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Original Research

Two-Stage Treatment of Chronic Periprosthetic Knee Infections With the Use of Gentamicin-Articulated Spacers: Success Rate and Predictors of Failure at the Minimum Seven-Year Follow-Up

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A B S T R A C T

Background: The purpose of this study was to assess the survivorship rates of 2-stage treatment with gentamicin-impregnated polymethylmethacrylate articulated knee spacer in patients with chronic periprosthetic joint infection and to identify risk factors associated with failure.

Methods: We conducted a retrospective study among 73 patients with chronic periprosthetic joint infection after primary total knee replacement with articulated polymethylmethacrylate gentamicin-impregnated spacers (Subiton, Medical Labs, Ind Argentina), performed in a single institution with a minimum follow-up of 7 years. Clinical and functional assessment was performed with Knee Society Score and Western and Ontario McMaster Universities Osteoarthritis Index. A univariate and multivariate analysis was performed to identify the variables that influenced the success and failure rates.

Results: We included 73 patients. There were 53 (71.3%) monomicrobial, 11 (15%) polymicrobial, and 10 (13.7%) negative cultures infections. The success and failure rates were 90.5% (n = 66) and 9.5% (n = 7), respectively. Multivariate analysis identified that age (odds ratio = 1.77; P = .039), greater erythrocyte sedimentation rate values prior to the first stage (odds ratio = 1.04; P = .006), and polymicrobial infections (odds ratio = 7.32; P = .0003) were independent variables associated with failure.

Conclusions: Two-stage revision with polymethylmethacrylate gentamicin-impregnated knee spacers is an effective strategy for the treatment of chronic periprosthetic joint infection after total knee arthroplasty. Age, higher erythrocyte sedimentation rate values prior first stage, and polymicrobial infections were independent risk factors for treatment failure.

Introduction

Periprosthetic joint infection (PJI) represents a serious complication and the most common cause of early failure after total knee arthroplasty (TKA) [1]. Despite advances and a better understanding of prophylactic efforts, its incidence ranges from 0.5 to 2.5% [2,3]. The gold standard treatment for chronic PJI is 2-stage revision [4,5], with success rates above 90% [6]. With this strategy, both static and articulated spacers have been described with similar rates of infection eradication [7–11]. Although, based on certain benefits such as better interstage functional capacity, less bone stock loss, and better functional outcomes with increased range of motion, there is a recent trend toward the use of articulated spacers [12].

For more than 15 years, we have been using articulated gentamicin-impregnated polymethylmethacrylate (PMMA) knee spacer in our department, and to our knowledge, there are no studies reporting its midterm clinical and functional results for the treatment of chronic PJI. Therefore, the purpose of this study was to assess the survivorship and clinical and functional outcomes of 2-stage revision for chronic PJI using these types of spacers. Secondarily, variables associated with failure due to recurrence of infection were evaluated. Our hypothesis is that these types of spacers achieve good clinical and functional outcomes with high treatment success rates.

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Material and methods

Study design

As per an institutional review board (protocol number 8177), a retrospective study of all patients treated consecutively between January 2009 and June 2015 for PJI after TKA was conducted. The inclusion criteria were patients older than 18 years with diagnosis of chronic PJI [13] who were treated with 2-stage revision using prefabricated gentamicin-impregnated PMMA articulating knee spacers (Subiton, Medical Labs SL; Buenos Aires, Argentina) and who completed a minimum follow-up of 7 years (after spacer placement).

Patients in whom TKA was performed for a diagnosis other than primary knee osteoarthritis (ie, post-traumatic osteoarthritis, history of periarticular osteotomies, and previous infections) and those who did not complete both stages of treatment were excluded. Out of 78 patients initially identified, 5 were excluded (3 for not having completed the 2 stages of treatment and 2 for not complying with the minimum follow-up).

PJI diagnosis

PJI was defined according to the MusculoSkeletal Infection Society criteria, with 1 major criterion or a minimum of 3 minor criteria [6].

