

C-reactive protein (CRP) in different types of minimally invasive knee arthroplasty

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Abstract

Purpose C-reactive protein (CRP) is an acute-phase biomarker responding to surgical trauma. Typically, a first peak is observed at day 2 with a reduction at day 4 and normalization 3–6 weeks after surgery. CRP is often linked to prosthetic joint infection when elevated values are present longer time after surgery. The aim of this study was to analyse the kinetics of CRP in different types of minimally invasive (MI) arthroplasty and to observe if there were significant differences in between MI total knee arthroplasty (TKA), patient-specific instruments (PSI) TKA and unicompartmental arthroplasty (UKA).

Materials and methods Three hundred and seventy-two patients were prospectively studied with a blood test measuring CRP at day 2, 4, 21 and 42 in 3 different groups of patients: 257 MI TKA, 55 PSI TKA and 60 UKA. Mean peak values and kinetics were compared in between different groups of MI arthroplasty.

Results There was a significant age difference in the three MI arthroplasty groups. The difference in mean age for the conventional MI TKA group of 68.8 ± 9.8 years, 58.5 ± 11.7 years for the unicompartmental group ($P < 0.05$) and

63.3 ± 9.6 years for the PSI group ($P < 0.05$) was significant. Mean CRP level, for the entire study group, on day 2 was 16.7 ± 8.8 mg/dl that gradually decreased to 13.6 ± 7.8 mg/dl on day 4. On day 21 and 42, median CRP level was 0.6 (0–20) and 0.4 (0–7) mg/dl, respectively. Peak CRP values were lower for UKA compared to TKA at day 2 (11.6 vs. 17.5 mg/dl) and day 4 (8.0 vs. 15 mg/dl), but this was not observed for PSI-assisted arthroplasty (18.9 vs. 17.5 mg/dl). There was a trend for faster CRP normalization in UKA compared to the two other groups at day 21 and at day 42 and for PSI TKA to have a lower mean level at 4 days (12.9 vs. 15 mg/dl). There was no statistical difference in the normalization rate of PSI-assisted versus MI TKA.

Conclusion Kinetics of CRP in MI arthroplasty are identical to the published kinetics of conventional TKA. Most patients normalize CRP at 3 weeks; however, 18 % does not by 6 weeks. This is not a sign of early prosthetic joint infection. Peak values are significantly lower for UKA but not for PSI TKA.

Level of evidence II.

Keywords C-reactive protein · Knee arthroplasty · Minimally invasive surgery · Patient-specific instruments · Unicompartmental arthroplasty

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Introduction

Total knee arthroplasty (TKA) is increasingly being used to alleviate pain and to improve mobility in arthritis for both younger and older patients [33, 34]. Postoperative pain and inflammation are part of the surgical process [23]. TKA represents a major surgical stress and is associated with a significant increase in the postoperative circulating levels of plasma hormones and inflammatory markers [3, 12]. The

release of neurogenic substances from the surgical area into the innervated tissues contributes to the establishment of peripheral inflammation [3]. Local cytokines like IL-6 and MCP-1 have been linked to surgical trauma in knee arthroplasty [35]. Systemic inflammatory parameters can be screened in the blood of surgical patients [1, 8]. Among those, C-reactive protein (CRP), an acute-phase protein produced in the hepatocytes is commonly used [14, 36]. Its synthesis is rapidly up-regulated under the control of the pro-inflammatory cytokines [14]. CRP plasma concentrations increase during inflammatory states, a characteristic that has long been employed for clinical purposes. Normal plasma levels of CRP in healthy adults are <1 mg/dl. The rapid increase in synthesis within hours of tissue injury or infection suggests that it contributes to host defence and that it is part of the innate immune response [1, 36]. Some authors have studied CRP kinetics after elective orthopaedic surgery [4, 7, 14, 19, 26, 36]. It has been shown that CRP levels rise after conventional knee and hip arthroplasty and that they reflect the degree of systemic trauma after surgery [23, 41].

Anaesthetic and surgical techniques have been optimized to facilitate rehabilitation after arthroplasty [10, 25, 30]. On the surgical side, minimally invasive approaches were developed without eversion of the patella [2, 21]. The anaesthesiologists introduced multimodal pain management combined with loco-regional anaesthesia [30]. The aim of this anaesthetic technique would be to modulate the surgical inflammatory response by a local block [3]. With the introduction of patient-specific instruments (PSI), the orthopaedic community wanted to address the issues of three-plane alignment and especially rotational alignment that was not fully covered with computer navigation [6, 15, 37]. The available peer reviewed data of PSI-assisted surgery are scarce up-to-date but eagerly waited for [24, 28].

