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ORIGINAL ARTICLE

Outcome of four weeks' intervention with probiotics on symptoms and endoscopic appearance after surgical reconstruction with a J-configurated ileal-pouch-anal-anastomosis in ulcerative colitis

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Abstract

Objective. Pouchitis is a common and troublesome condition in patients operated on with ileal-pouch-anal-anastomosis (IPAA). A disturbed microecology in the pouch has been suggested as one possible explanation. In a previous double-blind, randomized, controlled study we demonstrated clinical improvement of symptoms in patients with ulcerative colitis (UC) operated on with IPAA, during intervention with live probiotic microbes Lactobacilli and Bifidobacteriae. The aim of the present study was to confirm our previous results in a much larger material, including clinical symptoms, faecal flora and endoscopic evaluation, and to compare the results in UC/IPAA patients with those of patients with familial adenomatous polyposis (FAP) with IPAA and UC patients with ileorectal anastomosis (IRA). ***Material and methods.*** Five hundred millilitres of a fermented milk product (Cultura) containing live lactobacilli (La-5) and bifidobacteriae (Bb-12) was given daily for 4 weeks to 51 UC patients and 10 patients with FAP, operated on with IPAA, and six UC patients operated on for IRA. Stool samples were cultured for examination of lactobacilli, bifidobacteriae, fungi and pH before, during and after intervention. Before, during and after intervention, endoscopic evaluation was performed. Categorized symptomatology was examined prospectively using diary cards in addition to an interview, before and on the last day of intervention. ***Results.*** The number of lactobacilli and bifidobacteriae increased significantly during intervention in the UC patients operated on with IPAA and remained significantly increased one week after intervention. Involuntary defecation, leakage, abdominal cramps and the need for napkins (category I), faecal number and consistency (category II) and mucus and urge to evacuate stools (category III) were significantly decreased during intervention in the UC/IPAA group. In the FAP group there was a significant decrease in faecal leakage, abdominal cramps and use of napkins (category I) during intervention. The median endoscopic score of inflammation was significantly decreased during intervention in the UC/IPAA patients. Blood tests, faecal fungi and faecal pH did not change significantly during intervention. ***Conclusions.*** Results of this extended study, showing an effect of probiotics on symptoms and endoscopic inflammation in UC patients operated on with IPAA confirm our previously reported effect of probiotics on clinical symptoms and endoscopic score in a smaller, double-blind, randomized, controlled study. The significantly higher response to probiotics in families with increased risk of IBD will have to be repeated in future studies.

Key Words: *Bifidobacteriae, clinical chemistry, endoscopy, faecal fungi, faecal pH, ileal pouch, inflammation, lactobacilli, symptoms*

Introduction

Acute, recurrent or chronic inflammation of the ileal pouch, i.e. pouchitis, is a troublesome complication and a major problem in many patients operated on with ileal-pouch-anal-anastomosis (IPAA) [1,2]. The reported cumulative frequency of pouchitis ranges widely, depending on the definition of pouchitis and the duration and intensity of follow-up. Several scoring systems have been proposed to standardize the evaluation and response to therapy [3–5] with the Pouchitis Disease Activity Index (PDAI) [4] being the most widely used. An accurate diagnosis of pouchitis by the PDAI depends on a combination of clinical, endoscopic and histological assessment. Clinical assessment alone will result in

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unnecessary antibiotic treatment of pouchitis in up to 25% of patients [6]. Likewise, significant endoscopic and histologic inflammation of the pouch may be present with few clinical symptoms. The absolute risk of developing pouchitis appears to be greatest during the first 12 months after closure of ileostomy, ranging from 18% to 37% [7–9]. Within 10 years, at least 50% of patients will experience at least one episode of pouchitis [7]. Acute episodic pouchitis does not appear to affect the long-term pouch function [10,11]. Chronic pouchitis has in rare cases been associated with the development of dysplasia and carcinoma [12,13].

