CHAPTER

9

Revisions for culture-negative total knee arthroplasties, a case-control clinical evaluation of functional and patient reported outcome of two-stage revision versus one-stage revision

(submitted)

Ewout S. Veltman, MD[1,2]
Dirk Jan F. Moojen, MD PhD[1]
Rudolf W. Poolman, MD PhD[1,2]

[1]Department of orthopaedic and trauma surgery, OLVG, Amsterdam, the Netherlands
[2]Department of orthopaedic surgery, Leiden University Medical Center, Leiden, the Netherlands

ABSTRACT

Background Diagnosis of periprosthetic joint infections can be troublesome due to the low sensitivity of diagnostic tools. In case of infection a two-stage revision of a knee prosthesis is merited, while in aseptic cases one-stage revision provides a less strenuous treatment option. The differences in outcome between two-stage and one-stage surgery for aseptic cases have only scarcely been described.

Methods We selected all patients who underwent two-stage revision surgery, but that did not meet the infection criteria in retrospect. These patients were compared to a matched cohort of patients who underwent one-stage revision. Patients were matched using patient characteristics and reason for revision. Patient reported outcome measures (PROMs), knee function and complications of treatment were the outcomes.

Results We included twenty-three patients in the two-stage group and matched these to patients in the one-stage group. At final follow-up after mean thirty-eight months patients in the one-stage group achieved significantly better scores on the KOOS pain and symptom subscales, and slightly improved mean range of motion. Three patients in the two-stage group acquired an infection in between stages.

Discussion In the absence of a positive preoperative work-up for infection, orthopaedic surgeons should adhere strictly to the infection criteria when determining treatment strategies for patients they clinically suspect of infection, as two-stage revision surgery seems to lead to moderately impaired outcomes and increased risk of complications compared to one-stage revision in non-infected patients.

Keywords: two-stage revision; one-stage revision; knee arthroplasty; patient reported outcome.

INTRODUCTION

About one in every eight patients reports unsatisfactory results after total knee arthroplasty.[1,2] Aseptic loosening, prosthetic joint infection (PJI), malalignment, overstuffing, arthrofibrosis, fracture or fissure, and malrotation of prosthetic components are some of the many factors recognized as causes for persisting complaints after primary total knee arthroplasty.[1,2] The optimal type of treatment varies markedly for the different causes of persisting pain, therefore the importance of having the correct diagnosis before the initiation of treatment is eminent.

The Musculoskeletal Infection Society (MSIS), the Infectious Diseases Society of America (IDSA), the European Bone and Joint Infection Society (EBJIS) and the International Consensus Meeting have proposed criteria which can be used to qualify a patient as suspected for PJI or not.[4-6] Positive cultures of periarticular fluid or tissue, and the presence of a sinus tract around the prosthesis are considered to be major criteria and pathognomonic for PJI.[7] The presence of three minor criteria would also confirm the diagnosis of infection. Minor criteria are elevated serum CRP and ESR, elevated synovial white blood cell count, elevated polymorphonuclear neutrophil percentage or positive change on the leukocyte esterase test strip or alfa-defensin, positive histological analysis of periprosthetic tissue and a single positive culture.[7] Thus cornerstone of infection diagnosis, in absence of a sinus tract, remains a positive synovial fluid culture.[4] However, even with prolonged incubation of cultures a vast part of cultures remain negative.

The sensitivity of synovial fluid cultures for the detection of a periprosthetic joint infection (PJI) is low, making it impossible to definitely exclude infection as a cause of pain or loosening after primary knee arthroplasty only based on a negative culture result.[8,9] The percentage of culture-negative infection cases in published cohort studies is reported up to 22% of included cases, which is exemplary for this diagnostic dilemma.[10] Missing the diagnosis of infection may lead to under-treatment and subsequent worse outcome for the patient.[11] That is why many authors advocate treating patients suspected of infection but with negative cultures as aggressively as their culture-positive counterparts.[10,12-14] The diagnostic insecurities frequently lead to doubt about the optimal type of treatment in patients that preoperatively do not fully meet the infection criteria, for example patients with early postoperative loosening or with peroperative indistinct joint fluid, and can lead to subsequent two-stage treatment of non-infected patients. Probably, many patients are subjected to more rigorous treatment methods than would have been required, because of this diagnostic dilemma.

