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Original Article

Can serum C-reactive protein determine the timing of reimplantation in two-stage revised arthroplasty for periprosthetic hip infection?

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ABSTRACT

Background: There are no definitive guides to determine the timing of reimplantation in two-stage revision total hip arthroplasties (THA) for periprosthetic joint infection (PJI). This study was to design to support a rational strategy of surgical treatment using serum C-reactive protein (CRP).

Methods: We analyzed a total of 75 hips for PJI in the process of performing two-stage and multiple-stage revision THAs. CRP level was retrospectively evaluated every week and transformed to log2 (CRP) using a logistic regression model. Prosthesis survival from recurrent infection was determined by Kaplan-Meier analysis, using implant removal as the endpoint. Receiver operating characteristic curves were calculated using each log2 (CRP) to assess predictions of recurrent infection.

Results: The 10-year survival rates were 85% (95% confidence interval, 76–95) and 100% for two-stage and multiple-stage revision THAs, respectively. Preoperatively, at 1, 2, 3, and 5 weeks, log2 (CRP) was not associated with recurrent infection. In failed two-stage revision THAs, log2 (CRP) at 3 weeks divided by that at 2 weeks showed a significant difference. Failure was associated with a ratio of >4.0 for the CRP level between 3 and 2 weeks.

Conclusion: In two-stage revision THA for PJI, patients with CRP elevation from 2 weeks to 3 weeks, especially 4-fold elevation, suggests the need for further debridement and postponement of second-staged reimplantation.

1. Introduction

In total hip arthroplasty (THA), the incidence of prosthetic joint infection (PJI) requiring revision surgery has seen a notable rise globally, and the management of PJI presents major challenges [1,2]. The two primary options involve treatment with or without implant removal. Without removal, the indications and outcomes remain controversial. Therefore, the treatment for PJI is generally revision THA with implant removal, either as a one-stage or a two-stage procedure. One-stage revision THA is often preferred in Europe, while in the rest of the world, two-stage revision THA is considered the gold standard treatment for PJI [3,4]. Advantages of one-stage revision THA include shorter hospitalization, shorter duration of antibiotic treatment, lower mortality, lower rate of complications, and lower overall healthcare costs [5,6]. Two-stage revision THA is generally considered safe and secure, but includes the disadvantages of a second operation, higher costs, longer treatment periods, and greater economic burden [7,8]. Additionally, in a planned two-stage revision THA, debridement must be repeated if the infection was not controlled at the initial stage of surgery. The resulting procedure is called “multiple-stage revision THA” [9]. However, no definitive guides are available to determine the timing of reimplantation, and it is difficult to decide whether THA should be performed in the second stage of surgery during two-stage revision [10–15].

Serum C-reactive protein (CRP) is inexpensive, readily available, and the most popular marker for detecting PJI. Elevated CRP level is more accurate than other serum parameters and is included in the diagnostic criteria from the Musculoskeletal Infection Society (MSIS) [16–19]. However, some studies have suggested that the normalization of CRP was not associated with infection-free survivorship, especially for infected total knee arthroplasty (TKA) [20–22]. Particularly, the determination of CRP levels after the initial stage of surgery in two-stage revision THA remains equivocal

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because antibiotic therapy and resected joint instability can affect the CRP level. In the present paper, we ask, "In two-stage revision THA for PJI, can CRP levels predict reimplantation failure?" The aim of this study was to determine the timing of reimplantation in two-stage revision THA using serum CRP. We hypothesized that further debridement and a switch to multiple-stage revision THA can be selected if the CRP level does not decrease sufficiently after initial debridement.