The hypotheses of this prospective study were (1) that the observed peak levels of CRP would be lower in unicompartmental and PSI-assisted arthroplasty compared to TKA, (2) that CRP kinetics would be different between unicompartmental, minimally invasive and PSI-assisted TKA and (3) finally that non-normalization of CRP at 6 weeks after arthroplasty was not a sign for early prosthetic joint infection.

Materials and methods

This study was carried out on patients with a diagnosis of primary osteoarthritis of the knee who underwent conventional minimally invasive (MI) TKA, PSI-assisted MI TKA or unicompartmental arthroplasty (UKA) between 1 January 2010 and 30 March 2011 in a University teaching hospital. Data were collected prospectively on the electronic database

of our RCM registry, on the operating software for patient's medical records of our institution (Medical Explorer v3r9, Saint-Luc Hospital, 2008). Analysis of CRP was done using an immunoturbidometric technique on an auto-analyser (Olympus). The assay displays a limit of detection of 0.014 mg/dl with the normal programme. Results were obtained at one decimal precision. Patients with clinical signs of infection, neoplasia, inflammatory disease (rheumatoid arthritis, lupus, HIV) or who had had any operative procedures within 3 months before admission were excluded. Patients with C-reactive protein levels >1 mg/dl before surgery were also excluded. Patients who developed a prosthetic joint infection or other inflammatory or septic complications were also excluded during the 6 weeks course of the study. All preoperative and postoperative blood tests up to 6 weeks after surgery, were performed at the same laboratory. All patients were operated by a single surgeon under general anaesthesia. No loco-regional anaesthetic techniques were used. They all underwent a minimally invasive medial subvastus approach. The length of the skin incision and the arthrotomy were of course smaller for unicompartmental arthroplasty (9 vs. 14 cm). Cefalosporines were given 1 h before tourniquet inflation. The patella was displaced laterally but never everted. Intra-medullar alignment was used on the femoral side and extra-medullar alignment for tibial alignment. Minimal anterior dislocation of the tibia was performed at implantation of the tibial component. A postero-stabilized fixed-bearing implant (Vanguard, Biomet, Warsaw, US) was used in all patients with cemented components and patella resurfacing. For the unicompartmental arthroplasty, a cemented fixed-bearing prosthesis, the Zimmer Unicompartmental Knee (ZUK, Zimmer, Warsaw, US) was implanted. Extra-medullar alignment was used on the tibial side and a spacer technique for the femoral side. The PSI cases were all Signature (Biomet, Warsaw, US) with an MRI-based preoperative planning and production of surface matching pin locator guides (Materialise, Leuven, Belgium). If during the surgery conversion to conventional intra-medullary guides was necessary, the patient was excluded from the study. No drains were used. Full weight bearing without crutches was allowed the next day, and range of motion exercises were started immediately after surgery. No drains were used. Thrombosis prevention was done with nadroparin for 10 days after surgery. Blood specimens were collected before surgery and on day 2, 4, 21 and 42 after surgery as part of the standard arthroplasty follow-up in our institution. All patients were examined everyday during their 5-day hospitalization by the internist (JY) and at the outpatient's clinic on days 21 and 42, 3 months and 1 year after surgery by the surgeon (ET) to detect early postoperative complications. Less unicompartmental arthroplasties could be included in this study then performed during that time

period because few of them were ready to stay at least 4 days at the hospital to perform the day 4 blood test.

All patients, initially included in this study, were followed at least 1 year, clinically and radiologically, in order to detect the development of early prosthetic joint infection.

All patients were informed of the data collection and their future anonymous use for statistical purposes. All patients agreed orally to take part in this study upon admission to the ward. Institutional ethical committee approval was granted to this study.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences software, version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). All values were expressed as mean + standard deviation (SD) when the distribution was normal and symmetric and median (min–max) when the distribution was right-skewed. ANOVA testing was used for day 2 and 4 values and later on a Kruskal–Wallis test for day 21–42.