On a daily basis, orthopaedic surgeons who perform revision knee arthroplasties have to make decisions balancing on the delicate equilibrium between optimal treatment in case of infection versus less invasive treatment in case of a non-infected patient. As many orthopaedic surgeons are reluctant to expose their patients to the risk of under-treatment of infection, patients may be subjected to over-treatment by performing a two-stage revision where a one-stage revision would have been sufficient.

The aim of this matched-pair analysis is to determine whether patients, who retrospectively did not meet the infection criteria, achieve different patient reported outcome, functional outcome and complications after two-stage revision compared to patients with aseptic causes who received a one-stage revision. We hypothesize that patients who are treated with a two-stage revision, achieve worse patient reported and functional outcome compared to patients treated with a one-stage revision.

METHODS

We used the STROBE cohort checklist when writing our report.[15] This clinical evaluation study was approved by the local medical ethics committee, with number 15.080. Sample size calculation (with expected mean improvement of PROMS of 10% for the one-stage group, enrollment 1:1, alpha of 0.05 and 80% power) showed that at least 16 patients per group should be included.

After approval, we retrospectively reviewed the records of all patients who had two-stage revision knee arthroplasty between 2004 and 2016 and compared these to the infection criteria as postulated by Osmon and colleagues and Parvizi and colleagues in 2014.[4,6] All patients were assessed according to these criteria and cultures taken preoperatively and at first-stage surgery were evaluated. The reason for revision in the two-stage group was re-classified using chart data from the preoperative outpatient clinic evaluation (table 1). We then selected control cases from a cohort of patients treated with one-stage revision of a knee prosthesis for aseptic reasons, and matched the groups on patient characteristics (age, gender, BMI, comorbidity, ASA classification score, smoking status) and reason for revision. These patients were included in the one-stage (OS) group.

For both groups, during first-stage surgery we removed the infected prosthesis including all bone cement. Multiple tissue samples (at least four) were taken for culture, after which we administered cefuroxime antibiotic prophylaxis. After meticulous debridement, we implanted an antibiotic-loaded interval spacer with gentamicin

and vancomycin in the TS group and a (revision) knee prosthesis in the OS group. Postoperatively patients in the TS group were treated with cefuroxime until the definite culture results of first-stage surgery were available after two weeks. Patients in the OS group were prophylactically treated with cefuroxime for one to five days.

We retrieved general patient characteristics, complications during treatment, functional results and final outcome from patients' records. Patients were contacted to complete the patient reported outcome measures. At final follow-up, the Knee Osteoarthritis Outcome Score (KOOS) (range of scores 0-100, with 100 as the optimal score) with its subscores for pain, symptoms, activities of daily living (ADL), sports and quality of life (QoL), and the EQ-5D questionnaire (range of scores -.500 to 1.00, with 1.00 as the optimal score) and the EQ-5D QoL thermometer (range of scores 0-100, with 100 as the optimal score) were used to assess patient reported outcome.[12,13]

Primary outcomes were infection eradication and patient related outcome scores after revision surgery. Secondary outcomes were functional outcome and complications reported during the spacer period and at final follow-up. Patients were analyzed for the type of revision procedure they were treated with. Descriptive statistics, mean and range are used to represent the demographics of the patients. For numerical data t-test was used and for categorical data Chi-squared tests was used to assess the level of significance for differences between the groups, a p-value <0,05 was considered to be statistically significant. Calculations and statistical analyses were performed using Excel and SPSS software.

