

Smoking may prevent pouchitis in patients with restorative proctocolectomy for ulcerative colitis

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Abstract

Epidemiological studies have shown an increased risk of ulcerative colitis (UC) in non-smokers and particularly recent ex-smokers. Patients with UC have an increased risk of pouchitis following ileal pouch-anal anastomosis, which may be a manifestation of the original disease susceptibility. The aim of this study was to test the hypothesis that smoking habit may influence the incidence of pouchitis. All patients with a functioning pouch ≥ 12 months at one centre were assessed. Patients were excluded if (a) the original indication was not UC (n=5), (b) the excised pouch showed histology diagnostic of Crohn's disease (n=2), and (c) data were inadequate (n=4). Smoking data were collected by questionnaire, or direct interview, or both. Ex-smokers were those who had stopped smoking <7 years before colectomy. Non-smokers included ex-smokers who had stopped >7 years before colectomy. Pouchitis was defined as an increase in stool frequency >8/day with acute inflammation on biopsy specimen histology. Each presentation requiring treatment was regarded as an episode. For comparison smoking habit was assessed with regard to three other adverse outcomes - haemorrhage, sepsis, and pouch excision. Of 72 non-smokers (mean follow up 3.5 years) 18 had 46 episodes of pouchitis. Of 12 ex-smokers (mean follow up 3.3 years) four patients have had 14 episodes of pouchitis. Only one smoker from 17 has had a single episode of pouchitis. This shows that smokers have significantly less episodes of pouchitis compared with non-smokers ($p=0.0005$) and ex-smokers ($p=0.05$). There was no association of smoking habit with other adverse outcomes.

(Gut 1996; 38: 362-364)

Keywords: pouchitis, smoking, ileal pouch-anal anastomosis, ulcerative colitis.

Epidemiological studies show an increased risk of ulcerative colitis (UC) in non-smokers, particularly in recent ex-smokers.¹⁻⁹ The interval between cessation of smoking and subsequent onset of colitis in ex-smokers is comparatively short and in two thirds of patients occurs within seven years.⁹ Conversely in Crohn's disease there is a positive association with smoking.^{2 4 6 9 10} The mechanism for the association between smoking habit and inflammatory bowel disease is unknown.

Ileal pouch-anal anastomosis (IPAA) has become the operation of choice in patients with UC following proctocolectomy.¹¹⁻¹⁵ Despite this IPAA is associated with serious morbidity postoperatively and in the longer term.¹⁶ The most important longterm complication is pouchitis, which has a reported incidence of 7-45% depending on definition and whether histological confirmation is required.¹⁷⁻²¹ Although the pathogenesis of pouchitis is unknown, it is possible that chronic or recurrent pouchitis may represent recurrent inflammation similar to the UC disease process.¹⁷⁻²²

The aim of this study was to test the hypothesis that smoking habit may influence the occurrence of pouchitis in patients with UC prior to proctocolectomy.

Methods

Patients

The records of 112 consecutive patients from one hospital who had had a functioning IPAA for at least 12 months were reviewed. Patients were excluded if (a) the original indication was not UC (n=5), (b) the excised pouch showed histology diagnostic of Crohn's disease (n=2), (c) data were inadequate. The remaining 101 patients were the subject of this analysis.

Smoking data were collated by questionnaire (n=73) and direct interview (n=93) over a two year period. Ex-smokers were patients who had given up less than seven years prior to proctocolectomy. Non-smokers included ex-smokers who had given up more than seven years prior to proctocolectomy as well as lifelong non-smokers. Two patients had a sustained change in smoking habit after IPAA and the occurrence of pouchitis was related to the smoking habit at that time. All patients were followed up at designated clinics at one hospital and were followed up for two years (1990-1992) by one investigator (MM). For the purposes of this study pouchitis was defined as an increase in stool frequency to at least 8/day with biopsy specimen histology showing pronounced inflammation - that is, histopathology index ≥ 7 .²³ Patients usually had general malaise with occasional per anal bleeding and extraintestinal manifestations. Microbiological studies of stool were obtained routinely to exclude a specific pathogen as a cause for the diarrhoea. Each presentation requiring treatment was regarded as an episode. For comparison smoking habit was assessed against other adverse outcomes in this same patient group. These included haemorrhage, sepsis, and pouch excision.

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Accepted for publication
7 September 1995

TABLE I Smoking habit, pouch type, and follow up

	Number	Age (median)	Sex M/F	Total follow up	Pouch type
Non-smokers	72	33	39/33	255	8S/31W/33J
Smokers	17	32	12/5	71	3S/8W/6J
Ex-smokers	12	41	8/4	40	2S/5W/5J

Haemorrhage was defined as further surgical intervention requiring drainage of a haematoma. Sepsis was diagnosed in the presence of positive blood cultures or abscess formation, or both, confirmed either with imaging or at surgery.

Statistical analysis

The mean number of pouchitis episodes per group were compared with the mean score test.²⁴ The categorical data were formed into a contingency table and analysed with a log linear model, assuming that the distribution of frequencies was Poisson. The log likelihood ratio statistic was used to assess the 'fit' of the log linear model and to test any hypotheses. The log likelihood ratio statistic is χ^2 distributed.

