



C-Reactive Protein and Erythrocyte Sedimentation Rate in Orthopaedics

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Introduction

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are known as acute phase proteins, which reflect a measure of the acute-phase response. The term “acute phase” refers to local and systemic events that accompany inflammation. Local responses include vasodilation, platelet aggregation, neutrophil chemotaxis, and release of lysosomal enzymes. Systemic responses include fever, leukocytosis, and a change in the hepatic synthesis of acute phase proteins (a hepatic protein, which by definition, increases or decreases in serum concentration by at least 25%). Stimuli to the acute phase include many different forms of tissue injury, such as infection, immuno/allergic reaction, thermal injury, hypoxic injury, trauma, surgery, and malignancy. The clinical use of acute phase proteins is as an aid to diagnosis [15]. Because the acute phase response is relatively non-specific, the value of measuring acute-phase protein concentrations is to assess the extent of inflammation reflecting momentary disease activity. Similar to tumor markers, acute-phase proteins may monitor the course of disease in response to therapeutic intervention.

CRP and ESR are not the only acute phase proteins. Other acute-phase proteins include transport proteins (haptoglobin, ceruloplasmin, α 1-trypsin inhibitor, etc.), coagulation proteins (fibrinogen, prothrombin, etc.), and complement components (C3, C4, C5, etc.). What makes CRP and ESR markers of choice in monitoring the acute phase is that they increase in concentration relatively high compared to basal concentration, have a relatively short lag time from the moment of stimulus, and are cost-effective [15].

C-Reactive Protein

CRP was first discovered in 1930 by Tillet and Francis in the serum of patients with pneumonia, but it was not actually isolated until 1941. The name is derived from the ability of the C-reactive protein to react with C-polysaccharide isolated from pneumococcal cell walls. Early laboratory methods were only qualitative in nature until the late 1970s when significant advances in isolating CRP and measuring

to the picogram range were made. Most clinical laboratories now use laser nephelometric assay because of its ease of use, speed, and reproducibility. CRP is synthesized by hepatocytes and is classified as an acute-phase protein on the basis of its increase in plasma concentration during infection and inflammation. Cytokines, particularly IL-6, induce CRP synthesis in the liver [4]. The clearance rate of CRP is constant, therefore the level of CRP in the blood is regulated solely by synthesis. CRP acts as an opsonin for bacteria, parasites, and immune complexes, activating the classical complement pathway [3].

The plasma levels of CRP in most healthy subjects is usually 1 mg/L with normal being defined as <10 mg/L. Plasma levels begin increasing within 4–6 hr after initial tissue injury and continue to increase several hundred fold within 24–48 hr. CRP remains elevated during the acute-phase response, and returns to normal with restoration of tissue structure and function. The rise in CRP is exponential, doubling every 8–9 hr. The half-life is less than 24 hr [3]. CRP is a direct and quantitative measure of the acute phase reaction. Serial CRP measurements can be used as a diagnostic tool for infection, monitoring effect of treatment, or early detection of relapse.

Erythrocyte Sedimentation Rate

ESR was first introduced by Westergren in 1921. The Westergren method measures the rate of gravitational settling in 1 hour of anticoagulated red blood cells (RBCs) from a fixed point in a calibrated tube of a defined length and diameter held in an upright position [8]. Erythrocytes normally have net negative charges and therefore repel each other. High molecular weight proteins that are positively charged, such as fibrinogen, increase in the acute-phase reaction, favoring rouleaux formation, thereby increasing the ESR. Plasma viscosity correlates with ESR.

The importance of the ESR definition is that its value may be affected by the size/shape of red blood cells, plasma composition, and fluid status. CRP, in contrast, is independent of any physical properties. Normal ESR also increases with age. The upper limit of normal for males, less than 50 years of age, is 15 mm/hr, and for females, less than 50 years of age, is 20 mm/hr [1]. This increases to 20 and 30 mm/hr for males and females respectively over the age of 50 years. ESR is also affected by temperature, pregnancy,

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drugs (decreases with adrenal steroids and NSAIDs), and smoking.

ESR is an indirect measure of the acute phase reaction. Its value lies in the fact that it is a simple and inexpensive laboratory test for assessing inflammation. It has even been used for the prognosis of noninflammatory conditions, such as prostate cancer, coronary artery disease, and stroke. Most recent studies tend to favor CRP over ESR, mainly because of the fact ESR is affected by a multitude of factors [8]. A comparison chart is provided in Table 1.

