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ORIGINAL ARTICLE

Normative Temporal Values of CRP and ESR in Unilateral and Staged Bilateral TKA

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Abstract C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) play helpful roles in determining the presence of infection after TKA. To provide baseline values, we documented normative temporal values of CRP and ESR in unilateral and staged bilateral TKAs for osteoarthritis. Levels of CRP and ESR were evaluated before surgery and on the first, second, fifth, seventh, fourteenth, forty-second, and ninetieth postoperative days in 320 uncomplicated primary TKAs. C-reactive protein and ESR levels were compared in three groups: unilateral (108 knees), first knee bilateral (106 knees), and second knee bilateral (106 knees) groups. All three groups exhibited similar temporal patterns. Mean CRP levels increased rapidly, reaching a peak on the second day and decreased to less than the normal reference level on the forty-second day. They returned to preoperative levels on the ninetieth day. Mean ESR levels peaked on the fifth day and returned close to the preoperative levels only on the ninetieth day. Wide variations were observed and many cases (43%) did not follow the typical patterns. C-reactive protein had greater fold changes, less frequent atypical temporal patterns, and lower correlation between preoperative and postoperative levels than ESR. Our findings should help surgeons interpret CRP and ESR to determine the presence of infection after TKA.
Level of Evidence: Level I, diagnostic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.

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Introduction

Infection is one of the most serious complications after TKA. The crucial factor for successful management of an infectious condition at the site of a TKA is early and accurate diagnosis that allows prompt treatment [21, 28]. Especially in the early postoperative period, timely diagnosis could increase the likelihood of eradicating the infection while retaining the prosthesis [19, 31, 33]. Various diagnostic tools have been used to confirm the presence of infection or to identify the responsible pathogen after TKA [13, 21, 28]. Each diagnostic tool, however, has some limitations in terms of sensitivity and specificity, which tempers its clinical values, and the final decision of an infectious condition after TKA often relies on the physician's judgment. In practice, when the surgeon makes a decision about the presence of infection after TKA, the plasma CRP and ESR may play helpful or adjuvant roles [21, 28, 30, 33].

C-reactive protein and ESR are acute-phase reactants that reflect a measure of the acute-phase response after a stimulus and have been widely used to monitor the postoperative course after TKA because of their advantageous characteristics, including rapid increase in concentration, a relatively short lag time, and cost effectiveness [7, 21, 28]. Assessing the postoperative levels of CRP and ESR can be an important adjunct to making a correct diagnosis of infection after TKA [2, 21, 28, 33]. However, interpreting postoperative data of CRP and ESR is not straightforward because of their nonspecific nature and wide variations in perioperative levels [2, 12, 20]. Total knee arthroplasty is performed frequently as a bilateral procedure because many knee ailments involve both knees and staged procedures with an interval may be a good option to reduce the risks associated with a simultaneous bilateral procedure [15–17]. In staged bilateral TKAs, it might be more difficult to interpret the levels of acute-phase reactants because surgical trauma by the first procedure can influence their levels in the immediate postoperative period.

Numerous previous studies have reported perioperative levels of CRP and ESR after joint arthroplasty, but most of the studies had limitations, making it difficult to establish an efficient way to interpret postoperative data of CRP and ESR after TKA [1, 2, 4, 5, 8, 10, 14, 20, 22, 23, 25–27, 30, 32, 34]. Some of the previous studies used a very small series of fewer than 50 arthroplasties [1, 2, 8, 10, 25, 32, 34]. and some studies involved TKA and THA, which reportedly differ in postoperative levels of CRP and ESR [2, 5, 8, 10, 14, 20, 22, 25, 30]. Despite the well-known wide variations in postoperative levels of CRP and ESR, some previous studies report temporal patterns based on the mean values but without detailed normative data [2, 5, 8, 10, 20, 22, 25] and the proportion of cases not following the typical temporal pattern was not reported in these series. Also, these studies did not explore the association between preoperative and postoperative levels of CRP and ESR.

