RESEARCH ARTICLE

Computer-Assisted Surgery is Associated with Reduced Inflammatory Response in Total Knee Arthroplasty: A Randomized Double-Blinded Control Trial

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Abstract

Objectives: Total knee arthroplasty (TKA) is a standard treatment for advanced knee osteoarthritis (OA), but intramedullary reaming used in conventional (CON)-TKA may increase surgical trauma, blood loss, and systemic inflammation. Computer-assisted surgery (CAS)-TKA avoids canal entry and may reduce these adverse effects. This study compared postoperative inflammatory markers between CON-TKA and CAS-TKA.

Methods: The study was approved by the Institutional Review Board on September 25, 2019 (COA no. 161/61). Participants were recruited from May 2019 to August 2020, and the trial was retrospectively registered with the Thai Clinical Trials Registry on February 24, 2021 (TCTR20210224007). Forty patients with primary knee OA (mean age 67 years) were randomly assigned to CON-TKA or CAS-TKA. Serum inflammatory markers—interleukin-6, C-reactive protein, and erythrocyte sedimentation rate (sIL-6, sCRP, ESR)—were collected at baseline and at 24 h, 72 h, and 2 weeks after surgery. Synovial markers (jIL-6, jCRP) were obtained intraoperatively and from Hemovac drainage at 24 h. Functional outcomes were assessed using the Knee Osteoarthritis Outcome Score (KOOS) at 2 weeks.

Results: The sIL-6 and sCRP levels and ESR at 24 h, 72 h, and 2 weeks after surgery were significantly elevated compared with those at baseline. The CAS-TKA group had a significantly lower change in the sIL-6 and ESR at 2 weeks than the CON-TKA group (5.3 ± 2.9 vs 7.9 ± 4.8, P = 0.040, and 35 ± 16 vs 51 ± 22, P = 0.013). Synovial marker levels did not significantly differ between the two groups. Further, there were no significant differences in KOOS at 2 weeks between the two groups.

Conclusion: Compared with CON-TKA, CAS-TKA had a lower inflammatory response and a smaller change in sIL-6 and ESR levels at 2 weeks after surgery. However, its functional benefits should be further investigated.

Level of evidence: I

Keywords: Computer-assisted surgery, Inflammatory marker, Inflammatory response, Interleukin-6, Total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is a well-established treatment option for advanced osteoarthritis (OA) of the knee, with high patient satisfaction.[1] However, a significant number of patients still present with postoperative pain, which may be prolonged during the recovery period.[2] Postoperative pain can be caused by intraoperative soft tissue and bone injury, resulting in an inflammatory response.[3] A previous study showed that the level of inflammatory response could be directly related to the level of injury.[4] Other studies have revealed that post-surgical trauma-induced immune reactions increase the rates of postoperative infection and mortality in patients undergoing hip or knee surgery.[5-8] Therefore, perioperative management should aim to reduce pain and inflammatory response.[9,10]

The level of inflammatory response can be quantified

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through the assessment of proteins and cytokines, which can be detected systemically or locally. The erythrocyte sedimentation rate (ESR) and serum C-reactive protein (sCRP) level are widely used to measure the systemic response to inflammation. However, unlike the CRP level, a high ESR was not well correlated with inflammation. Although ESR has lower specificity compared to CRP in detecting acute inflammation, it remains a commonly used marker due to its simplicity and ability to reflect chronic low-grade inflammatory changes, making it relevant for longitudinal assessment. The CRP level has a high specificity and positive predictive value in screening infections, can reduce the cost of biological monitoring, and can assess physical symptoms. Moreover, it can be used in conjunction with other biological markers to diagnose surgical site infections.[11] IL-6 is a common inflammatory marker used to monitor inflammation after joint replacement.[12] High IL-6 levels in the joint fluid were associated with a slower recovery time[13] and postoperative arthrofibrosis[14] in TKA. Furthermore, the serum IL-6 level can regulate CRP release and affect ESR. Therefore, it can be a predictor of TKA outcome.[15]

Alternative techniques such as patient-specific instrumentation (PSI) and extramedullary femoral guides have also been introduced to avoid femoral canal violation. These methods aim to minimize surgical trauma and reduce intraoperative stress. PSI systems, for example, have shown logistical and potential clinical benefits, including improved mechanical alignment and less surgical time.[16] Similarly, extramedullary alignment systems have been used effectively even in standard TKA cases, showing comparable outcomes without femoral canal entry.[17]

