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Randomised clinical trial: colestyramine vs. hydroxypropyl cellulose in patients with functional chronic watery diarrhoea

F. Fernández-Bañares*,†, M. Rosinach*,†, M. Piqueras‡, A. Ruiz-Cerulla§, I. Modolell‡, Y. Zabana*,†, J. Guardiola§ & M. Esteve*,†

*Department of Gastroenterology, Hospital Universitari Mutua Terrassa, Terrassa, Spain.
†Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain.
‡Department of Gastroenterology, Consorci Sanitari Terrassa, Barcelona, Spain.
§Department of Gastroenterology, Hospital de Bellvitge, Barcelona, Spain.

Correspondence to:
Dr F. Fernández-Bañares, Department of Gastroenterology, Hospital Universitari Mutua Terrassa, Plaça Dr Robert 5, 08221 Terrassa (Barcelona), Spain.
E-mail: ffbanares@mutuaterrassa.es

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SUMMARY

Background
Idiopathic bile acid malabsorption (BAM) has been suggested as a cause of chronic watery diarrhoea, with a response to colestyramine in 70% of patients. However, the efficacy of this drug has never been investigated in placebo-controlled trials.

Aim
To evaluate the efficacy of colestyramine as compared with hydroxypropyl cellulose in the treatment of functional chronic watery diarrhoea.

Methods
Patients with chronic watery diarrhoea were randomly assigned to groups given colestyramine sachets 4 g twice daily (n = 13) or identical hydroxypropyl cellulose sachets (n = 13) for 8 weeks. The primary end-point was clinical remission defined as a mean of 3 or fewer stools per day during the week before the visit, with less than 1 watery stool per day. A secondary end-point was the reduction in daily watery stool number. SeHCAT test was performed in all patients, but an abnormal test was not a prerequisite to be included.

Results
All included patients had a SeHCAT 7-day retention ≤20%. There were no statistical differences in the percentage of patients in clinical remission at week 8 between colestyramine and hydroxypropyl cellulose with either intention-to-treat (53.8% vs. 38.4%; P = 0.43) or per-protocol (63.6% vs. 38.4%; P = 0.22) analyses. However, the mean per cent decrease in watery stool number was significantly higher with colestyramine than with hydroxypropyl cellulose (−92.4 ± 3.5% vs. −75.8 ± 7.1%; P = 0.048). The rate of adverse events related to study drugs did not differ between groups.

Conclusions
Colestyramine (4 g twice daily) is effective and safe for short-term treatment of patients with chronic watery diarrhoea presumably secondary to BAM. Clinical Trials Register number EudraCT 2009-011149-14.

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INTRODUCTION

Idiopathic bile acid malabsorption (BAM) has been suggested as a cause of watery diarrhoea in patients diagnosed with irritable bowel syndrome (IBS-D). Since the 1980s, the use of the ^{75}Selenium homocholic acid taurine (SeHCAT) test as a screening test for BAM has revealed that idiopathic (type 2) BAM is not a rare entity. A systematic review of studies investigating BAM in patients presenting with IBS-D symptoms showed that 10% of these patients had severe BAM (SeHCAT < 5%), and that 32% had moderate-to-severe BAM (SeHCAT ≤ 10%).[1] Colestyramine seems to be a successful therapy with improvement or cessation of diarrhoea in 70% (range, 63–100%) of patients who were able to tolerate it.[1, 2] However, due to a lack of randomised controlled trials, the scientific evidence for the use of colestyramine in this setting is scarce.[3]

In a previous study by our group, diarrhoea secondary to BAM, diagnosed on the basis of both an abnormal SeHCAT test and a long-term response to colestyramine, was the cause of diarrhoea in most patients suffering from chronic watery diarrhoea of functional characteristics when microscopic colitis and gluten-sensitive enteropathy had been ruled out.[4] However, the sensitivity of the SeHCAT test in detecting BAM is not well established, and no standardisation of the definition of a positive SeHCAT test exists.[3] Likewise, it has been suggested that response rate to colestyramine is not dependent on the severity of BAM, with a treatment success in 67% of patients with <5% retention in the SeHCAT test, 73% of patients with <8–12% retention and 59% of those with <15% retention.[2] For all these reasons, the necessity of performing a SeHCAT test to select patients with chronic watery diarrhoea to be treated with colestyramine is not well documented.