The pathogenesis of the disease is still obscure. It has been suggested that pouchitis may be due to either reduced mucosal perfusion [14,15] or microbial disturbance in the distal bowel [16–18]. The normal gut flora of adults constitutes a complex ecosystem comprising 400–500 different microbial species [19–21]. In pouchitis, the relative numbers of both lactobacilli and bifidobacteriae are decreased [16]. Most patients with acute pouchitis respond to antibiotic treatment [22], but 10% will develop chronic pouchitis that may require continuous therapy [23,24] and 10–15% of patients experience recurrences or symptoms refractory to antibiotic treatment [25–27]. Even in those patients with recurrent or chronic active pouchitis, sustained treatment with antibiotics will in most cases lead to healing [28]. Severe cases have been treated with a combination of antibiotic regimens, topical or oral mesalamine or corticosteroids, immune modulators, or biologic therapy. To maintain remission, continuous antibiotics may be used, with the risk of side effects or resistance. A tempting alternative is to try to modify the bacterial milieu with live bacteria, referred to as probiotics.

Since the time of Metchnikoff more than 100 years ago [29], it has been recognized that certain bacteria may have therapeutic value.

In 1989, Fuller defined probiotics "as a live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance" [30].

In a recent double-blind, placebo, controlled study, human Lactobacillus acidophilus (La-5) and Bifidobacterium lactis (Bb-12), in a commercially available product (Cultura; TINE Dairies BA, Oslo, Norway), given to patients with ulcerative colitis (UC) with IPAA improved faecal flora and stool frequency [31], as well as mucosal inflammation evaluated by endoscopy [32].

In the present study we sought to elaborate on our results of well-characterized UC patients operated on with IPAA by expanding the number of patients, to find out whether the results were repeatable in a much larger material. We also sought to compare the results with patients operated on with IPAA for familial adenomatous polyposis (FAP), and UC patients operated on with ileorectal anastomosis (IRA), to determine whether the results were related to the underlying disease or the surgical procedure.

Material and methods

The study was an open-label intervention comprising 69 patients. Patients were included from January 1996 through February 2001. The patients had surgery at least one year prior to inclusion and were all in a stable clinical condition. They were told to continue their ordinary diet as usual during the study. The surgery had been performed at Rikshospitalet.

Exclusion criteria were the use of anti-infectives-, anti-inflammatory- or motility-modifying drugs, with the exception of (Imodium) Loperamid during the preceding 3 months. Patients taking Loperamid were allowed to use an unchanged constant dose during the study. Patients with diabetes were not accepted. They were told to avoid probiotics during the 3 months preceding inclusion. Live lactobacilli and bifidobacteriae in 500 ml Cultura (TINE Dairies BA, Oslo, Norway), (100 g Cultura containing: 3.2 g protein, 1.5 g fat and 4.3 g carbohydrate) were given daily during the 4 weeks of intervention. The concentrations of both strains were 10^8 colony-forming units (cfu)/ml (Chr. Hansen A/S laboratory Horsholm, Denmark) [33]. Random samples of the milk product were quantitatively checked for bacterial content, at regular intervals during the study and found satisfactory. Compliance was checked for by counting returned empty packages. The study was performed according to the Declaration of Helsinki and approved by the regional ethics research committee.

Patient characteristics

Among the 51 patients in the UC group operated on with IPAA, 9 patients (18%) had one or more 1st-degree family members with UC or Crohn's disease. In the FAP group none of the patients had family members with inflammatory bowel disease (IBD). In the UC group operated on for IRA, one patient had 1st-degree relatives with IBD. Details of the surgical procedures were obtained in 39 of the 67 patients with respect to the construction and length of the reservoir, and in 29 of the 67 patients with respect to the length of the remaining rectum, whenever present. These measurements were checked endoscopically (Table I).

Table I. Length of the created reservoir and the remaining rectum ring whenever present in the three patient groups, described at surgery and endoscopy. Number of patients in parentheses.

