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Postoperative Complications in Children with Crohn's Disease: An Analysis of Risk Predictors

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Abstract: Crohn's disease is an incurable progressive disease of the gastrointestinal tract, in which up to 90% of patients undergo one or more operations during their life. Despite the active development and introduction of new surgical techniques for the treatment of patients with Crohn's disease, there is still a high incidence of postoperative complications - up to 25-30%. The problems of influence of various factors on the results of surgical interventions in children with Crohn's disease are still very controversial.

Keywords: Crohn's disease; surgical treatment; postoperative complications; diagnostics; children.

Purpose of the study: to investigate and identify possible risk factors for postoperative complications in children and adolescents with Crohn's disease.

INTRODUCTION: Crohn's disease (CD), an incurable disabling inflammatory gastrointestinal (GI) disease, has been rapidly spreading worldwide in recent decades. Currently, the incidence of BC in children reaches 12-13 cases per 100,000 population [1]. Progressive character of the disease leads to complicated course of CD in the majority of cases, up to 90 % of patients undergo one or several operations during their life, and the frequency of postoperative complications remains much higher than in routine abdominal surgery and colo-proctology - up to 30 % [2]. In children and adolescents CD is often represented by severe forms, with extended intestinal lesions, high disease activity, delayed physical development and is characterised by a more aggressive course than in adult patients, with a high risk of intestinal complications and the need for surgical treatment [3]. To date, the influence of various factors [4,6] on the results of

surgical interventions in children with inflammatory bowel disease remains very controversial, which necessitates further research.

Materials and methods of research:

A cohort retrospective analysis of the results of surgical treatment of 164 children with complicated forms of BC, including 106 (65%) boys and 58 (35%) girls, who were treated in the departments of surgery of the Andijan branch of the Republican Scientific Centre for Emergency Medicine 1998-2023 was conducted. The age of BC debut was 11.5 years (from 8.8 years to 14 years), the average age of surgery was 15 years (12.5-16 years). The interval from disease onset to BC diagnosis was 1 year (8 months to 2 years), as was the interval from first symptoms to first surgical intervention (3 months to 3 years). All 164 patients were divided into groups according to the Paris classification of the disease: stricturing BC, type B2 - 74 (45 %) people; penetrating with strictures BC, type B2B3 - 46 (28 %), inflammatory (nonpenetrating non-stricturing) BC, type B1 - 44 (27 %). The lag in physical development was registered in the form of growth retardation (type G1) in every second child - 94 (57 %) patients, and body weight deficit - in 118 (72 %) cases, and the expressed deficit with body weight index less than 16 kg/m2 was revealed in almost half of patients - 78 (48 %). Disease severity (or current exacerbation) was calculated by Pediatric Crohn's Disease Activity Index (PCDAI). High disease activity with PCDAI more than 30 points was registered in half of observations - 79 (48 %). The most frequent localisation was the lesion of the terminal ileum - isolated, type L1 (63 patients; 38 %) or in combination with the colon, type L3 (62; 38 %), in every fifth patient the colon, type L2 (35; 21 %) was detected. Localised form of BC (up to 30 cm) was registered in one third of observations (50; 30 %), and widespread lesion (more than 100 cm) was found only in single cases (4; 2 %). When analysing the results of laboratory investigations before the operation anaemia was detected in two thirds of BC patients (108; 66 %), of them severe anaemia with haemoglobin level less than 80 g/l was registered in 20 (12 %) cases. Decreased serum iron level (with anaemia or in the form of latent iron deficiency) was noted in 119 (73 %) observations. Increased erythrocyte sedimentation rate (133; 81 %) and C-reactive protein (137; 84 %) were noted in the vast majority of patients. Decrease of albumin level was detected in almost 113 (70 %) cases, including marked hypoalbuminaemia (with level below 30 g/l) in 23 (14 %) patients. Children with CD underwent surgical interventions taking into account the course and form of the disease, the localisation and prevalence of the lesion, the nature of intestinal or perineal involvement. The indications for surgery were acute and chronic intestinal complications of CD, perianal lesions, as well as ineffectiveness of conventional therapy. When analysing the number of surgical interventions in patients with CD it was revealed that half of patients underwent three and more operations (49 %), in a quarter of observations one (27 %) or two surgical interventions were performed (24 %). The average age of patients at the first operation was 14 years (from 11 to 16 years). The average time of surgery on the abdominal cavity organs, regardless of the surgical access (open or laparoscopic), was about 150 min (120-180)**.** When analysing the number of anastomoses per one operation it was noted that the overwhelming majority of patients (91 %), regardless of BC phenotype, had one intestinal anastomosis, several intestinal anastomoses were formed during one operation only in 5 patients with strictures (7 %) and in 6 patients with interintestinal fistulas (14 %). The results of the study of the types of intestinal anastomoses revealed that in every second observation a manual end-to-end anastomosis was applied (63 %), in one third of cases - a hardware anastomosis "side-to-side" (25 %), the other configurations were used much less frequently. The choice of intestinal anastomosis variant depended on the operative access: in open surgeries we used manual intestinal anastomosis "end-to-end", in laparoscopic access - hardware intracorporeal anastomosis "side-to-side".