Given the limitations in the literature, we compared normative temporal values of CRP and ESR in unilateral and staged bilateral TKAs performed for patients with osteoarthritis. We asked whether the second knee bilateral TKAs differed in the perioperative values of CRP and ESR from the unilateral or the first knee bilateral TKAs. We also sought to determine whether there were differences in the temporal values between CRP and ESR and whether CRP and ESR differed in the association between preoperative and postoperative levels.

Materials and Methods

We prospectively evaluated 228 consecutive patients with osteoarthritis (336 knees) who underwent primary TKAs from May 2003 to September 2004. We excluded 14 patients (16 knees). Five patients (five knees) were excluded owing to acute periprosthetic infection, which had been established (positive in microbiologic study and/or in intraoperative frozen biopsy) or clinically suspected (compatible clinical course with positive laboratory findings of the plasma and joint aspirate). We excluded five patients (six knees) because of postoperative delay in wound healing that could influence the laboratory findings despite the fact that the five patients (six knees) recovered without additional surgery. We excluded an additional four patients (five knees) because of systemic inflammatory conditions: one patient with a history of laparoscopic surgery for peritonitis; one with an operative history resulting from pulmonary fibroma; one with a recent history of pulmonary tuberculosis; and one patient (two knees) with long-lasting upper respiratory inflammation. Consequently, we included 320 osteoarthritic knees in 214 patients in the final analyses. In all cases, we confirmed the absence of infection by clinical evaluations (symptoms, signs, laboratory findings, and radiographic studies) made with a regular followup schedule (postoperatively, 6 weeks, 3 months, 6 months, 12 months, and yearly thereafter) for more than 1 year. This study was approved by the Institutional Review Board of our hospital and informed consent was obtained from all patients regarding use of their medical information for this study.

We divided 320 knees into three groups: a unilateral group (108 knees) in the patients who underwent TKA in only one knee, a first knee bilateral group (106 knees) of the first knees in the patients who underwent bilateral TKAs, and a second knee bilateral group (106 knees) of the second knees in the patients with bilateral TKAs. In the first knee bilateral group, we obtained relevant data for the period between the first and second operations (preoperatively and on the postoperative first, second, fifth, seventh, and fourteenth days). The second knee bilateral group included the same patients as the first knee bilateral group but with longer followup data. In the unilateral group, there were 102 women and six men with a mean age of 68.1 years (range, 51–82 years). The first and second knee bilateral groups included 103 women and three men with a mean age of 68.4 years (range, 55–84 years). There were no differences in these demographic data between the two groups (chi square test for gender and analysis of variance test for age, $p > 0.05$).

All TKAs were performed by one surgeon (KTK) using the standard surgical technique. We used a spinal block as the routine anesthesia method and administered general anesthesia when spinal anesthesia was ineffective. The standard parapatellar approach was used with a tourniquet. For patients with advanced osteoarthritis in both knees, bilateral TKAs were performed with an interval of 2 weeks. We resurfaced the patella in all cases and cement

fixation was used for all components. Intravenous patient-controlled anesthesia or patient-controlled continuous femoral nerve block anesthesia was administered for postoperative pain control. Prophylactic antibiotics were given preoperatively (2 hours before surgery) and postoperatively for 3 days.

We obtained blood samples before surgery and on the first, second, fifth, seventh, fourteenth, forty-second, and ninetieth postoperative days for patients having unilateral TKA. For patients having first knee bilateral TKAs, blood sampling was performed before surgery and on the first, second, fifth, seventh, and fourteenth postoperative days. For patients having the second TKA for the other knee a blood sample was obtained the morning of the second surgery (the fourteenth day). For patients having second knee bilateral TKAs, blood samples were obtained at the same postoperative time as samples were obtained for patients having unilateral TKA. Samples on the forty-second and ninetieth days were obtained from patients at the outpatient clinic because our routine followup schedule after discharge was 6 weeks and 3 months after surgery.

C-reactive protein was measured using the particle-enhanced light-scattering immunoassay on the TBA-200FR system (Toshiba, Tokyo, Japan) according to the manufacturer's instructions and the normal range was set to less than 5 mg/L (0.5 mg/dL). Erythrocyte sedimentation rate was measured using the photometric kinetic analysis of capillary-stopped flow on the Test-1 system (Alifax, Padova, Italy); the normal range of the laboratory at our hospital was less than 20 mm/hour.

