Periprosthetic Infections in Total Knee Arthroplasty: What Is Our Reality?

Infecciones periprotésicas en artroplastia total de rodilla: ¿Cuál es nuestra realidad?

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Abstract

Introduction Periprosthetic infection (PPI) is one of the most serious complications in total knee arthroplasty (TKA). Despite this, there is little Chilean literature regarding this pathology.

Objectives To determine the incidence, comorbidities, isolated microorganisms and their antibiotic susceptibility, morbidity, and mortality in patients with PPI.

Materials and Methods A descriptive and retrospective study in patients operated between 2001 and 2020 for gonarthrosis, with a primary TKA, in the same health center, with at least 1 year of follow-up. Patients operated on in other centers or with incomplete clinical records were excluded. Comorbidities, isolated microorganisms, antibiotic susceptibility, and survival were recorded through a systematic search of the clinical records of patients with PPI. Descriptive statistics were used to present the data.

Results We included 544 TKAs, 8 (1.47%) of which presented PPI, and the patients had an average age at presentation of 66 years ($\pm$ 5.7 years) and an average body mass index (BMI) of 30.3 ($\pm$ 4, 5) kg/m^2. The median time of presentation of the PPI was of 411 ($\pm$ 1,034) days. The main comorbidities recorded were arterial hypertension in 5 (62.5%), smoking in 4 (50%) cases, and dyslipidemia in 4 (50%) cases. In total, 5 (62.5%) patients presented polymicrobial etiology, and in 3 (37.5%), a single microorganism was isolated. The main isolated agents were *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, both multidrug-resistant, in 6 (75%) and 3 (37.5%) patients respectively. All patients received three doses of cefazolin as surgical prophylaxis. A sensitivity of 100% to vancomycin and rifampicin (12/12 cultures), and a resistance of 83.4% to ciprofloxacin (4/9 cultures) were described. Overall, 2 (25%) patients died 3 years after the TKA, due to causes unrelated to PPI. There were no cases of infectious relapse after the review.

Keywords
- periprosthetic infection
- knee
- microorganisms
- antibiotic resistance

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Conclusion An incidence of 1.47% (8 cases) of PPI was found. All patients with PPI presented some presurgical comorbidity. The main microbiological agents identified were multidrug-resistant and susceptible to vancomycin and rifampicin.

Resumen

Introducción La infección periprotésica (IPP) es una de las complicaciones más serias en una artroplastia total de rodilla (ATR). Pese a esto, existe poca literatura chilena respecto de esta patología.

Objetivos Determinar la incidencia, las comorbilidades, los microorganismos aislados y su susceptibilidad antibiótica, y la morbimortalidad en pacientes con IPP.

Materiales y Métodos Estudio descriptivo y retrospectivo en pacientes operados entre 2001 y 2020 por gonartrosis, con una ATR primaria, en un mismo centro de salud, con al menos 1 año de seguimiento. Se excluyeron pacientes operados en otros centros o con registros clínicos incompletos. Se registraron las comorbilidades, los microorganismos aislados, la susceptibilidad antibiótica, y la sobrevida por medio de una búsqueda sistemática de las fichas clínicas de los pacientes con IPP. Se utilizó estadística descriptiva para presentar los datos.

Resultados Se incluyeron 544 ATRs, de las cuales 8 (1,47%) presentaron IPP, y los pacientes tenían una edad promedio de presentación de 66 ($\pm$ 5,7) años, e índice de masa corporal (IMC) promedio de 30,3 ($\pm$ 4,5) kg/m^2. La mediana de tiempo de presentación de la IPP fue de 411 ($\pm$ 1.034) días. Las principales comorbilidades registradas fueron hipertensión arterial en 5 (62,5%), tabaquismo en 4 (50%) casos, y dislipidemia in 4 (50%) casos. En total, 5 (62,5%) pacientes presentaron etiología polimicrobiana, y en 3 (37,5%) se aisló un solo microorganismo. Los principales agentes aislados fueron *Staphylococcus aureus* y *Staphylococcus* coagulasa negativo, ambos multirresistentes, en 6 (75%) y 3 (37,5%) pacientes respectivamente. Todos los pacientes recibieron tres dosis de cefazolina como profilaxis quirúrgica. Se describe una sensibilidad del 100% frente a vancomicina y rifampicina (12/12 cultivos), y una resistencia del 83,4% al ciprofloxacino (4/9 cultivos). Un total de 2 (25%) pacientes fallecieron después de 3 años de la ATR por causas no relacionadas con la IPP. No hubo casos de recidiva infecciosa tras la revisión.

