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Review Article

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Surgery in Pediatric Crohn's Disease: Indications, Timing and Post-Operative Management

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Pediatric onset Crohn's disease (CD) tends to have complicated behavior (stricture or penetration) than elderly onset CD at diagnosis. Considering the longer duration of the disease in pediatric patients, the accumulative chance of surgical treatment is higher than in adult onset CD patients. Possible operative indications include perianal CD, intestinal stricture or obstruction, abdominal abscess or fistula, intestinal hemorrhage, neoplastic changes and medically untreatable inflammation. Growth retardation is an operative indication only for pediatric patients. Surgery can affect a patient's clinical course, especially for pediatric CD patient who are growing physically and mentally, so the decision should be made by careful consideration of several factors. The complex and diverse clinical conditions hinder development of a systemized treatment algorithm. Therefore, timing of surgery in pediatric CD patients should be determined with individualized approach by an experienced and well organized multidisciplinary inflammatory bowel disease team. Best long-term outcomes will require proactive post-operative monitoring and therapeutic modifications according to the conditions.

Key Words: Inflammatory bowel diseases, Crohn disease, Colorectal surgery, Child

INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory disease that mainly affects the gastrointestinal tract. It is thought to develop as a result of the abnormal immune reaction triggered by several environmental factors in genetically susceptible individuals. The incidence of CD is rapidly increasing worldwide, and up to 25% of patients are diagnosed during childhood or adolescence [1]. Pediatric onset CD tends to have a more complicated behavior (stricture or penetration) than elderly onset CD at diagnosis [2]. Furthermore, considering the longer duration of disease in pediatric patients, the accumulative chance of surgical treatment is higher than adult onset CD patient [3].

The paradigm of medical treatment for pediatric CD has changed with the emergence of effective biologic agents including infliximab and adalimumab [4]. Decreased surgery rate has been associated with

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successful use of immunomodulator or biologic agent [5,6]. However, other recent reports suggested that the rates of cumulative surgical treatment are not decreased significantly [7,8]. The dichotomy might be due to the extension of surgery indications or decreased physician reluctance to perform surgery in CD. Surgery is still needed for CD patients even in era of anti-tumor necrosis factor (TNF) use. However, surgery remains a critical decision for a patient; surgery can greatly affect one's clinical course, especially pediatric CD patients who are growing physically and mentally. The decision regarding surgery needs to involve careful consideration of several factors. In this article, we review operative indications and the proper timing of CD surgery and post-operative management.

ROLES OF SURGERY IN CD

CD is not a completely curable disease. So, surgery is not meant to be curative, but rather to relieve symptoms or complications of CD. Surgery can provide immediate relief of mechanical stress or focal inflammation, producing immediate improvements in symptoms and quality of life. Generally suggested surgery indications are listed in Table 1.

Physicians can rely on a medical treatment for too long. As well, patients can refuse surgery until their condition demands surgical intervention. Both can delay surgery and lead to increased morbidity [9]. Many patients and physicians can have an exaggerated fear of CD surgery, which can worsen the prognosis. This reluctance is regrettable. In one adult study, among 70 patients who have received ileocolonic resection and anastomosis for CD, no one regretted the decision for surgery, with the general view being that surgery should have been done 12 months earlier (95% confidence interval, 7 to 18 months) [10].

Table 1. Operative Indications in Crohn's Disease

Complex perianal fistula or abscess
Intestinal stricture or obstruction
Intra-abdominal abscess
Fistula (bowel to bowel, bowel to skin, bowel to adjacent organ)
Bowel perforation
Massive intestinal bleeding
Growth retardation
Neoplastic changes
Fulminant disease which is not responds to the medical treatment

But, the incidence of operation-related complications is not negligible. In one adult study, the rate of operation site infection was higher in inflammatory bowel disease (IBD) patients (18%) than in colon cancer patients (12%) or diverticulitis (12.8%) patients [11]. Similarly, the rate of reoperation within 30 days was also higher in IBD patients (7.3%) than in colon cancer patients (4.9%) or diverticulitis (4.4%) patients. Even if the clinical symptoms are relieved after surgical resection of intestine, bowel inflammation remains and clinical situations requiring further operation frequently occur. Other authors reported that cumulative clinical recurrence rates in pediatric patients at 1 year, 5 years and 10 years were 50%, 73% and 77%, respectively [12]. Consequences of bowel damage during surgery can accumulate with time and can result in digestive dysfunction in the long run [13]. For these reasons, decision making about surgery should be done prudently by multidisciplinary team approach considering the risks and benefits.

