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TREATMENT OF INFECTION AFTER TOTAL KNEE ARTHROPLASTY

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ABSTRACT

Objectives: To identify and compare the rate of success of therapeutic modalities applied in surgeries for the treatment of infections associated with total knee arthroplasty (TKA), and to evaluate the functional outcome and pain in different therapeutic modalities by means of quality of life scores. Methods: We evaluated all patients who developed periprosthetic infection after TKA for primary or secondary osteoarthritis, in the period from January 1st, 2008 to December 31st, 2010. Results: In the study period, 29 patients with TKA had infection, and 12 of these underwent debridement and retention of the prosthesis (D+R), seven received two-stage and six one-stage exchange arthroplasties, and four patients were treated with suppressive antibiotic therapy because they could not undergo another surgical procedure. Conclusion: The D+R, one-stage revision and two-stage revision success rates were 75%, 83.3%, and 100%, respectively. The best results of quality of life (QoL) and function occur in patients undergoing D+R. In contrast, the worst QoL and functional results were obtained in patients treated with two-stage revision arthroplasty. ***Level of Evidence II, Prognostic Studies - Investigating the Effect of a Patient Characteristic on the Outcome of Disease.***

Keywords: Arthroplasty. Infection. Prosthesis retention. Prosthesis-related infections. Knee prosthesis.

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INTRODUCTION

Periprosthetic infection is a major cause of failure of total knee arthroplasty[1] and its management is one of the most complex medical treatments. Even with the development of prophylactic antibiotic therapies, environmental control and improvements in surgical techniques, the incidence of infection varies between 1-2% in primary arthroplasties and 3.5-5% in revision surgeries.[2-4] The main risk factors associated with infection in knee arthroplasty are a previous surgery, advanced age, female gender, rheumatoid arthritis, obesity, diabetes and immunodeficiencies.[5]

The treatment of infection involves surgical removal of the focus of infection and prolonged antibiotic treatment against biofilm producing bacteria.[6,7] Several classifications and staging systems are used to determine the treatment and mostly consider the time interval between surgery and the appearance of signs and symptoms. The classification proposed by Zimmerli et al. differentiates early (developed earlier than three months after surgery), from intermediate (3-24 months) or late (after 24 months) infection cases and it is related to the pathogenesis of infection.[8] Early and intermediate infections are usually acquired during prosthetic implantation, whereas late infections results from hematogenous spread of the focus at a distance.[8,9]

Based on this classification, the therapeutic modalities proposed are: surgical debridement keeping the prosthesis and prolonged antibiotic therapy, change in one-stage or two-stages revision with short interval (2-6 weeks), two-stages revision with long intervals (6-8 weeks) and arthrodesis. In debridement with retention of the prosthesis, the hematoma is removed, as well as fibrous membrane, fistulae and dead bone and soft tissues, and the polyethylene component is changed.[10] The one-stage revision surgery consists in the removal of all material, debridement and prosthesis replacement in the same procedure.[11] In the two-stages exchange, the implementation of a new prosthesis is delayed for periods varying from four to six weeks (short interval) or more (long interval), and an antibiotic-loaded spacer can be inserted, allowing the maintenance of the limb alignment, soft tissue tension and partial mobility. The problem in this case is that the spacer acts as a foreign body, and thus, subject to displacement.[12,13] Arthrodesis is reserved for patients at high risk of reinfection or when the expected functional outcome is worse than in arthrodesis.

The objective of the present study is to identify therapeutic modalities applied in surgeries for the treatment of infections

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associated with knee arthroplasties, evaluating the success rate of each of them, and to evaluate the functional outcome and pain in different therapeutic modalities by means of quality of life scores.

METHODS

This is a retrospective cohort study, conducted at the Department of Orthopedics and Traumatology, in a public university hospital, Brazil, a university quaternary hospital, and a metropolitan referral center for trauma, with 105 beds for Orthopedics and Traumatology. The population consisted of all patients who developed periprosthetic infection after total knee arthroplasty (TKA) for primary or secondary osteoarthritis, in the period from January 1st 2008 to December 31st 2010. This study was approved by the Ethics Committee of the institution and patients signed Free and Informed Consent forms for the treatment.

