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REVIEW ARTICLE

Two-stage Revision for Periprosthetic Hip and Knee Joint Infections

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Abstract:

Background:

Periprosthetic joint infection (PJI) continues to be one of the leading causes of failure following hip and knee surgery. The diagnostic workflow of PJI includes detailed clinical examination, serum markers, imaging and aspiration/biopsy of the affected joint. The goals of treatment are eradication of the infection, alleviation of pain, and restoration of joint function. Surgical management of PJI consists of debridement, antibiotics and implant retention (DAIR) and single or two-stage revision procedures. Two-stage revision remains the gold standard for treatment of PJIs. We aim to discuss the two stage procedure in this article and report the outcomes.

Methods:

The first stage of the two stages consists of removal of all components and associated cement with aggressive debridement and placement of an antibiotic-loaded cement spacer. Patients are then treated with variable periods of parenteral antibiotics, followed by an antibiotic free period to help ensure the infection has been eradicated. If the clinical evaluation and serum inflammatory markers suggest infection control, then the second stage can be undertaken and this involves removal of the cement spacer, repeat debridement, and placement of a new prosthesis.

Results:

Common themes around the two-stage revision procedure include timing of the second stage, antibiotics used in the interim period, length of the interim period before consideration of reimplantation and close liaising with microbiologists.

Conclusion:

Successful eradication of infection and good functional outcome using the two stage procedure is dependent on a multidisciplinary approach and having a standard reproducible strategy.

Keywords: Infection, Hip, Knee, Prosthetic joint, Two-stage revision.

INTRODUCTION

Prosthetic joint infection (PJI) remains one of the most dreadful complications following total joint arthroplasty. Late PJI is reported in approximately 0.3%-1.7% of all total hip arthroplasties (THAs) and 0.8%-1.9% of all total knee arthroplasties (TKAs) [1 - 4], and is one of the leading causes of revision surgery. The diagnosis of infection can be challenging because no investigation is 100% sensitive and specific [5]. Therefore, a combination of clinical assessment, serologic tests, imaging, as well as aspirates and biopsies, has been used to confirm the diagnosis [6].

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More often than not, management of PJI requires multiple surgical interventions and prolonged courses of antimicrobial therapy [7 - 10]. Surgical options for treatment of PJIs include debridement, antibiotics and implant retention (DAIR), single or two-stage revision surgery, and salvage procedures (*e.g.*, arthrodesis or amputation) [11]. The goals of treatment include both eradication of the infection and reestablishment of a pain-free and well functioning joint. Two-stage revision is generally considered to be the gold standard procedure [12 - 15]. This involves removal of implants and the use of antibiotic loaded cement spacers for an interval period with intravenous antimicrobial therapy and the use of antibiotic loaded cement for prosthesis fixation at the time of reimplantation. A two-staged revision strategy has seen infection-free survival rates of 80% to 100% [16 - 30]. Two-stage revision ensures adequate delivery of antibiotics (both locally and systemically) and the opportunity for a second debridement if needed. Two-stage revision has several controversial aspects though, including the timing of the second stage procedure, the ideal duration of antibiotic dosage in between stages, the use of antibiotic-loaded cement at the second stage, the role of allograft bone grafting and the use of uncemented components [6]. Many factors like previous surgeries, co-morbidities, bone stock, soft tissue integrity, and organism virulence and resistance profile can also influence the outcome of two-stage revisions.

We aim to discuss the two stage procedure in this article and reported outcomes.

Indications

Indications for two over a single stage revision procedure in management of PJI include:

1. Patients with systemic manifestations of infection (sepsis);
2. Obvious clinical signs of infection but no organism has been identified;
3. Preoperative cultures identifying difficult to treat and antibiotic-resistant organisms;
4. Presence of a sinus tract;
5. Inadequate or non-viable soft tissue coverage.

Preoperative Workup

It is our routine practice to perform aspiration of the affected joint before surgery to identify the causative organism [6]. In cases where the infecting organism and its antibiotic sensitivity profile are identified pre-operatively, the antibiotics are adjusted accordingly. In all other cases with no identified growth, broad spectrum antibiotics such as vancomycin and an aminoglycoside are added to the cement mixture as they cover most organisms [6, 20].

