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A Randomized Clinical Trial of Ciprofloxacin and Metronidazole to Treat Acute Pouchitis

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Summary: Metronidazole is effective for the treatment of acute pouchitis after ileal pouch–anal anastomosis, but it has not been directly compared with other antibiotics. This randomized clinical trial was designed to compare the effectiveness and side effects of ciprofloxacin and metronidazole for treating acute pouchitis. Acute pouchitis was defined as a score of 7 or higher on the 18-point Pouchitis Disease Activity Index (PDAI) and symptom duration of 4 weeks or less. Sixteen patients were randomized to a 2-week course of ciprofloxacin 1,000 mg/d (n = 7) or metronidazole 20 mg/kg/d (n = 9). Clinical symptoms, endoscopic findings, and histologic features were assessed before and after therapy. Both ciprofloxacin and metronidazole produced a significant reduction in the total PDAI score as well as in the symptom, endoscopy, and histology subscores. Ciprofloxacin lowered the PDAI score from 10.1 ± 2.3 to 3.3 ± 1.7 (p = 0.0001), whereas metronidazole reduced the PDAI score from 9.7 ± 2.3 to 5.8 ± 1.7 (p = 0.0002). There was a significantly greater reduction in the ciprofloxacin group than in the metronidazole group in terms of the total PDAI (6.9 ± 1.2 versus 3.8 ± 1.7; p = 0.002), symptom score (2.4 ± 0.9 versus 1.3 ± 0.9; p = 0.03), and endoscopic score (3.6 ± 1.3 versus 1.9 ± 1.5; p = 0.03). None of patients in the ciprofloxacin group experienced adverse effects, whereas three patients in the metronidazole group (33%) developed vomiting, dysgeusia, or transient peripheral neuropathy. Both ciprofloxacin and metronidazole are effective in treating acute pouchitis with significant reduction of the PDAI scores. Ciprofloxacin produces a greater reduction in the PDAI and a greater improvement in symptom and endoscopy scores, and is better tolerated than metronidazole. Ciprofloxacin should be considered as one of the first-line therapies for acute pouchitis. **Key Words:** Pouchitis—Antibiotics—Therapy.

INTRODUCTION

Acute pouchitis is the most common complication of ileal pouch–anal anastomosis (IPAA) after total proctocolectomy (TPC) for ulcerative colitis (UC) (1–3). Pouchitis is generally considered acute if symptom duration is 4 weeks or less and chronic if symptom duration is greater than 4 weeks (4). Reported incidence rates for pouchitis vary with the duration of follow-up, diagnostic criteria, and the intensity of evaluation. The estimated 10-year cumulative incidence ranges between 24% (3) and 46% (5). In contrast to the high rate of pouchitis seen in patients with underlying UC, the cumulative incidence of pouchitis in patients with underlying familial adenomatous polyposis (FAP) ranges from 0% to 10% (6–10), suggesting that some aspect of the underlying disease predisposes to this complication.

The most frequent symptoms of pouchitis include increased stool frequency, fecal urgency, and abdominal cramping. Occasionally patients also have fever, pelvic discomfort, and extraintestinal manifestations. These symptoms suggest a diagnosis of pouchitis, but ideally, this diagnosis should be confirmed by pouch endoscopy with biopsy (1). To standardize diagnostic criteria, an 18-point Pouchitis Disease Activity Index (PDAI) has been developed (11). The PDAI calculates an overall score from three components of clinical symptoms, endoscopic findings, and histologic changes. Pouchitis is defined by a total of PDAI score of 7 or greater.

Most patients with acute pouchitis respond quickly to

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antibiotic therapy. Metronidazole is the only antibiotic to have been studied in a placebo-controlled, randomized clinical trial. Madden et al. (12) performed a crossover trial in which 11 patients with pouchitis each received a 1-week course of oral metronidazole 1,200 mg/d and a 1-week course of placebo. The overall response rate (defined as stool frequency of three or fewer per day) was 73% (8/11) for metronidazole versus 9% (1/11) for placebo ($p < 0.05$). Based on such results, and the low cost of metronidazole ($2.00 for a 2-week course), this agent has generally been considered as first-line therapy for pouchitis (1–3,10).

