

Temporal Value of C-Reactive Protein and Erythrocyte Sedimentation Rate after Total Knee Arthroplasty in Patients with Elevated Preoperative C-Reactive Protein: A Matched-Pair Analysis

Abstract

Background: We aimed to determine whether temporal values of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) after total knee arthroplasty (TKA) differ between patients with and without elevated preoperative CRP. We hypothesized that temporal pattern of CRP and ESR change would differ between the two groups. **Materials and Methods:** This retrospective study included 30 TKAs with a diagnosis of osteoarthritis with elevated preoperative CRP (>1 mg/dl) without clinical signs and symptoms of infection before surgery (elevated CRP group). Patients without elevated preoperative CRP were matched in a 1:10 fashion according to age, sex, number of comorbidities and whether TKA was unilateral or bilateral (nonelevated CRP group). The temporal values of CRP and ESR after TKA were compared between the two groups until 2 months after surgery. **Results:** The mean peak values of CRP and ESR after surgery were similar between the two groups in both unilateral and bilateral TKAs. In the unilateral TKA, mean values of CRP and ESR and the proportions of the knees with normal CRP and ESR at 2 months after surgery were similar in the two groups. However, in the bilateral TKA, mean values of CRP and ESR were higher and the proportions of the knees with normal CRP and ESR at 2 months after surgery were lower in the elevated CRP group compared to the nonelevated CRP group. **Conclusions:** When performing TKA in patients with elevated preoperative CRP, the fact that the levels of CRP and ESR may not be normalized until 2 months after surgery should be considered during followup.

Keywords: C-reactive protein, erythrocyte sedimentation rate, periprosthetic joint infection, total knee arthroplasty

Introduction

Periprosthetic joint infection (PJI) has been one of the major causes of revision surgery after total knee arthroplasty (TKA).¹⁻³ Many strategies to reduce the PJI have been applied during preoperative, intraoperative, and postoperative stages.⁴ In the preoperative stage, it is important to screen occult infections and controlling sources of bacteria.⁵ To screen for occult infection before performing TKA, preoperative C-reactive protein (CRP) is generally used.⁵ In addition, the preoperative level of CRP provides individual baseline value to compare the changes of the CRP levels after surgery. However, the level of CRP is not specific for diagnosing infections perioperatively.⁶

The elevated level of the CRP can be a rationale for delaying surgery and is used

as one of the diagnostic criteria of PJI after surgery.⁵ However, the level of preoperative CRP can be elevated in various clinical situations, such as concomitant cardiac disease, even if there is no obvious infection.⁷ If the CRP elevation is caused by the reasons other than infectious conditions, TKA does not need to be delayed.⁸ On the other hand, an elevated preoperative baseline value of CRP can affect the temporal change patterns of inflammatory markers including CRP and erythrocyte sedimentation rate (ESR) after surgery.⁹ This may cause confusion during the followup after surgery concerning whether additional diagnostic procedures are needed to confirm the presence of PJI.

We sought to determine whether temporal values of CRP and ESR differ between the patients with and without elevated preoperative CRP during the perioperative period. We hypothesized that the peak

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values of CRP and ESR would be higher in patients with elevated preoperative CRP and temporal pattern of CRP and ESR change would be different between the two groups.

Materials and Methods

This retrospective study included 30 TKAs with an elevated level of preoperative CRP (>1 mg/dl) and 300 TKAs without elevated preoperative CRP. Medical records of 1444 TKAs performed at the authors' institution from January 2009 to December 2010 were reviewed. The inclusion criterion was a diagnosis of primary osteoarthritis and patients with TKA who were followed up more than 2 years. Elevation of the preoperative CRP was defined as >1 mg/dl according to the diagnostic criterion of PJI reported previously.¹⁰ Among the patients eligible for inclusion, 30 TKAs had elevated preoperative CRP. These patients underwent TKA because they had no clinical signs and symptoms of infection on physical examinations before surgery (elevated CRP group). Patients without elevated preoperative CRP were matched in a 1:10 fashion according to age, sex, number of comorbidities and whether TKA was unilateral or bilateral using the propensity score matching. Thus, 300 knees without elevated preoperative CRP were selected (nonelevated CRP group) [Table 1]. All participants gave their informed consent to participate, and this study was approved by the Institutional Review Board of our hospital.

