devices (e.g., hip resurfacing systems)

Clinical studies selected for inclusion:

- Chiu and Lin. 2009 [9]. Antibiotic-impregnated cement in revision total knee arthroplasty. A prospective cohort study of one hundred and eighty-three knees. *J Bone Joint Surg Am.*
- Chiu et al. 2002 [10]. Cefuroxime-impregnated cement in primary total knee arthroplasty: a prospective, randomized study of three hundred and forty knees. *J Bone Joint Surg Am.*
- Chiu et al. 2001 [11]. Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus. A prospective, randomised study. *J Bone Joint Surg Br.*

Clinical studies excluded but of interest:

- van Kasteren et al. 2007. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. *Clin Infect Dis.* [single-group prospective cohort study]

- Bálint L et al. 2006. Detection of gentamicin emission from bone cement in the early postoperative period following total hip arthroplasty. *Orthopedics*. [outcome measure not related to patient outcomes]

- Hallan et al. 2006. Palamed G compared with Palacos R with gentamicin in Charnley total hip replacement. A randomised, radiostereometric study of 60 HIPS. *J Bone Joint Surg Br.* [all bone cements loaded with antibiotic]

- Digas G et al. 2005. Fluoride-containing acrylic bone cement in total hip arthroplasty. Randomized evaluation of 97 stems using radiostereometry and dual-energy x-ray absorptiometry. *J Arthroplasty*. [lack of control group]

- Malik et al. 2005. Primary total knee replacement: a comparison of a nationally agreed guide to best practice and current surgical technique as determined by the North West Regional Arthroplasty Register. *Ann R Coll Surg Engl.* [antibiotic loaded cement use comparison data only, not patient outcomes]

- Josefsson and Kolmert. 1993. Prophylaxis with systematic antibiotics versus gentamicin bone cement in total hip arthroplasty. A ten-year survey of 1,688 hips. *Clin Orthop Relat Res.* [lack of antibiotic-free cement control group]

  * Note: These authors conducted a prospective, randomized trial that compared deep infection rates of patients who received gentamicin-loaded bone cement vs. systemic antibiotics in 1688 hips. They reported a 0.4% infection rate with antibiotic-loaded cement compared to 0.9% with systemic antibiotics at 5-year follow-up.

- Brien et al. 1993. Antibiotic impregnated bone cement in total hip arhroplasty: an *in vivo* comparison of the elution properties of tobramycin and vancomycin. *Clin Orthop Relat Res.* [outcome measure not related to patient outcomes]

- Lindberg et al. 1991. The release of gentamicin after total hip replacement using low or high viscosity bone cement. A prospective, randomized study. *Int Orthop.* [outcome measure not related to patient outcomes]

Lastly, a search was conducted for clinical practice guidelines that refer to the use of antibiotic-loaded bone cement for total joint arthroplasty. Published guidelines by academic, professional societies and government were searched using Google. Particular attention was paid to literature available at the following organizations:

- American Academy of Orthopaedic Surgeons (AAOS)
- Canadian Orthopaedic Association (COA)
- Scottish Intercollegiate Guidelines Network (SIGN)
- National Guideline Clearinghouse (NGC)

One official guideline published by SIGN in July, 2008 (Antibiotic prophylaxis in surgery: A national practice guideline No. 104) [12] was selected for inclusion in the evidence review.

Quality control

The quality of the two selected prospective trials [9,10,11] was assessed by an independent reviewer. Study quality was measured using a validated scale [13] developed by the Cochrane Collaboration Back Review Group. With this assessment tool, quality assessment of a prospective comparative trial is based firmly on the study design, data collection and analysis processes. The studies included here were judged to have moderate to high-quality. Lastly, the AGREE Instrument [14] was used to appraise the selected clinical practice guideline. This instrument gauges the quality of a guideline based on six domains: scope and purpose; stakeholder involvement; rigour of development; clarity and presentation; applicability; and editorial independence. Based on this tool, the selected SIGN practice guideline was included in this evidence review.

Results

Prophylactic efficacy of antibiotic-loaded bone cement

A search of the major medical databases produced three prospective clinical trials which met this evidence review's inclusion criteria. These studies and their findings are discussed below.

