PROGNOSTIC FACTORS FOR ANASTOMOTIC INSUFFICIENCY IN ELECTIVE COLORECTAL SURGERY

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ABSTRACT

INTRODUCTION: Anastomotic insufficiency is a severe, potentially fatal complication of colorectal surgery. Its frequency, according to different authors, reaches up to 20%. It is related to two main types of risk factors: associated with the patient and associated with the therapeutic approach.

AIM: The aim of the study is to determine prognostic factors for anastomotic insufficiency. The collected data from patients operated on for a period of 5 years (2013-2017) in the Second Surgery Clinic, Alexandrovska University Hospital, Sofia, were analyzed.

MATERIALS AND METHODS: A total of 158 patients undergoing elective colorectal surgery have been retrospectively included. These on emergency, non-proven malignancies and with preoperative haemotransfusion were excluded from the study. All patients were evaluated by age, gender, BMI, ASA score, Charlson Comorbidity Score, localization, TNM stage and histological type. The surgical approach and the method of resection were determined. The postoperative period and complications were classified according to the Clavien-Dindo scale. The number of leukocytes, platelets, RDW, CRP and albumin were examined preoperatively, and on the day 1 and day 4, in the early postoperative period.

RESULTS: The average age of the patients was 67 (29-87). Of these, 100 (63.3%) were men, and 58 (36.7%) are women. The mean BMI was 27.1 (23-33). A total of 78.9% of the operated patients weree in TNM stage II and III. Histologically, 77.8% were moderately differentiated adenocarcinomas. The mean Charlson Comorbidity Score for the sample was 7.1 (range: 2-13), and the ASA score was 3 (2-4). The rectum was the most common localization - 40.1%, followed by right colon 22.8%, and the sigmoid colon 20.9%. Over the review period, most resections were conventional, with only 15.2% laparoscopic approach. The operations performed were right hemicolectomy - 36 (22.8%), left hemicolectomy -15 (9.5%), segmental resection - 38 (24.1%), total colectomy - 4 (2.5%) resection of the rectum - 44 (27.9%), and other - 21 (13.3%). In 12 (7.6 %) of the patients insufficiency was reported between day 2 and day 3, postoperatively. Five of them were treated conservatively and the other six were reoperated. Seven of the insufficiencies were after anterior resection of the rectum, 2 were after left hemicolectomy, 1 after resection of the sigmoid colon, one was after right hemicolectomy, which had been treated conservatively. The mean postoperative period of patients with insufficiency was 22 days (range: 9-45). For patients without complications, the postoperative period was 9.4 days (range: 4-21) and there was a strict statistical difference (P <0.05). All patients

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experienced an increase in leukocyte counts postoperatively, albumin drop, increased CRP and ESR. The mean platelet counts depended on the presence of insuffiency.

Conclusion: The anterior resection, which is associated with technically more difficult anastomosis and neoadjuvant radiotherapy is a potential risk factor for anastomotic insufficiency. The use of blood parameters in the postoperative period allows early diagnosis of the complication and possible change of the therapeutic strategy.

Keywords: *colorectal cancer, anastomotic insufficiency, colorectal surgery*

INTRODUCTION

Anastomotic dehiscence is severe, potentially fatal complication of colorectal surgery. It is responsible for 1/3 of the deaths in the early postoperative period (1). The quality of life of those patients is significantly worsened - strictures, fistulas, stoma, etc. In addition a two-way connection between the anastomotic leakage and local recurrence at the site of the anastomosis is observed (2-4). Last but not least, these patients have longer hospitalization duration, which generates huge expenses for the hospital, without any guarantees for the positive outcome of the treatment (5). Dehiscence rates vary a lot and can be up to 20%, depending on two big groups of risk factors – patient-associated and associated with the treatment approach and operative technique. In most of the cases, anastomotic leakage is diagnosed based on the complications it causes: in some cases it can be manifested severely as a septic shock, in others the symptoms can be blurred, the manifestation is tightened postoperative period and postoperative ileus. The fact that insufficiency risk is associated with many and different factors hints that the reasons should be searched on molecular level and risk determinants that are easy to evaluate should be found. They would allow adequate perioperative selection of the risk groups and early discovery of anastomotic leakage, before its clinical manifestation (6).

