THE SEPTIC COMPLICATIONS IN COLORECTAL SURGERY CAN MODIFY SERUM LEVELS OF C - REACTIVE PROTEIN IN EARLY TIME OF THE INCIDENCE?

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Abstract: *anastomotic leakage (AL) is a severe complication in colorectal surgery, and C-reactive protein (CRP) level can be a predictive marker of this complications. Material and method: this retrospective study analyses the evolution of 341 patients with colorectal cancer and primary anastomosis between 2003 and 2012, performed in the Ist Surgical Clinic, Emergency Academic Hospital Sibiu. Results: 7,3% of 341 patients developed AL, the mean day was 8,8 day postoperative of the patients with AL, 20 (80%) underwent reoperation, 20% of AL patients were treated conservatively. The high mortality in patients with AL (8%) caused by sepsis, versus 3,2% in larger group without AL and sepsis (p=0,20). The study of the serum CRP levels and WBC of patients say that CRP level in the two groups a peak on day 2, and in presence of AL, the CRP level not show a real decrease during the next few days. We observed high CRP levels in patients with pneumonia and other postoperative inflammations or sepsis. Conclusions: The serum CRP level is a relevant marker in diagnosis of the postoperative complications after colorectal resections.*

Cuvinte cheie: *fistulă anastomotică, protiena C reactivă, pneumonie*

Rezumat: *Fistula anastomotică (FA) este o complicație severă a chirurgiei colorectale, iar nivelul proteinei C reactive poate fi un marker predictiv al acestei complicații. Material și metodă: Studiul retrospectiv prezent analizează evoluția a 341 de pacienți cu cancere colorectale și anastomoze primare efectuate în intervalul 2003-2012 în Clinica Chirurgie I a Spitalului Clinic Județean de Urgență Sibiu. Rezultate: 7,3% din 341 de pacienți au dezvoltat FA, durata medie de apariție fiind 8,8 zile postoperator la toți pacienții cu FA. 20 (80%) din aceștia au fost reoperați, 20% dintre fistule au fost tratate conservator. Mortalitatea ridicată de 8% la pacienții cu FA s-a datorat sepsisului, în comparație cu 3,2% rată de mortalitate la pacienții fără FA și sepsis (p=0,20). Determinarea nivelului seric al PCR și leucocitelor la pacienții operați a arătat un vârf de creștere a PCR în a 2-a zi la ambele grupe, iar în prezența FA, nu se observă o scădere reală a PCR-lui în intervalul următor. Am observat un nivel crescut al PCR la cei cu pneumonie și în prezența altor infecții postoperatorii sau inflamații. Concluzii: Nivelul seric al PCR este un marker relevant în diagnosticul complicațiilor postoperatorii din chirurgia colorectală.*

INTRODUCTION

In 1991, the United Kingdom Surgical Infection Study Group defined anastomotic leak as the "leak of luminal contents from a surgical join between two hollow viscera".(1)

Clinical anastomotic leakage is accompanied by signs of peritonitis or abscess, septicemia, and fecal or purulent discharge from the wound, drain or abscess.(1,2) The incidence of anastomotic leak following colorectal surgery varies among institutions and by anatomic location of anastomosis in colo-anal or colo-rectal anastomosis leak 1% to 19%, colo-colic leak 0% to 2%, ileo-colic leak 0,02% to 4% and ileo-ileal leak 1%.(3,4,5,6,7,8,9)

Postoperative anastomotic leaks are one of the most devastating consequences of colorectal surgery. They occur in 2 to 51 percent of patients, and generally result in the need for emergent reoperation.(10-17) The anastomotic leaks occupy for approximately one-third of all deaths after colorectal surgery.(11,18,19) Because of the severity of the problems associated with an anastomotic leak, it is important and imperative in many cases to identify the complications and act it as early as possible.

Extra-peritoneal anastomotic leaks, by definition, leak an innervated peritoneal surface and therefore may develop insidiously without peritoneal signs.(20,21,22) The first sign of this type of anastomotic leak may be unexplained cardiorespiratory or urinary symptoms during early postoperative period.(23,24,25,26).