Service treatment protocol

All patients were treated individually according to the service protocol, based on the algorithm published by Zimmerli et al.[8] for the treatment of infected hip and knee artroplasties, which considers risk factors evaluated in previous studies.[8] Debridement with prosthesis retention is the option for patients with early or late infections with signs and symptoms lasting less than three weeks, with stable prosthesis, good skin and subcutaneous tissue conditions, who used anti-biofilm-forming pathogens antibiotics. Intravenous antibiotic therapy should have been kept for two to four weeks, followed by oral therapy for six months. The one-stage prosthesis replacement could have only been used if the conditions of skin and subcutaneous tissue were good, if there were no significant comorbidities and if the causative agent was sensitive to antibiotics. In patients with unfavorable conditions of the skin and subcutaneous tissue (skin fistulae), the option was two-stages replacement, and the interval between the two surgeries should have been four to six weeks. Antibiotic therapy was continued for six months. Permanent removal of the implant or arthrodesis was indicated for severe immunocompromised patients and those without mobility. Prolonged antibiotic therapy was indicated for patients without clinical possibilities of undergoing another surgery or those who refused surgery.

The cure of infection was defined as the absence of signs and symptoms of infection, C-reactive protein (CRP) < 2 mg/L or erythrocyte sedimentation rate (ESR) < 20 mm/h, and no radiographic signs of infection for two years after initiation of antibiotic therapy. Treatment failure was considered in patients who underwent a new surgical procedure or death resulting from infection, and successful cases were those who maintained TKA or had TKA reimplantation.

Statistical analysis

Cases were identified in the Knee Surgery Group services database. All medical records were reviewed and summarized by one author with a tool for collecting demographic data, clinical and surgical signs and symptoms, imaging and laboratory results and outcomes. Patients were interviewed by phone with the questionnaires Short Form-36 (SF-36) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Patient data were described with summary measures (mean, standard deviation) for age and absolute and relative frequencies by gender. Mean ages were compared between groups using analysis of variance (ANOVA)[14] and the association between gender and group was verified using the likelihood ratio test.[15] The quality of life (SF-36) and function (WOMAC) scores were described according to treatment groups, joining two treatments to obtain larger sample groups, using median, minimum and maximum values, and compared between groups using the Mann-Whitney test.[15]

RESULTS

In the study period, 29 patients were included and evaluated, 19 females and 10 males. Of these, 12 underwent debridement with prosthesis retention (D + R), seven had two-stages revision surgery and six patients had one-stage revision surgery, performed by one of the three orthopedic surgeons in the staff accompanied by an infectious disease specialist. Four patients were treated with suppressive antibiotic therapy because they did not agree with another surgical procedure or had no clinical conditions for the procedure. Of the 29 cases, nine (31%) had early infection, 12 (41.4%), intermediate infection and eight (27.6%), late infection. Causative agents identified in the culture are described in Table 1.

Among the 12 patients submitted to debridement but who kept the prosthesis, nine (75%) were cured. All seven patients undergoing two-stages revision surgery were also cured, and so did five from the six patients (83.3%) undergoing one-stage procedures.

Only cured patients who underwent surgical treatment (25 patients) were included in the multivariate analysis of quality of life: those not undergoing surgery were excluded from this analysis, and some were further excluded because they underwent debridement with prosthesis retention (D + R), but then it evolved into relapse (two cases), or died due to infection (two cases). From the remaining 21 patients, two were lost for follow-up (one died from causes not related to infection, one due to address change). Therefore, 19 patients answered the questionnaires, and these had a mean age of 70.3 years. The follow-up time free of relapses was 40.3 months in average.

Table 2 shows that there is no statistically significant association between gender and treatment group (p=0.306), no statistically significant difference in age between groups (p=0.962) and no

Table 1. Causative agents of periprosthetic infection in patients undergoing total knee arthroplasty, as identified by culture.

Agent	n (%)
Not identified (negative culture)	4 (13.8)
Staphylococcus aureus	9 (31)
Coagulase-negative *Staphylococcus*	5 (17.2)
Streptococcus	4 (13.8)
Pseudomonas aeruginosa	3 (10.3)
Escherichia coli	1 (3.4)
Staphylococcus pyodermides	1 (3.4)
Enterobacter sp.	1 (3.4)
Enterococcus sp.	1 (3.4)
Total	29 (100)

difference in the relapse-free follow-up times between treatment groups (p=0.426).

Table 3 shows that no statistically significant difference in scores between treatments regarding the domains physical functioning (p=0.003), physical role functioning (p=0.012) and general health perceptions (p=0.009) and in the body pain (p=0.007), function (p=0.003) and total functionality (p=0.002), comparing the three modalities of surgical treatment for infected arthroplasty.

