

Treatment of Rectal Cuff Inflammation (Cuffitis) in Patients with Ulcerative Colitis Following Restorative Proctocolectomy and Ileal Pouch-Anal Anastomosis

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BACKGROUND: Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the treatment of choice in the majority of patients with ulcerative colitis (UC) who require surgery. To ease the construction of the IPAA and improve functional outcome by minimizing sphincter related stretch injury, a stapling technique is being commonly used in the pouch-anal anastomosis. Despite its advantages, the procedure normally leaves a 1–2 cm of anal transitional zone or rectal cuff, which is susceptible to recurrence of residual UC or cuffitis. Cuffitis can cause symptoms mimicking pouchitis.

AIM: To conduct an open-labeled trial of topical mesalamine in patients with cuffitis.

METHODS: We treated 14 consecutive patients with cuffitis by giving mesalamine suppositories 500 mg b.i.d. (mean 3.2 months, range 1–9 months). The Cuffitis Activity Index (adapted from the Pouchitis Disease Activity Index) scores and improvement in symptoms of bloody bowel movements and arthralgias were measured as primary and secondary outcomes.

RESULTS: All patients had surgery for medically refractory UC. There were significant reductions in the total Cuffitis Activity Index scores after the therapy (11.93 ± 3.17 vs 6.21 ± 3.19 , $p < 0.001$). Symptom (3.24 ± 1.28 vs 1.79 ± 1.31), endoscopy (3.14 ± 1.29 vs 1.00 ± 1.52), and histology (4.93 ± 1.77 vs 3.57 ± 1.39) scores each were significantly reduced ($p < 0.05$). Ninety-two percent of patients with bloody bowel movements and 70% of patients with arthralgias improved after the therapy. No systemic or topical adverse effects were reported.

CONCLUSION: Topical mesalamine appears well tolerated and effective in treating patients with cuffitis, with improvement in symptom as well as endoscopic and histologic inflammation.

(Am J Gastroenterol 2004;99:1527–1531)

BACKGROUND

Restorative proctocolectomy (RP) with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for patients with medically refractory ulcerative colitis (UC), UC with dysplasia or cancer, or familial adenomatous polyposis (FAP) (1, 2). RP and IPAA have greatly improved health-related quality-of-life (QOL) scores in UC patients with medically refractory disease who require surgery (3, 4). The most common long-term inflammatory complication of IPAA is pouchitis (1–3). However, other inflammatory and noninflammatory complications also can develop, such as inflammation of the rectal cuff (cuffitis), Crohn's disease of the pouch, and irritable pouch syndrome.

When IPAA is performed, controversy exists about the optimal technique to be used for the pouch-anal anastomosis. Techniques vary between a hand-sewn IPAA with mucosectomy of the anal transition zone (ATZ) mucosa (or rectal cuff mucosa) or a stapled IPAA at the level of the anorectal ring without mucosectomy of the ATZ (5). To remove the rectal mucosa as completely as possible, a mucosectomy with hand-sewn anastomosis is necessary. This technique takes longer and has a relatively high risk for postoperative functional problems related to seepage and incontinence due to anal canal manipulation. In contrast, when the IPAA is stapled, the procedure is simpler and less likely to result in functional and septic complications (6). The preservation of ATZ is meant to optimize anal canal sensation, eliminate sphincter stretching, and preserve normal postoperative resting and squeeze pressures (5, 7, 8). However, to allow transanal insertion of the stapler head, it is usually necessary to leave

The work was partially presented at the 67th annual meeting of American College of Gastroenterology, Baltimore, MD, October 12, 2003.

a 1–2 cm strip of rectal cuff/ATZ mucosa that is at risk for developing symptomatic inflammation (cuffitis) or dysplasia (9–11). It is not uncommon to see some degree of inflammation of this rectal cuff/ATZ after the IPAA. However in a small percentage of patients, this can be symptomatic and further therapy may be needed (9). Patients with symptomatic cuffitis can present with similar symptoms to those with pouchitis and irritable pouch syndrome. However, in our previous study, bloody bowel movements were more commonly seen in patients with cuffitis. Endoscopic and histologic features of mucosal inflammation in cuffitis and pouchitis were similar, such as ulceration, erythema, and neutrophil infiltration (10). Our recent study demonstrated that patients with cuffitis, similar to patients with pouchitis or irritable pouch syndrome, have adversely affected QOL measured by poor scores in the Cleveland Global Quality of Life and the Irritable Bowel Syndrome Quality of Life scales (12). The aim of the study was to conduct an open-labeled trial of topical mesalamine in patients with cuffitis who underwent RP and IPAA.

