C-REACTIVE PROTEIN AS A MARKER OF POSTOPERATIVE SEPTIC COMPLICATIONS

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The aim of the study was to answer the question whether or not determination of C-reactive protein in patients after serious abdominal surgeries can be prognostic of septic complications.

Material and methods. 36 patients who underwent elective surgeries were included in the study. The patients were included either in the group where no postoperative SIRS developed or in the group where postoperative SIRS did occur. In the seven-day period after the surgery, in 26 patients SIRS was found, and in 10 – sepsis was suspected (according to the ACCP/SCCM definitions). In patients who underwent abdominal surgeries blood concentration of C-reactive protein was determined prior to the surgery (measurement ‘0’), and then on postoperative days 1, 2, 3, 5 and 7.

Results. The test for two variables (C-reactive protein on postoperative days five and seven) showed statistically significant difference, and for one variable (C-reactive protein on day three) – difference at the limit of significance. Thus, it was found that in the postoperative SIRS group the level of C-reactive protein is higher than in the non-SIRS group.

Conclusions. Serial measurements of C-reactive protein are useful in the first week after surgery, as they can be prognostic of postoperative septic complications. Such complications can be anticipated if CRP on postoperative day 5 is higher than 1/2 of the maximum CRP concentration on day 2 or day 3, or CRP > 150 mg/L as of postoperative day 3. Unfortunately, the severity of the disease cannot be projected based on C-reactive protein level.

Key words: C-reactive protein, postoperative septic complications

Monitoring patients after extensive abdominal surgeries is still an open issue. The number of recorded complications after such procedures ranges between 10 and 30%. They can be connected with all organs and systems, however, in the majority of cases (even up to 80%) they are surgical complications. It is estimated that the likelihood of sepsis in patients after serious abdominal surgeries is 9-12% (1). Early detection of postoperative complications followed by immediate management significantly reduces mortality associated with abdominal sepsis (1).

This study aimed at answering the question whether or not determination of C-reactive protein in surgical patients can be prognostic of development of septic complications.

MATERIAL AND METHODS

36 patients aged 33 to 78, who underwent elective surgeries, were included in the study. The patients were included either in the group where no postoperative SIRS developed (non-SIRS group) or in the group where postoperative SIRS did occur (SIRS group). In the seven-day period after the surgery, in 26 patients SIRS developed, and in 10 – sepsis was suspected (according to the ACCP/SCCM definitions). In 24 patients, surgical complications manifested as anastomotic separation, fistula, collection of fluid in the abdominal cavity, abscesses and massive bleeding. Patients were re-operated, had the ultrasound-guided transcutaneous drainage of fluid or abscesses, or
were treated conservatively. Patients with non-surgical complications were excluded from the study. Characteristic of the groups is presented in tab. 1. In patients who underwent abdominal surgeries, blood concentration of C-reactive protein was determined prior to the procedure (measurement 0), and then on postoperative days 1, 2, 3, 5 and 7. On the day of collection, the blood was centrifuged, and the plasma was frozen. Everyday, patients were evaluated for possible complications, e.g. respiratory or urinary, and the surgical wounds, as well as the contents drained from the peritoneal cavity, were inspected. Patients were also evaluated for symptoms of sepsis. C-reactive protein was determined by immunoprecipitation, using biochemistry analyzer Olympus AU-400; normal range was up to 5 mg/dL.

RESULTS

The Mann-Whitney U-test results, as well as mean values and standard deviation for C-reactive protein on successive postoperative days in the non-SIRS group and the SIRS group are presented in tab. 2 and fig. 1 (graphic presentation). Statistically significant difference was defined as p < 0.05. The test for two variables (CRP-5 and CRP-7) showed a statistically significant difference, and for one variable (CRP-3) – difference at the limit of significance. Thus, the level of C-reactive protein is higher more frequently in the SIRS.
group than in the non-SIRS group. Table 3 presents sensitivity and specificity of CRP.

**DISCUSSION**

C-reactive protein was discovered by Tillet and Francis in 1930 (2). However, determination of C-reactive protein had no clinical use for a long time. Only in mid-eighties, a method of quick and precise determination of C-reactive protein became feasible. The newest assay methods are inexpensive, the results are achieved within 15-30 minutes, and their sensitivity is ± 0.04 mg/L. In 99% of healthy persons, concentration of C-reactive protein should not exceed 10 mg/L (2), and the mean value should be 0.3-1.7 mg/L. In the case of pathology, the level of C-reactive protein usually ranges between 20 and 200 mg/L, and rarely exceeds 300 mg/L (3). In the studied group, CRP level increased postoperatively, reaching the maximum value on days 2 and 3, and on postoperative day 5 it was below 1/2 of the maximum concentration of day 2 (fig. 2).

