BMC Musculoskeletal Disorders

RESEARCH

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Natural course of postoperative C-reactive protein and erythrocyte sedimentation rate in unilateral and simultaneous bilateral total knee arthroplasty

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Abstract

Background C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are valuable markers for detecting periprosthetic joint infection (PJI) post-total knee arthroplasty (TKA). However, their prolonged elevation after TKA diminishes diagnostic reliability. This study investigates CRP and ESR trends in unilateral (U-TKA) and simultaneous bilateral TKA (SB-TKA) patients, comparing their patterns.

Methods Between 2017 and 2023, preoperative and postoperative (weeks 2, 4, 6) CRP and ESR levels were assessed in U-TKA (32 patients) and SB-TKA (29 patients) groups for gonarthrosis.

Results Median preoperative CRP levels were 1.13 mg/dL (U-TKA) and 0.2 mg/dL (SB-TKA), with corresponding ESR levels of 13.50 mm/h and 10 mm/h. While CRP and ESR increased more in SB-TKA, differences were statistically insignificant ($p > 0.05$). Both groups showed significant differences in CRP and ESR values at all time points ($p < 0.05$). U-TKA patients reached CRP < 5 mg/dL and ESR < 30 mm/h by the 6th postoperative week. SB-TKA patients did not exhibit significantly higher CRP and ESR levels at various intervals compared to U-TKA patients ($p > 0.05$).

Conclusion This study delineates postoperative CRP and ESR trends in U-TKA and SB-TKA for osteoarthritis. CRP values decreased below 5 mg/dL, and ESR values below 30 mm/h within 6 weeks in both groups. Statistically significant differences in CRP and ESR values were observed at all time points. No significant differences were found in CRP and ESR trends between both groups. These findings aid physicians in interpreting laboratory reports for PJI determination.

Level of Evidence: III.

Keywords Total knee arthroplasty, C-Reactive Protein, Erythrocyte Sedimentation Rate, Knee, Periprosthetic Joint infection

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Introduction

The trend of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as acute phase reactants in the early perioperative phase is a curious topic. A severe complication following total joint replacement surgery is known as periprosthetic joint infection (PJI), and it is responsible for a quarter of unsuccessful outcomes in total knee arthroplasty (TKA) [1]. Timely diagnosis of prosthetic joint infection is crucial as it enables the initiation of treatment at an earlier stage. The assessment of PJI involves various laboratory examinations, including CRP, ESR, white blood cell count (WBC), and more [2]. Nevertheless, there are notable issues associated with using ESR and CRP as diagnostic tools for PJI. One significant problem is that these serum markers tend to remain elevated for a relatively extended period after total knee arthroplasty (TKA), diminishing their diagnostic utility [3, 4].

Myriad studies have aimed to determine the trend of infection laboratory tests in total joint arthroplasty patients [5–8]. To best of our knowledge, there very few comparative studies that determined the trend of infection laboratory tests between unilateral (U-TKA) and simultaneous bilateral TKA (SB-TKA) [9, 10]. This study focuses on CRP and ESR due to their greater specificity in the context of PJI and their recognized importance in the 2018 MSIS criteria for diagnosing PJI, which exclude WBC count as a key serum laboratory parameter [11].

This study aims to delineate the distinct inflammatory responses elicited by U-TKA and SB-TKA, as the latter may induce a more pronounced inflammatory reaction due to increased surgical trauma, potentially influencing the interpretation of CRP and ESR levels in the diagnosis of PJI. This study seeks to determine the trend of CRP and ESR in both unilateral and simultaneous bilateral TKA patients to capture the dynamic phase of the inflammatory response, which is most critical for early detection of potential PJI, with CRP and ESR levels assessed at weeks 2, 4, and 6 postoperatively. It was hypothesized that the level of CRP and ESR remain elevated much longer in simultaneous bilateral TKA patients compared to unilateral TKA patients.

