C-reactive protein kinetics and its predictive value in orthopedic (trauma) surgery: A systematic review


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In Orthopedic Trauma Surgery (OTS), C-reactive protein (CRP) is a widely used marker for the diagnosis of postoperative wound infections (POWI’s) and other complications. The aim of this systematic review was to describe specific CRP kinetics and to evaluate the diagnostic value of CRP for detection of post-operative complications in OTS. The same pattern is reported consistently, where the highest levels of CRP are found at post-operative day two or three, returning to normal in three weeks. Amplitude varies per procedure. Persistently high CRP levels or secondary increases may indicate complications. A low CRP may be used to rule out complications.

Keywords: C-reactive protein; diagnostic tool; orthopedic surgery; surgical site infection.

INTRODUCTION

Postoperative wound infections (POWI) form one of the biggest challenges in orthopedic (trauma) surgery (OTS). It is estimated that POWI’s occur in 1-7% of all arthroplasty patients (8,11) and in approximately 3.3 % of patients following internal fixation for fracture treatment (7). Early diagnosis of POWI’s can be challenging, laboratory tests however may reveal POWI’s and other complications before clinical signs become apparent. Examples of these tests are Erythrocyte Sedimentation Rate (ESR), Leukocyte count and C-Reactive Protein (CRP). More recently revealed markers (e.g. Interleukine-6) also show promise as an accurate predictor of infection (5,11,14). To date, CRP is the most widely used marker for infection in daily practice.

C-reactive protein is an acute phase protein with a half-time of 4-6 hours. Serum levels in healthy individuals do not exceed 10mg/L (29). The serum levels can increase by a thousand-fold within 24-48 hours (26). A rise in CRP levels can be the result of a wide array of conditions, including local and general infections, and also tissue damage. An increase of CRP is a physiological phenomenon after surgical interventions, and its magnitude depends on the amount of surgical trauma (23). CRP levels may be also elevated by default in patients with underlying infections or systemic diseases, such as rheumatoid arthritis (25,32). Even though CRP is a sensitive test for the detection of post-operative complications, its low specificity

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limits its predictive value \((12,34)\). Early detection of POWI’s may lead to better treatment outcomes, as early treatment may avert serious adverse events such as chronic osteomyelitis or unplanned removal of implants.

Primary aim of this systematic review was to determine CRP kinetics after various types of OTS. Secondary aim was to evaluate the diagnostic value of post-operative CRP measurements in detecting POWI’s in orthopedic (trauma) surgery.

**METHODS**

This systematic review was performed according to the PRISMA guidelines \((21)\). A literature search was conducted up to the 8th of December 2016 to identify studies that concerned the postoperative course of CRP after OTS. The electronic databases of Pubmed, Cochrane and Embase were explored, using the following keywords and combinations (each modified to fit use in the different databases): ‘orthopedic surgery’, ‘trauma surgery’, ‘fracture’, ‘arthroplasty surgery’, ‘surgical wound infection’, and ‘C-reactive protein’. The full search is provided in the appendix. Using the Covidence online tool for reviews (www.covidence.org), all abstracts were reviewed by two independent researchers (JK and SD).

Eligible articles were those that considered patients undergoing fracture surgery or primary arthroplasty, with follow-up of the serum CRP of at least 5 days after surgery and on at least 3 separate days. A pre-operative CRP measurement was mandatory to rule out pre-existing elevated CRP levels. Only full versions of original articles were considered, there were no restrictions concerning publication date.

Articles concerning pediatric populations, spinal surgery and all revision arthroplasty surgery were excluded. Authors who did not exclude patients who suffered from any condition that might obscure the course of post-op CRP levels, such as rheumatic or chronic infectious diseases, were also excluded. Language was restricted to English, German and Dutch. In case of disagreement between the two reviewers, the differences were resolved through discussion. The search flowchart is shown in Figure 1. Of each study, data was extracted regarding the number of patients, the location of the fracture or arthroplasty, treatment, the number and timing of CRP measurements, the peak CRP moment and test accuracy if calculated. A separate analysis of total hip arthroplasty, total knee arthroplasty and open & closed fractures was performed. Studies that calculated test specifics (sensitivity, specificity and predictive values) were subjected to bias risk analysis using the QUADAS-2 questionnaire for diagnostic accuracy studies \((37)\). Four different domains were used to screen these studies; patient selection, index test, reference test and flow & timing. In each domain, a different number of signaling questions were answered, resulting in a high, low or unclear risk for bias in that domain. CRP kinetics were pooled for the uncomplicated THA and TKA using a fixed effect model.