Computer-assisted surgery (CAS)-TKA was introduced more than a decade ago. CAS can improve overall limb and prosthetic alignment without the need for femoral medullary canal violation.[18] Further, it can reduce the volume of blood loss and the number of blood transfusions.[19,20] Decreased femoral medullary canal violation resulted in a lower incidence of systemic emboli,[21-23] which can reduce marrow embolism-related morbidities. Based on these findings, compared with conventional (CON)-TKA, CAS-TKA may be associated with a lower incidence of microvascular injury caused by systemic microemboli. Therefore, CAS-TKA can be associated with a lower level of inflammatory response compared with CON-TKA. The current study aimed to compare the levels of multiple inflammatory biomarkers between CON-TKA and CAS-TKA. Our study utilized ESR and serum interleukin-6 (sIL-6), sCRP, joint fluid IL-6 (jIL-6), and joint fluid CRP (jCRP) levels to assess inflammatory response after surgery. The association between inflammatory response and functional recovery was also investigated. Then, all patients were followed up for at least 2 years.

The current study primarily aimed to compare the pre- and postoperative levels of sIL-6, sCRP, jIL-6, and jCRP, as well as ESR, between patients who underwent CON-TKA and those who underwent CAS-TKA. Furthermore, the functional outcomes, as measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS),[24] and the complications of TKA were evaluated.

Materials and Methods

This study was approved by the Institutional Review Board of the Faculty of Medicine (COA no.161/61). It was retrospectively registered with the Thai Clinical Trials Registry on February 24, 2021(Trial Registration Number: TCTR20210224007). All patients with primary OA of the knee who required TKA were recruited between May 2019 and August 2020. Written informed consent was obtained from each subject prior to their participation in this study. The anonymity of all patients was protected and preserved.

Patients were randomized using a stratified randomization method and categorized based on age and the Kellgren-Lawrence score [Figure 1]. Random numbers were computer-generated[25] to assign the participants into the CON-TKA and CAS-TKA groups. All of the patients were unaware of the study groups. The inclusion criteria were all patients with primary knee osteoarthritis who underwent unilateral TKA. The exclusion criteria were as follows: patients with previous knee surgery; those with previous or recent knee infection; those with underlying cerebrovascular and neuromuscular diseases affecting knee function; those with active lung disease, liver disease, end-stage renal disease, autoimmune disease, malnutrition, and hypoalbuminemia; those with non-steroidal anti-inflammatory drug-related allergy; those who received systemic non-steroidal anti-inflammatory drugs within 15 days; those with a previous history of intra-articular hyaluronic acid or steroid injection on the planned knee within 6 months; and those with drug abuse issues and those with an history of alcoholism. The surgeons performing the surgeries were not blinded due to the nature of the surgical procedures. However, both groups followed standardized surgical protocols, with the only difference being the use of CAS navigation in the CAS-TKA group and conventional techniques in the CON-TKA group. Furthermore, blinding of outcome assessors was maintained throughout the study. The assessors evaluating biomarkers (IL-6, CRP, ESR) and functional scores (KOOS) were unaware of the participants' group assignments.

The sample size required for each group was calculated using a priori power calculation (G*Power 3.1.9.2 software: http://www.gpower.hhu.de/en.html) and the two-tailed Wilcoxon signed-rank test. The results yielded 17 samples for each group (calculated effect size: 0.8, α level: 0.05, power: 80%, and allocation ratio: 1). We finally decided to enroll 20 patients in each group after referencing the pertinent publications.[26]

All patients underwent TKA performed by a senior surgeon (PC). All patients received a single shot of spinal anesthesia. A tourniquet with a pressure greater than 100 mmHg than the participants' systolic blood pressure was placed on the operated thigh. Then, it was inflated just before making the skin incision, and remained inflated until the completion of prosthesis cementation. The Cruciate Retaining Knee (Scorpio NRG, Stryker Corporation, Kalamazoo, MI, USA) was implanted with patellar resurfacing. All patients were selected for cruciate-retaining (CR) TKA based on preoperative clinical assessment of posterior cruciate ligament (PCL) function. Intraoperatively, PCL integrity was confirmed before proceeding with CR implant. No patients required conversion to posterior-stabilized components. All Patients had bone cement without antibiotics.

