The Use of Erythromycin and Colistin Cement in Total Knee Arthroplasty Does Not Reduce the Incidence of Infection: A Randomized Study in 2,893 Knees With a 9-year Average Follow-Up

Albert Pardo-Pol, MD, Albert Fontanellas-Fes, MD, Daniel Pérezez-Prieto, MD, PhD, Lluïsa Sorli, MD, PhD, Pedro Hinarejos, MD, PhD, Joan Carles Monllau, MD, PhD

Abstract

Background: One of the most severe complications of primary total knee arthroplasty (TKA) is prosthetic joint infection (PJI). Nowadays, the use of antibiotic-loaded cement for the prevention of infection is still controversial. The aim of the present study was to evaluate if the use of antibiotic-loaded cement reduces the infection rate in primary total knee arthroplasty in long-term follow-up.

Methods: This study is the follow-up extension of a prospective randomized study, with 2893 cemented TKA performed between 2005 and 2010 at our institution. Two different groups were formed depending on which bone cement was used, without antibiotic (control group) or loaded with erythromycin and colistin (study group). All patients received the same systemic prophylactic antibiotics. The patients were followed for a minimum of twelve months. The diagnosis of PJI was done according to Zimmerli criteria.

Results: In 1452 patients the prosthetic components were fixed using bone cement without antibiotics, whereas in 1441 patients was used bone cement loaded with erythromycin and colistin. Both groups were comparable in terms of all the possible risk factors studied. We found a total of 53 deep infections, with a mean rate of 1.8%. There were no differences between the groups, whether bone cement with or without antibiotics had been used group (p=0,58). The average duration of follow-up was 8.7 years. In terms of prosthetic revision due to aseptic loosening, there weren't differences between groups (p=0,32), performing 33 revision arthroplasties in the control group and 37 in the study group. Moreover, we analyzed the erythromycin resistance rate, with no differences between both groups (p=0.6).

Conclusions: The use of erythromycin and colistin-loaded bone cement in total knee arthroplasty did not lead to a decrease in the rate of infection in long-term follow-up, a finding that suggests that its use would not be indicated in the general population.

Keywords: total knee arthroplasty, antibiotic-loaded bone cement, periprosthetic joint infection, antibiotic resistance, aseptic loosening.

INTRODUCTION

Periprosthetic Joint Infection (PJI) is one of the most devastating complications, with a significant impact on a patient's health, economic, psychological, and social status [1]. Systemic antibiotic prophylaxis and improved operating room environments have effectively reduced its incidence. However, it is still estimated to be 1% to 2% among patients after total hip arthroplasty (THA) and 2% to 3% among patients after total knee arthroplasty (TKA) [2,3].

Since the use of antibiotic-loaded bone cement (ALBC) was introduced by Buchholz and Engelbrecht [4] in 1970, it has been widely used in prosthetic revision surgeries (infected or non-infected revisions), while its role as a prophylactic method to reduce the incidence of PJI is still controversial in TKA [5–7].

The main concerns about the routine use of ALBC include the potential detrimental effects on the mechanical properties of polymethylmethacrylate (PMMA) when antibiotics are mixed [8,9], systemic toxicity [10], allergic reactions, risk of selection of antibiotic-resistant bacteria [11] and a significant increase in the cost of the cement.

Over the last years, many studies have been published with variable results, not being able to resolve whether the prophylactic use of ALBC helps to decrease the incidence of PJI.

In 2013, our team published a prospective randomized of nearly 3000 primary TKA and found that the use of antibiotic-loaded bone cement did not lead to a decrease in the infection [12]. The short follow-up time (less than 5 years average follow-up) was considered a limitation of the study, as it would possibly misdiagnose chronic low-grade infections that would be diagnosed 1 year after surgery.

Therefore the main objective of the present study is to evaluate if antibiotic-loaded cement reduces the infection rate in primary TKA in long-term follow-up. The secondary objectives were to assess the incidence of aseptic loosening between the two groups and analyze the possible emergence of antibiotic-resistant bacteria.

Based on our previous workup data, we hypothesize that we will find no difference in long-term infection rates between the two treatment groups.

METHODS

This study shows the results of a single-center randomized clinical trial. The institutional ethics committee pre-approved the study and was registered at ClinicalTrials.gov (number NCT01631968). Written informed consent was obtained from all participants. Between September 1, 2005, and April 30, 2010, a total of 3,000 primary total knee arthroplasties were included in the trial.