Patient category	UC/IPAA ($n=51$)	FAP/IPAA ($n=10$)	UC/IRA ($n=6$)
Length of reservoir			
Endoscopic examination	16.5 cm (SD 2.5) (51/51)	16.3 cm (SD 0.3) (10/10	–
Described by the surgeon	17.5 cm (SD 4.5) (34/51)	18.4 cm (SD 3.7) (5/10)	–
Length of the remaining rectum			
Endoscopic examination	1.8 cm (SD 1.2) (51/51)	1.6 cm (SD 1.1) (10/10)	8.9 cm (SD 3.6) (6/6)
Described by the surgeon	1.7 cm (SD 1.2) (19/51)	1.6 cm (SD 0.9) (5/10)	6.6 cm (SD 5.1) (5/6)

Abbreviations: UC = ulcerative colitis; IPAA = ileal-pouch-anal-anastomosis; FAP = familial adenomatous polyposis; IRA = ileorectal anastomosis.

In the UC/IPAA group 34 of 51 patients had been operated on electively, the remaining had been operated on with acute colectomy with left-behind rectum for later pelvic pouch procedure. All those in the FAP group and four patients in the UC/IRA group had been operated on electively.

Reoperations because of complications were performed in 17 of 51 (33%) patients in the UC/IPAA group, in 1 of 10 (10%) in the FAP group and in 2 of 6 (33%) in the UC/IRA group.

Prior to inclusion, 28 patients (55%) in the UC group with IPAA had been treated for 59 episodes of pouchitis, with an average of 2.1 episodes in each of the 28 patients (range 1–9). In the FAP group one patient and in the IRA group none of the patients had been treated for inflammation.

In the UC group with IPAA, 33 patients (65%) had been dilated a total of 188 times for an anastomotic stricture. Three patients (33%) in the FAP group had been dilated once. None in the UC/IRA group had been dilated.

At inclusion, 10 patients (20%) in the UC/IPAA group described symptoms of ongoing pouchitis and 7 patients (14%) had strictures. In the two other groups no inflammation or strictures were present at inclusion. Two patients in the UC/IPAA group had been operated on without a temporary ileostomy, one electively and one in the acute stage.

In the UC/IPAA group, 12 of 51 (24%) patients were smokers, in the FAP group 3 of 10 (30%) and in the UC/IRA group 2 of 6 (33%) were smokers.

Recording of symptoms

Patient characteristics, including previous treatment, flares and symptomatology were recorded by interview at inclusion and on the last day of intervention.

Patient diary cards

Recording of clinical symptoms included faecal frequency day (d) and night (n), faecal consistency on a scale from 1 to 5 (1 = hard, 2 = formed, 3 = mash, 4 = soup-thin to 5 = water-like); blood or mucus (present or not), unintentional defecation (number in 24 h), pads, and/or napkins (number in 24 h), abdominal pain or cramps (present or not), urge, leakage and temperature in the morning were recorded daily, one week prior to, during and one week after intervention. Combinations of symptoms were processed using a factor analysis model, and divided into five categories:

Category I: Involuntary defecation, leakage, abdominal cramps and need for napkin.
Category II: Number and consistency of the stool.
Category III: Mucus and urge to evacuate.
Category IV: Use of sanitary towels.
Category V: Visible blood in stools and morning fever.

Extraintestinal symptoms in the skin, eyes, small and major joints were noted. All patients were also asked about nausea, gastro-oesophageal reflux, miction- and sexual function at inclusion and on the last day of intervention. Ongoing medication was noted as well as body mass index (BMI).

Stool examination

Microbiology. Stool samples were collected in the morning at baseline, after intervention (24 h after the last intake of 0.5 1 Cultura) and one week thereafter. The samples were brought to the microbiological laboratory within one hour and cultivated for lactobacilli (La-5) and bifidobacteriae (Bb-12). Quantitative counts of lactobacilli and bifidobacteriae were recorded as cfu/ml. The fermented milk product Cultura was used as the control. Growth of lactobacilli and bifidobacteriae were verified by colony morphology, Gram staining and biochemical tests.

