EARLY PROSTHETIC HIP JOINT INFECTION TREATED WITH DEBRIDEMENT, PROSTHESIS RETENTION AND BIOFILM-ACTIVE ANTIBIOTICS: FUNCTIONAL OUTCOMES, QUALITY OF LIFE AND COMPLICATIONS

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Introduction

Prosthetic joint infection (PJI) is a serious complication of arthroplasty that is difficult to cure, is associated with prolonged hospital stay and has significant costs [1]. The optimal treatment approach remains contentious. Traditionally treatment has been with one- or two-stage prosthesis exchange, which has resulted in high rates of success in treating infection but given the technically difficult and extensive surgery required, likely involves significant morbidity [2]. There is growing evidence demonstrating successful treatment of early PJI with surgical debridement, retention of prosthesis and the use of biofilm-active antibiotics such as rifampicin for staphylococcal infections and fluoroquinolones for gram-negative infections [3]. This approach has been favoured more recently as it involves less extensive surgery than prosthesis exchange and so ostensibly results in better function, quality of life(QOL) and less morbidity, however few studies have formally assessed these outcomes. Our aim was therefore to describe rates of successful infection treatment for patients undergoing treatment for PJI with surgical debridement, prosthesis retention and biofilm-active antibiotics and compare their functional outcomes, QOL and complication rates to patients without PJI.

Methods

Study Design

This was a case-control study performed at a single tertiary institution, St Vincent's Hospital in Melbourne, Australia(SVHM).

Study population

Cases and controls were identified from an arthroplasty registry that was prospectively compiled by a single researcher on consecutive patients undergoing primary hip arthoplasty at SVHM between January 2006 and December 2009. The registry, previously described[4], actively collected information on basic demographics, comorbidities, type of surgery, complications (including the presence of PJI) and pre-and 12-month post-procedure functional and QOL assessments. The Charlson comorbidity index (CCI), a score of comorbidities that includes age [5], was calculated pre-operatively.

Over the study period 981 hip arthroplasty operations were performed and minimum 12-month follow-up information was available on 952, with the remaining 39 unavailable because of death from causes unrelated to surgery (13 patients) or loss to follow-up (16 patients).

Eligible cases were patients who developed PJI some time prior to the 12-month post-arthroplasty assessment and had treatment with prosthesis debridement and retention. Patients were excluded if the infected prosthesis was a megaprosthesis for bone tumour surgery or if the primary surgical treatment was prosthesis removal or revision. Controls were patients who did not develop PJI within 12

months from arthroplasty and were matched at a ratio of 4 to 1 to cases by age and pre-arthroplasty Harris Hip Score [6].

During the study period a protocol existed where early PJI (<3 months from implantation) [2] or haematogenous PJI was treated with retention of the prosthesis and prompt, aggressive, repeated, open surgical debridement involving removal of infected soft tissue, large volume high-pressure lavage, and change of polyethylene liner at the last debridement operation. After an initial short period of intravenous antibiotics (10-14 days) patients were treated with oral antibiotic combinations depending on organism sensitivities and with preference given to agents with activity against biofilm-associated bacteria such as rifampicin, fusidic acid and/or ciprofloxacin[7].

PJI and infection outcome definitions

The presence of a prosthetic joint infection was defined as per the USA CDC definition of deep organ/space surgical site infection [8]. All microbiology cultures results were considered significant if the same microorganism/s were isolated on two or more intra-operative specimens [9].

Treatment failure was defined as persistence or recurrence of symptoms or signs of prosthetic infection, the isolation of the same or different organisms from subsequent operative samples, the removal of the prosthesis while antibiotic therapy continued or death from PJI.