One independent investigator performed the clinical evaluations by reviewing patient medical charts. All the data were stored in an electronic medical record system and obtained through a medical record review. The authors routinely evaluated the preoperative CRP and ESR the day before surgery. Although the level of CRP was higher than 1 mg/dl, TKA was performed if there were no clinical signs and symptoms of infection on the physical examination. Clinical signs and symptoms of infection included fever (>37.3°C), redness, and local heat sensation

on the index side of the knees. Patients with the elevated and nonelevated preoperative CRP were treated with the same protocol. All patients received the same prophylactic antibiotics (2 g cefazolin) within 1 h before incision. Intravenous antibiotic was also administered during the 1st 48 h after surgery. After surgery, the CRP and ESR were also checked at postoperative 3 days, 5 days, and 2 months.

A senior surgeon (one of the authors) performed all of the surgeries using a modified parapatellar approach with a tourniquet. All TKAs were performed using a posterior stabilized prosthesis. All patellae were resurfaced, and all components were fixed with cement. All of the bilateral TKAs were performed during the same day. The tourniquet was released after an elastic compression dressing was applied. A drain was kept in the joint for the 1st 2 days after surgery. All patients received the same perioperative management with regard to anesthesia, multimodal analgesics, and wound management. The 1st wound dressing was changed on the 2nd postoperative day, and then, a continuous passive motion machine was applied. On the 2nd postoperative day, all patients began ambulating with a walker.

The temporal values of the CRP and the ESR were compared between the elevated and the nonelevated CRP groups. The temporal values of CRP and ESR were separately described between unilateral and bilateral TKAs. The temporal values of CRP and ESR were described as the mean and standard deviation at each time point. In addition, the change in the patterns of CRP and ESR were compared between the two groups. For this comparison, knees with actual PJI development during the study were removed to eliminate the bias caused by the elevated levels of CRP and ESR of the infected joint. There was no PJI in the elevated CRP group. In contrast, there were 4 PJIs (1.3%) in the nonelevated CRP group. The PJI was diagnosed using the previously reported criteria.¹¹

The analyses were compared in two separate setups. First, the changes of mean values in CRP and ESR between preoperative and at postoperative 3 days, 5 days, or 2 months were compared between the elevated and the nonelevated groups. Second, mean values of CRP and ESR were compared between the two groups at each time point. The statistical significance of the differences was determined using the generalized estimating equations test. Finally, the proportions of the knees with normal CRP (≤ 0.3 mg/dl) and ESR (female, ≤ 27 mm/h; male ≤ 22 mm/h) 2 months after surgery were determined. The statistical significance of the differences in the proportion was determined using the Chi-square test.

Results

In the unilateral TKA, the level of CRP showed similar temporal patterns, whereas the temporal patterns of ESR differed between the two groups. The two groups showed a

Table 1: Demographic data of the elevated C-reactive protein and nonelevated C-reactive protein groups

Variable	Elevated CRP group (n=30)	Non-elevated CRP group (n=300)
Age (years)	67 (range, 43-81; SD, 8.4)	67 (range, 43-85; SD, 7.3)
Female patients	27 (90)*	270 (90)*
BMI (kg/m ²)	26.9 (range, 20-39; SD, 5.0)	26.9 (range, 16-42; SD, 3.5)
Bilateral TKA	18 (60)*	180 (60)*
Number of comorbidities	1.5 (range, 0-5; SD, 1.3)	1.5 (range, 0-6; SD, 1.0)

