Serum C-reactive protein levels correlate with clinical response in patients treated with antibiotics for wound infections after spinal surgery

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Abstract

BACKGROUND CONTEXT: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been used to diagnose postoperative infections after spinal surgery. However, it has not been demonstrated if resolution of the signs and symptoms of postoperative spinal wound infections in patients who are being treated with intravenous antibiotics correlates with these markers.

PURPOSE: The objective of this study was to determine if improvement of the signs and symptoms of postoperative wound infection after spinal surgery correlates with a decrease in serum CRP and ESR while intravenous antibiotics are administered.

STUDY DESIGN: Retrospective review.

PATIENT SAMPLE: The study consisted of 21 patients (mean age 63.8 years; 13 female, 8 male) with postoperative wound infections after spinal surgery. They were studied for a minimum of 20 weeks.

OUTCOME MEASURES: CRP and ESR were measured at the time of diagnosis and at serial time-points.

METHODS: All patients received intravenous antibiotic therapy for 6–8 weeks. Patients were monitored for clinical signs and symptoms of infection such as fever, drainage, erythema, or a need for continued wound packing at 4, 7, and 20 weeks after being diagnosed with a wound infection.

RESULTS: The average CRP for all 21 patients at time of diagnosis was 11.7±9.0 mg/dL (range 1.2 to 37.8 mg/dL). At the 4-week time-point, 16 patients (“early responders”) showed clinical improvement with no fevers, no wound drainage, no erythema, and no need for wound packing. The average CRP of this group at the 4-week time-point decreased to 0.3±0.5 mg/dL. In contrast, at the 4-week time-point five patients (“late responders”) still had signs and symptoms of infection (2 with continuing drainage requiring wound packing; 1 with vertebral osteomyelitis requiring irrigation and debridement; 2 with erythema without fevers). The average CRP for this group was still elevated at the 4-week time-point at 7.3±3.5 mg/dL. The CRP value difference was statistically significant between the two groups (p<.05). As treatment continued, at the 20-week time-point the average CRP of the late responders gradually decreased to 0.8±0.8 mg/dL, which was not statistically different from that of the early responders (average CRP=0.6±1.1 mg/dL). All 21 patients had resolution of infection at the 20-week time-point. The ESR did not correlate well with clinical improvement. At time of diagnosis, the ESR of both early responders (average=57.6±27.6 mm/hr) and late responders (average=64.0±21.9 mm/hr) was elevated. It remained elevated for both groups from the beginning of the study to the end at all time-points. The final ESR at the 20-week time-point was not different between the early responders and late responders (average=27.6±22.3 mm/hr vs. 31.0±2.6 mm/hr, respectively; p>.05).

CONCLUSIONS: Our data suggest that CRP may be of value in following the treatment response to antibiotics in wound infections after spinal surgery. The ESR can remain elevated in the presence of resolution of infection.
Introduction

Postoperative infection can be a serious complication of spinal surgery. Although countermeasures such as antisep ci tic techniques and antibiotic therapy have decreased their incidence, postoperative wound infections continue to be a problem for the patient and surgeon alike [1]. Early detection of such infections can be difficult because the signs and symptoms are often vague, nonspecific, and delayed. The physician has to rely on the clinical presentation and associated laboratory values such as leukocytosis with left-shift and a rise in acute-phase reactants for diagnosis. The rise in acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) has been successfully used as markers of infection after surgical procedures [2,3]. For example, data from total joint arthroplasty literature have demonstrated that increases in CRP value after the third postoperative day are highly suggestive of infection [4].

It is known that after uncomplicated spinal surgery CRP values rise sharply, reaching a peak value on the second postoperative day, followed by a rapid decline [5]. This spike in CRP levels is confined to a much shorter time period than other markers of inflammation, such as ESR, which may remain elevated for weeks. A second rise in the CRP value between postoperative days 4–7 has been shown to be a sensitive marker of infection after spinal surgery [5]. Interestingly, the same study showed that the peak CRP values after instrumented lumbar surgery are significantly higher than those after noninstrumented surgery. Because interleukins (IL) and tumor necrosis factor-α (TNF-α) are potent mediators of the inflammatory response [2], increased production of IL-1, IL-6, IL-8, and TNF-α by inflammatory cells upon contact with metallic implants is believed to be the reason for higher levels of CRP seen after instrumented spinal surgery [5].