2. Patients and methods

2.1. Study design and patients

Between January 2006 and December 2020, surgeons at our hospital performed 119 consecutive revision THAs for PJI in 111 patients. These procedures involved one-stage revision THA in 40 hips, two-stage revision THA in 73 hips, and multiple-stage revision THA requiring ≥2 debridements in 6 hips. Multiple-stage revision THA was defined as any procedure that required further debridement in the second stage of two-stage revision THA, so that the prosthesis would have to be reimplanted at a third or subsequent stage of surgery [9]. In multiple-stage revision THA, all 6 hips were reimplanted in the third stage of surgery, with no further debridement required. We diagnosed PJI based on the MSIS criteria [18]. A case was considered "successful" if we found no signs of infection at the follow-up visit >24 months after the first revision, and as "failure" if the implant was removed as a result of recurrent infection. We followed a total of 75 hips that involved two-stage revision THAs, including multiple-stage revision THAs, for a mean of 5 years (range, 0.3–16 years). Patients were 19 men and 56 women. Mean age was 68 years (range, 32–86 years) at the time of surgery. One patient developed infection in both hips, 6 patients relapsed and required re-replacement of the prosthesis, and 4 patients were lost to follow-up (follow-up rate, 95%) (Fig. 1). This cohort study was approved by our institutional review board, and each patient provided informed consent for the inclusion of patient data in the published findings.

2.2. Surgical procedures

We generally performed two-stage revision THA in patients who did not meet our criteria for one-stage revision THA, with the final decision made intraoperatively by the surgeon [9,23]. We obtained pre-operative aspirate for each patient, determined individual bacterial sensitivities, and custom-mixed an antibiotic-loaded acrylic cement (ALAC) for each patient (Fig. 2). ALAC was prepared in accordance with the protocol by Jiranek et al. [24], using over 3.6 g of antibiotic per 40 g of cement in the first stage of two-stage or multiple-stage revision THA. We selected antibiotics for ALAC, based on the results for individual bacterial sensitivities from pre-operative aspiration. In Gram-positive or unknown bacterial infections, a combination of vancomycin 3.0g and amikacin 0.6g were generally used because of the high elution levels that such blended antibiotics can provide [25,26]. For reimplantation, we used 1.0–2.0 g of antibiotic per 40 g (ENDURANCE Bone Cement, DePuy International, Leeds, United Kingdom).

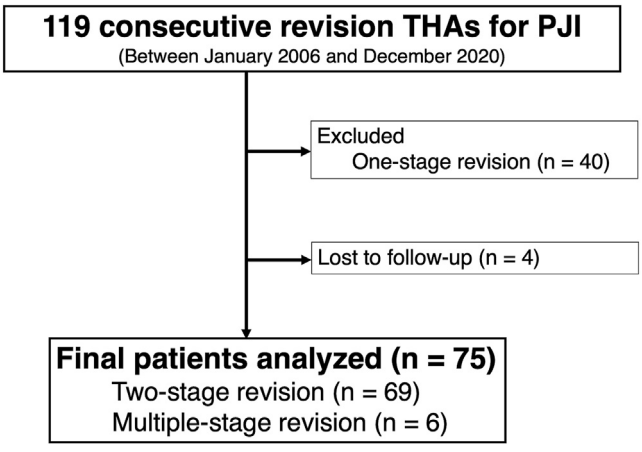

Fig. 1. Study flow chart. THA, total hip arthroplasty. PJI, periprosthetic joint infection.

PJI treatment requires thorough debridement and the use of sufficient local and systemic antibiotics [9]. We employed a transgluteal approach for debridement, with complete removal of all implant components, cement, granulation, and necrotic and infected tissues. Routine radiographs and computed tomography scans, along with radioisotopes if needed, were used to assess necrotic and infected tissues and ensure thorough debridement. Before initiating capsulotomy, we aspirated the hip joint and sent a sample for microbiological analysis. Periprosthetic tissue specimens were also submitted for microbiological and pathological testing. We then used hydrogen peroxide solution or povidone iodine to thoroughly flush the hip joint by pulse irrigation. Antibiotic-impregnated beads have shown characteristically higher elution and longer duration of antibiotic delivery than spacers, both *in vivo* and *in vitro*, due to the greater surface area of the beads [27,28]. For each two-stage or multiple-stage revision THA, we prepared a handmade rod and beads containing sufficient high-dose ALAC. After thorough debridement, we temporarily placed a handmade rod and beads including sufficient high-dose ALAC in the debrided area. We also provided appropriate intravenous systemic antibiotic therapy for 2 weeks after the surgery. Although we selected some antibiotics based on the results of individual bacterial sensitivities from pre-operative aspiration and intra-operative specimens, for Gram-positive or unknown bacteria we generally used both daptomycin and rifampicin [29]. After performing the initial debridement, we monitored the clinical signs and CRP levels for 6–8 weeks and then performed a second thorough debridement. If the infection had been successfully eliminated at that point, we performed THA using ALAC. If the infection was not yet fully controlled at this second stage, debridement was repeated (multiple-stage revision THA). ALAC antibiotic release was generally exhausted within 6–8 weeks [30], so whether implementing a two-stage or a multiple-stage revision THA, we continued debridement every 6–8 weeks until the revision was completed.