However, a drawback to metronidazole is that some patients experience side effects such as nausea, vomiting, metallic taste, dysgeusia, peripheral neuropathy, or seizure. Also, metronidazole is contraindicated in patients who use alcohol because of a disulfiram-like reaction (1,13). If patients fail to respond to or cannot tolerate metronidazole, second-line therapy has generally consisted of other broad-spectrum antibiotics, such as ciprofloxacin, tetracycline, clarithromycin, amoxicillin/clavulanic acid, doxycycline, or rifaximin (4,14). These antibiotics have never been directly compared with metronidazole in the treatment of pouchitis. In our practice, ciprofloxacin is the most commonly used second-line therapy. In noncontrolled trials, ciprofloxacin has been shown to be efficacious in treating acute episodes of pouchitis (15), and also in treating chronic pouchitis when combined with rifaximin (16). It also has a favorable side effect profile.

The purpose of this randomized clinical trial was to compare the effectiveness and tolerability of ciprofloxacin and metronidazole in the treatment of acute pouchitis.

PATIENTS AND METHODS

This study was approved by the Cleveland Clinic Foundation Institutional Review Board, and written informed consent was obtained from all patients. Subjects were recruited by advertising in a Cleveland Clinic Foundation newsletter for patients who had undergone TPC and IPAA.

Inclusion criteria were 1) age more than 18 years, 2) history of UC with IPAA, 3) an overall PDAI score of 7 or higher at study entry, and 4) acute pouchitis defined as symptoms lasting 4 weeks or less (4). Exclusion criteria were 1) current use (within 2 weeks of study entry) of antibiotics, corticosteroids, or 5-aminosalicylic acid products; 2) IPAA for FAP; 3) Crohn's disease; 4) history of adverse reactions to ciprofloxacin or metronidazole; 5) chronic pouchitis defined as symptoms lasting 4 weeks or longer; and 6) pregnancy.

The 18-point PDAI was used (11). The PDAI measures components of symptoms, endoscopic findings, and histologic findings with a maximum score of 6 points for each component. Based on the criteria proposed by Sandborn et al. (11), patients with a total PDAI score of 7 or higher were classified as having pouchitis. A total of 25 patients with typical symptoms of acute pouchitis were interviewed, examined, and underwent pouch endoscopy. Six patients with PDAI symptom scores of 3 or higher had no abnormal findings or only minimal inflammation on pouch endoscopy and histology. The total PDAI scores for these six patients were less than 7, and thus they were excluded. Three patients with acute pouchitis having had adverse effects to metronidazole in the past were excluded from the study. The remaining 16 patients were randomly assigned to one of two arms: ciprofloxacin 1,000 mg/d for 2 weeks ($n = 7$) or metronidazole 20 mg/kg/d for 2 weeks ($n = 9$). The treatment was not blinded.

Immediately after completion of the 2-week course of antibiotics, patients were reassessed with repeat history, physical examination, and pouch endoscopy with biopsies. Resolution of pouchitis was defined as a posttreatment PDAI score of less than 7. Adverse reactions from the antibiotics were recorded.

Pouch endoscopy was performed using a GIF-130 videoesophagoduodenoscope (Olympus America, Melville, NY, U.S.A.). Endoscopic scores (ranging from 0 to 6 points) were recorded based on a consensus between two endoscopists. Neither endoscopist was blinded to the treatment assignments. A gastrointestinal pathologist who was blinded to the patients' assignments, clinical presentations, endoscopic findings, and treatment assignment assessed the pouch biopsies for grading of acute inflammation (ranging from 2 to 6 points).