PERIANAL CD

Several kinds of perianal disease can occur in CD. Severity ranges from simple skin tags or anal fissures to complicated perianal fistulas or abscesses. Perianal CD is common in pediatric patients with an incidence ranging from 13.6% to 62% [14]. Prompt drainage of focal septic focus and conservative surgery with appropriate combined medical treatment are three general principles about perianal CD [15]. However, as the conditions are complex and have great diversity, it is difficult to suggest a systemized treatment algorithm, and individualized approaches according to the patient conditions are required [16].

Perianal skin tags generally do not regress completely, but usually do not require surgical treatment

as the lesions remain benign and stable. Anal fissures sometimes recur but usually can be healed with medical treatment [17].

Diverse types of perianal abscesses can occur in CD. Their exact mechanisms of pathogenesis are not fully understood. These lesions are frequently related with bowel inflammation and are not treatable using one treatment modality. Surgical intervention and medical treatments, such as antibiotics, immunomudulators, or biologic agents, should be combined in most cases. Antibiotics like metronidazole and ciprofloxacin are used as first-line treatment for perianal abscess. The abscess cavity should always be drained if it is not resolved with medical treatments [18]. Simple skin incision or silastic drain can be placed according to the abscess location and size. Internal drainage from the anal canal or rectum without external skin incision is not preferred because the abscess can recur in a short time [17].

Simple perianal fistula confined to the anal canal or located superficially heals spontaneously without surgical management in 50% of cases [19]. In contrast, complex fistula or fistula to adjacent organ require surgical treatment because those lesions do not heal completely with a medical approach [17]. Because treatment strategies differ according to the type of perianal disease, thorough assessment about the lesions is necessary before treatment. Rectal examination, endoscopic ultrasound, magnetic resonance imaging (MRI), and examination under anesthesia are usually used. Due to its high sensitivity and specificity and lack of radiation exposure, MRI is considered to be the radiologic study of choice in most cases [17]. Seton procedures, which drain inflammatory exudates from the fistula track, are frequently used and are useful for complex perianal fistula. Combined medical treatment, such as with anti-TNF antibody, can control the bowel inflammation and result in delayed healing of perianal fistula [20]. In patients with severe, complicated perianal disease, fecal diversion with ileostomy or colostomy can be an option. After controlling perianal inflammation, ostomy can be repaired. Although data from pediatric studies are insufficient, adipose-derived mesenchymal stem cell treatment for complex perianal fistulas in CD showed efficacy [21].

STRICTURE

Stricturing lesions can develop from anywhere in the gastrointestinal tract in CD. These lesions can cause symptoms that require some kind of intervention. Intestinal stricture due to inflammation should first be managed with medication. Symptomatic fibrostenotic lesions require physical dilation. Computed tomography enterography and MR enterography have high sensitivity and specificity in discriminating inflammatory and fibrostenotic lesion, sometimes it is difficult to figure out the character of the lesions and in many cases both characters are combined. Endoscopically accessible short segment (<5 cm) stenosis is a good candidate for endoscopic dilatation [22]. Although the evidence for endoscopic dilatation in CD is from adult studies, it can be effective for pediatric patients as well [23]. However, stricture connected to the fistula or abscess is a contraindication for endoscopic dilatation [24]. Surgery is indicated for patients with symptomatic bowel strictures that do not respond to medical therapy or lesions for which endoscopic approaches are impossible or contraindicated. Bowel resection or surgical stricureplasty can be performed for those lesions. As strictureplasty can reserve bowel length, it is preferred over bowel resection for nonphlegmonous strictures.

OBSTRUCTION

Intestinal obstructions are a common indication for surgery in CD; approximately 25% of all CD patients will undergo surgery for this reason [25]. There are several mechanisms of intestinal obstruction for CD patients. Chronic gradual fibrosis can cause obstructive symptoms and acute inflammation can also cause intestinal obstruction due to edematous intestinal mucosa. In many cases both acute and chronic lesions exist at the same time and cause obstruction simultaneously. In patients who

have previously had surgery, physicians should take into account intestinal adhesion induced obstruction. Fiber rich food can become stuck in the stenotic intestine and occasionally seed of the fruit or capsule endoscopy can also induce acute intestinal obstruction. Most cases of obstruction response to conservative management, such as nasogastric tube decompression, with nil per os and intravenous hydration. If CD flares and the obstruction is due to inflammation, an anti-inflammatory treatment like corticosteroid can be helpful. Surgery is indicated in a medically unresponsive patient or those with frequently repeated obstruction [16].

