Review Article

Anastomosis after Large Bowel Resection in Adults: Two Specific Risk Factors in Maturation and Function

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Abstract

Anastomotic leakage is a dreadful complication of colorectal surgery, as it greatly increases the morbidity and mortality, irrespective of the type of anastomosis performed. It has also been associated with increased local recurrence in malignant cases and reduced survival. However, despite proper caution and excellent surgical technique, some anastomotic leaks are inevitable. The frequency of anastomotic leakage is high in certain circumstances, such as emergency colorectal surgery, resection of low rectal tumours and malnutrition. This report seeks to highlight the importance of two special risk factors in adult anastomotic healing and function, the impaired immune defense and the colonic and rectal neuronal malformations.

INTRODUCTION

After decades of research, various factors have been identified to promote successful healing of the anastomoses, while others increase therisk for anastomotic disruption despite all the progress noted in the techniques of colonic resection/anastomosis [1-4]. In general, the risk rate of anastomotic leakage in stable patients, irrespective of the surgical approach and the type of anastomosis, may be influenced by: a) local anatomic conditions (tumor site and stage -with decreasing tumor distance from the anal verge being a major risk factor-, obstruction, inflammation and peritonitis); b) technical problems in anastomosis construction (ischemia, disproportionate stumps, undue tension); c) underlying special gastrointestinal (GI) pathology, which might be either progressive, such as the mesenteric thrombo-embolic disease, or known inflammatory bowel disease (IBD) with fistulating potentiality, such as Crohn's disease; and d) complex factors associated with the patient's history and status, such as age, diabetes mellitus, obesity (BMI >25), malnutrition, smoking, corticosteroid administration, non-steroidal anti-inflammatory drugs, and preoperative chemo-radiation. Other factors, such as prolonged operative time (>200 min), presence of abscess or fistula at the time of laparotomy, intraoperative blood loss (>200ml), massive blood transfusion-hypotension, positive margin of histologic specimen (cancer, IBD, aganglionosis), intramural or general disorder of the blood circulation and chronic renal failure, have been also implicated in various studies [1-4]. If more than one of these factors arepresent, the cumulative risk for anastomotic rupture is highly increased, and a primary anastomosis should better be avoided. All these factors should be taken into account in perioperative decision-making regarding the stoma formation, irrespective of the primary disease (either a malignancy, a benign disease, or coexistence of the two) [1]. In patients with such adverse factors, ileo-colostomies may not be safer than colo-colostomies [3].

Until recently, colonic mucosal immunity received relatively little attention, and the underlying molecular mechanisms of host-microbiota interactions were incompletely understood in a variety of infection and inflammatory conditions [4-7]. Similarly, colonic innervation defects and dysmotility are poorly understood in adults; it has been suggested that they may have an impact on anastomosis but, unfortunately, they are often neglected [8-11].

Anastomosis to colon/rectum and immunology

The GI tract has normally a physical and immunologic barrier that keeps pathogens within the intestinal lumen[12]. Indeed, the intestinal mucosal immune defense, including both humoral and cellular immunity, provides both barrier function and immediate effective recognition of bacteria invading the mucosa [5-12]. The enteric nervous system, including the myenteric (Auerbach's) and the submucosal (Meissner's) plexuses, provides the intrinsic innervation of the gut, controlling various functions, such as motility, mucosal secretion/absorption and growth, local blood flow, and the immune function [8,9,12,13].

Under steady conditions, the resident micro biota continuously provides signals to the innate immune system, maintaining this way a healthy inflammatory tone within the intestinal mucosa;it promotesthus resistance to infection by enteric pathogens [5,12]. Defense mechanisms of the GI system -including the enteric nervous system and the immune responses- rely on a delicate balance of multidirectional interactions of the different components of the GI mucosa in order to maintain immune homeostasis [8,12]. In cases when the gut microbial exposure increases (because of increased epithelial permeability, genetic deficiencies in local defense mechanisms, imbalances in local immune regulation or GI pathogenic bacterial infections), or when the compartmentalization between systemic and gut mucosal immunity is breached, systemic immune response to gut microbes is impaired [5]. Consequently, intestinal bacteria gain access to extra intestinal sites (translocation), may be more virulent, and cause systemic infection and subsequent multiple organ dysfunction in immune compromised or injured patients, as well as in patients in surgical stress [8,12]. Inhibition of the various pathways of the normal immune defense, angiogenesis and collagen synthesis may increase the risk of infections and impair wound healing in patients after surgery. Disruptors of mucosal defense mechanisms include pathogens, allergens, chemicals, drugs and radiation [13].