Using the mid-vastus approach, the menisci and osteophytes were removed. Then, the proximal tibia was resected initially using the extramedullary alignment guide in the conventional group and using articular surface-mounted (ASM) navigation (Stryker, Kalamazoo, MI, USA) in the CAS group. Thereafter, the distal femur was resected using the intramedullary femoral guide in the conventional group, and the ASM was utilized in the CAS group. There was no femoral canal violation in the CAS group. Soft tissue balancing was performed in a stepwise manner, beginning with the extension gap using spacer blocks to assess and correct medial-lateral tension through selective ligament release. Once a satisfactory extension balance was achieved, a flexion gap assessment was conducted using a tensioning device to confirm that the knee could flex to an appropriate angle without excessive tightness, while maintaining the function of the posterior cruciate ligament (PCL). In all cases, flexion balancing ensured that the femoral component could be appropriately rotated and the PCL tension remained functional throughout the arc of motion. After completing the bone cut, pulsatile lavage was conducted to clean all debris. Then, the prosthesis was implanted with the standard bone cement without antibiotics. A 1/8-in Hemovac (Zimmer Hemovac; Zimmer, Warsaw, IN, the USA) was left in place for 24 h.

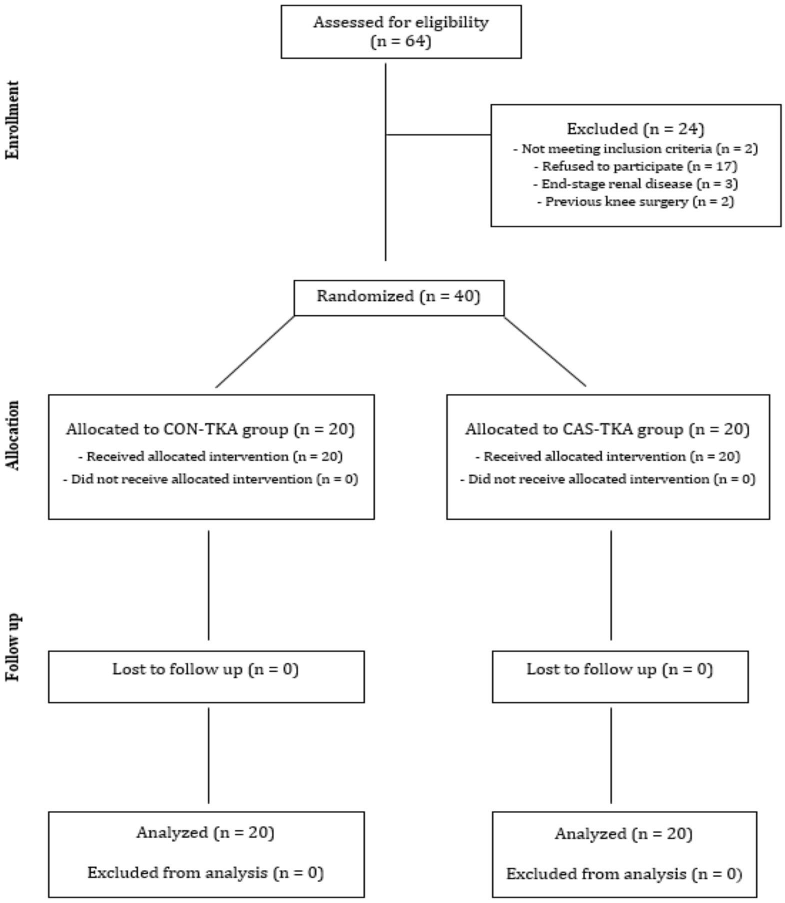

Figure 1. CONSORT flow diagram illustrating the enrollment, allocation, follow-up, and analysis of study participants

The postoperative pain management and rehabilitation protocol were similar in all patients. All patients were admitted 1 day before surgery and discharged if they met the discharge criteria. Length of stay was determined based on the day of admission to the day when the patient met the discharge criteria. The Hemovac drain was routinely removed 24 hours postoperatively, unless drainage exceeded 200 mL; in such cases, the drain was maintained for an additional 12–24 hours, based on clinical judgment. The volume of blood loss was interpreted.[27,28] The patients could perform a range of motion and progressive weight-bearing exercises with the operated knee as tolerated. At 2 weeks after surgery, the KOOS was assessed. The patients were followed up for complications after TKA for at least 2 years. After the 2-week postoperative visit, patients were followed at 6 weeks, 3 months, 6 months, 1 year, and annually thereafter to assess complications or functional deterioration. All outcome assessors were blinded to patient group allocation.