Non-drop or repeated increase in CRP suggested infection. Thus, the Lindberg’s (4) and Cox’s (5) results were confirmed. No correlation between surgery type and the maximum level of CRP was found, which was observed also by other authors (6, 7).

The statistical analysis showed that statistically significant differences between the non-SIRS group and the SIRS group occurred on postoperative day 3, and only since then it was possible to differentiate between patients from both groups based on CRP level. Similarly designed studies can be found in literature. In the studies conducted in 104 patients after injuries or surgeries (8), concentration of CRP on day one from the occurrence of a stimulus did not differentiate patients with or without infection. However, on day 6 the con-

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**Table 3. Sensitivity and specificity of C-reactive protein in the non-SIRS/SIRS group**

<table>
<thead>
<tr>
<th></th>
<th>C-reactive protein</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>96%</td>
</tr>
<tr>
<td>Specificity</td>
<td>79%</td>
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</tbody>
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**Fig. 1. CRP values (mg/dL) in the non-SIRS group and the SIRS group in the successive periods**

**Fig. 2. CRP concentration in uncomplicated postoperative period**
centration of CRP was significantly higher in patients with septic complications than in patients without complications (216 mg/L versus up to 57 mg/L). On day 6, the concentration > 130 mg/L had the 85% sensitivity and 83% specificity for detecting infection. In another study (151 patients after pneumonectomy (9)), C-reactive protein reached the maximum level on postoperative days 3 and 6, and then it decreased in the uncomplicated course, and after 12 days it was < 50 mg/L. The concentration > 100 mg/L after 12 days indicated postoperative septic complications (100% sensitivity and 94.5% specificity). In another study, septic complications were indicated by CRP > 190 mg/L after three days from surgery (10). In our study, the statistical analysis showed that complications are indicated by CRP > 150 mg/L as of postoperative day 3. The Falcoza thesis (11) that CRP > 100 mg/L on postoperative day 2 is associated with increased risk of septic complications was not confirmed. However, not all authors recognize usefulness of determination of C-reactive protein. They point out to slow kinetics of CRP (12). C-reactive protein provides little information in the initial 48 hours from the surgery – it is elevated in reaction to postoperative trauma, its level is often high even in an uncomplicated course (4), and significant fluctuation occurs even in the case of low-grade local infections. Mokart (13) ascertained that postoperative concentration of C-reactive protein remains elevated for a long time, both in the group of complicated patients and uncomplicated ones. In our study, we also attempted to find out if a single measurement of C-reactive protein is effective in diagnosis of sepsis. There have been a few studies that provide an answer to this question. According to Povoa (14), the concentration > 50 mg/L has the sensitivity 89.5% and the specificity 79% in detecting sepsis; and according to Ugarte (15), the concentration > 80 mg/L has the sensitivity of 72% and specificity of 66.6%. Castelli says that sepsis can be detected when CRP > 128 mg/L (16). In other studies, the cut-off values of CRP that could indicate sepsis range between 50 and 100 mg/L (16, 17).

Authors emphasize that determination of C-reactive protein is less effective than determination of procalcitonin (PCT). Other researchers emphasize that C-reactive protein has low specificity and cannot be used as the only marker to confirm infection. Sometimes the level of CRP is not elevated at all, despite clinical symptoms of a disease. The kinetics of CRP is slow (18); the maximum level of CRP is reached after about 48 hours from the occurrence of a stimulus. The decrease in CRP is also slow. It is often the case that a clinically healthy patient continues to have a high level of C-reactive protein. Our studies confirmed that a single measurement of CRP is of limited usefulness for detecting sepsis. On many occasions, C-reactive protein in the studied groups exceeded the levels reported by other authors, and it was not associated with confirmation of SIRS or infection. Concentration of CRP increases also in non-infectious complications or as a reaction to a postoperative trauma. Another thesis verified in the study was whether or not it is possible to determine the severity of septic syndromes based on CRP concentration. According to some researchers, a single measurement of CRP reflects its secretion, which in turn corresponds with inflammatory response; based on that, the severity of the septic process can be defined.