Although several studies in the literature have demonstrated that CRP can be used to diagnose postoperative spinal infections [5–7], we are not aware of any studies that have documented if serum CRP levels in patients with wound infection after spinal surgery correlate with the resolution or persistence of infection while antibiotic therapy is being administered. Therefore, the purpose of this study was to retrospectively study a cohort of patients clinically diagnosed with a postoperative wound infection after spinal surgery who were being treated with intravenous antibiotics. The CRP and ESR values were recorded at serial time-points. We wanted to find out if clinical improvement was accompanied by a decrease in CRP and ESR values.

Materials and methods

Data were collected through a retrospective chart review on 62 consecutive patients who were diagnosed with a postoperative wound infection after spinal surgery between 2000 and 2004. Forty-one patients who did not have postoperative serial CRP and ESR measurements or who did not have a minimum of 20-week follow-up data were excluded from the study. The final number of patients thus obtained was 21 (13 female, 8 male; average age 63.8 years; range 29–82). To minimize observer bias, at the beginning of this retrospective study the authors did not check to see whether or not the CRP or ESR values were elevated for these patients.

The procedures included anterior cervical decompression and fusion (n=2), thoracic/lumbar discectomy (n=4), thoracic/lumbar instrumented fusion (n=12), lumbar laminectomy (n=2), and lumbar hemangioma resection with instrumented fusion (n=1). The average duration between the index surgical procedure and a clinical diagnosis of postoperative infection was 26 days. A specialist from the Division of Infectious Diseases was consulted who followed each patient from time of diagnosis onwards. Seventeen patients underwent operative irrigation and debridement. Because of the retrospective nature of this study, the criteria for operative irrigation and debridement were not predetermined, and were made by the principal surgeons on a case-by-case basis. Fluctuance, persistent or purulent drainage were the most common indications for operative irrigation and debridement. Thirteen of the 17 patients had implanted metal hardware. Three of the 17 patients had deep infections whereas the rest had superficial infections. Intraoperative cultures were obtained, and the results of the intraoperative cultures were as follows: methicillin-sensitive Staphylococcus aureus (4 patients), Staphylococcus epidermidis (4 patients), gram-negative rods (3 patients), polymicrobial cultures (2 patients), and negative cultures (4 patients). The patient characteristics and results of all 21 patients are shown in Table 1. All patients received 6 to 8 weeks of intravenous antibiotics. Serial CRP and ESR values were measured at the time of diagnosis. The patients were seen in clinic for follow-up at 4, 7, and 20 weeks post-diagnosis, at which point CRP and ESR values were measured.

Chart review was performed to see if patients had any signs or symptoms of wound infection at the various time-points, such as fever, erythema, drainage, or need for continued wound packing. Specifically, at the 4-week time-point each one of the patients was assigned to either a group that had a favorable response to antibiotic therapy
ie, absence of the aforementioned signs and symptoms of wound infection) or to a group that did not have a favorable response to antibiotic therapy (ie, persistent signs and symptoms of wound infection). Once this assignment was made based on the clinical response, then the CRP and ESR values were examined for each patient.

**Results**

The average CRP of all 21 patients at the time of clinical diagnosis of a wound infection was 11.7±9.0 mg/dL (range 1.2 to 37.8 mg/dL; normal <1.2 mg/dL). Figure 1 shows the changes in CRP with time.