Assessment of IL-6 and CRP levels and ESR

The blood samples used to assess sIL-6 and sCRP levels and ESR were collected upon admission, which is <24 h before and at 24 h, 72 h, and 2 weeks after TKA. The joint fluid samples utilized to examine jIL-6 and jCRP levels were obtained during TKA by aspirating 3 mL of fluid from the knee joint before arthrotomy and at 24 h after surgery via the clamped suction tube drainage. Joint fluid samples were immediately placed on ice for transfer and then centrifuged at 1,000 g for 15 minutes to remove cells. Then, the serum samples were stored at −80ºC until analysis.

The sIL-6 concentration was determined using the electrochemiluminescence immunoassay (cobas®; Roche Diagnostics GmbH, Mannheim, Germany). The jIL-6 concentration was determined using the human enzyme-linked immunosorbent assay (Human IL-6 DuoSet ELISA) by plotting the standard concentration-optical density curve. The ESR was analyzed using the Monitor-20 ESR analyzer (DIESSE®, Italy). The sCRP level was determined using the particle-enhanced turbidimetric immunoassay technique (Dimention®, Siemens Healthcare GmbH, Erlangen, Germany). The jCRP level was identified using the human CRP/CRP DuoSet ELISA.

Statistical analysis

The normality of data distribution was assessed using the Shapiro-Wilk test. This test was selected because it is commonly used for small to moderate sample sizes and is effective in determining whether the data follow a normal distribution. Parameters that passed the normality test were expressed as mean ± standard deviation (SD), while data that were not normally distributed were presented as median (interquartile range, IQR).

For comparisons between groups, the Student's t-test was used for normally distributed data, and the Mann-Whitney U test was applied for non-normally distributed data. The Pearson's chi-square test was used to analyze categorical demographic data between groups. Differences in the levels of sIL-6, jIL-6, sCRP, jCRP, and ESR within the same group at baseline and subsequent time points were compared using the Friedman test, as it is appropriate for non-parametric repeated measures data.

When comparing ESR between groups, a Student's t-test was used, as ESR data followed a normal distribution. Spearman's rank correlation coefficient (Spearman's rho, ρ) was used to assess the relationship between inflammatory marker levels (sIL-6 and jIL-6) and the 2-week KOOS, given the ordinal nature of the KOOS data.

To account for multiple comparisons and reduce the risk of Type I errors, Bonferroni or Holm-Bonferroni corrections were applied where appropriate. These corrections adjust the significance threshold for multiple tests, thereby controlling for the inflated probability of a false-positive result when performing multiple statistical tests.

A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 22.0.

Results

Overall, 40 patients were included in this analysis and randomly distributed into the CON-TKA and CAS-TKA groups [Figure 1]. There was no statistically significant difference in terms of preoperative demographic characteristics, tourniquet time, and operative time between the CON-TKA and CAS-TKA groups. The CAS-TKA group experienced a lower volume of blood loss compared to the CON-TKA group. Table 1 shows the demographic and clinical characteristics of the patients [Table 1]. All participants completed the examination of inflammatory markers using blood and joint fluid samples.

Table 1. Demographic and clinical characteristics of 40 patients undergoing total knee arthroplasty, comparing conventional (CON-TKA) and computer-assisted (CAS-TKA) techniques. Data are presented as numbers (%), mean ± standard deviation, or median (interquartile range). P-values reflect the results of an independent samples t-test, Mann–Whitney U test, chi-square test, or Fisher's exact test.