Aspiration is ideally performed under strict aseptic conditions after having discontinued all antibiotics for duration of at least 4 weeks. Samples should be placed in aerobic/anaerobic blood culture bottles as well as universal containers. In cases where infection is suspected, arthroscopic biopsy is carried out with a minimum of six samples taken from the prosthetic surfaces and synovium [6].

Sensitivity of pre-operative aspiration and/or tissue biopsy in diagnosing infected TKA has been reported as 12% -100% [31 - 35]. Meermans *et al.* [36] performed a prospective study of 120 patients who underwent aspiration and biopsy for suspected joint infection (64 with THAs and 56 with TKAs) . The sensitivity reported was 83% for aspiration, 79% for biopsy, and 90% for the combination of both techniques. The specificity was 100% for aspiration and biopsy and the combination. The overall accuracy was 84%, 81%, and 90%, respectively [36]. They inferred that routine aspiration must be followed by a biopsy in the work up of septic joints.

FIRST STAGE

The original incision is utilised to expose the joint. Radical debridement that entitles removal of all cement, membranes and potentially infected and devitalised tissue is performed. Intramedullary reaming of the canal followed with copious use of saline pulse lavage is recommended. Well fixed implants are carefully extracted so as to avoid iatrogenic damage to the bone and neighbouring viable soft tissues. There should be a low threshold to perform an osteotomy to remove well fixed implants or cement mantle. Studies have confirmed that extended trochanteric osteotomies in the hip heal reliably even in the setting of infection [37, 38].

Antibiotics are withheld until all microbiological samples have been taken. A minimum of 3 and ideally 5 or 6 periprosthetic intraoperative tissue samples or the explanted prosthesis itself should be sent for aerobic and anaerobic cultures to maximize the chance of obtaining a definitive diagnosis [6]. Using a minimum of two positive samples, the sensitivity has been reported to be 94%, specificity 97%, positive predictive value 77% and negative predictive value

99% [39]. At completion of debridement, all drapes, gowns, gloves and surgical instruments are changed to maintain sterility.

Spacers

Cement spacers can be classified as articulating (dynamic) or nonarticulating (static), pre-fabricated or custom-made. The use of a static spacer block makes exposure at reimplantation difficult due to quadriceps contracture. There is also a risk of additional bone loss attributable to migration of the spacer block [18, 24, 40].

Articulating spacers avoid prolonged immobilization of the joint and prevents soft tissue contractures by permitting range of movement and partial weight bearing [18, 19, 40, 41]. Improved patient mobility preserves the soft tissue envelope that is crucial during the reimplantation procedure.

The spacer also helps maintain the native tension of the collaterals. This serves to preserve and identify planes better during subsequent revision, avoiding further soft tissue damage and aiding recovery. After thorough debridement, an antibiotic-laden cement spacer is then implanted. Commonly used spacers are Prostheses of Antibiotic-Loaded Acrylic Cement (PROSTALAC) articulating spacers to which 3 g of vancomycin and 2 g of gentamicin per sachet of Palacos R cement (Schering Plough Ltd, Labo nv, Belgium) is added. The objective is to deliver a high concentration of local broad spectrum antibiotics against most common causative pathogens prior to culture results. The antibiotics are also adjusted when preoperative sensitivity pattern of the microorganisms is known. A five-day course of intravenous teicoplanin or vancomycin is also continued post-operatively, by which time microbiological sensitivities are available.

