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ORIGINAL ARTICLE

Diversion proctocolitis and response to treatment with short-chain fatty acids—A clinicopathological study in children

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Abstract
Objective Diversion proctocolitis (DPC) frequently develops in the colorectum after diversion of the fecal stream characterized by bleeding from the inflamed mucosa. Short-chain fatty acids (SCFA) are responsible for growth and differentiation of enterocytes. Adult series have reported variable response of DPC to luminal SCFA. There is dearth of studies in children. We aimed to study incidence, clinical, endoscopic, and histopathological characteristics of DPC and effect of SCFA in children.
Methods Prospectively clinical, endoscopic, and histopathological evaluation was done for DPC in children undergoing fecal diversion. Patient characteristics, type and duration of stoma, symptoms, endoscopy and biopsy findings, duration of treatment and response to SCFA, time of closure of stoma, and any associated gut anomaly were recorded.
Results Fifteen children completed the study. Anorectal malformation was the commonest indication for stoma. Sixty percent were symptomatic within 2–9 months, excessive mucous discharge being the commonest symptom. All had at least one positive endoscopic finding; erythema, edema, and exudates being the commonest findings. All DPCs improved clinically and endoscopically following SCFA. Histological resolution was seen in 78 %, while 22 % had persistent disease. Closure of stoma showed complete resolution of DPC.
Conclusion DPC was common (87 %) following stoma formation in children with strong male preponderance (6.5:1). The commonest indication for stoma was anorectal malformation (67 %). Clinical, endoscopic, and histopathological changes appeared within 2–9 months with symptomatic DPC in 60 %. All patients (100 %) had at least one positive endoscopic finding, histopathological examination confirmed the diagnosis. SCFA led to symptomatic, endoscopic, and histopathological resolution of DPCs. Closure of stoma cured all the persistent DPCs.

Keywords Children · Diversion proctocolitis · Endoscopy · Histopathology · Short-chain fatty acids

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Introduction

Diversion proctocolitis (DPC) is an inflammatory process that occurs in segments of the colorectum after surgical diversion of the fecal stream. The condition persists indefinitely unless the excluded segment is reanastomosed [1]. It is believed to result from bacterial overgrowth, antibiotics, intraluminal toxins, and nutritional deficiency [2]. The condition is usually asymptomatic, but it may be manifested by rectal discomfort, diffuse abdominal pain, mucous discharge, tenesmus, and bleeding [3,4]. Its incidence may be as high as 100 % when it is observed prospectively, with the onset occurring between 3 and 36 months after diversion [5].

The diagnosis is established by colonic or rectal biopsy. Endoscopic and histologic features of DPC are almost universally present in defunctioned bowel; however, clinically, symptoms are reported to occur in 6 % to 100 % of cases [5–8].

Possible mechanisms postulated are bacterial overgrowth of normal colonic flora, invasion of bypassed segment by pathogenic organisms, and a nutritional deficiency of the

colonic epithelium, specifically due to absence of short-chain fatty acids (SCFA) normally present in colonic contents [2,9]. Harig et al. [1] reported absence or near absence of SCFA from the excluded rectosigmoid and reversal of the disease after surgical reanastomosis or topical application of SCFA. SCFA are predominant solutes in the aqueous phase of colonic contents and stool. About 90 % of the SCFA content is accounted for by acetic, propionic, and *n*-butyric acid [10]. These acids are produced by anaerobic bacterial fermentation of carbohydrates, a process of which mammalian cells are incapable [9]. Short-chain fatty acids are readily absorbed by the colon in humans and animals in exchange of bicarbonate with simultaneous stimulation of water and sodium absorption [11]. Roediger [8] demonstrated that SCFA are the major and preferred energy source for human colonic epithelium. The colonocytes must assimilate these SCFA from the lumen because the plasma concentration is negligible [12]. Among the SCFA normally present in colonic contents, *n*-butyric acid is most avidly metabolized [9]. This observation led them to prepare a SCFA solution in which the *n*-butyric acid was in excess as compared with its physiologic concentration in molar ratio to other SCFA [10]. Rolandelli et al. [12,13] demonstrated in rats that the instillation of SCFA or pectin (a substrate for bacterial production of SCFA) accelerates the healing of colonic anastomoses, and that the oral administration of pectin leads to healing of experimentally induced colitis [14]. In dogs, luminal perfusion of the colon with SCFA increases regional blood flow and oxygen uptake [15]. Even the enterocyte healing effect of parenteral SCFA on small intestine have been demonstrated by Koruda et al. [16,17]. Harig et al. [1] used enteral SCFA effectively in the management of DPC, albeit Guillemot et al. [18] were unable to reproduce the similar results and questioned the efficacy of this treatment.