In patients with stricturing BC radical intestinal resections in half of observations were performed by open surgical access (56 %), in more than one third of patients laparoscopic endosurgical interventions were performed (40 %). At penetrating BC with strictures radical intestinal resections in the overwhelming majority of cases were also performed by open surgical

access (74 %), only in a quarter of observations (26 %) laparoscopic endosurgical interventions were performed.

In patients with penetrating with strictures BC in the overwhelming majority of cases intestinal fistulas (42/46 - 91 %) and/or intra-abdominal infiltrates (37/46 - 80 %) were revealed. In patients with fistulas in two thirds of cases interintestinal accesses were found (26/42 - 62%), of which in several observations in combination with retroperitoneal fistulas (4) or with external intestinal-dermal fistulas (3). Isolated retroperitoneal fistulas were found in a quarter of patients with fistulas (11/42 - 26 %), and intestinal cutaneous fistulas - only in 12 % of observations (5/42). The average interval from detection of intra-abdominal infiltrate before surgical intervention was 3.5 months (from 1 to 5 months), and from detection of intestinal fistulae before surgery - 2.7 months (from 1 to 5 months). Abscessation of the infiltrate was noted in half of the observations (20/37 - 54 %), of them retroperitoneal psoas abscess was revealed in four patients (4/20 - 20 %). In the vast majority of cases abscesses were detected intraoperatively (14/20 - 70 %), only in one third of cases (6/20 - 30 %) abscess was detected and drained before radical surgery. In the majority of clinical observations resection of the affected part of the intestine with dissection of the intra-abdominal infiltrate and/or intestinal fistula with primary intestinal anastomosis (29/46 - 63 %) or with removal of the intestinal stoma (17 %) was performed. In one in five patients a stoma proximal to the intestinal conglomerate was applied in the first stage without interintestinal fistula separation, and radical surgery with intestinal resection was performed in the delayed period (20 %). Every third child with inflammatory BC refractory to therapy underwent intestinal surgery (15/44 - 34 %). Approximately in half of observations (6/15 - 40 %) the indication for surgery was uncontrollable intestinal bleeding, mainly these were patients with refractory colitis (5) and only in one child the source of bleeding was detected in the terminal ileum (he underwent ileocecal resection with ileo-ascendostomy). Out of five patients with refractory colitis three patients underwent colectomy with primary ileorectal anastomosis, in two cases double-barrel ileostomy with delayed colectomy was performed. In half of the cases with severe active colitis combined with perianal lesions (7/15 - 47 %) a diverting ileostomy was formed. Two patients with refractory colitis underwent total colectomy with a terminal ileostomy. Specific anti-inflammatory therapy of BC before operation was prescribed to the overwhelming majority of patients (150/164 - 91 %). Most often patients received immunosuppressive therapy with thiopurines or methotrexate before the operation (58 %), every third patient (38 %) received biological therapy with drugs directed against tumour necrosis factor (anti-TNF drugs) or hormonal treatment with steroids (29 %). In the preoperative period patients with severe hypoalbuminemia were transfused with 20 % albumin solution (12 %), in case of severe iron deficiency anaemia parenteral iron preparations were administered (9 %). Children with weight deficiency were corrected with therapeutic enteral mixtures (46 %) and in 10 % of observations patients received parenteral nutrition. Two thirds of patients (77%) received antibiotic therapy in the preoperative period. Statistical processing of the results was carried out on a personal computer using the free programming language R and the free software development environment RStudio. Standard methods of parametric and nonparametric statistics were used. To determine the risk factors in case of dichotomous variables we constructed conjugacy tables with calculation of odds ratio (OR) and their 95% confidence interval (CI). To study the independence of dichotomous variables, conjugacy tables were constructed with calculation of Pearson's chi-square statistic (x2). For small samples we used Fisher's exact test with calculation of probability p. For pairwise study of independence of numerical variables we used Student's t-test for normally distributed data and Mann-Whitney U-test in other cases.