Material and methods

Study population

Following the approval of institutional review board on 10122021–9-3, patients underwent unilateral and simultaneous bilateral TKA between 2017 and 2023 were examined. 61 patients fulfilled all eligibility criteria and were enrolled in the study. Among the TKA patients who were screened, 32 U-TKA patients and 29 SB-TKA patients were found in archive records. Inclusion criteria were (1) patients with advanced osteoarthritis of the knee (Grade 4, bone on bone) affecting the quality of life and daily activities, (2) patients who underwent U-TKA or SB-TKA for gonarthrosis due to unresponsive conservative treatment, (3) patients whose CRP and ESR values were checked at preoperatively and after surgery on week 2, 4 and 6. Patients were excluded according to the following exclusion criteria: (1) a history of previous knee surgery, (2) having inflammatory arthritis such as rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, Hashimoto's thyroiditis, psoriasis, systemic lupus erythematosus and (3) having postoperative adverse events like skin site infection, deep prosthetic joint infection, and urinary tract infection. After exclusions, a total of 61 patients with advanced osteoarthritis of the knee underwent U-TKA or SB-TKA, were included in the study.

Sample collection

Venous blood samples were collected preoperatively and after surgery on week 2, 4 and 6. Samples were collected in Vacutainers containing EDTA-K2, sodium citrate, and serum clot activator (Greiner Bio-one, UK). CRP was measured using an immunoturbidometric technique on a Roche Cobas Integra 400 Plus autoanalyzer (Roche Diagnostics Ltd, Switzerland). Westergren method was used for measurement of ESR (Greiner Bio-One, Austria). The mean and peak values for CRP and ESR were determined. Normal values of CRP and ESR in our institution are 5 mg/dl and 30 mm/h, respectively.

Statistical analysis

Whether the data had a normal distribution was tested with the Shapiro–Wilk test. The independent sample t test was used to compare normally distributed data between two independent groups, and the Mann–Whitney U test was used to compare non-normally distributed data between two independent groups. Wilcoxon was used to compare two dependent groups. Fisher's Exact Chi-Square test was applied to compare categorical data. Descriptive statistics of data with non-normal distribution are shown as mean (min–max), and descriptive statistics of data with normal distribution are shown as mean ± deviation. Categorical variables are given with n (%) values. All statistical analyzes were performed in IBM SPSS Statistics 26 program with a significance level of 0.05 and a confidence level of 95%. As a result of the post hoc power analysis conducted according to the findings obtained from the study, considering the difference between the means for CRP (primary variable) as 9.12 and the combined standard deviation as 10.95 and the effect size as 0.833, the power of the study was obtained as 88% for n1 = 32, n2 = 29, n = 61 people. and the sample size is sufficient.

Results

Table 1 provides a summary of the patient characteristics. In the U-TKA group, the median preoperative serum CRP level was 1.13 (with a range of 0–4.48) mg/dL, and the ESR level was 13.50 (with a range of 4–40) mm/h. In the SB-TKA group, the median preoperative serum CRP level was 0.2 (with a range of 0–4.63) mg/dL, and the ESR level was 10 (with a range of 3–33) mm/h. Table 2 presents the levels of these two serum tests both before and after the surgery, at weeks 2, 4, and 6. While there was a greater increase in CRP and ESR levels in the SB-TKA group compared to the U-TKA group, these differences were not statistically significant ($p > 0.05$).

In U-TKA cases, the CRP level on the 2nd postoperative week ranged from 0.67 to 48.78 mg/dL, with a median of 8.58 mg/dL. In SB-TKA cases, the CRP level on the 2nd postoperative week ranged from 0 to 67.51 mg/dL, with a median of 9.26 mg/dL. Similarly, in unilateral cases, the ESR level on the 2nd postoperative week ranged from 9 to 71 mm/h, with a median of 28 mm/h. In SB-TKA cases, the ESR level on the 2nd postoperative week ranged from 10 to 88 mm/h, with a median of 29 mm/h. Notably, both CRP and ESR values showed statistically significant differences at all measured time points in both groups ($p < 0.05$), as shown in Table 3.

In the U-TKA group, CRP and ESR values returned to levels below 5 mg/dL and 30 mm/h, respectively, by the 6th postoperative week (Figs. 1 and 2). Furthermore, SB-TKR patients did not exhibit statistically significant higher CRP and ESR levels compared to U-TKR patients at various time intervals, including the 2nd postoperative week, 4 weeks, and 6 weeks after the operation ($p > 0.05$), as detailed in Table 2.

