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Periprosthetic hip and knee infections: comparison of etiology, perioperative management and costs

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Abstract. – OBJECTIVE: We compared two series of patients treated at our Hospital for periprosthetic hip and knee infections (PHI; PKI), in order to evaluate etiology, perioperative management (duration of spacer, antibiotic therapy, quality of life during the treatment), length of hospital stay, and costs.

PATIENTS AND METHODS: We included in the study 32 patients with PHI and 30 patients with PKI. The average age of the patients was 74.8 in PHI and 71.2 in PKI. Treatment consisted of a two-stage revision associated with antibiotic therapy. All patients were followed up for at least two years after surgery. We analyzed the causative microorganism responsible for the infection, duration of the spacer and antibiotic therapy, quality of life during this time, length of hospital stay, and total hospital cost of treatment.

RESULTS: The gram-negative microorganisms were more common in PHI, without any statistically significant difference compared to PKI. Duration of the spacer for PHI was 7.4 months and 5.5 months for PKI (p=0.005). Length of antibiotic therapy was 6.2 months for PHI and 4.1 months for PKI (p<0.001). Most patients in the two series had an acceptable quality of life during treatment. The mean length of hospitalization was 54 days in PHI and 26 days in PKI (p<0.001). The cost averaged 38,300 euros for PHI and 22,100 euros for PKI (p<0.001).

CONCLUSIONS: Our study showed statistically significant differences between periprosthetic hip and knee infections as regards etiology, duration of treatment and global costs. Periprosthetic hip infections are caused by more virulent microorganisms that are harder to eradicate, require a longer length of treatment and have a greater economic impact on the healthcare system.

Key Words

Periprosthetic infection, Hip, Knee.

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are two of the most common orthopedic surgical procedures. Their number is expected to grow due to a constant increase in life expectancy and in functional requirements even in the elderly population[1,2]. The large number of primary total hip and knee arthroplasties performed in the world has resulted in an increase of periprosthetic joint infections (PJI) that represent one of the most common causes of failure of joint arthroplasty[3]. Recent studies report that PJI is becoming the leading cause for TKA revision[4-6] and one of the top three causes for THA revision, after aseptic loosening and instability[7-9]. Another cause of the growing number of PJI is a progressive increase in resistance to antibiotics, partly due to their inappropriate use, which reduces the efficacy of perioperative antibiotic prophylaxis[10,11].

Compared to other causes of THA and TKA failure, like aseptic loosening and instability, PJI generally require longer and multidisciplinary treatment. This has a greater impact on the patient's quality of life and entails higher healthcare costs. Although there have been many improvements in the prevention of PJI, such as laminar air flow, use of body exhaust suits, decreasing the number of people in the operating room, screening and treatment for active oral and nasal infections, preoperative cleansing of the skin with chlorhexidine gluconate and the use of ultraviolet light[12,13], the rate of periprosthetic hip and knee infections ranges from 0.4% to 2.2% and 1.7% to 2.4% respectively[14-16].

While cost-effectiveness for THA and TKA has been well documented[17], the cost of treating PJI is variable and represents an important burden for the

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healthcare system. It is around four times as much as primary joint replacement and is associated with longer hospital stays, a decrease in the quality of life of the patients, the risk of arthrodesis (3%) and amputation (4%), and an increased mortality rate[18-22].

Several studies have reported on periprosthetic hip and knee infections. However, to the best of our knowledge, few studies analyze possible differences between the two procedures regarding etiology, perioperative management, and costs.

The aim of our study was to compare two groups of patients treated for periprosthetic hip or knee infections in terms of etiology, length and efficacy of treatment, and costs.

Patients and methods

This is a retrospective observational study in which we compared two series of patients treated for chronic periprosthetic hip or knee infections. The first series included 32 patients with periprosthetic hip infection; 18 were male and 14 female. The average age of the patients at diagnosis of the infection was 74.8 years (range from 68 to 80). All prosthetic implants were cementless, and most patients had had primary arthroplasty in another hospital (24 cases). Nine patients were affected by type II diabetes mellitus, 7 patients had heart disease, 4 patients suffered from depression; no patient was affected by rheumatoid arthritis. The second series included 30 patients with periprosthetic knee infections; 16 were male and 14 female. The average age of the patients at diagnosis of the infection was 71.2 years (range from 50 to 78). All prosthetic implants were cemented, and most patients had had primary arthroplasty in another hospital (22 cases). Twelve patients were affected by type II diabetes mellitus, 8 patients had heart disease, 3 patients suffered from depression; no patient was affected by rheumatoid arthritis.