There is dearth of clinical and experimental studies on DPC and role of SCFA in the pediatric age group. Therefore, we aimed at studying the incidence, clinical, endoscopic, and histopathological characteristics of DPC in the pediatric population, and the role of enteral SCFA in the resolution of the same in a prospective manner.

Methods

Following the Institutional Review Board (IRB) approval and informed consent, children (0–13 years) undergoing diversion ileostomy or colostomy between September 2003 and February 2007 were recruited prospectively. Patient demography, indication, type and duration of the stoma, symptoms, endoscopy and biopsy findings, duration of treatment with SCFA, patient's compliance, any clinical, endoscopic, and histopathological improvement in DPC, and the time of closure of the stoma were recorded. In patients with bleeding per rectum, a digital examination was done to rule out a polyp or other local anal cause. All these children underwent endoscopic examination of the distal limb of the diverted segment monthly to look for any evidence of inflammation. A punch biopsy was taken at the time of scopy and subjected to histopathological examination. The incidence of DPC was calculated from positive histopathological findings as described by Haque et al. [19]. The specific endoscopic findings included presence of erythema, friability, edema, nodularity, aphthous ulcers, exudates, and frank bleeding. The histopathological features monitored for DPC under hematoxylin and eosin staining were presence of lymphoid follicular hyperplasia, chronic inflammation, acute inflammation, paneth cell metaplasia, goblet cell depletion, aphthous ulcers, and presence of eosinophils, crypt abscess, cryptitis, edema, and patchy involvement.

In children with proven DPC, a mixture of SCFA was instilled into the lumen according to the following protocol. SCFA mixture was made in the pharmacy section of the hospital. The sodium salt of propionate (30 mmol/L), acetate (60 mmol/L), and butyrate (40 mmol/L) were constituted into a single mixture. Citric acid was added to bring the pH to 7. Instillation of this mixture was carried out by an infant feeding tube no. 8 or 10, inserted into the defunctioned stoma at a dose of 10 mL twice daily. Parents were trained to instill this at home.

Response was evaluated monthly with clinical, endoscopic, and histological examinations until they showed complete resolution of DPC or until the closure of the stoma, whichever was earlier. A written consent for the use of above-mentioned SCFA for irrigation of the distal segment of the defunctioned stoma was taken from the parent or attending guardian. Exclusion criteria included anorectal agenesis with rectourinary fistula in males, anorectal agenesis with rectovaginal fistula in females, inflammatory bowel disease, and distal malignancies (gut, pelvic).

Results

A total of 15 children (mean age 2 months; M/F 6.5:1) completed the study. Anorectal malformation was the commonest indication for stoma (10/15, 66.7 %), none had rectourinary or rectovaginal fistula. Three children had Hirschsprung's disease, and two children had necrotizing enterocolitis. All of patients had the stoma formation within 0–3 months of age, mostly within days following the birth. Out of 15 patients enrolled, 13 developed DPC and two did not have DPC. Nine were symptomatic and four had asymptomatic DPC. Among symptomatic cases, excessive mucous discharge per stoma/rectum was the commonest symptom observed (Table 1). Patients became symptomatic 2–9 months

Table 1 Types of symptoms in diversion proctocolitis (Harig et al. [1], Kiely et al. [2])

Symptoms	Number $n=15$	Percentage	Time of onset of symptoms (months)
Excessive mucous discharge (alone)	4	26.6	2.5
Bleeding (alone)	2	13.3	6.0
Excessive mucous discharge with bleeding	3	20	7.2
Abdominal pain	2	13.3	8.4

following the diversion of the fecal stream (Table 1). Seven (46.7 %) of the patients were anemic (Hb below 10 gm/dL).