Results

A total of 372 arthroplasty patients (113 M/259 F) with a mean age of 66.1 ± 10.7 years were included in this study. Two hundred and fifty-seven patients underwent minimally invasive TKA; 55, PSI-assisted (Signature, Biomet, Warsaw, US) TKA; and 60, unicompartmental arthroplasty. The MI TKA population had a mean age of 68.8 ± 9.8 years. A significant younger age was observed for both unicompartmental; 58.5 ± 11.7 years ($P < 0.05$), and PSI-assisted arthroplasty; 63.3 ± 9.6 years ($P < 0.05$). Demographic data are summarized in Table 1. Thirteen patients left the hospital before their day 4 blood test leaving 359 patients available for a second CRP value.

For the entire study group ($N = 372$), CRP rose gradually with peak levels on the 2nd day after surgery. Mean CRP level on day 2 was 16.7 ± 8.8 mg/dl and gradually decreased to 13.6 ± 7.8 mg/dl on day 4. On day 21 and 42, median CRP levels were 0.6 (0–20) and 0.4 (0–7) mg/dl, respectively (Table 2). However, on day 21 and 42, 32.1 % (104/324) and 18.7 % (48/256) of patients had not reached normal CRP levels yet (CRP < 1 mg/dl) (Table 3).

In Table 4, the mean CRP peak values are compared for each different technique of minimally invasive arthroplasty. Peak CRP values were statistically lower for unicompartmental arthroplasty compared to MI TKA at day 2 (11.6 vs. 17.5 mg/dl) and day 4 (8.1 vs. 15 mg/dl) ($P < 0.0001$), but this was not observed for PSI-assisted arthroplasty (18.9 vs. 17.5 mg/dl) ($P = \text{n.s.}$). There was a trend for faster CRP

normalization in UKA compared to the two other groups at Day 21 (80.4 vs. 65.6 %) ($P = 0.05$) and at day 42 (92.1 vs. 78.5 %) ($P = 0.05$) (Table 5).

When PSI-assisted TKA was compared to MI TKA, a slightly higher peak at day 2 (18.9 vs. 17.5 mg/dl) was observed but a lower mean CRP peak at 4 days postoperative (12.9 vs. 15 mg/dl) (n.s.) (Table 6). There was no statistical difference in the normalization rate of PSI-assisted versus conventional MI TKA.

None of the patients with abnormal CRP on D21 and D42 after TKA have been diagnosed with early prosthetic joint infection at 1-year follow-up.

Discussion

The most important findings of this study were that MI TKA shows a CRP kinetics pattern similar to one of conventional TKA published earlier in the literature. PSI-assisted TKA does not reduce the systemic inflammatory response (peak value of CRP) after surgery, nor does it allow for a faster return to normal values of this inflammatory serum parameter. There was a lower CRP peak at day 4 in the PSI group, probably because of less bone marrow damage by not opening the medullary canal, but without statistical significance.

Another important finding was that a lower CRP peak with faster recovery of CRP kinetics was observed after unicompartmental arthroplasty. Finally, it was observed that CRP values that are not normalized at 6 weeks post-arthroplasty did not result in early prosthetic joint infection.

The acute-phase response after surgery is diverse and complicated. Serum IL-6 level, CRP level, WBC count and fever are representative markers for surgical trauma [14]. Some authors have studied CRP in different types of orthopaedic surgery [4, 7, 14, 19, 23, 26, 36]. Their conclusion is that CRP levels reflect the extent of tissue damage during surgery [4, 19, 23]. Recently, Shen et al. compared CRP levels after four different types of arthroplasty and found that the peak CRP levels after hip resurfacing and computer navigation-assisted TKA were lower than those after conventional primary total hip arthroplasty (THA) and TKA. They considered these two former types of arthroplasty as “systemic minimally invasive” arthroplasties [36].

The same findings for PSI TKA were not confirmed, but we compared it to MI TKA, which has lower CRP peak values compared to published CRP values for conventional TKA. Tsujii et al. [39] found no differences in CRP in a MI and a conventional total knee group, but did not specify their values. Moerschini et al. [22] found no differences between THA and TKA. Larsson et al. [19] showed that the increase in CRP depended not only on the amount of tissue

Table 1 Demographics of study groups

Number of patients <i>N</i> (%)	372 (100 %)	257 TKA (69 %)	55 PSI (15 %)	<i>P</i> value	60 UNI (16 %)	<i>P</i> value
Age mean (SD)	66.1 (10.7)	68.8 (9.8)	63.3 (9.6)	<0.001	58.5 (11.7)	<0.001
Sex <i>N</i> (%)	M/F	113 M (30.4 %)	259 F (69.6 %)			
Laterality (%)	L/R side	197 L (52.9 %)	175 R (47.1 %)			
BMI (SD)		30.4 (5.6)	30.3 (6.08)	n.s.	29.8 (4.8)	n.s.