Variables	CON-TKA group (n = 20)	CAS-TKA group (n = 20)	p-value
Age (years)	66.60 ± 5.10	66.30 ± 5.36	0.857
BMI (kg/m²)	27.90 ± 4.42	26.02 ± 4.17	0.358
Sex			
Male	2 (10.0)	2 (10.0)	1.000
Female	18 (90.0)	18 (90.0)	
KL score			
Grade 3	10 (50.0)	10 (50.0)	1.000
Grade 4	10 (50.0)	10 (50.0)	
Side			
Left	4 (20.0)	13 (65.0)	0.004
Right	16 (80.0)	7 (35.0)	
Coronary artery disease & #equivalents	9 (45.0)	9 (45.0)	1.000
HbA1c (%)	5.88 ± 0.61	5.81 ± 0.53	0.498
Preoperative HKA angle*	10.97 ± 6.18	9.99 ± 8.76	0.733

Table 1. Continued

Postoperative HKA angle*	0.93 ± 2.26	1.46 ± 2.65	0.513
Length of hospital stay (days)	6.00 ± 1.34	5.95 ± 0.83	0.151
Operative time (min)	125.80 ± 19.55	118.80 ± 16.12	0.302
Tourniquet time (min)	63.05 ± 9.50	56.00 ± 15.98	0.207
Blood loss volume (mL)	690 ± 216	626 ± 149	0.372

Data are presented as numbers (%), mean ± standard deviation, or median (interquartile range).

P-values reflect the results of an independent samples t-test, Mann–Whitney U test, chi-square test, or Fisher's exact test.

The equivalents included diabetes, chronic kidney disease, carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm.

* Positive values indicate varus alignment.

Abbreviations: BMI= body mass index; KL= Kellgren and Lawrence; HKA=hip–knee–ankle

The patterns of serum inflammatory markers are shown in [Figures 2-4]. Serum IL-6 levels [Figure 2] increased after surgery in both CAS-TKA and CON-TKA groups, reaching their peak at 24 hours and subsequently declining over time. Although there were no significant differences at individual time points, the CAS-TKA group showed a steeper reduction by 2 weeks, with lower IL-6 levels compared to the CON-TKA group.

Serum CRP levels [Figure 3] peaked at 72 hours in both groups. While not statistically different, the CAS-TKA group consistently exhibited slightly lower CRP levels throughout the follow-up period. ESR [Figure 4] gradually increased after surgery in both groups. By the 2-week follow-up, the CAS-TKA group had a lower ESR than the CON-TKA group, suggesting a milder inflammatory response.

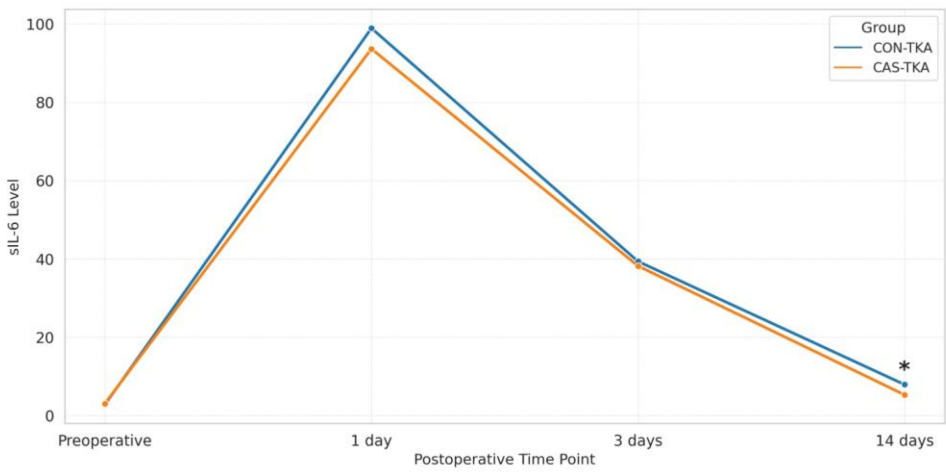

Figure 2. Serum IL-6 levels (pg/mL) were measured at baseline, 24 hours, 72 hours, and 2 weeks postoperatively in CAS-TKA and CON-TKA groups. Error bars represent interquartile ranges. *Statistical significance at 2 weeks ($p < 0.05$)