METHODS

The Institutional Review Board of the Cleveland Clinic Foundation approved the study. From June 2002 to May 2003, a total of 123 symptomatic UC patients with IPAA were evaluated in our Center for Inflammatory Bowel Disease. All patients underwent clinical, endoscopic, and histologic evaluation. Forty-two patients (34.1%) had pouchitis diagnosed by Pouchitis Disease Activity Index (PDAI) scores (13). Nineteen patients (15.4%) had Crohn's disease of the pouch diagnosed by findings of inflammation and ulcers of the afferent limb, perianal disease, or granulomas on histology. Thirty-five patients (28.5%) had irritable pouch syndrome diagnosed by having abdominal pain and diarrhea in the absence of endoscopic and histologic inflammation of the afferent limb, pouch, and cuff. Seven patients (5.7%) had concomitant pouchitis and cuffitis on endoscopy and histology. Twenty patients (16.3%) had symptomatic cuffitis, who were all treated with mesalamine suppositories (Canasa®, Axan Pharma, Birmingham, AL) 500 mg b.i.d. The medicine was given as induction and maintenance therapy since cuffitis was considered to be a remnant of UC, which often requires long-term medical therapy. All the patients were scheduled for a follow-up visit and repeat pouch endoscopy with biopsy in 2 months (actual range from 1 to 9 months) after initiation of therapy. Fourteen patients (70%) returned for a clinic visit and underwent repeat pouch endoscopy within 9 months after initial visit while six patients (30%) were lost to follow-up. In this paper, we present our data on these 14 patients with UC, IPAA, and cuffitis where follow-up is complete. The mean duration of therapy was 3.19 ± 2.39 months with a range from 1 to 9 months. All the patients underwent pouch endoscopy and biopsy as a part of pre- and posttreatment evaluation and no interim clinic visit and pouch endoscopy evaluations were done. Segmental biopsies from the neo-terminal ileum,

pouch, and cuff were obtained. A gastrointestinal pathologist (A.E.B.), blinded to demographic, clinical, and endoscopic data, assessed and scored inflammation of biopsied specimens of the afferent limb, pouch, and cuff. Patients with pouchitis, irritable pouch syndrome, Crohn's disease of the pouch, and concurrent pouchitis and cuffitis, were excluded from the study. Cuffitis was diagnosed based on the presence of symptoms of diarrhea, urgency, abdominal pain, or bleeding, and endoscopic and histologic inflammation of the cuff and absent or minimal endoscopic inflammation of the pouch body and prepouch neo-terminal ileum.

The primary outcome measurements were total Cuffitis Activity Index and its subscores. The Cuffitis Activity Index was adapted from the PDAI instrument. The 18-point PDAI instrument was specifically designed for the diagnosis and quantification of disease activity of pouchitis (13). The PDAI consists of three subscores, symptoms (0–6 points), endoscopy (0–6 points), and histology (2–6 points). An 18-point Cuffitis Activity Index adapted components of the PDAI scoring system for the quantification of symptom and inflammation of the cuff. The Cuffitis Activity Index scores, specifically used for this study, consisted of symptom assessment (0–6 points), endoscopy (0–6 points), and histology (2–6 points) of the cuff, instead of pouch. Endoscopic and histologic inflammation of the afferent limb also was quantified in a similar fashion, with a range of 0–6 points and 2–6 points, respectively.

We documented separately the improvement in bloody bowel movements and extraintestinal manifestations (arthralgias) after therapy as a secondary outcome measure. Complete response was defined as the absence of blood in stools or in patients with arthralgias complete resolution of the symptom, and partial response was defined as decreased amount or frequency of blood in stools or improvement of arthralgia symptoms. Student *t*-test was used for the statistical analysis and *p* values < 0.05 were considered as statistically significant.

