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Clinical Effect of Fibre Supplement in Patients with Ulcerative Colitis Treated with 5-ASA

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Abstract

Ulcerative colitis (UC) is frequently treated with 5-ASA in active disease or to maintain remission. As dietary fibres binds 5-ASA in vitro, we wanted to investigate if a daily supplement of 30 ml of Isphagula Husk in patients with UC in remission or relapse affects disease activity and urinary excretion of 5-ASA.

It is a paired intervention study (trial I) and randomised controlled trial (trial II). The participants with UC in remission received 30 ml of fibre/day (trial I). Participants with relapsing UC were randomised to either 30 ml of fibre or blended breadcrumbs for two-three months (trial II).

The main outcome measures is C-reactive protein and 24 hours' urine collection of total 5-ASA (trial I). In trial II the disease activity was determined by Inflammatory Bowel Disease Questionnaire (IBDQ) and Simple clinical colitis activity index (SCCAI) questionnaires.

22 participants with UC in remission and 12 with relapsing UC were included. In trial I no significant effect of fibre on CRP or on disease activity was found, whereas a decreased urinary excretion by a median of 6.3 percentage point (range: -50.6-33.6; p=0.03) of total 5-ASA was found. No significant differences were found between fibre and placebo groups in trial II.

A decreased urinary excretion of total 5-ASA was seen in patients with UC in remission, but not in patients with relapsing UC. The number of patients was low and different factors could affect the results, but the results confirm that the in vitro results can be reproduced in patients.

Keywords: Ulcerative colitis; Dietary fibre; 5-Aminosalicylic acid (5-ASA); Isphagula Husk

Introduction

Ulcerative colitis (UC) is treated with 5-aminosalicylic acid (5-ASA) in mild to moderate disease and maintains remission. How 5-ASA affects the disease is not known, but it is assumed that it exerts its effect from colon lumen. For this reason it is attractive to increase the intraluminal concentration of 5-ASA in the colon, by a reduced absorption in the intestine [1,2]. Such an effect may be obtained by binding of 5-ASA to dietary fibres. The fibre Isphagula Husk, which consists of psyllium from the Indian plant 'Plantage Ovata', binds 5-ASA more efficient than wheat bran, citrus-pectin and wheat flour in vitro [3].

Isphagula Husk is moderately fermented in colon and consequently 5-ASA may be liberated and the intraluminal concentration of 5-ASA in colon may thereby be increased [4]. Also the side effects of 5-ASA may be decreased because they are mainly attributed to the absorbed fraction. This binding capacity might thereby be a therapeutic gain in the treatment of UC with 5-ASA. Low compliance with intake of medicine is observed also among patients with UC [5], and that increases the attraction to decrease the need for medicine. Kidney damage by 5-ASA is rare [6], but this only add to the wish for a non-toxic dietary way of decreasing the absorption of 5-ASA.

The purpose of this study were to investigate if a daily supplement of Isphagula Husk in patients with UC in remission or relapse affects disease activity and urinary excretion of 5-ASA.

Methods and Materials

Trial Design

Trial I is a paired intervention study, whereas trial II is a randomized double-blind placebo-controlled trial, where randomisation was conducted after collection of baseline data to either fibre or placebo using sealed envelopes with tinfoil to ensure blindness.

All patients were recruited consecutively at the outpatient clinic at Aalborg University Hospital.

Inclusion and Exclusion Criteria

Adult patients (18-75 years) with a diagnosis of Ulcerative colitis were suitable for inclusion in the trials.

In trial I, patients with inactive UC with a 'Simple clinical colitis activity index' (SCCAI) score [7] of 0-3 were recruited.

In trial II, patients with active UC with an SCCAI score of 4-10 were recruited.

All patients were in a stable-dose, oral treatment with 5-aminosalicylic acid (5-ASA) for minimally one month before inclusion and throughout the studies. Rectal 5-ASA was allowed and was to be stable as the oral dose of 5-ASA.

Exclusion criteria in both trials included the use of steroids, patients with impaired renal or liver function, use of gluco-corticosteroids within 1 month prior to study entry or during study period, ileostomy, pregnancy, coeliac disease and not being able to communicate in Danish.

Patient Recruitment

In both trials, suitable patients were recruited at their regular control visits in the out-patient clinic. Furthermore, potential patients were searched for in the departments' patient registry – a registry of all patients with gastrointestinal diseases in the North region of Denmark. These were contacted by phone. All gave informed consent.

