

Frequency, Clinical Features and Factors Associated with Pouchitis after Proctocolectomy with Ileo-Pouch-Anal Anastomosis in Patients with Ulcerative Colitis: A Latin-American Country Retrospective-Cohort Study

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Key Words

Inflammatory bowel disease · Ulcerative colitis · ileo-pouch-anal anastomosis · Pouchitis

Abstract

Background: Pouchitis is the most common complication of proctocolectomy with ileo-pouch-anal anastomosis (IPAA) for ulcerative colitis (UC). No previous study in Mexico has evaluated this issue; our aim was to evaluate its frequency, clinical characteristics and factors associated with its presence in Mexican patients with UC and IPAA. **Methods:** Retrospective-cohort study including 70 patients with histopathological diagnosis of UC and IPAA between 1983 and 2014 from inflammatory bowel disease clinic of a tertiary care center. The statistical analysis used descriptive statistics, chi-square and Fisher's exact test for categorical variables and Student's t test for numeric variables. Univariate analysis was performed to identify the factors associated. **Results:** Patients presenting with pouchitis accounted for 48.6%. From the 34 cases, 12 (35.3%) had inactive pouchitis; 7 (20.6%) active acute pouchitis; 15 (44.1%) chronic active pouchitis. On average, pouchitis occurred 5.37 years after IPPA. Factors probably associated with its occurrence were the presence of autoimmune concomitant diseases (ACDs; $p = 0.06$, OR

4.40, 95% CI 0.84–22.9) and extra-intestinal manifestations (EIMs; $p = 0.05$, OR 2.53, 95% CI 0.96–6.64), which was also probably associated with chronic active pouchitis ($p = 0.06$, OR 0.31, 95% CI 0.07–1.31). **Conclusions:** The frequency of pouchitis is high in Mexican UC patients after IPAA. ACDs and EIMs were probably associated with its development.

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Introduction

Along the clinical course of ulcerative colitis (UC), which is one of the 2 forms of inflammatory bowel disease (IBD), 15% of the patients will present a severe clinical course and 20–30% will require surgical treatment [1]. Even patients hospitalized for the first time due to severe UC have a 20% risk of requiring colectomy [2]. With the aim of relieving the symptoms, minimizing cancer risk, achieving good functional results and improving quality of life [3], the procedure that is most commonly chosen is ileo-pouch-anal anastomosis (IPAA) [4], which is pursued when medical treatment has not been useful or when complications like toxic megacolon, perforation, uncontrollable colorectal bleeding, dysplasia or colon carcinoma appear [5–7]. This type of surgical procedure is sought

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to restore intestinal continuity, preserve sphincter function and prevent incontinence [2], besides the fact that it offers excellent long-term functional results, removes all the affected mucosa and entails a lower risk of developing cancer [8]. Even though it leads to remission of disease in its intestinal expression, it also carries on several complications that drastically impact the patients' quality of life and bowel habits, especially at the beginning of the adaptation process. Some of the complications that may arise from this procedure are the anastomosis failure, pelvic sepsis [8, 9], a 3 times higher infertility risk in young women [8, 10], pelvic nerve damage, portal vein thrombosis [8, 11], presence of fistulae, abscess, inflammation of the afferent limb, Crohn's disease of the pouch [12–14], the infrequent and auto-limited anal-transition zone dysplasia [7, 15] and finally, one that has shown to have a frequency that varies from 12 to more than 50% [15–18], and thus the most common of all, pouchitis. This term refers to the inflammation of the ileal reservoir that appears *de novo*, whose multifactorial etiology, although still poorly understood, relies predominantly between immunologic and bacterial interactions [19], besides the fact that an autoimmune mechanism may be implicated in its pathogenesis, as it is frequently related to the presence of extra-intestinal manifestations (EIMs) and other diseases of immune origin [20]. In the same context, a common pathway has also been suggested to exist between pouchitis and primary sclerosing cholangitis (PSC) [21]. There are several studies that evaluate the frequency of pouchitis appearance among patients with UC that have been through IPAA around the world, and the vast majority of them confirms its high frequency, found to be of 18.8% in a meta-analysis that included 43 observational studies [22]. Independently, in the United States, approximately 50% of the patients experience an acute episode during the first 5 years after IPAA [23]. In other regions like Belgium, pouchitis is reported in 46% of the patients [24]. In the Irish population, on the other hand, pouchitis appears in 48.5% of the cases [25], and Scotland data report pouchitis in 34% of the patients [26]. Talking about Latin American countries, there are Brazilian data that report pouchitis in 21.7% of the patients [27] and a study of the Puerto Rico experience that reports pouchitis in 44% of them [28]. Conversely, all these data contrast with what happens in China and Japan. China reports that pouchitis appears only in 5.3%, although the incidence of UC has increased progressively in this country [29]. Japan, on the other hand, reports pouchitis in 10% of the patients [30]. Although an explanation for this fact remains unknown, the generally high frequency of pou-