Even though the rate of anastomotic leaks in patients with anastomoses after resection for colon cancer in low, it remains a significant morbidity and mortality.(27,28,29,30)

Identification of the best methods to discovered the presence of sepsis, it is justify, because, unfortunately, despite the progress in basic and clinical research efforts, mortality from septic shock remains unchanged or greater than 50%.(27-31)

Anastomotic leakage apart from the early consequence, like postoperative morbidity, increased mortality, has been proven to have an independent negative impact on long – term survival after potentially curative resection of colorectal cancer.(32-39)

Increased levels of C- reactive protein have already been established in acute pancreatitis and pancreas

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transplantation for signalling an unfavourable outcome and for early detection of necrosis.(40,41)

The C- reactive protein is a pentameric protein, and it's considered an indicator of postoperative surgical and nonsurgical complications.(42,43)

The recent studies has been shown that CRP (C-reactive protein) elevation after rectal resection in carcinoma is predictive of septic complications in postoperative evolution of the patients, including anastomotic leakage (AL) and may be an indicator of anastomotic leakage.(44,45)

The advance in rectal cancer surgery, in areas such adjuvant chemo-radiotherapy, stapling anastomoses, total mesorectal excision, has increased the sphincter preservation rate, this situation may contribute to an increase risk of anastomotic leakage.(46-49)

This retrospective study was designed to evaluate the role of CRP in the early prediction of AL following colorectal resection.

Acute phase protein and some hormones have been clinically and experimentally used as indicators of the inflammatory state induced by infections, thermal injury and surgical procedures.(46-50) However we have often seen a discrepancy between the condition of patients and these indicators. This discrepancy might exist because these factors do not mediate subsequent response against exogenous stress.

We previously found an elevation during surgery in serum C- reactive protein and to investigate these questions we measured the changes in CRP levels during and after surgery in colorectal carcinoma patients.

METHODS

Between January 2003 and January 2012, 341 colorectal resections with primary anastomosis were performed for carcinoma and benign disorders, the patient data were analysed retrospectively with the incidence and outcome of AL.

In this retrospectively study we analysed the serum CRP levels.

In table no. 1 are presented the studied patients details and underlying diagnose.

Table no. 1. Details of 341 patients with colorectal resection

Diagnosis	
Cancer	183/341 (53%)
Emergency resections	40/341 (12%)
Crohn's disease	12/341 (3,5%)
Diverticulitis	13/341 (3,8%)
Age (mean +/- range)	60,0 +/- 33 (27-93)
ASA score (mean +/- range)	2,5 +/- 0,6

In 341 patients studied total colectomy represent 3,4% (11 case), 100 (29,5%) with sigmoid resection, 88 (25,8%) right colectomy, 24 (7%) left colectomy, 55 (16%) low rectal resection, 38 (11%) Dixon resection.

In this studied patients, all received prophylactic antibiotics, for the longer antibiotic therapy, we used third generation cephalosporin in combination with metronidazole, or imipenem (cylopen). At the time of diagnosis the presence of AL, antibiotic therapy was restarted.

Tumours were classified according to site, and cancer arising at the recto-sigmoid junction was classified as rectal cancers. The extent of tumour spread was assessed by Duke's classification based on histological examination of the resected specimen.

Anastomotic leakage was defined as any clinical or radiological evidence of dehiscence of anastomosis (51), and the definition included all patients with a localized or generalized leak.

In the study protocol, serum CRP simultaneous with white blood counts (WBC) were determinate daily. The analysis started before the operation until the postoperative day 7.

A WBC between 4.000/ml to 10.000/ml was considered normal, and CRP up to 0,5mg/dl were considered elevated.

In case of suspicious clinical symptoms of the anastomotic leakage, and X- ray, or CT was performed.

Statistical analysis was performed with SPSS and Fisher- test, and to compare the values student's t- test were used. The confidence interval 95%, p value < 0,05 was considered significant.

RESULTS

The in-hospital mortality was 3,5%.

In the postoperative evaluating, 24 of 341 (7,05%) patients developed an anastomotic leakage, diagnosed at a main of 8,8 days (range 3- 28 days) postoperatively.

In the presence of anastomotic leakage, the patients present acute abdominal pain in 5 (23%) cases, feces in the drain in 5 (16%) case and fever in 14 (61% cases).

Of the patients with anastomotic leakage 80% underwent reoperation, 20% of AL patients were treated conservatively.

The evolution of the patients with AL was more complicated in postoperative period, with significantly longer hospital stay (30 +/- 12) than of those without AL (13 +/- 8) days; $P < 0,001$.

The high mortality in patients with AL, 8% caused versus 3,2% in larger group without AL and sepsis (p=0,20).

In this study we compared the serum CRP levels and WBC of patients with AL, vs. patients without AL. In patients with AL, the CRP level have a peak of 17,2 +/- 8,6 mg/dl on mean postoperative day, and decreased thereafter.

In all patients the CRP level increase in first two days, with highest increase in day 2, but after this period, in patients without AL decrease over the next few days.

In evaluation of the two categories, with and without AL, in Al patients, the CRP levels was in 3 and 7 days postoperative higher ($p < 0,001$). This difference did not show in evolution of WBC levels in both groups, and was no significant difference in the course of WBC between the two groups.

In complicated postoperative evolution 3% of the patients developed pneumonia. In this category, without AL, the CRP levels was high on postoperative day 3, 4, 5, 7, comparing with others without complications in postoperative evolution.