Functional and Quality of life assessments

Functional assessments were performed using the Harris Hip Score (HHS), a disease specific scoring system that assesses hip pain, function, range of motion and deformity [6, 10]. The maximum HHS is 100 and outcomes have been interpreted as: 100-90=excellent; 89-80=good; 79-70=fair; <70=poor [11]. An adverse functional outcome in this study was defined as a HHS < 70, equating to a poor result. QOL and general health was assessed using the 12-item Short Form Health Survey (SF-12), a generic measure of health status that has been validated previously in the setting of joint arthroplasty [12]. The SF-12 has physical health (Physical Component Summary [PCS]) and mental health (Mental Component Summary [MCS]) scores, with maximum scores (56.58 for PCS and 60.76 for MCS) based on population norms. Scores are interpreted as: >50=no disability; 40-50=mild disability; 30-40=moderate disability; <30=severe disability [13]. An adverse QOL outcome for this study was defined by a PCS or MCS score <40, equating to moderate-severe disability. Baseline HHS and SF-12 assessments were administered 2-8 weeks prior to hip arthroplasty and outcome assessments were performed 12-months post-arthroplasty. The factors analysed as potential predictors of 12-month functional and QOL outcomes were pre-operative functional and QOL scores, gender, BMI, age-adjusted CCI, smoking status, previous contralateral hip arthroplasty, operation duration, cemented prosthesis, superficial wound complications and presence of PJI.

Complications

Complications were defined as medical or surgical events related to treatment that occurred up to 12-months post-operatively and lead to a change in patient management. Superficial wound complications were excluded as these could not be distinguished from presenting features of PJI cases.

Statistical analysis

The Kaplan–Meier method was used to estimate survival free of treatment failure. The Mann–Whitney U-test and Student's t-test were used for comparison of continuous variables. Fisher's exact test and the chi-squared test were used for categorical variables. Logistic regression analysis was used to produce odds ratios (OR). Multivariate logistic regression models were used in assessment of risk factors for adverse outcomes by forward stepwise selection of factors significantly predictive of outcomes in the univariate analysis ($P< 0.1$). All reported p values were two-tailed, and for each analysis, $p <0.05$ was considered statistically significant. Data were analyzed in SPSS version 19.0; 2010(SPSS Inc).

Ethics approval

Ethics approval was granted by the SVHM Human Research Ethics Committee.

Results

Over the study period there were a total of 21 PJI identified. One patient was excluded from further examination as they underwent primary prosthesis resection and another was excluded because they underwent 2-stage prosthesis exchange. The remaining 19 cases were managed by debridement and prosthesis retention. Baseline demographic information of cases and controls is shown in Table 1. For cases, the median duration from joint insertion until first debridement (joint age) was 14 days (IQR 12-20). The median duration of symptoms until debridement was 4 days (IQR 3-9). The median duration of follow-up for cases from the time of infection was 24 months (IQR 15-37).

Microbiology

Eleven of the PJI cases were polymicrobial, 7 were monomicrobial and 1 was culture negative. Staphylococcus aureus was isolated in 9 cases (3 of these methicillin-resistant), coagulase-negative staphylococci in 10, gram-negative bacilli in 7 and enterococci in 6. The microbiology of individual cases is shown in Table 2.

Surgical treatment

The median number of debridement operations per case patient was 3 (range 3 to 6). All debridements were performed by open arthrotomy. Three patients in the control group required 1 wound debridement operation for treatment of superficial wound complications.

Medical treatment

All cases of PJI received an initial course of intravenous antibiotics followed by oral antibiotics. The median duration of intravenous antibiotics was 15 days (IQR 12-34) and involved a glycopeptide and/or beta-lactam antibiotic in all cases. The median duration of oral antibiotics was 356 days (IQR 230-395). Rifampicin-based regimens were used in 17 patients (in combination with fusidic acid in 15 cases). Ciprofloxacin was used in 7 cases, including all but 1 case involving a gram-negative organism. All patients had ceased antibiotics at the time of last review. The median duration of follow-up post-cessation of antibiotics was 12 months (IQR 5-24). Oral antibiotic regimens used for individual cases and outcomes are shown in Table 2.

