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C-Reactive Protein in Orthopaedic Surgery

C-reaktivní protein v ortopedické chirurgii

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SUMMARY

C-reactive protein (CRP) is a common laboratory infection marker in blood-serum of patients.

In all diverse medical departments CRP is often used, and also in orthopaedics CRP is proved to be very helpful in diagnosis and monitor of infections. CRP in most fields is superior to conventional and newer infection parameter and is a basic parameter for inflammation. Especially for detection of an early postoperative infection CRP can be very helpful as an objective parameter easy to obtain. In uneventful operative treatment a similar evolution in CRP concentrations was found: the peak level occurred on the second or third postoperative day and reflected the extent of surgical trauma. A second rise of CRP in the postoperative course indicates a complication. Highest levels are reached in bacterial infection after the forth postoperative day with a cut-off level about 10 mg/dl. CRP can also be used as a preoperative marker for risk stratification and newer times CRP is reported as an independent fracture-risk-factor. In general CRP is the basic inflammatory parameter in orthopaedic surgery and is more significant and common than WBC or ESR. But CRP is only a laboratory parameter and must always be correlated with clinical signs of infection.

INTRODUCTION

C-reactive protein (CRP), an acute-phase reactant, was discovered in the serum of patients with pneumonia by Tillett and Francis in 1930 (33). At this early time CRP was accepted as a parameter of severity for clinical diseases. After a time of oblivion in the 1970s and 1980s in which the erythrocyte sedimentation rate predominated, CRP now is considered to be a valid marker of inflammation and infection. CRP is superior to the conventional parameters (leukocyte counts, erythrocyte sedimentation rate) in detecting surgical complications with bacterial infection (6, 9, 10, 19).

Newer serum parameter for infection like IL-6, TNFα or PCT seems to be helpful for special indications but mostly not superior to CRP in detecting bacterial infections (8, 24).

CRP also is considered to reflect the extent of surgical trauma (20). Preoperative CRP-levels are considered to be a risk factor for the postoperative outcome. However, CRP is thought to be a basic parameter for the surgeon to monitor patients (11).

Immune parameter CRP

CRP has been linked to the development of systemic inflammatory response syndrome. CRP belongs to the natural immunity and host defence, activates the complement pathway and modulates the cellular defence (31). CRP synthesis is induced promptly after tissue injury by cytokines (IL-6, IL-1, IFNγ, TNFα), and elevated plasma levels can be detected 4 hours after injury. The plasma concentration can increase of several hundredfold within 24 hours after tissue injury from a normal resting state CRP concentration of 0.5 mg/dl (11). CRP is very powerful in detecting acute inflammatory processes, especially those caused by bacteria. CRP is routinely available in most laboratories or even can be quick measured with a simpl rapid test (ELISA-Kit).

Natural CRP response after trauma/operation

After trauma or operation a rise of CRP-levels in serum were seen as expression of inflammatory response (11). In conservative fracture treatment CRP levels shows a slight elevation around 5-10 fold of normal levels. In almost the same manner a rapid CRP rise can be observed after orthopaedic surgery, reaching the maximum value at the second day after surgery. After femoral fracture treatment we see a CRP rise with the peak level on the second postoperative day (13.6 mg/dl) and afterwards a continuous decline to normal values in about two weeks (Fig. 1).

CRP levels about 10 to 16 mg/dl can be seen after total hip or knee arthroplasty (1, 22, 25, 35). In fracture treatment of the tibial shaft CRP levels reach values of 6.7 mg/dl (17), and in malleolar fracture treatment 4.5 mg/dl (3).

In arthroscopically assisted anterior cruciate ligament reconstruction peak level were seen at 9.5 mg/dl (18). In spine surgery CRP levels depend on extend of operation. For fracture treatment we have seen values about

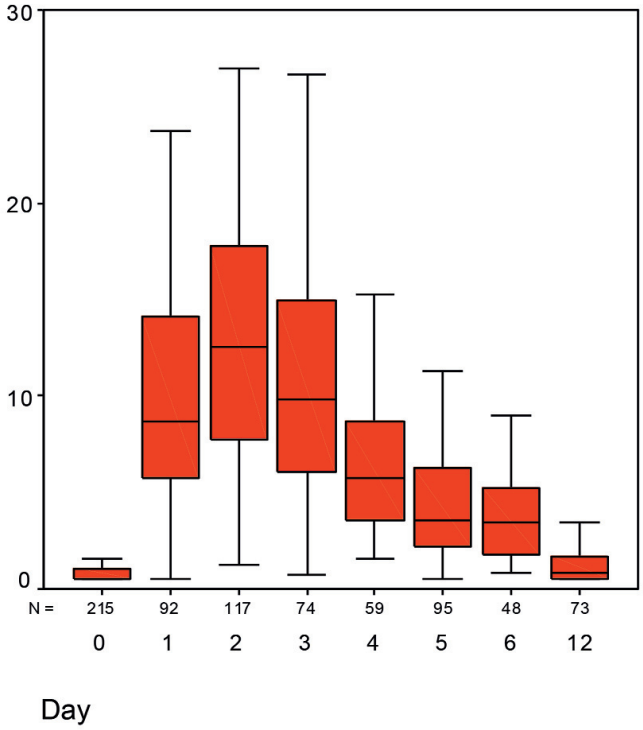

Fig. 1. CRP levels after uneventful femoral fracture surgery. (Boxplot with median, interquatiles and 10/90 percentiles.)

