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Ismayilova Z.✉, Aghayev E., Israfilova S.
Azerbaijan Medical University, Baku, Azerbaijan

Preoperative Risk Factors for Anastomotic Leaks in Colorectal Surgery

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Contacts: doktorrufat@yandex.ru

Abstract

Anastomotic leak remains a severe complication after colorectal surgery with considerable morbidity, higher rate of reoperations, and higher mortality. There is generally accepted idea that arterial ischemia or tension in the anastomotic line will lead to healing complications. But it's noteworthy that even well perfused, under no tension anastomoses may develop leakage, hence it continues to be a challenging issue in colorectal surgery. Over the past several decades of investigation are determined a lot of preoperative, intraoperative and postoperative risk factors for anastomotic leak, as well as, some conclusive recommendations are justified, whereas others are still open to discuss. The primary goal of present review was to analyze the literature on the problem of anastomotic leakage, determine preoperative risk factors for this complication. Data concerning patients' general condition, main disease and comorbidities, as well as preoperative preparation of gastrointestinal tract were evaluated. The most frequent preoperative risk factors for leakage revealed are male sex, smoking and alcohol intake, preoperative anemia and hypoproteinemia, body mass index, high age, preoperative chemical therapy and radiotherapy, omitting mechanical bowel preparation and oral antibiotic therapy.
Keywords: colorectal anastomoses, high risk anastomoses, anastomotic leakage, risk factors for anastomotic leakage

Исмаилова З.Е.✉, Агаев Э.К., Исрафилова С.Б.
Азербайджанский медицинский университет, Баку, Азербайджан

Предоперационные факторы риска несостоятельности анастомозов в колоректальной хирургии

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Резюме

Основной целью настоящего обзора является систематический анализ мировой литературы по проблеме несостоятельности анастомоза, определение предоперационных факторов риска этого осложнения и изучение связи этих факторов с несостоятельностью анастомоза после открытой или лапароскопической колоректальной хирургии. В статье представлена клиническая классификация степени тяжести (степень A, B и C) несостоятельности анастомоза. Оценивались данные об общем состоянии пациентов, основном и сопутствующих заболеваниях, а также о предоперационной подготовке желудочно-кишечного тракта. Были подробно изучены предоперационные факторы риска несостоятельности, основными из которых являются мужской пол, курение и частое употребление алкоголя, предоперационная анемия, гипопротеинемия и гипоальбуминемия, высокий индекс массы тела, пожилой и старческий возраст, предоперационная химиотерапия и лучевая терапия, длительное лечение кортикостероидами, отсутствие механической подготовки кишечника и пероральной антибиотикотерапии.
Ключевые слова: колоректальные анастомозы, анастомозы высокого риска, несостоятельность колоректальных анастомозов, факторы риска несостоятельности анастомозов

Complications in colorectal surgery encompass a wide range of clinical manifestations. Advanced technology has allowed many of the most severe complications of intestinal surgery, to be detected early and often to be treated without surgical intervention. Anastomotic leakage (AL) is one of the most feared complications following any type of intestinal anastomosis due to increased risk of morbidity, mortality, overall impact on functional outcome and expenditure on hospital resources [1–3].

AL is in the general accepted guidelines defined as a "defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extraluminal compartments" and graded according to Grade A, Grade B and C depending on severity of AL [2, 4]. Despite these general guidelines published, surgeons still have different opinions regarding definitions of AL and what actions are needed in order to prevent AL [4].

Many different definitions and approaches to the problem can be found in the medical literature, but the mechanism behind this complication still is not fully understood.

Colorectal anastomotic leak rates have been found to vary depending on the urgency of surgical procedures, anatomic location of the anastomoses, and different other factors. Clinical studies determining causes of anastomotic insufficiency are based on retrospective analyses of associated risk factors. In some studies, the risk factors are classified as modifiable (adjustable), non-modifiable (non-adjustable) and intraoperative. Modifiable risk factors (smoking, alcohol intake, anemia, hypoproteinemia, the use of corticosteroids and immunosuppressive medicines in preoperative period etc.) can be corrected prior to surgery to improve clinical outcomes. Non-modifiable risk factors (age, gender, some chronic co-morbidities) cannot be liquidated, but awareness of these problems may affect intraoperative decision making. Lastly, intraoperative factors such as excessive blood loss, decreased perfusion of and high tension on the anastomosis, fecal contamination of operating field can also increase the risk of anastomotic complications [4, 5].

According to most authors risk factors are categorized into preoperative; intraoperative; and postoperative factors [6–8].

Herein, we conducted a systematic review of recent years' literature analyzing the preoperative risk factors for colorectal AL, regardless of the type of pathology.

