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Original Research

Decrease in acute periprosthetic joint infections incidence with vancomycin-loaded calcium sulfate beads in patients with non-modifiable risk factors. A randomized clinical trial

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ABSTRACT

Objectives: The influence of local antibiotic therapy in orthopedic surgery remains unclear. In this trial, we evaluated the incidence of periprosthetic joint infections (PJI), after local or intravenous (IV) antibiotic prophylaxis. The aim of this intervention was to compare the PJI incidence in a population with non-modifiable risk factors after local prophylaxis with vancomycin-loaded calcium sulfate beads versus a control group.
Methods: A total of 83 subjects were evaluated, inclusion criteria included participants over 60 years of age, with at least one main risk factor for PJI who underwent total hip or knee joint replacement between June 2019 and May 2020. Cases were randomized, and the intervention group received local prophylactic antibiotic therapy with calcium sulfate beads impregnated with vancomycin; conventional IV prophylactic antibiotic therapy was administered for the control group. C-reactive protein (CRP) and erythrocyte sedimentation rate (ERS) serum biomarkers were analyzed on the day 5 and weeks 4, 8, and 12. When needed, the synovial fluid sample was obtained and cultured for the early acute PJI diagnosis.
Results: Acute PJI was found in 27 patients (67.5%) in the control group and 4 (9.3%) in the intervention group. The variable analysis identified that local prophylaxis with calcium sulfate beads reduces the incidence of acute knee or hip PJI in patients with non-modifiable risk factors compared to conventional prophylaxis ($p < 0.0001$) with a relative risk of 0.13 (CI:0.05–0.35). Length of hospital stay was also shorter in the intervention group at 4.6 days, compared to 15.25 days in the control group; $p < 0.001$.
Conclusions: Local antibiotic prophylaxis in patients with non-modifiable risk factors undergoing hip or knee replacement reduces the incidence of acute PJI compared to IV antibiotics.
Clinical trials: NCT03976466 (clnicaltrials.gov)
Level of evidence: II.

What are the new findings

- Local antibiotic prophylaxis with vancomycin in patients with non-modifiable risk factors reduces the incidence of periprosthetic joint infections compared to IV antibiotics.
- It is safe to apply calcium sulfate beads as an antibiotic carrier at the implant/bone interface.
- Decreasing the incidence of acute periprosthetic joint infections with local antibiotic prophylaxis using calcium sulfate beads reduces the length of hospital stay.

Introduction

Knee and hip joint replacements are some of the most recognized and successful orthopedic surgeries worldwide; however, they are not exempt of complications; the most challenging and devastating one for the patient and physicians is periprosthetic joint infections (PJI) [1,2]. There are many important topics to evaluate for a PJI; non-modifiable risk factors may be influenced by the socio-economic status of the patients, becoming a challenge for physicians and having adverse effects on the economic burden of health institutes. It has been estimated that by the year 2030, more than $1.85 billion will be spent in the USA on

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PJI and about 15,000 dollars per patient in México [3,4]. In México, the demand of patients seeking health services exceeds the capacity of the institutes; therefore, making it impossible to adequately evaluate patients with a multidisciplinary approach before undergoing joint replacement. This leads physicians to use their own criteria and assess the risks and benefits of joint replacement surgery not only to improve the quality of life in patients but also to allow them to resume their economic activities and avoid prolonged disability. However, it has been proven that the joint replacement benefits far exceed the complications; this explains why, even though a patient could have one or more risk factors, the procedure is not contraindicated and remains the best option of treatment [5].

It has been proved that some patient co-morbidities are key factors in complications following total joint arthroplasty (TJA), leading to the identification of those risk factors in relation to PJI, as well as strategies to mitigate them. The choice of risk factors as inclusion criteria in this trial was according to a meta-analysis by Y. Zhu et al., who describes the main risk factors found in PJI [6], as illustrated in Table 1.