Clinical Significance of CRP and ESR

The recognition of post-operative infection or established osteomyelitis usually occurs with the onset of clinical symptoms. By that stage, the disease is already well-advanced. The difficulty in assessing post-operative patients for infection, lies in the common signs masked by the effects of the procedure itself, such as pain, fever, tachycardia, mental status changes, and elevated white count.

The majority of the literature on CRP levels predicting post-operative infection has originated in Europe, where CRP has essentially replaced ESR. Mustard et al. conducted a study of 108 patients undergoing clean-contaminated, contaminated, and dirty procedures [7]. Blood was drawn every day from immediately pre-op to post-op day 14. CRP results were analyzed at a later date so that results would not influence clinical decisions. A positive CRP response was defined as meeting two criteria:

- (1) A CRP level on days 3 and 4 that is >80% of day 2 (positive diagnosis by day 4).
- (2) After day 4, CRP rising on 2 consecutive days with level greater than 15 mg/L on each day (positive diagnosis by day 6).

The sensitivity was 63%, specificity 82%, positive predictive value (PPV) 68%, and negative predictive value (NPV) 78%. It was concluded that CRP testing is very predictive. A normal CRP response to surgery without secondary rise may exclude the possibility of post-operative septic complications. Positive CRP response was less predictive but still useful. In either case, CRP was determined to be a better marker for post-operative infection than fever, WBC, or ESR, which are more easily affected by the surgical procedure itself.

Larsson et al. performed a prospective study focused on CRP levels in 193 patients undergoing 4 types of uncomplicated elective orthopaedic procedures [5]. The prerequisite for use of CRP as a diagnostic tool is to first know the natural CRP course for uncomplicated surgery. Once the natural CRP response after uncomplicated surgery is known, then deviation from normal should raise clinical suspicion that a complication may be surfacing. Four groups of patients underwent the following procedures: primary hip arthroplasty ($N = 109$), revision arthroplasty ($N = 9$), unicondylar knee arthroplasty ($N = 39$), and lumbar microdiscectomy ($N = 36$). The CRP levels were measured days 0–5, 10, 14, 21, and 42. Results are shown in Fig. 1A–D.

The average peak CRP level after THA occurred post-op day 3 at 116 mg/L. For revision hip arthroplasty CRP peaked post-op day 3 at 136 mg/L. After unicondylar knee arthroplasty, CRP peaked on post-op day 2 at 140 mg/L. The maximum CRP after lumbar disc surgery was significantly less than the other procedures occurring on post-op day 2 at 48 mg/L. This is most likely due to the minimal tissue trauma.

All four procedures had a peak CRP response 2 to 3 days after surgery followed by a biphasic rapid decline. In the

Table 1. Comparison of ESR and CRP (used with permission from Ng [8])

| | | ESR | CRP | |
|-----------------------------|-------------------------------------|------------------|---------|----|
| Results affected by | Gender | Yes | No | |
| | Age | Yes | No | |
| | Pregnancy | Yes | No | |
| | Temperature | Yes | No | |
| | Drugs (e.g., steroids, salicylates) | Yes | No | |
| | Smoking | Yes | No | |
| | Level of plasma proteins | Yes | No | |
| | Red blood cell factors | Hematocrit | Yes | No |
| | | Morphology | Yes | No |
| Aggregability | | Yes | No | |
| Response to disease process | Intermediate | Early | | |
| Clinical assessment | Normal range of results | Wide | Narrow | |
| | Specificity | Moderate | High | |
| | Sensitivity | Moderate | High | |
| | Reproducibility | Low/moderate | High | |
| | Check for technical errors | May be difficult | Readily | |
| Availability | >60 min | <20 min | | |
| Relative cost | x1 | x2–3 | | |