Conclusión Se encontró una incidencia de 1,47% (8 casos) de IPP. Todos los pacientes con IPP presentaron alguna comorbilidad prequirúrgica. Los principales agentes microbiológicos identificados fueron multirresistentes y susceptibles a vancomicina y rifampicina.

Palabras claves
- infección periprotésica
- rodilla
- microorganismos
- resistencia antibiótica

Introduction

Periprosthetic infection (PPI) is one of the most serious complications in total knee arthroplasty (TKA), with an incidence of around 0.29% in the United States and 2% in Spain.[1,2] It is significantly associated with high morbidity and mortality, in addition to greater economic expenses and the need for surgical reintervention, with an estimated price of 6,815.4 dollars for each revision arthroplasty.[3] The main current advances are focused on the prevention, early diagnosis and treatment of PPIs, in order to reduce the rate and improve patient outcomes.[4]

Among the main risk factors related to PPIs, those linked to the patient's lifestyle stand out, such as obesity, excessive alcohol intake, active smoking, and the use of intravenous drugs. Factors related to comorbidities, such as diabetes, psoriasis, rheumatoid arthritis, and ankylosing spondylitis, are also relevant. On the other hand, there are risks associated with surgery, such as a surgical time longer than 90 minutes.[2,5,6]

The strategies for the prevention of PPIs are mainly preoperative antibiotic prophylaxis, preoperative skin cleaning, and the use of cemented prostheses loaded with antibiotics.[7]

Based on the current evidence, many centers continue to recommend the use of antibiotic prophylaxis with first- or second-generation cephalosporin, intravenously, during the preoperative period and in the following 24 hours after arthroplasty.[8]

The diagnosis of PPI remains a challenge due to multiple factors such as: false negative cultures, non-diagnostic laboratory tests, and heterogeneous clinical presentations.[9–11] In search of a more conclusive diagnostic tool, different classifications have been proposed, such as those by Tsukayama

Criterios Mayores (por lo menos 1 de los siguientes)	Decisión
2 cultivos positivos para el mismo organismo	Infectado
Tracto sinusal con evidencia de comunicación o visualización de la prótesis	

Table 1 Criteria for the diagnosis of PPI.

et al.[12] in 1996 or by the Musculoskeletal Infection Society (MSIS)[13] in 2011, which have undergone modifications until reaching the classification most used currently, published in the 2018 International Consensus on Musculoskeletal Infection by Parvizi et al.[9] (►**Table 1**).

There are various ways of classifying PPIs, with the presentation time being one of the most widely used. One of the first classifications of this type is the one proposed by Coventry[15] in 1975, which was soon modified by Fitzgerald et al.[16] in 1977, who group them into acute, subacute and late (►**Table 2**).[14–16]

For the correct treatment of a case of PPI, it is essential to isolate and identify the etiological agent. The main microorganisms described are gram-positive bacteria, gram-negative bacteria, and fungi in third place.[17,18]

Given the scarcity of data published in this regard in Chile, the present study becomes necessary in order to know the regional reality in terms of the most prevalent microorganisms, their sensitivity, and the characteristics of patients affected by PPI.

Materials and methods

We obtained the complete casuistry of patients who underwent TKA due to severe gonarthrosis in a public hospital in Santiago de Chile. A descriptive and retrospective study of these patients was carried out, including all those who underwent primary total knee arthroplasty between 2001 and 2020, with a minimum follow-up of 1 year.

Until 2018, patients who met the PPI criteria according to the main international guidelines (Tsukayama et al.[12] and MSIS[13]) were identified and included; after 2018, the diagnostic method was guided by the Philadelphia consensus of the same year.

We excluded all patients operated on at other health centers, those with revision prostheses, and those who had incomplete clinical records.

The surgical technique used followed the manufacturer's instructions and the prosthesis model. In addition, surgical protocols and asepsis and antisepsis techniques were used, respecting the quality standards of the hospital, with three doses of cefazolin as the antibiotic surgical protocol (vancomycin in the case of patients allergic to cephalosporins). All interventions were performed with medial parapatellar approach, use of ischemia handle, and without the use of drainage.

Regarding the patients with PPI, the following variables were analyzed:

- Demographics: age, gender, previous illnesses and body mass index (BMI).
- Surgical: surgical time and antibiotic prophylaxis.
- Microbiological: isolated microorganism, and antibiotic susceptibility and resistance.

Each infection was classified according to its temporality between the TKA and the moment of PPI diagnosis, using the classification described by Fitzgerald et al.,[16] and recording the microbiological variables found for each case.