2.3. Follow-up protocol

During the waiting period for implantation, wheelchair use was permitted on the second postoperative day following the first surgical procedure. Full weight-bearing was not advised until the second postoperative day after implantation, and patients began walking on the 5th postoperative day. All patients received weekly follow-up for the first 2 months, then at 3, 6, and 9 months, and biannually thereafter. Two orthopaedic surgeons blinded to patient identities provided retrospective analysis. Microorganisms that had been isolated pre- and intraoperatively were identified from patient records, and changes over time in serum CRP levels (mg/L) were assessed.

2.4. Statistical analysis

Prosthesis survival was calculated from Kaplan-Meier analysis with 95% confidence intervals (CI), with the endpoint being the removal of implants due to recurrent infection. For the logistic

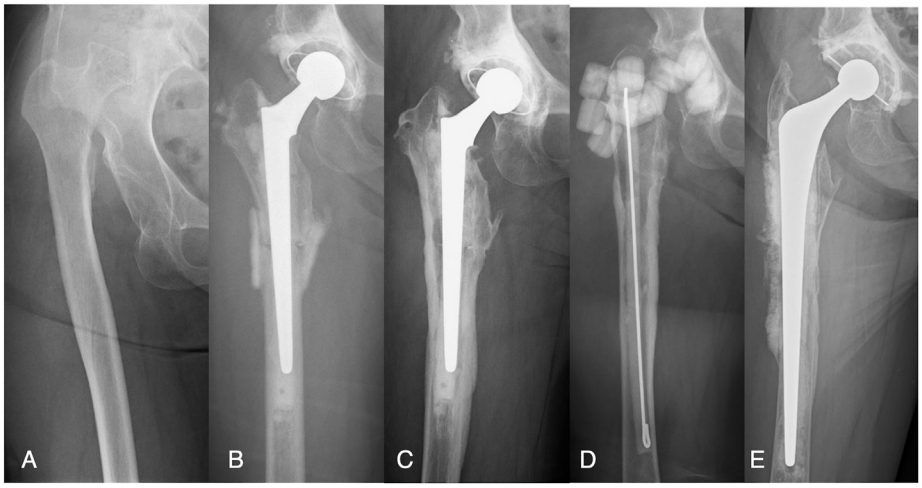

Fig. 2. Radiographs of a 65-year-old female who had undergone two-stage revision total hip arthroplasty (THA): (A) before primary THA, showing dysplasia classified as Crowe group IV, (B) primary THA with subtrochanteric shortening osteotomy, (C) five years after primary THA, showing implant loosening and subsidence, (D) antibiotic-loaded acrylic cement beads 7 weeks after the first-staged surgery, and (E) four years after revision THA using a cemented long stem, no recurrence.

regression model, we transformed CRP levels to log2 (CRP) because the values on the log scale often approximate the normal curve reasonably well, which could allow us to calculate more reliable odds ratio estimates. We used univariate logistic regression to model a linear relationship between the independent variable (X) and the probability of failure. When the expected probability of failure at a given log2 (CRP) is p, the regression coefficients represent the intercept (α) and slope (β) of this line

$$\log\left(\frac{p}{1-p}\right) = \alpha + \beta X$$

We calculated receiver operating characteristic (ROC) curves, using each log2 (CRP) to assess our performance in predicting failure. This enabled examination of the area under the curve (AUC). All data were analyzed using one-way analysis of variance with SAS version 9.2 (SAS Institute, Cary, NC). P value < 0.05 was considered significant.