Biring *et al.* [42] in their study of 99 patients treated with PROSTALAC articulating hip spacers (DePuy, Warsaw, Indiana) have quoted long-term infection control rate of 89% at a mean follow up of 12 years (range 10-15 years). Gooding *et al.* [43] reported 98% infection control rate (113 of 115 infected TKRs) using the PROSTALAC knee spacers (DePuy, Warsaw, Indiana) at a minimum of 5 years follow up. Van Thiel *et al.* [41] retrospectively reviewed post-operative function and control of infection in 60 patients using an articulating antibiotic spacer made intra-operatively from prefabricated silicone moulds. Seven patients (12%) developed recurrent infection, and one spacer (femoral component) fractured but did not require specific treatment. No bone loss was identified between stages. The mean Knee Society score improved from 53 preoperatively to 79 at a mean follow-up of 35 months and the mean flexion improved from 90.6° to 101.3°. This study illustrated control of deep infection in 88% of patients while preserving knee motion [41]. Various studies [19, 44] have found a significant increase in knee society function scores in patients with dynamic spacers but no difference in pain scores. Brunnekreef *et al.* [45] reported better and faster recovery of knee function with the use of dynamic spacers resulting in shorter operation times. Garg *et al.* [46] suggested that static spacers not only reduce the range of motion of the knee joint but can also cause difficulty in exposure during second stage with the potential for additional bone loss due to scarring of the capsule and quadriceps muscle. Faschingbauer *et al.* [47] enlisted complications associated with using antibiotic loaded spacers in 138 patients. 27 patients (19.6%) developed complications including spacer fractures in 12 cases (8.7%), dislocation in 12 cases (8.7%), one periprosthetic femoral fracture (0.7%) with a spacer *in situ*, one dislocation with a simultaneous spacer fracture (0.7%), and one protrusion into the pelvis.

Interval Period

Intravenous (IV) antibiotic therapy for 4-6 weeks with subsequent cessation of antibiotics for 2-8 weeks prior to reimplantation is most commonly employed regimen and has resulted in overall good infection control rates [27, 48]. Best results are obtained in cases where the pathogen is not resistant and systemic antibiotics are administered simultaneously [2, 49]. Studies have suggested that prolonged time intervals result in suboptimal restoration of patient function and eradication of infection. However, in one study, there was no difference in functional outcomes between patients who underwent two-stage exchange procedure with more than 6 month interval between resection and reimplantation and those who had reimplantation within 6 months of resection [50].

At our institution, it is common practice to start a course of intravenous antibiotics, usually teicoplanin until the sensitivity pattern of the culture samples are known. The results are discussed in the multidisciplinary meeting, and the antibiotics are modified accordingly. Our patients receive antibiotics for at least six weeks following which the antibiotics are stopped for two weeks prior to the second stage to foresee the patient's response. We perform routine aspiration of the involved joint in all cases prior to revision surgery. Stopping the antibiotics provides another opportunity to grow any residual microorganisms at the time of reimplantation. The decision to proceed with prosthesis implantation is determined by clinical evaluation, resolution of blood markers and a negative joint aspirate. Any

suspicion of residual infection mandates redoing the first stage with debridement and placement of a new spacer.

A normal C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) alone do not guarantee eradication of infection, particularly with coagulase negative staphylococcal infections. Kusuma *et al.* [51] in a recent study suggested that synovial white cell count is the most accurate indicator of control of infection, and although the levels of inflammatory markers tend to fall with control of infection, they do not show a clear pattern.

SECOND STAGE

The second stage of revision hip and knee arthroplasty involves spacer removal, tissue sampling, debridement and reimplantation. Contraindications to reimplantation at the second stage include persistent infection or significant medical comorbidities. However the majority of patients usually proceed to reimplantation [52]. In the second stage procedure, the principles of operative technique are similar for both hip and knee revision arthroplasty. We use previous surgical scars to approach the joint [53]. Once the joint is explored, joint fluid samples are obtained for bacterial culture. It is of prime importance to remove the spacer and cement without losing native bone. The synovial membrane of the pseudosynovial cavity formed around the spacer is curetted and sampled for bacterial culture. We usually send at least five samples for bacterial culture and sensitivity. A thorough debridement to any necrotic tissue is undertaken. This is followed by copious irrigation with pulsed lavage to the bone and surrounding soft tissues. Debridement and irrigation reduces the burden of devitalised and infected tissues. It also removes any cement abrasion debris originating from the antibiotic spacer which is a potential cause of future third body wear. Bone allograft is then used to reconstruct bone defects if necessary followed by reimplantation of the appropriate prosthesis as per the pre-operative planning. Antibiotics are given for five days following the procedure till the results of bacteriology are available.