Faecal fungi. Fungi in the stools were examined. The samples were brought to the microbiological

laboratory within one hour and cultivated for species of fungi. Growth of fungi was verified by the morphology of the colonies and biochemical tests.

Faecal pH. Stool samples were additionally examined on pH by dry chemistry in fresh stool samples before, immediately after and one week after the end of the intervention.

Endoscopy

The degree of mucosal inflammation was evaluated by endoscopy of the ileal pouch (UC/IPAA, FAP/IPAA)/distal bowel (UC/IRA), performed before and after intervention by the same investigator. The endoscopic part of the PDAI [4], with a scale from 0 to 6, including oedema, granularity, fibrin, loss of vascular pattern, mucus and ulceration, was applied.

Clinical chemistry

Routine blood samples were collected in the morning on the last day before and the last day of intervention, including ANA and ANCA.

Statistical analysis and calculations

The different items from the diaries as well as the blood sample variables are summed up with mean values and standard deviations. Variables showing a more skewed distribution are summed up with median values and range. Some of the variables such as the numbers of bifidobacteriae and fungi were log-transformed before the tests were performed.

Paired t-tests were used to compare results pre- and post-intervention. The different groups were compared with one-way ANOVA models. Bonferroni corrections were performed to correct for multiple comparisons.

The 21 items derived from the diary cards were grouped into 5 categories based on an explorative factor analysis. A 5-factor model explaining 58.9% of the total variance of the data was chosen. The method of maximum likelihood estimation was used to extract the different categories.

To study the development of the different factors with time, generalized additive models were used [34]. The expected value of the dependent variables (5 factors) was assumed to be a function of time. The response variable was assumed to follow the Poisson distribution, introducing a logarithmic link.

To test the nil hypothesis of no relationship between the dependent variables (factors) and the independent variable time, a likelihood ratio statistic was computed. Models were estimated for the three groups and for the five categories as dependent variables.

The procedures in Splus were used to fit the different general additive models. SPSS 9.0 for Windows was used to perform the factor analysis. Logistic regression was used to model whether or not improvement was related to a set of independent variables. The following variables were independent variables: endoscopic score before and after intervention, IBD in the family, smoking habits, number of episodes with pouchitis and number of ileo- anal stenoses that needed dilatation before inclusion, the patient's opinion of ongoing pouchitis and/or anastomotic stenosis at inclusion, elective- or acute surgery, numbers of reoperations, BMI, gender, age and groups of patients.

Results

Sixty-seven patients completed the study. One closed perforation occurred after biopsies in the distal gut, treated conservatively. This patient was excluded. One woman refused to continue after the first endoscopy. The remaining 51 patients (25 F, 26 M, mean age 40 years) operated on with IPAA, the 10 FAP patients operated on with IPAA (5 F, 5 M, mean age 35 years) and the 6 UC patients (3 F, 3 M, mean age 42 years) operated on with IRA were all examined according to the study protocol, acting as their own controls.

All patients completed the treatment period and reported intake of Cultura according to schedule. The empty packages were returned for counting and none were found missing. The BMI was within normal limits in all three groups. The analysis of blood clinical chemistry did not show significant changes, including p-ANCA (data not shown).

Medication

Medication for bowel symptoms was used by 24 of 51 patients in the UC/IPAA group, by 4 of 6 in the UC/IRA group and by 3 of 10 in the FAP group. In the UC/IPAA group, 24 of 51 patients used Imodium, in the FAP/IPAA group 3 of 10 and in the IRA group 4 of 6 used Imodium. The median number of daily tablets was 2.7 (0.5–11), 1 (1–1) and 5.9 (5–6.5), respectively.