AIM

The goal of this study is to determine the prognostic and predictive factors for anastomotic leakage. The analyzed data is from the Second Surgery Clinic in Alexandrovska University Hospital, for a 5-year period (2013-2017).

MATERIALS AND METHODS

Involved in the study were 158 patients, evaluated retrospectively. Patients who underwent emergency surgery, unproven carcinomas and those with preoperative hemotransfusion were excluded. Inclusion criteria were those with elective colorectal surgery with proven malignant disease and with complete medical records. Patients were evaluated based on their age, gender, BMI, ASA score, Charlson Comorbidity Score (CCS), tumor localization, TNM stage, histological type of the carcinoma. Statistical significance was calculated by the Chi-square method, with Yates correction. The operative approach and the type of resection were taken into account. All of the surgeries were performed by skilled and experienced surgeons from the Alexandrovska University Hospital. The postoperative period and postoperative complications were classified by the Clavien-Dindo scale. From the laboratory tests the ones that were of interest to us were WBC count, platelets count, RDW, CRP and albumin, preoperatively, on first and on fourth postoperative days. All blood tests were performed fasting, in accordance with the standards for good medical practice. Lab results were reviewed in certified laboratories, in referent ranges.

RESULTS

The mean age of the patients was 67 (29-87). Of them 100 (63.3%) were men, and 58 (36.7%) were women. The mean BMI was 27.1 (23-33). A total 78.9 % of the patients underwent surgery in second and third TNM stage. Histologically 77.8% were with moderately differentiated adenocarcinoma. The mean value of CCS was 7.1 (2-13), and the ASA score - 3 (2-4). The rectum was involved in 40.1% of the cases, followed by the right colon 22.8%, and the sigmoid colon 20.9%. For the period of this study, most

of the resections were conventional, and only 15.2% were performed laparoscopically. The volume of resection was as follows: right hemicolectomy in 36 (22.8%), left hemicolectomy - 15 (9.5%), segmental resection – 38 (24.1%), total colectomy– 4 (2.5%), anterior resection of the rectum - 44 (27.9%), combined - 21 (13.3%). Anastomotic leakage was reported in 12 (7.6 %) of the patients, between the 2nd and 3rd postoperative days. Five of them were treated by a conservative approach and the others were reoperated. Ten (83.3%) of the patients with leakage were men (p-value 0.039377). Eight of them had undergone anterior resection of the rectum, 2 were after left hemicolectomy, 1 after resection of the sigmoid colon, and 1 after right hemicolectomy, which was treated conservatively. The mean postoperative hospitalization time of patients with anastomotic leakage was 22 days (9-45). In comparison for patients without complications it was 9.4 days (4-21), which had statistical significance ($P<0.05$). Out of all blood tests, significant were WBC count, platelets count, albumin value, RDW, CRP and ESR. In all patients WBC rise, albumin drop, high values of CRP and ESR were recorded. RDW showed rise in all patients with complications and was considered non-selective in regard to anastomotic leak. The mean platelet values showed difference in patients with and without insufficiency. Empirically, in patients with dehiscence, a tendency of rise in platelets count was observed.