Highlights of the surgical technique

After removing the prosthesis, aggressive surgical debridement and irrigation was performed, where a minimum of 5 and 3 samples were sent for bacteriologic [14] and histologic analyses, respectively. This was followed by placement of a Subiton's gentamicin-impregnated and articulating cement spacer (Fig. 1a). This spacer is available in 3 sizes RF58, RF65, and RF79 with gentamicin impregnated between 1.38 and 2.82 grams depending on the size. Femoral and tibial components were then fixed with 1 dose of 40-gram low-viscosity cement (Simplex P, Stryker, USA) and 1 gram of vancomycin was added per dose of cement. All patients underwent the same rehabilitation protocol. They were allowed full weight bearing with the aid of a walker the first day after surgery. Active knee mobility was allowed after the third week.

Figure 1. (a and b) antero-posterior and lateral view of left knee with osteoarthritis. (c and d) postoperative x-ray of primary TKR. (e and f) articulating gentamicin-impregnated cement knee spacer. (g and h) anteroposterior and lateral views of knee spacer before reimplantation. (i and j) postoperative x-ray after second stage with femoral and tibial stems. (k and l) x-ray 6 years after surgery. TKR, total knee replacement.

Postoperative visits were performed at 3 and 6 weeks after each stage, at 3, 6, and 12 months and then annually.

Initially, all patients received intravenous antibiotic therapy according to the isolated microorganism for 2-3 weeks monitored by the infectious disease department. After this, antibiotic therapy was administered orally. Two weeks prior to the second stage, patients did not receive any antibiotics. Prosthetic reimplantation was decided when the following conditions were observed: no clinical signs of inflammation or joint pain, absence of radiological signs of infection, and downward trend of the erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and white blood cell levels (WBC).

After the second stage, operative cultures were assessed for 3 weeks, and if no microorganism was observed, no antibiotic was not administered.

Variables analyzed

Information was collected from the institutional medical records. Demographic data, body mass index, and comorbidities (using Charlson comorbidity index and American Society of Anesthesiologists classification) were collected.

We recorded the time elapsed between primary TKA and first stage operation for PJI, size of the implant, isolated microorganism from bacteriologic and histologic analysis, length of hospital stay, the time elapsed between stages, and duration of antibiotic therapy. Serum marker values prior to each stage (normal values, ESR: 16 mm/h; CRP: <0.9 mg/dl; and WBC: <10,000 mm^3) were also registered. Complications and reoperations for any cause up to the end of the study were documented.

Clinical and functional assessment was performed at baseline and at the end of follow-up using the Knee Society Score [15] and Western Ontario and McMaster Universities Osteoarthritis Index [16]. We compared preoperative and postoperative range of motion in the last control with use of a goniometer. The surveys were completed by an orthopaedic surgeon trained in knee arthroplasty.

Treatment success was defined as the absence of clinical signs of infection, with no requirements for additional procedures after reimplantation and no deaths related to PJI (criteria concluded in an International Multidisciplinary Consensus applying the Delphi method) [17].

Failure was defined as the persistence or recurrence of the infection (patients in whom a new infection was observed after the second stage, regardless of the isolated microorganism) [18].

Statistical analysis

Categorical variables were described as frequencies and percentages, while continuous variables were expressed as mean and standard deviation. Quantitative variables were compared using Student's t-test and qualitative variables were compared using the chi-square test (X^2) or Fischer's exact method. After comparative assessment between patients with failure and success, a multiple regression analysis was performed with significant variables. A difference of $P < .05$ was considered statistically significant. All data were entered into an Excel spreadsheet (Redmon, WA, USA) and statistical calculations were performed using GraphPad Prism 8.0 software (LaJoya, CA, USA).

Results

The series consisted of 73 patients with a median follow-up of 7.9 (7.0-10.3) years. The description of the series is detailed in Table 1.

Table 1
Variables recorded prior to the first stage.