Trial Endpoints

The primary endpoint in trial I was the change in CRP and the secondary endpoint was the change in total urinary 5-ASA excretion in patients with UC in remission. The participants are their own controls in trial I.

In trial II, the primary endpoint was change in SCCAI and Inflammatory Bowel Disease Questionnaire (IBDQ) and the secondary endpoint was the change in total urinary 5-ASA excretion in patients with UC in relapse. In trial II the control and intervention groups are compared.

The SCCAI includes questions regarding bowel frequency (day and night), urgency of defecation, blood in stools, general wellbeing, and extra colonic manifestations. A score was given for each of the questions and a final score between null and 19 is given. The higher the score, the more and worse the symptoms.

Trial Protocol

In trial I, patients received a box with Isphagula Husk and in trial II patients received a box with Isphagula Husk or blended breadcrumbs. In both trials the patients were supposed to take an amount of 30 ml powder per day mixed with food or a cold beverage for one week (trial I) or two or three months (trial II) at the same time as proceeding with 5-ASA in unchanged dose. Before and at the last day with powder intake a blood sample was collected from the patients. At the same point of time, the patients collected a faeces sample and urine for 24-hours.

The box included more powder (Isphagula Husk or blended breadcrumbs) than the patients needed and compliance was measured by weighing the amount of returned powder.

In both trials, all patients remained on an unrestricted diet and stable maintenance therapy for their UC throughout the trial, but were asked to keep everything as constant as possible.

Intake of dietary fibre in trial II was assessed by using a food frequency questionnaire with focus on fibre containing food items, especially fibre rich food items. The questionnaire was developed by the authors for this trial and therefore not validated.

Measurement of Urinary 5-ASA Excretion, CRP and f-calprotectin

The total urinary 5-ASA excretion was measured as the sum of 5-ASA and its metabolite acetyl-5-ASA in urine. The method of analysis was based on liquid chromatography using an Agilent 1100 series chromatograph (Agilent Technologies, Palo Alto, CA, USA) equipped with a Quatpump, a degasser, a column oven, an autosampler, a DAD UV detector operated at

240 nm and a fluorescence detector operated with excitation at 315 nm and emission at 430 nm. The reversed phase column was a Xterra MS (Waters, Milford, MA, USA) C18, 100 x 2.1 mm with 3.5 µm particles. The mobile phase consisted of acetonitrile + 0.05 M sodium phosphate pH 6.2 (40:60 v/v) delivered with a flow rate of 0.25 ml/min. The column was maintained at 30°C.

Urine was either measured directly after mixing and centrifugation (for 5-ASA using fluorescence detection) or after dilution 100 times (for acetyl-5-ASA using UV at 240 nm).

Measurement of CRP and f-calprotectin was conducted as part of the routine of the laboratory methodology (accredited laboratory).

For measurement of f-calprotectin all patients were given a set containing a little spoon, a glass and a franked envelope. All patients were instructed to send the test to the laboratory the day it was taken.

Statistical Analysis

The Mann-Whitney rank sum test and the Wilcoxon signed rank sum test were used for unpaired and paired comparisons respectively. Kruskal-Wallis and Friedmans test were used for excretion of 5-ASA in the urine in trial II due to three measurements.

The treated as protocol population was defined as a subset of all randomised patients excluding all patients with major protocol violations as well as participants who did not complete the study.

Quantitative variables are described using median (range) in trial I and range and percent in trial II whereas qualitative variables are described by frequency in both trials.

Statistical analysis was conducted using GraphPad Prism 5.

Ethics

The trials were approved by the regional ethical committee (case number H-3-2011-124), and conducted in accordance with the standards of the Declaration of Helsinki.

Results

Patients

Trial I: Of 64 patients, 25 declined or could not be contacted and 17 did not meet the inclusion criteria. A total of 22 patients were included. Two patients were excluded from the final analysis because of change in the dose of medicine or relapse, and in addition, two patients did not show up for the follow-up visit. A total number of 18 patients were eligible for analysis. Thirteen patients took Asacol and three patients took Mesasal. Two patients took Pentasa. Table 1 shows the baseline characteristics for trial I.