Table 1 Between-group comparison of demographic data

n = 61	Unilateral (*n* = 32)	Bilateral (*n* = 29)	*p*-value
Age	68.94 ± 7.39	66.45 ± 7.09	0.186*
Surgery Time	114(95–197)	176(137–254)	**< 0.001****
Weight	84.50(65–120)	83(63–105)	0.707**
Height	156(145–172)	160(147–170)	0.878**
BMI	32.67(24.22–49.95)	32.81(27.89–42.60)	0.937**
ASA	2(1–3)	2(1–3)	0.423**
Gender			
Female	30(%93.8)	28(%96.6)	1***
Male	2(%6.3)	1(%3.4)	
Blood transfusion			
Yes	0(%0)	7(%24,1)	0.003***
No	32(%100)	22(%75,9)	

Data are expressed as mean ± standard deviation, frequency(percentage) or median (min–max)

* *p*-values are the values of the t-test

** *p*-values are the values of the Mann Whitney U test

*** *p*-value is the values of the Fisher's Exact Chi Square test

Table 2 Comparison of inter-group laboratory parameters according

	Unilateral (*n* = 32)	Bilateral (*n* = 29)	*p*-value
Preoperative			
CRP	1.13(0–4.48)	0.20(0–4.63)	0.251**
ESR	13.50(4–40)	10(3–33)	0.060**
2 Weeks			
CRP	8.58(0.67–48.78)	9.26(0–67.51)	0.270*
ESR	28(9–69)	29(10–72)	0.452*
4 Weeks			
CRP	7.49(3.44–17.33)	6.26(2.39–16.97)	0.607*
ESR	23(6–49)	12(3–38)	0.470*
6 Weeks			
CRP	2.77(0–24.25)	2.86(0–15.72)	0.554*
ESR	19(5–35)	16(3–41)	0.409*

Data are expressed as median (min–max)

* *p*-values are the values of the Wilcoxon test

** *p*-values are the values of the Mann Whitney U test

Discussion

In this study, we investigated natural course for serum CRP and ESR after unilateral and simultaneous bilateral TKA. The most important finding of this study was that the CRP value decreases below 5 mg/dl in 6 weeks

Table 3 Comparison of intra-group laboratory parameters according to pre-op

	CRP	ESR
Unilateral (n = 32)		
Pre-op[1]	1.13(0–4.48)	13.50(4–40)
2 weeks[2]	8.58(0.67–48.78)	28(9–69)
4 weeks[3]	7.49(3.44–17.33)	23(6–49)
6 weeks[4]	2.77(0–24.25)	19(5–35)
p-value[1–2]	**< 0.001**	**< 0.001**
p-value[1–3]	**0.028**	**0.043**
p-value[1–4]	**0.001**	**0.005**
Bilateral (n = 29)		
Pre-op[1]	0.20(0–4.63)	10(3–33)
2 weeks[2]	9.26(0–67.51)	29(10–72)
4 weeks[3]	6.26(2.39–16.97)	12(3–38)
6 weeks[4]	2.86(0–15.72)	16(3–41)
p-value[1–2]	**< 0.001**	**< 0.001**
p-value[1–3]	**0.001**	**0.046**
p-value[1–4]	**< 0.001**	**< 0.001**

p-values are the values of the Wilcoxon test. Data are expressed as median (min–max)