RESULTS

The demographic and clinical data of the 14 patients were listed in Table 1. All patients had total proctocolectomy with IPAA and ATZ preservation for UC refractory to medical therapy. A majority of patients (11/14, 78.6%) had their pouch surgery at our institution. The three who had their IPAA done elsewhere were evaluated at our institution for "refractory" pouchitis and were found to have cuffitis. Only one of the 14 patients had a family history of IBD in his first-degree relatives. Two patients regularly used nonsteroidal antiinflammatory drugs. All patients had diarrhea, abdominal pain, urgency, perianal pain, or bloody bowel movements. Extraintestinal manifestations were common, especially arthralgias. No granulomas, dysplasia, or neoplasia were found in the mucosal biopsies of the neo-terminal ileum, pouch, or cuff.

The endoscopic manifestations of cuffitis were edema, erythema, nodularity, granularity, mucous exudates,

Table 1. Demographic and Clinical Data

Age, yr (\pm SD)	37.07 \pm 12.06
Gender, male (%)	3 (21%)
Duration of UC, yr (\pm SD)	12.64 \pm 8.05
Duration of IPAA, yr (\pm SD)	5.14 \pm 3.99
Pancolitis, cases (%)	14 (100%)
J-pouch, cases (%)	14 (100%)
Refractory UC as an indication for IPAA, cases (%)	14 (100%)
Excessive alcohol use, cases (%)	0
Current tobacco use, cases (%)	0
Nonsteroidal antiinflammatory drug use, >weekly use, cases (%)	2 (14.29%)
Family history of inflammatory bowel disease, cases (%)	1 (7.14%)
Presenting symptoms, cases (%)	
–Diarrhea	14 (100%)
–Urgency	14 (100%)
–Abdominal pain	11 (78.57%)
–Perianal pain	13 (92.86%)
–Bloody bowel movement	13 (92.86%)
–Incontinence	10 (71.43%)
Extraintestinal manifestations, cases (%)	
–Arthralgias	10 (71.43%)
–Primary sclerosing cholangitis	1 (7.14%)
–History of pyoderma gangrenosum	1 (7.14%)

ulcerations, loss of vascular pattern, hemorrhage, and friability. A majority of patients with cuffitis (13/14) had a normal length of cuff, ranging from 1–2 cm. One nonobese patient had a 4 cm long cuff.

Topical mesalamine significantly reduced the total Cuffitis Activity Index score and subscores of symptom, endoscopy (Fig. 1), and histology (Fig. 2). There were no significant changes of endoscopic and histologic scores of the pouch or afferent limb after the therapy (Table 2).

Bleeding was one of the predominant symptoms in patients with cuffitis. The majority of patients responded to topical mesalamine therapy, completely or partially. In addition, arthralgia symptoms also improved with therapy (Table 3).

Two patients showed complete resolution of symptoms of both bleeding and arthralgias, three patients stopped bleeding completely, and one patient had complete resolution of arthralgias. Eleven patients had partial response to the therapy with either decreased frequency and amount of bleeding or improvement of their joint symptoms. Because of the small sample size, predictors for response to the therapy, such as duration of treatment, could be not analyzed in a meaningful statistical way. No systemic and topical adverse effects were reported.

DISCUSSION

Patients with cuffitis experienced symptoms of urgency, abdominal pain, diarrhea, and bleeding. Topical mesalamine was well tolerated and no systemic and topical adverse effects were reported. In this open-labeled, noncontrolled study, we found that topical mesalamine suppositories appear effective in treating patients with cuffitis, by reducing the total Cuffitis Activity Index scores, and symptom, endoscopy, and histology subscores. The majority of patients who had blood in stools and arthralgias improved symptoms.

A majority of patients (13/14, 92.9%) with cuffitis had symptoms of bloody bowel movements. In our previous study of 61 consecutive symptomatic patients with IPAA, 4 patients had cuffitis and all of them had bloody bowel movements, while the remaining 57 patients with pouchitis or irritable pouch syndrome did not have bleeding symptoms (10). We observed from the data in this and our previous studies that the bleeding symptoms are a highly specific findings in cuffitis. Our unpublished data show that bleeding also is rare in patients with Crohn's disease of the pouch.