One important topic is the biomaterials used in arthroplasty, although biomedical implants such as joint prosthetics have revolutionized medicine, they also have an increased risk of infections, primarily caused by *Staphylococcus aureus* and secondly by *Staphylococcus epidermidis* [7,8]. The biofilm forms on avascular zones and requires high concentrations of antibiotics and debridement to eliminate it. Sub-lethal antibiotic doses cause persistence and resistance of the infections; therefore, methods to release antibiotics at the necessary concentrations locally and for a prolonged time have been sought [9]. Polymethyl methacrylate (PMMA) has been used for years either as a bone cement spacer or as beads to carry antibiotic. However, it has been shown that PMMA does not eliminate biofilm, and 90% of the antibiotic remains trapped in the compound becoming more susceptible to bacterial colonization and biofilm formation [10].

To reduce the risk of periprosthetic infection, the application of local antibiotic at the surgical site may be a promising concept; for this purpose, calcium sulfate beads have been used as a carrier, and these begin to degrade within 4–8 weeks releasing antibiotic gradually over time, presenting minimal risk to damage the prosthesis components and having a low setting temperature which allows them to be mixed with thermo-sensitive antibiotics, whereas PMMA cannot [11].

There are still not enough in vivo investigation reports on the use of calcium sulfate in prosthetic implants [11,12]. A randomized controlled trial in patients with non-modifiable risk factors for PJI was performed, comparing the intervention group where prophylactic local calcium sulfate impregnated with vancomycin was applied versus a control group with a standard IV antibiotic prophylaxis. We hypothesized that the incidence of acute PJI and hospital length of stay would be lower in the intervention group compared to the control group.

Methods

Trial design

A prospective, longitudinal, and randomized controlled trial was designed. The intervention was performed at the department of orthopedics in our institution and approved by the ethics and research committee.

Participants

The eligibility criteria for this intervention were as follows: being over 60 years of age, having one or more non-modifiable risk factors, and patients who underwent total hip or knee joint replacement between June 2019 and May 2020. The exclusion criteria were as follows: patients with an active systemic infection, kidney or liver failure, and known allergies to vancomycin or cephalosporin [6,8].

Table 1
Risk factors for periprosthetic joint infection.

Risk factor	
BMI	>40 kg/m^2
Diabetes mellitus	>7% HbA1c
Nosocomial infection	Yes/No
Albumin in blood	<3 g/dl
Immunosuppression	Yes/No
Malignancy	Yes/No
Steroid therapy	Yes/No
Rheumatoid arthritis	Yes/No
Active wound infection	Yes/No
History of joint arthroplasty	Yes/No
Excessive surgical bleeding	Blood transfusion indication Yes/No
Operative time	(>120 min)

Note: BMI, Body mass index; HbA1c, Glycosylated hemoglobin test.

Outcomes

Our primary outcome was to determine the relationship between antibiotic prophylaxis with local calcium sulfate beads in patients with non-modifiable risk factors for PJI and its clinical progress with or without infection, compared with a standard antibiotic prophylaxis control group. The secondary outcome was to determine if there was an improvement in hospital length stay, which could be translated into a lower rate of economic burden.

Sample size

According to our biostatistics department records, in 2018, a total of 354 knee and hip arthroplasties were performed. Out of the total procedures, 94 had one or more non-modifiable risk factor [6,8]. This population was used for the sample size determination, with a desired 95% confidence level and a maximum acceptable error percentage of 5%. These data were calculated (STATS 2.0 Software), and a minimum number of participants were 76 to obtain a statistically significant different p-value. At the enrollment period, we obtained 87 participants, 4 of whom were excluded due to the expiration of health insurance ending with a total of 83.

Blinding and randomization

All participants who met the selection criteria were invited to be part of the intervention, detailing that they will not know which group they would be in, and could have a systemic or local prophylactic therapy according to the group randomly assigned (Randomizer v.0.2.6.). Once the ethics and procedures of the research were explained, the participants signed a letter of informed consent agreeing to join the randomized clinical trial.