Diagnóstico Preoperatorio	Criterios Menores		Puntaje	Decisión
	Sangre	PCR oDimero D elevado	2	>o igual a 6, Infectado
		Velocidad de hemosedimentación elevada	1	
	Líquido sinovial	Recuento de Leucocitos elevados o Estereasa leucocitaria elevada	3	2-5 Posiblemente infectado
		Alfa-Defensina positiva	3	
		Polimorfonucleares elevados (%)	2	0-1 No infectado
		PCR elevada	1	

Diagnóstico Intraoperatorio	Puntaje preoperatorio no concluyente o muestras secas	Puntaje	Decisión
	Puntaje preoperatorio	-	> o igual a 6, Infectado
	Histología positiva	3	
	Purulencia positiva	3	4-5 Inconcluso
	Un único cultivo positivo	2	
			< o igual a 3, No infectado

Table 2 Classification according to presentation time of PPI.

Secondly, we analyzed the antibiotic and/or surgical management that was carried out in the PPI patients and the morbidity and mortality after the treatment.

Finally, a descriptive analysis of the different variables was performed using Microsoft Excel 2020 (Microsoft Corp., Redmond, WA, United States).

The study was approved by the institutional ethics committee.

Results

Between 2001 and 2020, a total of 544 TKAs were performed, and 8 patients (1.47%) presented PPIs in their subsequent evolution.

Of those 8 patients (1.47%), 3 were male, and 5, female, with a mean age at the time of installation of the primary prosthesis of 66 (± 5.7) years, all with a presurgical diagnosis of severe gonarthrosis.

Among the morbid conditions, the obesity of the patients stands out, with an average BMI of 30.3 (± 4.5) kg/m^2; all patients had an associated comorbidity (hypertension, smoking, diabetes, or other).

All patients received antibiotic prophylaxis with 1 g of intravenous cefazolin preoperatively and 2 doses postoperatively. The mean operative time was of 114 (± 23.3) minutes.

The time elapsed between the primary TKA and reoperation ranged from 12 to 3,324 days, with a median of 411 days. Regarding the presentation, it was acute in 3 (37.5%) patients, subacute in 3 (37.5%) and late in 2 (25%) cases (►**Table 3**).

The main reason for consultation was joint pain in 6 cases, while the remaining 2 were joint stiffness. No patient presented with fever, and only 1 (12.5%) presented a fistula.

Regarding the laboratory tests, C-reactive protein (CRP) on admission was elevated in 7/8 patients and the leukocytes were elevated in 3 cases.

In total, 5 (62.5%) of the patients with PPI presented polymicrobial etiology, while the other 3 (37.5%), a single causal bacterial agent was found. The main isolated agent was multidrug-resistant *Staphylococcus aureus*, which occurred in 75% of the patients. The other causal agents found are described in ►**Table 4**.

Table 3 Time of evolution time from primary total knee arthroplasty to infection

Patient	Days
Patient 1	455
Patient 2	367
Patient 3	14
Patient 4	12
Patient 5	614
Patient 6	3,315
Patient 7	1,125
Patient 8	43

Regarding antibiotic sensitivity, we found that all cultures that were positive for *S. aureus* were sensitive to vancomycin and rifampicin. On the other hand, a high resistance against ciprofloxacin was observed.

The remaining sensitivity rates of other antibiotics are described in ►**Table 5**.

Of the total number of patients, 7 (87.5%) underwent revision prostheses in 2 stages, while the remaining patient (12.5%) underwent removal of the infected prosthesis and 3 surgical knee cleanings, subsequently dying from septic shock secondary to endocarditis.

Discussion

Though it can result in serious complications such as PPI, TKA has been increasingly performed. The incidence of PPI in our center was of 1.47%, which is within the percentages described in the literature.[19,20]

Among the main risk factors for developing a PPI, we find obesity, diabetes mellitus and rheumatoid arthritis, among others.[5,21] It is noteworthy that most of the patients in the present study had a high BMI, in addition to some of the other risk factors mentioned, which suggests that not only the conditions of the health center are important, but also patient's medical condition.

Table 4 Infectious agents isolated per patient

	SA	EF	CNS	SE	EC	AB	KBL	SH	SP	PAE
Patient 1	+	+	-	-	-	-	-	-	-	-
Patient 2	-	-	+	+	-	-	-	-	-	-
Patient 3	+	-	-	-	-	-	-	-	-	-
Patient 4	+	-	-	-	-	-	-	-	-	-
Patient 5	+	-	+	-	+	+	-	-	-	-
Patient 6	+	-	-	-	-	-	+	-	-	-
Patient 7	-	-	-	-	-	-	-	+	-	-
Patient 8	+	-	-	-	-	-	-	-	-	+

Abbreviations: AB, *Acinetobacter baumannii*; CNS, coagulase-negative *Staphylococcus*; EC, *Escherichia coli*; EF, *Enterococcus faecalis*; KBL, *Klebsiella* producing extended-spectrum β-lactamase (ESBL); PAE, *Pseudomona aeruginosa*; SA, *Staphylococcus aureus*; SE, *Staphylococcus epidermidis*; SH, *Staphylococcus hominis*; SP, *Streptococcus pyogenes*.

