

# Relationship of C-reactive protein, erythrocyte sedimentation rate and knee skin temperature after total knee arthroplasty: A Prospective study

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## Abstract

Knee osteoarthritis is a common cause of severe pain and functional limitation. Total knee arthroplasty is an effective procedure to relieve pain, restore knee function, and improve quality of life for patients with end stage knee arthritis. The aim of this study was to investigate the inflammatory process in patients with primary knee osteoarthritis before surgery and in subsequent periods following total knee arthroplasty. A prospective study of 14 patients undergoing primary total knee replacements was conducted from October 2014 to May 2015 in our institution. The patients were evaluated by monitoring serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), knee skin temperature and clinical status. Measurements were carried out preoperatively and postoperatively on day 2 and 2nd week, 6th week, 14th week and 24th week during follow-up review. The CRP was elevated on the 2nd postoperative day but fell to preoperative values at two weeks postoperatively. CRP returned to within the normal range by six weeks postoperatively. In addition, the postoperative ESR showed a slow rise with a maximum level at two weeks after surgery and returned to within normal range at 14 weeks postoperatively. The difference in skin temperature between operated and contralateral knee had a mean value of 3.9C at two weeks. The mean value decreased to 3.4C at six weeks, 2.3C at 14 weeks, and 1.0C at 24 weeks. The difference in skin temperature decreased gradually and eventually there was no statistically significant difference at 24 weeks after surgery. A sustained elevation in serum CRP, ESR, and skin temperature must raise the concern of early complication and may suggest the development of postoperative complication such as haematoma and or infection.

**Keyword:** Total knee replacement, C-reactive protein, knee temperature, erythrocyte sedimentation rate

## Introduction

Osteoarthritis is one of the most common degenerative joint diseases that progressively results in loss of joint function and can lead to substantial morbidity and disability in the elderly <sup>[1]</sup>. Total knee arthroplasty (TKA) is an effective procedure to relieve pain, restore knee function, and improve quality of life for patients with end stage knee arthritis. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are very useful routine laboratory

screening tests for diagnosis of potential infection. ESR is a nonspecific haematological test

routinely used as an indirect parameter of increased acute phase reactants. CRP is a major acute phase reactant that is produced by the liver in response to inflammation, infection, malignancy, and tissue damage<sup>[2, 3]</sup>. The synthesis of CRP is rapidly upregulated, primarily in hepatocytes, under the control of the proinflammatory cytokines mainly Interleukin-6. Interleukin-6 (IL-6) is produced substantially by monocytes and macrophages after antigen activation, even though other cells (such as fibroblasts, endothelial cells, and T-lymphocytes) may also synthesise it<sup>[4]</sup>. Surgery may instantly mediate IL-6 release by these cells, or IL-6 release may be activated by other locally released cytokines. Synthesis of IL-6 in fibroblasts can be upregulated by both IL-1 and tumour necrosis factor (TNF)-<sup>[5]</sup>. However, levels of TNF-, IL-1, and IL-8 are often very low for detection. TNF and IL-1 are most difficult to measure in the systemic circulation even in severely infected patients<sup>[6]</sup>. Furthermore, IL-6 is principally responsible for activating the hepatic synthesis of CRP, which has been considered the inflammatory biomarker of choice in orthopaedic surgery<sup>[7, 8]</sup>. The objective of this study was to investigate the inflammatory process in patients with primary knee osteoarthritis before surgery and in subsequent periods following total knee replacement. This study was designed to evaluate the CRP, ESR, knee skin temperature, and clinical status after uncomplicated TKA. In addition, we further determined the relationships of these parameters with knee skin temperature post TKA.

### Patients and Methods

**Patients:** Fourteen patients, aged 50–78 years, diagnosed with primary knee osteoarthritis (six females and eight males; mean age 67.8) were recruited in this prospective study over a 24-week period. We excluded any patients with inflammatory arthritis, a systemic inflammatory or autoimmune disorder, or a history of any type of cancer or chronic illness. All patients underwent total knee arthroplasty at our institute from October 2014 to April 2015 and were operated upon by one surgeon (AT) using the standard surgical technique.