ABDOMINAL ABSCESSES

Besides perianal lesions, intra-abdominal abscesses are distinguishing characteristics of CD. These abscesses typically originate from intestinal perforations or penetrating deep ulcers. Abdominal abscesses are mainly located in the ileocecal area and are commonly associated with intestinal fistulae [16]. According to the proposed algorithm for spontaneous intra-abdominal abscess in in pediatric CD patients, broad spectrum antibiotics such as piperacillin-tazobactam, ticarcillin-clavulnate, meropenem or advanced-generation cephalosporin with metronidazole combination should be an initial treatment in the case of small sized ($\leq$2 cm) abscess [26]. Radiology guided percutaneous drainage is indicated for larger abscesses unable to be treated with antibiotics alone. The success rate of percutaneous drainage exceeds 90% and about half of the patients treated this way can avoid short-term surgery [27]. However, percutaneous drainage is not always feasible and is often unsuccessful, especially in the case of multiloculated or multifocal abscess [22]. In the case of absence of clinical improvement within 3 to 5 days, in spite of antimicrobial treatment with percutaneous drainage, follow up image study is required and surgical drainage should be considered if the abscess persists [26]. To avoid unnecessarily extensive bowel resections or post-operative recurrence, prudent preoperative evaluations and combined medical treatments are necessary. Ideally, to avoid operation related complications, corticosteroid should be reduced to $<$20 mg/d before surgery if the patient was on steroid treatment [21].

ABDOMINAL FISTULA

As CD involves intestine transmurally, fistulae can arise from the intestine. Fistulas can develop between regions of the intestine and also can occur between intestine and adjacent organ such as skin, urologic organ or gynecologic organ. Although intra-abdominal fistulae can arise from anywhere in the bowel, most common location is the ileocecal area, frequently combined with abscesses [16]. If the enteroenteric fistulas have no clinical symptoms, they may not be required surgical treatment. However if they are symptomatic, surgery is required. Inflamed bowel should be resected but noninflamed bowel or a secondarily affected adjacent organ, such as bladder or vagina, also can be managed with primary closure [22]. The conditions are usually not urgent, so preoperative nutritional supplement and inflammation controls should precede surgical repair for better prognosis. A significant percentage of fistulas occur combined with intraabdominal abscesses; the abscesses should be drained before the surgery if feasible [22].

HEMORRHAGE

Only 0.9-6% of CD is complicated with acute severe lower gastrointestinal bleeding [28]. Although rare, management can be challenging. The bleeding focus can be multiple, sometimes difficult to find, and often not possible to control or approach with endoscopy. Medical treatment includes anti-TNF therapy, which is regarded as the most effective medical treatment; angiographic interventions can be tried as well as a therapeutic approach, but those are not always successful and occasionally require surgical resection of affected lesion [29]. For patients with massive bleeding who are not stabilized despite multiple (>4 units) transfusions of packed red blood cells

within 24 hours, those who fail medical management, or with recurrent massive hemorrhage, surgery is recommended [30].

GROWTH RETARDATION

Pediatric IBD has distinct features compared to adult IBD. Therefore, the therapeutic approach can differ, and consideration to growth is one of the most important issues for treating children with IBD. Severe growth retardation is thought to be a predictive factor of poor clinical outcome. Insufficient attention to linear growth and bone health may result in impaired final adult height and increased risk for fractures [31,32]. About 20% of CD children continue to have abnormal growth despite CD treatment [33]. If growth continues to be impeded despite medical treatments like exclusive enteral nutrition (EEN), immunomodulator therapy, and use of biologics, intestinal resection should be considered. Timely surgery can improve growth in patients who are unresponsive to medical treatment [15,34]. However, resection surgery should be done for patients who have definite localized lesion; surgery needs to be performed before the adolescent growth spurt for the effective catch-up of growth [32].