Study participants

Subjects enrolled in the control group received a prophylactic intravenous cefuroxime dose of 750 mg, 20 min before joint replacement surgery and every 8 h for 24 h.

Regarding the patients assigned to the intervention group, none received parenteral antibiotic prophylaxis. In the operating room and before the final implantation of the prosthesis, the commercially pure calcium sulfate beads were impregnated with 3 g of vancomycin and applied locally. For the local prophylaxis, we utilized a STIMULAN Kit (Biocomposites Ltd, UK) [12]; which includes 10 cc (20 g) of calcium sulfate hemihydrate powder, a pre-mixing solution bulb, mold of 3, 4.8, and 6 mm sizes of beads and spatula. A total of 3 g of vancomycin powder was mixed with each 10 cc of calcium sulfate in the mixing bowl, after 30 s, the resulting paste was applied to the molds using the spatula and allowed to set for 10–15 min. In the hip joint, the 3 mm beads were pulverized and applied on the previously reamed acetabular cavity. For

the proximal femur, the beads were inserted into the medullary canal, and the final components were placed by impaction, ending the placement of the beads at the interface zones. The remaining beads were applied to the soft tissue around the prosthesis. For the knee joint, the 4.8 mm beads were applied inside the femoral and tibial medullary canals (Fig. 1), and the remaining beads were placed into the soft tissue around the prosthesis before cementation (Fig. 2). Antibiotic-loaded PMMA was not used in any subject.

After surgery, the acute PJI diagnosis algorithm was established in accordance with Della Valle, Jarvad Parvizi et al., clinical practice guideline by measuring acute phase reactants, cell count, and synovial culture; C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) biomarkers were analyzed on day 5 and weeks 4, 8, and 12 for acute periprosthetic infection. A CRP >93 mg/L and ESR >44 mm/h were considered the cutoff value for infection risk [13]. If CRP was elevated alone or with ESR, then a synovial fluid sample was obtained and analyzed. A threshold of leukocytes >12,800 cells/μL and/or a positive culture was defined as an acute PJI [14,15].

Statistical analysis

Statistical analysis was performed using SPSS Statistics 26 IBM software. Prospectively recorded data included patient demographics; biomarkers values before and after surgery, diagnosis and kind of arthroplasty replacement, non-modifiable risk factors for PJI, synovial fluid analysis, and length of hospital stay. The presence of periprosthetic infection in both groups was evaluated by two-sided chi-square and Fisher's exact tests for dichotomous nominal and qualitative variables with longitudinal direction and relative risk test; Cramer's V test was analyzed to assess the strength of relationship between variables. Length of hospital stay and continuous data with normal or skewed distribution were reported as mean (and SD) and median, respectively, and Student's *t*-test and Mann–Whitney U test were used for independent continuous variables. A two-tailed α value <0.05 was set as significant.

Results

A total of 87 subjects were enrolled in the period between June 2019 to May 2020, and four of them were excluded (the institutional insurance of the four patients expired; therefore, no postoperative follow-up was obtained). The remaining 83 patients were evaluated, 44 cases were female (53%), and 39 cases were male (46.9%). The mean age was 76.6 (61–90) years old. BMI was found to be the main risk factor (19.28%), followed by uncontrolled diabetes mellitus type 2 (18.07%). All the patients had at least one main risk factor for presenting periprosthetic infection (Table 2). Although both knee and hip prostheses were placed, differences between these were not considered because of a small sample size. A total of 38 knees were placed (52.5% for control group versus 39.5% for the intervention group), and 45 hips were treated (47.5% and 60.5% for control and intervention groups, respectively). There was no difference in demographic variables for either treatment group ($p > 0.05$).

Fig. 1. Calcium sulfate beads with vancomycin before be applied inside the femoral and tibial medullary canals for knee prosthesis.

Fig. 2. X ray of the knee showing the beads inside and outside the medullary canal in a knee prosthesis.