Infection outcomes of cases

Eighteen of the 19 patients retained the original prosthesis at the time of last review. One patient had 2-stage prosthesis exchange because of ongoing signs of infection. There was no evidence of treatment failure in 17 patients. Survival free of treatment failure at 1 year was 95%(95%CI, 68-99%) and at 2 years 88% (95% CI, 59–97%).

Functional and QOL outcomes

Mean pre- and 12-months post-arthroplasty HHS and SF-12 scores for cases and controls can be seen in Table 3. There was significant change in HHS from pre-arthroplasty to 12 months post-arthroplasty for both cases (+35.9[SD20.1]; p<0.001) and controls (+44.6 [SD 18.7]; p<0.001). Similarly, for the SF-12 PCS score, there was improvement for both cases (+10.9[SD10.4]; p<0.001) and controls (+15.7[SD11.0]; p<0.001). SF-12 MCS scores did not show a significant change from pre-arthroplasty to post-arthroplasty for either cases or controls. There was no significant difference between cases and controls for improvement from pre-arthroplasty to 12 months post-arthroplasty in HHS, SF-12 PCS score or SF-12 MCS scores (p=0.08, p=0.09 and p=0.12 respectively).

Univariate analysis showed that PJI was not a significant risk factor for adverse outcomes according to HHS (OR, 2.07 [95% CI 0.74-5.78]; p=0.16), SF-12 PCS (OR, 2.06 [95% CI 0.71-5.97]; p=0.19) or SF-12 MCS (OR, 0.53 [95%CI 0.14-1.99]; p=0.34). Results from multivariate logistic regression analysis can be seen in Table 4. From multivariate analysis, predictors of an adverse HHS outcome were higher BMI and age-adjusted Charlson co-morbidity index. Predictors of an adverse SF-12 PCS outcome were being female and a higher age-adjusted Charlson co-morbidity index. Higher pre-operative PCS and MCS scores were protective against adverse PCS and MCS outcomes respectively.

Complications

The majority of complications were medical and were made up of drug reactions, delerium, venous thromboembolism, cardiac arrhythmias and pneumonia. Cases

(6/19[32%]) were more likely than controls (9/76[12%]) to have a medical complication (p=0.04) but not when drug reactions were excluded (2/19[11%] vs 7/69[11%]; p=1.0). Surgical complications were similar between cases and controls (1/19[5%] vs 4/76[5%]; p=1.0) and were due to transient sciatic nerve palsy, fractured acetabulum, fractured greater trochanter and dislocation.

Discussion

The treatment of PJI with debridement, retention of prosthesis and biofilm-active antibiotics in our cohort was successful, with only 2 of 19 patients showing evidence of infection relapse over a median duration of follow-up of 24 months and an 88% survival free from treatment failure at 2 years. Early studies examining outcomes of PJI treatment with prosthesis retention had poor outcomes, with success rates of <70% [14]. More recent studies, where patients mainly with early PJI were included and where antibiotic treatment was with biofilm-active antibiotic combinations, especially rifampicin, have reported good outcomes similar to our study. These results are comparable to treatment with 1 or 2-stage prosthesis exchange, approaches traditionally regarded as superior to prosthesis retention in successfully eradicating PJI but which involve more extensive surgery [14]. Given that results for successful infection eradication for these different management approaches appear to be similar in appropriately selected patients, it is important to consider other issues that may influence treatment decisions such as functional outcomes, QOL and treatment-associated

complications, which have been infrequently reported previously in studies examining PJI management.

Despite having a PJI, cases in this study treated with debridement and retention of prosthesis had a significant improvement from pre-arthroplasty to 12-months post-arthroplasty in functional outcome according to HHS (+35.9; p<0.001). This improvement was not significantly different to that seen in control patients with no PJI and is similar to results of +33 and +39.1 reported in 2 previous studies examining treatment of PJI with mainly prosthesis exchange [15, 16]. Other studies have reported mean post-treatment HHS after treatment of PJI with prosthesis exchange at between 69 and 84[17] and after debridement and prosthesis retention at 79[9]. The mean post-arthroplasty HHS of 68.5 seen in cases in this study is at the lower end of these scores, however adequate comparison is difficult as these studies do not report pre-arthroplasty HHS and administered the score much later than in this study.