Total, n	Intention-to-treat (n=22)	Per protocol (n=18)
Age, years	46.5 (21.0-71.0)	48.0 (21.0-71.0)
Sex, n		
Women	15 (68)	13 (72)
Men	7 (32)	5 (28)
BMI, kg/m ²	24.6 (19.1-31.8)	24.9 (19.1-31.8)
SCCAI, point	1.0 (0.0-3.0)	1.0 (0.0-3.0)
Disease extent, n		
Proctitis	4 (18)	3 (17)
Proctosigmoiditis	3 (14)	3 (17)
Left sided colitis	2 (9)	2 (11)
Extensive colitis/pancolitis	13 (59)	10 (56)
CRP, mg/L	1.3 (0.49-15.0)	1.5 (0.6-15)
Type of medicine, n		
Pentasa®	2 (9)	2 (11)
Asacol®	17 (77)	13 (72)
Asacol® + Mesasal®	3 (14)	3 (17)
Dose of medicine, mg/day		
5-ASA	4000 (800-6000)	3700 (800-6000) **
Total urinary 5-ASA excretion, %		
Pentasa®	38 (13.5-62.5) *	38 (13.5-62.5) *
Asacol®	28.4 (5.7-64.7)	28.4 (5.7-64.7)
Medicine compliance, %	100 (89-100)	100 (92-100)

BMI = Body mass index, SCCAI, Simple clinical colitis activity index, CRP = C-reactive protein.

Quantitative variables are described using median (range) and qualitative variables are described by frequency (%).

* Estimated from 18 participants. ** Estimated from 17 participants.

Trial II: A total of 12 patients were randomly assigned to Isphagula Husk ($n=8$) or placebo ($n=4$). One patient was excluded from the final analysis due to change in the dose of medicine, and additionally two patients never started their assigned treatment and one patient did not want to continue due to lack of effect. A total number of eight participants were eligible for analysis - four

from the intervention group and four from the placebo group. All the patients in the intervention group took Asacol. In the placebo group, two patients took Asacol and one patient took Mesasal. Only one patient took Mezavant. There were no significant differences between the two treatment groups at baseline (Table 2).

	Fiber group	Placebo group	p-value
Total, n	8 (4)	4	-
Age, years	23-54 (23-33)	35-53	0,35 (0,029)
Sex, n			-
Women	4 (1)	2	
Men	4 (3)	2	
BMI, kg/m ²	19,6-27,7 (20,3-26,6)	20,5-25,4	0,67 (1,0)
FFQ, g/day	9-26 (16-26)	13-29	0,39 (1,0)
IBDQ, point	135-199 (158-199)	133-196	0,67 (0,38)
SCCAI, point	4-8 (4-8)	10-Apr	0,93 (0,56)
f-calprotectin, µg/g	29-2444 (29-2444)	78-2924	0,51 (0,69)
CRP, mg/L	0,4-9,9 (0,4-7,5)	0,4-12	0,78 (0,56)
Disease extent, n			-
Proctitis	3 (2)	1	
Proctosigmoiditis	1 (0)	1	
Left sided colitis	2 (1)	1	
Extensive colitis/pancolitis	2 (1)	1	
Type of medicine, n:			-
Mezavant®	0 (0)	1	
Asacol®	7 (4)	2	
Asacol® + Mesasal®	1 (0)	1	
Dose of medicine, mg/day	2400-4500 (2400-4000)	2400-4800	0,93 (0,77)
Total urinary 5-ASA excretion, %	(0,5-27,1) *	2,7-26,0	(0,89)
Medicine compliance, % ***	43-100** (94-100)	68-100***	0,48 (0,24)

BMI = Body mass index, FFQ = Food frequency questionnaires, IBDQ = Inflammatory bowel disease questionnaire, SCCAI = Simple clinical colitis activity index, CRP = C-reactive protein.

Quantitative variables are described using range and qualitative variables are described by frequency.

Data are estimated as intention-to-treat, and in brackets are shown data as treated as protocol.

* $n=5$. ** $n=6$. *** $n=3$.

Clinical Outcomes Trial I

After one week with fibre supplement the primary endpoint, CRP, decreased with 7.7 mg/L ($p=0.27$). Total urinary excretion of 5-ASA, decreased 6.3 percentage point (range: -50.6-33.6) ($p=0.03$) in absolute values (treated as protocol population). Post hoc analysis without the patient, who was noncompliant with the medicine ($n=17$) showed an even more significant decrease of 6.3 percentage point (range: -50.6-33.6) ($p=0.008$) in total urinary excretion of 5-ASA. Data is shown in table 3 and figure 1 and 2.

Clinical outcomes (trial I).