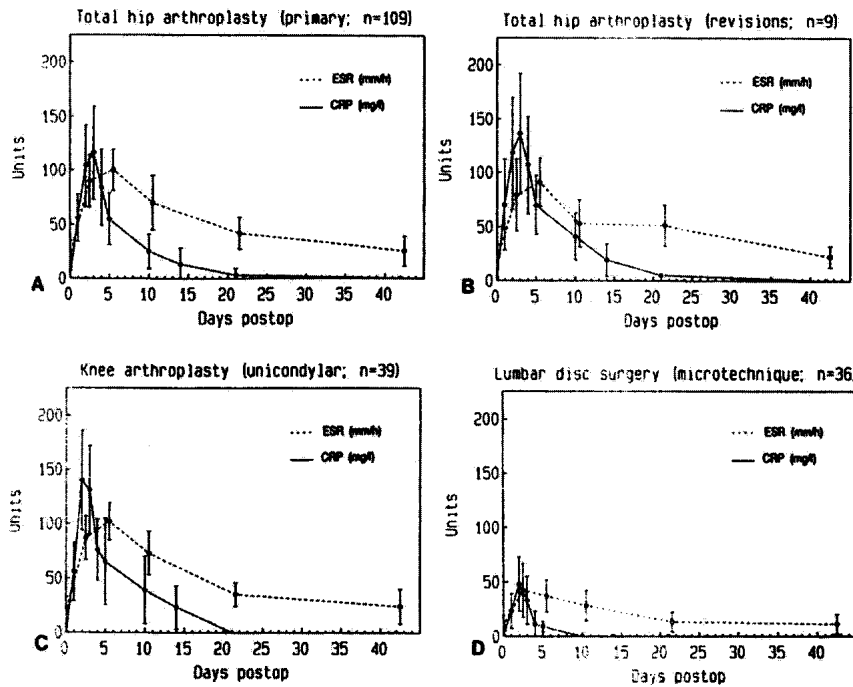


Fig. 1. (A–D) Graphs demonstrating CRP and ESR levels after various orthopaedic procedures (used with permission from Larsson et al. [5]).

first phase there is a rapid decline 3 to 5 days after surgery. In the second phase there is a more gradual decrease until 14 to 21 days after surgery. ESR tends to be more variable, remaining elevated after 42 days and up to 1 year in hip revisions. The conclusion from the study is that a normalized CRP response that follows a typical biphasic response seems to indicate an uneventful recovery.

Waleczek et al. further supported Larsson’s work by studying orthopaedic procedures in which post-operative CRP was compared to ESR, WBC, body temperature, and clinical symptoms. Normal patterns of CRP levels were seen in 101 patients. Of the 7 patients with an atypical CRP pattern, all had a wound infection [16].

Meyer et al. examined the use of CRP in detection of early infections after lumbar microdiscectomy [6]. Although the hospitalization stays have decreased with recent advances in microsurgery, early postoperative infections, such as spondylodiscitis and/or subfascial abscesses, have not been eliminated. Classical screening, namely clinical examination, WBC, ESR, and elevated temperature, all have a high number of false positives and false negatives. Expensive examinations such as MRI often produce unclear findings in a very non-economical manner. The study

pushed for using CRP as a simple, reliable, and inexpensive screening test.

In his study, 400 patients were operated for single-level, unilateral lumbar disc herniation. CRP, ESR, and WBC were drawn pre-op (day 0), and post-op days 1 and 5. Ninety-six percent ($N = 385$) had an uneventful course, while 4% ($N = 15$) suffered from post-operative infections confirmed by blood culture. The graphs in Fig. 2A–C demonstrate the differences between CRP, ESR, and WBC between the infected and uninfected groups.

All 15 patients (4%) who developed post-operative infection had a CRP value on day 5 above that of day 1. A large number (98.5%) of 385 ($N = 369$) infection-free patients had a CRP value on day 5 below their post-surgery peak level. The sensitivity of CRP was thus determined to be 100%, specificity 95.8%, and negative predictive value to be 100%. Comparison with ESR and WBC is shown in Table 2.