There was improvement for cases in this study in QOL outcomes according to SF-12 PCS score from pre-arthroplasty to 12-months post-arthroplasty of +10.9(p<0.001) and this was not significantly different to controls. The 12-month mean SF-12 PCS score of 33.7 for cases is similar to that reported in 1 previous study examining outcomes after treatment with 2 stage-exchange[18].

There was no improvement between pre-arthroplasty and post-arthroplasty SF-12 MCS score for either cases or controls and no differences between the groups, however pre-operative MCS scores were already in the high range, minimising potential for further improvement. Smaller gains in the SF-12 MCS score have been

seen previously post-arthroplasty [12] suggesting that mental health is not significantly impacted by hip arthroplasty regardless of the presence of PJI.

In this study, factors such as age and comorbidities (Charlson comorbidity index), higher BMI and female sex were predictors of poor functional and QOL outcomes whereas the presence of PJI treated with debridement and retention was not a predictor. Similar factors have been demonstrated in previous studies to predict worse functional and QOL outcomes[19, 20].

Medical complications occurred more commonly in patients with PJI compared with controls in this study but these were mainly drug reactions to intravenous or oral antibiotics to which controls were obviously not exposed. Rates of other medical or surgical complications occurred at similar rates in cases and controls despite the extra surgical and medical treatment required for PJI cases, suggesting that, aside from the risk of drug reaction, this treatment approach is well tolerated. Very few previous studies examining PJI outcomes report treatment complication rates however 1 study reported a high rate of 58 complications occurring in 68 patients treated with prosthesis exchange [17].

It is important to note that the results of the present study cannot be generalised to all prosthetic joint infections treated with debridement and retention. Each case patient in the study exhibited features that have been shown previously to be associated with good treatment success rates. In particular, they were all early PJI, with a short joint age (14 days) and short duration of symptoms (4 days) until initial debridement [2]. These factors may also be associated with better function and QOL and less complications, however this association is yet to be studied.

The retrospective design of this study is an obvious limitation given the risk of incomplete or variably recorded information, especially the occurrence of complications. However the prospective collection of data by a single researcher and using standard definitions minimised biases arising from this. The relatively small sample size in this study means it was not powered to detect smaller differences in outcomes or infrequently occurring risk factors for poor outcomes. This study suggests that patients treated for early PJI with debridement, prosthesis retention and biofilm-active antibiotics results in not only successful treatment of infection but also significant improvements in functional and QOL outcomes, which are similar to patients without PJI. Treatment is well tolerated however is associated with the risk of drug reaction. Given the good results in successful PJI treatment obtained from both debridement and retention as well as prosthesis exchange, future studies are required directly comparing these approaches and should include functional outcomes, QOL outcomes and complication rates to better inform management decisions.

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Table 1. Demographic and co-morbidity data for cases (PJI) and controls (no PJI)

Variable	Cases (n=19)	Control (n=76)	p value
Mean age (years)(SD)	68.5(10.1)	68.5(9.9)	1.0
Female gender (n=59)	10(53%)	49(64%)	0.34
Aetiology			0.06
Osteoarthritis	14(74%)	69(91%)	
Rheumatoid arthritis	2(11%)	1(1%)	
Avascular necrosis	3(16%)	4(5%)	
Congenital hip dysplasia	0	2(3%)	
Mean BMI (kg/m^2)(SD)	33.3(6.9)	30.5(5.7)	0.06
Diabetes	4(21%)	9(12%)	0.29
Hypertension	12(63%)	38(50%)	0.30
Cardiovascular disease	2(11%)	8(11%)	1.0
Obstructive airway disease	2(11%)	9(12%)	1.0
Malignancy	4(21%)	8(11%)	0.25
Current smoker	2(11%)	6(8%)	0.66
Median age-adjusted Charlson co-morbidity index (IQR)	3(0-4)	0(0-3)	0.18