Preoperative risk factors

A recent systematic analyses identified several preoperative risk factors including male sex, age, smoking, obesity, alcohol intake, preoperative anemia and hypoproteinemia (hypoalbuminemia), steroid and non-steroidal anti-inflammatory drug use, radiotherapy, advanced tumor stage that makes surgery technically difficult, mechanical bowel preparation, and preventive oral antibiotic therapy [2]. Some of adjustable preoperative risk factors can be corrected before surgical procedure. Consequently, detection and management of these factors in preoperative period will lead to decreased postoperative complications, mortality and length of stay.

Male gender. According to most authors' studies male gender is one of the preoperative risk factors due to a narrow and deeper pelvis, which makes dissection of tissues and creating colorectal anastomosis more hard, and they tend to have more complications in comparison to female patients [4, 8].

There is information that hormonal functions (plasma level of androgen) may impair anastomotic healing as well. Some study results showed marked gender-specific differences in the intestinal microcirculation and perfusion pressure. According to the study conducted Zhang et al. (2017) male gender was an independent risk factor of AL (OR 2.898, 95% CI 1.265–6.637, p=0.012) [9].

Smoking and alcohol intake. In some literature sources have been emphasized that smoking and alcohol intake exceeding 35 drinks per week are associated with AL, regardless of patient age. In one study has been shown that anastomotic leak rate in smokers was 17% versus 5% in non-smokers [10]. Smokers had over 4 fold more chance of leak. The impact of smoking might be secondary to ischemia caused by smoking-related microcirculatory problems in the intestinal wall. Specialists recommend for patients to quit smoking four to eight weeks before surgery and throughout the postoperative period [11].

Age. In several studies patients' age was evaluated as risk factor [12–14]. The negative impact of age on anastomotic healing was indicated by Menegozzo et al. (2019). Their study involved a retrospective analysis of patients who underwent emergency surgery for complicated colorectal cancer. The median age of patients was 72 years. 65.7% of patients had some form of postoperative complication, AL rate was 11.7%. The study confirmed that elderly patients with complicated colorectal cancer undergoing emergency surgical procedures have high morbidity including AL rates. Consequently, advanced age is associated with worse outcomes [13].

Researches carried out by Vacante et al. (2019) demonstrated that colorectal cancer surgery for elderly patients still represent a challenge for the surgeon due to frequent comorbidities such as cardiovascular and pulmonary diseases, which increase operative risk as well as the risk of AL. There is also evidence that patients with comorbidities receive various treatment, compromising anastomotic healing. Laparoscopic surgery for colorectal cancer in elderly patients shows some advantages compared to open surgery such as less postoperative pain, rapid return to prior activities and a decrease in costs [15].

Body mass index (BMI). Several studies have shown obesity (BMI >25–35 kg/m^2) to increase the risk of AL [4, 14, 16].

According researches performed by McDermott et al. (2015) waist circumference to hip ratio and visceral fat area measured in laparoscopic assisted surgery are more sensitive parameters than BMI [6].

A systematic search of electronic databases (PubMed, Embase, Cochrane CENTRAL, Scopus Database, and Wanfang Database) was conducted by Hui Qu et al. (2015) to quantify the risk factors predictive for AL in patients who underwent laparoscopic anterior resection (LAR). Several patient related factors including BMI >25 kg/m^2 were found to be significantly associated with the development of AL [17].

However, there are conflicting opinions about the impact of obesity on AL rate. Suwa et al. (2020), Kazama et al. (2020) compared outcomes for robotic and laparoscopy-assisted colectomy between obese and non-obese patients. In terms of postoperative complications, they observed no differences between two groups. Therefore, they note that robotic and laparoscopic surgery for obese patients with colon cancer provide equivalent safety and advantages in terms of early outcomes and should be offered as alternative procedures [18, 19].

Preoperative nutritional status. Preoperative anemia and hypoproteinemia are common findings in colorectal diseases, particularly in colon cancer. Many authors reported that malnutrition represents one of the risk factors for AL [2, 20, 21].

Anemia and hypoproteinemia (hemoglobin ≤100 g/L or albumin ≤32 g/L) impair anastomotic healing by decreasing collagen synthesis and synthesis of sulfated mucopolysaccharides or fibroblast proliferation [20]. Meyer et al. (2019) identified several adjustable risk factors including anemia, albumin <3.5 g/dL, hypotension [2].

It is known that in the process of healing are identified 3 phases: inflammation, proliferation and remodeling. High risk to the anastomosis is thought to occur during first phase when proteolytic activity is greatest. After forty-eight hours, colonic anastomoses lose 70% of their initial strength. Anastomotic strength gradually increases as fibroblasts and smooth muscle cells synthesize new collagen, hence protein deficiency and anemia in this period may contribute to the development of anastomotic leak [20].