The diagnosis of chronic periprosthetic infections, in both series, was made if at least three of the following criteria were present: painful joint with restricted range of motion, hot and swollen joint; sinus tract or persistent wound drainage; increased inflammation markers (C-reactive protein and erythrocyte sedimentation rate), x-ray signs of infections, like periosteal elevation and focal osteolysis and positive joint aspiration culture[23].

In both series, treatment consisted of a two-stage revision, associated with antibiotic therapy prescribed by our hospital specialists in infectious diseases and based on the intraoperative culture obtained during our first surgical procedure. All patients observed a washout period of at least two weeks before the first surgical operation, by suspending any antibiotic therapy.

The first-stage procedure consisted of removal of the infected prosthesis, accurate surgical debridement, and application of an antibiotic spacer, both in the hip and knee periprosthetic infections. During this stage, both microbiological cultures and histopathological periprosthetic tissue were collected for examination. The spacer was maintained until the infection was considered eradicated by the infectious disease specialist who analyzed the normalization of C-reactive protein and the absence of clinical and radiographic signs of infection. The second stage consisted of removal of the antibiotic spacer with the same surgical approach and application of a revision prosthetic implant (cementless or cemented in the hip and always cemented in the knee).

All the patients of both series were followed up for at least two years after the second-stage procedure. We analyzed the causative microorganism of the periprosthetic infections, the length of time between the first and the second-stage procedure during which the antibiotic spacer was maintained, quality of life during this interval time as evaluated through a patient-administered survey, length of antibiotic therapy, duration of hospital stay in both the orthopaedic and infectious disease Departments, and total hospital cost of treatment. This was calculated by adding up the cost of the hospital stay, the cost of the antibiotic spacer and revision implant used, the cost of the operating room, and the cost of the antibiotic therapy administered during the stay. The survey asked the patients whether they were satisfied, partially satisfied or unsatisfied.

Statistical Analysis

We performed a descriptive analysis of our study parameters (Tables I and II). Data are expressed as means ± standard deviation or median and range. The Student's t-test and Mann-Whitney U test were used to evaluate the significance of differences in interval time for the antibiotic spacer, length of antibiotic therapy, length of hospitalization and cost. A chi-squared test or Fisher's exact test was used to evaluate the significance of differences in the age, sex, causative organisms, comorbidities, quality of life, and overall rate of treatment success. All statistical analyses were performed using the SigmaStat Version 4.0 program (Systat Software). p-values less than 0.05 were considered significant.

Table I. Demographic characteristics of patients.

	Periprosthetic hip infections (32)	Periprosthetic knee infections (30)	*p*-value
Age	74.8 ± 9.4	71.2 ± 6.3	> 0.05
Sex			> 0.05
• F	44%	47%	
• M	56%	53%	
Comorbidities			
• DM type II	9 (28%)	12 (40%)	> 0.05
• Depression	4 (12.5%)	3 (10%)	> 0.05
• Heart disease	7 (22%)	8 (27%)	> 0.05

Results

There was no statistical difference between the two series when comparing for sex, age and presence of medical comorbidities, including diabetes mellitus, heart diseases and depression (Table I).

The causative microorganism was isolated in 81% of the periprosthetic hip infections and in 87% of the periprosthetic knee infections. Regarding the periprosthetic hip infections, the isolated microorganisms in order of frequency were: *Staphylococcus aureus* in 5 cases (15.6%) (methicillin-resistant in 2 cases); *Escherichia coli* in 5 cases (15.6%); *Staphylococcus epidermidis* in 4 cases (12.5%); *Klebsiella pneumoniae* in 3 cases (9.4%); *Pseudomonas aeruginosa* in 2 cases (6%); *Staphylococcus lugdunensis* in 1 case (3%); *Proteus mirabilis* in 1 case (3%); *Mycobacterium tuberculosis* in 1 case (3%). Polymicrobial infections were diagnosed in 4 cases (12.5%), whereas 6 cases were culture negative (19%). For the periprosthetic knee infections, the

Table II. Causative microorganisms of periprosthetic joint infections.