The results of Meyer were further confirmed by another German study by Schmidt-Matthiesen and Oremek [11]. CRP values were compared to WBC, ESR, body temperature, and clinical symptoms. The results of that study showed that CRP had a PPV = 85% and a NPV = 98%. In

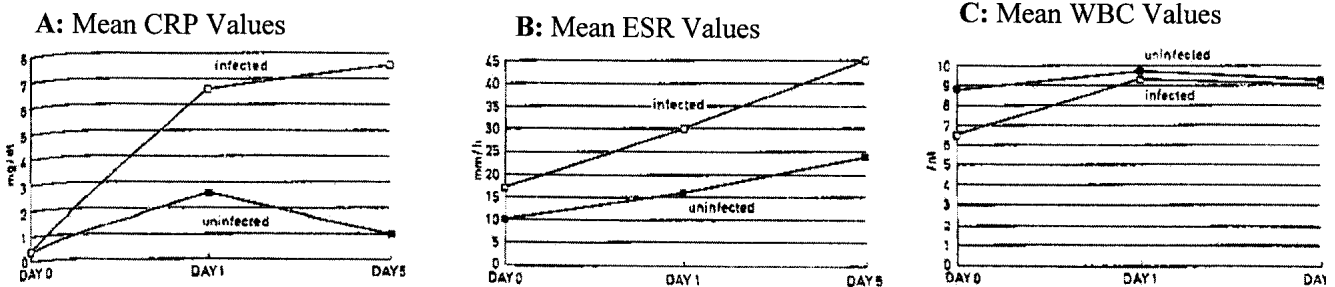


Fig. 2. (A–C) CRP, ESR, and WBC levels after single-level, unilateral discectomy (used with permission from Meyer et al. [6]).

Table 2. CRP, ESR, and WBC in predicting post-operative infections in single-level unilateral discectomy (used with permission from Meyer et al. [6])

| | CRP | ESR | WBC |
|-------------|-------|-------|-------|
| Sensitivity | 100% | 78.1% | 21.4% |
| NPV | 100% | 98% | 96.4% |
| Specificity | 95.8% | 38.1% | 76.8% |
| PPV | 48.4% | 4.4% | 3.2% |

contrast, only half (46.5%) of all patients with an elevated WBC count were actually infected. Even WBC correlated with temperature had a PPV of only 75.6%.

Ellitsgaard et al. conducted a study on 140 elderly patients with hip fractures that measured CRP and ESR during the week after operation [2]. Eighty-two fractures were reduced with a dynamic compression screw, 20 with cancellous screws only; and 38 received a hemiarthroplasty. The ESR and CRP levels did not differ with the type of fixation used. In 113 cases, prophylactic antibiotics were used without any direct correlation with changes in CRP and ESR values. The postoperative ESR in uncomplicated cases remained elevated 1 week after surgery, while the CRP peaked at day 2 and normalized by day 7. In five cases of deep wound infection, the ESR level varied within the normal post-operative range while the CRP level was significantly raised, and remained elevated until the infection cleared. The conclusion of the study was that CRP measurements were more reliable than ESR in indicating a post-operative infection after hip fracture surgery.

Peltola et al. compared CRP, ESR, and fever in septic arthritis in a pediatric population treated with antibiotics [10]. Defervescence occurred after an average of 5 days, with CRP normalized after 7 days, ESR normalized after 22 days. In the study antibiotics were administered for 16 days. The study suggested that CRP could be used as a tool to monitor the effect of antibiotic therapy.

Sell and Schleh investigated CRP as an early indicator of heterotopic ossification (HO) after total hip arthroplasties involving 95 patients [12]. In this study CRP was measured in 3 groups of patients on post-op day 1 and on post-op days 5–7. The first group had Brooker classification 0, the second group Brooker classification 1, and the third group was combined classes 2–4 labeled as “significant HO.” The average CRP values on post-op day 1 was 6.33, 7.04, and 7.65 mg/dL the day after surgery for the respective groups. On post-op days 5–7, the average values were 4.22, 5.57, and 6.38 mg/dL. Thus it was demonstrated that CRP, on average, was increasingly elevated with the amount of HO. The difference in CRP elevation in patients without ossification (first group) as compared to patients with ossification (second and third groups) was statistically significant ($P = 0.036$) [12].

Conclusion

There is a wealth of literature supporting the use of CRP, and to a lesser extent, ESR in the diagnosis and monitoring of treatment of infection in post-operative patients. It is important to realize that a single CRP reading holds very limited value, and that a trend must be observed in order to maximize its full usefulness. It is not practical to set numeric limits or cutoffs for this reason, although it is useful to be aware of the natural CRP response curve after uncomplicated surgery. CRP rises early and before the onset of clinical symptoms, and declines with the resolution of infection. It is a biologic warning sign that should raise an index of suspicion for infection if a rising trend, discordant from that of established normal patterns, is observed.

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