In 2016, Frasson et al. performed prospective, observational study including 1102 patients that underwent right hemicolectomy to determine risk factors for postoperative morbidity and mortality. According to their investigations preoperative serum protein was the only independent risk factor for anastomotic failure (p<0.0001, OR 0.6 per g/dL) [22].

Shimura et al. (2018) analyzed the treatment results in total 200 colorectal cancer (CRC) patients undergoing laparoscopic surgery. AL was observed in 5.6% cases. Postoperative serum albumin levels in AL group were significantly lower than in non-anastomotic leakage group. Therefore, they concluded that lower early postoperative serum albumin levels are a valuable indicator of AL in CRC patients [95% confidence interval (CI)] = 7.53 (1.60–55.80), p=0.0095 undergoing curative surgery, and correction of hypoalbuminemia allows to reduce AL rate [23].

Effect of drug therapy on anastomotic healing. Multivariable analyses conducted by Nicolian et al. (2017), Uysal (2017), Zarnescu et al. (2021) have demonstrated some medication use may affect the development of AL. According to their study results the use of corticosteroids and some immunosuppressive medicines may delay and impair anastomotic healing [14, 24, 25].

In multivariable analyses performed by Nicolian et al. were identified several risk factors of AL of colorectal anastomoses and one of them was preoperative immunosuppressive medication use (2017). According to their studies the use of immunosuppressive drugs increases the risk of anastomotic leak 2.62 times [14]. This finding is supported by other studies showing that use of immunosuppressive drugs increases the risk of anastomotic leakage in colorectal surgery. Uysal et al. (2017) studied the effects of preoperative treatment with immunosuppressant cyclosporine A and tacrolimus on colon anastomosis recovery. Their study showed that tacrolimus and cyclosporine A might have a negative effect on colon anastomosis recovery. Average anastomosis bursting pressure was 115.6±5.3 mmHg in the control group, 66.2±3 mmHg in tacrolimus group, and 91.1±4 mmHg in cyclosporine A group. There were statistically significant differences among bursting pressures of groups (P<0.001). The value was significantly lower in tacrolimus group compared to control group (P<0.001) [24].

A systematic search of literature of recent years was conducted Eriksen et al. (2014). The authors in their analysis concluded that prolonged use of corticosteroids in preoperative period is a risk factor for anastomotic leakage. Overall, the anastomotic leakage rate was 6.77% (95% CI: 5.48–9.06) in the corticosteroid group and 3.26% (95% CI: 2.94–3.58) in the non-corticosteroid group. It is known that corticosteroids impair wound healing by decreasing activation and infiltration of inflammatory cells. These inflammatory cells, macrophages and polymorph leucocytes, are essential in the first phase of wound healing. Additionally, corticosteroids inhibit the expression of growth factors and matrix proteins such as collagen synthesis [25].

Preoperative chemotherapy and radiotherapy. There are multiple reports showing an association between pre-operative chemotherapy and radiotherapy and incidence of anastomotic leakage. Some studies demonstrate that the use of intraperitoneal Methotrexate, Cisplatin, Doxorubicin, Mitomycin C, and postoperative chemotherapy including Bevacizumab can lead to delayed anastomotic insufficiency and colocutaneous fistula from the anastomosis [25, 26].

There is strong evidence that preoperative radiotherapy for colorectal cancer increases the risk for anastomotic leakage. Neoadjuvant radiotherapy that's routinely used in many patients may cause tissue edema, loss of tissue planes, pelvic fibrosis, bowel obstruction, necrosis and anastomotic failure [1, 26].

According to the data published by the Dutch Colorectal audit and Sparreboom et al. (2018) the risk factors for early and late anastomotic leakages might be different. Their hypothesis was that early anastomotic leakage is mostly related to technical failure of the anastomosis, whereas late anastomotic leakage is mostly related to healing deficiencies, that occur due to preoperative tumor complications, extensive resection because of tumor growth, ASA score III to V, and preoperative radiation (OR 2.0; p=0.010) [27].

Nevertheless, the literature on this question is controversial [28]. N. Asratova et al. (2021), conducted retrospective file scans of patients, who were older than 18 years, were diagnosed with rectal cancer, underwent surgery, and were given AT or NT. They found no difference in terms of AL development between patients receiving neoadjuvant chemo- (p=0.758) and radiotherapy (p=0.827 and p=0.1) and patients receiving adjuvant therapy. The use of neoadjuvant therapy did not increase the risk of AL [29].