Chiu et al. (2001) conducted a Taiwan-based prospective, randomized trial with 78 consecutive primary TKA patients with diabetes during the period between 1993 and 1998. In that study, the authors assessed for post-operative deep infections, as confirmed by ESR and CRP measurements and joint fluid cultures, among the intervention group patients (n=41 knees) that received cefuroxime-impregnated bone cement compared to the control group patients (n=37 knees) who received standard bone cement during arthroplasty. Simplex P cement was used in all cases and the intervention group cement had 2 g of cefuroxime added in 40 g of cement. Intervention and control group patients did not differ in pre-, peri- and post-operative measures such as age, duration of diabetes mellitus, tourniquet time, operation time, blood transfusion volume, pre- and post-operative blood sugar levels, and superficial infection rates (one case in each group). One surgeon performed all of the procedures in standard operating theatres without routine UV lights for disinfection, laminar air flow ventilation

or isolation suits. To compensate for the poor operating environment a lengthy seven-day course of systemic antibiotics was administered to all patients. At a mean follow-up period of 4.2 years (range: 2.2 to 7.3 years) no case of deep infection was observed in the intervention group while 5 deep infections (13.5%) were noted among the control group patients. Moreover, no incidence of implant loosening was observed at final follow-up and allergic reactions to the antibiotic were absent. Clearly, this prospective study suggests reasonable prophylactic efficacy of antibiotic-loaded bone cement as a means to prevent deep tissue infection in high-risk primary TKA patients.

Although this study was a prospective, randomized clinical trial design, which is widely regarded as the most valid method for determining the efficacy of a therapeutic intervention, the limitations, and thus interpretation, of this study are worth noting. These include the use of a quasi-random method for the allocation of the intervention, a lack of surgeon and outcome assessor blinding, a failure to report compliance and intent-to-treat analysis, and the failure to report the follow-up periods for the outcome assessment of both groups separately. These potential forms of selection, retention and measurement bias could serve to exaggerate the prophylactic efficacy of antibiotic-loaded bone cement although both intervention and control group patients did not differ in pre-, peri- and post-operative measures. Conversely, the risk of random error is likely minimal given the decent study sample size (n=78). Finally, generalizability of the results of this Taiwan-based study to arthroplasty patients in Alberta may be viewed favorably given that the study sample's mean age was nearly 70 years and the primary indication for total joint replacement being osteoarthritis, albeit the ethnicity of the patients was not outlined and all were high-risk (diabetic) for post-operative deep tissue infection.

In the following year, Chiu et al. (2002) reported a nearly identical prospective, randomized clinical trial setup which examined the prophylactic efficacy of cefuroxime-loaded bone cement in the prevention of deep tissue infection following primary TKR. The unique aspect of this trail was that its 340 consecutive arthroplasties, performed from 1994 to 1998, were done on non-diabetic (low-risk) patients. As in their previous study, patients were divided into two groups; Group 1 (n=178) received antibiotic-loaded bone cement (2 g of cefuroxime to 40 g of Simplex P cement), and Group 2 (n=162) received standard bone cement. There were no differences between the groups in terms of demographics, pre-op and post-op knee scores, surgical time, tourniquet use, or the amount of blood transfused perioperatively. At an average follow-up time of 4.1 years (range: 0.5 to 6.7 years), no deep tissue infections were observed among Group 1 patients, whereas 3.1% (n=5) developed deep infection in Group 2. Although one (0.6%) out of the 178 arthroplasties in Group 1 had loosened at 2 years follow-up while no loosening was observed in the control group, this difference was not statistically significant. Further, no other complications were noted in this study sample. Based on their results, the authors concluded that cefuroxime-impregnated cement is an effective method of minimizing the risk of early to moderate deep infection following primary aseptic TKA with no adverse clinical effect, such as loosening of the component, after intermediate-term follow-up. Given the nearly identical study design as their previous trial (discussed above), similar concerns regarding the internal validity and generalizability of the study's results are justified.

Recently, a prospective, randomized study was published by Chiu et al. (2009) which assessed for infection rates and other adverse complications following aseptic revision TKA in a study sample of 183 arthroplasties. Specifically, the authors examined the effect of vancomycin-loaded bone cement (1 g of vancomycin in 40 g of Simplex-P cement) in 93 knees compared to the outcomes observed in 90 knees done with standard bone cement. All procedures were performed between 1993 and 2004 in standard operating theatres without routine UV lights for disinfection, laminar flow ventilation or isolation suit, and all joints were found to be aseptic pre- and intra-operatively. At a mean follow-up of 7.4 years, none of the revisions performed with antibiotic-loaded bone cement incurred deep infection whereas 6 (7%) deep infections occurred in implants with cement lacking antibiotic (p=0.013). The results of this recent trail with aseptic revision TKA patients demonstrates excellent intermediate-term outcomes with the use of Vancomycin-loaded boned cement used in conjunction with systemic antibiotics during arthroplasty.