DISCUSSION

From a surgical point of view, anastomotic insufficiency is defined as "necrosis of the anastomosis, discovered during surgery" or "intraperitoneal collection, radiologically diagnosed, and needing percutaneous drainage" (7). In a wider aspect, it can be defined as any disruption of bowel integrity, at the site of the anastomosis, regardless of its clinical manifestation. Patient-associated risk factors are male gender (8), older age, atherosclerosis and ischemic heart disease, bowel dysbiosis, malignancy, comorbidities, anemia, dysproteinemia, abdominal emergency. Operation-associated risk factors are – lower anastomosis site, long operative time, big blood loss, neoadjuvant therapy (9,10). Empirically as risk factors are determined male gender, obesitas, alcohol and cigarettes, malnutrition, hypoproteinemia, high tumor stage, emergency surgery, left-sided anastomosis, intraoperative complications, corticosteroids use in the postoperative period. They can combine or act alone in the pathogenesis of anastomotic dehiscence, putting at risk even perfectly build anastomosis (11). Three are the main pathogenetic mechanisms of anastomotic dehiscence - disrupted integrity of extra- and intraluminal surfaces of the gut, in anastomotic construction; infection of the anastomotic site; disrupted healing process. From here follows the three-way rule of anastomotic quality - hermeticity, adequate perfusion and no tension (12). Colonization with *E. faecalis* and other collagenase-producing microorganisms participate in anastomotic leakage pathogenesis. Activation of MMP9 (tissue matrix metalloprotease-9) by these bacteria plays an essential role in collagen remodeling in the extracellular matrix (13). Changes in the bowel microbiome can lead to tumor genesis, local recurrence at the site of the anastomosis, and anastomotic insufficiency. They cause disruption of local immunity, with consequences for the anastomotic blood supply and healing. The preoperative use of antimicrobial medications, neoadjuvant therapy and bowel preparation can affect the microbiome of the gut, and compromise the outcome of the surgery. These effects are not observed in all patients. Genotyping of an individual's microbiome, by so individualizing the approach to every patient, is a step towards personalized medicine and the future (14). The incidence of anastomotic leakage rises with distal anastomoses. It is most common in colorectal and colo-anal anastomoses, which correlates with worse perfusion of the left colon (15,16,17). With the main goal of reducing leakage occurrence, many surgical methods have been developed and studied, but none showed superior to the others, including the use of mechanical stapling devices (18,19).

Comorbidities are evaluated by the CCS, to facilitate statistical derivation. Charlson comorbidity Index can be calculated, based on CCS, which predicts overall survival, morbidity and hospitalization time, individualized for each patient, based on his concomitant diseases (20,21). Comorbidities associated with high rates of anastomotic dehiscence are cardiovascular, pulmonary, diabetes, anemia, hypoproteinemia. Calculation of the risk, based on CCS is appropriate. A high risk correlates with more complications, morbidity and mortality, and a lower one

- with better recovery and survival. In most of the studies, a strong connection between emergency surgical intervention and anastomotic leakage is observed, in comparison to scheduled surgeries (22,23). ASA score calculation is a standard preoperative algorithm to determine the risks of perioperative mortality and complications. It shows correlation with the overall patient status. High ASA score can predict the risk of anastomotic insufficiency (24).

The *Clavien-Dindo* classification is easy and convenient to use, and also a good predictor of morbidity and mortality, following surgical complications. This model is accepted successfully by many lead medical centers across the world. It is based mainly on the therapeutic approach for treatment of these complications, and the consequences of the them - organ dysfunction, disabilities and death. It has 7 grades, in ascending order, the last of which is death of the patient, by the complications (25,26).

Blood tests are mostly used for early diagnosis of anastomotic leakage. In particular CRP (C-reactive protein), as acute inflammatory protein, rises early and its values correlate with the severity of inflammatory response (27,28). Together with ESR, they have high predictive value for morbidity and mortality in the early postoperative period. Despite this, they should not be interpreted individually, but in combination with WBC count and clinical findings. Drop in albumin levels is not specific marker for dehiscence, but lower values in the postoperative period may be predictive, to determine the leakage risk groups (29). Rise of platelets count could be an interesting field of further exploration. Experimental model on pigs, by Giusto et al., shows good outcomes in anastomotic healing, after application of PDGF (platelet derived grout factor) and PRP (platelet rich plasma), in the early postoperative period (30). The rise of the platelet number may be a compensatory reaction of the organism to overcome the condition. More data and bigger statistical sample are needed to confirm this statement.

Our main limitations are: small statistical sample, gained by patients in only one center, retrospective character of the study, lack of uniform volume of information for all of the patients; no data from long-term follow-up.

CONCLUSION

Anterior resection of the rectum, associated with technically harder anastomosis and conduction of neoadjuvant radiotherapy, is a potential risk factor for anastomotic leakage, in patients undergoing elective colorectal surgery. In males the incidence is higher. Lab testing in the postoperative period is good way diagnose this complication, respectively to adjust or change the therapeutic strategy.

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