Inclusion and exclusion Criteria

Patients with any diagnosis leading to total knee arthroplasty were included. The only exclusion criteria were a history of infection (including infection-derived osteoarthritis) in the knee or a history of allergy to one or both antibiotics used in the cement.

Randomization

The randomization was performed intraoperatively with a computer-generated list. In the control group, the prosthesis was cemented with Simplex cement without antibiotics

(Stryker, Mahwah, New Jersey); in the study group, the prosthesis was cemented with Simplex P cement loaded with 0.5 g of erythromycin and 3 million units of colistin in 40g of cement (Stryker, Mahwah, New Jersey). In both cases, the cement was mechanically mixed under vacuum conditions.

Surgical procedure

All patients had primary TKA in the same surgical theater with laminar airflow exchange. Body exhaust suits for the surgical team were not used in any case. In all patients, preoperative intravenous prophylactic antibiotics were administered with 2 g of cefazolin in a ten to fifteen-minute infusion thirty to sixty minutes before incision or 1 g of vancomycin in a one-hour infusion sixty to ninety minutes before incision if the patient had a type 1 beta-lactam allergy. The antibiotic prophylaxis was complemented by 1 g of cefazolin every eight hours or 1 g of vancomycin every twelve hours for the first twenty-four hours after surgery.

Outcomes and follow-up

Patients were evaluated by the surgeon at two weeks, two months, six months, and twelve months after surgery. From one year after surgery, the follow-up has been variable according to the surgeon; some patients with annual follow-up, some with biannual follow-up.

The diagnosis of PJI was made according to Zimmerli criteria [13]. In positive culture PJI, bacteria were identified, and the susceptibility to erythromycin was evaluated.

Cases of PJI were treated by means of Debridement, Antibiotics, and Implant Retention (DAIR) in acute postoperative infection or late acute hematogenous (LAH) cases. Chronic PJI was treated using one or two-stage replacement, depending on each patient and according to the aforementioned Zimmerli algorithm.

Aseptic loosening was considered in all patients with clinical symptoms of pain in the knee, together with imaging tests compatible with loosening that needed revision of the prosthesis. In all of them, infection was ruled out preoperatively and intraoperatively. In every revision case, the same protocol was used to rule out the infection of the prosthesis: culture of 5 samples of tissue, joint fluid culture and cellularity, sonication of every implant that has been removed, and histologic study of the synovium and interface tissue.

The clinical history of all patients initially included in the study was reviewed. We considered the follow-up time of patients who died during these years to be the year of death.

Patients who, for some reason, changed residence during follow-up and were no longer monitored at our hospital could be followed up using the database of the Catalan Health System.

Patients who moved outside Catalonia and did not respond to follow-up visits have been excluded from the study since it was impossible to establish if they had undergone reoperation or had any complications.

All surgeries performed on all patients included in the study were collected and classified as follows:

1- Surgeries due to acute non-septic complications (extensor apparatus injury, stiffness, and acute mobilization of prosthetic component).

2- Surgeries due to septic (acute and chronic) complications (DAIR, one-stage replacement, and two-stage replacement).

3- Prosthetic revision due to non-septic complications (aseptic loosening, instability, painful prosthesis, malalignment, and others).

4- Periprosthetic fracture treated without implant exchange.

5- Surgeries for chronic non-infectious complications, treated without changing prosthetic components (patellar clunk syndrome and extensor apparatus chronic injury).

Data Analyses and Sample Sizes

A power study was done to evaluate the size of the sample. Accepting an alpha risk of 0.05 and a beta risk of 0.20 in a one-sided test for two independent proportions, 1370 subjects were necessary for the first and second groups to recognize a decrease in the infection incidence ratio from 2.2% in the conventional group to 1% in the experimental group as significant. A patient dropout rate of 5% was anticipated.

Pearson's Chi-square test was used to perform power analyses for the secondary objectives. The continuous variables were compared with the Mann-Whitney U test, and the categorical data were compared using the chi-square test or Fisher exact test, as appropriate. P values of <0.05 were considered significant.

Source of funding

There was no external funding source for this investigation.

RESULTS

A total of 2893 knees with a minimum follow-up of twelve months were analyzed: 1452 knees (50.01%) were assigned to the control group (plain cement), and 1441 knees (49.98%) were assigned to the study group (erythromycin and colistin-loaded bone cement).