RESULTS

We identified twenty-three patients that were treated with a two-stage revision arthroplasty of the knee between 2004 and 2016, and who did not meet the PJI criteria preoperatively and had negative preoperative joint aspirate and negative peroperative tissue cultures at first stage. These patients were included in the two-stage (TS) group. In these patients suspicion of infection was mainly present due to early postoperative loosening of the prosthesis, persistent pain or repetitive swelling of the joint. The reason for revision was retrospectively re-classified using chart data from the preoperative outpatient clinic evaluation (table 1). We then matched these patients to twenty-three patients treated with one-stage revision of a knee prosthesis for aseptic reasons. These patients were included in the one-stage (OS) group. General patient characteristics, infection characteristics and reasons for revision are listed in table 1. There were no statistically significant differences between the groups.

Two-stage vs. One-stage

Peroperative cultures of first stage surgery were negative in all 46 patients (table 1). The complications, range of motion at follow-up, KOOS and EQ-5D scores, and statistical analysis of the outcomes are displayed in table 2.

Table 1: Patient characteristics, infection characteristics and reason for revision

	Two-stage group	One-stage group	p
Patient characteristics			
Number of patients	23	23	N.S.
Age (range)	66 (58-76)	68 (54-78)	N.S.
Gender female	16	18	N.S.
BMI (range)	28 (20-35)	30 (22-42)	N.S.
BMI > 30	8	9	N.S.
Diabetes	3	3	N.S.
Active smoker	5	6	N.S.
ASA 1/2/3	5 / 14 / 4	4 / 14 / 5	N.S.
Preoperative flexion (range)	103 (45-140)	100 (80-130)	N.S.
Preoperative extension (range)	-4 (-25 – 5)	4 (-5 – 35)	N.S.
Months from primary surgery (range)	33 (12-96)	48 (12-132)	N.S.
Months follow-up (range)	46 (12-120)	37 (12-62)	N.S.
Infection characteristics			
Soft tissue involvement	0	0	N.S.
Mean preoperative CRP (range)	6 (1-26)	4 (1-28)	N.S.
Mean preoperative Leukocytes (range)	8 (5-13)	7.4 (4-13)	N.S.
Preoperative culture neg/pos	23/0	23/0	N.S.
Peroperative cultures neg/pos	23/0	23/0	N.S.
Reason for revision			
Aseptic loosening	11	11	N.S.
Persisting pain/restricted ROM	10	10	N.S.
Component malrotation	2	2	N.S.

N.S. = Not significant. BMI = Body mass index. ASA = American Society of Anesthesiologists score.

The spacer interval in the TS group was a mean five weeks (range 2-8). Three patients in this group had (two or more) positive cultures at second-stage reimplantation, with a coagulase-negative Staphylococcus in two cases and a Streptococcus species in the latter case. All three infections were successfully treated with 3 months of antibiotics.

All other patients had negative cultures at second-stage surgery. In the OS group there were no infections.

Table 2: Follow-up results: score (range)

	Two-stage group	One-stage group	p
Complications			
Persisting pain	9	10	N.S.
Arthrofibrosis	3	0	N.S.
Infection	3	0	N.S.
ROM			
Flexion	102 (70-125)	108 (90-140)	N.S.
Extension	-1 (-10 - 0)	-1 (-10 – 5)	N.S.
KOOS			
Pain	55 (8-86)	68 (33-92)	0.03
Symptom	62 (32-86)	73 (39-93)	<0.01
ADL	53 (9-85)	62 (22-100)	N.S.
Sport	21 (0-69)	28 (0-70)	N.S.
QoL	40 (0-75)	50 (6-88)	N.S.
EQ-5D			
Score	0.540 (-0.259 - 1)	0.534 (-0.128 - 1)	N.S.
QoL	63 (40-80)	69 (40-80)	N.S.

ROM = range of motion. ADL = activities of daily life. QoL = quality of life.