Table 2 Mean and SD of CRP for entire study group (*N* = 372)

<i>N</i> = 372	Mean (SD)	Median (min–max)
<i>CRP blood test</i>		
Day + 2	16.7 (8.8)	(1–48)
Day + 4	13.6 (7.8)	(1–41)
Day + 21	1.3 (0.21)	0.6 (0–20)
Day + 42	0.8 (0.93)	0.4 (0–7)

Table 3 Normalization of CRP in total study group

Blood test (<i>N</i> = 372)	% patients with CRP < 1 mg/dl
Day 2	1.1
Day 4	0.6
Day 21	67.9
Day 42	81.3

Table 4 Peak values CRP (SD) for each type of arthroplasty

	<i>N</i>	CRP mean (SD)	<i>P</i> value
<i>Day 2</i>			
TKA	257	17.5 (8.9)	0.0001
UKA	60	11.6 (7.5)	
PSI	55	18.9 (7.4)	
<i>Day 4</i>			
TKA	252	15 (7.9)	0.0001
UKA	53	8 (5.8)	
PSI	54	12.9 (6.7)	
CRP median (min–max)			<i>P</i> value
<i>Day 21</i>			
TKA	227	0.7 (0–20)	n.s.
UKA	46	0.5 (0–4)	
PSI	51	0.6 (0–9)	
<i>Day 42</i>			
TKA	181	0.4 (0–5)	n.s.
UKA	38	0.4 (0–7)	
PSI	37	0.4 (0–5)	

injured, but also on the type of tissue being damaged, such as bone, fat or muscle. No relation between alignment, soft tissue releases and CRP levels was found.

Table 5 Normalization of CRP in time for different groups

	<i>N</i>	% CRP < 1 mg	<i>P</i> value
<i>Day 2</i>			
TKA	257	0.8	n.s.
UKA	60	3.3	
PSI	55	0.0	
<i>Day 4</i>			
TKA	252	0.4	n.s.
UKA	53	1.9	
PSI	54	0.0	
<i>Day 21</i>			
TKA	227	65.6	0.05
UKA	46	80.4	
PSI	51	66.7	
<i>Day 42</i>			
TKA	181	78.5	n.s.
UKA	38	92.1	
PSI	37	83.8	

Table 6 CRP MI TKA versus PSI TKA

	<i>N</i>	CRP mean (SD)	<i>P</i> value
<i>Day 2</i>			
MI TKA	257	17.5 (8.9)	n.s.
PSI	55	18.9 (7.4)	
<i>Day 4</i>			
MI TKA	252	15 (7.9)	n.s.
PSI	54	12.9 (6.7)	
		CRP median (min–max)	<i>P</i> value
<i>Day 21</i>			
MI TKA	227	0.7 (0–20)	n.s.
PSI	51	0.6 (0–9)	
<i>Day 42</i>			
MI TKA	181	0.4 (0–5)	n.s.
PSI	37	0.4 (0–5)	

Neumaier et al. suggested that trauma to the bone marrow is crucial for the CRP response. Opening of the femoral canal, extrusion of bone marrow from the medullary cavity, and loading of the lungs with bone marrow would result in higher CRP values [19, 23].

Peak levels of CRP after TKA have been found to be higher than those after THA [7, 26, 41]. TKA is more traumatic, and the severity of bone and bone marrow trauma seems to be an influencing factor [36]. This can probably be explained by macrophages that are more present in bone than in muscle [4, 19]. In TKA, the degree of inflammation was higher, and the duration, longer. In contrast, the type of anaesthesia used, the extent of blood loss or blood transfusion, use of cement or tourniquet, antibiotics or anti-inflammatory drugs, operative time, and patient age and gender have no impact on CRP levels [4, 19, 31].

Niki et al. studied the difference in surgical trauma of different minimally invasive approaches with different muscle enzymes. They found no difference between conventional and minimally invasive surgery and even more muscle damage with a midvastus approach [25].