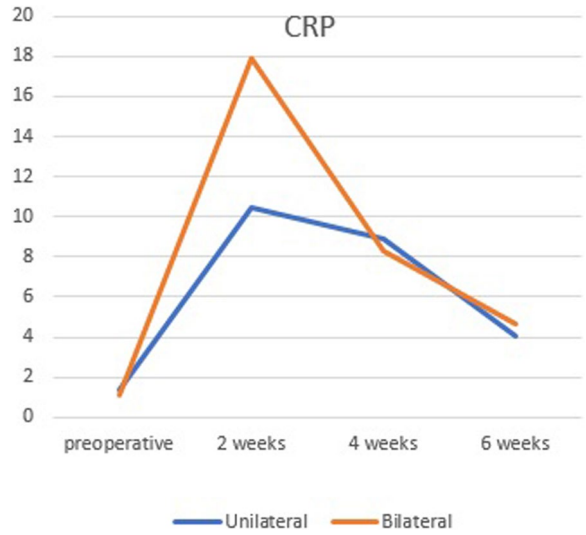

Fig. 1 CRP Levels Timeline for Unilateral and Bilateral TKA

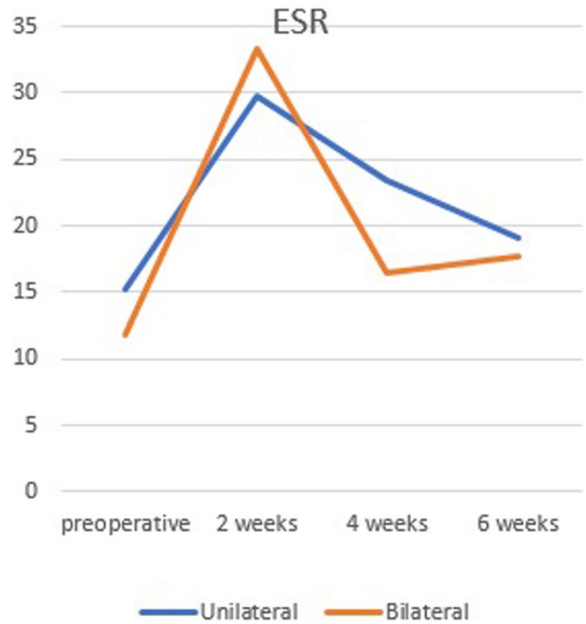

Fig. 2 ESR Levels Timeline for Unilateral and Bilateral TKA

in U-TKA group and SB-TKA group. Additionally, in U-TKA and SB-TKA groups ESR were below 30 mm/h at all measured times.

Obtaining a precise and prompt diagnosis of PJI continues to pose difficulties because of various factors such as patient comorbidities [12], the virulence of the infecting organism [13], and the duration of symptoms [14]. Failing to correctly diagnose or adequately treat PJI can result in a persistent infection, the need for further surgical revisions, impaired function, and an increased risk of mortality [15]. Most diagnostic algorithms for PJI still primarily rely on serological markers, with different consensus statements suggesting a range of options like CRP, ESR, D-dimer, alpha defensin and interleukin 6 [11, 16, 17]. The damage to bone and bone marrow during TKA can lead to an increase in CRP and ESR levels [3]. Hence, it is crucial to understand the natural course of serum CRP and ESR levels following U-TKA and SB-TKA in order to make a diagnosis of PJI.

As per previous research conducted in North America and Europe, CRP levels typically reach their highest point on the first and second days following surgery, gradually returning to normal within 6 to 8 weeks postoperatively [3, 18–20]. A study by Londhe et al. found that a significant proportion of our patients who underwent unilateral TKA (60%) and simultaneous bilateral TKA (92%) did not reach normal CRP levels even 8 weeks after their operations. Notably, the research also revealed that Indian TKA patients required a longer time for their CRP values to return to normal compared to their Anglo-Saxon counterparts [9]. Ethnicity may have an impact on the natural course for serum CRP. In present study, the CRP value decreases to normal levels in 6 weeks in U-TKA group and SB-TKA group. It seems Turkish postoperative CRP trend is compatible with North-American and European counterparts. Only a limited number of studies have investigated the initial post-operative changes in CRP and ESR levels in a specific group of Turkish individuals [4, 5]. The current research aims to address this gap in the existing literature by examining the CRP trends within a Turkish population. Furthermore, the majority of previously published literature has primarily examined CRP trends in total hip arthroplasty and unilateral TKA. In contrast, our study takes a more comprehensive approach by analyzing the CRP trends in both U-TKA and SB-TKA.