Symptomatic cuffitis can occur in UC patients with IPAA. A few studies have addressed incidence and prevalence of cuffitis. In a study of 217 UC patients with stapled IPAA with and without symptoms, Lavery *et al.* (9) reported 48 patients (22%) had endoscopic and histologic inflammation of the rectal cuff (cuffitis), of which 32 patients had

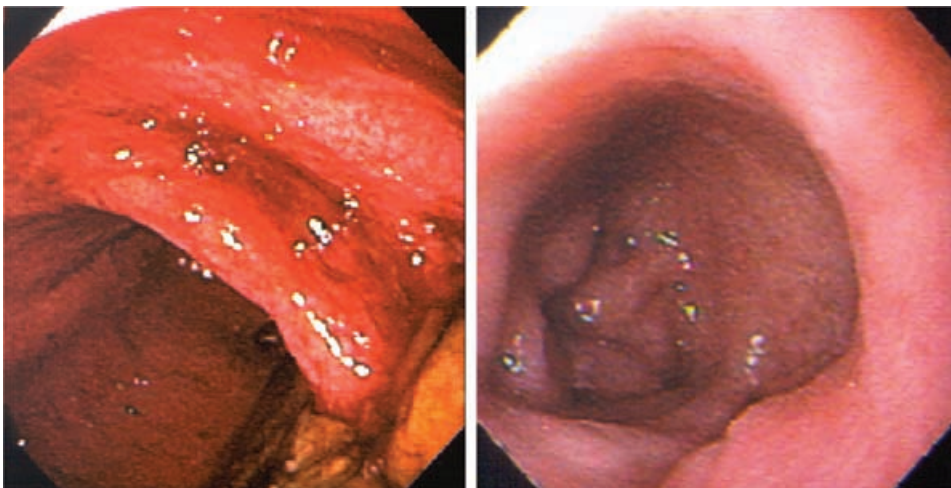


Figure 1. Endoscopy of cuff area before (left) and after (right) topical mesalamine therapy in a 41-yr-old patient with cuffitis.

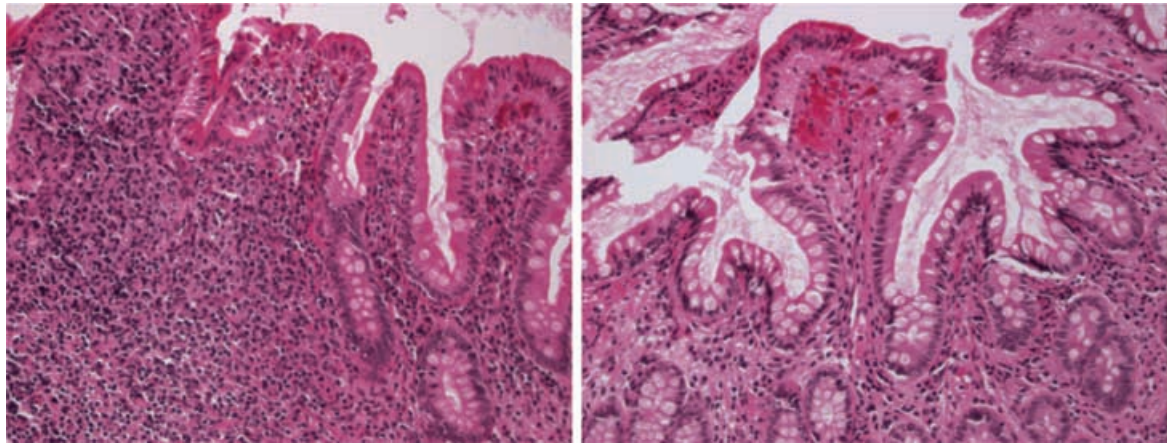


Figure 2. Histology of cuff area before (left) and after (right) topical mesalamine therapy in the patient.

symptoms. Only symptomatic patients with cuffitis require medical therapy. Of the 48 patients with endoscopic and histologic cuffitis, 18 patients had a normal pouch and 30 patients had concurrent pouchitis. In our previous study of 61 consecutive symptomatic patients with IPAA, 4 patients (7%) were diagnosed with cuffitis (10). Cuffitis is characterized by bleeding, urgency, perianal pain, and diarrhea, which mimic symptoms of pouchitis (10). Seven patients with concurrent pouchitis and cuffitis were excluded from the study. These seven patients were treated with 2 wk of ciprofloxacin 500 mg b.i.d., of whom six responded with improvement of symptoms. One patient who failed to respond to therapy was then treated with mesalamine suppositories and his symptoms improved.