chitis is clear. In this respect, several risk factors have been proposed for its occurrence, such as the presence of EIMs, younger age at proctocolectomy [24], being a non-smoker, having PSC [20], as well as the expression of p-ANCA and anti-CBir1 [31]. Turning to the clinical presentation of pouchitis, as symptoms may not be quite specific and they do not correlate with endoscopic and histologic findings, diagnosis must be made based on those 3 and on the consideration that these are independent factors, in order to avoid unnecessary antibiotic treatment [32]. According to the second-European evidence-based consensus, the most frequent clinical symptoms of pouchitis include increased number of liquid stools, urgency, abdominal cramping and pelvic discomfort; although fever and bleeding may appear, they are considered to be rare [33]. Even when there is a wide variety of data describing the incidence of pouchitis, and its clinical characteristics are well known, there are a very few studies about the Latin American experience and still none that describes its frequency or clinical characteristics in Mexican patients, despite the fact that we already know that UC frequency has increased 2.6-fold in this population [34]. For this reason, IBD characteristics vary widely and depend on multiple factors, including the ethnic background and geographic location [35]. The aim of this study was to describe the frequency, clinical characteristics and factors associated with pouchitis in Mexican patients with UC and IPAA.

Methods

This is a retrospective-cohort study from the IBD clinic of a tertiary care center (National Institute of Medical Sciences and Nutrition 'Salvador Zubirán'), where 137 patients with UC diagnosis and history of IPAA in the period between 1983 and 2014 were considered and 67 patients were excluded. The following characteristics were considered for the analysis: gender, history of smoking habit, family history of IBD and family history of other immune-mediated diseases, such as rheumatoid arthritis, type 1 diabetes mellitus, ankylosing spondylitis (AS), Graves disease, autoimmune hepatitis, systemic lupus erythematosus, immune thrombocytopenic purpura, Sjögren's syndrome, Hashimoto's thyroiditis, polyarteritis nodosa and vitiligo. Other variables were age at diagnosis of UC, years of UC evolution, extent of disease according to Montreal classification (E1: proctitis, E2: left or distal colitis, E3: extense colitis or pancolitis), frequency of relapses (appearance of symptoms requiring attendance to the urgency department and hospitalization) of disease before IPAA (infrequent when occurred less than once in a year, frequent when they happened twice or more and continuous when remission was never achieved), the presence of EIMs such as arthritis, arthralgia, AS, sacroiliitis, PSC, pyoderma gangrenosum, erythema nodosum or uveitis; medical treatment before IPAA and the reason for no response (steroid dependence, steroid resistance, resistance to im-

