

THE ROLE OF ELECTIVE SURGERY IN CHILDREN WITH LOCALIZED CROHN'S DISEASE

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Background: Substantial proportions of children with Crohn's Disease (CD) are non-responsive to standard medical therapy and/or nutritional treatment. For many children impairment of growth will also be an associated medical problem.

Aim: The aim of our study was to investigate a role of elective surgical treatment on the induction and duration of remission, and on growth improvement in paediatric patients with localized CD, who were refractory to conservative treatment.

Methods: We retrospectively analyzed the data of 55 newly diagnosed CD patients among whom 22 children (40%) had undergone surgical treatment.

Results: Post surgery all patients had significant PCDAI decline and the great majority of them (90.9%) had stable remission for more than 2 years. Following surgery 86.4% patients had a significant improvement in growth: an improvement in Z score for height ranging from 0.2 to 0.5 SD (9 months to 2 years after resection, $p < 0.01$).

Conclusion: Elective surgery, if properly timed and in well prepared patients, has a significant relapse preventive and steroid sparing role, and also results in major growth improvement.

Descriptors: SURGICAL PROCEDURES, OPERATIVE; CROHN DISEASE – surgery

INTRODUCTION

Crohn's disease (CD), as a chronic inflammatory bowel disease (IBD), may cause inflammation of any part of the digestive tract and has an estimated incidence in the paediatric population of 1.36-2.0/100,000 per year (1, 2, 3).

Signs and symptoms in children with CD may be vague or non-specific, depending on the severity of the disease and site of involvement. For those children with involvement of the coecum and terminal ileum this may be especially true. However, abdominal pain is the most common symptom (in 72% of patients), and wasting and stunted growth the most common clinical findings in children with CD (4, 5).

Important linear growth retardation occurs in 20-30% of children with CD, in almost 90% of patients height velocity is reduced, and 46% experience a decrease in growth even before gastrointestinal symptoms have appeared (6). If not corrected by medical or surgical treatment, growth failure will persist into adulthood, resulting in stunted growth, which is present in 19-35% of adults with IBD and stunted height was seen in 37% of patients (7).

Although the underlying mechanisms of growth retardation are not fully understood, the most likely causal factors are poor nutrition, hormonal abnormalities, frequent use of corticosteroids and active intestinal inflammation itself (8, 9, 10, 11, 12, 13).

Different medical and nutritional treatment modalities, adjusted to the clinical condition of the individual patient, could be applied, particularly following the recently published guidelines of the European Crohn's Colitis Organization (ECCO) (14). For remission maintenance immunomodulatory drugs, Infliximab or surgery can be used. Immunomodulatory drugs such as azathioprine or 6-mercaptopurine showed a beneficial effect on remission duration and postoperative recurrence of CD, but there was no positive effect on linear growth (15, 16). On the other hand, it has been published that Infliximab usage may improve growth in paediatric CD patients (17, 18), however, the wider use of biological agents has been compromised by a series of cases of Hepatosplenic T cell lymphoma (HST-CL), all in young CD patients, and in most of them lethal outcome was imminent (19). Regarding surgical treatment, there are several studies which have showed that well-timed surgical intervention often modifies the outcome and may initiate impressive catch-up growth (20, 21, 22, 23, 24, 25).

We therefore decided to re-evaluate the role of elective surgery in the treatment of children with localized CD, with special emphasis on the effect on growth and on remission duration.

MATERIALS AND METHODS

Data on all newly diagnosed CD patients treated at the Children's Hospital, Zagreb from 1993 to 2006 were retro-

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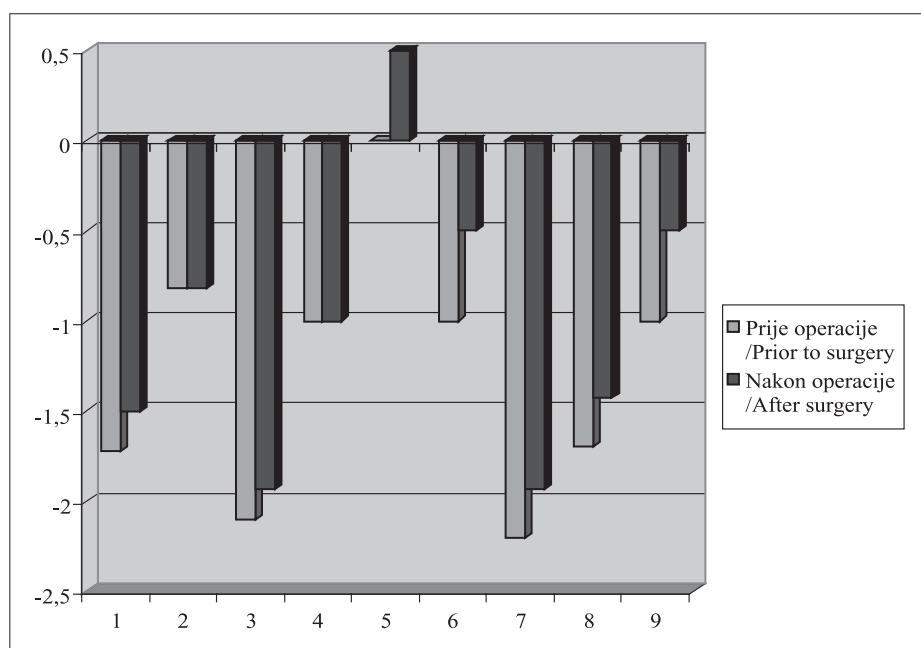