General assumption about postoperative ESR trend is that the postoperative normalization of ESR may take 4 months in TKA patients [4, 21] and that the normalization after surgery takes longer than CRP [3, 4, 22]. In this current investigation, both groups exhibited a notably elevated CRP value during the 2nd, 4th, and 6th-week follow-ups in comparison to the preoperative baseline. However, in U-TKA and SB-THA groups ESR were below 30 mm/h at all measured times. A study about ESR's cut-off value for PJI would illuminate diagnostic level of ESR in Turkish population.

The generation of reactive oxygen species (ROS) following TKA can trigger oxidative stress and contribute to postoperative inflammation [23]. This inflammatory response, marked by elevated levels of inflammatory markers like CRP and ESR, can complicate the differentiation between normal postoperative recovery and

periprosthetic joint infection (PJI) [11]. While studies have shown that tourniquet use during TKA can induce ischemia and further contribute to oxidative stress [24], our institution does not employ tourniquets during TKA procedures. This approach may help to mitigate the negative effects of ischemia on mitochondrial function and ROS production [24].Understanding the role of ROS in TKA is crucial for optimizing patient recovery and accurately diagnosing potential complications like PJI, especially given the challenges in interpreting CRP and ESR trends in the early postoperative period [11].

The present study has some limitations. First, we excluded individuals with pre-existing inflammatory conditions from our research. Such patients typically exhibit elevated preoperative CRP and ESR levels. In the future, it would be beneficial to investigate whether CRP and ESR levels in this specific group of patients with inflammatory arthritis return to their preoperative levels within six weeks following TKA. Second, blood samples were not taken in the first week after TKA. It will be useful to to determine the trend of CRP and ESR in TKA patients in first days after TKA. Third, present study has a limited follow-up duration of 6 weeks, focusing on the early postoperative period most relevant for acute PJI, and did not assess long-term outcomes or the potential for late-onset infections, which may require a longer follow-up period, such as 3 months. Fourth, this study did not include a control group of patients with PJI. Future research directly comparing CRP and ESR trends between infected and non-infected patients is necessary to further evaluate the diagnostic utility of these markers in the context of PJI. Fifth, it is worth noting that this study did not account for the effect of blood transfusions on CRP and ESR levels, which could be a confounding factor. However, our analysis of CRP and ESR levels at 2, 4, and 6 weeks postoperatively did not reveal any significant differences between the unilateral and bilateral groups (Table 2), suggesting that the difference in transfusion rates between our groups did not translate into a clinically significant difference in CRP and ESR levels at these time points. This is consistent with the findings of Han et al. [25], who reported no significant difference in CRP response between allogeneic and autologous transfusions in patients undergoing total hip arthroplasty.

Our study documents the postoperative trend of CRP and ESR values in unilateral and simultaneous bilateral TKAs in patients with osteoarthritis, excluding those with pre-existing inflammatory conditions and those with postoperative complications such as infection. We found that the CRP value decreases below 5 mg/dl in 6 weeks in U-TKA group and SB-TKA. We also found that in U-TKA and SB-TKA group ESR were below 30 mm/h at all measured times. Both CRP and ESR values showed statistically significant differences at all measured time points in both groups. There was not statistically significant between trends of both group. 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 PJI.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Gemini in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Human Ethics and Consent to Participate declarations

This study was approved by the Bezmialem Vakif University Institutional Review Board (reference number 10122021–9-3). Informed consent was obtained from all participants included in the study.

Trial registration

This study was an observational cohort study and did not involve any intervention. Therefore, it was not registered as a clinical trial.

Authors' contributions

All authors have read and agreed to this manuscript being submitted for publication. All listed as authors meet the criteria, and nobody who qualifies for authorship has been omitted from the list. Contributors have been properly acknowledged, and all authors and contributors have approved their being listed and/or acknowledged. Mustafa Alper Incesoy conceived the idea of the study and supervised the IRB proposal, study design, collection of data and wrote the first and edited subsequent drafts. Cemil Burak Demirkiran, Hakan Batuhan Kaya, Muhammed Ali GECKALAN and Aysegul Yabaci Tak worked in collection and analysis of the data. Nurzat Elmali, Fatih Yildiz and Gokcer UZER participated in study design and edited the subsequent drafts.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 7 January 2025 Accepted: 12 March 2025
Published online: 14 March 2025

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