Of the 2893 knees, 77.5% were women. The patients' mean age (and standard deviation) was 72.3 ± 7.19 years. The average duration of follow-up was 8.7 years (range, 1 to 14). Overall, 1,619 patients were followed up to 5 years after surgery, 639 patients were followed up to 9 years, and 214 patients were followed up to 12 years. We have detected that a total of 539 patients died during follow-up. Both groups were comparable in terms

146 of all the possible risk factors studied (Table 1). No patient had an allergic reaction, local
147 or systemic, attributable to the cement's antibiotic. No patient had toxicity related to the
148 antibiotic.

149 As for the study's primary aim, 53 deep infections were identified, with a mean rate of
150 1.8% (95% confidence interval [CI], 0.8% to 2.1%). There were no differences between
151 the groups (p= 0.58), whether bone cement with or without antibiotics had been used
152 (Table 2). There were 29 cases of deep infection in the control group and 24 in the study
153 group, of which 18 were acute postoperative infections (10 in the control group and 8 in
154 the study group). There are 3 cases of 1-time replacements (2 cases in the control group
155 and 1 case in the study group). Twenty-two cases of 2-time replacement (10 in the control
156 group and 12 in the study group), with a mean time from surgery of 26.25 months (SD
157 32.44). There are 10 cases of hematogenous infection treated with a DAIR (6 in the
158 control group vs. 4 in the study group), with a time from implantation to infection of 4.7
159 years (SD 3.6).

160 The deep infection rate was not influenced by age (p= 0.73). However, it was greater
161 among men than women (p=0.004) (Table 3). The odds ratio of infection in men
162 compared with women was 2.39 (95% CI, 1.30 to 4.38). The weight of patients with deep
163 infection was also more significant than those without infection (p= 0.037), yet the
164 difference in BMI in patients with an infected knee was not significant (p = 0.954) (Table
165 3). After multivariate analysis, 3 factors were related to a higher incidence of deep
166 infection: men, weight, and a surgical duration of > 125 minutes (Table 4).

167 The most common infecting organisms were *staphylococcus* spp (60%), followed by
168 gram-negative bacteria (17%). The rest of the microorganisms are described in Table 5.

169 In terms of prosthetic revision due to aseptic loosening, there weren't differences between
170 groups (p = 0.83), performing 33 revision arthroplasties in the control group and 37 in the

171 study group (Table 6). An early reintervention was observed in the ALBC group (Figure
172 1), without being statistically significant (p = 0.16). When erythromycin resistance rate
173 has been analyzed in gram-positive infections in both groups, there were no differences
174 (p = 0.77) (Table 7).

175 We have made a graph representing dropouts for each reason separately (Figure 1). In
176 this case, we cannot compare the survival curves since the reason for dropout is an
177 intrinsic characteristic of the event.

178 The resulting power for Pearson's Chi-squared test (pooled variance) was 46.97%, so it
179 was low. The second analysis concerned the erythromycin resistance rate; the result was
180 5.58%, very low.

181 **DISCUSSION**

182 The primary focus of this prospective study was to extend the follow-up of almost 3,000
183 TKA and analyze if there was a substantial difference in deep infections between groups.
184 In that sense, antibiotic-loaded cement did not reduce the incidence of infection after total
185 knee arthroplasty in long-term follow-up; therefore, the hypothesis was confirmed. This
186 may be an expected result considering that most of the antibiotic is released in the first
187 few days [14,15].

188 In the previously published study [12], a total of 45 superficial infections that did not
189 require surgery were described, with no differences between the 2 groups. There have
190 been no new cases of superficial infections in this study with the extended follow-up.

191 The data published in the literature remain ambiguous. In TKA, there is some evidence
192 from the Finnish Registry [16] of a lower infection incidence when ALBC is used.
193 Otherwise, data from other Registries do not support the Finnish data [17]. Another
194 important registry of arthroplasties [18], in this case, hip arthroplasties, did find a slight
195 difference (absolute risk reduction of 0.12%) in the number of revisions due to prosthetic

196 infection, and therefore its use has been recommended. Another study, by Sanz et al. [19],
197 in addition to finding more critical differences in the rate of periprosthetic infection,
198 counted the economic impact it represented, estimating that the use of antibiotics in
199 cement provided a saving per patient of $1,775 ($1,295 in cases of TKA vs. $2,811 in
200 cases of THA). Two other studies obtained different cost-effectiveness results when
201 comparing the use of ALBC with cement without antibiotics, without a significant
202 difference in the incidence of infection [20,21].