The aim of the present study was to evaluate the efficacy and tolerability of short-term treatment with colestyramine as compared with hydroxypropyl cellulose in patients presenting with either functional chronic diarrhoea or IBS-D symptoms in a double-blind, randomised, controlled trial. Hydroxypropyl cellulose was chosen as a placebo although, as discussed below, we subsequently became aware that it may be an active drug in treating BAM.

The presence of BAM (as assessed by a SeHCAT test ≤10% 7-day retention) was not a prerequisite for inclusion in the present trial.

METHODS

Study design and setting

The study was designed as a double-blind, randomised placebo-controlled, phase IV, noncommercial, independent, comparative clinical trial conducted in three centres in Spain. The study was funded by a Spanish health ministry grant on Independent Drug Research (grant number EC08/00085). Patients were included from July 2010 to September 2014. The study protocol was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and in full conformity with relevant regulations. It was approved by the ethical committees of the three participating centres. The study protocol was registered at www.clinicaltrialsregister.eu (EudraCT 2009-011149-14). All authors had access to the study data and reviewed and approved the manuscript.

Study population

Men and women aged 18 years or more were eligible for randomisation if they met the following inclusion criteria: (i) presence of chronic watery diarrhoea defined as >2 watery stools per day (type 6–7 in the Bristol Stool Scale); (ii) fulfilling Rome III criteria of IBS-D or functional diarrhoea; (iii) normal physical examination and blood analysis, including blood biochemistry (fluid/electrolyte status; kidney and liver function; prothrombin time; ferritin; folate; serum protein/globulins; cholesterol and triglycerides; calcium; magnesium; C-reactive protein), complete blood count, ESR, serum T4-TSH and serum IgA-human anti-tissue transglutaminase antibodies; (iv) negative faecal bacterial cultures and exam for ova and parasites; (v) women of child-bearing potential were required to use appropriate contraceptive methods; and (vi) all participants provided written informed consent.

A SeHCAT test was performed on all participants at baseline to quantify the extent of BAM. Patients were included if they had an abnormal SeHCAT test (≤10% 7-day retention) or if after an extensive diagnostic work-up, there was no aetiology of the diarrhoea (idiopathic chronic watery diarrhoea). Exclusion criteria for participation included previous treatment with colestyramine; significant ileal and colonic diseases (i.e. microscopic colitis – normal multiple colonic biopsies were required, polyps >2 cm, ulcerative colitis, Crohn's disease, ischaemic colitis); ileal and/or colonic resection, vagotomy, cholecystectomy; other intestinal diseases with structural

damage; infectious diarrhoea; coeliac disease [negative coeliac serology and normal (Marsh 0) duodenal biopsies, if positive HLA-DQ2 and/or HLA-DQ8, were required]; malignant disease; severe co-morbidity; abnormal hepatic function or liver cirrhosis; bile conduct obstruction; renal insufficiency; either alcohol or drug abuse; chronic intake of NSAIDs or olmesartan; participation in other randomised controlled trial in the previous 4 weeks; pregnancy or breast-feeding.

As inclusion/exclusion criteria refer to patients without clinical history, signs or symptoms, or analytical abnormalities supporting either pancreatic insufficiency or bacterial overgrowth as the cause of the chronic diarrhoea, tests to rule out these entities were no routinely indicated.

Treatment allocation

A computer-generated list of random numbers was used for allocation of participants. This list was prepared by the Pharmacy Department of Hospital Universitari Mutua Terrassa without any clinical involvement in the trial. Eligible patients were randomly assigned to one of two treatment groups. The study medication was packed in boxes, and consecutively numbered for each patient according to the randomisation schedule. The investigators at the centres enrolled the patients and dispensed the study medication according to the randomisation schedule. Patients received either 4 g colestyramine sachets twice daily or identical placebo sachets for 8 weeks in a double-blind fashion. It was very difficult to select a placebo of similar organoleptic properties than colestyramine. Hydroxypropyl cellulose was chosen for comparison although, as discussed below, we subsequently became aware that it may be an active drug in treating BAM.