	Periprosthetic hip infections	Periprosthetic knee infections
Total	**32**	**30**
Gram Positive	**10**	**20**
• *Staphylococcus aureus*	5	12
- Methicillin resistant	2	5
• *Staphylococcus epidermidis*	4	5
• *Staphylococcus lugdunesis*	1	1
• Staphylococcus warneri		1
• Streptococcus agalactiae		1
Gram Negative	**11**	**4**
• *Escherichia coli*	5	3
• *Pseudomonas aeruginosa*	2	
• *Proteus mirabilis*	1	
• *Klebsiella pneumoniae*	3	
• *Acinetobacter baumannii*		1
Mycobacterium	**1**	
• *Tuberculosis*	1	
Polymicrobial	**4**	**2**
• *S. aureus + K. pneumonie + A. baumani*	1	
• *S. aureus + Providencia stuartii*	1	
• *S. epidermidis + P. mirabilis*	1	
• *E. coli + K. pneumonie*	1	
• *Staphylococcus ominis + Morganella morganis + Serratia marcescens*		1
• *S. epidermidis + E. coli*		1
Culture Negative	**6**	**4**

isolated microorganisms in order of frequency were: *Staphylococcus aureus* in 12 cases (40%) (methicillin-resistant in 5 cases); *Staphylococcus epidermidis* in 5 cases (16.7%); *Escherichia coli* in 3 cases (10%); *Staphylococcus lugdunensis* in one case (3.3%); *Staphylococcus warneri* in one case (3.3%); *Streptococcus agalactiae* in one case (3.3%); *Acinetobacter baumannii* in one case (3.3%). Polymicrobial infections were diagnosed in 2 cases (6.7%), while 4 cases were culture negative (13.3%) (Table II).

The Gram-negative microorganisms were more common in periprosthetic hip compared to periprosthetic knee infections, without any statistically significant difference between the two series. On the other hand, the overall prevalence of gram-positive bacteria was statistically significantly higher in the periprosthetic knee infections (p=0.005). Although polymicrobial infections were twice as common in the hip, resulting in 12.5% of cases compared to 6.7% in the knee, there was no statistically significant difference. Values for the negative culture cases were 19% and 13% in the hip and knee respectively, without any statistically significant difference.

All patients in both series were treated with two-stage revision, with antibiotic spacer implantation during the first stage. The interval between the first and the second stage, during which the patients maintained the spacer, was 7.4 months for the hip infections (from 2.8 to 13.5 months), whereas for the knee infections it lasted 5.5 months (from 2.5 to 9.8 months). There was a statistically significant difference between the two series (p=0.005). In most cases, the spacer was maintained for at least one more month after the end of antibiotic therapy (Table III).

The length of antibiotic therapy for the hip infections was 6.2 months (from 1.8 to 12.5 months), while it was 4.1 months for the knee infections (from 1.5 to 8.3 months). There was a statistically significant difference between the two series (p < 0.001). In all patients, it was administered until the inflammatory markers were normalized and the radiological examination showed no signs of infections.

In 2 periprosthetic hip infections and 6 periprosthetic knee infections, we postponed the reimplantation procedure (second stage) for either patient-related or clinical reasons. The patient- related reasons were either personal or determined by the fact that the patient had an acceptable quality of life with the spacer. The clinical reason was a lack of normalization of the inflammatory markers. No case required an additional debridement with the replacement of the spacer, although in two cases (one hip and one knee) the spacer broke before the final reimplantation. All patients, even those that had a postponed procedure, eventually had a reimplantation arthroplasty.

In spite of the presence of the spacer, most patients in the two series had an acceptable quality of life. In the group of hip infections, 22 patients out of 32 (69%) were satisfied or partially satisfied with their quality of life, while in the knee infections group 24 out of 30 patients (80%) were satisfied or partially satisfied. There was no statistically significant difference between the two series.

The mean length of hospitalization was 54 days (from 22 to 95 days) in the periprosthetic hip infections, whereas it was 26 days (from 15 to 52 days) in the periprosthetic knee infections. There was a statistically significant difference between the two series (p<0.001).

Table III. Duration of treatment, quality of life and costs of hip and knee periprosthetic infections.

	Periprosthetic hip infections (32)	Periprosthetic knee infections (30)	*p*-value
Duration of antibiotic spacer*	**7.4 ± 3.1**	**5.5 ± 1.8**	**0.005**
Duration of antibiotic therapy*	**6.2 ± 2.9**	**4.1 ± 1.5**	**< 0.001**
Quality of life during treatment:			
• Satisfied	5 (16%)	10 (33%)	> 0.05
• Partially satisfied	17 (53%)	14 (47%)	> 0.05
• Not Satisfied	10 (31%)	6 (20%)	> 0.05
Total length of hospitalization*	**1.8 ± 0.8**	**0.9 ± 0.4**	**< 0.001**
Cost of hospital treatmentt^	**38300 ± 14300**	**22100 ± 7100**	**< 0.001**

*results in months. ^in euros

The entire hospital cost for treating periprosthetic hip infections averaged 38,300 euros (range 19,500-64,500), whereas for periprosthetic knee infections it averaged 22,100 euros (range 13,300-37,700), with a statistically significant difference between the two series ($p<0.001$).