Variables	(n = 73)
Male gender (n, %)	26 (35.6)
Age (median, IQR)	70.0 (62.0-74.0)
BMI (median, IQR)	28.5 (26.2-34.6)
CCI (n, %)	
III	37 (50.7)
IV	26 (35.7)
V	2 (2.7)
VI	5 (6.8)
VII	1 (1.3)
VIII	2 (2.7)
ASA (n, %)	
I-II	23 (31.5)
III-IV	50 (68.5)
DBT (n, %)	26.0 (35.7)
KSS (median, IQR)	57.0 ± 8.7
KSS functional (median, IQR)	58.0 ± 7.2
WOMAC (median, IQR)	44.5 ± 6.8
WBC (median, IQR)	9800 ± 4320 (mm^3)
ESR (media, DE)	110 ± 11.4 (mm)
CRP (media, DE)	11.5 ± 3.7 (mg/dl)

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; CRP, C-reactive protein; DBT, diabetes; ESR, erythrocyte sedimentation rate; IQR, interquartile range; KSS, Knee society score; WBC, white blood cell count; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

The time elapsed between primary TKA and diagnosis of PJI was 6.1 (range 4-48) months. Regarding the implanted spacer size, Subiton's RF65 was used in 53 (72.7%), RF58 in 15 (20.4%), and RF79 in 5 (6.9%) patients. The length of hospital stay during the first stage was 16 (14-24) days.

There were 51 (69.9%) monomicrobial infections, 12 (16.4%) polymicrobial infections, and 10 cases (13.7%) with negative cultures (Table 2).

Complications between stages

One (1.4%) spacer dislocation was observed. This occurred after a fall from the patient's own height 4 weeks after implantation. The patient underwent open reduction of the same spacer, without recurrence until the reimplantation. In no case, the first stage of treatment had to be repeated.

ATB treatment, laboratory values, and reimplantation

Systemic antibiotic therapy was administered for 13.9 ± 8.3 days. After this, oral antibiotic therapy was indicated during 60.8 ± 18.8 days.

Table 2
Frequencies of isolated microorganism.

Microbiology	N (%)
Methicillin susceptible *Staphylococcus*	18 (24.6)
Culture negative (−)	10 (13.7)
Staphylococcus epidermidis	9 (12.2)
Polymicrobial infection	12 (16.4)
Streptococcus agalactiae	6 (8.0)
Enterococcus faecalis	3 (4.1)
Stenotrophomonas maltophilia	2 (2.8)
MR *Staphylococcus epidermidis*	2 (2.8)
MR *Staphylococcus aureus*	2 (2.8)
Klebsiella pneumoniae ESBL	2 (2.8)
Finegoldia magna	2 (2.8)
Enterococcus cloacae	2 (2.8)
Coagulase-negative *Staphylococcus*	1 (1.4)
Staphylococcus lugdunensis	1 (1.4)
Escherichia coli	1 (1.4)

ESBL, extended spectrum beta-lactamase; MS, methicillin susceptible; MR, methicillin resistant.

Prior to the first stage, the values of serum markers were: ESR = 110 ± 11.4 ml/1 h, CRP = 11.5 ± 3.7 mg/dl and WBC = 9800 ± 4320. After reimplantation these decreased to ESR = 49.2 ± 12.5, CRP = .4 ± 0.3 and WBC = 6500 ± 3425.

All patients underwent the second stage of treatment after a mean of 18.5 (13.5 − 20.0) weeks after the first stage. The length of hospital stay after this procedure was 6.4 ± 6.0 days (Fig. 1b).

Functional outcomes

At the end of the study, the clinical and functional Knee Society scores were 84.9 ± 8.7 and 82.3 ± 4.1, respectively; the mean Western Ontario and McMaster Universities Osteoarthritis Index score observed was 89.2 ± 9.6. This represented a statistically significant improvement in both the scores ($P < .001$). The range of motion registered was 111.2° ± 10.6 after 7.2 years of mean follow-up.