Various dietary fibre preparations were used in 11 of 51 UC/IPAA patients, in 3 of 6 in IRA patients and in none of the FAP patients. The median number of daily doses (2–3 spoons in a glass of water) was 2.8 (1–9) and 3 (3–3), respectively.

Medication for the gut was continued unchanged during the study as for other medication used on a regular basis.

Symptom registration by diary card

Factor analysis showed a significant decrease in symptoms concerning category I ($p < 0.0005$), II ($p = 0.0354$) and III ($p = 0.0053$) in the UC/IPAA group (Figure 1A). In the FAP group a significant decrease in symptoms was shown for category I ($p = 0.0005$) (Figure 1A). In the UC/IRA group no significant decrease was found in any of the categories (data not shown).

Symptoms before and after intervention examined by interview

A non-significant symptom reduction was found in all five categories in the UC/IPAA group. Among the FAP/IPAA patients, category II and category IV did not show any significant changes, as for categories II, IV and V in the UC/IRA group. No significant changes in symptoms were found in any of the three groups during the week after intervention (Figure 1B).

There was a significant reduction in eye symptoms in 12 patients recorded before to 7 patients after intervention ($p = 0.02$). Small-joint symptoms were recorded in 18 patients before and 15 patients after intervention (NS). Skin symptoms were recorded in 14 patients before and 11 patients after intervention (NS). Symptoms from major joints were recorded in 19 patients before and 15 patients after intervention ($p = 0.04$). There was no significant change in nausea, gastro-oesophageal reflux, miction or sexual function during intervention.

Patients with IBD among 1st-degree relatives were significantly improved regarding stool frequency and consistency compared to patients without IBD in the family ($p = 0.01$). Categories III and V were significantly improved regarding mucus or urge to evacuate ($p = 0.02$) and blood in stools and morning fever ($p = 0.03$) among the patients who described ongoing pouchitis at inclusion.

Faecal microbiology, fungi and pH

Faecal microbiology. The number of lactobacilli and bifidobacteriae increased significantly from baseline values during intervention in the UC/IPAA group, $p = 0.017$ and $p = 0.006$, respectively, and changed non-significantly in all three groups one week after intervention (Table II).

Faecal fungi. No significant changes in fungal number were seen in any of the groups or in the differences between groups.

Faecal pH. Faecal pH was unchanged in and between the groups, during the study period.

Endoscopy

In the group of 51 UC patients operated on with IPAA, the endoscopic score decreased for 30 patients, 19 were unchanged and the condition of 2 patients worsened. The mean endoscopic score was significantly decreased from 4.5 at inclusion, to 3.0 on the last day of intervention ($p = 0.0001$) (Table III).

In the FAP group, 4 patients had decreased endoscopic scores, 5 were unchanged, and none had increased scores (NS). In the UC/IRA group, 4 of the 6 patients had decreased scores, 2 remained unchanged and none had increased score (NS).

Discussion

Several reports support a role for the intestinal microflora in the pathogenesis of pouchitis [16–18,35]. The probiotic bacteria used in the present study were originally isolated from human gut content and have been used as additives to dairy products for decades, thus assuring their safety [36].

In the present study, duration of disease, age, frequency of acute or elective surgery, length of the created reservoir and remaining rectum all corresponded well to other published patient materials [4,16].

The symptomatic improvement observed in both groups with a pelvic pouch, but not in those without, may indicate that the container function of the pouch leads to a sufficiently long exposure time, which may be necessary to obtain an influence of the probiotic or probiotic modified flora on the mucosa.

It has been proposed that pouchitis might be due to an ecologic imbalance of the gut flora, sometimes called dysbiosis [16]. The supposed effect of probiotic bacteria has hence been that they could have a stabilizing effect on the ecosystem and thus act as true probiotics. An alternative explanation could be that the actual lactobacilli and/or bifidobacteria might exert immune modulating effects on the mucosa on their own. The present study cannot answer this question. Unlike others [16], we did, however, not observe any change in faecal pH or faecal fungi in the pouch content that could indicate a more profound effect on pouch ecology.