To compare the normative temporal values of CRP and ESR among the unilateral, the first knee bilateral, and the second knee bilateral groups, we summarized data of the CRP and ESR at each time as means with standard deviations. The ranges of the ESR and CRP levels were obtained in three ways: the overall range (minimum to maximum), the 90% range (5^{th} percentile to 95^{th} percentile), and the 50% range (25^{th} percentile to 75^{th} percentile). We performed comparisons of the mean values among the groups using parametric methods (Student's t test and paired t test) or nonparametric methods (Mann-Whitney U test and Wilcoxon signed-rank test), depending on whether the data were normally distributed. The data on the forty-second and ninetieth postoperative days only were compared between the unilateral and the second knee bilateral groups. Because the levels of CRP and ESR are influenced by the presence of other systemic conditions (diabetes mellitus, cardiac diseases, chronic lung and kidney disease, and cancers) [6, 9, 18, 24], proportions of patients with the systemic conditions were compared between the unilateral and the staged bilateral groups. There were no differences in the prevalence of systemic conditions between the unilateral and staged bilateral groups (20.3% versus 27.9%; $p > 0.05$, chi square test). Analysis was performed using SPSS for Windows statistical package (Version 11.5; SPSS Inc, Chicago, IL) and a p value less than 0.05 was considered significant.

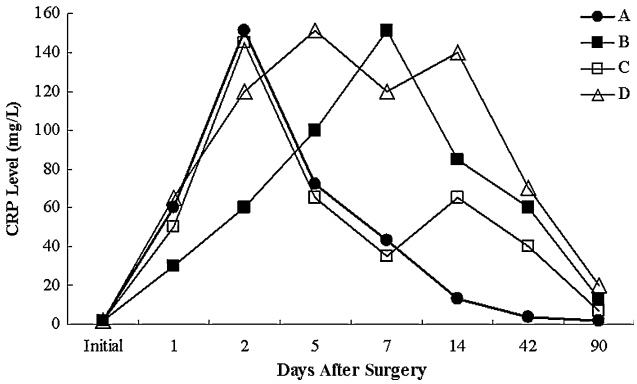

Fig. 1 A schematic graph shows the temporal patterns of CRP and ESR: A, the typical type; B, the type with the peak at a different time; C, the type with deviation from the decreasing levels pattern after a peak; and D, the combined type with deviation from the decreasing pattern and the peak at a different point.

To determine whether CRP and ESR differed in temporal patterns of postoperative levels, we analyzed the temporal pattern of postoperative changes of CRP and ESR levels by fold changes calculated as the ratio of the value at each time to the preoperative value. In addition, we investigated the proportions of cases not following a typical temporal pattern; we defined a typical temporal pattern as the pattern with the peak (CRP, the second day; and ESR, the fifth or seventh day) accompanied by the following decreasing pattern based on previous studies [2, 22, 32].

The temporal pattern of each case was classified into four types: the typical type, the type with the peak at a different time, the type with deviation from the decreasing level pattern after a peak, and the combined type with deviation from the decreasing pattern and the peak at a different point (Fig. 1). To determine whether CRP and ESR differed in the extent of association between preoperative and postoperative levels, we performed Pearson correlation analysis and extent of association was represented by a correlation coefficient [11].

Results

The second knee bilateral group exhibited similar temporal patterns of postoperative changes in CRP and ESR as the unilateral and first knee bilateral groups (Tables 1, 2). The second knee bilateral group had higher CRP levels at several times, but the basic temporal patterns were similar in all three groups and the differences were not great (8.6%–18.1%). For ESR, the second unilateral group had

Table 1. Comparison of perioperative C-reactive protein levels among the unilateral, first bilateral, and second bilateral groups