Two-tailed Student *t* test and Fisher exact test were used for statistical analysis. Descriptive statistics were presented as mean ± 1 SD; $p < 0.05$ was considered statistically significant.

RESULTS

Nine men and seven women with a mean age of 41.4 ± 13.3 years were entered into the study. The mean time since IPAA was 92.3 ± 58.1 months. The duration of UC before TPC was 55.1 ± 32.5 months, and all the patients had pancolitis before TPC. The two groups were similar in terms of age, sex, time since IPAA, duration and extent of UC before TPC, indication for TPC, extraintestinal manifestations, history of smoking, and family history of inflammatory bowel disease (Table 1).

Three patients in the metronidazole group and 1 pa-

TABLE 1. *Demographic characteristics*

	Ciprofloxacin (N = 7)	Metronidazole (N = 9)	p value
Age (y)	43.6 ± 16.9	39.7 ± 10.5	0.59
Males	4 (57%)	5 (56%)	>0.99
Time since IPAA (mo)	89.1 ± 57.9	96.0 ± 52.3	0.81
Duration of UC before TPC (mo)	53.1 ± 61.9	58.7 ± 56.0	0.85
Pancolitis	7 (100%)	9 (100%)	>0.99
Extraintestinal manifestations of IBD	1 (14%)	1 (11%)	>0.99
Indication for TPC			
Steroid-dependent colitis	3 (43%)	2 (22%)	0.60
Steroid-refractory colitis	4 (57%)	6 (67%)	>0.99
Dysplasia	0	1 (11%)	0.99
Current smokers	1 (14%)	2 (22%)	>0.99
Family history of IBD	1 (14%)	1 (11%)	>0.99

IPAA, ileal pouch–anal anastomosis; UC, ulcerative colitis; TPC, total proctocolectomy; IBD, inflammatory bowel disease.

tient in the ciprofloxacin group were diagnosed with their first episode of pouchitis, documented with PDAI scores, when enrolled into the study. The remaining 13 patients had been diagnosed with pouchitis in the past based on symptoms alone, but had not previously undergone endoscopic and histologic evaluation to confirm the diagnosis of pouchitis.

The mean PDAI scores of the entire study group before therapy were symptom subscores of 2.6 ± 1.1, endoscopy subscores of 4.2 ± 1.5, histology subscores of 3.0 ± 0.8, and total PDAI scores of 9.9 ± 2.2. There were no statistically significant differences in the pretreatment PDAI scores between the two groups.

Both ciprofloxacin and metronidazole significantly lowered total, symptom, endoscopic, and histologic PDAI scores (Table 2). However, when compared with the metronidazole group, patients in the ciprofloxacin group experienced significantly larger reductions in mean total PDAI scores (6.9 versus 3.8; $p = 0.002$), symptom subscores (2.4 versus 1.3; $p = 0.03$), and endoscopy subscores (3.6 versus 1.9; $p = 0.03$) (Table 3). The difference in reduction of pre- to posttreatment total PDAI scores between the two groups was 3.2. The ciprofloxacin group also experienced larger reductions in histology subscores, but this did not reach statistical significance.

All seven patients (100%) in the ciprofloxacin group achieved resolution of pouchitis as defined by a posttreatment PDAI score less than 7. In contrast, six of the nine patients (67%) in the metronidazole group achieved resolution of pouchitis. The other three patients (33%) in the metronidazole group had posttreatment PDAI scores ranging from 7 to 9. The difference in rates of resolution of pouchitis between the two groups did not reach statistical significance ($p = 0.21$).

None of patients in the ciprofloxacin group experienced adverse effects, whereas three patients in the metronidazole group (33%) developed nausea, vomiting, dysgeusia, or transient paresthesias of fingers and lips (peripheral neuropathy). These side effects were not severe enough to prevent the three patients from completing the course of antibiotics.