Data are presented as means and number of patients. *Proportions are presented in the parentheses. CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate, BMI=Body mass index, SD=Standard deviation, TKA=Total knee arthroplasty

similar temporal pattern of changes in CRP levels [Figure 1]. There was no difference in change patterns from the preoperative period to 3 days postoperatively ($P = 0.853$), from preoperative to 5 days ($P = 0.171$) and from preoperative to 2 months ($P = 0.074$) between the two groups. In addition, there was no difference in mean values of CRP at 3 days, 5 days, and 2 months between the two groups. Furthermore, at 2 months after surgery, the proportion of the knees with normal CRP was similar between the two groups [Table 2]. In contrast, the ESR changes partly differed between the two groups [Figure 2]. The mean values of ESR increased more from preoperative to 5 days after surgery in the nonelevated CRP group compared to the elevated CRP group ($P = 0.045$), although there was no significant difference in the change patterns from preoperative to 3 days ($P = 0.057$) between the two groups. In addition, the mean values of ESR decreased from preoperative to 2 months in the elevated CRP group, whereas the mean values increased from preoperative to 2 months in the nonelevated CRP group ($P = 0.003$). However, at 2 months after surgery, mean values and the proportion of the knees with normal ESR were similar between the two groups [Table 2].

In the bilateral TKA, the two groups showed a similar temporal pattern of changes in terms of CRP and ESR

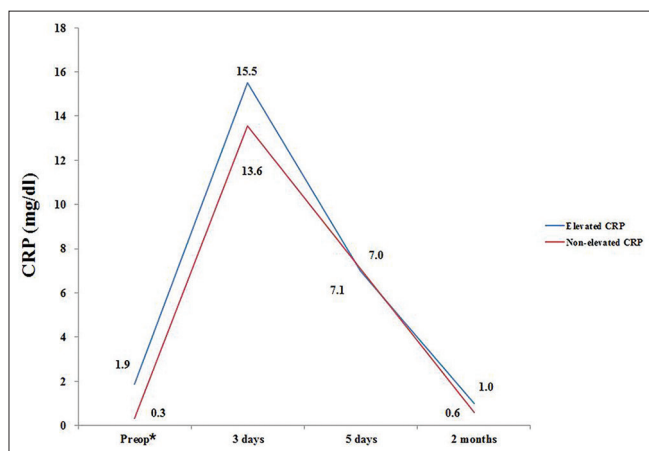


Figure 1: Comparative data of temporal values of C-reactive protein in the unilateral total knee arthroplasty have a similar temporal pattern between the elevated C-reactive protein and nonelevated C-reactive protein groups. *Mean value of C-reactive protein at each time point only differed preoperatively (preoperative, $P = 0.011$; postoperative 3 days, 0.429; postoperative 5 days, 0.925; postoperative 2 months, 0.306)

during 2 months after surgery [Figures 3 and 4]. In addition, there was no difference in terms of mean peak values of CRP and ESR between the elevated CRP and the nonelevated CRP groups during the 2 months after surgery. In contrast, at 2 months after surgery, mean values of CRP and ESR were higher and the proportions of the knees with normal CRP and ESR were lower in the elevated CRP group than in the nonelevated CRP group [Table 2].

Discussion

In the present study, the mean values of CRP and ESR of the elevated CRP group were still higher than those of the nonelevated CRP group at 2 months following bilateral TKA. Moreover, the levels of CRP and ESR were not normalized until 2 months after surgery in a substantial portion of the knees treated with bilateral TKA in the elevated preoperative CRP group.