Colestyramine sachets were re-packed for masking from Resincolestiramina sachets (Rubió Laboratories, Barcelona, Spain), by an independent company that also prepared the identical hydroxypropyl cellulose sachets. Resincolestiramina sachets contain strawberry flavoured colestyramine (4 g) powder to be dissolved in water, and as excipient, it includes carboxymethyl cellulose. Rubió Laboratories did not have any role in the present independent, noncommercial research.

Interim visits were made at weeks 1, 2 and 4. Patients nonresponsive after 2 weeks were allowed to increase the study drug dose to three sachets daily. Adherence to the study treatment was monitored by sachet count at each study visit and with the patient diary. During the entire study period, the use of anti-diarrhoeals, spasmolytics and other drugs causing constipation was not permitted.

Clinical outcomes evaluation

Our primary end-point was clinical remission at 8 weeks, defined as a mean of 3 or fewer stools per day during the week before the visit, with less than 1 watery stool per day.[5] A secondary end-point was the reduction in number of watery stools (type 6–7 in Bristol Stool Scale) per day. Additional end-points were changes in health-related quality of life as assessed with the Gastrointestinal Quality of Life Index (GIQLI),[6] and tolerability and safety.

Safety evaluation

At baseline and final visit, patients underwent physical examination and general laboratory tests. In addition, at each appointment, previous (at baseline) and concomitant medications were recorded, and adverse events were noted.

Statistical analysis

Sample size was calculated assuming rates of clinical remission of 70% in the colestyramine group.[1, 2] As there were no previous data about placebo response in this setting, we select a arbitrarily 20% response rate for the placebo comparison group. With an alpha value of 5% and an 80% statistical power to yield a statistically significant result, the calculated sample size was 12 patients per group.

Efficacy was analysed for the intention-to-treat (ITT) population with a sensitive analysis for the per-protocol (PP) population. Patients with lack of compliance, violation of eligibility criteria or early discontinuation due to adverse event without causal relationship with study drug were excluded from PP population. Safety analysis was performed descriptively for the safety population.

Results are given as mean ± S.E.M. or percentages. Fisher's exact test and paired or unpaired *t*-test were used for the statistical analysis, and type 1 error rate was two-sided with alpha = 0.05. All statistical analyses were conducted using the SPSS for Windows statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient population

We randomised a total of 26 patients (colestyramine, 13; hydroxypropyl cellulose, 13) eligible for ITT analysis. The flow of patients throughout the study is described in Figure 1. A total of two patients in the colestyramine group had adverse events that prompted their withdrawal, but there was no causal relationship with the