In the Suprin study (19), patients with septic syndromes were grouped by the ACCP/SCCM definition, which yielded the following mean CRP results: SIRS patients – 70 mg/L, sepsis patients – 98 mg/L, severe sepsis patients – 145 mg/L and septic shock patients – 173 mg/L. Ugarte (15) on the other hand received the following results: SIRS – 66 mg/L, sepsis – 108 mg/L and septic shock – 126 mg/L. Castelli (16) claims that based on determination of C-reactive protein, one cannot differentiate between grades of severity of septic syndromes; one can however differentiate SIRS from sepsis; in sepsis, CRP concentration is considerably higher. A different opinion is held by the other group of researchers. They claim that determination of CRP is not useful for defining the severity of inflammatory response; high values can be found even in local inflammations (18). Also, there is no relation between the concentration of CRP and the SOFA scale of multiorgan failure (18). In our studies, the validity of the letter thesis was confirmed. When monitoring postoperative C-reactive protein, it is difficult to associate postoperative concentration of CRP with severity of inflammatory reaction. During observation, SIRS and sepsis were found, but no severe sepsis or septic shock occurred. Comparing CRP in various SIRS patients, no mean
value of CRP, characteristic of this disease entity, was defined; in various patients it ranged between 52 mg/L and 350 mg/L. Usefulness of C-reactive protein as a prognostic marker of death was evaluated. It was found that CRP concentration in patients who died was considerably higher than in those who survived. In the Cox study (5), C-reactive protein on admission was 70 mg/L in the case of those who died, and 18 mg/L in the case of convalescents. Also in another study, CRP concentration determined during hospitalization was higher in those patients who died, compared with those who survived (20). However, in most publications the predominating opinion is that one cannot prognosticate the patient’s survival or death based on CRP determination in the initial stage of sepsis (12, 18), which was confirmed by our studies. Serial measurements are more significant than a single measurement. They allow monitoring the course of inflammatory reaction and response to treatment – CRP decreases in the case of effective therapy, and increasing concentration of CRP suggests incorrect diagnosis or inappropriate therapy. C-reactive protein has a much higher diagnostic value than determination of WBC count and measurement of body temperature.

Infection should always be suspected in the event that CRP concentration gradually increases in 2-3 days, and there has been no intervention (e.g. surgery) that could have caused such inflammatory reaction (21). In another study, it was ascertained that increase in CRP concentration by 25% compared to the previous day value suggests sepsis (22). However, one should bear in mind a relatively slow kinetics of C-reactive protein. Once sepsis has developed, C-reactive protein increases to the maximum level within 2-3 days, and when the disease is resolving, the decrease is also delayed (99). Our studies have confirmed usefulness of serial measurements. It seems that C-reactive protein is useful for postoperative evaluation of the patient. For a surgeon, elevated CRP is a useful sign in the case of non-infectious complications (e.g. fistula and fluid collection in the abdominal cavity, which are not associated with infection in the initial stage). Without question, serial measurements should be done, and CRP should necessarily be determined on postoperative day 2, in order to have a point of reference for successive measurements. Increase in C-reactive protein was noted one or two days prior to clinical diagnosis of complications. Unfortunately, one cannot predict the development of complications based on CRP determined on the first postoperative days, and thereby assess, in a sense, the correctness of the surgery. The level of CRP on postoperative day one and day two did not differentiate patients from the non-SIRS group and SIRS group. Differences occurred only in successive days.

High levels of CRP on initial postoperative days are associated with the development of SIRS. It is a physiological response to surgical trauma. It was found in 33% of patients in whom no postoperative complications occurred, and in as many as 92% of complicated patients. SIRS that occurs in subsequent days is connected with manifestation of surgical complications. In 10 patients, sepsis was suspected. In postoperative week one, no severe forms of septic syndromes were noted – severe sepsis, septic shock or MODS. It was probably connected with normal functioning of the immunological system and prophylactic antibiotic therapy. Changes in C-reactive protein concentrations in this period have been presented above. In the first period, deaths were caused by cardiovascular and respiratory failure, not by infection.

Observation of the subsequent course of the disease in complicated patients showed that severe septic conditions occurred in postoperative week 2 or week 3. They were connected with hospitalization-related superinfection with bacterial strains resistant to many antibiotics. At that time, also impairment of the systemic immunologic functions developed. Such complications occurred in patients who were repeatedly re-operated, as the first reoperation was ineffective.

CONCLUSIONS

In our opinion, serial measurements of C-reactive protein are useful in the first week after surgery, as they can be prognostic of postoperative septic complications. Such complications can be anticipated if CRP on postoperative day 5 is higher than 1/2 of the maximum CRP concentration on day 2 or day 3, or CRP > 150 mg/L, as of postoperative day 3. Unfortunately, the severity of the disease cannot be projected based on C-reactive protein level.
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