In the clinical practice, "spontaneous" GI micro perforation (small leakage) has been reported during combined neoadjuvant treatment of colonic (rectal) cancer with bevacizumab, a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF), as well as in patients with non-GI tumours [1]. Probably this results from inhibition of neoangiogenesis. Similarly, the use of anti-Tumour Necrosis Factor (TNF)-a agents in Crohn's disease is associated with an increase in post-operative infections or anastomosis-related complications, probably due to the fact that TNF plays an important role in immune defense, angiogenesis and collagen synthesis [14].

Surgery for IBD, either Crohn's disease or ulcerative colitis, is well known to have an increased risk of anastomotic complications and morbidity [2,6,7]. Although the indications for surgical management of IBD and its complications are clear, there is still controversy regarding the best surgical colonic excision and the required anastomosis. In Crohn's disease affecting the colon, the extent of excision and the choice of the type of the required anastomosis or the fashioning of an ostomy are determined by the localization of the disease itself (i.e., if it is proximal: limited resection with primary anastomosis, or distal: major colonic resection, better without anastomosis), the presence of fistula or abscess, and the high rate of recurrence after surgery [7]. On the contrary, few studies have investigated the risk factors for surgical site infection in patients undergoing surgery for ulcerative colitis, and no precise evaluation of risk factors has been presented to date because of the various confounding factors, such as disease specificities, different surgical procedures and patient's characteristics. Restorative proctocolectomy with ileal pouch-anal anastomosis is often performed in order to treat these patients [7]. However, chronic pouchitis is common and may be associated with extra intestinal manifestations and other diseases of immune origin, suggesting an overlap in the disease pathogenesis. There is also emerging evidence of the role

of autoimmunity in a subgroup of patients with pouchitis, such asco existence of primary sclerosing cholangitis, seropositivity for immunoglobulin G4, or infiltration of immunoglobulin G4-expessing plasma cells in the pouch mucosa [15]. Due to the need for both long-term treatment of proctitis or pouchitis and close endoscopic surveillance for cancer, most authors suggest total proctocolectomy with end-ileostomy as a viable alternative at some point in the evolution of this disease [6,7].

In their report with 53 immuno compromised and 63 immuno competent patients emergently treated for perforated diverticulitis, Golda et al [4], used the Peritonitis Severity Score (PSS) to facilitate decision making in GI continuity after resection. They performed 42 vs 15 Hartmann's procedures and 11 vs 48 primary anastomoses with or without ileostomies in immune supressed and immune competent patients, respectively; they pointed out that Hartmann's procedure is safer as surgical option in patients with a PSS superior to 11.

Anastomosis to colon/rectum and organ innervation

The colon is innervated via the sympathetic and parasympathetic nervous systems. Sympathetic stimulation inhibits colonic peristalsis, which is promoted by the parasympathetic system. Sympathetic innervation consists of fibers from the six lower thoracic neurotomes that join in the paravertebral ganglia (preaortic, celiac, and superior mesenteric), form the splanchnic nerves, and then the superior and inferior hypogastric plexuses. Parasympathetic fibers derive from the vagus nerve and the sacral outflow andinnervate the caecum, the ascending and the transverse colon (via the preaortic plexus); fibers from the sacral outflow join the hypogastric plexuses to innervate up to the splenic flexure. These fibers synapse with the ganglia of Auerbach's and Meissner's plexuses [8,11,16,17].

The aganglionicmega colon or Hirschsprung's disease (HD), a true congenital malformation, is a well-known pathologic condition in which the basic defect is the total absence of ganglia of the intermuscular and submuscular plexuses of the undilated distal bowel, along with hyperthrophy of the dilated segment; the proximal bowel is normally innervated [8,16]. However, it is an infancy disease and lacks objecting interest in this report.