munomodulators, intolerance to immunomodulators or lack of optimization); time between diagnosis and IPAA (at the moment of diagnosis, during the first 5 years, 5–10 years after diagnosis, more than 10 years after diagnosis); clinical symptoms such as increased stool frequency, liquid stool, abdominal cramping, urgency, tenesm, discomfort, fever or EIM exacerbation; endoscopic and pathological findings were considered for the diagnosis of pouchitis at least 3 months after IPAA; pouchitis was classified as acute (symptoms for less than 4 weeks), chronic (symptoms for more than 4 weeks) or in remission (without symptoms after medical treatment) if it was idiopathic or secondary; the frequency of pouchitis relapses (infrequent when occurred less than once a year, frequent when they were 2 or 3 per year and continuous when they were more than 3); response to antibiotic treatment (responsive, dependent or refractory); the number of years between IPAA and the first episode of pouchitis; complications of pouchitis (none, abscesses, fistulae, stenosis of the pouch-anal anastomosis and adenocarcinoma of the pouch); antibiotic used for the treatment of the acute episode (metronidazole, ciprofloxacin, other) or chronic pouchitis (2 antibiotics, budesonide, infliximab); and reason for surgical treatment (perforation, toxic megacolon, massive bleeding, lack of response to medical treatment, dysplasia and cancer). This research was approved by the local ethics committee.

Statistical Analysis

Demographic and clinical characteristics are presented as mean, SD, median, and range. On the basis of advice from a statistician, the Kolmogorov–Smirnov test was used in order to check the normal distribution of the population. Chi-square was used to compare categorical variables. The unpaired t test was used to compare differences in the means of continuous variables. OR and 95% CI assessing the risk of pouchitis were estimated by univariate analyses using multiple logistic regression analysis, adjusted for confounding variables. A p value ≤ 0.05 was considered statistically significant and Bonferroni correction for p value was applied for multiple-comparison calculated as α/n . All statistical analyses were conducted using the statistics program SPSS/PC version 17.0.

Results

A total of 70 patients with a history of proctocolectomy and IPAA were evaluated: 40 (57.1%) men and 30 (42.9%) women, divided into 2 groups: (1) 34 patients (48.6%) with pouchitis (cases) and (2) 36 (51.4%) without pouchitis (controls). The detailed demographic and clinical characteristics are shown in tables 1 and 2, respectively.

Patients with Pouchitis

From the 34 cases, 12 (35.3%) had pouchitis in remission, 7 (20.6%) had active acute pouchitis and 15 (44.1%) chronic active pouchitis. Figure 1 shows the distribution according to different types of pouchitis. The development of pouchitis was present at 5.37 years after the IPPA. The first episode of pouchitis was most frequent in the first year

Table 1. Demographic variables of patients with IPAA and UC

Variables	Cases (n = 34) (48.6)	Controls (n = 36) (51.4)
Gender		
Male	21 (61.8)	19 (52.8)
Female	13 (38.2)	17 (47.2)
Family history of autoimmune diseases	6 (17.6)	6 (16.7)
Smoking habit	11 (32.4)	14 (38.9)
ACDs	7 (20.6)	2 (5.6)
Appendectomy	3 (8.8)	6 (16.7)
Tonsillectomy	4 (11.8)	4 (11.1)
History of oral contraceptives intake	5 (14.7)	3 (8.3)
History of NSAID intake	4 (11.8)	4 (11.1)
History of PPI intake	9 (26.5)	6 (16.7)

NSAID = Non-steroidal anti-inflammatory drugs; PPI = proton-pump-inhibitors.

Data are represented as n (%).

Table 2. Clinical characteristics of patients with IPAA and UC

Variables	Cases (n = 34) (48.6)	Controls (n = 36) (51.4)
Relapses of UC before IPAA		
Infrequent relapses	10 (29.4)	10 (27.8)
Frequent relapses	29 (85.3)	21 (58.3)
Continuous activity	5 (14.7)	5 (13.9)
EIMs	21 (61.8)	14 (38.9)
Reason for surgical treatment		
Perforation	3 (8.8)	5 (13.9)
Toxic megacolon	3 (8.8)	1 (2.8)
Massive bleeding	0 (0)	1 (2.8)
Lack of response to medical treatment	24 (70.6)	21 (58.3)
Cancer	0 (0)	7 (19.5)
Dysplasia	3 (8.8)	1 (2.8)
Previous treatment		
None	4 (11.8)	4 (11.1)
5-ASA	5 (14.7)	10 (27.8)
5-ASA + steroids	16 (47.1)	15 (41.7)
5-ASA + steroids + thiopurines	9 (26.5)	5 (13.9)
Steroids	0 (0)	1 (2.8)

5-ASA = 5-aminosalicylates. Data are represented as n (%).