**RESULTS**

The search yielded a total of 1580 articles, of which 482 were duplicates, which were removed. One thousand ninety-eight titles and abstracts were screened, after which 1020 articles were excluded. The remaining 78 articles were eligible for full-text review. Fifty-five articles were excluded after reading full text for following reasons: incompatible intervention \((n = 10)\) (i.e. revision surgery, spinal surgery, implant removal), incompatible study design \((n = 29)\) (i.e. no exclusion of possible influential factors such as rheumatic disease or chronic infections, infection at baseline, short follow-up and insufficient post-surgical CRP measurements), language other than English, Dutch or German \((n = 10)\) and full text unavailable \((n = 6)\). The remaining 23 articles were cross-checked for references, and no additional articles of interest were identified.

**CRP kinetics**

Total hip arthroplasty (THA) was the most extensively researched procedure. We found 16 articles describing CRP kinetics after THA, with a total number of 629 patients \((1,2,5,10,13,18–20,22,23,27,30,33,35,36,39)\). Results are available in Table I. Serum CRP peaked at postoperative day
C-REACTIVE PROTEIN KINETICS

Twelve authors studied CRP kinetics after total knee arthroplasty (TKA) in a total number of 1607 patients (Table II) \((13,15,18–20,22,28,30,35,36,38,39)\). CRP kinetics in uncomplicated cases were similar to those in THA patients. Pooled CRP kinetics following uncomplicated TKA are shown in figure 3.

There were six studies describing fracture surgery and other miscellaneous procedures \((6,9,20,24,31,39)\). All of these authors excluded multi-trauma patients. It was reported that operative treatment of fractures of the Femur, Tibia, Humerus, Forearm, Ankle and small bones have a lower CRP peak than THA and

Fig. 1. — Flow-chart literature search according to the PRISMA 2009 Guidelines

(POD) two or three, and reached a mean peak amplitude ranging from 66 mmol/L \((22)\) to 185 mmol/L \((18)\). In uncomplicated cases, there was a relatively rapid decline after the peak on day 2-3, to POD 5-7, after which CRP returned slowly to pre-operative levels in three weeks (figure 1). One study analyzed 32 hip fractures in elderly patients of whom 23 were treated by intramedullary nailing and 9 by hemiarthroplasty. CRP peaked at 48-60 hours post-surgery at 165 mg/L \((± 15)\) \((3)\). Pooled CRP kinetics following uncomplicated THA are shown in figure 2.
TKA surgery (Table III). CRP kinetics however after fracture surgery follow a similar pattern to joint arthroplasty surgery. The magnitude of the CRP response is different for each intervention. Two studies describe multiple types of fracture surgery separately (24,31). These studies report highest peak levels in proximal femur fractures (165 (9) and 154 mg/L (31)), followed by Humerus (82 mg/L) (24) and Tibia fractures (79 mg/L) (Table 3) (31).

Open and closed fractures

Bourguignat et al. analyzed a population of open fractures, and reported a peak mean CRP of 77,3 mg/L. The population consisted of Femur,
### C-Reactive Protein Kinetics

#### Table III. — CRP kinetics after miscellaneous procedures

<table>
<thead>
<tr>
<th>Fracture site</th>
<th>Peak day</th>
<th>Peak amplitude (mean, in mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourguignon 1996: Femur (n = 4)</td>
<td>4</td>
<td>71.5</td>
</tr>
<tr>
<td>Knee (n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibia (n = 51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle (n = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot (n = 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulut 2010: Proximal femur (n = 29)</td>
<td>2</td>
<td>165</td>
</tr>
<tr>
<td>Kallio 1990: Tibia: Conservative (n = 27)</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>Tibia: Intramedullary nailing (n = 10)</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>Tibia: Open reduction, internal fixation (n = 5)</td>
<td>2</td>
<td>105</td>
</tr>
<tr>
<td>Larsson 1992: THA (n = 109)</td>
<td>3</td>
<td>116</td>
</tr>
<tr>
<td>TKA revisions (n = 9)</td>
<td>3</td>
<td>136</td>
</tr>
<tr>
<td>Knee, unicortil (n = 39)</td>
<td>2</td>
<td>140</td>
</tr>
<tr>
<td>Microdisectomy (n = 36)</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>Neumaier 2008: Femur (n = 362)</td>
<td>2</td>
<td>136</td>
</tr>
<tr>
<td>Tibia (n = 113)</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>Humerus (n = 88)</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>Elbow &amp; forearm (n = 61)</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>Ankle &amp; small bones (n = 163)</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>Scherer 2001: Femur (n = 81)</td>
<td>2</td>
<td>154</td>
</tr>
<tr>
<td>Tibia + anterior cruciate ligament rupture (n = 57)</td>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>Humerus (n = 17)</td>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>Elbow + fore arm (n = 40)</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>Ankle + small bones (n = 85)</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Implant removal (n = 24)</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>Yoon 1993: Long bone fractures (n = 57)</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>(Humerus n = 6, forearm n = 8, femur n = 19 tibiofibular n = 24)</td>
<td></td>
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</tr>
</tbody>
</table>