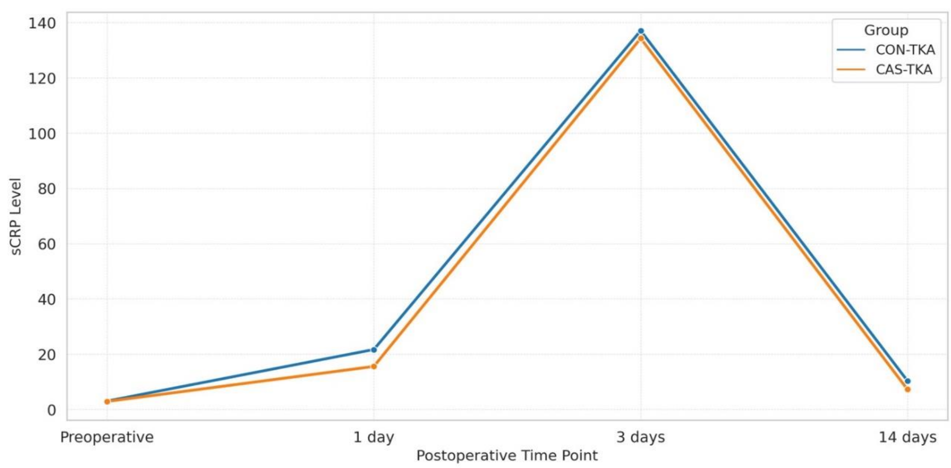

Figure 3. Serum CRP levels (mg/L) were measured at baseline, 24 hours, 72 hours, and 2 weeks postoperatively in CAS-TKA and CON-TKA groups. Error bars represent interquartile ranges

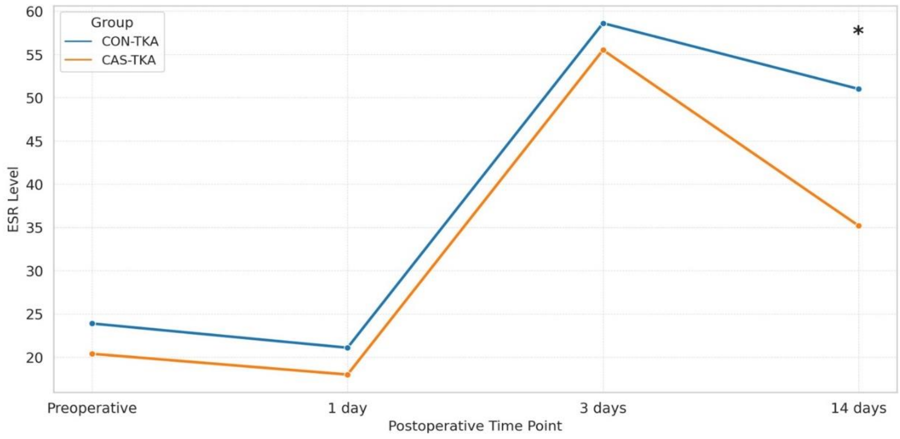

Figure 4. Erythrocyte sedimentation rate (mm/hr) measured at baseline, 24 hours, 72 hours, and 2 weeks postoperatively in CAS-TKA and CON-TKA groups. Error bars represent interquartile ranges. *Statistical significance at 2 weeks ($p < 0.05$)

Consistently, both groups showed significantly elevated sIL-6, CRP, jIL-6, jCRP, and ESR levels at all postoperative time points when compared to baseline. The median sIL-6 peaked at 24 hours, while jIL-6 and jCRP were notably elevated at 24 hours in both groups, with slightly higher values in the CON-TKA group [Table 2]. By 72 hours, sIL-6 levels had declined in both groups without a significant intergroup difference. However, at the 2-week mark, the CAS-TKA group demonstrated significantly lower changes in IL-6 and ESR compared to the CON-TKA group [Table 3].

Table 2. Comparison of joint C-reactive protein (jCRP) and joint interleukin-6 (jIL-6) levels in synovial joint fluid samples and drain fluid between CON-TKA and CAS-TKA groups. Data are presented as median (interquartile range). P-values reflect the results of an independent samples t-test or the Mann–Whitney U test.

Time	CON-TKA group		CAS-TKA group		p-value
jCRP level					
Synovial joint fluid	246	(175–382.5)	249	(171.5–323.5)	0.589
Drain	3,154	(3,147.5–3,154)	3,140.5	(3,087.5–3,154)	0.189
jIL-6 level					
Synovial joint fluid	118	(110–141)	119.5	(111.5–156.5)	0.787
Drain	25,366	(20,408.5–45,356)	25,074.5	(22,578–28,720.5)	0.725

Data are presented as median (interquartile range).
P-values reflect the results of an independent samples t-test or the Mann–Whitney U test.