Times	Unilateral group (n = 108)*					Second bilateral group (n = 106)					p Value†
	Mean (mg/L)	SD	Range			Mean (mg/L)	SD	Range			
			Overall (minimum–maximum)	90% (5^{th}–95^{th} percentile)	50% (25^{th}–75^{th} percentile)			Overall (minimum–maximum)	90% (5^{th}–95^{th} percentile)	50% (25^{th}–75^{th} percentile)	
Preoperative	1.64 [1.39]	2.23 [1.80]	0.1–8.8 [0.1–9.8]	0.2–7.6 [0.1–4.8]	0.2–1.9 [0.1–2.0]	18.11	17.91	0.1–86.2	1.8–67.9	6.0–25.7	< 0.001‡ [< 0.001‡]
PO first day	59.08 [56.37]	35.42 [25.63]	11.2–185.6 [11.2–130.5]	13.9–128.1 [17.6–101.4]	33.8–72.8 [37.4–73.0]	66.49	26.58	20.0–136.3	25.9–122.0	47.5–82.8	0.160 [< 0.001‡]
PO second day	151.26 [157.16]	54.34 [56.28]	34.2–282.2 [52.4–299.8]	74.4–252.4 [71.5–263.6]	111.5–189.0 [116.7–193.4]	165.33	53.13	47.7–294.3	80.8–258.5	124.5–203.0	0.133 [0.145]
PO fifth day	71.67 [68.51]	35.50 [37.19]	12.5–187.2 [12.5–183.9]	19.8–129.9 [26.1–156.1]	47.2–96.8 [41.8–87.5]	78.42	37.06	12.7–208.7	26.1–154.3	56.6–96.3	0.321 [0.009‡]
PO seventh day	43.83 [41.48]	30.95 [32.84]	4.4–127.4 [4.4–178.3]	7.1–106.5 [9.7–123.4]	23.0–55.8 [17.6–49.0]	46.33	30.17	7.2–159.9	11.2–119.7	26.1–60.8	0.285 [0.009‡]
PO fourteenth day	12.78 [18.11]	15.49 [17.91]	0.1 –90.6 [0.1–86.2]	1.6–39.5 [1.8–67.9]	3.7–15.3 [6.0–25.7]	15.61	12.97	1.5–63.3	2.4–45.4	6.5–22.9	0.016‡ [0.523]
PO forty-second day	3.66	6.61	0.1–33.8	0.1–23.3	0.1–3.7	2.78	3.66	0.1–18.4	0.1–12.6	0.1–3.6	0.743
PO ninetieth day	1.48	1.78	0.1–7.2	0.1–6.8	0.1–1.9	1.72	1.51	0.1–6.6	0.1–4.7	0.1–2.6	0.254

* Numbers in brackets are the values of the first bilateral group (n = 106); †preliminary analyses (Kolmogorov-Smirnov test) to determine whether the data had a pattern of normal distribution found only the data of PO first and second days had normality; logarithmic transformation made the data of PO seventh and fourteenth days have normality, but the data of the preoperative and PO fifth, forty-second, and ninetieth days remained without normality even after the logarithmic transformation; comparisons between the unilateral and the second bilateral groups were performed using the independent t test for the variables with normality (the data of the PO first and second days and the logarithmically transformed data of PO seventh and fourteenth days) and a nonparametric test (Mann-Whitney U test) for the variables without normality (the data of the preoperative and PO fifth, forty-second, and ninetieth days); comparisons of the first bilateral and second bilateral groups were done using the paired t test for the variables with normality and the Wilcoxon signed-rank test for the variables without normality; numbers in brackets are the p values of the comparisons between the first bilateral and second bilateral groups; ‡values are significantly different ($p < 0.05$); the comparisons between the unilateral and the first bilateral groups revealed no significant differences in any variables but in the data of PO fourteenth day ($p = 0.032$); SD = standard deviation; PO = postoperative.

Table 2. Comparison of perioperative erythrocyte sedimentation rate levels among unilateral, first bilateral, and second bilateral groups