All patients were followed up for at least 2 years after the reimplantation arthroplasty. In 5 cases of the first series (hip infections) and 4 cases of the second series (knee infections), we observed persistent clinical and laboratory signs of infection of the revision arthroplasty. Therefore, the overall success rate in our study was 84% and 87% in the two series respectively, without any statistical difference.

Discussion

Periprosthetic infection is one of the most common and most devastating complications of total hip and knee replacement. Despite the many improvements in its prevention, prophylaxis, and treatment, this serious complication continues to have a relatively high incidence and entails an important economic impact for the healthcare system[2,4,6,18-20,24,25].

Several studies have shown a prevalence of gram-positive bacteria in periprosthetic hip and knee infections[9,23,26-28]. Recently, in a multicenter study conducted in USA and Europe on a large series of patients, Aggarwal et al[26] reported that the two most common pathogens that cause periprosthetic hip and knee infections are *Staphylococcus aureus* and coagulase-negative Staphylococcus followed by Streptococcus and Enterococcus. We observed similar data for knee infections, while in our series there was a predominance of gram-negative bacteria in the hip infections, although this result was not statistically significant. We could speculate that this difference, although not statistically significant, may be related to possible urinary tract infections often present in elderly patients who represent an important predisposing risk factor for periprosthetic hip infections[23,29-31]. However, since our case series is relatively small, we believe that the preponderance of gram-negative pathogens in hip infections needs further confirmation in the future. As regards the culture-negative periprosthetic infections, we observed no difference between the two series, in accordance with previous studies[26,27,32]. Only Aggarwal et al[26] in their European series observed a statistically significant difference in culture-negative periprosthetic infections that were more common in the knee.

Gomez et al[27] reported no difference in the duration of the spacer between hip and knee periprosthetic infections; in their series, this time averaged 4.4 months for the hip infections and 4.1 months in the knee infections. In our study, the patients of both series maintained the spacer for a longer time, and we observed a longer period of spacer implantation in the periprosthetic hip infections, with a significant statistical difference between the two series. There are two main reasons to explain our different results. First, in our series, there was a larger number of gram-negative pathogens in the hip infections, which are usually more difficult to eradicate, as reported by other authors[9]. Second, the treatment protocol suggested by our infectious disease specialists is very cautious; they generally prefer to wait a longer mean time before considering the second-stage procedure. Another reason is related to the advanced mean age of our patients who were often retired at the time of surgery and had fewer functional requirements. Moreover, as mentioned in the Results, in some cases, the patient decided to postpone the reimplantation arthroplasty. Lastly, the quality of life with the spacer, as reported by the patients through a questionnaire, was acceptable, especially in patients with a knee infection.

Although most studies[27,33-37] have reported an approximately 80% incidence of reimplantation arthroplasty, some authors[38-42] performed the second-stage procedure in about 100% of the patients, in accordance with our results.

Length of hospital stay and costs are important aspects that need to be carefully studied in both hip and knee periprosthetic joint infections, in order to try to reduce them. Some studies have reported that length of stay was longer and the economic impact was greater for infected hips than infected knees[18,24]. In accordance with this observation, both length of hospitalization and costs in our study were significantly higher in periprosthetic hip infections compared to periprosthetic knee infections. We attributed these findings to the different causative micro-organisms, which required more expensive antibiotic therapy for a longer time in the hip infections series. Moreover, some antibiotics used in this series could be administered only in a hospital setting and required stricter clinical and laboratory controls, to avoid antibiotic toxicity and other medical complications. This is in agreement with Cunningham et al[9], who showed that some gram-negative bacteria, along with methicillin-resistant *Staphylococcus aureus*, entail a worse prognosis and longer hospitalization. On the other hand, most periprosthetic knee infections were caused by gram-positive microorganisms that responded well to oral antibiotic therapy.

Finally, it should be noted that the economic impact of periprosthetic hip and knee infections is not only determined by the direct medical cost but also by the limitation of work and everyday activities of the patient affected by this pathology. This negative social impact is seen not only in employed patients, but also in older patients who lose their self-sufficiency.

There were limitations to this study. It was a retrospective observational study that analyzed two small series of elderly patients who often need particular attention related to the risk of comorbidities. Regarding the total cost, we did not calculate the cost of the surgical team and the anesthesiologists or other minor costs such as radiological exams, laboratory exams, etc.

In conclusion, our study showed statistically significant differences between periprosthetic hip and knee infections, as regards etiology, duration of treatment and global costs. Periprosthetic hip infections are caused by more virulent microorganisms that are harder to eradicate, require a longer length of treatment and have a greater economic impact on the healthcare system.

Conflict of Interests

The authors declare that they have no conflict of interest.

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