Our findings partly affirm the hypothesis that temporal value of CRP and ESR would differ between the elevated CRP and the nonelevated CRP groups. The levels of CRP and ESR are important inflammatory markers for

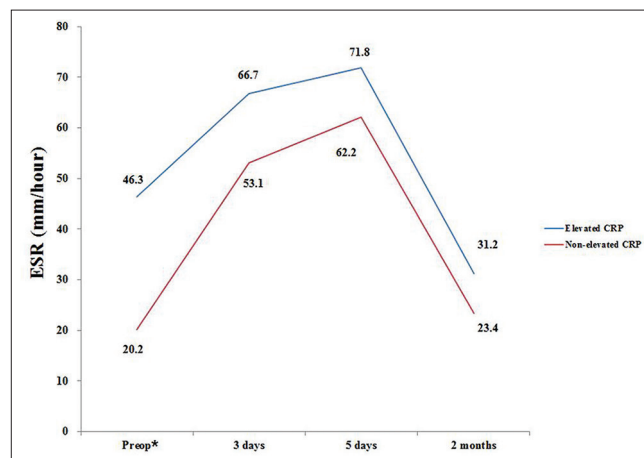


Figure 2: Comparative data of temporal values of erythrocyte sedimentation rate in unilateral total knee arthroplasty. The mean values of erythrocyte sedimentation rate showed higher increase at 5 days after surgery in the nonelevated C-reactive protein group compared to the elevated C-reactive protein group ($P = 0.045$). The mean values of erythrocyte sedimentation rate decreased from preoperative to 2 months in the elevated C-reactive protein group, whereas the mean values increased from preoperative to 2 months in the nonelevated C-reactive protein group ($P = 0.003$). *Mean value of erythrocyte sedimentation rate at each time point only differed preoperatively (preoperative, $P = 0.010$; postoperative 3 days, 0.117; postoperative 5 days, 0.278; postoperative 2 months, 0.265)

Table 2: The proportions of the knees with normal C-reactive protein and erythrocyte sedimentation rate levels 2 months after total knee arthroplasty

Variable	Normal CRP on 2 months after TKA		P	Normal ESR on 2 months after TKA		P
	Elevated CRP group (%)	Nonelevated CRP group (%)		Elevated CRP group (%)	Nonelevated CRP group (%)	
Unilateral TKA	6/12 (50)	88/119 (74)	0.082	7/12 (58)	80/119 (67)	0.372
Bilateral TKA	5/18 (28)	112/177 (63)	0.004	5/18 (28)	101/177 (57)	0.016

Data are presented as numbers and proportions in the parentheses. TKA=Total knee arthroplasty, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate

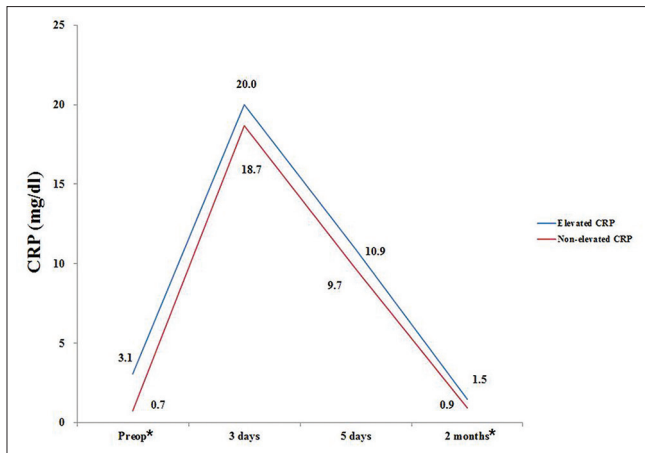


Figure 3: Comparative data of temporal values of C-reactive protein in bilateral total knee arthroplasty have a similar temporal pattern between the elevated C-reactive protein and nonelevated C-reactive protein groups. *At 2 months after surgery, mean values Erythrocyte sedimentation rate of the elevated C-reactive protein group were higher than those of the non-elevated C-reactive protein group (preoperative, $P < 0.001$; postoperative 3 days, 0.387; postoperative 5 days, 0.286; postoperative 2 months, 0.003)