6.5 mg/dl for dorsal stabilisation and 17.4 mg/dl in ventral fusion operation (29).

CRP values seems to depend on different trauma regions and may reflect the extend of surgical trauma. Studies from abdominal surgery showed that CRP levels after laparoscopic approach for fundoplicatio or cholecystectomy were significantly lower than after conventional operation (15, 30).

In orthopaedic surgery we can also see operation-depending CRP levels: In cervical neck fractures of the femur CRP peak levels (reached on the second postoperative day) depends significant on operation technique (20). For osteosynthesis CRP levels were about 10 mg/dl (medians: screws: 8.7 mg/dl; dynamic hip screw: 12.0 mg/dl) and for hip replacement significant higher with CRP levels about 15 mg/dl (medians: total hip replacement: 15.6 mg/dl bipolar hemiarthroplasty: 16.0 mg/dl).

Levels of CRP following surgical trauma can be used to quantify the tissue damage and invasiveness of a procedure and reflects the perioperative stress for the patient. The CRP response objectifies the individual surgical trauma.

CRP in infection

CRP has demonstrated to be the most sensitive parameter for monitoring infections and the results of antibiotic treatment (11). In orthopaedic surgery CRP can help to detect complications earlier and differentiate between bacterial infection and abacterial infections or complications.

CRP can be used to monitor infections under therapy with antibiotics. In the case of the right antibiotic therapy

Table 1. CRP level of complication past 5 days after orthopaedic surgery

Complication	Number	C-reactive protein mg/dl, mean (standard error)
No complication	283	1.9 (0.15)
Aseptic loosening	5	5.3 (2.77)
Thrombosis (periphery)	2	3.7 (0.60)
Hematoma	10	8.0 (2.34)
Skin infection, necrosis	9	3.6 (0.66)
Urinary tract infection	6	4.6 (1.58)
Sepsis	1	12.0 (–)
Pulmonary infection	2	18.2 (9.25)
Deep wound infection	9	26.0 (3.42)

CRP-levels decline. In case of antibiotic resistance a persistent high CRP-level is seen and antibiotic therapy must be changed.

In the treatment of **pediatric osteoarticular infection** CRP can be used to monitor the therapy (5). In effective antibiotic therapy the initial high CRP-levels (15.7 ±9.8 mg/dl) were reduced about 50% over 4 days. In complicated cases persistently elevated CRP-levels were seen.

Also in patients with **bloodstream infection** CRP reach high levels approximate around 10 mg/dl. In Gram-negative bacterial bloodstream infection levels were significant higher than in Gram-positive bacterial bloodstream infection (11.2 ±5.7 mg/dl versus 7.6 ±5.7 mg/dl), (4).

CRP can be helpful in diagnosis and management of **primary pyogenic spinal infection** (39). Primary CRP-levels of 6.7 mg/dl were seen in pyogenic spinal infections. 80% were initially treated with long term antibiotics and successful monitored by CRP. In spondylodiscitis with multiresistant bacteria CRP levels reach values of 13 ±9 mg/dl (28).

Postoperative infection

In orthopaedic surgery it may be difficult to differentiate between CRP elevation caused by postoperative infection and CRP elevation caused by surgery.

For **early detection of postoperative complications**, the time-dependent values were an indicator. The kinetics of CRP levels after fracture surgery shows the difference between uneventful cases and complicated cases: The important point of detecting complications is the second rise and a persistent elevation of C-reactive protein (21). In our study all patients with postoperative bacterial infections had an increase with a large CRP-value. "Simple" infections (e.g. urinary tract) and "serious" infections (e.g. sepsis, pulmonary, deep wound infection) can be differentiated with CRP-levels. Abacterial complications, like mechanical loosening, show mostly no or only slightly increased CRP-levels. Wound hematomas can cause intermediate high CRP values (Table1).

The values were time-dependent with the onset of the complication. In the first days after surgery all patients have high CRP-serum-values because of the operative trauma. So it is difficult to differentiate between CRP elevation caused by postoperative infection and CRP elevation caused by surgery in the first 4 days. In extended operations higher CRP levels were seen on the second postoperative day than in minimal invasive operations. CRP shows the reflection of the surgical trauma to the patient. Higher CRP-values on the second postoperative day belongs to extended surgery and also may have more likely any complication because of the major operative trauma with higher risk. But no detection of complication can be made with CRP in the first 3-4 days.

The clinical appearance of an early wound infection occurs first time about the 5 day after surgery. The second rise of CRP for detection of wound infection is in average one day prior than the clinical appearance (29). For deep wound infection highest CRP-levels were seen, a cut-off level of 10 mg/dl (sensitivity 92%, specificity 93%) after the fourth day of **fracture surgery** was calculated. But the CRP values must always be correlated to the clinical situation because every bacterial inflammation can cause high levels of CRP (e.g. pulmonary infection). No laboratory value alone can account for clinical decision making.