Table 4 shows that patients treated with two-stages revision surgery show lower quality of life scores in the physical functioning domain than patients receiving other treatments ($p < 0.05$), and also in the WOMAC areas of pain, function and total ($p < 0.05$) score. The scores of physical limitations are significantly lower in patients treated with two-stages revision compared to patients treated with debridement and retention (D+R; p=0.003), and general health scores of patients treated with debridement (D + R) have significantly higher scores than patients undergoing other treatments ($p < 0.05$).

Table 5 shows that patients treated with debridement and retention (D+R) have significantly higher scores for the quality of life in the domains functional capacity, physical impairment, pain and general health status, and in the scores pain, functionality and total score than patients treated with two-stages or one--stage revision surgery ($p < 0.05$).

Table 6 shows that patients treated with two-stages revision surgery have significantly lower scores of quality of life in functional capacity, physical limitation and pain domains, and WOMAC scores for pain, function and total score than patients treated with D + R or one-stage revision surgery ($p < 0.05$). (Table 6)

Table 2. Age, gender and recurrence-free follow-up time according to the treatment group: patients treated with debridement plus prosthesis retention (D+R), two-stages or one-stage revision surgery.

Variable	Groups			Total (n = 19)	p
	D+R (n = 8)	Two-stages (n = 7)	One-stage (n = 4)		
Gender (n%)					
Female	4 (50)	6 (85,7)	3 (75)	13 (68,4)	0,306*
Male	4 (50)	1 (14,3)	1 (25)	6 (31,6	
Age (years old)					
Mean (SD)	70,3 (8,2)	69,9 (6,6)	71,3 (,9)	70,3 (7,6	0,962†
Recurrence-free follow-up time (months)					
Mean (SE)	37,9 (4,7)	47,0 (0,0)	37,7 (6,7)	40,7 (3,3)	0,426‡

*Results of the likelihood ratio test; † ANOVA result; ‡Result of the long-rank test.

Table 4. Multiple comparisons between treatment modalities for scores in the quality of life and functionality domains that showed statistical differences.

Variable	Comparison	Z value	*p*
Functional capacity	D + R *versus* two-stage	3.47	0.001
	D + R *versus* one-stage	0.50	0.0619
	Two-stages *versus* one-stage	-2.38	0.017
Physical limitation	D + R *versus* two-stage	2.97	0.003
	D + R *versus* one-stage	0.78	0.433
	Two-stages *versus* one-stage	-1.69	0.092
General health status	D + R *versus* two-stage	2.86	0.004
	D + R *versus* one-stage	2.49	0.013
	Two-stages *versus* one-stage	0.06	0.949
WOMAC pain	D + R *versus* two-stage	3.17	0.002
	D + R *versus* one-stage	0.57	0.566
	Two-stages *versus* one-stage	-2.06	0.039
WOMAC function	D + R *versus* two-stage	3.58	< 0.001
	D + R *versus* one-stage	0.88	0.379
	Two-stages *versus* one-stage	-2.10	0.036
WOMAC total	D + R *versus* two-stage	3.68	< 0.001
	D + R *versus* one-stage	0.92	0.359
	Two-stages *versus* one-stage	-2.14	0.032

Table 3. Quality of life and functionality scores according to treatment modality: patients treated with debridement plus prosthesis retention (D+R), two-stages or one-stage revision surgery.

Variable	Grupos			Total median (minimum; maximum)	p
	D+R median (minimum; maximum)	Two-stages (minimum; maximum)	One-stage (minimum; maximum)		
Functional capacity	6.5 (55; 85)	35 (30; 55)	62.5 (50; 85)	55 (30; 85)	0.003
Physical limitation	62.5 (50; 100)	25 (0; 50)	50 (25; 100)	50 (0; 100)	0.012
Pain	58 (30; 74)	41 (22; 54)	51.5 (41; 62)	51 (22; 74)	0.057
General health status	82 (62; 100)	62 (30; 72)	59.5 (47; 67)	67 (30; 100)	0.009
Vitality	85 (50; 95)	70 (35; 100)	65 (30; 95)	70 (30; 100)	0.280
Social aspect	81.5 (50; 100)	75 (63; 100)	69 (39; 88)	75 (38; 100)	0.338
Emotional aspect	100 (66.6; 100)	67 (0; 100)	67 (33; 100)	67 (0; 100)	0.304
Mental health	84 (56; 100)	64 (32; 88)	68 (52; 96)	64 (32; 100)	0.315
WOMAC pain	17.5 (16; 20)	14 (11; 16)	17 (15; 19)	16 (11; 20)	0.007
WOMAC rigidity	8 (7; 8)	7 (2; 8)	8 (6; 8)	8 (2; 8)	0.245
WOMAC function	57.5 (43; 62)	40 (30; 47)	49.5 (47; 55)	48 (30; 62)	0.003
WOMAC total	85.9 (70.8; 90.6)	64.6 (44.8; 72.9)	78.1 (72.9; 82.3)	76 (44.8; 90.6)	0.002