The trend towards a parallel decrease in mean symptom score recorded by interview before and at the end of intervention did not reach statistical significance.

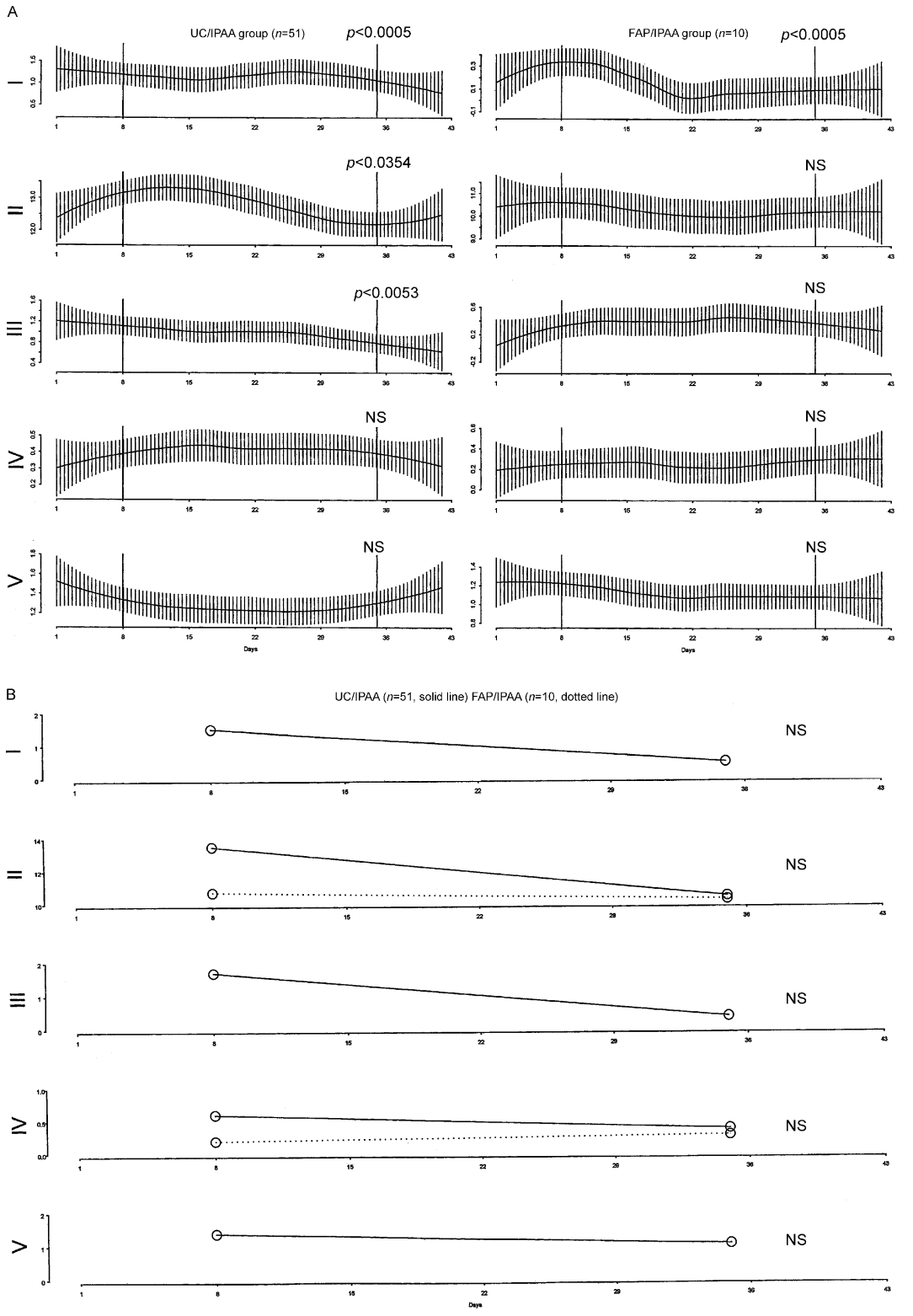

Figure 1. Symptom scores for categories (I–V) registered prospectively before, during and after intervention (accessible results for evaluation of all five categories (A)), and the same categorized symptoms examined by interview on the first (day 8) and last day (day 35) of intervention, (accessible results for evaluation of all five categories in the UC/IPAA group, and accessible results for evaluation of categories II and IV in the FAP/IPAA group (B)). Symptom score for each of the symptom categories on the y-axis, and time in days on the x-axis. UC = ulcerative colitis; IPAA = ilealpouch-anal-anastomosis; FAP = familial adenomatous polyposis; IRA = ileorectal anastomosis. Category I: Involuntary defecation, leakage, abdominal cramps and use of napkins. Category II: Stool frequency and consistency. Category III: Mucus and urge to evacuate. Category IV: Use of sanitary towels. Category V: Blood in stools and morning fever. UC/IPAA ($n = 51$), FAP/IPAA ($n = 10$).

Table II. Number of lactobacilli and bifidobacteriae (given as cfu/ml), before (A), during (B) and after intervention (C) with probiotica in, UC patients with IPAA ($n=51$) (1), FAP patients with IPAA ($n=10$) (2) and in UC patients with IRA ($n=6$) (3). Results given as median and range.

	A	B	C
Lactobacilli			
1. UC patients with IPAA			