All had at least one positive finding on endoscopy. Erythema, edema, and presence of exudates were the commonest findings (Table 2). Edema and presence of exudates was noted in two of the patients not diagnosed to be having DPC.

Based on histopathology, 13 out of 15 (87 %) patients in the study were diagnosed to be having DPC in the defunctionalized portion of bowel (Table 3). All 13 patients with DPC showed presence of lymphoid follicular hyperplasia and chronic inflammation (100 %), 12 (92.30 %) had edema, 8 (61.54 %) had aphthoid ulcers, 6 (46.15 %) had acute inflammatory infiltrate, and 5 (38.46 %) had cryptitis. Three (23.07 %) had patchy involvement of the defunctioned bowel and presence of eosinophils, 2 (15.38 %) had goblet cell depletion, and 1 (7.70 %) had Paneth cell metaplasia (Figs. 1, 2, 3, 4, 5, and 6). Crypt abscess was not found in any patient.

Both the patients who did not have DPC were asymptomatic. Thirteen out of 15 patients (87 %) had endoscopic and histopathologic evidence of the DPC. Four out of 13 (30.7 %) had closure of the stoma done at the time of the first endoscopic and histopathologic examination itself. The remaining 9 patients (69.3 %) underwent treatment with SCFA.

Eight out of nine (88.88 %) of the patients received treatment with the SCFA for a period of 1 month. One (11.11 %) of the patients received treatment with SCFA for a period of 2 months due to persistent DPC. All 9 (100 %) patients were compliant with the treatment.

The majority of patients showed improvement in the clinical symptoms of DPC in response to SCFA (Fig. 7).

Table 2 Endoscopic findings of defunctioned bowel (Ma et al. [3], Ordein et al. [4])

Endoscopic findings	Number ($n=15$)	Percentage
Erythema	11	73.3
Friability	6	40.0
Edema	11	73.3
Nodularity	4	26.7
Aphthous ulcers	6	40.0
Exudates	11	73.3
Frank bleeding	3	20.0

The endoscopic findings showed definitive improvement at 1 month (Fig. 8). Edema, friability, and frank bleeding showed complete disappearance. Erythema, exudates, and aphthous ulcers subsided significantly in the repeat scopy. Repeat biopsy showed resolution of DPC in 7 out of 9 (77.78 %) patients, while 2 (22.22 %) had persistent disease (Table 4).

Eight (88.9 %) stomas were closed after 1 month of the treatment. One (11.1 %) stoma was closed after 2 months of treatment with SCFA. Closure of stoma led to complete resolution of all the symptoms such as excessive mucous discharge/bleeding per stoma/rectum and abdominal pain, and endoscopic and histological changes.

Discussion

DPC is an iatrogenic disorder which develops in the segment of the colorectum after surgical diversion of the fecal stream. In the pediatric population, fecal diversion in form of ileostomy or colostomy is commonly done for Hirschsprung's disease, anorectal malformations, meconium ileus, complex intestinal atresias, necrotizing enterocolitis, and unusual rectal or colonic perforations or injuries. The fecal stream is diverted for a variable duration leading to trophic

Table 3 Histopathological findings

Histologic findings	Diversion proctocolitis	
	($n=13$)	Percentage
Lymphoid follicular hyperplasia	13	100
Chronic inflammation	13	100
Acute inflammation	6	46.1
Paneth cell metaplasia	1	7.7
Goblet cell depletion	2	15.3
Aphthous ulcers	8	61.5
Eosinophils	3	23.0
Cryptitis	5	38.4
Crypt abscesses	0	0
Edema	12	92.3
Patchy involvement	3	23.0

All of the above findings were absent in non-diversion proctocolitis patients ($n=2$)