Success and failure rate

The success rate was 90.5% (n = 66), with no deaths reported.

Seven (9.5%) failures were registered, at a mean of 28.2 ± 9.7 weeks from the second stage. Of these 7 patients, 6 were re-treated with a 2-stage revision and all of them achieved infection control. The remaining 1 continued with suppressive antibiotic therapy due to high surgical risk.

Comparative analysis between patients with and without failure

Regarding patients with and without treatment failure, we found significant differences in age, polymicrobial infections, and ESR values prior to first- and second-stage surgeries (Table 3).

Multivariate analysis

Multivariate analysis showed an increased failure risk related to age at the time of surgery, polymicrobial infections, and ESR values prior to the first stage of treatment (Table 4).

Table 3
Univariate analysis between patients with and without failure.

Variables	Failure (n = 7)	Success (n = 66)	*P* value
Age (mean, SD)	81.1 ± 6.7	68.1 ± 9.9	<.01
BMI (mean, SD)	29.3 ± 2.9	27.4 ± 2.2	.59
Diabetes (n, %)	2 (28.6)	5 (6.9)	.66
ASA (n, %)			
I	1	34	.10
II	1	17	.55
III	3	12	.34
IV	2	3	.08
CCI (n, %)			
II	-	6 (9.1)	.07
III	-	25 (37.9)	
IV	-	32 (48.5)	
V	-	2 (3.0)	
VI	4 (57.1)	1 (1.5)	
VII	1 (14.3)	-	
VIII	2 (28.6)	-	
Time between TKA and first stage (wk) (mean, SD)	18.3 ± 9.5	17.3 ± 10.9	.9
KSS before first stage (mean, SD)	57.2 ± 7.3	57.1 ± 8.2	.83
KSS before first stage (functional) (mean, SD)	55.0 ± 8.6	58.4 ± 7.6	.10
First stage			
WBC (mean, SD)	8543 ± 2015	9145 ± 3204	.92
ESR (mean, SD)	106.3 ± 30.0	64.3 ± 29.9	<.01
CRP (mean, SD)	14.5 ± 4.6	11.5 ± 5.2	.26
Infection type n (%)			
Monomicrobial	1 (14.3)	50 (75.7)	<.01
Polymicrobial	6 (85.7)	6 (9.1)	
Negative culture	0 (0)	10 (15.2)	<.01
Length of hospital stay (d) (mean, SD)	12.4 ± 1.2	13.3 ± 7.1	.78
Second stage			
Time between spacer and re-implantation (mean, SD)	16 (14.7-19.5)	14 (12-20)	.79
WBC/mm3 (mean, SD)	5406 ± 1309	6318 ± 1606	.09
ESR (mean, SD)	38.2 ± 18.9	21.3 ± 12.5	.012
CRP (mean, SD)	1.1 ± 0.7	1.0 ± 0.6	.65
Length of hospital stay (mean, SD)	4.4 ± 1.1	5.1 ± 0.7	.47
KSS (clinical) (mean, SD)	66.5 ± 9.3	74 ± 8.1	<.01
KSS (functional) (mean, SD)	67.2 ± 7.9	77.3 ± 9.5	<.01
Follow-up (mean, SD)	87.1 ± 3.9	86.9 ± 4.3	.69

ASA, American Association of Anesthesiologist; BMI, body mass index; CCI, Charlson comorbidity index; ESR, erythrocyte sedimentation rate.

Discussion

The most important finding of this study was that in the 2-stage treatment of chronic PJI after TKA, the use of commercially available articulating spacers impregnated with gentamicin had a 90.5% success rate at 7.9 years of follow-up. Potential benefits of prefabricated articulated antibiotic-impregnated knee spacers include shorter surgical time, trials and modularity, articular congruency and sustained antibiotic elution and has demonstrated comparable results to custom spacers regarding infection eradication [19].