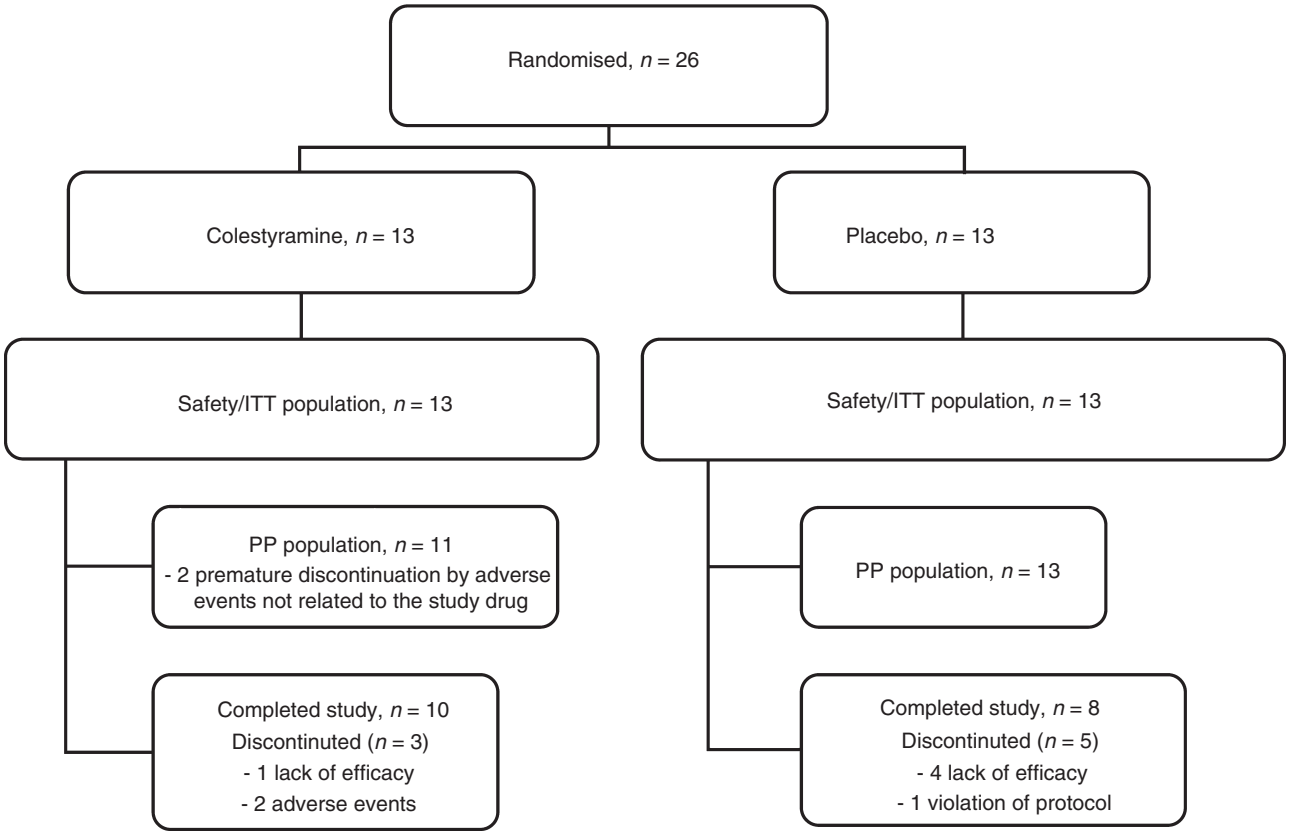

Figure 1 | Study flow of randomised patients.

Table 1 | Baseline demographic and clinical characteristics of each group

Characteristics	Colestyramine (n = 13)	Hydroxypropyl cellulose (n = 13)	P
Age (years)*	50.0 ± 4.9	49.3 ± 4.5	NS
Sex (% women)	7/13 (53.8)	11/13 (84.6)	NS
Duration of diarrhoea (months)*	69.7 ± 23.6	80.1 ± 29.8	NS
Daily stool number*	5.0 ± 0.46	4.9 ± 0.43	NS
IBS (%)	8/13 (61.5)	10/13 (76.9)	NS
Functional diarrhoea (%)	5/13 (38.5)	3/13 (23.1)	NS
%SeHCAT 7-day retention			
≤20	13/13 (100%)	13/13 (100%)	NS
≤15	10/13 (77%)	12/13 (92.3%)	
≤12	10/13 (77%)	11/13 (84.6%)	
≤10	10/13 (77%)	7/13 (53.8%)	
≤5	7/13 (53.8%)	7/13 (53.8%)	
GIQLI*	119.7 ± 6.2	116.1 ± 8.9	NS

NS, nonsignificant.

* Mean ± S.E.M.

study medication (see below), leaving 24 patients for the PP analysis. The baseline demographic and clinical characteristics of the ITT population were similar for the two treatment groups (Table 1). All included patients in both groups had a SeHCAT 7-day retention ≤20% (Figure 2). Adherence to study drug was excellent, higher than 80% in all patients and without differences between study groups.