DISCUSSION

The cause of pouchitis still is not clear, but is likely to be multifactorial. Most patients with acute pouchitis respond promptly to antibiotic therapy, but 5% to 10% develop refractory or rapidly relapsing symptoms that require long-term therapy (17,18). Of patients with acute pouchitis, 39% have a single acute episode that responds

TABLE 2. *PDAI scores before and after antibiotic therapy*

	Ciprofloxacin (N = 7)				Metronidazole (N = 9)			
	Pre-Rx	Post-Rx	Difference (95% CI)	p value	Pre-Rx	Post-Rx	Difference (95% CI)	p value
Total PDAI score	10.1 ± 2.3	3.3 ± 1.8	6.9 (5.7–8.0)	0.0001	9.7 ± 2.3	5.8 ± 1.7	3.8 (2.5–5.2)	0.0002
Symptom score	2.7 ± 1.1	0.4 ± 0.8	2.4 (1.4–3.2)	0.0007	2.6 ± 1.2	1.2 ± 0.7	1.3 (0.7–2.0)	0.0017
Endoscopy score	4.3 ± 1.4	0.6 ± 0.9	3.6 (2.4–4.7)	0.0003	4.1 ± 1.6	2.2 ± 1.7	1.9 (0.7–3.1)	0.0035
Histology score	3.1 ± 1.2	2.3 ± 0.5	0.9 (0.02–1.7)	0.045	2.9 ± 0.3	2.3 ± 0.5	0.6 (0.2–1.0)	0.01

PDAI, pouchitis disease activity index; CI, confidence interval.

TABLE 3. *Comparison of reduction of the PDAI scores after antibiotic therapy between ciprofloxacin and metronidazole groups*

	Post Rx mean reduction			
	Ciprofloxacin (N = 7)	Metronidazole (N = 9)	Difference (95% CI)	p value
Reduction in total PDAI score	6.9 ± 1.2	3.8 ± 1.7	3.2 (1.3–4.6)	0.002
Reduction in symptom score	2.4 ± 0.9	1.3 ± 0.9	1.1 (0.3–2.1)	0.03
Reduction in endoscopy score	3.6 ± 1.3	1.9 ± 1.5	1.8 (0.2–3.2)	0.03
Reduction in histology score	0.9 ± 0.9	0.6 ± 0.5	0.4 (–0.4–1.1)	0.41

PDAI, pouchitis disease activity index; CI, confidence interval.

to treatment with antibiotics, whereas the remaining 61% of patients go on to develop at least one recurrence (7).

The response of pouchitis to antibiotics suggests an infectious cause. Interestingly, probiotics also appear to be effective in preventing flare-ups of acute relapsing pouchitis. A recent trial evaluated the use of a probiotic named VSL#3 for the maintenance of acute relapsing pouchitis after remission was induced using ciprofloxacin and rifaximin (19). Only 3 of 20 patients (15%) in the probiotic group relapsed within the 9-month follow-up, whereas all 20 patients (100%) in the placebo group developed a relapse ($p < 0.05$) (19,20). Proposed mechanisms of probiotics as maintenance therapy for pouchitis include 1) suppression of resident pathogenic bacteria, 2) stimulation of mucin glycoprotein production by intestinal epithelial cells, 3) prevention of adhesion of pathogenic strains to epithelial cells, and 4) induction of host immune responses (14).

The results of our randomized clinical trial demonstrate that both ciprofloxacin and metronidazole were efficacious in treating acute pouchitis by significantly reducing the total PDAI scores, and by leading to a significant improvement of clinical symptoms, and endoscopic and histologic scores. Our results also indicate that ciprofloxacin led to a greater degree of reduction in the PDAI scores than metronidazole. When we compared the changes for each component of the PDAI between the two treatment groups, we found significantly greater reductions in the symptom and endoscopy subscores and a trend towards reduction in the histology subscores for the ciprofloxacin-treated patients. Furthermore, all seven patients (100%) in the ciprofloxacin group achieved a posttreatment PDAI score less than 7 compared with six of nine (66.7%) patients in the metronidazole group. Ciprofloxacin also was better tolerated than metronidazole, with no adverse effects in patients receiving ciprofloxacin.