Wan et al [20] reported a 90.9% success rate after 2 years of follow-up, evaluating 33 patients with chronic knee PJI treated with the use of commercial articulating spacers. This result is consistent with those of a recent meta-analysis published by Spivey et al [21]. They evaluated 34 studies involving 1016 knee spacers for the treatment of PJI and reported a success rate ranging from 73% to 100%.

On the other hand, our results are worse than the ones reported by Vecchini et al [22], who observed 100% success rates after treating 16 patients with the use of articulated gentamicin-impregnated knee spacers with PJI. We believe that this difference could be explained by the fact that these authors did not include polymicrobial infections, a variable that in our analysis proved to be an independent risk factor for recurrence.

Previously, different authors have tried to identify the variables related to failure after 2-stage knee revision for PJI. In the present study, we found that age, polymicrobial infections, and ESR values prior to spacer implantation were significantly associated with this condition.

We observed that for each year of increasing age in first stage, the risk of failure significantly increased 1.77 times. This contrasts with recent reports by Vielgut et al [23] and Claassen et al [24] in which they described that this variable was not related to reinfection. They also found that polymicrobial infection was a variable that significantly affected their success rate ($P < .001$). Similarly, Drexler et al [25] reported a success rate of 85.4% in a study of 82

Table 4
Multivariate analysis.

Variables	OR	CI95%	*P* value
Age	1.77	1.29-36.23	.039
ESR before first stage	1.04	1.01-1.08	.006
ESR before second stage	0.94	0.81-1.15	.06
Polymicrobial infection	7.32	2.30-43.79	.0003

CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds-ratio.

patients treated with ceftazidime and vancomycin spacers, associating their failure rate with polymicrobial infections. Consistent with these authors, our analysis showed that polymicrobial infections presented a significant difference between patients with and without failure, being identified as an independent variable that increased the risk of failure 7.32 times.

Another independent variable found in this study was ESR values before the first stage. Similarly, Carrega et al [26] reported lower ESR values in successfully treated patients compared to those who failed. Although our analysis showed that each point increase in this value prior to the first stage, the risk of failure increased 1.04 times. On the other hand, Stambough et al [27] reviewed 291 the ESR and CRP serum values of 291 hip and knee arthroplasties and observed that the preresection and prereimplantation values were poor markers for recurrence or persistent infection.

The authors of this study consider that the value of serum markers in isolation should not determine the appropriate time for reimplantation or predict treatment failure. This depends on multiple variables that must be considered by the orthopedic surgeons in order to perform properly a 2-stage treatment.

Another point to note in this study is that after the first stage, patients received intravenous antibiotic treatment for a mean of 13.9 $\pm$ 8.3 days. This could be considered a short period of time compared to the 4-6 weeks reported in multiple studies [28,29]. However, there are studies such as those by Hsieh et al [30] who looked at 99 patients with hip PJI treated in 2 phases with an antibiotic preformed cement spacer. Two study groups were formed, one with patients treated for 1 week with intravenous antibiotic therapy and the other for 4-6 weeks. After a mean follow-up of 43 months, no significant differences were observed. Similarly, Hoad-Reddick et al [31] went further and published a series of 59 patients with knee PJI treated for a mean of 4.6 days with intravenous antibiotics, obtaining an eradication rate of 89%. The limitations of the present study are those inherent to its retrospective design, in which we evaluated a complex entity such as chronic PJI, where the causes of failure can be influenced by different bias. Also, the small number of failures makes it difficult to draw strong conclusions. Nevertheless, the multivariate analysis performed allows us to suppose that the effect of these co-founders has been addressed in an acceptable way. Another limitation is the number of patients and the absence of randomization.

Conclusions

Two-staged treatment with the use of PMMA gentamicin-impregnated spacers had a 90.5% success rate at 7.9 years of follow-up. The risk of failure was related to age, ESR values prior to the first stage of treatment, and polymicrobial infections.

Conflicts of interest

The authors declare there are no conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2023.101177.

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