Median	2.8×10^{7}	$8.0\times10^{7}\star$	$3.0\times10^{7\mathrm{NS}}$
Range	$(3.0\times10^{4}-2.5\times10^{9})$	$(2.0\times10^{5}-4.0\times10^{9})$	$(3.0\times10^{4}-2.5\times10^{9})$
2. FAP patients with IPAA			
Median	1.0×10^{8}	$3.5\times10^{8\mathrm{NS}}$	$3.5\times10^{6\mathrm{NS}}$
Range	$(4.0\times10^{5}-9.0\times10^{8})$	$(3.5\times10^{6}-9.0\times10^{8})$	$(4.0\times10^{5}-6.0\times10^{8})$
3. UC patients with IRA			
Median	3.5×10^{7}	$5.0\times10^{7\mathrm{NS}}$	$1.8\times10^{8\mathrm{NS}}$
Range	$(3.0\times10^{4}-1.5\times10^{8})$	$(3.0\times10^{7}-2.5\times10^{9})$	$(3.5\times10^{6}-9.0\times10^{8})$
Bifidobacteriae			
1. UC patients with IPAA			
Median 7.8×10^{6}		$8.3\times10^{7}\star\star$	$1.5\times10^{7\mathrm{NS}}$
Range	$(1.0\times10^{4}-1.0\times10^{9})$	$(1.0\times10^{4}-6.0\times10^{9})$	$(2.0\times10^{4}-1.0\times10^{9})$
2. FAP patients with IPAA			
Median 3.0×10^{7}		$1.5\times10^{9\mathrm{NS}}$	$3.5\times10^{7\mathrm{NS}}$
Range	$(1.0\times10^{6}-3.0\times10^{8})$	$(2.0\times10^{6}-8.0\times10^{9})$	$(2.5\times10^{5}-2.0\times10^{9})$
3. UC patients with IRA			
Median 1.3×10^{7}		$4.0\times10^{7\mathrm{NS}}$	$6.8\times10^{6\mathrm{NS}}$
Range	$(1.0\times10^{4}-1.0\times10^{8})$	$(7.5\times10^{4}-6.0\times10^{8})$	$(1.5\times10^{5}-6.5\times10^{7})$

Abbbreviations: UC = ulcerative colitis; IPAA = ileal pouch-anal-anastomosis; FAP = familial adenomatous polyposis; IRA = ileorectal anastomosis; cfu = colony-forming units.
$\star\star p<0.01$. $\star p<0.05$
Asterix ($\star$) shows comparison with the previous value.