In a study with **open extremity fractures** CRP at day 4 after transfixation was significant higher with upcoming infection (mean: 1.7 mg/dl) than without infection (mean: 0.8 mg/dl) with a sensitivity of 100% (8).

In **spine surgery** also CRP was the best parameter for detection of early wound infection (13). In two studies CRP were prior to WBC, ESR and PCT with high sensitivity 100% respectively 90% and specificity 96% and 89% respectively for a second rise of CRP (19, 34). The absolute median value on postop day 5 was 7.5 mg/dl for early infection after lumbar microdiscectomy (19).

In **total hip arthroplasty** (THA) and revision hip arthroplasty CRP is useful in the early postoperative period, but not in long term problems like low-grade infections. In a study with over 6000 primary THA in 36 patients an early infection occurred within 6 weeks (38). The best test for diagnosis of periprosthetic joint infection was the synovial fluid WBC (cut-off 12,800 cells/μL) followed by serum CRP (cut-off 9.3 mg/dl). CRP seems to be an excellent screening test, whereas the synovial fluid WBC count is more specific, but even more difficult in sample taking and analysis (16). In metal-on-metal bearings the synovial fluid WBC can frequently be falsely positive in automated cell count and should be manual count (37). A good sensitivity with 94% for CRP in detection of periprosthetic infection was reported in the same study.

Chronic or **low grade infections** after joint replacement are much more difficult in diagnosis and therapy. Differential diagnosis of aseptic loosening and allergic reactions needs a complex diagnostic algorithm to reveal low grade infection. Slightly elevated CRP values (>0.3 mg/dl) can be useful in combination with IL-6 (10), but often CRP reported to be normal in chronical infections (36). Analysis of synovial fluid seems to be more powerful in chronic periarticular infection. CRP can also be measured in synovial fluid and recent studies have suspected that CRP concentrations in synovial fluid might hold promise as a superior diagnostic marker (26,

27). A comprehensive study showed a cut-off level of 0,66 mg/dl for synovial fluid CRP, but also the same significance as serum CRP (AUC for both 0.90), (32). So measurements of CRP in synovial fluid did not offer a distinct advantage over serum CRP in chronic periprosthetic infections. Newer synovial fluid parameters like antimicrobial peptides HBD-3 and LL-37 showed promising results for the diagnosis of periprosthetic joint infection (12). Difficult aspiration of synovial fluid and missing standard laboratory measurements for special synovial parameters at the time let still appear CRP as a good basic parameter for chronic infection.

A portuguese meta-analysis of the predictive value of CRP in postoperative infections revealed an average of 85% sensitivity and 86% specificity (AUC: 0.906; OR: 23.56), (23). This again shows the need to match high CRP values to the clinical situation, because other bacterial infection like pneumonia can cause high levels. For early detection of acute postoperative Infection CRP seems to be the best and easily to get marker at the time. Interpretation of CRP kinetics permit establishment of early detection of surgical complications after orthopaedic surgery.

CRP: preoperative risk factor

CRP proved helpful as a marker in risk stratification. The preoperative CRP-level based on unsuspected infection or trauma predicts the postoperative course. High levels have a poor outcome. In femoral neck fractures treated with bipolar hemiarthroplasty 80% of the patient with a postoperative infection had CRP levels over 5 mg/dl upon admission (2). The C-reactive protein levels of patients with fracture might be preoperatively increased because of the trauma. It is known that a distinctive pattern of natural C-reactive protein response occurs after an accident or surgery (11). However, the preoperative C-reactive protein level (based on unsuspected infection or trauma) predicts the postoperative course, and patients with high C-reactive protein levels should be evaluated and closely monitored.

CRP: Fracture risk factor

Higher CRP levels are associated with increased fracture risk (14). A multivariate prospective analysis of 1872 women over 7 years shows an increased fracture risk for CRP levels over 0.3 mg/dl. Inverse association with the composite strength index but not with bone mineral density were even registered. In another study the increased fracture risk with elevated CRP was confirmed. Women shows a 39% higher risk for fractures and in men 80% higher fracture risk with CRP-values in the upper tertile of collective (7). There were suspicions that low-grade inflammation is associated with fractures, therefore CRP may be increased because it is a high sensitive inflammatory marker. But the relationship between inflammation (CRP) and bone mineral density (fracture risk) is less clear now.

CONCLUSION

C-reactive protein is a useful parameter to detect and monitor musculoskeletal infections treated with antibiotics. In operative fracture treatment and joint replacement CRP helps to estimate risks and to indicate early infections. An increased preoperative C-reactive protein level presents a risk factor for postoperative complications. The C-reactive protein value on the second/third postoperative day characterizes the surgical trauma, and a second rise in the postoperative course or a level beyond 10 mg/dl indicates there may be a deep infection. Monitoring C-reactive protein levels may help to detect complications earlier, to plan the correct treatment sooner, and to gain a better outcome for patients with postoperative infections.

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