The routine anaesthesia method was Epidural anaesthesia. In each case the standard parapatellar approach was used with a tourniquet. A wound drain with vacuum suction was used and was removed on the second day after surgery. All patients were mobilized on the second operative day. The skin temperature of both knees was evaluated preoperatively and postoperatively at day 2, day 14, 6th week, 14th week and 24 weeks during follow-up review. The temperature was determined using skin surface thermometer at four different locations on the anterior aspect of the knee (superomedial, superolateral, inferomedial, and inferolateral border of the patella). The mean of the two readings was taken as the final temperature. A similar measurement was also carried out on the contralateral knee, which served as the control. Assessment taken at midday was selected as the time for taking readings for the rest of the study. For each patient, the same thermometer was used throughout the course of the study. **Laboratory methods:** Venous blood samples were obtained before surgery, and on the second postoperative day and at 2 weeks, 6 weeks, 14 weeks and 24-weeks follow-up. C-reactive protein was measured using the latex particle enhanced nephelometric immune assay.

### Statistical Analysis

All values were expressed as mean  $\pm$  standard deviation (SD). Comparison between groups were employed using Student's t-test and Mann-Whitney U-test. A P-value < 0.05 was considered to be statistically significant.

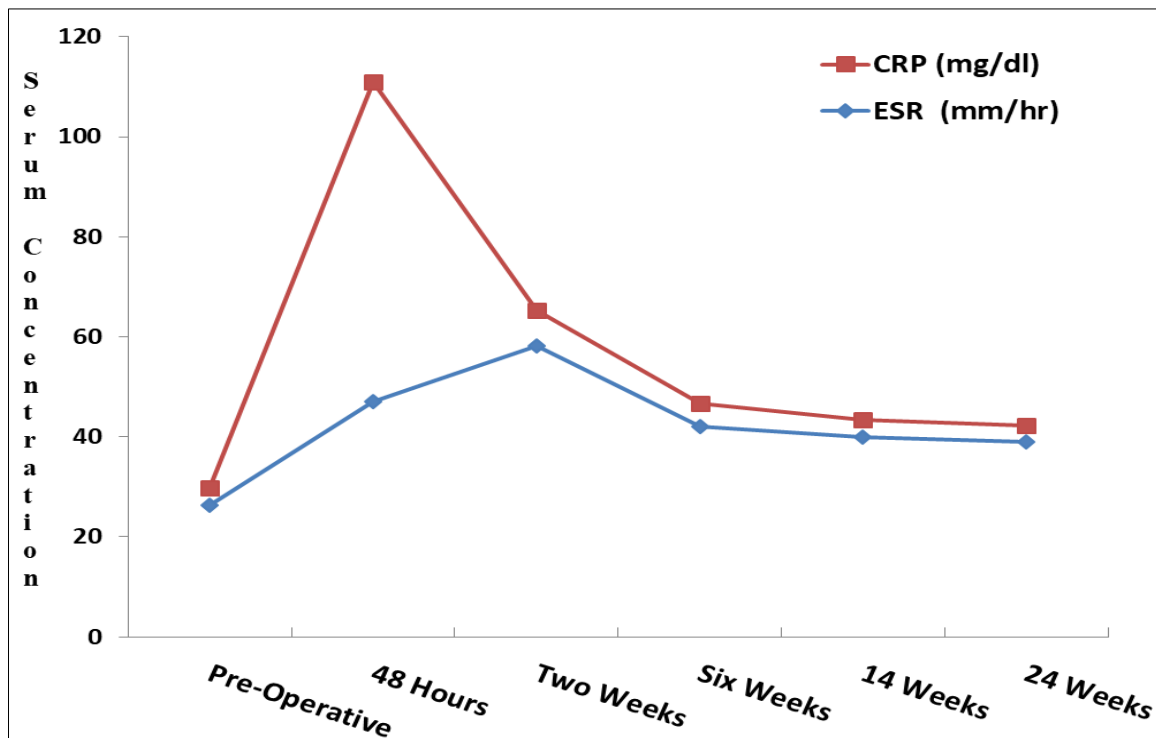
**Analysis Table**

**Table1:** Comparison of ESR and CRP levels before and after Surgery

Parameter	Pre-Operative			Post-Operative		
	Time Period					
	Pre-Operative	48 Hours	Two Weeks	Six Weeks	14 Weeks	24 Weeks
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ±sd	Mean ±sd	Mean ± sd
ESR (mm/hr)	26.36 ± 6.30	47.07 ± 8.56	58.14± 9.49	42.00± 7.72	39.93± 7.66	38.93± 7.66
CRP (mg/dl)	3.34 ± 1.21	63.78 ± 9.10	7.22 ±1.06	4.60± 0.72	3.53± 1.16	3.30± 1.11
ESR Pre Vs Post		0.0001	0.0001	0.0001	0.0001	0.0001
CRP Pre Vs Post		0.0001	0.0001	0.01	0.004	Not Significant

**Table 2:** Comparison between the Temperatures of operated Knee and Contralateral knee

Parameter	Temperature (Degree Celsius)			
	2 Weeks	6 Weeks	14 Weeks	24 Weeks
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
Operated Knee	36.32 ± 0.28	36.15 ± 0.39	35.59 ± 0.34	35.19 ± 0.26
Contralateral Knee	32.28 ± 0.23	32.88 ± 0.46	33.34 ± 0.55	34.33 ± 0.36
OK vs CK p-value	0.0001	0.0001	0.0001	0.0001