203 A large retrospective study including more than 22000 TKA from Namba et al. [5] did
204 not find that the use of tobramycin or gentamicin-loaded cement prevented infection after
205 TKA in the general population. Two recently published meta-analyses, the first by Zhou
206 et al., which included five comparative trials to assess the efficacy of ALBC in primary
207 TKA, found no differences in the deep infection rate [22]. Another recent meta-analysis
208 has studied the protective effect of ALBC in TKA and total hip arthroplasty (THA),
209 analyzing randomized controlled trials (RCT) or cohort studies. They found that the
210 superficial infection rate was similar, but it may reduce the rate of deep infection[2]. Of the
211 ten trials included, the five that concluded that ALBC reduces the infection rate after
212 primary total joint arthroplasty had no laminar flow in the operating rooms or lacked a
213 description of air control. One of the possible explanations for this is that infection rates
214 may be significantly reduced by laminar flow in the operating room, such that ALBC had
215 no significant effect since infection rates were already reduced to a relatively low level.

216 In the study by Chiu et al [23]. it was observed that the risk of periprosthetic infection
217 was reduced when using Cefuroxime-impregnated cement in diabetic patients (the
218 relative probability of not developing a deep infection was 0.865 times lower than the
219 group without ALBC). Leong et al. [18] found in their registry of primary hip
220 arthroplasties a protective effect of the antibiotic on the cement which in turn had a

reduction in the risk of revision due to aseptic loosening or osteolysis in the follow-up period of > 4.1 years after primary THA, HR 0.57 (95% CI 0.45 to 0.72) in cases with cement without antibiotic and 0.54 (95% CI 0.41 to 0.72) in patients with an antibiotic. This result is similar to other studies, such as that of Lenguerrand et al. [24] and Bohm et al. [17] In our case, we found no difference in the rate of aseptic replacement due to loosening or osteolysis (33 patients vs. 37, p >0.05), so the concern of some authors [25] about the biomechanical alteration of the cement, when used with an antibiotic had no clinical relevance in our case.

The deep infection rate in our study (1.8%) is just below the previously reported range of 2 to 3% [2,3]. We can affirm that men and heavier patients had a higher risk of infection, as previously described [26-28]. Although some studies have established diabetes mellitus as a possible risk factor for PJI after TKA, [28,29] we have seen a tendency, but without statistical significance. Moreover, we found that a longer duration of the surgery was associated with a higher risk of deep infection, as has been reported in previous studies [26,30–32].

Another important aspect related to the antibiotic-loaded into bone cement is whether antibiotic exposure causes resistance. Aminoglycoside cement spacers (4 g of antibiotic/40 g of PMMA) used in 2-stage revision arthroplasty seem to increase the gram-positive cocci resistance [11], suggesting the risk of selecting resistant strains when using ALBC is real. Our study findings suggested that its routine prophylactic use in primary TKA had not resulted in a significant impact on infectious pathogens and antibiotic resistance profiles, as it was found in 2014 by Hansen et al. [33].

The duration of the release of the antibiotic from the cement is still an issue under debate [30-32]. Some studies claim that most of the cement is released in the first 72 hours, being effective against most broad-spectrum organisms causing periprosthetic infections [32].

Fletcher et al. [30] detected antibiotic (gentamicin) concentrations in the synovial fluid of 13 patients years after implantation of the prosthesis (up to 15 years), without finding a relationship between antibiotic levels with the time of implantation of the prosthesis, thus demonstrating that the cement mantle can release substantial levels of antibiotics many years after implantation.

We used the commercially available combination of erythromycin and colistin because they tend to be less expensive and have shown a spectrum in vitro as broad as aminoglycosides against gram-positive, gram-negative, and anaerobic bacteria[34]. We are not aware of any clinical studies comparing the efficacy of one antibiotic-loaded bone cement with another.

This study has some limitations; the first to consider is that although all the patients were operated on in our center and most of them have been followed up in our outpatient clinics, some patients may have decided to be treated in private centers, whose medical records are not shared with the public hospital network to which we have access, so it is possible that some complications have not been detected in the follow-up.

Another limitation is that we have used colistin and erythromycin as antibiotics in the cement. The results should not be extrapolated to using other frequently used antibiotics, such as vancomycin or aminoglycosides. Moreover, with only fifty-three deep infections, the ability to develop a robust list of risk factors is minimal; some of these factors may not even have been detected.

CONCLUSIONS

Using erythromycin and colistin-loaded bone cement in total knee arthroplasty did not decrease the infection rate in long-term follow-up. In addition, neither a high incidence of aseptic loosening nor germen-resistant selection was found.

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