(10 patients, 29.4%) and then 2 peaks during the ninth (4 patients, 11.8%) and tenth year (4 patients, 11.8%) of follow-up. Regarding the frequency of pouchitis relapses, 10 patients (29.4%) had them infrequently (less than once a year), 19 (55.9%) had them frequently (2 or 3 per year) and 5 (14.7%) continuously (>3 per year); from the group of ac-

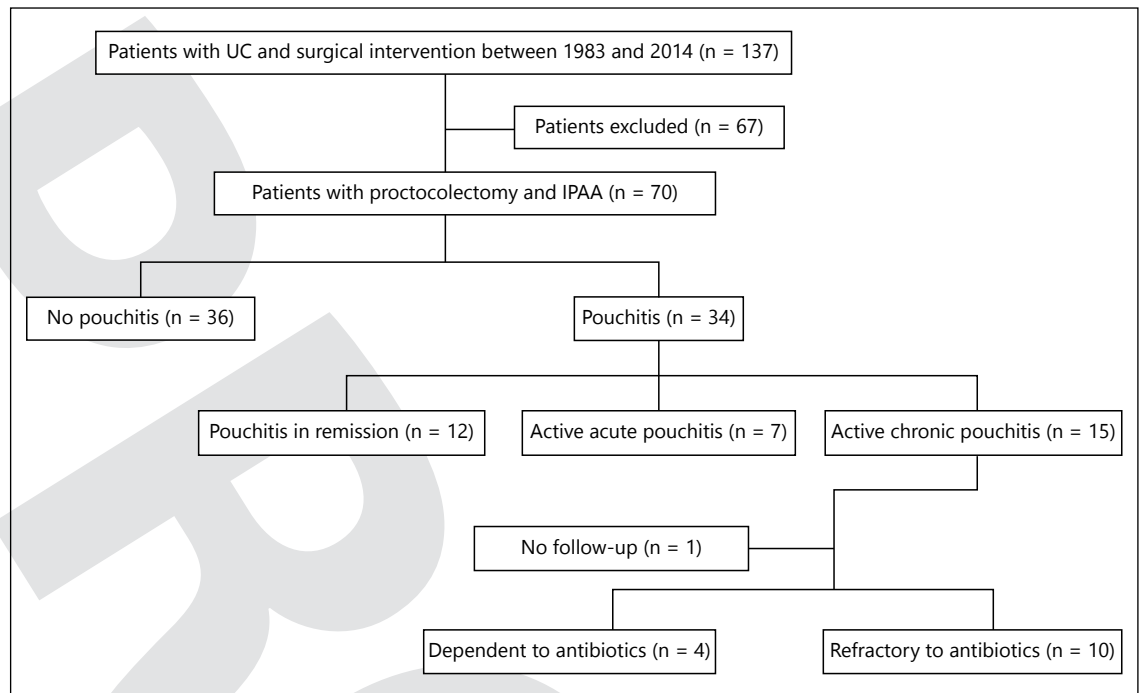


Fig. 1. Flowchart of patients included in the study.