determining treatment plans during followup after TKA.¹² However, reportedly, the level of CRP and ESR is not specific for diagnosing PJI and varies widely in terms of the perioperative level.^{6,13,14} The sensitivity of serum CRP for diagnosing the PJI was reported as 97% in a previous study, but its specificity was only 76%.⁶ Thus, most surgeons probably have more confidence in the temporal pattern than the level at one-time point.¹² The temporal values of CRP and ESR after surgery have been used as one of the clues to perform additional diagnostic procedures to confirm the presence of PJI after surgery.¹⁵ We initially thought that patients with elevated CRP and ESR levels can show higher peak values of CRP and ESR during followup. However, there was no difference in the peak values of both parameters between the two groups. Our findings are in line with a previous study that reported an inconstant correlation between preoperative values and postoperative peak values of CRP and ESR after TKA.¹² In the previous study, the peak value of CRP was found at the 2nd postoperative day and the correlation coefficient between preoperative values and values of the 2nd postoperative day was only 0.191.¹² Although the peak value does not show difference, postoperative pattern of the values of CRP and ESR showed difference between the two groups. In the present study, in the patients with elevated CRP, the CRP level was still higher than normal level 2 months after TKA in a substantial proportion of the patients, especially in bilateral TKA.

Among the TKA candidates, a subset of patients will have elevated preoperative CRP levels. Most of those patients probably have inflammatory arthritis including rheumatoid arthritis.⁹ However, sometimes, patients with a diagnosis of osteoarthritis show elevated CRP without an infection

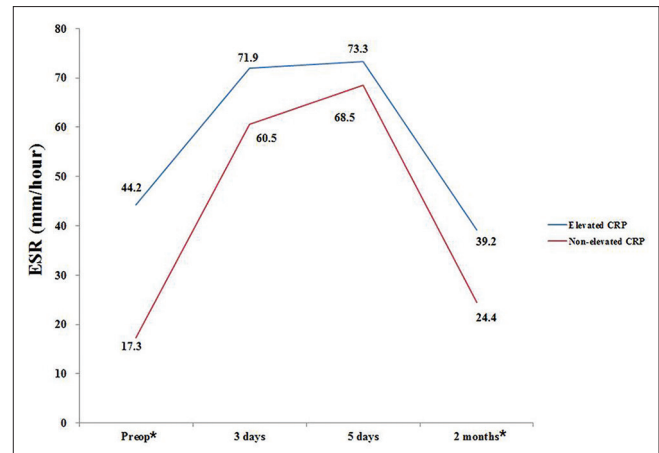


Figure 4: Comparative data of temporal values of erythrocyte sedimentation rate in bilateral total knee arthroplasty have a similar temporal pattern between the elevated C-reactive protein and nonelevated C-reactive protein groups. *At 2 months after surgery, mean values erythrocyte sedimentation rate of the elevated C-reactive protein group were higher than those of the non-elevated C-reactive protein group (preoperative, $P < 0.001$; postoperative 3 days, 0.105; postoperative 5 days, 0.457; postoperative 2 months, 0.009)

focus. In this situation, surgeons can delay surgery and/or add diagnostic tests, such as knee joint aspiration or whole body bone scans. Even after thorough diagnostic evaluations result in no sign infection, some patients still show elevated level of CRP. When TKA is performed in such cases, PJI after TKA is difficult to diagnose due to lack of baseline information in these subset of patients. In this regard, our findings would be helpful for surgeons to make a diagnosis of PJI after surgery in patients with the elevated preoperative CRP.

This study has several limitations. First, the majority of the patients in the elevated CRP group had limited elevation of CRP levels, even though it was higher than 1 mg/dl. The mean preoperative CRP was only 2.3 mg/dl. Thus, we were not able to provide information about the level of CRP that is tolerable for TKA. Second, CRP and ESR data were available only preoperatively and postoperatively after 3 days, 5 days, and 2 months because we obtained blood samples according to the routine followup schedule. However, this time period is probably reasonable followup period after TKA.

Conclusions

In patients with elevated preoperative CRP, the levels of CRP and ESR may not be normalized until 2 months after surgery, especially in bilateral TKA. Our findings should be considered when deciding the timing of TKA and during followup after surgery. Further study is needed to obtain concrete evidence about the association between preoperative elevated CRP and PJI after surgery.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given

their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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