Mechanical bowel preparation (MBP) and preventive oral antibiotic therapy (OA)

Some authors note that intestinal microbes with the capacity to produce collagenases and to activate host matrix metalloproteinase MMP-9 may break down collagen in the gut tissue contributing to AL [7, 30].

Therefore, Sparreboom et al. (2019) conducted international multicenter prospective cohort study to find out possible correlation between AL after colorectal surgery and MMP-9 activity. A total of 292 patients were analyzed; 38 (13.0%) patients suffered from AL, with a median interval to diagnosis of 6.0 (interquartile ratio 4.0–14.8) days. The prediction model of postoperative day 3, including CRP and MMP9, had a c-index of 0.78. This c-index indicated that for 78% of the time the model assigned a higher probability to a patient with AL than a patient without AL. The study demonstrated that MMP-9 activity was highest in the direct surroundings of an anastomosis. As well as, MMP-9 activity was significantly low in areas further proximally and distally from the anastomosis and was nearly or completely absent in uninjured tissue. Their study demonstrated unambiguous interconnection between MMP-9 activity and colorectal AL [31].

It is generally accepted that preoperative bowel preparation has a significant role in AL prevention. MBP is performed before colorectal surgery to reduce massive bowel contents, which can be a source of colorectal AL and bacterial pathogens. Many studies have supported combined MBP and OA prior to planned colorectal surgery [32, 33].

496 patients undergoing colorectal surgery with anastomosis were included for analysis in the study of Ambe et al (2019). Cases undergoing MBP + OA were included in the study group, patients undergoing MBP – OA were included in the control group. Preoperative MBP was performed using either polyethylenglykol or sodium-magnesium sulfate 24 h prior to surgery. Oral antibiotics (1 g vancomycin and 400 mg metronidazole) were added to the above preparation. The rate of AL was significantly higher in the control group (MBP – OA) compared to study group (MBP + OA) (9.1% vs. 4.0%, p=0.03). The effectiveness of MBP with additive OA was confirmed. In conclusion, they recommended mechanical bowel preparation with additive non-absorbable oral antibiotics in preoperative period for elective colorectal surgery [33].

Toh et al. (2017) conducted retrospective analysis of 5729 patients to study the effectiveness of MBP and OA in both laparoscopic and open left-sided restorative colorectal surgery. Patients were divided into four groups: patients who had MBP with OA, MBP alone, OA alone and no preparation. MBP with OA had a protective effect on anastomotic leak in both the laparoscopic and open cohorts (laparoscopic multivariable adjusted OR=0.42 (0.19–0.94), P=0.035; open multivariable adjusted OR=0.3 (0.12–0.77), P=0.012). MBP alone and OA alone was not associated with a significant decrease in complication rate [34].

Numerous studies have recommended routine use of MBP and OA in patients undergoing colon resection. Especially for Hirschsprung's disease (HSCR), preoperative MBP is a widely accepted dogma, but MBP is a most unpleasant experience for both children and parents. It can cause some discomforts to patients such as nausea, vomiting, abdominal pain, distension, hypocalcemia, dehydration, and fatigue [35]. However, some authors note that the MBP and OA does not reduce surgical site infections or the overall morbidity of colon surgery compared with no bowel preparation. Therefore, they propose that current recommendations of using MBP and OA for colectomies to reduce surgical site infections or morbidity including AL should be reconsidered [35, 36].

In order to analyze the effectiveness of MBP and OA Liang et al. (2021) performed a retrospective review of all available medical records of pediatric patients diagnosed with Hirschprung disease and who underwent colostomy closure. Patients were divided into two groups based on whether preoperative MBP and OA was performed or not. Information was collected and compared for demographics, symptoms and pre-hospital status (based on clinical assessment), postoperative condition, including any postoperative complications, duration of antibiotic therapy, combination of antibiotics, hospitalization, and total hospital cost. Complications included anastomotic leaks, intra-abdominal infection, wound infection, intestinal obstruction etc. In their study, omitting MBP and OA did not increase the occurrence of postoperative intra-abdominal infections, wound infections, anastomotic leak and intestinal obstruction. There were no statistically significant differences in terms of AL rate [35]. Consequently, it is suggested that bowel cleansing can be safely omitted in colonic surgery without inducing a higher complication rate.

The literature analyses of recent years demonstrated that a lot of preoperative risk factors have been investigated although some of data remain controversial, and it remains hard to accurately predict the development of AL. Complete awareness of risk factors is necessary for identifying high risk patients and properly select them for diverting stomas in order to reduce the AL rate or mitigate the clinical effects of leakage. However, the present analysis cannot determine to what extent each factor's prevention contributed to the reduction in AL rate. Further high-quality research is of great importance to reduce the risk and subsequent consequences associated with AL.

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