No lower CRP peak levels were found either, and it has to be concluded that PSI-assisted knee arthroplasty is not less traumatic at the bone level, resulting in comparable CRP levels as minimally invasive TKA. This finding seems logical since in PSI TKA, the bone cuts are the same. A possible difference would only be observed at the intra-medullary canal level. The hypothesis of bone trauma was further confirmed in this study since significant lower CRP levels were observed in the unicompartmental group, where less bone surface is cut resulting in less surgical trauma [23, 36]. This could be an important argument why unicompartmental arthroplasty is better tolerated by patients [27].

A lower CRP peak value at 4 days was observed in the PSI group. This could mean that the initial peak at day 2 is determined by the surgical trauma (approach and bone cuts) and that the more important reduction at day 4 is related to the absence of intra-medullary canal bone exposure [23]. Maybe a significant difference between both groups was not observed because the surgeon aspirates the bone marrow extensively after opening the canal before rodding, avoiding fat and bone marrow to enter the circulation [9]. Another explanation would be that the patients of the MI TKA group were older and that a less important CRP response has been observed in that group because of their older mean age [4].

CRP kinetics after orthopaedic surgery has been studied by several authors [4, 7, 14, 19, 23, 26, 36]. Plasma CRP levels fluctuate after elective knee arthroplasty with maximum values observed between the 2nd and 3rd postoperative days, followed by an ulterior decrease [4, 19]. CRP usually reaches normal levels 3–6 weeks after surgery [4, 7, 19, 23, 26]. Neumaier et al. studied 16 conventional TKA and found a mean preoperative CRP of 0.5 mg/dl with a mean peak of 26.0 mg/dl on day 2. A regression to 0.9 mg/dl was observed at 2 months and only a complete normalization at 3 months postoperative [23, 26].

Park et al. described well the time to return to normal of the CRP with a rapid increase until the peak at day 2 and then

a decreasing pattern in two phases. A gradual decrease to less than the normal reference level on the 42nd day and a return to the preoperative levels on the ninetieth day [31]. Bilgen et al. [4] too observed normal values only after 3 months.

In our study, the mean CRP level for MI TKA on day 2 was 17.5 mg/dl (SD 8.9). Other authors have shown that peak CRP levels could vary between 10 and 26.02 mg/dL [4, 19, 23]. A typical drop of the mean CRP to 15 mg/dl was observed. It is interesting to note that in our study, though median CRP values were almost normal on day 21 (0.7 mg/dl) and 42 (0.4 mg/dl), 34.4 and 21.5 % of patients, respectively, had not reached normal CRP levels yet after 6 weeks. No blood tests were performed after this period, if clinically the patient's evolution was reassuring. We did not observe a faster reduction in CRP levels in MI TKA compared to previously published papers [8] despite that 68 % of patients had normalized (<0.8 mg/l) their CRP at 3 weeks.

Specific data on the value of kinetics of CRP and particularly the value of CRP at day 21 and day 42 to predict the occurrence of prosthetic joint infection in the year of follow-up are scarce in the modern literature [1, 8] (Fig. 1).

In general, the rapid decline in CRP after uncomplicated TKA will be interrupted by a second rise or by a persisting elevated level if infectious complications occur [1, 26, 41]. Serial measurement of CRP levels is thus the most useful tool in the early detection of surgical complications [8, 41].

Finally, a significant difference in the different age groups was observed. The younger unicompartmental arthroplasty patient is not new to literature [27, 34]. However, a younger age for the PSI-assisted group was observed too. There was no bias from the surgeon in patient selection. Most patients who had PSI-assisted TKA came with a specific demand for that type of surgery. We believe that the bias in this age group is created by the Internet. Younger patients browse the Internet more and decide based on that information what they want. It is up to the orthopaedic community to provide papers like this one to inform our peers about the Internet-based information on PSI and knee arthroplasty.

