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Infection After Primary Total Knee Arthroplasty: A Randomized Controlled Prospective Study of the Addition of Antibiotics to Bone Cement*

Infecção após artroplastia total primária de joelho: Estudo randomizado prospectivo controlado da adição de antibiótico ao cimento ósseo

Hugo Alexandre de Araujo Barros Cobra[1] Alan de Paula Mozella[1] Pedro José Labronici[2] Amanda S. Cavalcanti[3,*] João Antonio Matheus Guimarães[3]

[1] Center for Specialized Care in Knee Surgery, Instituto Nacional de Traumatologia e Ortopedia, Rio de Janeiro, RJ, Brazil
[2] Department of Orthopedics and Traumatology, Universidade Federal Fluminense, Niterói, RJ, Brazil
[3] Research Division, Instituto Nacional de Traumatologia e Ortopedia, Rio de Janeiro, RJ, Brazil

Address for correspondence Hugo Alexandre de Araujo Barros Cobra, Praia do Flamengo, 66, sala 1313, Flamengo, Rio de Janeiro, RJ, 22210-030, Brasil (e-mail: hmcobra@uol.com.br).

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Abstract

Objective The present prospective, randomized and controlled study was conducted with 286 patients submitted to primary total knee arthroplasty (TKA) with the objective of evaluating the efficacy of the addition of antibiotics to bone cement as a way to prevent post arthroplasty infection (PAI).

Methods The patients were randomized into two groups: bone cement without antibiotic (No ATB, $n = 158$) or cement with antibiotic (ATB, $n = 128$), in which 2 g of vancomycin was added to 40 g of cement. The patients were followed up for 24 months after surgery.

Results Regarding preoperative demographic data, the distribution of patients between groups was homogeneous ($p < 0.05$). In the 24-month period, the overall infection rate was of 2.09% (6/286), with no difference (odds ratio [OR] = 1.636; 95% confidence interval [CI]: 0.294–9.080; $p = 0.694$) between the ATB group (1.56%; 2/128) and the No ATB group (2.53%; 4/158). In the No ATB group, the infection was caused by methicillin-resistant *Staphylococcus aureus* (MRSA) ($n = 2$), methicillin-sensitive *S. aureus* (MSSA) ($n = 1$) and *Eschirichia coli* ($n = 1$). *Proteus mirabilis* and MSSA were isolated from patients in the ATB group. Among the comorbidities, all patients with PAI

Keywords
- antibiotic
- arthroplasty, replacement, knee
- bone cements
- prosthesis-related infections

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were hypertensive and nondiabetic. Two rheumatoid arthritis patients who developed PAI were from the ATB group.

Conclusion The use of cement with ATB reduced the absolute number of infections, but without statistical difference between the groups; thus, routine use should not be encouraged.

Resumo

Objetivo O presente estudo prospectivo, randomizado e controlado foi realizado com 286 pacientes submetidos à artroplastia total primária do joelho (ATJ) com o objetivo de avaliar a eficácia da adição de antibiótico ao cimento ósseo como forma de prevenção da infecção pós-artroplastia (IPA).

Métodos Os pacientes foram randomizados em dois grupos: cimento ósseo sem antibiótico (Sem ATB, $n = 158$) ou cimento com antibiótico (Com ATB, $n = 128$), ao qual foram adicionados 2 g de Vancomicina para 40 g de cimento. Os pacientes foram acompanhados por 24 meses após a cirurgia.

Resultados No que diz respeito aos dados demográficos pré-operatórios, a distribuição dos pacientes entre os grupos foi homogênea ($p < 0,05$). No período de 24 meses, a taxa global de infecção foi de 2,09% (6/286), não havendo diferença (odds ratio [OR] = 1,636; intervalo de confiança [IC] 95%: 0,294–9,080; $p = 0,694$) entre o grupo Com ATB (1,56%; 2/128) e Sem ATB (2,53%; 4/158). No grupo Sem ATB, a infecção foi causada por *Staphylococcus aureus* resistente à meticilina (MRSA, na sigla em inglês) ($n = 2$), *S. aureus* sensível à meticilina (MSSA, na sigla em inglês) ($n = 1$) e *Eschirichia coli* ($n = 1$). *Proteus mirabilis* e MSSA foram isolados dos pacientes do grupo Com ATB. Dentre as comorbidades, todos os pacientes com IPA eram hipertensos e não diabéticos. Dois pacientes com artrite reumatoide que desenvolveram IPA eram do grupo Com ATB.