**Fig 1:** Comparison between mean creative protein and erythrocyte sedimentation rate

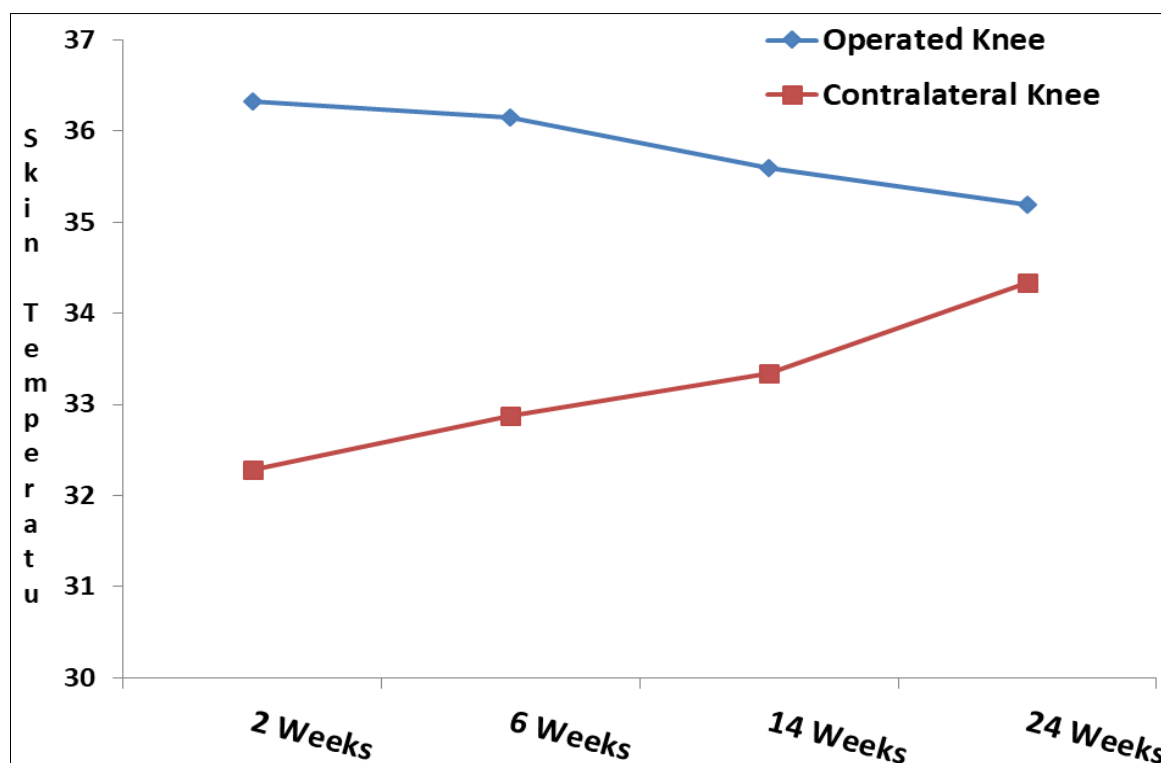


Fig 2: Mean skin temperature of both knees in osteoarthritis patients

## Discussion

Infection following joint arthroplasty is a major concern for Surgeons. Nonspecific clinical presentation makes it difficult to distinguish from those indicating infection. Objective data are needed to exclude the possibility of infection despite suspicious clinical symptoms and signs. CRP and ESR have been extensively used to examine the presence of infection following surgery. IL-6 appears to be a major endogenous protein mediator of fever and the acute phase response after surgery<sup>[5]</sup>. IL-6 also plays a crucial role in the induction and regulation of the acute phase protein response, particularly that of CRP synthesis by hepatocytes<sup>[9]</sup>. Elevated CRP, ESR, and skin temperature can raise concern that infection may be present following TKA<sup>[10]</sup>. It is imperative therefore to investigate the temporal patterns of CRP, ESR, and knee skin temperature after uncomplicated TKA. Our results have demonstrated that there is a significant rise in CRP. In comparison, ESR differs in the temporal pattern of postoperative level after TKA. ESR had slower temporal changes and lower amplitude changes. These findings are in accordance with those of previous studies reporting the postoperative levels of IL-6, CRP, and ESR after total joint replacement<sup>[11, 12]</sup>. Serum IL-6 and CRP correlate with a high degree of inflammatory activity with a more rapid increase and a faster return to normal values than ESR, suggesting that IL-6 and/or CRP measurements could be more favourable than ESR measurements in determining the presence of infection during the early postoperative period. Moreover, previous studies have indicated that IL-6 may be a better indicator of postoperative inflammatory response<sup>[13-15]</sup>. IL-6 levels reach the maximum level in the first six to 12 hours following surgery and fall back to their baseline range by 48 to 72 hours postoperatively<sup>[13, 16, 17]</sup>. CRP levels peak two to three days after surgery and return to normal values approximately three weeks postoperatively<sup>[18-20]</sup>. This study has also shown that the skin temperature of the operated knee is significantly raised following surgery and gradually decreased by 24 weeks postoperatively. This temperature difference is presumably attributed to the postoperative inflammatory response in the operated knee. In accordance with our findings, Mehra *et al.