Results

The three groups had similar ages, male/female ratio, and pouch design, although an increase in age of ex-smokers was noted (Table I) ($p=NS$). The mean score test was used to test the null hypothesis that the average number of pouchitis episodes was equal for non-smokers, smokers, and ex-smokers (Table II). The test of the hypothesis gave a χ^2 of 15.854 on 2 degrees of freedom (df), which is significant at the 0.001 level. The mean number of pouchitis episodes was similarly assessed in paired analysis. The number of pouchitis episodes for non-smokers is significantly more than for smokers ($p=0.0005$), however the difference between non-smokers and ex-smokers was not significant. Ex-smokers had more pouchitis episodes than smokers ($p=0.05$).

Contingency table analysis (Table II) was used to assess the hypothesis of no dependence between patients group and the occurrence of pouchitis. Of 72 non-smokers, 18 suffered episodes of pouchitis compared with only one

TABLE II Smoking habit and number of pouchitis episodes

Group	Number	Number of pouchitis episodes							Mean score
		0	1	2	3	4	5	6	
Non-smokers	72	54	5	6	2	3	1	1	0.639
Smoker	17	16	1	0	0	0	0	0	0.059
Ex-smoker	12	8	0	1	2	0	0	1	1.167

TABLE III Other complications in patients with pouch function ≥ 1 years (including early complications)

	Number	Bleeding	Sepsis	Pouch excision (and indication)
Non-smokers	72	7	9	1 PF, 4S
Smokers	17	2	3	0
Ex-smokers	12	0	1	1P

PF=poor function, S=sepsis, P=pouchitis.

of 17 smokers ($\chi^2=3.717$ on 1 df $p=0.054$). Of 12 ex-smokers four had episodes of pouchitis compared with smokers) ($\chi^2=3.779$ on 1 df $p=0.052$) at the 0.06 level (borderline significance). The hypothesis was accepted for non-smokers and ex-smokers. There was no association between smoking habit and three other adverse outcomes – haemorrhage, sepsis, and pouch excision (Table III).

Two patients had a sustained change in smoking habit. Patient 1, a 52 year old woman stopped smoking one year before proctocolectomy in 1983. The patient recommenced smoking immediately after the IPAA procedure and continued for six years with excellent pouch function. In 1989 she again stopped smoking and suffered pouchitis within 12 months and has since had five further episodes with associated arthritis. Patient 2, a 24 year old man did not smoke before IPAA and for two years after the procedure. During those two years, there were three episodes of pouchitis with an asymmetrical polyarthritis. At this time he started smoking for the first time and has continued for six years to the time of assessment. He has not had any further pouchitis or acute flares of arthritis although some joint deformity persists.

Discussion

Pouchitis is a poorly understood late complication of IPAA. Much of the confusion particularly with regard to incidence relates to the variability of criteria used to diagnose pouchitis. The use of clinical criteria alone is unsatisfactory as patients with IPAA may develop diarrhoea for reasons other than inflammation in the ileal reservoir. Recently a pouch disease activity index has been proposed, which combines clinical, endoscopic, and histological appearance.²⁵ Endoscopic appearances of 'inflammation' are highly subjective (in our experience) with significant interobserver error and so was not included. In this study we used both clinical criteria and biopsy specimen histology²³ to diagnose pouchitis.

The aetiopathogenesis of pouchitis is unknown and it seems plausible that pouchitis may be the end result of a number of essentially different disease processes.^{14 17-22} Using clinical criteria Rauh *et al* identified two major subgroups of pouchitis. The first group experience one or two episodes only and respond well to antibiotics. The second group, however, suffer serious illness and have recurrent or chronic pouchitis, which is often resistant to antibiotics. This group often require sulphasalazine or corticosteroids to control symptoms.²² The last subgroup of pouchitis occurs exclusively in patients with prior UC and may resemble the original disease process with regard to clinical manifestations and histological level. Other mechanisms proposed for pouchitis include bacterial overgrowth and changed bile acid metabolism,^{18-21 26-28} ischaemia,^{29 30} and unrecognised Crohn's disease.

The protective role of smoking against UC is well reported.¹⁻⁹ However, this is the first

report of smoking habit in relation to the incidence of pouchitis. Our finding that smoking is protective against the subsequent onset of pouchitis needs to be confirmed with a larger series, but pouchitis needs to be accurately defined and include histological criteria.

The mechanism(s) by which smoking protects against intestinal inflammation (UC) are unknown. Smoking has been reported to affect mucosal immune function in both the respiratory tract³¹⁻³³ and gastrointestinal tract³⁴ although in the last study only minor differences in IgA concentrations were identified. Smoking also affects mucus production³⁵ and rectal blood flow,³⁴ however the significance of these reports is unknown. Perhaps the most important finding is that smoking reduces mucosal permeability as measured by urinary recovery of ⁵¹chromium-EDTA.³⁶

Regardless of the mechanism the finding that smoking (and probably nicotine) protects against pouchitis raised the possibility of therapeutic intervention. We have shown that barrier function (⁵¹chromium-EDTA permeation) is low in preclosure ileal pouch, which suggests that the ileal mucosa is at greatest risk in the first few weeks when exposed to a large antigen/toxin faecal load.¹⁹ The importance of these early events is underlined by the findings that the first episode of pouchitis usually occurs soon after ileostomy closure (mean=3.5 months).²² There is insufficient evidence at this stage to support the use of nicotine (and smoking) to prevent pouchitis. However, a controlled trial would be worthwhile.

This paper was an oral presentation at the Digestive Disease Week, Boston, USA, 1993.

The authors would like to thank Dr Bridget Hsu-Hage and Dr Phillip McCloud for help with the statistical analysis and Dr Shao Kai Lin for his help with preparation of the manuscript.

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