It has been described that patients who have an extended reservoir length of between 20 and 30 cm have more clinical symptoms, including pouchitis, than patients with reservoir lengths between 15 and 20 cm [37], as for the patients in the present study.

In the present study both the endoscopically measured length of the reservoirs and the length of the remaining rectums were similar to the measurements given in the surgeon's description.

The increased number of lactobacilli and bifidobacteriae in the UC/IPAA group during intervention, was in accordance with our previous randomized placebo-controlled study [31].

Table III. Endoscopic evaluation before (A) and after (B) intervention with probiotica in: UC patients with IPAA ($n=51$) (1), FAP patients with IPAA ($n=10$) (2) and UC patients with IRA ($n=6$) (3). Results given as mean value, after the PDAI endoscopic score.

	A	B
1. UC patients with IPAA	4.5	$3.0\star\star\star$
2. FAP patients with IPAA	3.9	$2.2\star\star$
3. UC patients with IPAA:	3.0	$1.8\star$

Abbreviations: UC = ulcerative colitis; IPAA = ileal-pouch-anal-anastomosis; FAP = familial adenomatous polyposis; IRA = ileorectal anastomosis.
$\star\star\star p=0.0001$. $\star\star p=0.066$. $\star p=0.058$.

It is reasonable to assume that this originated from ingested Cultura, indicating that the lactobacilli and bifidobacteriae of Cultura are able to survive the passage through the gastrointestinal tract [38,39]. The maintained elevation in the numbers of lactobacilli and bifidobacteriae one week post-intervention indicates that these species are able to multiply in the pouch for some time, indicating that a transient colonization may take place. The reduction in symptom score one week after intervention could also indicate a prolonged post-probiotic effect.

The significant improvement in passing of mucus and the urge to evacuate (category III), blood in stools as well as morning fever (category V) observed among the patients with pouchitis at inclusion strengthens the basis for recommendation of probiotics as a treatment in active pouchitis. These findings suggest that the probiotic bacteria seem to act more effectively in patients with severe compared to light to moderate inflammation in their pouch mucosa.

The lack of significance in the increase in the number of lactobacilli and bifidobacteriae in the FAP group and the IRA group may be due to an insufficient number of patients in those groups.

The endoscopic improvement and also the significant decrease in symptoms, particularly in the UC/IPAA group, indicate that the probiotics exert

some beneficial effects on the inflammation and the function of the pouch.

According to logistic regression analysis testing for possible risk factors related to changes in symptoms, patients with IBD among 1st-degree relatives were significantly improved regarding stool frequency and consistency (category II), compared with patients without IBD in the family. To the best of our knowledge, this observation has not been reported previously. It could be speculated that this might be due to a genetic susceptibility to microbial imbalance in the gut in families with IBD, and possibly also disposes towards a better effect of probiotics, or that immune modulation as an answer to probiotics might be genetically determined.

Colectomy has not been shown to reduce extra-intestinal manifestations [40]. In the present study, a significant decrease in symptoms from eye and major joints in the UC/IPAA group was demonstrated after intervention. It is tempting to see this as a result of a reduction in the degree of pouch inflammation.

As the risk of pouchitis has been reported to be increased in patients with a history of extraintestinal manifestations, primary sclerosing cholangitis, positive serology for perinuclear antineutrophil cytoplasmic antibodies (ANCA), and backwash ileitis [41,42], it is tempting to suggest a relationship between the present effect of probiotics on pouchitis.

Our findings suggest that bacteria may play a role in the causation of pouchitis and may also be useful in the treatment of pouchitis, and that probiotics may be a good alternative to antibiotics in some patients with pouchitis.

Future studies will be needed to elucidate more specifically the choice of microbes and the necessary quantities and length of treatment. The surprising finding of a better effect of probiotics in patients belonging to families with more than one member with IBD will have to be confirmed in future studies.

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