* have demonstrated that skin

temperature of the operated knee increases in the early postoperative period but returns to normal at 18 weeks postoperatively<sup>[21]</sup>. Haidar *et al.* have also shown a decrease in the mean difference between the operated and contralateral knee over time<sup>[22]</sup>. Significant postoperative elevations in CRP, ESR, and knee skin temperature should be a normal response to surgical trauma and not an indication of complications. Measurements of these parameters, including at least one preoperative measurement, are required when the clinical significance of the postoperative values of these parameters is indicated. If postoperative values of these parameters continue to be elevated for several days with respect to the preoperative value, or even show a tendency to rise, further investigation for this must be carefully evaluated. The limitations of our study are firstly, we did not collect blood specimens during the early postoperative period when CRP and ESR are elevated. This made it difficult to determine precisely when peak CRP and ESR was achieved. No blood sampling was collected between the first and 14th postoperative days, which made it impossible to tell the exact time when CRP and/ or ESR reach the maximum level. Secondly, our study was based on a relatively small number of enrolled patients. A further investigation with a larger number of subjects would be needed to make a strong conclusion. In conclusion, this study demonstrates the temporal patterns of CRP, ESR, and knee skin temperature in osteoarthritis patients undergoing TKA. The use of IL-6 in conjunction with CRP and ESR was suggested to verify infection following surgery.

### Conclusion

A sustained elevation in CRP, ESR and skin temperature must raise the concern of early complication and may suggest the development of postoperative complication such as haematoma and/or infection.

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