The limitation of this study lies in the fact that not all patients did their blood tests up to day 42. Until day 4, this was because some patients left the hospital before the second blood test. At 21 and 42 days, the main reason was that the patients forgot to do the blood test before seeing the surgeon and because a normal blood test from the previous clinic was present or an excellent clinical result was observed. At that stage, the blood test was cancelled for economical reasons. A very small group was excluded because of prosthetic joint infection (0.8 %) or superficial wound complications (1.2 %). None of the patients that remained in the study developed a joint infection at 1 year follow-up. Five patients in the conventional MI TKA group

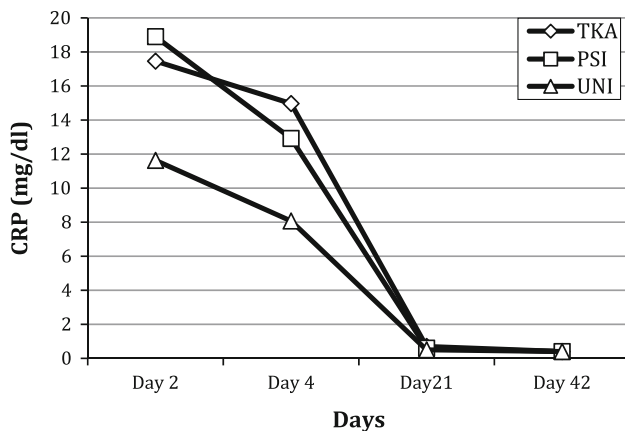


Fig. 1 Kinetics of CRP for different types of MI arthroplasty

were excluded because of medical complications interfering with the interpretation of CRP. All these patients were followed up for 1 year at least and did not present infection problems later on.

Another limitation would be that by following CRP values only the systemic inflammatory response with one biomarker would be evaluated [14]. Maybe the use of PSI would make a difference in the liberation of local cytokines by the absence of femoral canal opening and could make a local difference in the inflammatory response [13, 40].

Another limitation lies in the decision to study early infection, with a clinical follow-up of 1 year, on the abnormal CRP's at 6 weeks [1]. The 28.7 % of patients that did not normalize their CRP levels at 6 weeks can still develop a low-grade infection later on maybe with a bio-film producing bacteria [16]. The follow-up was also only based on clinical and radiological examination. The long-term infection rate of the studied surgeon is, however, 0.8 %, and this correspond well to the infection rate that was observed in this study group.

An important limitation of this study is that we did not have age-matched groups. If age matters in the reduction of the peak levels of CRP, this will have an influence on both the PSI-assisted and unicompartmental group. In general, younger age would elicit a stronger immunologic and pain response after surgery as found by other authors [17, 20, 32]. Controversial data was found on CRP and age with some authors saying it does not matter [4, 31] and other authors finding the elderly have a lower CRP response [38]. If that is the case the peak CRP of the MI TKA group is lower, then it would be in an age-matched study and maybe PSI would make a significant difference then, as found in some navigation studies [36]. However, no other clinical differences on cognition or other co-morbidity in between both groups were observed [5, 11].

A final limitation would be that we did not measure fat embolism at the right atrium with transesophageal

echocardiography and compare conventional MI with PSI-assisted TKA with this technique [18, 29]. The studied CRP response can only be considered as a measure of surgical trauma and systemic inflammation [19, 23]. At day 4, a lower CRP peak was observed in the PSI group suggesting an early advantage without statistical significance, however. Recent literature showed, however, no major differences in the prevalence of fat embolisation in between conventional and computer-assisted surgery, suggesting it is related to the bone cuts and not only the rodding of the femoral canal [18, 29]. Technically speaking, the main advantage of PSI guides would be that there is no need to position femoral or tibial trackers. If that surgical activity would be responsible for the creation of fat and bone marrow emboli, a significant difference should be observed.

The clinical importance of this study lies in the observation that elevated CRP values are a response to the cut bone surfaces and that lower values were found in unicompartmental arthroplasty. This study also showed that elevated CRP levels 6 weeks after surgery do not result in prosthetic joint infection at 1 year postoperatively.

Conclusion

CRP is an important postoperative biomarker in minimally invasive TKA follow-up. This study confirms comparable CRP kinetics after MI TKA as published for conventional TKA. CRP peaks are observed on day 2 with an initial reduction at day 4. Normal levels are reached between 21 and 42 days after surgery for the different types of MI arthroplasty. On the other hand, it highlights that a significant number of patients do not have normal CRP levels after 3–6 weeks in minimally invasive surgery, though it is not a predictive factor of early prosthetic joint infection. Using PSI does not reduce peak levels or does not change the kinetics of CRP. Lower peak levels and faster return to normal levels have been observed in unicompartmental arthroplasty, suggesting CRP measures the soft tissue trauma and especially the cut bone surfaces.

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