Table 3. Changes in erythrocyte sedimentation rate (ESR), serum C-reactive protein (sCRP), and serum interleukin-6 (sIL-6) levels over time in CON-TKA and CAS-TKA groups. Data are presented as mean ± standard deviation or median (interquartile range). P-values reflect the results of an independent samples t-test or the Mann–Whitney U test.

Time	CON-TKA group	CAS-TKA group	p-value
ESR			
Preoperative	23.9 ± 20.2	20.4 ± 10.5	0.4956
1 day	21.1 ± 16.8	18.0 ± 8.8	0.4681
3 days	58.6 ± 18.2	55.5 ± 15.2	0.5622
14 days	51.0 ± 21.9	35.2 ± 16.2	0.0134*
sCRP level			
Preoperative	3.01 ± 3.23	2.86 ± 2.35	0.8675
1 day	21.67 ± 15.74	15.55 ± 12.38	0.1797
3 days	137.07 ± 65.97	134.31 ± 62.47	0.8927
14 days	10.32 ± 8.23	7.23 ± 10.60	0.3096

Table 3. Continued

sIL-6 level			
Preoperative	2.75 ± 1.29	3.03 ± 1.16	0.4748
1 day	98.89 ± 68.67	93.63 ± 62.82	0.8018
3 days	39.34 ± 23.72	38.17 ± 25.02	0.8802
14 days	7.87 ± 4.79	5.26 ± 2.86	0.0402*

Data are presented as mean ± standard deviation or median (interquartile range).
P-values reflect the results of an independent samples t-test or the Mann–Whitney U test.

There were no significant differences in terms of the 2-week KOOS between the two groups [Table 4]. Furthermore, the sIL-6 and jIL-6 levels, as well as the 2-week KOOS, showed no significant difference [Table 5]. One patient in the CON-TKA group presented with an intra-hospital acute ischemic stroke. Furthermore, one patient in the CAS-TKA group developed a periprosthetic joint infection during the 20-month follow-up period.

Table 4. Knee injury and Osteoarthritis Outcome Score (KOOS) two weeks postoperatively in CON-TKA and CAS-TKA groups. Data are presented as mean ± standard deviation. P-value reflects the result of the Mann–Whitney U test.

Variables	CON-TKA group (n = 20)	CAS-TKA group (n = 20)	p-value
KOOS	78.90 ± 9.32	78.75 ± 8.84	0.959

Abbreviations: KOOS= Knee Injury and Osteoarthritis Outcome Score
Data are presented as numbers (%), mean ± standard deviation, or median (interquartile range).
The p-value reflects the result of the Mann–Whitney U test.

Table 5. Correlations of ESR, sCRP, and sIL-6 levels with KOOS scores at two weeks postoperatively, analyzed in total, CON-TKA, and CAS-TKA groups. Pearson correlation coefficients (r) and 95% confidence intervals (CI) are reported.

Groups	Variables	KOOS		
		r	95% CI	p-value
Total (n = 40)	*ESR*	−0.104	(−0.403–0.214)	0.522
	sCRP	−0.069	(−0.372–0.248)	0.674
	sIL-6	−0.088	(−0.389–0.230)	0.591
CON-TKA (n = 20)	*ESR*	−0.246	(−0.621–0.220)	0.296
	sCRP	−0.196	(−0.588–0.270)	0.408
	sIL-6	−0.263	(−0.632–0.204)	0.263
CAS-TKA (n = 20)	*ESR*	0.066	(−0.388–0.494)	0.754
	sCRP	0.03	(−0.418–0.466)	0.900
	sIL-6	0.192	(−0.273–0.585)	0.416

Abbreviations: KOOS= Knee Injury and Osteoarthritis Outcome Score; r= Pearson correlation coefficient

Discussion

This randomized controlled trial demonstrated that CAS-TKA was associated with a significantly lower inflammatory response at 2 weeks postoperatively, as indicated by reduced changes in serum IL-6 and ESR levels compared to CON-TKA. These findings support the hypothesis that minimizing femoral canal violation through computer-assisted techniques can attenuate postoperative systemic inflammation.