Table 2. Organisms isolated, antibiotics used and infection treatment outcome for PJI cases

Patient	Organisms isolated	Oral antibiotics	Treatment failure
1	CNS, *P. mirabilis*	R,F, C	No
2	CNS, *E. faecalis, E.coli*	R, F, Amox/clav	No
3	MSSA, *E. coli*	R, F, C	No
4	CNS	R, F	No
5	CNS, *E. faecalis*	Amox	No
6	CNS	R, F	No
7	Corynebacterium	R, F, Amox	No
8	MSSA, *E. coli*	R, C	No
9	*E. faecalis, E. coli, Proteus sp*	Amox, C	No
10	MSSA, CNS, *E. faecalis*	R, F, pristinamycin	No
11	MRSA	R, F	No
12	Culture negative	R, F, C	No
13	MRSA, *P. mirabilis, Morganella sp*	R, F, C	No
14	CNS x 2	R, F	Yes
15	MSSA	R, F	No
16	MRSA, CNS, *E. faecalis, E. coli*	R, F, C	Yes
17	MSSA	R, F	No
18	MSSA, CNS, *E. faecalis*	R, F, Amox	No
19	CNS	R, prinstinamycin	No

CNS, coagulase-negative staphylococcus; P.mirabilis, *Proteus mirabilis*; *E.coli, Escherichia coli;* MSSA, methicillin-sensitive *Staphylococcus aureus*; *E.faecalis, Enterococcus faecalis;* MRSA, methicillin-resistant *Staphylococcus aureus*; R, rifampicin; F, fusidic acid; C, ciprofloxacin; Amox, amoxicillin; clav, clavulanic acid.

Table 3. Functional and QOL scores for cases (PJI) and controls (no PJI)[a]

Score	Cases	Controls	p value[b]
HHS			
Pre-arthroplasty[c]	32.6(11.1)	32.4(10.9)	0.99
12 months post	68.5(20.7)	77.0(18.0)	0.08
Change	+35.9(20.1)	+44.6(18.7)	0.08
p value[d]	<0.001	<0.001	
SF-12 PCS			
Pre-arthoplasty	22.8(7.2)	24.0(6.5)	0.48
12 months post	33.7(11.6)	39.7(11.7)	0.05
Change	+10.9(10.4)	+15.7(11.0)	0.09
p value[d]	<0.001	<0.001	
SF-12 MCS			
Pre-arthoplasty	42.6(13.2)	46.9(14.6)	0.26
12 months post	50.8(9.7)	49.0(12.2)	0.56
Change	+8.2(17.8)	+2.1(13.9)	0.12
p value[d]	0.06	0.18	

Statistically significant p-value (≤0.05)
[a]Values are median(SD)
[b]Cases vs controls
[c]Along with patient age, pre-arthroplasty HHS was used to match cases and controls.
[d]Pre-arthroplasty vs 12 months post-arthroplasty

Table 4. Multivariate models for factors associated with adverse functional (HHS<70;poor result) and QOL (SF-12 PCS and MCS<40;moderate-severe disability) outcomes.

	Variable	OR(95% CI)	p value
Total HHS<70 (n=32)	Age adjusted Charlson co-morbidity index	1.36(1.09-1.69)	0.006
	Female gender	2.47(0.88-6.97)	0.09
	BMI	1.08(1.00-1.17)	0.05
SF-12 PCS<40 (n=52)	Pre-operative SF-12 PCS	0.83(0.74-0.94)	0.002
	Female gender	3.66(1.29-10.39)	0.02
	Age adjusted Charlson co-morbidity index	1.35(1.06-1.72)	0.02
SF-12 MCS<40 (n=23)	Pre-operative SF-12 MCS	0.96(0.93-0.99)	0.01