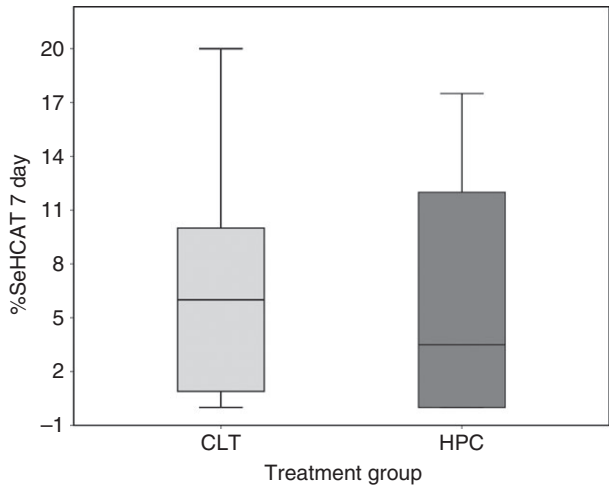

Figure 2 | Box plots describing the basal SeHCAT 7-day retention in both study drug groups. There were no significant differences between groups.

Clinical efficacy

Regarding the primary end-point, the proportion of patients in clinical remission at week 8 was higher with colestyramine than with hydroxypropyl cellulose, but the difference did not reach statistical significance either with the ITT or the PP analysis (Table 2). The differences persisted nonsignificant for the different cut-offs of SeHCAT test, but they were more marked in the cut-offs used in literature to define both moderate-to-severe malabsorption (SeHCAT 7-day retention ≤10%) and severe malabsorption (SeHCAT 7-day retention ≤5%) (Table 2). In these subgroups, a trend was observed but the small sample size precluded to achieve statistical significance.

The effect of study drugs on the daily stool number throughout the trial is shown in Figures 3 and 4. Both colestyramine and hydroxypropyl cellulose significantly reduced the mean number of watery stools per day from 5.0 ± 0.46 to 0.18 ± 0.20 ($P < 0.0005$), and from 4.9 ± 0.43 to 1.29 ± 0.42 ($P < 0.0005$) respectively. However, the mean per cent decrease was significantly greater with colestyramine than with hydroxypropyl cellulose (−92.4 ± 3.5% vs −75.8 ± 7.1%; $P = 0.048$). The effect depending on the SeHCAT 7-day retention is described in Figure 5a,b. The mean per cent decrease was greater with colestyramine than with hydroxypropyl cellulose for all SeHCAT 7-day retention values, achieving statistical significance in the ≤10% cut-off value for both daily total stool number and daily liquid stool number, and in the ≤20% cut-off value for the daily liquid stool number.

The daily dose of colestyramine was increased to 12 g/day in four nonresponsive patients after 2 weeks, two of them achieving clinical remission. Eight nonresponsive patients required a dose increase to three daily sachets in the hydroxypropyl cellulose group, being effective in two of them.

Health-related quality of life

Both colestyramine and hydroxypropyl cellulose improved health-related quality of life as assessed with the GIQLI, but the difference was more marked with colestyramine (Table 3). In the colestyramine group,

Table 2 | Clinical remission rates at week 8 by ITT and PP depending on the %SeHCAT 7-day retention. All included patients had a SeHCAT 7-day retention ≤20%; therefore, this value corresponds to the whole series of patients

%SeHCAT 7-day retention	Colestyramine (n = 13)	Hydroxypropyl cellulose (n = 13)	P value
≤20			
ITT (n = 26)	7/13 (53.8%)	5/13 (38.5%)	0.43
PP (n = 24)	7/11 (63.6%)	5/13 (38.5%)	0.42
≤15			
ITT (n = 22)	4/10 (40%)	5/12 (41.6%)	0.93
PP (n = 20)	4/8 (50%)	5/12 (41.6%)	0.71
≤12			
ITT (n = 21)	4/10 (40%)	5/11 (45.4%)	0.80
PP (n = 19)	4/8 (50%)	5/11 (45.4%)	0.84
≤10			
ITT (n = 18)	4/10 (40%)	2/8 (25%)	0.50
PP (n = 16)	4/8 (50%)	2/8 (25%)	0.30
≤5			
ITT (n = 13)	3/6 (50%)	2/7 (28.6%)	0.43
PP (n = 12)	3/5 (60%)	2/7 (28.6%)	0.28