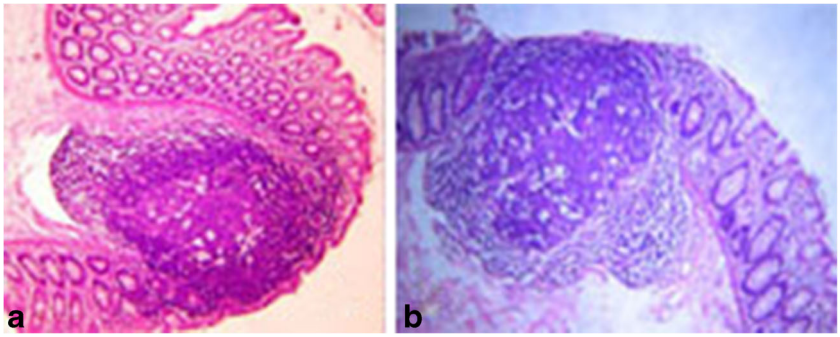

Fig. 1 Diversion proctocolitis showing hyperplastic lymphoid follicle (**a**) and superficial ulceration and congestion (**b**) (H&E, ×100)

changes in the colon manifesting as signs and symptoms of DPC. It persists indefinitely unless the excluded segment is reanastomozed. Endoscopic and histological analysis would help in reducing the diagnostic confusion with inflammatory bowel diseases or other forms of colitis, and thus will reduce the morbidity and delay in closure of the stoma.

DPC has been reported to occur in all age groups involving children and adults [1–3,19,20]. There has been no mention of specific peak of incidence in any particular age, although higher incidence is reported in pediatric age group compared to adults (78 % to 100 % [4,19,20] vs. 6 % to 100 % [3,21,22]). This may be primarily due to the nature of the study and the modalities used to diagnose DPC. Prospective studies involving histological examinations have revealed consistently higher incidences.

In the present study, all were children under 3 years of age, 13 (86.6 %) patients, later proven to have DPC, had the stoma made when they were neonates, and the histological examination has been done on the endoscopic biopsies. DPC was confirmed in 13 out of 15 patients (86.7 %) similar as reported in the first report in international literature by Glotzer et al. [21]. There was male preponderance (6.5:1) as reported by others in pediatric [2,19,20] as well as in adult patients [1,3,18].

In the literature, various reasons for diversion in pediatric patients included Hirschsprung's disease, anorectal malformation, or severe gastrointestinal motility disorders, meconium ileus, complex intestinal atresias, necrotizing enterocolitis, and mucosal rectal or colonic perforations or injuries; and in adults, the common reasons for diversion included fecal incontinence, diverticular diseases, rectal and anal cancers, perineal injuries/sepsis/fistula, inflammatory bowel disease, pseudomembranous colitis, and sphincter saving surgeries for large-bowel cancers. The diversion in our series were mostly due to anorectal malformation without fistula (n=10) and Hirschsprung's disease (n=3) akin to others [2,19,20].

There is wide variation in the percentage (6% to 100 %) of the patients who become symptomatic with DPC in the literature [2,3,19–22]. The clinical symptoms observed were excessive mucous discharge and bleeding per stoma or rectum, vague abdominal pain, and tenesmus similar to typical colitis. In our series, 60 % were symptomatic. Excessive mucous discharge per stoma/rectum alone was the commonest symptom (26.6 %). Bleeding and/or mucus discharge in combination were the most common presenting symptoms (Table 1). This is in consistency with Haque et al. [19] and Vujanic et al. [20]. However, Ordein [4] reported poorly localized abdominal pain in all of his 14 patients. Abdominal pain was present in 2 (13.3 %) of our patients who had excessive mucous discharge and bleeding as well, albeit there were no cases of tenesmus. Therefore, high index of suspicion of DPC in such

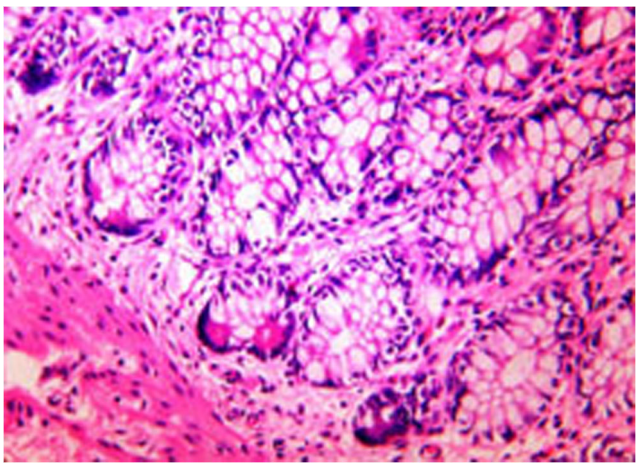

Fig. 2 Diversion proctocolitis showing Paneth cell metaplasia (*arrows*) (H&E, ×200)