Times	Unilateral group (n = 108)*					Second bilateral group (n = 106)					p Value†
	Mean (mm/hour)	SD	Range			Mean (mm/hour)	SD	Range			
			Overall (minimum–maximum)	90% (5^{th}–95^{th} percentile)	50% (25^{th}–75^{th} percentile)			Overall (minimum–maximum)	90% (5^{th}–95^{th} percentile)	50% (25^{th}–75^{th} percentile)	
Preoperative	22.25 [17.03]	12.14 [10.63]	3.0–46.0 [2.0–39.0]	5.6–43.0 [2.0–36.0]	11.0–32.8 [8.0–24.0]	51.23	23.43	2.0–120.0	12.2–88.0	34.8–64.8	< 0.001‡ [< 0.001‡]
PO first day	16.31 [13.71]	14.73 [10.13]	2.0–56.0 [2.0–44.0]	2.0–49.4 [2.0–34.8)]	5.00–22.0 [5.3–21.0]	32.49	17.29	2.0–81.0	5.4–67.1	19.0–44.5	< 0.001‡ [< 0.001‡]
PO second day	42.13 [37.37]	20.48 [15.28]	10.0–87.0 [3.0–83.0]	12.6–80.2 [16.3–65.0]	24.0–59.0 [26.0–45.0]	49.82	16.80	14.0–82.0	17.6–80.0	38.0–61.0	0.039‡ [< 0.001‡]
PO fifth day	69.07 [68.47]	21.98 [22.70]	35.0–120.0 [16.0–120.0]	38.0–118.4 [29.1–110.5]	51.0–86.0 [53.0–83.8]	70.08	24.04	16–120	26.0–110.0	55.0–90.0	0.806 [0.311]
PO seventh day	67.25 [65.59]	22.29 [23.56]	32.0–120.0 [3.0–120.0]	33.8–113.7 [26.5–106.8]	51.0–82.5 [51.0–82.0]	66.95	23.25	17–120	27.2–102.3	51.8–83.0	0.940 [0.434]
PO fourteenth day	56.38 [51.23]	22.43 [23.43]	16.0–104.0 [2.0–120.0]	21.0–97.8 [12.2–88.0]	41.0–72.0 [34.8–64.8]	56.05	23.69	12–120	19.1–97.9	39.5–71.3	0.935 [0.213]
PO forty-second day	31.26	19.76	2.0–80.0	2.8–73.6	17.0–45.0	26.68	16.13	2.0–73.0	4.5–55.3	14.3–38.5	0.210
PO ninetieth day	23.00	16.57	4.0–69.0	4.3–65.3	12.0–27.5	17.98	9.44	2.0–47.0	5.1–37.0	10.0–23.5	0.173

* Numbers in brackets are the values of the first bilateral group (n = 106); †preliminary analyses (Kolmogorov-Smirnov test) to determine whether the data had a pattern of normal distribution found the data had normality at all time points; comparison of the second bilateral group with the unilateral and first bilateral groups was performed using the independent t test and the paired t test, respectively; numbers in brackets are the p values of the comparison between the first bilateral and the second bilateral groups; ‡values are significantly different ($p < 0.05$); the comparisons between the unilateral and the first bilateral groups using the independent t test revealed no significant differences in any variables but in the data of the preoperative day ($p = 0.004$); SD = standard deviation; PO = postoperative.

higher levels than the other groups only on the preoperative and first and second postoperative days, but after the second postoperative day, all three groups exhibited similar temporal patterns.

The temporal changes of CRP values were faster and greater than those of ESR (Table 3; Fig. 2). The amount of fold changes in the CRP levels was much greater than the amount of fold changes of the ESR levels. C-reactive protein levels increased rapidly, reaching a peak on the second day. The decreasing pattern of the CRP levels was biphasic. The first phase occurred during the first 2 weeks, when the CRP level decreased rapidly from the peak levels, and the second phase came with a gradual decrease by the forty-second postoperative day. It decreased to less than the normal reference level (5 mg/L) on the forty-second day but returned to preoperative levels on the ninetieth day. In contrast, ESR levels decreased slightly on the first postoperative day and increased to peak on the fifth day. The peaked level gradually decreased and remained elevated above the normal reference level (20 mm/hour) on the forty-second postoperative day. It returned close to the preoperative levels only on the ninetieth postoperative day. Of the 214 patients in the unilateral or the second knee bilateral groups, 93 (43%) did not have the typical pattern in either CRP or ESR. The proportion of cases not following the typical pattern was higher ($p < 0.001$) in the ESR levels than in the CRP levels (32.2% [69 of 214] versus 11.7% [25 of 214]). Of the 25 knees with an atypical pattern in CRP levels, six (2.8%) showed the peak at a different time and 19 (8.9%) deviated from the typical decreasing pattern after a peak. For ESR levels, 15 (7.0%) cases showed the peak at a different time and 41 (19.2%) cases deviated from the decreasing pattern. Thirteen (6.1%) knees showed the combined type in ESR levels.