3. Results

Two-stage revision THA was successful in 61 of the 69 hips, with a 10-year implant survival rate of 85% (95% CI, 76–95). There were no failures in multiple-stage revision THA (Table 1). For the 8 hips that failed two-stage revision THA, the mean duration from revised THA to implant re-removal because of recurrent infection was 1.9 years (range, 0.3–6.2 years). Among those 8 hips, re-revision THA was successful in 6, and for the remaining 2 hips the patient died subsequent to implant removal. All patients showed a final infection control rate of 97% (73/75 hips). Microorganisms that were isolated preoperatively and intraoperatively are shown in Table 2.

Table 2
Isolated microorganisms: preoperative and intraoperative.

Isolates	Two-stage Success group	Two-stage Failure group	Multiple-stage Success group
CNS	19	2	1
MRSA	14	2	2
MSSA	9	0	0
MRSE	6	0	0
MRCNS	3	0	1
MSSE	3	0	0
Pseudomonas aeruginosa	1	1	0
Streptococcus sp.	1	0	1
Staphylococcus sp.	2	1	0
Peptostreptococcus sp.	2	1	0
Group B *Streptococcus*	3	0	0
Serratia	1	0	0
Enterococcus	1	0	0
Bacteroides sp.	1	0	0
Proteus vulgaris	0	1	0
Escherichia coli	1	0	0
Mycobacterium tuberculosis	1	0	0
Fungus	1	0	0
Unknown	17	1	1

CNS: coagulase-negative *Staphylococcus*, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSE: Methicillin-resistant *Staphylococcus epidermidis*, MRCNS: Methicillin-resistant coagulase-negative *Staphylococcus*, MSSE: Methicillin-sensitive *Staphylococcus epidermidis*.

Table 1
Patient demographics.

Type of surgery	Two-stage Success group n = 61	Two-stage Failure group n = 8	Multiple-stage Success group n = 6
Mean age at surgery (y) (range)	68 (32–86)	67 (50–81)	71 (59–84)
Male:Female	15:46	3:5	1:5
Diabetes mellitus (number)	10	2	2
Steroid therapy	4	1	0
Mean time from primary procedure to first-stage revision (y) (range)	4 (0.1–14)	5 (0.3–16)	4 (0.5–12)
Mean time from first-stage to second-stage revision (wk) (range)	7 (5–13)	8 (6–9)	5 (4–7)
Mean time from revised THA to final follow-up (y) (range)	4 (0.3–16)	6 (0.7–13)	6 (1–10)

THA: total hip arthroplasty.

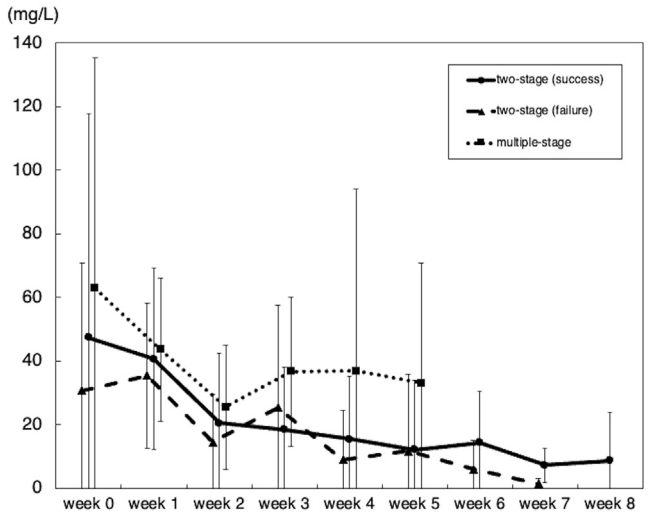

Fig. 3. The progression of mean C-reactive protein levels treated in two-stage and multiple-stage revision total hip arthroplasty. Data are expressed as the means and standard deviations.