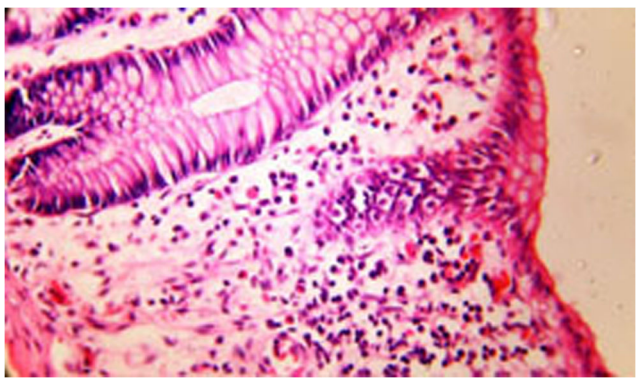

Fig. 3 Diversion proctocolitis showing scattered eosinophils (*arrows*) in the lamina propria (H&E, ×400)

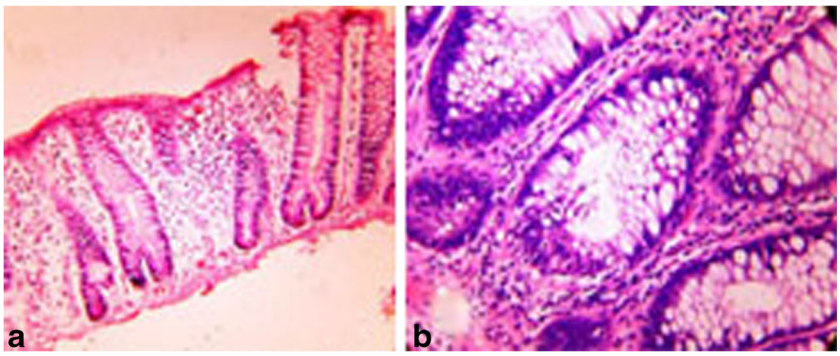

Fig. 4 Diversion proctocolitis showing branching of crypts (**a**) (H&E, ×200) and cryptitis (**b**) (H&E, ×400)

patients would obviate unnecessary treatment of other forms of colitis.

The authors [2,4,19,20] have reported the development of symptoms as early as 2 weeks of stoma formation in children. Others have reported onset of DPC from 1 month to 17 years in adults [1,3,22]. In our study, patients developed symptoms 2–9 months following fecal diversion. Therefore, it is quite evident that enterocytes can undergo inflammatory and trophic changes very soon, thereby warranting early screening for diagnosis and intervention.

Gross endoscopic findings of DPC include mucosal erythema, bleeding, ulceration, petechiae, edema, loss of vascular pattern, contact friability, granularity, and pseudopolyp formation [3,4,19,21–23]. The degree of inflammatory changes can vary from mild to severe and tend to be most prominent in the rectum, although the entire diversion segment including ileum may be involved confluently or in a patchy distribution. The endoscopic appearance of DPC may be indistinguishable from that of Crohn's disease or ulcerative colitis [4,5]. All of our 15 patients had at least one positive endoscopic finding. Erythema, edema, and presence of exudates were the commonest findings and were present in 11 (73.3 %) patients. The next commonest finding was friability and aphthous ulcers, present in 6 (40 %) out of the 15 patients. Nodularity was seen in 4 (26.7 %), and frank bleeding in 3 (20 %) patients. Haas et al. [23] showed that out of 85 patients who underwent endoscopic examination of the colon and rectum distal to a colostomy, 80 % had abnormal endoscopic findings. The most common and also the least serious endoscopic findings were mucous plugs and scybala.