Figure 1. Z score for height in female patients prior to and after surgery
Slika 1. Z vrijednost za visinu za djevojčice, prije i nakon operacije

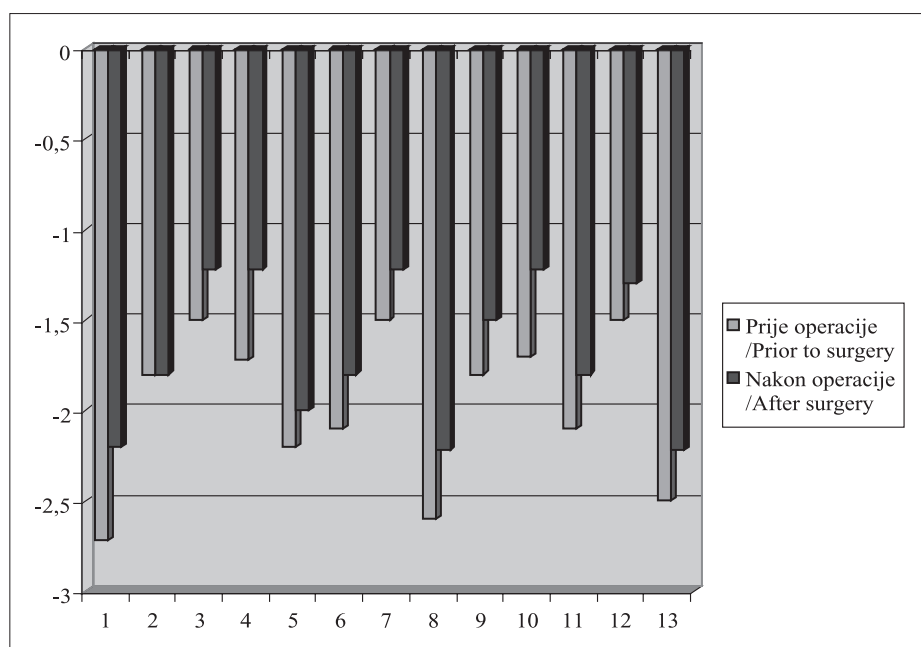


Figure 2. Z score for height in male patients prior to and after surgery
Slika 2. Z vrijednost za visinu za dječake, prije i nakon operacije

spectively analyzed. We identified 55 patients (33 males, 22 females) with newly diagnosed CD (age range: 9-17.8 years; mean: 13.8 years). All patients underwent both upper endoscopy and colonoscopy with ileoscopy completed with biopsies of all sites and barium small intestine examination. Surgical intervention was performed in 22 (40%) of all treated patients, (13 males, 9 females) in the period from 4 months to 5.5 years (mean 21.2 months)

after diagnosis. Indications for surgery were as follows: a) localized disease refractory to conservative treatment (N=19; 86.36%); b) intestinal perforation (N=2; 9.1%); c) uncontrolled bleeding (N=1; 4.54%). A refractory disease was defined as a steroid dependent/resistant disease, also one resistant to immunomodulatory treatment with azathioprine and/or methotrexate. Prior to surgery, all our patients were treated with enteral nutrition, corti-

costeroids and azathioprine and in 8 patients methotrexate was also introduced. Median age at the time of surgery was 14.6 years for female and 15.2 years for male patients. All patients were followed up for at least two years.

For all patients the Paediatric Crohn's Disease Activity Index (PCDAI) was calculated prior to and after the surgery (26) Severe disease was defined as a PCDAI score above 40, moderately severe as a PCDAI score from 30 to 40 and remission was defined as a PCDAI score below 15. Growth rate was evaluated using Z scores for height, adjusted for age and sex. Clinical activity of the disease and growth were compared prior to and after the surgery, and the differences were tested by the T test. A p value of less than 0.05 was used as the criterion for statistical significance.