Fig. 3 shows progression in mean CRP level. In two-stage revision THA, mean CRP levels at the second stage of surgery (reimplantation) in successful and failed cases were 8.8 ± 12.3 and 10.3 ± 22.8, respectively ($p = 0.78$). In multiple-stage revision THA, mean CRP levels at the second and third stages of surgery were 27.8 ± 19.2 and 5.3 ± 3.7, respectively ($p < 0.001$). In the event of failure after two-stage revision THA and multiple-stage revision THA, mean CRP levels at 3 weeks were increased.

Table 3 shows findings for mean log2 (CRP) using logistic regression. To predict failure preoperatively, sensitivity and specificity were plotted on an ROC curve (AUC 0.567; 95% CI 0.334–0.800). At 5 weeks, when the second-staged surgery was scheduled, log2 (CRP) showed an AUC of 0.634 (95% CI 0.406–0.861). Preoperatively, at 1, 2, 3, and 5 weeks, log2 (CRP) was not associated with failure of the procedure. A number of parameters were also calculated using log2 (CRP) at 3 weeks after the first-staged surgery (Table 3) because mean CRP levels at 3 weeks were increased in the event of failure following two-stage or multiple-stage revision THA. The log2 (CRP) at 3 weeks divided by that at 2 weeks showed a significant difference (AUC 0.444; 95% CI 0.154–0.734), and a ratio of >4.0 between the 3-week and 2-week CRP levels values was associated with failures following two-stage revision THA.

4. Discussion

PJI continues to be one of the most severe complications in THA and is the second most common cause of revision in the United Stated and the third in the United Kingdom [1,2]. Two-stage revision THA is considered the gold standard treatment for PJI worldwide, although for certain selected patients the one-stage revision procedure can be feasible [3,4,9,31]. However, the two-stage revision process makes it difficult to assess the optimal timing of reimplantation. This difficulty stems from two reasons: first, prolonged antibiotic therapy can confound results, and second, the presence of unremoved ALAC may act as a scaffold to which biofilms attach and serve as foci of reinfection [32]. Thus, in the second stage of two-stage revision THA, surgeons struggle with two decisions: when to plan for reimplantation, and whether to actually proceed to reimplantation at that point or to continue with further debridement (i.e. multiple-stage revision). In the current study, we verified the timing of reimplantation in two-stage revision THA using serum CRP.

PJI diagnosis progressed after the introduction and modification of MSIS criteria, but efforts continue to identify a reliable biomarker that can be measured accurately and less invasively. CRP, an archetype acute phase protein first identified in 1930, is a very commonly available serum biomarker [33]. It continues to be used in first-line screening tests for PJI and plays an important role in effective monitoring during therapy. However, CRP often fails to normalize after the infection is eradicated [20–22]. In two-stage revision THA, some authors have reported difficulty in determining from CRP alone whether to perform THA or to perform further debridement [10–15]. Dwyer et al. [14], reviewed 205 two-stage revisions (132 TKAs and 73 THAs), compared hips with and without recurrent infection, and found no difference in mean preoperative serum CRP level between these two groups ($p = 0.40$). Stambough et al. [15] reviewed 291 two-stage revision procedures (146 TKAs and 145 THAs), and found that serum CRP levels were a poor marker of recurrent infection when compared between preresection and 6 weeks after resection (AUC = 0.539). Nevertheless, these past reports did not compare CRP levels over time, and attempts to perform detailed CRP analysis across systemic reviews and meta-analyses proved problematic.