Conclusão O uso de cimento com ATB reduziu o número absoluto de infecções; porém, sem diferença estatística entre os grupos. Desta forma, o uso rotineiro não deve ser encorajado.

Palavras-chave
- antibiótico
- artroplastia do joelho
- cimentos ósseos
- infecções relacionadas à prótese

Introduction

Deep infection after total knee arthroplasty (TKA) is one of the most devastating complications and it generates great frustration for both the patient and the surgeon. Its incidence varies between 0.5 and 2%,[1,2] but it is the most common etiology (20.4%) in the TKA revisions in the United States.[3] Data from a Brazilian center show that infection is responsible for 49% of early failures and for 25% of late failures.[4]

Despite their relatively low incidence, post-arthroplasty infections (PAIs) and their treatment have great economic impact. The cost of a single treatment can range from US$ 30,000 to US$ 50,000; and treating serious infections caused by resistant microorganisms can cost up to US$ 100,000.[5] The cost of treating a periprosthetic infection in the Brazilian public system is estimated at ∼ BRL 55,000 (∼ US$ 14,000).[6]

As a measure to prevent infection in TKA, the American Academy of Orthopedic Surgeons (AAOS) recommends systemic antimicrobial prophylaxis 1 hour before surgical incision. However, the drug does not readily reach the implant-tissue interface. Thus, local administration of systemic antibiotics is recommended by some authors to provide higher *in situ* antibiotic concentrations, with lower risk of systemic toxicity.[7]

The manual mixing of the antibiotic powder with bone cement during surgery or the commercially available premixed product are the most commonly used methods for local antibiotic intake.[8] Alternatively, other authors suggest the application of antibiotic powder directly to the surgical wound, the so-called intrawound antimicrobial prophylaxis. However, there is still no consensus in the literature regarding the effectiveness of these methods, and more evidence with prospective studies is necessary.[9–11]

From the clinical point of view, the use of antibiotic-impregnated cement reduced septic and aseptic failure rates in TKA.[8,10,12] With a 60.6% reduction in the occurrence of infections and savings of EU801,00 per patient, its cost-benefit was considered favorable.[13] Conversely, a systematic review with > 34,000 patients undergoing TKA showed that the use of antibiotics did not reduce the prevalence of PAI and may be an unnecessary cost to the health system.[14] Given the controversial evidence, we investigated the efficacy of adding antibiotics to bone cement in primary TKA as a way to prevent deep infection.

Material and Methods

Selection criteria

The present study was approved by the Research Ethics Committee (CAAE 0036.0.305.00-10). All volunteers consented in writing before being included in the study. Patients with primary and secondary osteoarthritis (OA) with indication for TKA were included. There was no age limit and no restriction on gender. The exclusion criteria were patients submitted to unicompartmental knee arthroplasty, revision arthroplasty or any previous joint surgery, and patients with evidence of joint infection or congenital or acquired coagulopathies, as well as a previous history of allergy to vancomycin.

Study groups

All patients ($n = 286$) submitted to TKA between July, 2010 and December, 2013 were prospectively recruited. The patients were submitted to primary TKA with Press Fit Condylar Sigma prosthesis (DePuy-Synthes, West Chester, PA, USA) and randomized according to the use of antibiotics in bone cement. In 158 patients, called the No ATB group, conventional bone cement (DePuy-Synthes) was used, and in 128 patients, 2 g of vancomycin was added to every 40 g of bone cement, and they were called the ATB group. Patients with medical records with an uneven ID number were allocated to the No ATB group, and patients with an even medical records ID number were allocated to the ATB group.