Gold standard of diagnosing DPC is the presence of positive histopathological findings as described by Haque et al. [19]. Lymphoid follicular hyperplasia and lymphoplasmacytosis are the commonest histopathological findings [2,3,19–21,24]. The chronic inflammatory infiltrate in DPC differs from those with an underlying mucosal disorder, because there is relative preservation of mucosal architecture in DPC and presence of superficial rather than a basal lymphoplasmacytotic infiltrate. Other findings included presence of features of acute inflammation, mucin depletion, and aphthous ulcerations in majority of cases; occasional findings were Paneth cell metaplasia, architectural distortions, and crypt abscesses. Based on these criteria, DPC could be distinguished reliably from other colitis. The following minor variations were however observed in our series: acute inflammation was seen in 46 %, unlike their series (100 %). Cryptitis was observed in 38 % as compared to 100 %

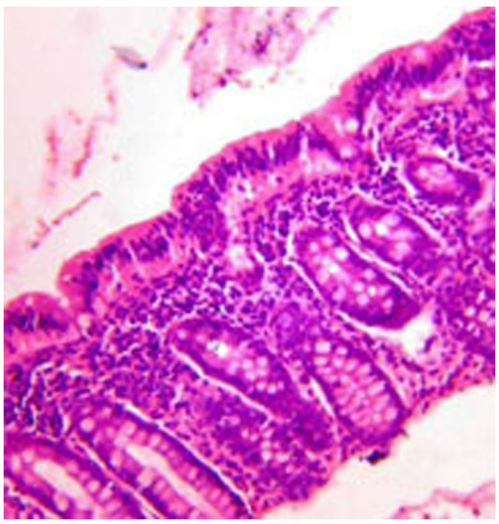

Fig. 5 Diversion proctocolitis showing increase in intraepithelial lymphocytes and dense chronic inflammatory infiltrate in the lamina propria (H&E, ×200)

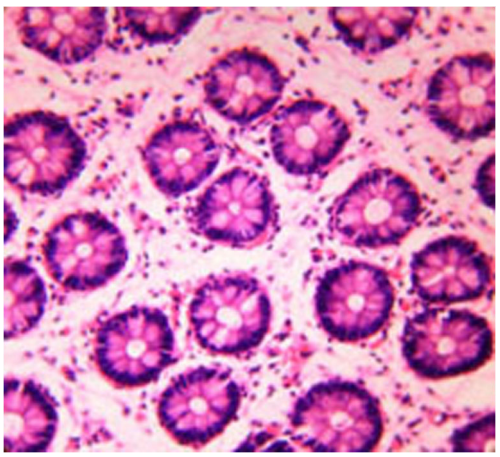

Fig. 6 Diversion proctocolitis posttreatment with short-chain fatty acids showing normal number of inflammatory cells in the lamina propria (H&E, ×400)