ǂ = Both complicated and uncomplicated cases

^ = Including open fractures

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**Fig. 4.** — Different CRP kinetics after THA

**Fig. 5.** — Different CRP kinetics after TKA
peak at POD two or three. In uncomplicated cases, CRP will then decline to normal levels in two to three weeks. The decline is initially rapid, and evens out when it approaches normal levels. A secondary peak was explicitly found to be indicative of post-operative complications in 5 studies (3,17,20,31,36).

Diagnostic value of CRP

Five studies evaluated CRP measurements as a diagnostic tool for detecting complications (table IV) (3,6,24,30,31). Neumaier and Bourguinat were

<table>
<thead>
<tr>
<th>Study</th>
<th>RISK OF BIAS</th>
<th>APPLICABILITY CONCERNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PATIENT SELECTION</td>
<td>INDEX TEST</td>
</tr>
<tr>
<td>Beloosesky 2004</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>Bourguignat* 1996</td>
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<tr>
<td>Neumaier* 2008</td>
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<tr>
<td>Sastre 2006</td>
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<td>☒</td>
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<tr>
<td>Scherer 2001</td>
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</tbody>
</table>

*= exclusively postoperative wound infections Sens = sensitivity. Spec = specificity. PPV = positive productive value. NPV = negative predictive value.

Table IV. — Diagnostic test characteristics

Table V. — Risk of bias analysis, using Quadas-2 tool

Tibia and foot fractures (6). Kallio et al. reported a slightly higher CRP in open fractures (58.4 mg/L) compared to closed fractures (54.7 mg/L). However, this difference was not significant (17). Yoon et al. reported a secondary CRP rise in conservatively treated fractures. Authors attribute this second rise to the required repeated debridement of the open wounds and secondary closure. There was no difference in CRP levels at the three-week mark (39).

The global pattern of CRP behavior was similar in all types of fractures and interventions. There is a peak at POD two or three. In uncomplicated cases, CRP will then decline to normal levels in two to three weeks. The decline is initially rapid, and evens out when it approaches normal levels. A secondary peak was explicitly found to be indicative of postoperative complications in 5 studies (3,17,20,31,36).

Diagnostic value of CRP

Five studies evaluated CRP measurements as a diagnostic tool for detecting complications (table IV) (3,6,24,30,31). Neumaier and Bourguinat were
C-reactive protein kinetics follow the same pattern after different types of surgical procedures. The amplitude of the CRP peak however, differs between the procedures. Notably, it has been stated that even an untreated femur fracture causes a rise in CRP and thus the total post-surgical increase can be partly explained by the trauma itself. Therefore, we believe that the different CRP peak is partially the consequence of the trauma mechanism and partially of the surgical treatment, with both factors causing a certain amount of tissue damage. CRP kinetics after abdominal surgery follow a similar pattern, also with a peak at POD two or three.

Some studies have compared uncomplicated procedures with complicated procedures, calculating test accuracy ratings for post-operative CRP. Authors calculated different optimal cutoff values for CRP on different post-operative days. Unfortunately there were methodological differences between those studies and authors used different patient groups for their analysis. Four authors pooled different procedures. We believe their results are inaccurate, since each procedure produces a different CRP peak.

Chapman et al. developed a predictive model for the expected CRP value on a certain POD, accurate between POD five and thirty; 500/d (d = POD). A CRP higher than the predicted value raises suspicion for post-operative complications.