Surgical technique

All patients were submitted to spinal anesthesia and peripheral block of the sciatic and femoral nerves with the aid of electrostimulation. The procedures were performed with or without ischemia, with pneumatic tourniquet of inflated thigh with a pressure of 300 mmHg. The cement/antibiotic mixture was prepared according to McLaren et al.[12] by the main surgeon during the surgical procedure (►**Supplementary Figure S1**). A single 4.8 mm drain (Hemovac, Zimmer) was maintained in all patients for 24 hours. All surgeries were performed in a single institution by two surgeons who were members of the Brazilian Society of Orthopedics and Traumatology and of the Brazilian Knee Society (Cobra H. A. A. B. and Mozella A. P.).

Postoperative care

All patients received 2 g of intravenous cefazolin supplemented with 2 additional doses of 1g every 8 hours. The prevention of thromboembolic events was performed with a single daily dose of 40 mg subcutaneous low molecular weight heparin (Clexane, Sanofi Aventis, Paris, France) started 12 hours after the end of surgery and maintained for 10 days.

Diagnosis of infection

The diagnosis of infection was based on the criteria defined by Parvizi et al.,[15,16] considering the clinical findings, the increase in C-reactive protein levels, an increase in the speed of hemosedimentation, and positive microbiological culture of tissue fragments obtained in the intraoperative period. The presence of flushing, erythema and pain associated or not with fever were considered positive clinical signs of infection. Once the patient underwent the first stage of the revision surgery, three femur fragments, three tibia and soft tissue fragments for microbiological culture were collected. The diagnosis of infection was established when bacterial growth of the same microorganism occurred in at least two samples.

Follow-up

The patients were evaluated at 15 days, and at 2, 6, 12 and 24 months after surgery at the outpatient clinic of the institution. The occurrence of postoperative complications, such as time and presence of superficial or deep infection, skin necrosis, deep vein thrombosis, acute myocardial infarction, and symptomatic allergic reactions were investigated.

Statistical analysis

The distribution analysis of the numerical data was performed by the Shapiro-Wilk test. The Student and Mann-Whitney *t*-tests were applied to the variables with normal and non-normal distribution, respectively. The significance of 5% was adopted. Categorical data were analyzed by the Fisher chi-squared or exact test. GraphPad Prism version 7.00 for Windows (GraphPad Software, San Diego, CA, USA) was used.

Results

Characteristics of the patients

Preoperative data were analyzed to verify the randomization of individuals in the treatment groups. The study groups were homogeneously distributed without differences in gender ($p = 0.221$), American Society of Anesthesiologists (ASA) score ($p = 0.348$), age (68 versus 66 years old; $p = 0.429$), body mass index (BMI) (30.4 versus 29.3; $p = 0.579$), plasma globulin levels (2.8 versus 2.7; $p = 0.566$), plasma albumin levels (3.5 versus 3.3; $p = 0.555$), duration of surgery (90 versus 85 minutes; $p = 0.087$), for the groups with and without ATB, respectively (►**Tables 1** and **2**).

From the 286 patients undergoing TKA, 212 (70.6%) had primary OA, 101 (78.9%) in the ATB group and 111 (70.2%) in the No ATB group. Osteoarthritis secondary to rheumatoid arthritis was the diagnosis in 25 (19.5%) patients in the ATB group and in 24 (15.2%) patients in the No ATB group. Two patients in the ATB group developed OA secondary to osteonecrosis, and two other patients in the No ATB group developed OA secondary to trauma. Regarding the presence of comorbidities, 3 patients in the No ATB group had diabetes mellitus (DM), 94 had systemic arterial hypertension (SAH), and 32 had the association of the 2 comorbidities. In the ATB group, 3 were diabetic, 74 were hypertensive, and 23 had the association between DM and SAH. There was no difference between the groups for the presence of DM ($p = 0.706$), SAH ($p = 0.474$) or both conditions in association ($p = 0.654$). Serum albumin < 3.5 g/dL levels were observed in 96 of the 286 patients. The diagnostic prevalence and distribution of comorbidities were similar between the groups (►**Table 2**).