NEOPLASTIC CHANGES

The risk of colon cancer is increased in those with CD compared to the normal population. Although uncommon, neoplastic changes can develop in adolescents or young adults. While debatable, long-term duration, extensive colitis, chronic active inflammation, and presence of primary sclerosing cholangitis may be influential factors for the development of colorectal malignancies [22,35]. Guidelines in the United States, Britain, and European Crohn's and Colitis Organisation (ECCO) recommend surveillance colonoscopy every 1-2 years after 8-10 years duration of disease. For high-risk patients, earlier and more frequent surveillance should be considered [22,35,36]. Identification of carcinoma or non-adenoma-like dysplasia associated lesion or mass, high-grade dysplasia, or multifocal low grade dysplasia from the colon or rectum should prompt consideration of total proctocolectomy. Sporadic adenoma can be managed safely with polypectomy in patients without CD [22].

FAILED MEDICAL TREATMENT

Although many medical options are effective for treating CD, none are perfect. EEN is relatively safe but is difficult to continue for life. Corticosteroids are generally effective, but treatment duration needs to be limited due to side effects. Anti-TNF agents are one of the most potent medicines for CD, but not all patients respond. Even the combination of infliximab and azathioprine achieved only 56.8% corticosteroid-free clinical remission at 26 weeks for adult patients [37]. Similarly in moderate to severe pediatric CD patients, adalimumab could have achieved clinical remission in 33.5% of patients at week 26 [38]. Patients with an insufficient response to the medical treatment, patients who develop CD complications even during medical treatment, patients with severe drug-induced adverse events, and poorly compliant patients should be considered for surgery as an option. When the disease is localized in a short segment of the gut, the patient is a good candidate for surgery. Acute severe colitis or toxic megacolon in CD is also an indication for surgery if response to the medical treatment is poor [16,22].

POST-OPERATIVE MANAGEMENT OF CD

Surgery is not the final solution in CD. An appreciable number of patients experience recurrence despite surgery. Danish data of 115 pediatric CD patients who had surgery chronicled that 50% and 73% showed clinical recurrence at 1 year and 5 years, respectively [12]. If endoscopic recurrence is included, the rate of postoperative recurrence becomes much higher [39]. Endoscopic recurrences are thought to precede clinical recurrence and postoperative endoscopic surveillances are used to predict and prevent

clinical recurrence. The Rutgeerts endoscopic recurrence scoring system is the most frequently used system [40]. In this system, i0 indicates no lesions; i1 indicates <5 aphthous lesions; i2 >5 aphthous lesions with normal mucosa between the lesions, skipped areas of larger lesions, or lesions confined to the ileocolonic anastomosis site; i3 indicates diffuse aphthous ileitis with diffusely inflamed mucosa; and i4 indicates diffuse inflammation with larger ulcers, nodules and/or narrowing. Most (90%) of patients scoring i4 score will experience recurrence within 3 years [41]. Active smoking is the most well-established risk factor of postoperative recurrence. Penetrating disease, perianal disease, prior intestinal resection, and extensive small bowel resection (>50 cm) are also risk factors of recurrence [39]. Monitoring for disease recurrence and proper actions are required to maintain remission and better prognosis. The ECCO guideline [32] recommends continued maintenance treatment in children and adolescents after surgically induced remission, with thiopurine as the treatment of choice in patients with extended disease and those at risk for relapse. Like other treatment strategies for adult patients, ileocolonoscopy should be considered 6-9 months after surgery to optimize treatment for pediatric patients [42,43]. If the Rutgeerts score shows i2 or higher, step-up treatment should be considered [43].

CONCLUSION

Medical treatments are evolving and several new medications are under development or undergoing clinical trial evaluation [44]. Treatment targets have changed from clinical remission to mucosal healing or deep remission. Patient-reported outcome has become a treatment target as well [45]. In the same manner, newer surgical techniques have reduced invasiveness or complications [46]. During the disease course, surgery can be a turning point and should be regarded as a possible treatment option. It should not be regarded as an option to avoid at all costs [16]. Although timely surgery is the core in treating CD, it is extremely difficult to establish an operation guideline in CD, especially in children, due to the great diversity between patients and due to the lack of supporting evidence [47]. Gastroenterologists and surgeons can have different points of view of the best course and it is essential to discuss about the individual patient before making a decision. Patients and their parents should be also involved in formulating a treatment plan. Radiologists and other specialists should be part of the multidisciplinary IBD team. In conclusion, surgery in pediatric CD patients requires an individualized approach by an experienced and well-organized multidisciplinary IBD team. For the best long-term outcome, proactive post-operative monitoring and therapeutic modifications according to the conditions are essential.

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