The length of postoperative stay contributes significantly to the cost of general surgical care. The main length of postoperative stay was 10 days.

An increase in the length of postoperative stay was associated with:

1. Postoperative ventilation (mean 18 days)
2. Wound infection (11,7 days)

   In this study 3,5% (12/341) of patients had a postoperative abdominal wall infection six of those cases suffered from AL. In this patients with wound infection with or without AL did not show any difference in CRP levels.
3. Stoma (4,5 days)
4. Urinary complications (5 days)
5. The length of postoperative stay was increased by 3,7 days for each 10 g/l decrease in preoperative serum albumin

DISCUSSIONS

Of pre-operative factors, a low albumin level was associated with a prolonged postoperative stay, with higher risk in AL. Since albumin is the most specific of the variable reflecting nutritional status (46,47), the present dates indicates an association between poor nutrition and prolonged postoperative stay.

The incidence of AL of colorectal surgery range from 2 to 6%, with higher as 11% for low anterior resection of the rectum with total mesorectal excision.(36,37,48,49,50,51)

In study of Alves et al. (48), postoperative mortality after AL complications is high as 25- 40%, and AL accounts for more than one third of all deaths after colorectal surgery.

Postoperative complications are usually considered to be the most responsible factors for prolonging postoperative stay.

In one study, the length of postoperative stay was almost doubled in patients with postoperative complications.(52)

AL is an independent negative factor in long-term survival in colorectal cancer.(36,38,39)

Alves et al. observed that early reoperation in AL improves survival (0% mortality in patients re-operated before day 5 after primary surgery compared to 18% re-operated after day 5).

It is possible that the adverse impact of anastomotic leakage on long-term survival was simply a reflection of the high postoperative mortality rate associated with development of intra-abdominal sepsis.(53,54,55)

Recent studies have shown that the presence of a systemic inflammatory response, as evidenced by raised circulating concentrations of CRP is associated with poor survival in patients undergoing resection for colorectal cancer.(49,54)

It is therefore possible that the duration and magnitude of the SIRS is an important factor in determining long-term outcome in patients who develop an anastomotic leak. It is well established that there is a self-limiting process as SIRS after surgery in patients with uncomplicated postoperative evolution. However, patients who develop an AL, suffer a "double hit", the first as a result of surgery and the second as a result of sepsis, and an increased magnitude and duration of SIRS. The release of cytokine and growth factors as part of SIRS, response secondary to intra-abdominal sepsis, and the associated immunosuppression may have a direct effect on the growth of residual tumour cells.(50,56) The serum CRP level is known to increase after different kinds of surgery, showing a peak after 48 to 96 h.(42,57)

In present study we showed in patients with or without leakage an increase CRP level, with a peak in postoperative day 2 and 2,5 respectively, the level decrease after the peak of day 2 in patients without postoperative AL.

Matthiessen et al. (44) describe a prolonged increase in CRP level to be an indicator of impending leakage in patients with Dixon resection.

Welsch et al (45) observed a correlation between persistent CRP elevation as predictive of sepsis following rectal surgery, and in that study no significant difference in CRP elevation in patients with AL, infection of wound, pneumonia. The persistent increase level of CRP from preoperative to postoperative values seems to be even more predictive. The development of an AL it's very important because it might be hypothesized that patients who develop an AL after apparently curative resection have more residual tumors, and if this is the case, disease free survival at 2 years might be expected to be worse in these patients.(58-61)

Using the CRP levels in diagnosis of AL, we can reduce time to treatment. The higher CRP levels were identified on postoperative day 3 and 7, AL could be suspected about 2 to 6 days in advance of its actual appearance. The mean time of leakage was 8,8 days postoperatively. The highest CRP was measured 1 day before the leakage was evident in only 19% of the cases. The increase of CRP and the presence of AL might be secondary a persistent impairment of microcirculation with local ischemia.(62-65)

Millan et al. (61) showed that a reduced intra-mucosal pH at the anastomotic site was significantly associated with AL, and the date from Vignoli (65) say that the reduction of blood flow at the rectal stump measured by laser-Doppler flowmetry was associated with increased risk of AL.

A possible correlation between anastomotic perfusion and microcirculation with CRP levels needed others studies to prove.

In the study by Welsch et al. (45) WBC did not indicate an unfavourable outcome as early as CRP elevation did, and in our data we have bad a slight postoperative increase in WBC in both groups without any significant difference.

PCR has been shown to be made more sensitive in identifying AL, that WBC.

CONCLUSIONS

Serum CRP is a predictive marker for detecting postoperative septic complications.

The persisting elevation in the CRP level without decrease precedes the occurrence of AL after colorectal surgery.

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