Table 5 Antibiotic sensitivity

Antibiotic	Sensitivity: % (sensitive/cultures studied)
Vancomycin	100% (12/12)
Rifampicin	100% (12/12)
Sulfamethoxazole-trimethoprim	100% (10/10)
Linezolid	100% (9/9)
Gentamicin	100% (9/9)
Ceftaroline	100% (8/8)
Clindamycin	50% (6/12)
Erythromycin	45% (5/11)
Oxacillin	45% (5/11)
Ciprofloxacin	44% (4/9)

The follow-up of patients after TKA has not been defined, and it varies according to the guideline or medical center. We can observe, for example, that the Arthroplasty Society of Australia[22] recommends an annual follow-up from the first to the tenth postoperative years and, thereafter, every three to five years. On the other hand, Mending et al.[23] followed up 11,019 TKAs, investigating the temporal peaks of risk of failure, and concluded that the optimal moments of follow-up include 6 and 12 months, then 3, 8, 12, and 17 years, and these last 2 periods are recommended for those with a BMI greater than 40 kg/m^2. In the present study, we observed infections with a median of 411 days and great dispersion, ranging from 12 to 3,315 days (9 years); based on what was previously published and according to what we found in the present study, it seems reasonable to us to recommend an annual clinical follow-up after the first postoperative year, continuing up to 10 years after surgery.

Once the diagnosis of PPI is suspected, the choice of the empirical antibiotic regimen should be made considering the main and most likely etiologies. There is great variability within the literature in this regard; Jaén et al.[24] conducted a multicenter study in Spain in which they isolated *Staphylococcus epidermidis* as the main infectious agent, while Girón-Cornelio[25] in a literature review with a focus on health centers in Peru, found that the main etiology was coagulase-negative *Staphylococcus*. In the present study, on the other hand, we found multidrug-resistant *S. aureus* as the main infectious agent, which does not correlate with the previously-described etiologies and shows that there is a high variability regarding the main agent in each center.[24,25]

The study by Leijtens et al.[26] showed a high sensitivity to the combination of clindamycin and rifampicin, while Gellert et al.[27] showed the treatment with various antibiotic biofilms, including rifampicin, ampicillin and ciprofloxacin, according to the susceptibility. In our local population, we were able to identify multirug-resistant *S. aureus* as the most prevalent agent, with vancomycin and rifampicin as the ideal antibiotics to eradicate the infection, while we observed high resistance to ciprofloxacin and erythromycin. It should be noted that the antibiotics sulfamethoxazole-trimethoprim, linezolid, and gentamicin presented high sensitivity; however, they were studied in a smaller number of cases. Given this difference that is observed within the different health centers, it seems reasonable to recommend using the international treatment guidelines only as a first approach, but that each center has its own study of etiological agents with regards to the identification of the most frequent pathogens and their antibiotic susceptibilities.

Within the limitations of our study, we can mention both the low number of TKAs and PPIs in the sample, which could exaggerate the rates of the variables measured. On the other hand, we did not perform a comparison of the risk factors for PPI with a control group that did not present infection. This motivates us to propose a new line of research, with a regional and national multicenter study, to describe the incidence, isolated microorganisms, and susceptibility, in order to analyze trends and develop a national management and treatment guide.

Another point to consider is that, although the sample of the present study is kept under strict and closely-monitored follow-up due to their health insurance, it is possible that a patient has made a change of address or city and developed PPI, which could affect the final incidence of PPI. In any case, we estimate that it should not correspond to a relevant factor, since all the patients adhered to the follow-up in our center in the years following their intervention.

As strengths, we highlight the long period covered by the present study (18 years), a standardized intervention by the same team, the diagnosis based on the latest relevant international guidelines, and the analysis of the microbiological variables for each of the PPI cases, also detailing the antibiotic susceptibility study, which could serve as a guide for the different groups when deciding which empirical antibiotic treatment to use in a case of PPI.

Conclusion

The incidence of PPI found in the present study was of 1.47%. All patients with PPI presented some preoperative comorbidity. The main microbiological agents identified were multidrug-resistant and susceptible to vancomycin and rifampicin.

Conflict of interests

The authors have no conflict of interests to declare.

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