Five studies exclusively considered POWI’s, with incidence rates ranging from 2.7% to 11.4%. Others also considered other complications as an endpoint, these include urinary tract infections and pneumonia. This reflects the main weakness of CRP as a diagnostic tool, namely its low specificity.

Open fractures produce a slightly higher CRP peak. This may be caused by the increased energy of the trauma in these injuries.
debridement and secondary closure may cause a secondary increase of serum-CRP, as a result of surgical trauma (39). Evidence on open versus closed fractures is limited.

Blood transfusions, amount of blood loss, type of anesthesia and administered drugs do not correlate with a higher CRP peak (20,24). The use of a tourniquet seems to increase CRP production in the first 15 minutes after perfusion, but it is unclear whether longer-term CRP is affected (16). A high body mass index (BMI) seems to significantly increase post-operative CRP levels after both THA and TKA procedures (35). The largest cohort study on uncomplicated TKA so far found significantly higher CRP values in men on POD 2-5 and 7-8 (38).

One earlier systematic review by Nunes et al. was performed on CRP kinetics after surgery including orthopedic trauma surgery. A pooled test sensitivity and specificity were calculated, resulting in a sensitivity of 85% and a specificity of 86%. The validity of the calculations may be disputed, as the authors pooled results from both gastrointestinal and orthopedic trauma studies. Also, no references are provided to the original studies and their outcomes (26).

In gastro-intestinal surgery, two systematic reviews calculated test characteristics for CRP. They found very similar kinetics to orthopedic and trauma surgery. Pooled cutoff values were 159 mg/L (12) and 140 mg/L on POD 3 (34). Authors state that the positive predictive value is limited, but a low CRP can be used to rule out complications with high certainty. Furthermore, additional diagnostic evaluation is recommended in case of a CRP > 215 mg/L on POD 5 (34). We believe that the same characteristics may apply to CRP in OTS, but the cutoff value may vary per trauma/intervention.

In OTS several authors have pooled different surgical procedures to establish a ‘common’ cutoff-value. We believe such cut-off values are certainly useful in clinical practice but should be intervention specific. Another option would be to follow CRP levels on designated moments after surgery. A deviation from the ‘normal’ course is more predictive for complications than one single CRP value. If there is a higher-than-expected peak at day 2 or 3, or if there is a secondary increase in CRP, a complication may be present and additional diagnostics might be indicated.

Several limitations have to be taken into account. Firstly, there is no standard definition for the diagnosis of POWI’s. Many studies use different diagnostic criteria, hampering interpretation of the different test characteristics (i.e. sensitivity and specificity). Secondly, the studies we included in our analysis show great methodological heterogeneity, making it impossible to perform meta-analysis. Thirdly, most of the reports in our review are not designed to look at POWI’s specifically. The incidence of POWI’s is usually low and most authors focus on any major complication, including general infections such as urinary tract infections and pneumonia.

However, this is the first attempt to establish a practical interpretation of CRP values in OTS, following similar studies in abdominal surgery.

We believe that the high negative predictive value of a normal CRP is the most valuable asset and CRP is less suitable to differentiate between various types of complications, as any septic complication will cause an increase in CRP level. Clinical evaluation remains the prime tool for a patient with suspected post-operative complications. In order to establish an accurate model for the predictive value of CRP testing after orthopedic trauma surgery, a large prospective study is needed, with regular CRP evaluation at fixed intervals and a uniform golden standard for clinical evaluation of POWI’s and other complications. This could especially be of value in high-risk surgery such as surgery for open fractures or calcaneal fractures.

**CONCLUSION**

In uncomplicated cases, CRP values peak at POD two or three. Each intervention has its own distinct peak value. In current literature, authors established a sensitivity between 60% and 100% and specificity between 65% and 98% for CRP as a diagnostic tool. Low CRP levels following OTS may rule out- and a secondary rise may be indicative of postoperative complications. However more prospective research towards the clinical value of CRP measurements as a diagnostic tool is needed especially in the light of its low specificity.

C-reactive protein (CRP) is a non-specific inflammatory biomarker that is often elevated in the presence of infection. However, the diagnostic value of CRP levels in the early postoperative period for predicting periprosthetic joint infection remains unclear. The current study aimed to assess the diagnostic value of CRP levels for predicting periprosthetic joint infection in patients undergoing elective total hip arthroplasty.

Compliance with ethical standards: The authors declare that they have no conflict of interest.

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Research involving human participants and/or animals: This article does not contain any studies with human participants or animals performed by any of the authors.

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REFERENCES