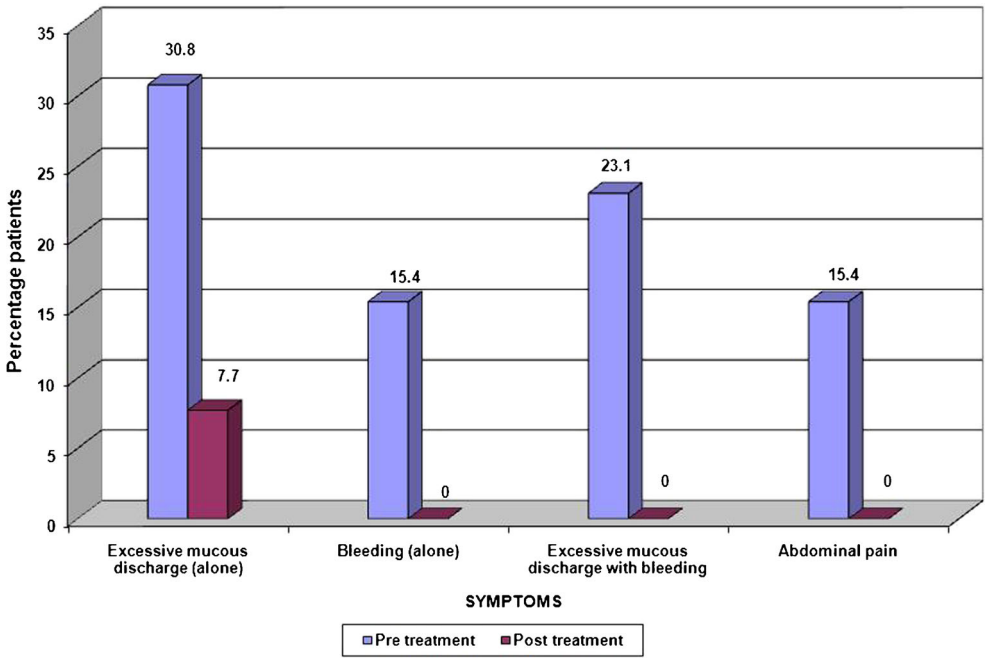

Fig. 7 Clinical response to short-chain fatty acids

reported by Haque et al. [19]. Aphthous ulcer was seen in 62 %, similar to those reported by them. Mucin depletion (15 %) and Paneth cell metaplasia (7.7 %) were uncommon histopathological findings in our series.

Complete clinical response was seen in 89 % symptomatic patients with SCFA.

Kiely et al. [2] have reported effective symptomatic relief in three out of five children with SCFA, while the remaining two needed adjunctive anti-inflammatory drugs. Harig et al. [1] showed the effectiveness of treatment with SCFA in a group of four adult patients in whom bloody discharge ceased in three. In a study on 13 adult patients by Guillemot et al. [18], only one was symptomatic with abdominal pain with occasional bleeding before starting therapy. The clinical effect of treatment is not mentioned.

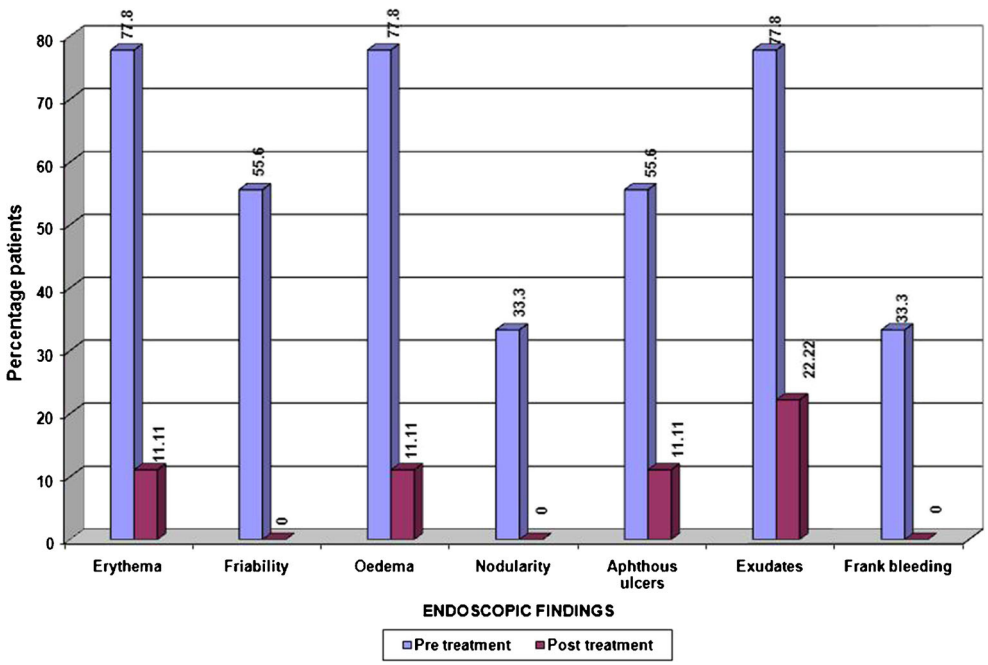

Fig. 8 Endoscopic response to short-chain fatty acids

Table 4 Comparing histopathologic findings in patients with diversion proctocolitis (DPC) (n=9) before treatment, with the patients showing resolution of DPC (n=7) after treatment with short-chain fatty acids and those having persistent DPC (n=2)

Histologic findings	DPC prior to SCFA		Resolved DPC after SCFA		Persistent DPC after SCFA	
	(n=9)	Percentage	(n=7)	Percentage	(n=2)	Percentage
Lymphoid follicular hyperplasia	9	100.00	0	0	2	100
Chronic inflammation	9	100.00	0	0	2	100
Acute inflammation	4	44.44	0	0	0	0
Paneth cell metaplasia	1	11.11	1	14.3	0	0
Goblet cell depletion	1	11.11	0	0	0	0
Aphthous ulcers	5	55.56	0	0	0	0
Eosinophils	2	22.22	0	0	0	0
Cryptitis	2	22.22	0	0	0	0
Crypt abscesses	0	0.00	0	0	0	0
Edema	8	88.89	0	0	2	100
Patchy involvement	2	22.22	0	0	0	0