RESULTS:

Early results of operations on abdominal organs (within 30 days after surgical intervention) were evaluated according to the Clavier-Dindo scale. Postoperative complications in patients with BC after the first operation on the abdominal cavity organs were noted in 15% of observations (20/133), their detailed characteristic is presented in the table. When analysing the early results of treatment after the first operation on the intestine, the high frequency of complications in

patients with inflammatory refractory form of BC B1 (40%) was noted, while the general frequency of complications in all operated patients did not exceed 15%. Purulent-septic complications were the most frequent (11 %).

When assessing the early postoperative results of repeated interventions, a high complication rate was also noted in patients with inflammatory phenotype of BC (25%), while the overall complication rate in all operated patients did not exceed 14%. The main type of complications was purulent-septic (9), of which infection and divergence of the postoperative wound edges were also leading (5).

Fatal outcome occurred in two cases against the background of sepsis with multiorgan failure (in boys with very early onset of CD and unspecified primary immunodeficiency), despite emergency surgical interventions with the formation of an intestinal stoma.

In order to clarify and identify possible risk factors, we analysed the correlation of postoperative.

features of CD, phenotype and localisation of the lesion, surgical tactics and variants of surgical treatment, with the volume of drug therapy in the perioperative period, as well as with some event intervals in the treatment of patients.

The reliable connection of postoperative complications with severe variants of CD - refractory inflammatory form and penetrating with strictures, as well as with extended GI lesions and high need for colectomy - was noted. Clinical manifestations of CD in the form of intra-abdominal infiltrates/abscesses and intestinal fistulas (mainly inter-intestinal) are important unfavourable factors associated with the complicated period after surgery. The state of refractoriness to therapy (including hormone resistance), the occurrence of irreversible changes in the intestinal wall (presence of fibrosis) and iron deficiency anaemia requiring correction are also considered as risk factors for complications after surgery.

In our study the collinearity of statistically reliable risk factors of postoperative complications was checked in order to identify independent factors, taking into account that patients may have an integral impact of certain parameters on the course of the disease in the perioperative period. The following independent predictors were identified: penetrating type of BC with strictures ($p = 0.0047$), extraintestinal manifestations in the form of recurrent infections ($p = 0.0105$), intestinal fistulas ($p = 0.0047$) and fibrosis in the biopsy of the intestinal mucosa ($p = 0.0093$), as well as hormonal therapy before surgery ($p = 0.0105$).

When analysing and testing for collinearity of factors associated with mortality after surgery, the following independent predictors were noted: age of BC debut less than 6 years (OR 10.8; 95% CI 1.16-137, $p = 0.0177$), combination of BC of any localisation with upper GI lesions (OR 13.8; 95 % CI 1,01-143, $p = 0,0247$), preoperative examination revealed significant hypoalbuminaemia less than 30 g/l (OR 9,62; 95 % CI 1,04-122, $p = 0,0228$), as well as absence of specific therapy after surgery (OR 10,8; 95 % CI 1,16-137, $p = 0,0177$).

DISCUSSION

In adult patients with CD such factors as intraoperatively detected intra-abdominal abscesses, combined lesions of the upper GI tract, severe anaemia and hypoalbuminaemia, detection of morphological changes in the resection margins, specific preoperative therapy and high disease activity are significantly associated with an increase in the incidence of septic complications [7-9].

Our study analysing the results of surgical treatment of children with CD and searching for possible risk factors of postoperative complications is a pilot one in the national literature and includes a large number of observations, although it has a disadvantage due to retrospective data collection

The influence of preoperative conservative therapy in adults with CD on postoperative surgical complications has been largely studied [10]. In most studies it is proved that previous hormonal

therapy of CD increases the risk of postoperative complications, for example, the use of prednisolone at a dose of 20 mg/day (or its equivalent) for 6 weeks before surgery is a significant risk factor for infectious postoperative complications [11]. Data of several meta-analyses and retrospective studies have shown that treatment with anti-TNF drugs in adult patients with CD before surgery can increase the incidence of surgical complications, such as postoperative sepsis, wound infections, intra-abdominal abscesses and anastomosis failure [12]. The combination of steroid hormones and anti-TNF drugs significantly increases the risk of complications [13]. At the same time, monotherapy with immunosuppressors (thiopurines - azathioprine, 6-mercaptopurine) can be safely performed in the peri-operative period [14].