Our results are consistent with previous studies, which have reported lower serum IL-6 and CRP levels following CAS-TKA. For instance, Kim et al. and Jiang et al. similarly observed attenuated inflammatory biomarker responses in navigated TKA.[29,30] Moreover, elevated IL-6 levels at 24 hours after total hip arthroplasty (THA) were found to correlate with delayed ambulation, suggesting systemic inflammation may negatively impact early recovery.[31] It supports earlier findings that postoperative inflammation can impair functional recovery following TKA.[32] However, in contrast to several prior studies that found superior short-term functional outcomes in the CAS group, our 2-week KOOS scores did not differ significantly between groups. This may be due to the limited follow-up period or small sample size, as early inflammation may not directly translate into immediate functional gains.

Beyond serum analysis, we also evaluated synovial fluid biomarkers. While both jIL-6 and jCRP levels peaked at 24 hours postoperatively, the intergroup differences were small and did not reach statistical significance. These findings align with previous research suggesting that while synovial markers may be more sensitive to joint-level responses, their short half-life and variability limit their utility for between-group comparisons in small samples.[33]

Although CAS-TKA enables more precise bone resection and alignment, recent meta-analyses have failed to demonstrate meaningful clinical superiority or implant survival benefit over conventional TKA.[34,35] Nevertheless, a prior biomarker study showed reduced expression of endothelial cell adhesion molecules after CAS-TKA, suggesting less vascular endothelial stress.[36]

This study has several strengths. It aimed to assess the potential benefit of CAS-TKA by evaluating surrogate biomarkers associated with postoperative complications and recovery. Notably, it is among the first randomized controlled trials to investigate both serum and synovial fluid inflammatory markers in TKA. All procedures were standardized and performed by a single surgeon using a cruciate-retaining, cemented implant with patellar resurfacing. Operative variables, including tourniquet time and blood loss, were well controlled and comparable between groups. Blinding was effectively maintained for patients, clinical assessors, and laboratory personnel through the use of ASM navigation and securely coded specimens.

This study has several limitations. First, the relatively small sample size may have reduced the statistical power to detect significant differences in joint fluid biomarkers and functional outcomes. Second, the short duration for joint fluid sampling, restricted to 24 hours postoperatively, may not adequately capture the full temporal profile of the inflammatory response. Third, as a single-center study with all procedures performed by a single surgeon, the generalizability of our findings is limited. Additionally, the low incidence of complications, such as the isolated case of in-hospital acute ischemic stroke, prevents definitive conclusions regarding the association between surgical technique and postoperative ischemic events. Finally, the short follow-up period of only two weeks is insufficient to assess the long-term clinical impact of the surgery. A follow-up period of 6 months to 1 year is needed to evaluate the sustained effects of CAS-TKA on functional outcomes, pain reduction, and joint stability. Future studies should also include KOOS scores at 2 years postoperatively to better understand long-term recovery and the benefits of CAS-TKA. Larger, multicenter studies with extended follow-up are necessary to confirm these findings and explore their clinical implications.

Conclusion

CAS-TKA, which can be performed without causing medullary canal violation, is associated with a lower level of inflammatory response compared with CON-TKA at the early postoperative period. Nevertheless, the association between the extent of the inflammatory response and clinical outcome, as well as the development of major complications, should be investigated further.

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Authors Contribution: Authors who conceived and designed the analysis: Pruk Chaiyakit, Theerasak Tempaiboolkul/Authors who collected the data: Pruk Chaiyakit, Theerasak Tempaiboolkul, Ittiwat Onklin/Authors who contributed data or analysis tools: Ittiwat Onklin/Authors who performed the analysis: Pruk Chaiyakit, Theerasak Tempaiboolkul, Ittiwat Onklin/Authors who wrote the paper: All authors/ Other contribution: Sittisak Honsawek performed laboratory investigation and contributed to final manuscript review

Declaration of Conflict of Interest: The author(s) do NOT have any potential conflicts of interest for this manuscript.

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Declaration of Ethical Approval for Study: This study was approved by the Institutional Review Board of the Faculty of Medicine, Vajira Hospital on September 25, 2019 (COA no. 161/61). It was retrospectively registered in the Thai Clinical Trials Registry (TCTR20210224007) on February 24, 2021. Available at: https://www.thaiclinicaltrials.org/show/TCTR20210224007.

Declaration of Informed Consent: All patients provided written informed consent prior to participation. Patient anonymity was strictly maintained.

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