At the 4-week time-point 16 patients (henceforth referred to as “early responders”) had shown clinical improvement with no fevers, no wound drainage, no erythema, and no need for wound packing. We defined these patients as having a favorable response to antibiotic therapy. The average CRP of this group at time of diagnosis was 11.5±9.1 mg/dL, which decreased to 0.3±0.5 mg/dL at the 4-week time-point. The other five patients (henceforth referred to as “late responders”) were still symptomatic at the 4-week time-point. Unlike the early responder group, these patients had one or more clinical signs or symptoms of continued infection (ie, fever, wound drainage, erythema, need for wound packing). This group consisted of three patients who underwent lumbar

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**Table 1**

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Instrumentation/Hardware</th>
<th>I&amp;D performed?</th>
<th>Superficial vs. deep infection</th>
<th>Organism</th>
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<td>Early responders (n=16)</td>
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<td>—</td>
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<tr>
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<td>Lumbar hemangioma resection and fusion</td>
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<td>Deep</td>
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<td>Yes</td>
<td>Deep</td>
<td>MSSA</td>
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<td>Yes</td>
<td>Superficial</td>
<td>GNR</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>SE</td>
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<td>Yes</td>
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</table>

MSSA=methicillin sensitive staphylococcus aureus, SE=staphylococcus epidermidis, GNR=gram-negative rods, I&D=irrigation and debridement.

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Fig. 1. Values of C-reactive protein (CRP) (±SD) versus time for early responders (ER; n=16) and late responders (LR; n=5). Unlike the late responder group, the early responder group had a rapid resolution of clinical signs and symptoms of infection, which was accompanied by a rapid normalization of C-reactive protein. *p<.05.
instrumented fusion and two patients who underwent thoracic/lumbar discectomy. In this group, one patient developed vertebral osteomyelitis requiring an irrigation and debridement (CRP 9.1), two patients had continued drainage requiring wound packing (CRP 12.0 mg/dL, 2.9 mg/dL), and two had persistent erythema but without fevers (CRP 7.4 mg/dL, 5.0 mg/dL). The average CRP of the late responders at time of diagnosis was 12.5±9.8 mg/dL, which decreased to 7.3±3.5 mg/dL at the 4-week time-point. At the 4-week time-point the CRP difference between the two groups was statistically significant (p<.05).

By week 20, the CRP values of both early responders and late responders had normalized to 0.6±1.1 mg/dL and 0.8±0.8 mg/dL respectively (p>.05), and they had no clinical signs and symptoms of a wound infection.

Figure 2 shows the corresponding ESR values. At time of diagnosis, the ESR of both early responders (average=57.6±27.6 mm/hr) and late responders (average=64.0±21.9 mm/hr) was elevated. At the 4-week time-point, the average ESR for the 16 early responders was 48.6±29.3 mm/hr, whereas the average ESR of the 5 late responders was 42.3±11.6 mm/hr (p>.05). At the 20-week time-point, the ESR of the early responders had decreased to 27.6±22.3 mm/hr while that of the late responders had decreased to 31.0±2.6 mm/hr, but there was no statistical difference between the two groups (p>.05).

Discussion

Tillett and Francis first described CRP in 1930 in patients being treated for pneumococcal pneumonia [8]. It was named as such because of its ability to react to the C-polysaccharide component of the pneumococcal wall. CRP is secreted by the liver in response to a variety of inflammatory cytokines, particularly IL-6, after trauma, inflammation, or infection [9]. CRP acts as a pattern recognition molecule to activate the adaptive immune response via the innate immune system.