As a standard procedure, all our CD patients received enteral nutrition two weeks before surgery and 10-14 days after surgery. Immunomodulatory drugs such as azathioprine or methotrexate were also used following the surgery in order to help maintain remission.

RESULTS

The majority of our patients who underwent intestinal resection (N=22) had limited resection of ileocecal segment, followed by an ileocolonic anastomosis (12/22 – 54.54%) and 8 (36.36%) of them had a segmental ileal resection, followed by ileoileal anastomosis. In as few as 2 patients (9.1%) resection was limited to the colon only, resulting in a colostomy. In both of them the operation was due to acute symptoms such as perforation and refractory bleeding. In contrast to those two children, 19 of 22 CD patients who underwent ileal or ileocecal resection had elective surgery due to localized disease refractory to conservative treatment. Duration of remission after surgical treatment was >2 years for 20 patients (90.9%) and only two patients (9.1%) had short remission (1 year) and needed steroid treatment. Prior to surgery all the patients had severely active disease despite the treatment prescribed; the median PCDAI score for male patients was 40.4 (ranging from 35-45) and 42.2 (ranging from 35-45) for female patients. Three months after surgery the PCDAI significantly declined to 12.7 for male and 12.8 for female patients (ranging from 10 to 15) indicating inactive disease in remission (p<0.0001).

Table 1. Main patient characteristics prior to and after surgery

Tablica 1. Karakteristike bolesnika, prije i nakon operacije

Patient number/ Broj bolesnika	Reason for surgery/Razlog operacije	Type of surgery (resection of)/Tip operativnog zahvata (resekcija)	PCDAI prior to surgery/PCDAI prije operacije	PCDAI after surgery/PCDAI nakon operacije	Duration of remission/Trajanje remisije (god)	Z score prior to surgery/Z vrijednost prije operacije	Z score after surgery/Z vrijednost nakon operacije
Male/Dječaci							
1	UB	LC	45	10	1	-2,7	-2,2
2	LD+RT	TI+C	40	10	2	-1,8	-1,8
3	LD+RT	TI	45	15	2	-1,5	-1,2
4	LD+RT	TI+C	45	15	2	-1,7	-1,2
5	LD+RT	TI+C	35	15	2	-2,2	-2
6	LD+RT	TI	35	10	2	-2,1	-1,8
7	LD+RT	TI+C	40	15	2	-1,5	-1,2
8	LD+RT	TI	45	15	2	-2,6	-2,2
9	LD+RT	TI	35	10	2	-1,8	-1,5
10	LD+RT	TI+C	45	15	2	-1,7	-1,2
11	LD+RT	TI+C	40	10	2	-2,1	-1,8
12	IP	TI	35	10	2	-1,5	-1,3
13	LD+RT	TI+C	40	15	2	-2,5	-2,2
Female/Djevojčice							
1	LD+RT	TI+C	45	15	2	-1,7	-1,5
2	IP	LC	40	15	2	-0,8	-0,8
3	LD+RT	TI	45	10	2	-2,1	-1,9
4	LD+RT	TI+C	45	15	1	-1	-1
5	LD+RT	TI+C	45	10	2	0	0,5
6	LD+RT	TI+C	40	10	2	-1	-0,5
7	LD+RT	TI+C	45	15	2	-2,2	-1,9
8	LD+RT	TI	35	15	2	-1,7	-1,4
9	LD+RT	TI	40	10	2	-1	-0,5

UB – uncontrolled bleeding/nekontrolirano krvarenje; LD+RT – localized disease refractory to conservative treatment/lokalizirana bolest koja ne odgovara na konzervativno liječenje; IP – intestinal perforation/perforacija crijeva; TI – terminal ileum/terminalni ileum; C – cecum/cekum; LC – left part of colon/lijeva strana kolona; PCDAI – Paediatric Crohn's Disease Activity Index/Pedijatrijski indeks aktivnosti za Crohnovu bolest

Almost all patients prior to the surgery had growth impairment: median Z score for height for female patients prior surgery was -1.27 standard deviation (SD) (ranging from -2.2 to 0 SD, Figure 1) and for male patients -1.98 SD (ranging from -2.7 to -1.5, Figure 2). As the result of the stable remission achieved after resection a significant improvement in growth was detected in 86.4% (N=19) of patients, irrespective of the type and extent of the operation or gender. The median Z score for female patients before surgery was -1.28 SD (ranging from -2.2 to 0 SD) and following the resection it was -1.01 SD (ranging from -1.9 to 0.5 SD, Figure 1). For boys with CD it was -1.98 SD before (ranging from -2.7 to -1.5 SD) and -1.67 SD after the operation (ranging from -2.2 to -1.2 SD, Figure 2). This improvement in the Z score for height was statistically significant ($p<0.01$), ranging from 0.2 to 0.5 SD in the period from 9 months to 2 years post surgery (Table 1).