The goal in hip revision surgery is to achieve biological fixation with bony ingrowth whenever possible. Bone stock is restored with impaction grafting underneath a cementless cup in most of the acetabular revisions. Concerns have been raised in the past regarding the use of bone allograft in revision surgery following PJIs [54, 55]. However, recent studies have failed to show any significant difference in the re-infection rates following the use of allografts in revision surgery. Hence they have been safely used in cases that present with significant bone loss [56]. Technique involves mixing bone milling and bone chips of various sizes. Morselised allograft is then inserted, packed, and/or reverse reamed into any bony defects in order to create a hemisphere. We aim to obtain biological fixation of the acetabular component to the underlying viable host bone which requires intimate host bone contact and rigid implant stability. The implant of choice is mostly an uncemented, porous, coated acetabular components augmented by screw fixation in the majority of acetabular revisions [57]. The choice of the femoral component is dictated by the bone quality, bone stock and femoral canal deformity if any. This is particularly important in cases where bone loss or altered anatomy requires customized implants. Preferred implant is an uncemented, porous, coated femoral stems in the majority of hip revisions. Uncemented fixation of an intramedullary stem of standard proportions avoids the problems presented in a reinfected, distally cemented prosthesis.

Cemented knees have taken precedence over their uncemented counterpart in revision knee arthroplasty. This is attributed to earlier reports of loosening of cementless stems [58] and the potential biomechanical advantages [59]. Conlisk *et al.* [60] in an *in vitro* study examined the influence of stem fixation method on the pattern and level of relative motion at the bone-implant interface. They found that uncemented constructs have significantly higher level of relative motion compared to cemented implants. Uncemented stems when used in cases of severe bone loss may result in stress shielding of the surrounding bone. This consequently affects loading of any bone allograft used to deal with bone defects [61].

Interestingly though, recent studies have shown comparable clinical results between cemented and uncemented components in revision TKR. In a comparative study, Edwards *et al.* [62] demonstrated similar re-infection rates following cemented and uncemented revision of infected TKRs. Furthermore, they showed that the repeat revision rate for aseptic loosening were comparable between the two groups.

Outcomes of infection control after two stage revision procedures from various studies reported in the literature have been summarized in Tables 1 and 2.

Reimplantation Microbiology

The role of reimplantation cultures as well as intraoperative frozen section in the two-stage revision arthroplasty remains controversial. Banit *et al.* [63] prospectively compared the accuracy of intraoperative positive frozen section

(>10 polymorphonuclear leukocytes per high power field) with intraoperative cultures in 121 revision hip and knee arthroplasty. They found that frozen sections had 67% sensitivity and 93% specificity in detecting infection with 67% positive predictive value and 93% negative predictive value. Low sensitivity of frozen sections was similarly reported in other studies [39, 64]. This could be attributed to sampling errors, which emphasizes the importance of wide sampling [64]. Therefore, the reliability of frozen section as a diagnostic tool for infection in reimplantation procedures remains questionable.

Table 1. Summary of studies reporting on the results of two-stage revision hip arthroplasty.

Study	Year	Number of patients	Follow up (months)	Rate of infection control (%)
Wilson and Dorr	1989	15	>36	91
Hope <i>et al.</i>	1989	19	21	100
Nestor <i>et al.</i>	1994	34	47	82
Garvin <i>et al.</i>	1994	30	>24	95
Fehring <i>et al.</i>	1999	25	41	92
Haddad <i>et al.</i>	2000	50	68	92
Koo <i>et al.</i>	2001	22	44	95
Hoffman <i>et al.</i>	2005	27	76	94
Kraay <i>et al.</i>	2005	33	>24	92
Masri <i>et al.</i>	2007	29	>24	90
Fink <i>et al.</i>	2009	36	35	100
Oussedik <i>et al.</i>	2010	39	60	95
De Man <i>et al.</i>	2011	50	>24	92
Leung <i>et al.</i>	2011	38	58	79
Klouche <i>et al.</i>	2012	46	>24	98
Berend <i>et al.</i>	2013	186	53	83
Ibrahim <i>et al.</i>	2014	125	>60	96

Table 2. Summary of studies reporting on the results of two-stage revision knee arthroplasty.