The spacer interval in the TS group was a mean five weeks (range 2-8). Three patients in this group had (two or more) positive cultures at second-stage reimplantation, with a coagulase-negative Staphylococcus in two cases and a Streptococcus species in the latter case. All three infections were successfully treated with 3 months of antibiotics. All other patients had negative cultures at second-stage surgery. In the OS group there were no infections.

The number of patients with persistent pain was comparable in both groups. At final follow-up one patient in the TS group had an above-the-knee amputation because of persistent pain. There was no sign of infection at any stage before amputation. This patient did complete the EQ-5D, but logically not the KOOS. Three additional patients

underwent manipulation under anesthesia due to stiffness of the knee. No patients' knees were manipulated under anesthesia in the OS group.

The knee flexion was slightly, but not significantly, better in the OS group with a mean 108 (range 90-140) versus 102 (range 70-125) degrees respectively (p>0,05).

For the patient reported outcomes, one-stage patients scored significantly better on the Pain and Symptom subscores of the KOOS (table 2). On all other KOOS subscores and the EQ-5D scores the one-stage patients had better scores as well, but not significantly.

DISCUSSION

Our retrospective clinical evaluation shows that patients in the OS group achieved slightly more improvement in range of motion and significantly better scores for pain and symptoms, without reaching statistical significance for the other subscores of the KOOS and EQ-5D.

Three patients on the TS group had positive cultures at second-stage surgery, while cultures at first-stage surgery were negative. Probably, the causative pathogens were introduced perioperatively during first-stage surgery. All three patients were treated with antibiotics for three months, no further operative procedures were performed to treat the infection. We found no infectious complications in the OS group.

Persistent pain at follow-up was present in a comparable number of patients in both groups. Pain was the reason for revision in seven out of the nineteen patients with persisting pain postoperatively (four in the TS group and three in the OS group). Pain as reason for revision did not predict persisting pain postoperatively in this study.

Several studies have been performed comparing patients with culture-negative and culture-positive PJI. Li and colleagues have compared a group of culture negative patients treated with two-stage revision surgery to two groups of patients with positive cultures that were treated with one- or two-stage revision surgery.[12] They found similar outcomes at follow-up and, surprisingly, a similar chance of reinfection for both the infected and the non-infected patients. Patient reported outcome was not reported. Wang and colleagues, Santoso and colleagues and Reisener and colleagues all report comparable results of two-stage revision surgery for culture-negative and culture-positive patients.[13,14,17] Furthermore, Konrads and colleagues report comparable outcome in their group of patients treated with one-stage revision for aseptic reasons

compared to patients treated with two-stage revision surgery for PJI.[18] A group of patients that retrospectively did not meet the infection criteria and that was treated with two-stage revision surgery, has not been described before.

This study has several limitations. Selection bias can exist because of the retrospective design of this study. The number of patients included in this study is small, which is caused by the scarcity of two-stage revisions performed in patients with a low suspicion of infection in this single center study. PROM results are only available at follow-up, so a comparison of the preoperative PROM results is not possible, this may lead to bias if one group actually had better preoperative scores. Since our clinical evaluation lacks an experimental design we cannot draw causal conclusions.

For future studies, authors should aim at combining groups of patients from multiple centers to achieve a greater sample size. Results of such multicenter studies could greatly improve the power of studies and our understanding of the optimal treatment for patient with suspected periprosthetic joint infection.

To summarize, this study suggests that aseptic patients undergoing revision surgery seem to have a greater risk of poor outcome when treated with a two-stage procedure. Next to this, the extra procedure in case of two-stage surgery imposes a burden to the patient, hospital resources and healthcare system expenses. Obtaining the correct preoperative diagnosis is therefore essential for the patient, their treating orthopaedic surgeon and the healthcare system in general. Recently, the infection criteria have been adjusted and validated to improve the specificity and sensitivity. It has yet to be studied whether these findings are reproducible in larger sample sizes using experimental study designs.[19] Despite the urge not to miss any infections, orthopaedic surgeons should be wary to overtreat their patients as this may lead to unnecessary costs for the healthcare system and worse outcome for their patients.

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