Preoperative and postoperative CRP values correlated inconsistently (Table 4). We found no correlation on the second postoperative day when the CRP levels peaked, suggesting the peak level of CRP was not determined by the preoperative level. However, we found consistent correlations between preoperative and postoperative ESR values (Table 4). The strength of correlation was weaker during the early postoperative periods at approximately the peak time (fifth, seventh, and fourteenth days) than in the times before the peak (first and second days) or during the late postoperative days (forty-second and ninetieth days).

Discussion

Infection is a persistently recurring fear for the physician caring for patients with TKA. Nonspecific clinical symptoms and signs make it difficult to differentiate from those suggesting infection, and we frequently need objective data to exclude the possibility of infection despite suspicious clinical symptoms. C-reactive protein and ESR have been widely used to determine the presence of infection after TKA, but appropriate interpretation of the levels of CRP and ESR is not easy, particularly during the early postoperative period. To obtain helpful guidelines for interpretation, we asked whether the second knee bilateral TKAs differed in perioperative values of CRP and ESR from the unilateral or the first knee bilateral TKAs. We also sought to determine whether there were differences in the temporal values between CRP and ESR and whether CRP and ESR differed in the association between preoperative and postoperative levels.

Several limitations should be noted in our study. We performed bilateral TKAs with an interval of 2 weeks. Different findings might be found with different intervals between the two TKAs. Second, we included only uncomplicated cases based on our clinical assessment. The absence of infection was not verified with measures such as a bone scan. It is conceivable for subclinical infection to exist and to present as a clinical infection later. However, it might not be practical to perform an expensive examination without the presence of infection. Instead, we confirmed no patient had relevant symptoms or signs suggesting the presence of infection through 1-year followup. Third, we did not collect specimens on the third postoperative day, which made it impossible to tell whether the day peak CRP was attained was the second or third postoperative day. No blood sampling was performed between the fourteenth and forty-second postoperative days, which made it difficult to determine the exact time when the CRP decreased to less than the normal reference level. However, we believe we covered typical times for routine practice. Fourth, the levels of CRP and ESR are influenced by the presence of systemic conditions [6, 9, 18, 24]. In our study, we found no differences in the prevalence of the systemic conditions between the unilateral and staged bilateral groups. However, the presence of systemic conditions might have influenced the normative data and it may be difficult to directly extrapolate our findings to other patient populations with a different prevalence of systemic conditions. Finally, the dominance of female patients in the current series should be considered. Erythrocyte sedimentation rate levels vary with gender [3, 35], whereas CRP levels do not have a similar variation [5, 29].

Because many of the bilateral TKAs were performed as staged procedures with an interval, we were particularly interested in determining whether the second knee bilateral TKAs differed from the unilateral or the first knee bilateral TKAs in CRP and ESR levels. The second knee bilateral group did not have many differences from the first knee bilateral or unilateral groups. The typical temporal

Table 3. Changes by fold in perioperative levels of erythrocyte sedimentation rate and C-reactive protein