	Difference	p-value
CRP, % (n=18)	7.7	0.27
Total urinary 5-ASA excretion, % (n=18)	6.3	0.03
Total urinary 5-ASA excretion, % (n=17)	6.3	0.008

Figure 1 Urinary 5-ASA excretion – per protocol analysis

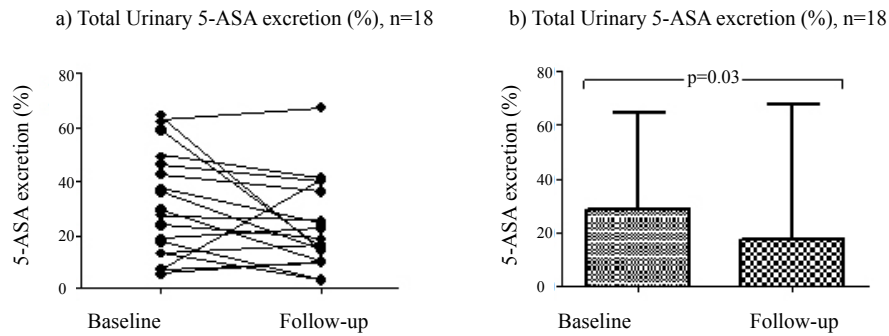


Figure 1: Total urinary 5-ASA excretion before and after seven days fiber intake according to treated as protocol analysis ($n=18$) ($p=0.03$).

a) Shows the excretion for each single patient.

b) Shows the both the median before (28.4 %) and after (17.5 %) for the excretion (range 50.6-33.6 %).

Figure 2 Urinary 5-ASA excretion – post hoc analysis

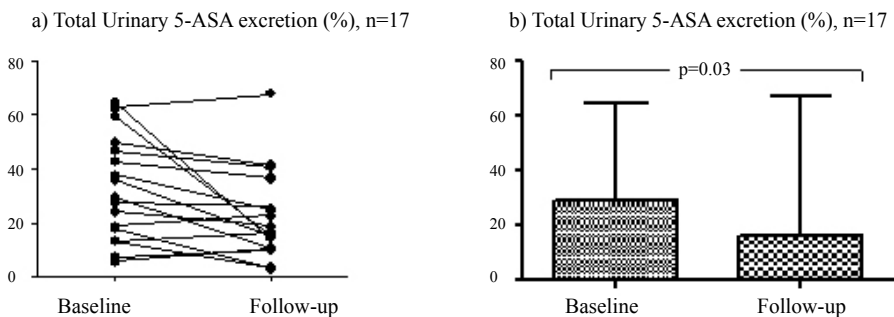


Figure 2: Total urinary 5-ASA excretion before and after seven days fiber intake according to post hoc analysis ($n=17$) ($p=0.008$).

a) Shows the excretion for each single patient.

b) Shows the both the median before (29.4 %) and after (16.4 %) for the excretion (range 50.6-33.6 %).

Treatment Compliance in Trial I

At follow-up, 15 participants delivered the remaining fibre, thus resulting in a compliance with fibre intake of 104 (87-140) %. At follow-up all patients took the prescribed dose of medicine.

Clinical Outcomes in Trial II

In trial II no significant changes were found neither within nor between fibre and placebo group with in respect to IBDQ and SCCAI score, faeces samples, and excretion of 5-ASA and ac-5-ASA, (Table 4).

The results for disease activity score at baseline (1.) and follow-up (2. or 3. if three measurements) together with the effect over time (E).

Patient	IBDQ			SCCAI			F-calprotectin			Total urinary 5-ASA excretion			
	1	2	E	1	2	E	1	2	E	1	2	3	E
5	192	165	↓	8	8	↔	2444	472	↑	0.5	0	0.8	↓
10	199	189	↓	5	5	↔	98	116	↓	26.7	18	21	↑
11	158	175	↑	4	3	↑	<30	<30	↔	27.1	27.3	17.2	↑
12	161	199	↑	5	2	↑	283	152	↑	7.7	7.9	16.5	↓
3	133	166	↑	6	5	↑	2924	614	↑	2.7	3.7	0.6	↑
4	142	122	↓	10	11	↓	1076	>3600	↓	14.9	11.5	11.5	↑
7	161	189	↑	7	2	↑	115	24	↑	23.9	36.6	44.7	↓
9	196	198	↑	4	4	↔	78	233	↓	26	33	33.2	↓

Treatment Compliance in Trial II

At follow-up all patients delivered the remaining powder, thus resulting in a compliance with intake of fibre of 72-117% (range) and intake of breadcrumbs of 61-100% (range). At follow-up all patients in the fibre group took the prescribed medicine, whereas the medicine compliance was 90.6-100% (range) in the placebo group. The patients in the fibre group had an intake of dietary fibre of 16-26 g/day at baseline and 21-37 g/day at follow up whereas the intake was 13-29 g/day at baseline and 22-26 g/day at follow up in the placebo group (data as range) measured by food frequency questionnaire.