The subjects were randomly assigned in two groups for the longitudinal design intervention. Forty subjects (48%) were enrolled for the control group and received standard IV prophylactic antibiotic therapy with cephalosporin for a total of 24 h. For the intervention group, 43 patients (51.8%) received local antibiotic therapy with calcium sulfate beads mixed with vancomycin during the surgery. Although prophylactic treatment was supplied in both groups, the presence of early periprosthetic infection was found in 37.3%. Acute PJI was found in 27 subjects (67.5%) enrolled in the control group, while 4 (9.3) were found in the study group.

All 31 participants with acute PJI had a positive synovial fluid culture. According to the analysis of presence or absence of PJI, we identified that local prophylaxis with calcium sulfate beads compared to standard prophylaxis can further prevent the presence of acute knee or hip periprosthetic infection in patients with non-modifiable risk factors ($p = 0.0001$) with a 0.13 of relative risk C.I. (0.05–0.33). The incidence of acute PJI is 87% less in patients with local prophylaxis with calcium

Table 2
Demographics and non-modifiable risk factors.

Parameter/group	Standard prophylaxis	Local prophylaxis	Total	P-value
Demographics				
Age (mean ± SD)	77.3 ± 8.94	75.9 ± 8.14	76.6 ± 8.51	0.41
Gender	(%)	(%)		0.72
Female	22 (55.0)	22 (51.2)	44 (53%)	
Male	18 (45.0)	21 (48.8)	39 (47%)	
Joint				0.23
Hip	19 (47.5)	26 (60.5)	45 (54.3%)	
Knee	21 (52.5)	17 (39.5)	38 (45.7%)	
Non-modifiable risk factors for PJI				
Preoperative				
BMI	6 (15%)	10 (23.2%)	16 (19.2%)	0.41
History of nosocomial infection	3 (7.5%)	3 (6.9%)	6 (7.2%)	0.99
Decompensated diabetes mellitus	7 (17.5%)	8 (18.6%)	15 (18%)	0.99
Serum albumin	4 (10%)	1 (2.3%)	5 (6.0%)	0.19
Immunosuppression	1 (2.5%)	0	1 (1.2%)	0.48
Malignancy	0	3 (6.9%)	3 (3.6)	0.24
Steroid therapy	0	1 (2.3%)	1 (1.20%)	0.99
Rheumatoid arthritis	5 (12.5%)	2 (4.6%)	7 (8.4%)	0.25
Active wound infection at a distant zone	4 (10%)	2 (4.6%)	6 (7.2%)	0.42
History of joint arthroplasty	1 (2.5%)	3 (6.9%)	4 (4.8%)	0.61
During operative time				
Excessive surgical bleeding	5 (12.5%)	7 (16.2%)	12 (14.4%)	0.75
Prolonged operative time	4 (10%)	3 (6.9%)	7 (8.4%)	0.70

Table 3
Acute PJI comparison for patients who underwent standard versus local antibiotic prophylaxis. Leucocytes were measured only in patients with elevated CRP and ESR.

	Periprosthetic joint infection				Without periprosthetic joint infection				p-value
Total	31 (37.3%)				52 (62.7%)				<0.001
	Standard group n = 40		Local group n = 43		Standard group n = 40		Local group n = 43		
	27 (67.5%)		4 (9.3%)		13 (32.5%)		39 (90.7%)		<0.001
	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	
CRP	84.64 ± 14.3	93.53 ± 14.6	77.85 ± 14.9	77.45 ± 18.0	32.57 ± 42.5	16.21 ± 9.5	17.38 ± 17.5	21.4 ± 22.1	
ERS	45.29 ± 5.6	48.7 ± 5.2	46.0 ± 2.8	52.5 ± 5.2	26.25 ± 7.9	25.8 ± 10.8	20.06 ± 7.9	20.04 ± 10.8	
LEUCOCYTES	6682.3 ± 3776.9 (17)	6570 ± 2852.6 (10)	4750 ± 70.7 (2)	8950 ± 6434.6 (2)	- (0)	- (0)	1300 ± 0 (1)	1590 ± 1404.8 (4)	

sulfate beads impregnated with vancomycin than those with standard prophylaxis (Table 3). Length of stay was also shorter in the intervention group at 4.6 days (range: 2–23 days) compared to 15.25 days in the control group (range: 2–32 days; $p < 0.001$) (Table 4).