Table 5. Quality of life and functionality scores comparing the group receiving debridement plus retention of the prosthesis (D + R) with the other groups, joined. Results of the Mann-Whitney test.

Variable	Groups		Total median (minimum; maximum)	p
	D + R median (minimum; maximum)	Two-stage/one-stage (minimum; maximum)		
Functional capacity	67.5 (55; 85)	40 (30; 85)	55 (30; 85)	0.009
Physical limitation	62.5 (50; 100)	25 (0; 100)	50 (0; 100)	0.016
Pain	58 (30; 74)	41 (22; 62)	51 (22; 74)	0.041
General health status	82 (62; 100)	62 (30; 72)	67 (30; 100)	0.001
Vitality	85 (50; 95)	70 (30; 100)	70 (30; 100)	0.129
Social aspect	81.5 (50; 100)	75 (38; 100)	75 (38; 100)	0.272
Emotional aspect	100 (66.6; 100)	67 (0; 100)	67 (0; 100)	0.152
Mental health	84 (56; 100)	64 (32; 96)	64 (32; 100)	0.152
WOMAC pain	17.5 (16; 20)	15 (11; 19)	16 (11; 20)	0.016
WOMAC rigidity	8 (7; 8)	7 (2; 8)	8 (2; 8)	0.351
WOMAC function	57.5 (43; 62)	45 (30; 55)	48 (30; 62)	0.004
WOMAC total	85.9 (70.8; 90.6)	69.8 (44.8; 82.3)	76 (44.8; 90.6)	0.003

Table 6. Quality of life and functionality scores comparing the group receiving debridement plus retention of the prosthesis (D + R) joined with patients receiving one-stage revision surgery and those receiving two-stages revisions. Results of Mann-Whitney test.

Variable	Groups		Total median (minimum; maximum)	p
	Two-stages (minimum; maximum)	D + R/one-stage median (minimum; maximum)		
Functional capacity	35 (30; 55)	67,5 (50; 85)	55 (30; 85)	< 0,001
Physical limitation	25 (0; 50)	50 (25; 100)	50 (0; 100)	0,004
Pain	41 (22; 54)	58 (30; 74)	51 (22; 74)	0,022
General health status	62 (30; 72)	77 (47; 100)	67 (30; 100)	0,056
Vitality	70 (35; 100)	82,5 (30; 95)	70 (30; 100)	0,261
Social aspect	75 (63; 100)	75 (38; 100)	75 (38; 100)	0,967
Emotional aspect	67 (0; 100)	83,5 (33; 100)	67 (0; 100)	0,340
Mental health	64 (32; 88)	80 (52; 100)	64 (32; 100)	0,299
WOMAC pain	14 (11; 16)	17,5 (15; 20)	16 (11; 20)	0,001
WOMAC rigidity	7 (2; 8)	8 (6; 8)	8 (2; 8)	0,142
WOMAC function	40 (30; 47)	53 (43; 62)	48 (30; 62)	< 0,001
WOMAC total	64,6 (44,8; 72,9)	80,7 (70,8; 90,6)	76 (44,8; 90,6)	< 0,001

DISCUSSION

The treatment of periprosthetic infections, involving multiple surgical interventions and prolonged antibiotic therapy, fails in 10% to 20% of cases.[16,17] Although the literature presents rates between 1% and 2% of infection in primary arthroplasties,[2,3] a recent survey from 1994 to 2008 at our university public hospital (Santa Casa de São Paulo, São Paulo, SP, Brazil) showed an incidence of 6.4%.[18] Even evaluating a small number of subjects, the present study verified that less than one quarter of patients with infection were treated with two-stages exchange arthroplasty, the most common surgical procedure in the literature.[19] According to the literature[8,20,21] D+R surgery was the most frequently offered surgical modality in order to rescue arthroplasty without having to remove all components.