Discussion

In this study we examined the binding effect of 5-ASA to Isphagula Husk by examining urinary excretion of 5-ASA in patients with UC in remission and relapse (trial I and II). We also examined the effect on disease activity in patients with UC in remission and relapse (trial II).

In trial I we observed no changes in CRP level over the study period ($p=0.27$), whereas a significant decrease of 6.3 percentage point in the amount of 5-ASA excreted in the urine was found in patients with UC in remission ($p=0.03$). The reason that less 5-ASA was excreted in the urine may be due to that a binding effect between 5-ASA and Isphagula Husk is seen and 5-ASA may as a consequence be transported to the colon together with Isphagula Husk. In the colon Isphagula Husk is moderately fermented Eswaran et al. [4] and 5-ASA may be liberated and the intraluminal concentration in colon may thereby be increased.

In trial II no changes were found in active UC in respect to changes in disease activity and excretion of 5-ASA in the urine, but it seems that patients in the fibre group did not worsen over time. The possible coherence between disease activity and fibre intake may be due to increased production of short chain fatty acids in the colon [8]. The risk of errors of type 2 is, however, very large due to the small number of patients included in trial II, and this may be the reason that we see a decreased excretion of 5-ASA in trial I and not in trial II.

In trial I and II several factors could have influenced the results. E.g. both trials included patients with different extensions of colitis and it is impossible to know if the colonic absorption of fibre and 5-ASA differ because of that. One patient in trial II took Mezavant, which have a more distal 5-ASA release than e.g. Asacol and Pentasa. The different release systems could have influenced the results [1,9].

Most patients had very small variations in the CRP-concentrations - the largest decrease was 2.0 mg/L and the largest increase was 2.7 mg/L. In these well-treated patients, one could hardly expect to detect a difference in disease activity unless the number of patients was very large.

Compliance turned out to be satisfying in this study, although methods for measurement are imprecise. The intake of fibre in trial I reached a compliance rate at 104%, which illustrated that the patients used a larger amount of powder than instructed.

Ingestion of 30 g/day of Isphagula Husk over 4 weeks has shown a decrease in pH of 0.5 in colon [10]. Also pH values of 2.3-4.3 were found in patients with active UC, only in three out of seven patients, though. These were the

patients with the most active disease. In the rest of the patients pH values of 5.0 and 7.4 were found, and these are considered normal [11]. Although pH has a large impact on the absorption of 5-ASA in colon with a maximum absorption at pH 5.5, this is hardly relevant to the effect on urinary excretion as most of the absorption takes place in the small intestine, where dietary fibres do not alter pH.

Also the side effects of 5-ASA may be decreased because they are mainly attributed to the absorbed fraction. This binding capacity might therefore be a therapeutic gain in the treatment of UC with 5-ASA.

Intake of dietary fibre was determined using a food frequency questionnaire, which was constructed for trial II in particular and therefore not validated in other studies.

The participants were asked not to change their intake of dietary fibre and fibre rich food items while participating in trial II. Despite this, three participants in the fibre group and two in the placebo group increased their fibre intake, while two in the placebo group decreased their intake. Only one patient in the fibre group had a stable intake of fibre. Other sources of fibre than Isphagula Husk may have an impact on the absorption of 5-ASA, but the importance of this is not known [3], although other fibres had a much lesser binding capacity for 5-ASA in vitro.

The accuracy of the urine collection is always a crucial point, and several patients in both trials had very small amounts of total urine, but this was equally distributed in both randomization groups although adding to the variance in a small study. The variability of 5-ASA excretion in the urine has earlier been seen to increase with 24-36% after Asacol, 25-37% after Pentasa and 33-57% after Mesasal intake [5,12,13]. A decrease of 6.3%, as seen in this study, could therefore be a natural variation and maybe not an effect of the dietary fibre intake.

Conclusion

In patients with quiescent UC a decreased excretion of 5-ASA was found, but this was not seen in eight patients with active UC, possible due to the small number of participants. No effects on disease activity was found in either trial, but participants in the placebo group in trial II seemed to have worsened activity whereas participants in the fibre group did not worsen, generally seen from SCCAI, IBDQ, faecal calprotectin and CRP.

From these trials it seems that a fibre supplement does not worsen patient's symptoms, and this may allow for larger studies investigating the potential positive effect of fibre supplement on disease activity or risk of flare ups.

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