For the current study, we retrospectively evaluated CRP levels every week, and we used log2 (CRP) which yields more reliable odds ratio estimates. Consequently, we were unable to predict failure in the first-staged surgery based on preoperative CRP levels, and we were also unable to make predictions about the second-staged surgery based on CRP levels during the first 5 weeks. However, we found a significant difference in the log2 (CRP) at 3 weeks divided by that at 2 weeks, and we also found that a CRP ratio of 4.0 or higher between week 3 and week 2 was associated with failure following two-stage revision THA. Similarly, Simon et al. [34] reviewed 61 two-stage revision THAs for PJI without an ALAC spacer and reported elevation of CRP levels in the failure group from week 2 to week 3 after resection. The AUC after ROC was 0.813 between the matched failure group and success group on day 24 (±1) postoperatively ($p = 0.001$). Based on these findings, in two-stage revision THA for PJI, patients who show elevated CRP from 2 to 3 weeks after the first stage should be considered for further debridement prior to reimplantation.

Table 3
Mean log2 (CRP) using logistic regression.

Mean log2 (CRP)	Logistic regression coefficient	Odds ratio (95% CI)	*p* value
Preoperatively	−0.094	0.937 (0.767–1.145)	0.5233
At 1 week	−0.243	0.845 (0.501–1.426)	0.5285
At 2 weeks	−0.075	0.949 (0.706–1.276)	0.7298
At 3 weeks	−0.039	0.973 (0.692–1.368)	0.8760
At 5 weeks	−0.071	0.952 (0.756–1.199)	0.6758
(3 weeks−1 week)	incalculable	incalculable	incalculable
(3 weeks−2 weeks)	0.469	1.384 (0.928–2.064)	0.1109
(3 weeks/1 week)	0.154	1.113 (1.022–1.212)	0.0136
(3 weeks/2 weeks)	0.498	1.412 (1.124–1.774)	0.0031

CRP: C-reactive protein, CI: confidence intervals.

There are some limitations to this study. First, the small number of cases, short follow-up period, and relatively few failed cases made statistical analysis challenging and yielded a relatively flat AUC. Infection risks, including diabetes mellitus or steroid therapy, also could not be statistically evaluated because of the small number of failed cases. Second, treatment of PJIs involves the use of a wide variety of antibiotics, so the conditions of treatment can vary considerably. In the second stage of surgery, the decision to reimplant the prosthetic or to switch to multiple-stage revision was made by the surgeon, with no firm criteria provided. Furthermore, in two-stage revision THA using cement spacers, the normalized time interval of CRP level in the culture-negative PJI group was shorter than in the culture-positive PJI group [35]. We did not collect specific data regarding culture-negative PJI vs. culture-positive PJI, which may have also affected our results. Third, for diagnosing PJI, several other markers including plasma fibrinogen, synovial tests, interleukin-6, procalcitonin, tumor necrosis factor-α, flow cytometry, and next-generation sequencing, have proven to be superior diagnostic tools, although serum CRP evaluation is more accurate than other serum traditional parameters such as white blood cell count, percentage of neutrophils, or neutrophils to lymphocytes ratio [10,13,17,19]. Multiple variables may now be included in decisions for reimplantation, since the modified MSIS criteria included several new biomarkers [18].

In conclusion, 10-year survival rates were 85% (95% CI, 76–95) and 100% for two-stage and multiple-stage revision THA, respectively. All of those who failed two-stage revision THA and all of those who succeeded at multiple-stage revision THA showed elevated CRP levels 3 weeks after the first surgery. In patients whose multiple-stage revision was successful, CRP levels at the third staged surgery were significantly lower than at the time scheduled for the second-staged surgery. These findings emphasize the importance of waiting until CRP has dropped to an appropriate level before performing reimplantation. When the ratio of CRP levels between 3 weeks and 2 weeks exceeds 4.0, further debridement without reimplantation should be considered in the second stage of surgery.

IRB approval

This study was approved by our institutional review board.

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Authors' contributions

Each author made substantial contributions to the following components of the project: conception, design, interpretation of data, drafting of the manuscript. All authors read and approved the final manuscript.

Study design

Clinical research (Retrospective cohort study). The study was approved by our institutional review board (H120167).

Declaration of competing interest

All authors have no conflicts of interest relevant to this article to declare.

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