Table 1 Numerical clinical data of patients submitted to total primary knee arthroplasty with Press Fit Condylar Sigma prosthesis (DePuy-Synthes, West Chester, PA, USA)

	ATB group ($n = 128$)					No ATB group ($n = 158$)					*p-value*
	Median	IQR		Min.	Max.	Median	IQR		Min.	Max.	
Age (years old)	680	61.0	73.0	33.0	83.0	66.0	61.0	72.3	30.0	82.0	*0.429*[a]
BMI (kg/m^2)	30.4	26.8	32.6	15.0	43.8	29.3	25.7	33.2	18.0	44.9	*0.597*[a]
Globulin (g/dL)	2.8	2.2	3.2	0.4	4.5	2.7	2.1	3.3	0.06	5.5	*0.566*[b]
Albumin (g/dL)	3.5	3.2	4.0	1.9	7.1	3.6	3.3	3.9	*2.2*	6.9	*0.555*[a]
Duration of surgery (minutes)	90.0	78.0	105.5	40.0	150	85.0	72.0	100.0	46.0	147.0	*0.087*[a]

Abbreviations: ATB, antibiotic; BMI, body mass index; IQR, interquartile range; min., minimum; max., max.
The patients were randomized into two groups: bone cement without antibiotics (No ATB, $n = 158$) or cement with antibiotic (ATB, $n = 128$), in which 2g of vancomycin was added to 40g of cement.
[a]Mann-Whitney nonparametric test

Table 2 Categorical clinical data of patients undergoing total primary knee arthroplasty with Press Fit Condylar Sigma prosthesis (DePuy-Synthes, West Chester, PA, USA)

	ATB ($n = 128$)	No ATB ($n = 158$)	*p-value*
Gender			
Male	21.8% (28/128)	15.8% (25/158)	*0.221*[a]
Female	78.1% (100/128)	84.1% (133/158)	
ASA			
1	6.2% (8/128)	5.1% (8/158)	*0.348*[b]
2	92.2% (118/128)	90.5% (143/158)	
3	2.3% (3/128)	3.2% (5/158)	
Diagnosis			
Osteoarthritis	78.9% (101/128)	70.2% (111/158)	*0.911*[b]
Rheumatoid arthritis	19.5% (25/128)	15.2% (24/158)	
Other	1.6% (2/128)	1.3% (2/158)	
Comorbidities			
Diabetes mellitus	2.3% (3/128)	1.9% (3/158)	*0.653*[a]
Systemic arterial hypertension	57.8% (74/128)	59.5 (94/158)	
Both	18.0% (23/128)	20.3% (32/158)	
No	21.9% (28/128)	18.4% (29/158)	

Abbreviations: ATB, antibiotic; ASA, surgical risk classification according to the American Society of Anesthesiology; Other, osteonecrosis, hemophilia or sequelae of trauma.
The patients were randomized into two groups: bone cement without antibiotics (No ATB, $n = 158$) or cement with antibiotic (ATB, $n = 128$), in which 2 g of vancomycin was added to 40 g of cement.
[a]Fisher's Exact Test
[b]Chi-Squared Test.

Post knee arthroplasty infection in patients who used cement with or without antibiotics

In the 24 months of follow-up, the percentage of infection was 2.09% (6/286), with no difference (odds ratio [OR] = 1.636; 95% confidence interval [CI]: 0.294–9.080; $p = 0.694$) between the ATB group (1.56%; 2/128) and the No ATB group (2.53%; 4/158) (►**Figure 1**). The mean time between surgery and diagnosis of infection was 250 days (27–158 days). One patient developed infection within 915 days. Exceptionally, this patient was not excluded from the study, because he was from another state and was in the out-of-home (OOH) treatment program of the Brazilian Unified Health System (SUS, in the Portuguese acronym), which led to his delay in returning. Patients who evolved with PAI underwent revision surgery. The mean length of hospital stay after the review was 46.6 days (16–90 days).