Several authors have studied CRP as a potential diagnostic tool for postoperative infection after spinal surgery. A prospective study of 89 patients who underwent uncomplicated spinal surgery (lumbar microdiscectomy, conventional lumbar discectomy, anterior lumbar fusion, posterolateral interbody fusion) showed that CRP rises within the first two postoperative days and then sharply declines [10]. These findings were supported by another study of 89 patients who underwent spinal surgery which demonstrated that CRP reaches a peak level on the second postoperative day and then rapidly decreases [11]. Additionally, both these reports commented that the postoperative rise in ESR is more irregular and unpredictable, and that the ESR can remain elevated for up to several weeks postoperatively even in the absence of any infectious complications [10,11]. Because there were no cases of infections in the two aforementioned studies, the authors were only able to speculate that CRP was likely to be a more sensitive diagnostic marker of postoperative infection. This hypothesis was shown to be correct by Rosahl et al. who prospectively studied 51 patients undergoing anterior cervical fusion [6]. The authors found that CRP is indeed superior to ESR for early detection of postoperative infection. Meyer et al., who prospectively studied 400 patients undergoing lumbar microdiscectomy, came to a similar conclusion [7]. The investigators concluded that CRP was 100% sensitive and 95% specific in detecting postoperative infections. However, there were only nine cases of surgery-related wound infections, and the CRP was not measured after postoperative day 5. Therefore, these studies were not able to comment if clinical improvement of wound infections was correlated with a decrease in CRP. Schultz and Assheuer studied 31 patients prospectively who underwent one-level discectomy and showed that postoperative CRP elevation was correlated with an infection [12]. In another prospective study of 73 patients undergoing instrumented or noninstrumented spine surgery, Takahashi et al. showed that although both types of patients reached a peak CRP value on the second postoperative day, the peak is much higher in the instrumented group compared with the noninstrumented group [5]. There were three cases of postoperative infections (all with instrumentation), and they all had a second rise in CRP between postoperative days 4–7. The authors concluded that a second rise in the immediate postoperative period of the CRP value was strongly indicative of an infection. Therefore, the bulk of the current literature seems to indicate that CRP is much more sensitive and specific than ESR in the diagnosis of postoperative infection after spinal surgery.

Even though the aforementioned studies have demonstrated the usefulness and validity of CRP as an aid in establishing a diagnosis of postoperative infection after spinal surgery, the question posed in the present study was different; namely, whether or not CRP and ESR values
in patients with postoperative wound infection after spinal surgery, who are being treated with intravenous antibiotics, correlate with clinical improvement. Our study differs from previous studies because we first made a diagnosis of postoperative infection clinically and then measured and subsequently monitored serial CRP and ESR values at specific time-points while antibiotic treatment was being administered. CRP and ESR were used not just as diagnostic tools, but also as potential objective markers of wound infection resolution. It is interesting to note that simply administering antibiotics in the absence of an infection has no effect on CRP values [13]. Therefore, our study suggests that while antibiotic treatment is being undertaken, a persistently elevated CRP value indicates an active, persistent infection, whereas a declining/normalizing CRP indicates a resolving infection. There is support for this hypothesis in the literature. A study of 16 patients with pyogenic discitis demonstrated that radiographic improvement of paravertebral/epidural abscesses using magnetic resonance imaging was correlated with a decrease in serum CRP levels [14]. However, the aforementioned study included patients with pyogenic discitis only, not those with postoperative wound infections after spinal surgery.

In the current study, 16 of the 21 patients had clinical improvement within the first 4 weeks of antibiotic treatment. In those same 16 patients, the CRP values declined dramatically. On the other hand, the ESR had a wide degree of variability and did not show a rapid decrease. This variability in the ESR is in agreement with other studies in the literature [7,10,11]. Therefore, we propose that CRP is a better marker than ESR for following the course of postoperative wound infections after spinal surgery in patients being treated with intravenous antibiotics, and that CRP may be useful for guiding antibiologic therapy.

The strength of this study is that it attempts to provide an objective laboratory marker for monitoring a specific clinical process, namely postoperative wound infection after spinal surgery. To our knowledge, this is the first report to specifically address this question. We suggest that the surgeon and the infectious disease specialist can serially follow the CRP values of patients diagnosed with postoperative wound infections while antibiotics are being administered. Measuring CRP is a convenient, readily available, and inexpensive test. There are some limitations to our study. The first and most obvious is that it consists of a relatively small number of patients who were studied retrospectively. Also, because all of our patients had a favorable clinical response to treatment at the end of the study period, it remains to be seen how the CRP values of persistently poor responders change with time. We are mindful of the fact that the patient sample studied in this report was heterogeneous, because it consisted of patients with several different types of bacterial organisms. Prospective studies with larger numbers of patients are needed to address these issues.

Conclusion

Based on this small retrospective study, serial CRP level measurement may be helpful in monitoring the treatment of postoperative wound infections after spinal surgery. However, ESR does not appear to be a sensitive marker of infection resolution.

References