tive chronic pouchitis, 4 (26.7%) were dependent on antibiotic treatment and 10 (66.7%) were refractory; 1 patient did not have enough follow-up to confirm this fact. The most frequent complications of the pouch were fistulae in 3 patients (8.8%) and stenosis of the IPAA in 13 (38.2%). The antibiotic used for the treatment of the acute episode was metronidazole in 5 cases (71.4%) and ciprofloxacin in 2 (28.6%); the antibiotics used for chronic pouchitis were ciprofloxacin and metronidazole in 12 cases (80%) and budesonide in 3 (20%). In the group with pouchitis in remission: 6 (50%) were treated with metronidazole, 4 (33.3%) with ciprofloxacin and 2 (16.7%) with double antibiotic. The presence of autoimmune concomitant diseases (ACDs) was more common in patients who had developed pouchitis (20.6%) than in controls (5.6%); one or more ACDs were present in 8.4% of the patients with pouchitis in remission, 28.6% of the patients with active acute pouchitis and 26.7% of the patients with active chronic pouchitis. The presence of EIMs was associated with chronic active pouchitis ($p = 0.06$, OR 0.31, 95% CI 0.07–1.31); the presence of ACDs was not associated with chronic active pouchitis ($p = 0.23$, OR 1.93, 95% CI 0.36–10.43). Relapses of UC before IPAA were infrequent (<1 per year) in 29.4% of cases and 27.8% of controls; frequent (>2 per year) in 85.3% of cases and 58.3% of controls; continuous activity (persistent symptoms) of disease was reported in 14.7%

Table 3. Symptoms of patients with pouchitis

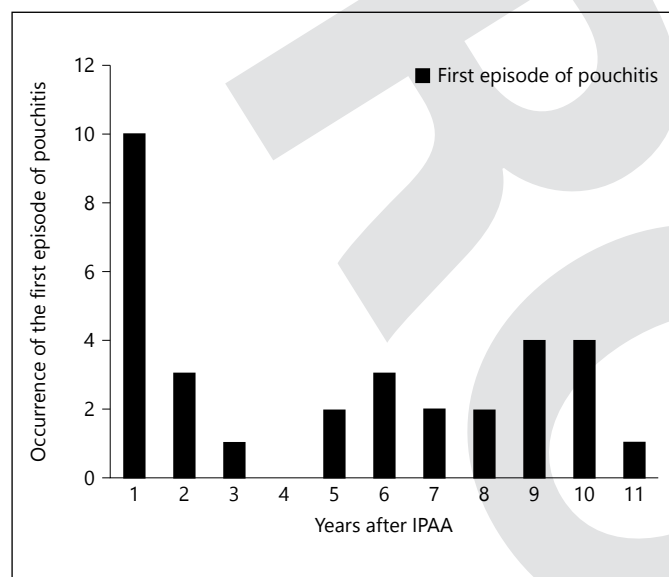
Variables	Cases (n = 34) (48.6)
Symptoms of pouchitis	
Increased stool frequency	29 (85.3)
Liquid stool	23 (67.6)
Abdominal cramping	8 (23.5)
Urgency	2 (5.9)
Tenesm	12 (35.3)
Discomfort	23 (67.6)
Fever	14 (41.2)
EIM exacerbation	3 (8.8)
Data are represented as n (%).	

of cases and 13.9% of controls. Table 3 shows the symptoms of pouchitis our patients presented and their respective frequency. The most common symptoms were increased stool frequency (85.3%), liquid stool (67.6%) and discomfort (67.6%). The presence of EIMs was more frequent in cases (61.8%) than in controls (38.9%); one or more EIMs were present in 23.5% of the patients with pouchitis in remission, 17.6% of the patients with active acute pouchitis and 20.6% of the patients with active chronic pouchitis. The most frequent presentation of the first episode of pouchitis was in the first year after IPAA as shown in figure 2.

Table 4. Factors associated in the patients with UC, IPAA and pouchitis

Analyzed factors	Cases (n = 34) (48.6)	Controls (n = 36) (51.4)	p value	OR (95% CI)
Autoimmune concomitant disease	7 (20.6)	2 (5.6)	0.06	4.40 (0.84–22.9)
EIMs	21 (61.8)	14 (38.9)	0.05	2.53 (0.96–6.64)
Smoking habit	11 (32.4)	14 (38.9)	0.62	0.75 (0.28–2.0)
Lack of response to medical treatment as reason for surgery	23 (67.6)	26 (72.2)	0.32	1.41 (0.53–3.73)
Young age at diagnosis (<40 years)	25 (73.5)	29 (80.6)	0.57	0.67 (0.21–2.06)

Data are represented as n (%).