Discussion

The present study provides information that local antibiotic prophylaxis may have a greater influence on the prevention of acute PJI in patients with non-modifiable risk factors. Nevertheless, there were some limitations, the first one is that this study only evaluates acute joint infections from post-operative to 3 months, and no cases of chronic infection were considered. Another limitation was that the guidelines for PJI diagnosis could not be followed using biomarkers like d-dimer, Alpha-defensin, and histologic analysis [15]. Therefore, the diagnosis was made by CRP and ESR biomarkers, as well as synovial white blood cell count and culture. In our country, the socio-cultural conditions of the population do not allow adequate knowledge of diseases, leading to underestimation of repercussions on their health conditions due to poor adherence in their treatments. We have found in this study that some patients who require surgical joint replacement treatment do not have adequate control of their chronic conditions, increasing the risk of infection by having risk factors that cannot be modified in the short or medium term [16]. Although adequate preoperative preparation is mandatory, in our population, it is not feasible to control all the risk factors because of our socio-cultural environment [4]. Despite this, in many cases, replacement surgery is necessary to provide a better quality of life [5]. During the trial, 367 arthroplasties were carried out, including primary and revisions, and 280 of them did not comply with the eligibility criteria; therefore, 83 participants with non-modifiable risk factors for PJI risk were enrolled. Once the acute infection has been diagnosed, the treatment that follows is complex and not without complications; in patients, who also have risk factors or active diseases, treatment becomes even more difficult and expensive [2].

Table 4
Days of hospital stay.

Length of hospital stay				
	Standard group n = 40	Local group n = 43	Total n = 83	p-value
Hip	15.15 ± 10.70	4.15 ± 3.49	8.80 ± 9.16	
Knee	15.33 ± 9.71	5.47 ± 5.99	10.92 ± 9.55	
Total	15.25 ± 10.06	4.67 ± 4.62	9.77 ± 9.34	<0.0001

In previous years, we found that the prevalence of PJI in our institution was very high compared with the international references; for this reason, we initiated protocols to reduce this prevalence found among some procedures, like the local application of antibiotics, which has been studied on several occasions [17]. However, the direct application to the prosthetic bone interface areas has not yet been well established. In the present research, we were able to identify that the application of a local antibiotic in contact with the prosthetic components and surrounding tissue is beneficial for patients. Periprosthetic infections will continue to be an issue with devastating consequences for the patient, the surgeon, and the health system.

Similar findings were reported by Parvizi et al. showing that one of the greatest challenges in PJI prevention is risk factor recognition, whether modifiable or non-modifiable. Recognition of these factors will allow us to focus on better prevention strategies [18]. Michael M. Kheir

et al. have also published the relationship between risk factors and the increased susceptibility to infection, as well as antibiotic prophylaxis, and their study demonstrates that extended oral antibiotic prophylaxis by seven days postoperatively may reduce the prevalence of infection by counteracting poor host factors up to one year [19]. The present study found that medicated calcium sulfate beads, when used as a local release method of prophylactic antibiotic therapy, have the potential to reduce PJI in patients with non-modifiable risk factors by 86.6%, as well as their associated complications and economic burden; however, more studies are required to corroborate long-term results.

Conclusions

Antibiotic-loaded calcium sulfate beads as a local antibiotic prophylaxis method in patients with non-modifiable risk factors undergoing hip or knee replacement provide adequate protection, reduce the risk of presenting an acute PJI, and shorten the length of hospital stay.

Declaration of competing interest

None.

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