What is the best strategy to treat concurrent pouchitis and cuffitis? Should we treat pouchitis first with antibiotics and use topical mesalamine as a salvage therapy? Should we treat cuffitis first with topical mesalamine and use antibiotic therapy as a salvage regimen? Should we use a combined therapy of antibiotics and topical mesalamine? In the authors' opinion, if a patient with concurrent pouchitis and cuffitis has bleeding and perianal pain as predominant symptoms and had cuff inflammation on endoscopy, a trial of topical mesalamine first would be beneficial.

Table 2. Response to Topical Mesalamine in the 14 Patients with Cuffitis—Primary Outcome Measurement

	Pretreatment	Posttreatment	<i>p</i>
Total Cuffitis Activity Index scores (± SD)*	11.93 ± 3.17	6.21 ± 3.19	<0.001
Symptom scores (± SD)	3.24 ± 1.28	1.79 ± 1.31	<0.001
Endoscopy scores (± SD)			
–Cuff	3.14 ± 1.29	1.00 ± 1.52	<0.001
–Pouch	0.86 ± 0.86	0.29 ± 0.61	0.054
–Afferent limb	0.14 ± 0.36	0	0.15
Histology scores (± SD)			
–Cuff	4.93 ± 1.77	3.57 ± 1.39	0.033
–Pouch	3.43 ± 1.74	2.57 ± 0.65	0.096
–Afferent limb	2.29 ± 0.61	2.14 ± 0.36	0.46

*Total Cuffitis Activity Index scores were calculated based on the sum of symptom, endoscopy, and histology (of cuff) scores.

The data on management of cuffitis are scant (9). Cuffitis can be considered as a remnant piece of UC-affected mucosa. Topical or oral mesalamine has been used as a first-line therapy for mild to moderate UC. We observed that similar to patients with UC, topical mesalamine would be effective in cuffitis. Our anecdotal experience suggested that antibiotics, which were effective in the treatment of patients with pouchitis, were not effective in cuffitis.

The decision on hand-sewn IPAA with mucosectomy versus stapled IPAA with preservation of ATZ are based on several factors, such as patients' age and preference, indications for IPAA (refractory disease vs dysplasia), and risk for cuffitis and dysplasia (9, 11, 14–18). Our current study showed that cuffitis responded favorably to topical mesalamine therapy. Dysplasia in the anal transition zone or cuff is rare (6, 19), although cuffitis may theoretically predispose to the development of dysplasia. A recent study has shown that 5-aminosalicylate therapy may reduce the risk for dysplasia in patients with UC (20). We speculate that by effective therapy with topical mesalamine, we might be able to reduce the risk of dysplasia in the rectal cuff. Nonetheless, mucosectomy with hand-sewn IPAA has been recommended for UC patients with dysplasia or cancer (6, 11).

None of our patients needed surgical treatment for their cuffitis. We have a small case series with medically refractory cuffitis or with dysplasia, which required surgical intervention. Some of these patients had an excessively long cuff. Surgical options included transanal mucosectomy with excision of the inflamed or dysplasia-retained anorectal mucosa followed by pouch advancement and a neo-IPAA or pouch resection (11, 18, 21).

Table 3. Response to Topical Mesalamine in Patients with Cuffitis—Secondary Outcome Measurement

	Number of Cases	Complete Response	Partial Response
Bleeding	13	5 (38.46%)	7 (53.85%)
Arthralgias	10	3 (30%)	4 (40%)

The patients with cuffitis in this study had stapled IPAA with the preservation of rectal cuff/ATZ mucosa. Whether cuffitis can occur in patients with IPAA with mucosectomy is not known. Rectal mucosa islands still can exist even with mucosectomy (22). The incidence of cuffitis in patients with IPAA and mucosectomy needs to be studied. Although this is an uncontrolled study involving a small number of patients, it raises several important issues that warrant further investigation. What are the risk factors for patients to develop cuffitis? Does cuffitis disease activity correlate with extraintestinal manifestations, especially arthralgias as in UC? What is the natural course of cuffitis? How long should patients with cuffitis be treated? Is maintenance therapy needed? Will topical corticosteroids be useful as well?

In summary, topical mesalamine appears effective and safe to control symptoms and improve endoscopic and histologic scores of cuffitis. A diagnostic instrument specifically designed for cuffitis needs to be validated. A randomized clinical trial comparing topical mesalamine with topical corticosteroid or placebo is warranted.

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Received December 30, 2003; accepted February 27, 2004.

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