**Fig. 2.** Frequency of pouchitis after IPAA during the follow-up.

Factors Associated with the Presence of Pouchitis

The univariate analysis showed that the probably factors associated with the presence of pouchitis were the presence of ACDs ($p = 0.06$, OR 4.40, 95% CI 0.84–22.9), and EIMs ($p = 0.05$, OR 2.53, 95% CI 0.96–6.64). Other factors were not associated as shown in table 4.

Discussion

The frequency of pouchitis in Mexican patients with severe UC treated with IPAA is high; however, to the best of our knowledge, this is the first study in Mexican patients that describes the frequency and clinical characteristics of pouchitis.

The high frequency in our population (48%) was similar to that reported in other countries such as United States [23], Belgium [24], Irish population [25] and Puerto Rico [28]. This data differs from other countries where 34% was reported in Scotland [26] and 21.7% in Brazil [27], and differ widely from China (5.3%) [29] and Japan (10%) [30]. To date, there is still no clear explanation for this fact, but it may be influenced by ethnic background, geographic location [35], genetic information [36], diet [37] and some features of the UC, for example, the clinical course [38]. In our study, 20.6% of the patients had active acute pouchitis and 35.3% presented pouchitis in remission due to the adequate response to antibiotic treatment, in contrast with United States where 96% of the patients responded to antibiotic treatment [23]. Other countries like Scotland reported that 77% of the patients achieved remission after the acute episode [26], and it was 87% in Japan [30]. On the other hand, 44.1% of the patients presented chronic active pouchitis similar to that reported in the United States (46%) [39]. On the other hand, other countries have reported a low frequency of chronic pouchitis such as Scotland in 19% [26] contrasting with 47% in Japan [30].

Data discussed above indicate that, compared to other countries, our population has fewer patients achieving remission, which could be because of an inadequate adherence to medical treatment from the patients, an inadequate prescription from the physicians or maybe a more aggressive clinical course of the disease in this population. Further studies could focus on elucidating the reason for this fact. The similar and high number of patients who developed chronic pouchitis could confirm the fact that this is one of the most challenging complications of IPAA in the context of UC. In our population, the first episode of pouchitis occurred at an average of 5.37 years after IPAA, being more frequent during the first year (29.4%). Our findings are similar to

that reported in other countries such as United States, where 56% of the patients develop pouchitis during the first 12 months [23]; Scotland at 18 months [26] and Japan, where 74% of the patients developed it within the first 2 years after IPAA [30]. The appearance of pouchitis at different periods of follow-up may be influenced by microbiota, immune response, diet and ethnic background or geographic location [35]. It is important to note that our population with pouchitis had a higher presence of ACDs (20.6%) compared to those patients without pouchitis (5.6%); as also, the presence of EIMs was more frequent in patients with pouchitis (61.8%) than without pouchitis (38.9%). Similar results have been previously described in other countries. For instance, Brazilian data have described that 92.3% of their patients with pouchitis had any kind of EIMs [27]. In Belgium, the presence of EIMs was found to be a risk factor for developing pouchitis [24]. In the United States, only 11% of the patients with pouchitis had at

least one EIM [39]. It is well known that an evaluation that includes assessment of symptoms, endoscopy and histology are required to make the diagnosis of pouchitis [32]. It is important to consider some limitations such as this in a retrospective study and the small number of patients included due to the low frequency of IBD in our country.

In conclusion, the frequency of pouchitis was 48.6% in our population. The presence of ACDs and EIMs might be factors associated with the development of pouchitis.

Disclosure Statement

The authors declare no conflict of interest.

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None.

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