Among the six patients who developed infection, all were hypertensive, and none were diabetic and/or obese. In the ATB group, 2 of the 25 patients with OA secondary to RA

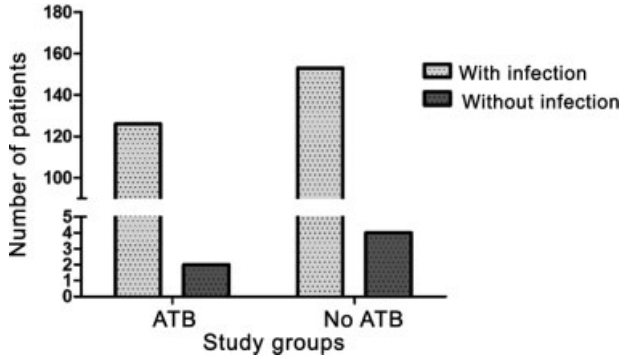

Fig. 1 Infection after knee arthroplasty in patients undergoing total primary knee arthroplasty with Press Fit Condylar Sigma prosthesis (DePuy-Synthes, West Chester, PA, USA). The patients were randomized into 2 groups: bone cement without antibiotics (No ATB, $n = 158$) or cement with antibiotic (ATB, $n = 128$), in which 2 g of vancomycin was added to 40g of cement.

developed infection. In the No ATB group, among the four infected patients, none of them had AR. One patient in each group had serum albumin levels < 3.5 g/dL.

In the No ATB group, the infection was caused by methicillin-resistant *Staphylococcus aureus* (MRSA) ($n = 2$), methicillin-sensitive *S. aureus* (MSSA) ($n = 1$) and *Escherichia coli* ($n = 1$). In the ATB group, MSSA was isolated in one of the patients, and *Proteus mirabilis* in the other. The earliest infection was detected 27 days after TKA, and the later, in 915 days (OOH patient), both caused by MRSA (►**Table 3**).

No local or systemic allergic reactions or adverse events have been reported.

Discussion

The results of the present prospective randomized study with 286 patients submitted to primary TKA with and without the addition of antibiotics to bone cement showed that the use of bone cement impregnated with vancomycin reduced the absolute number of deep infections, but without statistical significance. The use of the antibiotic was also not related to the occurrence of adverse reactions.

Table 3 Profile of infection after total knee arthroplasty with bone cement without antibiotic (No ATB, $n = 158$) or with bone cement plus antibiotic (ATB, $n = 128$), in which 2 g of vancomycin was added to 40 g of cement

Patient	Group	Time to diagnosis of infection (days)	Microorganism
1	No ATB	915	MRSA
2	No ATB	449	MSSA
3	No ATB	29	*Escherichia Coli*
4	No ATB	27	MRSA
5	ATB	46	MSSA
6	ATB	39	*Mirabilis*

Abbreviations: ATB, antibiotic; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, *Staphylococcus aureus* susceptible to methicillin.

In our study, the overall infection rate was similar to the infection rate reported in the literature (0.5 to 2%).[1,2,17] Few randomized prospective studies have evaluated the effects of antibiotic-impregnated bone cement on infection rates. A prospective randomized study with 340 patients found that the addition of cefuroxime (2 g / 40 g) was effective in preventing deep infections (0 versus 3.1%; $p = 0.024$).[10] Another study with 1,625 patients revealed no difference between the use of a commercial formulation containing tobramycin (2.2%; 18/814) and the control group (3.1%; 25/811).[18] In another cohort study, the use of bone cement with gentamicin did not reduce the infection rate, even in patients considered part of a risk group.[5] In the present study, most infections occurred within the first 60 days after surgery. We cannot exclude the hypothesis that the 2 longest infections that occurred within 449 and 915 days and were caused by *S. aureus* are a consequence of acute hematogenous infection.