In single publications of paediatric specialists there is information about possible high risk of complications in the preoperative period with hormonal [11] and biological therapy [15]. In our study we obtained similar data confirming that hormonal therapy before surgery can be an independent predictor of septic complications.

Body weight deficiency

Undernutrition with body weight deficiency is classified as a reliable risk factor for postoperative complications, including anastomosis failure [16-18]. Loss of 10% or more of body weight over a three-month period appears to be a pronounced weight deficit and is accompanied by physical developmental delay [19]. In our cohort of patients every second patient had physical development delay with weight deficit, but statistically significant increase in the incidence of postoperative complications in these children was not revealed.

Hypoalbuminaemia

Some publications [20-22] present data on hypoalbuminemia as a reliable predictor of early complications in adult patients with CD, but the authors estimated different levels of serum albumin: below 35 g/l, less than 30 g/l or below 25 g/l. In the pre-available literature, there are single publications in which a decrease in serum albumin level is considered as a reliable predictor of the need for early surgical treatment in children with CD [23].

Our study revealed statistically reliable association of severe hypoalbuminaemia (less than 30 g/l) with septic complications in the early postoperative period**.**

Type of surgical access, resection variant and intestinal anastomosis

Current literature presents studies on the possible influence of specific configurations of intestinal anastomoses and surgical access on adverse outcomes, and various authors have reported that side-to-side apparatus anastomosis may lead to a lower incidence of overall postoperative complications (with anastomosis failure) as well as laparoscopic access [24]. In a retrospective review of the Paediatric Centre for Inflammatory Bowel Diseases from the UK [25], postoperative complications in children with CD after intestinal resections were reported in 22% of cases. None of the considered possible risk predictors (resection volume, open or laparoscopic access, anastomosis technique, number of anastomoses per operation, histological changes in the resected intestine edges) was significantly associated with the complication rate. On the contrary, in the works of other authors there are data that the high risk of septic complications is significantly higher in children with colorectal CD, when it is necessary to perform surgery for emergency indications, as well as when morphological inflammatory changes are detected in the resection margin [26]. A significant association of septic postoperative complications with the volume of resection (total or subtotal colectomy, $p = 0.003$ [2] was revealed. In our study we also did not reveal the connection of different operative techniques with the increase of complication rate, but we noted a statistically significant dependence of the risk of postoperative complications with extended GI lesions, with the need for total colectomy and with the detection of morphological changes in the intestinal wall (mucosal fibrosis).

Crohn's disease phenotype

Our work revealed a high frequency of complications in inflammatory refractory and penetrating with strictures form of CD (in particular, in the presence of intestinal fistulas and/or intra-abdominal infiltrates and abscesses). Similar data are available in publications of European paediatric surgeons [6]. At the same time, in adult patients with CD, according to some authors [4], only detected intra-abdominal abscesses, but not the CD phenotype itself, are reliably associated with postoperative complications.

As in previous studies [2], we identified predictors of disease severity in children: early age of onset, combination of CD of any localisation.

with upper GI lesions and the presence of extra-intestinal manifestations, a reliable association of these risk factors with postoperative complications was noted.

One of the latest publications presenting a multicentre retrospective study [9] revealed factors influencing the risk of postoperative infections, such as male gender, urgent surgery, intervention with laparotomy access, anaemia with haemoglobin level below 100 g/l and high level of C-reactive protein. In our cohort of patients, no similar statistically significant association of these predictors with adverse outcomes was found, which may be due to insufficient sample size.

CONCLUSION

In our study statistically reliable and independent risk factors influencing early outcomes of surgical interventions in children with complicated forms of CD have been established. When choosing individual tactics of treatment it is necessary to take into account the available predictors to ensure optimal treatment strategy with correction of homeostasis disorders in the preoperative period (anaemia, hypo-albuminemia, weight deficit), selection of specific therapy (with reduction of the dose of hormonal drugs) and determination of the terms of surgical intervention.

Thus, correct assessment of the balance of risk and benefit of the therapy, improvement of the patient's preoperative condition, timeliness of surgical intervention based on the identified risk predictors will improve the results of surgical treatment of children with complicated Crohn's disease.

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