Colonic hypoganglionosis (CH) is a rare disease. It is actually a developmental abnormality with epidemiological and clinical features similar to HD, although the age at diagnosis is higher [10,11,16]. CH is a hypogenetic variant of intestinal innervation deficiency, actually a dysganglionosis, which is characterized by small and sparse myenteric ganglia, low or absent acetyl cholinesterase (AchE) activity in the lamina propria and hypertrophy of the muscularis mucosa [10,11]. In some patients, ganglia extend into the rectal region of the normal variation in the level of the lowest ganglia, but apparently their fibers do not reach or innervate the internal sphincter [8]. CH appears in two subtypes, the hypoganglionosis associated with HD, and the isolated CH [11]. Isolated CH is similar to the hypoganglionosis of the transitional zone between affected and normal segments of intestine in HD. However, HD affects both submucosal and myenteric plexuses, whereas isolated CH is characterized by a decreased number of ganglia only in the myenteric plexus while the submucosal plexus is normal [8,10,11]. The isolated

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CH causes visceral neuropathy and is usually symptomatic and diagnosed in infancy or childhood. The isolated CH accounts for 5% of all intestinal neuronal malformations and may also be diagnosed in adulthood [11]. Patients usually present with chronic or acute constipation, pseudo-obstruction and enterocolitis or, occasionally, with sigmoid volvulus. In these cases, the diagnosis of hypoganglionosis can only be established by histopathological staining of full-thickness bowel specimens. Immuno histo chemical staining for AchE, the most frequent staining method for isolated CH, can only be performed on frozen sections, and confirms the diagnosis [11]. The aim of this practice may be double, as some patients may be successfully treated by a minimal intervention (i.e. anal dilatation or anal myectomy in "anal achalasia"), and the anastomosis after excision of the estimated affected segment can be performed on healthy ends. The principles of the surgical treatment in diagnosed cases are, firstly, to remove all the hypoganglionic segments and secondly, to achieve bowel continuity between the normally innervated bowel and the anal canal [11]. The most commonly used procedures for pull-through surgery are recto sigmoidectomy (Swenson's), retrorectal approach (Duhamel's), and the endorectal approach (Soave's). In emergency patients and in cases where there is no possibility to perform frozen sections for AchE staining, gross removal of the obviously affected segment and an ostomy is a wise surgical option; bowel continuity can be established later, after achieving negative full-thickness biopsies of the two bowel ends.

A different group of cases of megacolon or mega rectumun associated with a ganglionosis has also been described. This acquired condition, which is much larger than the previous category, includes simple megacolon or megarectum, dolichocolon and colonic or rectal inertia (slow transit constipation) and is found in late adolescent or adulthood [16]. Three subgroups are identified: a) megasigmoid with a normal or only slightly dilated rectum; b) megarectum without significant megacolon; and c) megarectum with gross megasigmoid or more extensive megacolon [8-16]. The first group of mega sigmoid is possibly a distinct entity and is sometimes complicated by recurrent volvulus. The two other groups resemble to rectal inertia in childhood, but they have obscure etiology; they are possibly due to habitual constipation associated with prolonged conservative treatment [16]. No deficiency of intramural innervation is found in biopsies, and previous studies have failed to disclose any consistent abnormality [8]. In some patients, rectal sensation to balloon distension is greatly reduced or almost completely absent, and the normal inhibition of the external anal sphincter in response to prolonged rectal distension is absent or impaired. Also, pressure studies on the sigmoid colon indicate that its activity may be diminished, increased or normal [8]. Patients with non-HD colonic dilatation, scheduled for elective surgical intervention, should have anextended preoperative evaluation, including a careful rectal examination, barium enema examination, anorectalmanometry, and colonic transit times [11,16]. Treatment of the non-HD variant of megacolon and megarectum should favor conservative methods, including daily wash-outs and aparients, hospitalization for manual diss impaction, and regular follow-up examinations [16]. However, operative treatment may occasionally be chosen, although there

is little consensus regarding its precise indications and the type of operation to be applied. In cases with recurrent volvulus characterized by long dilated sigmoid and normal rectum and pelvic floor function, an elective sigmoidectomy with end-to-end anastomosis could be an effective option. As for the much more common cases with gross megarectum or megacolon of variable degree that are resistant to conservative treatment, various surgical options have been suggested, depending on the presence of normal or dysfunctioning pelvic floor; they include resection of the grossly dilated sigmoid or rectum and ileorectal, ileosigmoid or caecorectal anastomosis, or a proximal iliac colostomy [8,16].

CONCLUSION

More systematic prospective studies are required to further understand the natural history and the risk factors of anastomotic failures, both in elective and emergent colorectal surgery. Further research of mucosal immunity is promising in order to elucidate the GI immune mechanisms and the pathogenesis of several GI and systemic diseases. Patients with symptomatic colonic dilatation, unassociated with aganglionosis or associated with some neuronal malformation, should undergo detailed preoperative evaluation. Surgeons have to pay attention to adverse effects in various circumstances, and consider temporary colostomy in presence of particular risk factors.

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