Time	Unilateral group (n = 108)			First bilateral group (n = 106)			Second bilateral group (n = 106)		
	Mean level[†]	Change by fold (ratio to preoperative value)		Mean level[†]	Change by fold (ratio to preoperative value)		Mean level[†]	Change by fold[*] (ratio to preoperative value)	
		Mean	Minimum–Maximum		Mean	Minimum–Maximum		Mean	Minimum–Maximum
C-reactive protein									
Preoperative	1.6	1.0		1.4	1.0		18.1	1.0	
PO first day	59.1	252.8	2.4–1298.0	56.4	255.4	1.9–1064.0	66.5	284.6	3.3–1363.0 [15.8 (0.7–565.0)]
PO second day	151.3	637.0	10.2–2566.0	157.2	712.2	8.3–2649.0	165.3	775.8	14.0–2787.0 [40.7 (2.0–1651.0)]
PO fifth day	71.7	257.7	5.9–1105.0	68.5	314.2	2.9–1605.0	78.4	371.3	5.9–2087.0 [21.2 (1.0–966.0)]
PO seventh day	43.8	140.3	2.9–916.0	41.5	172.2	1.1–1783.0	46.3	212.9	1.7–1599.0 [10.8 (0.5–446.0)]
PO fourteenth day	12.8	40.1	1.0–306.0	18.1	74.6	1.0–701.0	15.6	84.3	0.5–633.0 [3.7 (0.1–150.0)]
PO forty-second day	3.7	16.7	0.0–207.0				2.8	9.5	0.0–148.0 [2.6 (0.0–148.0)]
PO ninetieth day	1.5	4.9	0.1–27.0				1.7	6.90	0.0–47.0 [0.8 (0.0–36.0)]
Erythrocyte sedimentation rate									
Preoperative	22.3	1.0		17.0	1.0		51.2	1.0	
PO first day	16.3	0.7	0.1–2.7	13.7	0.8	0.1–9.5	32.5	3.1	0.1–38.5 [0.9 (0.1–11.8)]
PO second day	42.1	2.4	0.4–7.8	37.4	2.2	0.9–20.5	49.8	4.3	0.5–22.5 [1.4 (0.2–9.8)]
PO fifth day	69.1	4.4	0.9–15.3	68.5	4.0	1.7–42.5	70.1	7.1	0.5–47.0 [2.0 (0.3–14.0)]
PO seventh day	67.3	4.0	0.8–15.0	65.6	3.9	1.4–46.0	67.0	6.7	0.8–47.5 [1.8 (0.4–10.3)]
PO fourteenth day	56.4	3.2	0.7–16.0	51.2	3.0	0.2–43.0	56.1	5.3	0.4–38.5 [1.5 (0.3–8.6)]
PO forty-second day	31.3	1.4	0.3–3.8				26.7	2.3	0.3–21.5 [0.7 (0.1–6.0)]
PO ninetieth day	23.0	1.2	0.3–4.5				18.0	1.7	0.2–11.5 [0.4 (0.1–2.5)]

[*] Data were calculated with the reference of the preoperative level of the first bilateral group; numbers in brackets are the data calculated using the preoperative level of the second bilateral group, which had been examined on the operation day of the second TKA; [†]the units for the mean levels of CRP and ESR are mg/L and mm/hour, respectively; PO = postoperative.

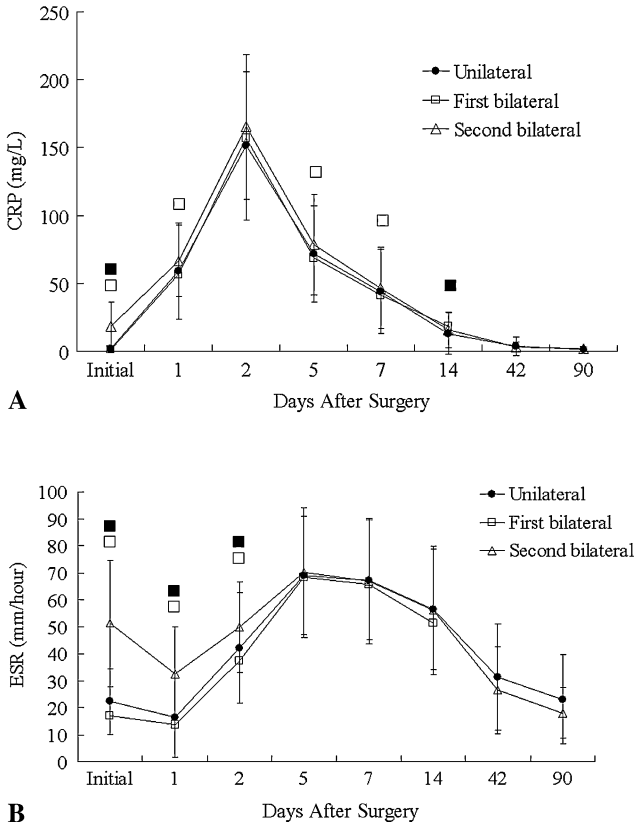

Fig. 2A–B The line graphs show the temporal patterns of perioperative mean levels of (**A**) CRP and (**B**) ESR in the unilateral, first knee bilateral, and second knee bilateral groups. Data are presented as the mean ± standard deviation. The values with statistical significance are marked with a black box (■) for the comparisons between the unilateral and the second knee bilateral groups and with a white box (□) for the comparisons between the first knee bilateral and the second knee bilateral groups.

patterns of the mean values of CRP and ESR were identical in all three groups. These findings indicate the identical strategy can be applied to the second knee bilateral TKAs in interpreting the laboratory reports of CRP and ESR.