Lastly, an official clinical practice guideline is included in this evidence review for completeness. SIGN has prepared a 2008 guideline which presents a literature summary and recommendation on the prophylactic use of antibiotic-loaded bone cement in total joint replacements. The excerpt summary from that guideline is as follows:

"A large retrospective study [15] showed that a combination of IV prophylactic antibiotic and antibiotic-impregnated bone cement is more effective than IV prophylaxis alone in reducing the risk of SSI (surgical site infection). Compared to the combined regimen, patients who received antibiotic prophylaxis only systemically had a 1.4 times higher revision rate with all reasons for revision as the end point (p=0.001), 1.3 times higher with aseptic loosening (p-0.02) and 1.8 times higher with infection as the end point (p=0.01)." (p.33)

Furthermore, this guideline recommends that "in addition to intravenous antibiotics,

impregnated cement is recommended for cemented joint replacements" and the strength of this recommendation is B, corresponding to a judgment based on high-quality case-control study where the risk of bias is deemed very low and with a high probability of the relationship being causal.

Related Issues of Concern

The common concerns regarding the prophylactic use of antibiotic-loaded bone cement in primary and revision aseptic THA and TKA focus on potential antibiotic-induced allergic reactions, toxicity, dosage and weakening of the cement, and the development of drug-resistant organisms in hospital settings. The prospective clinical trials and guideline included in this evidence review did not test nor encounter these issues. Chiu et al. [9,10] used cefuroxime-loaded bone cement (2 g per 40 g of Simplex P cement) in relatively healthy and diabetic (high-risk) aseptic primary TKA patients and their short- to intermediate-term follow-up results did not present these concerns. Chiu et al.[11] used 1 g of vancomycin per 40 g of Simplex-P cement in aseptic revision TKA and also did not observe these potential adverse complications. Chiu et al. [9] cite literature that indicates up to 2 g of antibiotic powder may be added to a 40 g pack of bone cement without altering its static tensile and compressive strengths, although its fatigue strength may be diminished slightly but not enough to produce adverse outcomes. Certainly, the results of their randomized clinical trials do not contradict this.

The potential development of drug-resistant microorganisms with routine prophylactic antibiotic-loaded cement use is a major concern as a future revision of the joint could be ineffective to the primary antibiotic. For example, Hope et al. [16] observed that of 91 revision THAs performed in their study, 80 patients (88%) had gentamycin-resistance if they received gentamycin-loaded bone cement during the primary arthroplasty, as compared to 16% of the patients who received standard cement during the primary THA. Others [17] have recommended that antibiotic-loaded bone cement should be reserved for arthroplasties at higher risk for infection. These patients would include those with a history of previous infection or multiple surgeries of the involved joint, particularly those with failed internal fixation of periarticular fractures. Additional high risk patients may include those with insulin-dependent diabetes mellitus, those with some degree of immune suppression, including patients with organ transplantation on immunosuppressive agents, steroid-dependent patients (asthma, inflammatory arthritis), patients with malnutrition (decreased albumin, decreased lymphocyte count), and patients $\geq$80 years of age [17]. The development of drug-resistant microorganisms in this context is a serious possibility and one that represents a management issue with regards to the choice of antibiotic for treatment or revision implants, and continued monitoring for the emergence of antibiotic-resistant organisms is warranted.

Summary

The prospective clinical studies presented in this evidence review lend support to the routine prophylactic use of antibiotic-loaded bone cement in aseptic primary and revision total joint replacement. Furthermore, adverse outcomes, such as implant loosening, toxicity, allergic reactions, and revisions, were none existent or similar to that observed with standard antibiotic-free bone cement use.

The current Alberta Hip & Knee Arthroplasty care path recommends the following:

- Low-dose (1-2 g antibiotic per 40g cement) antibiotic-impregnated bone cement to be used for all primary hip/knee arthroplasties.
- High-dose (>2 g antibiotic per 40g cement) antibiotic-impregnated bone cement is appropriate for high-risk patients.

In light of and limited to the evidence presented here, 1 or 2 g antibiotic per 40 g of cement ought to be used in all aseptic primary and revision THA and TKA procedures, particularly with patients deemed to be at high-risk for post-operative deep infection.

Clinical Committee Comment

On October 15, 2009 the Hip and Knee Clinical Committee discussed the findings of this evidence review. Committee members agreed that the current recommendations made by the Hip and Knee Care Path are consistent with best evidence and best practice.

Care Path Recommendation

The current Alberta Hip & Knee Arthroplasty care path recommends "Appropriate cement – antibiotic impregnated cement unless patient has allergy."

Based on the results of this evidence review, there is no contradictory information observed in the included studies to warrant amendment to the current ABJHI recommendations. The Hip and Knee Clinical Committee agreed current recommendations are to remain unchanged.

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