Factors associated with higher rates of infection are previous knee surgeries, advanced age, female gender, rheumatoid arthritis, obesity, diabetes and other immunodeficiencies.[5,22]

Infection onset earlier than three months post-surgery was the most frequent in our study, and this is probably explained by the virulence of microorganisms found in these cases, such as *S. aureus* and Gram-negative bacilli. The most frequent agent was *S. aureus*, similarly to the findings by Marculescu, with 32% rate of infection by this pathogen.[10] However, we also found several other bacteria, as three cases of *Pseudomonas aeruginosa* and *Escherichia coli*, *Enterobacter sp* and *Enterococcus sp*.

The main finding of the study was the best results of quality of life, according to SF-36, found in patients undergoing debridement and retention (D+R) as compared to the other treatments. The analysis of each component of SF-36, by calculating raw scale, showed higher scores in physical functioning, physical limitations, pain and general health. According to WOMAC questionnaire, these patients experienced better outcomes in pain, function and overall score. The success rate in D+R, one-stage and two-stages revision at a time in two days was 75%, 83.3% and 100%, respectively.

Two-stages revision arthroplasty is the most widely used procedure, with a success rate close to 90%.[19,23] The infected prosthesis is removed, soft tissue and bone are debrided and a cement spacer impregnated with antibiotics is used. Although widely used, our study shows the worst results of quality of life and WOMAC scores with this treatment. Two-stages revision is not indicated in patients with severe immunosuppression or with unfavorable clinical conditions for surgery. The patients in our study treated with two-stages revision had the worst results in SF-36 domains functional capacity, physical limitation and pain. The results of WOMAC scores were also worse for pain, function and overall score as compared to the other patients.

There are few comparative studies on the effectiveness of one-stage revision surgery, and this modality is seldom indicated as compared to standard two-stages procedure.[24,25] Indication is more frequent in infected hip arthroplasties. In our service, this procedure is performed in patients with early symptoms of infection without signs of loosening, good soft tissue condition and absence of fistula. It is, however, not indicated in methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus sp*, fungi or other multiresistant microorganism infections. A long period of parenteral antibiotic therapy is required after the procedure, with a success rate in the literature of up to 80%.[20]

Currently the D+R has gained space in the treatment of early and acute hematogenous infections. The success rate in the literature varies between 19.5% and 89.5%.20,26 One of the key success factors is the type of infection: Byren et al., in a prospective study with 112 infected TKA treated with D+R, had a success rate of 66.7% in patients with late onset infection, while early and late hematogenous infections showed a rate of 100% and 92.3%, respectively.[21] Other factors related to failure are a delay on revision surgery greater than two weeks after the onset of symptoms, the presence of fistula, articulated prostheses and immunocompromised patients. In our protocol, D+R is indicated for patients with symptoms for less than two weeks, with no signs of implant loosening and no fistula, with negative cultures or microorganisms susceptible to antimicrobial agents for surface-adherent microorganisms (e.g.: rifampicin).

Other therapeutic modalities, such as arthrodesis, amputation and resection, without reimplantation and long-term suppressive antibiotic therapy, are exceptions in our view, due to the large functional limitation and low patient satisfaction, indicated only as rescue procedures. In our series, four patients were submitted to suppressive antibiotic therapy, all due to lack of clinical conditions for surgery.

The goal of antibiotic therapy in patients with infected TKA is to cure or control the infectious process. There are few randomized trials evaluating the efficacy of drug therapy in patients with infected TKA. The choice depends on *in vitro* susceptibility data, allergic reactions and intolerance, patient preferences, and type of procedure performed.[20]

Our study demonstrated a success rate of 84%, with 8% of deaths and other two (8%) cases of failure undergoing revision surgery. During the period 1994-2007, before starting the protocol, our death rate was 12.8%.[18]

We believe that there is an indication for each therapeutic modality, however, the better result of quality of life is obtained upon choosing for debridement and prosthesis retention (D+R). This result underscores the importance of a precise and early diagnosis, and knowledge on the best indications for each case. Parenteral antibiotics for two to six weeks followed by oral antibiotics for a prolonged period, oriented by an infectious disease specialist, is fundamental for the protocol success.

CONCLUSION

In our series, the success rate in debridement plus prosthesis retention (D+R), one-stage and two-stages revision was 75%, 83.3% and 100%, respectively. The best results of quality of life and functional outcome, according to the SF-36 and WOMAC, occur in patients undergoing D+R as compared to the other treatments. In contrast, the worst quality of life and functional results were obtained in patients treated with two-stages revision arthroplasty.

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