Our randomized study is valuable because the treatment of pouchitis has been largely empiric. Although our study was unblinded, we used the PDAI scoring system as an objective measurement of outcome, which should minimize potential bias. Uncontrolled trials have reported benefits for many treatments including amoxicillin/clavulanic acid, erythromycin, tetracycline, mesalamine enemas, corticosteroid and budesonide enemas, oral sulfasalazine and mesalamine, oral corticosteroids, allopurinol, azathioprine, and bismuth subsalicylate (4). However, there is a paucity of randomized clinical trials for pouchitis. In one randomized clinical trial, bismuth carbomer enemas were not better than placebo (21). Another randomized clinical trial evaluated 19 patients with chronic pouchitis and found that relapse rates were 67% (6/9) in patients receiving glutamine suppositories compared with 40% (4/10) in those receiving butyrate suppositories ($p > 0.05$) (22).

Broad-spectrum antibiotics are the mainstay of treatment of pouchitis. Metronidazole was used in this study because it has been considered the first-line therapy for treating acute pouchitis. Metronidazole is inexpensive, with a cost of $2 for a 2-week course, but it is not well tolerated in some patients. Reported serious adverse reactions include seizures and peripheral neuropathy. Persistent peripheral neuropathy has been reported in some patients with prolonged use of the medicine. In a prospective study of 17 patients receiving metronidazole (1,200 mg/d) for 2 to 4 weeks for a variety of infectious diseases, 4 patients had diminished deep tendon ankle jerks, and 2 patients had paresthesias (23). The most common adverse reactions to metronidazole are gastrointestinal in origin and include nausea, vomiting, anorexia, and diarrhea. Three of the nine patients (33%) taking metronidazole in our study reported adverse effects of the gastrointestinal or neurologic systems, although all nine patients in the metronidazole group were able to complete the 2-week course of treatment. We used a relatively high dose of metronidazole (20 mg/kg/d) in this study, which might have affected the rate of adverse effects. The optimal dosage and duration of treatment with antibiotics for pouchitis has not been established. We chose a high dose of metronidazole based on they study by Madden et al. (12), in which a dose of 1,200 mg/d of metronidazole was used, which

represents 17 mg/kg/d for a 70 kg person. We empirically chose a 2-week course based on our clinical practice and previously published controlled trials, in which courses of antibiotics ranging from 7 to 28 days (12,19) were used. It is possible that a lower dose of metronidazole or a shorter course of treatment may have led to fewer adverse effects, but response rates also may have been lower.

The greater efficacy of ciprofloxacin as compared with metronidazole that we found in this study could be caused by several factors, including different spectra of antibacterial activity. Ciprofloxacin is well tolerated (15,16), although it is more expensive, with a cost of $127 for a 2-week course. The low side effect profile might have led to better adherence. No adverse reactions were reported in a study using the combination of rifaximin and ciprofloxacin to treat 18 patients with chronic pouchitis (16). In a randomized, placebo-controlled trial of ciprofloxacin (1,000 mg/d for 3 months) in 30 patients with reactive arthritis, the prevalence of side effects for ciprofloxacin was not different from placebo (24). The six patients treated with ciprofloxacin in our study experienced no side effects, including the unique but rare side effect of tendon ruptures.

In summary, our study demonstrates that a 2-week course of either ciprofloxacin or metronidazole is effective for the treatment of acute pouchitis. Ciprofloxacin was associated with a larger reduction in the PDAI score, with no adverse effects. Metronidazole also was effective but produced a smaller reduction in the PDAI score, and three patients did not achieve a posttreatment PDAI score less than 7. Adverse effects occurred in 33% of metronidazole-treated patients. We suggest that the improved clinical outcome and better safety profile with ciprofloxacin may justify higher costs. Therefore, ciprofloxacin should be considered as one of the first-line therapies for acute pouchitis.

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