Growth improvement did not occur in three patients. These included two fe-

males – one after partial colon resection following intestinal perforation, the other due to the short duration of the remission; and one male patient who entered stable remission but the surgery was performed at postpubertal age (almost 18 years).

DISCUSSION

The aim of treatment in children with IBD is not only to induce and maintain remission, but also to achieve normal growth and development, followed by a reasonably good quality of life. Compared to adults, children have high rates of disease complexity and disease at onset is more extensive (27). Moreover, both the inflammation itself and the medical treatment – steroids in particular – have a negative effect on growth (8, 9, 10, 11, 12). If not timely corrected, these defects will result in the permanently stunted growth (7).

It has been said that surgery can be a good choice for remission maintenance but it has also been underlined that it has to be well planned because high rates of

postoperative CD recurrence are associated with severe disease at the time of surgery, colonic CD, and the preoperative use of 6-MP (28).

It has already been shown that after four years of follow-up, operated patients have a lower relapse rate compared to patients treated medically (20% vs. 51%) (29). Moreover, after the elective bowel resection, significant improvement in growth was also achieved (20). Griffiths showed that the mean height velocity of patients with growth potential increased from 2.4 (2.3) cm per year preoperatively to 8.1 (3.4) cm per year in the first postoperative year ($p=0.0001$) (30).

We performed the study to evaluate the role of elective surgery in the treatment of children with localized CD. The influence of surgical treatment on duration remission, PCDAI and growth improvement was measured. In our albeit retrospective study, we could clearly show that children with localized severe CD, unresponsive to conservative treatment entered stable remission following resection of the in-

flamed bowel segment, confirmed by a significant PCDAI decline; 91% of them did not need any further steroid treatment for more than 2 years.

Stable remission and no steroid treatment are necessary prerequisites for catch-up of growth. Our study showed a significant improvement in height z-scores post-surgically and it confirms earlier findings (31) that if remission cannot be achieved by medically treatment, surgical removal of inflamed tissue is a good option (32). However, a role of proper timing cannot be overemphasized. If the surgery was performed in the pre- and early pubertal stage, postsurgical height velocities increased dramatically, while the results are much less impressive if the surgery was performed in late puberty (20, 22, 33, 34). Our study showed that prepubertal as well as patients in puberty (median age at surgery was 14.6 years for female and 15.2 years for male patients) have growth improvement after surgery (improvement in Z score for height ranged from 0.2 to 0.5 SD ($p < 0.01$)).

In conclusion, in paediatric CD patients who do not respond to conservative treatment and have localized disease, properly timed and not prolonged elective surgery can provide optimal management of the disease and result in remission followed by an appropriate growth improvement.

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S a ž e t a k

ULOGA ELEKTIVNE KIRURGIJE U DJECE S LOKALIZIRANOM CHRONOVOM BOLEŠĆU

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Uvod: Značajan postotak djece s Crohnovom bolešću (CD) ne reagira na konzervativno liječenje lijekovima i/ili enteralnom prehranom. S druge strane, za velik broj djece koja boluju od Crohnove bolesti jedan od najvećih problema je zaostajanje u rastu.

Cilj: Cilj ovog istraživanja bio je odrediti ulogu kirurškog liječenja u poticanju i održanju remisije te utvrditi postoji li poboljšanje rasta nakon operacije u djece koja boluju od lokaliziranog oblika Crohnove bolesti, koja ne odgovara na konzervativno liječenje.

Metode: Retrospektivno smo analizirali podatke 55-ero novodijagnosticiranih bolesnika sa CD-om, od kojih je 22-je djece (40%) liječeno kirurškom resekcijom.

Rezultati: Nakon operacije svi su bolesnici imali značajno smanjenje PCDAI-a, a velika većina (90,9%) ostala je u stabilnoj remisiji dulje od 2 godine. Nakon operacije, kod 86,4% bolesnika zabilježen je zamah rasta; poboljšanje Z vrijednosti za visinu od 0,2 do 0,5 SD (9 mjeseci do 2 godine nakon operacije, $p < 0,01$).

Zaključak: Elektivni kirurški zahvat, dobro planiran i u pomno odabranih bolesnika, značajno smanjuje broj relapsa bolesti i potrebu za uporabom kortikosteroidnog liječenja, te posljedično rezultira značajnim zamahom rasta.

Deskriptori: KIRURŠKI ZAHVAT, OPERATIVNI; CROHNOVA BOLEST – operacija

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