Diabetic patients are 1.28 times more likely to be infected.[19] Although Chiu et al.[20] have shown the efficacy of using cement with cefuroxime in the prevention of deep infection in primary TKA in diabetic patients, Namba et al.[21] did not observe a reduction in the infection rate in these patients. In the sample of our study, 37 diabetic patients were included in the No ATB group and 29 in the ATB group, but none of them developed infection. It is possible that the rigid preoperative control of blood glucose contributed to this finding. Although it is not possible to establish, from our results, a protocol for the use of antibiotics in bone cement in primary TKA in patients considered at risk, its use is supported by the literature.[7]

Morbid obesity ($BMI \geq 40$ Kg/m^2) and obesity ($BMI > 30$ Kg/m^2) combined with diabetes are risk factors for PAI after TKA.[23] In a series with ~ 7,000 primary TKAs, the infection rate was of 0.37% in patients with normal BMI and of 4.66% in the morbidly obese group.[24] In our sample, none of the obese patients developed infection.

Serum albumin concentration is one of the most relevant and simple indicators of nutritional status assessment.[25] The recommended parameter for patients undergoing arthroplasties is between 3.5 g/dL and 5.0 g/dL.[26] From the patients with serum albumin level < 3.5 g/dL, 1 of each group presented PAI. In Brazil, the prevalence of malnutrition in patients hospitalized in the SUS is high.[27] In the future, it would be interesting to investigate the impact of malnutrition and protein deficiency, as well as the cost associated with malnutrition.

Similarly, surgery time is considered a risk factor for periprosthetic infection, especially when it exceeds 210 minutes.[17] The mean surgery time was 85 minutes in the No ATB group and 90 minutes in the ATB group; the small difference can be explained by the extra time required to mix the cement with the antibiotic. Even so, the maximum time spent in this group was 150 minutes, much less than the 210 established as a limit in the literature. Surgeons should consider this aspect in planning the surgery or even consider the use of bone cement premixed with antibiotics.

Regarding safety, local use of antibiotics requires caution due to the potential risk of toxicity, allergic reactions, resistant microorganisms, and decreased mechanical resistance.[18] In

the present study, we did not observe local or systemic allergic reactions or adverse events attributable to the antibiotic. It is important to note that the choice of vancomycin was based on a recommendation from the Hospital Infection Control Commission, due to the greater sensitivity of bacterial microbiota associated with post-TKA infections to this antibiotic. Although the addition of >0.5 g of vancomycin affects the mechanical properties of bone cement, doses <2 g lose their antimicrobial property.[28] Further studies should be conducted to determine the effect of vancomycin on the mechanical properties and elution of the antibiotic on DePuy-Synthes bone cement, used here. These results do not rule out the influence of other factors on PAI after primary TKA in our sample population – a tertiary public orthopedic center. Infection rates can be controlled through stricter patient care measures, and there is not a single determining factor for periprosthetic infection, but a set of factors.[29] Thus, in the future, the analysis by subgroups, such as RA, obese and transfused patients, may guide the surgeon's decision-making on the use of antibiotics in primary TKA in our population.

We considered as a strong point of the present study the long follow-up time (24 months) without loss to follow-up. However, we recognize as limitations not having performed the sample calculation, which made it impossible to analyze not only subgroups by comorbidities, but also other factors, such as ischemia, transfusion, and nutritional aspects. Additional prospective studies with larger Brazilian sample sizes and based on the most recent infection diagnostic criteria are required.[30] Another point to be considered is that microbiological analysis of the prosthesis explanted by the sonication method was not performed. This analysis could increase the sensitivity of the diagnosis of infection. In addition, the cost-benefit ratio of bone cement impregnated with antibiotics should also be investigated. As far as we know, only 1 study, including 34 patients, evaluated the economic impact of periprosthetic knee joint infection in Brazilian hospitals. The total additional cost was estimated at US$ 91,843.75,[31] while 2 g of Vancomycin cost $\sim$ BRL120 ($\sim$ US$ 30.00) in the Brazilian market. Another study estimated the cost of treating hip arthroplasty infection at BRL 55,821.62 ($\sim$ US$ 14,561) per patient.[6]

Conclusion

Finally, the use of antibiotic-impregnated cement should not be encouraged in primary total knee arthroplasties. We believe that our results may direct the conduct of orthopedic surgeons and contribute to the reduction of inappropriate use of antibiotics.

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Conflict of interests
The authors have no conflict of interests to declare.

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