C-reactive protein and ESR frequently are examined together and comparative information of their temporal patterns of perioperative levels would bring a synergized value to a clinician to determine the presence of infection after TKA. Our study shows CRP and ESR differ in the temporal patterns of postoperative levels after TKA. In comparison to ESR, CRP had faster temporal changes, greater folder changes, less frequent atypical patterns, and weaker associations between preoperative and postoperative levels. Our findings concur with those of previous studies evaluating the postoperative levels of CRP and ESR after TKA or THA [1, 8, 10, 20, 22, 27, 34] and suggest CRP might be more advantageous than ESR in determining the presence of infection, particularly during early postoperative days.

In practice, it may not be rare to have abnormal levels of CRP or ESR while there are no clinical symptoms and signs suggesting the presence of infection. In those situations, we might tend to speculate patients who had higher preoperative levels would maintain higher levels even after acute postoperative periods had elapsed. In our analysis correlating preoperative and postoperative levels, ESR had a consistent association at all times. In contrast, CRP revealed a variable correlation depending on the times, and the strength of the correlation was weaker than that of the ESR. This finding leads us to speculate CRP is influenced more by surgical trauma than ESR, the levels of which are more influenced by preoperative levels in addition to surgical trauma.

Table 4. Correlation analysis of preoperative levels of C-reactive protein and erythrocyte sedimentation rate to their postoperative levels*

Time	Unilateral group (n = 108)				Second bilateral group (n = 106)			
	C-reactive protein†		Erythrocyte sedimentation rate†		C-reactive protein		Erythrocyte sedimentation rate	
	Correlation coefficient	p Value	Correlation coefficient	p Value	Correlation coefficient	p Value	Correlation coefficient	p Value
PO first day	0.185 [0.249]	0.165 [0.023‡]	0.590 [0.565]	< 0.001‡ [< 0.001‡]	0.219	0.049‡	0.277	0.015‡
PO second day	0.191 [0.056]	0.163 [0.623]	0.553 [0.505]	< 0.001‡ [< 0.001‡]	0.021	0.002‡	0.394	0.002‡
PO fifth day	0.336 [0.065]	0.011‡ [0.565]	0.426 [0.409]	< 0.001‡ [< 0.001‡]	–0.023	0.833	0.320	0.004‡
PO seventh day	0.394 [0.108]	0.002‡ [0.330]	0.463 [0.376]	< 0.001‡ [< 0.001‡]	0.034	0.757	0.322	0.003‡
PO fourteenth day	0.397 [0.158]	0.003‡ [0.170]	0.452 [0.327]	0.001‡ [0.006‡]	0.023	0.838	0.363	0.001‡
PO forty-second day	0.355	0.037‡	0.601	< 0.001‡	0.450	< 0.001‡	0.535	< 0.001‡
PO ninetieth day	0.182	0.394	0.585	0.003‡	0.217	0.096	0.472	< 0.001‡

* The initial preoperative values before the first TKAs were used for the correlation analyses in the second bilateral group; †numbers in brackets are the values for the first bilateral group (n = 106); ‡values are significantly different ($p < 0.05$); PO = postoperative.

Our study documents the normative temporal values of CRP and ESR in unilateral and staged bilateral TKAs in patients with osteoarthritis. We found the perioperative levels of CRP and ESR after the second TKA were similar to those in the first or unilateral TKAs in bilateral TKAs staged 2 weeks apart. We also found CRP and ESR differed in the temporal patterns of the postoperative levels and the extent of association between the preoperative and postoperative levels. Our findings should facilitate a physician's interpretation of the laboratory reports of CRP and ESR, which can assist the physician in determining the presence of infection after TKA.

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