Four stomas had closure prior to SCFA instillations

DPC diversion proctocolitis, *SCFA* short-chain fatty acids

Since eight out of the nine symptomatic patients in our study showed a complete clinical response, we conclude that treatment with SCFA is effective.

Kiely et al. [2] observed that all the five children with DPC showed a definite reduction in the endoscopic index after treatment with SCFA for 6 weeks. Of the four adult patients studied by Harig et al. [1], one patient was available only for 2 weeks of therapeutic trial. The other three showed a definitive improvement of endoscopic scores with remission therapy. However, it is mentioned that two patients needed maintenance therapy; one for 14 months and the other for 6 months. In a prospective double blind trial reported by Guillemot et al. [18], no improvement was detectable after SCFA irrigation as compared with isotonic sodium chloride. The possible factors as discussed by them were shorter duration of therapy (2 weeks), longer length of excluded bowel, variation in the etiology of diversion, and the total amount of SCFA infused (less than that used by Harig et al. [1]).

In the nine patients in our study, treated for DPC, there was highly significant response to treatment with SCFA in seven patients at 1 month (Fig. 8). We attribute this to proper dosing, compliance and adequate duration of therapy.

Only two series [1,18] have described findings of a repeat histopathological examination following treatment with SCFA.

Harig et al. [1] have reported their findings in the small series of four patients, where one patient had treatment only for 2 weeks and two had to be on maintenance therapy with SCFA for 14 and 6 months, respectively. They observed that the histopathological findings of superficial erosions, exudates, and edema of lamina propria disappeared after treatment with SCFA irrigation. When endoscopy demonstrated remission, the biopsies showed an intact mucosa with return of adequate mucin secretion and the absence of crypt abscesses and acute inflammation of lamina propria. Persistent changes included increase in the numbers of plasma cells and lymphocytes and prominence of lymphoid follicles.

Guillemot et al. [18] did not find any improvement in the histological score of biopsies done in 13 patients before and after treatment with SCFA for 14 days.

In our study, a repeat biopsy has been done in a total of nine children. Seven out of 9 (77.7 %) have shown a definite improvement in histopathological findings (this is similar to endoscopic improvement). We attribute this to a proper dose of SCFA and appropriate duration of therapy (4 weeks). A majority of the patients (77 %) showed complete resolution of all histopathological findings (except Paneth cell metaplasia in one patient) after 4 weeks treatment with SCFA (Table 4). In two patients who had persistent disease, lymphoid follicular hyperplasia, chronic inflammation, and edema were the only unremitting histopathological findings, rest other histopathological changes had responded to SCFA.

Haque et al. [19] and Keily et al. [2] in their study on DPC in children have observed that DPC is reversed by restoration of the intestinal continuity. Similarly, Harig et al. [1], Glotzer et al. [21], and Haas et al. [23] concluded in adults that the treatment of choice for DPC is restoration of the continuity of the intestine.

In the present study, two patients had persistent DPC. With the closure of stoma, all the symptoms, i.e. excessive mucous discharge per stoma/rectum, bleeding per stoma/rectum, and abdominal pain, showed complete resolution. Endoscopic and histopathological findings too resolved following restoration of intestinal continuity.

We found that DPC was common following stoma formation in children. There was a strong male preponderance. Clinical, endoscopic, and histopathological changes appeared in 2–9 months time following fecal diversion. Children were usually symptomatic. All patients had at least one positive endoscopic finding and histopathological examination confirmed the diagnosis. After treatment with SCFA, resolution of symptoms and histological changes occurred in the majority. All symptomatic patients had complete cure with restoration of intestinal continuity.

Conflict of interest KP, ST, HAl-B, and VPS declare that they have no conflict of interest.

Ethics statement The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights, and the authors followed the policy concerning Informed Consent as shown on Springer.com.

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