Study	Year	Number of patients	Follow up (months)	Rate of infection control (%)
Goldman <i>et al.</i>	1996	64	90	91
Hirakawa <i>et al.</i>	1998	55	62	75
Haddad <i>et al.</i>	2000	45	48	91
Fehring <i>et al.</i>	2000	55	>24	93
Mont <i>et al.</i>	2000	69	>36	91
Lonner <i>et al.</i>	2001	53	56	83
Meek <i>et al.</i>	2004	54	41	96
Haleem <i>et al.</i>	2004	96	86	91
Hofman <i>et al.</i>	2005	50	73	88
Hart <i>et al.</i>	2006	48	49	88
Freeman <i>et al.</i>	2007	114	71	94
Westrich <i>et al.</i>	2010	75	52	91
Van Thiel <i>et al.</i>	2011	58	35	88
Gooding <i>et al.</i>	2011	115	>60	77
Mortazavi <i>et al.</i>	2011	117	45.6	72
Ferrari <i>et al.</i>	2011	50	>24	92
Mahmud <i>et al.</i>	2012	253	48	93
Pelt <i>et al.</i>	2014	58	38	66

Positive cultures have varied from 0% to 28% at reimplantation [29, 65 - 67]. Many a times it has been reported that the microbes cultured at reimplantation were different from those cultured at excision. Hart *et al.* [28] reviewed 48 patients who underwent two-stage revision TKAs. At the time of second-stage surgery, 11 patients (23%) had positive cultures and two of those developed recurrent infection. The cultured microbe was different in seven cases and rest four cases revealed persistent coagulase-negative *staphylococcus*. Out of the remaining 37 patients with negative cultures, four developed recurrent infection. Authors concluded that the possible reason for growth of different organisms during

the second stage could be due to sample contamination during the first surgery.

Puhto *et al.* [68] in their series of 107 cases reported that the reimplantation microbiology was available in 90.7% of cases, and the samples were positive in 5.2%. Only one of the 5 samples that were reported positive had the same organism isolated at the time of implant excision (*Candida albicans*) and the treatment failed in this case. The other four patients were treated as having an acute postoperative PJI with a short-course of antibiotics and prosthesis retention. Eighty percent of patients with positive reimplantation samples were cured of infection as compared to 96% with negative reimplantation samples.

Bejon *et al.* [65] in a series of 152 cases found that routine cultures sent at reimplantation were positive in 21 patients (14%). Reimplantation cultures were frequently more positive in knees than in hips (21% vs. 6%). The same organism was isolated at both excision and reimplantation in 4 cases and different in 10 cases. Moreover, seven cases reported positive reimplantation cultures following previous negative cultures. There was no evidence that positive reimplantation cultures were associated with worse outcome. Contrary to many studies that recommend second stage after a trial of antibiotic free period and testing, the authors suggested that reimplantation may be considered without an antibiotic-free period, with additional antibiotic prophylaxis before reimplantation. A limited antibiotic course may also be prescribed when reimplantation cultures are positive in the absence of clinical signs of ongoing infection [65].

There is sparse data on studies that compare patient reported outcome measures (PROMs) in single *versus* two-stage revision for infection. Baker *et al.* [69] compared patient outcome scores (Oxford knee scores, Euroqol-5D) of single *versus* two stage septic knee revisions in 195 patients. They found no differences in post-operative knee scores, general health perception or satisfaction between the study groups. Hence, the recommendation was that decision making should take into account other factors including infection control rates when comparing both groups.

CONCLUSION

The management of PJIs after hip and knee arthroplasty remains challenging. In delayed presentations, two-stage revision with an interval prosthesis using an articulating spacer has been associated with low recurrence of infection. Such spacers also facilitate restoration of good range of motion, mobility in the interim period and maintenance of soft tissues tension which makes subsequent revision easier and less complex.

CONFLICT OF INTEREST

Each author certifies that he or she, or a member of his or her immediate family, has no commercial interests that might pose a conflict of interest in connection with this work.

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