Aliment Pharmacol Ther 2015; 41: 1132–1140

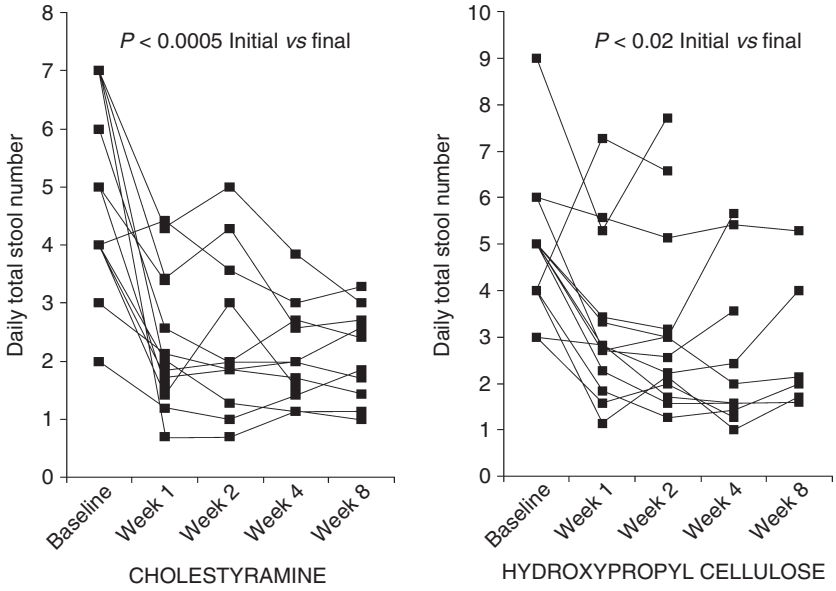

Figure 3 | Evolution of the daily total stool number throughout the trial by patient in each study group. Each point represents the mean value of the previous week at every visit.

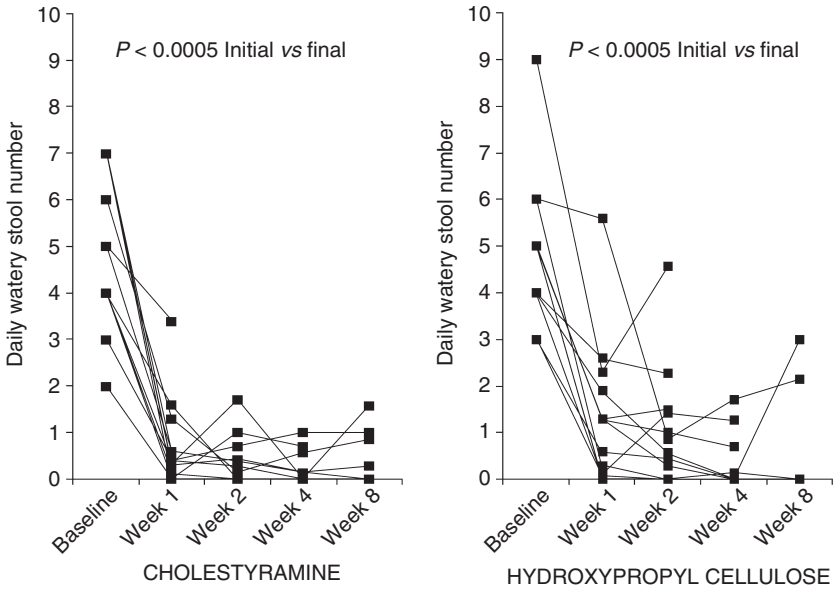

Figure 4 | Evolution of the daily watery stool number throughout the trial by patient in each study group. Each point represents the mean value of the previous week at every visit.

there were significant improvements in symptoms, physical and emotional scales; in the hydroxypropyl cellulose group, the significant differences were in the symptom and social dysfunction scales (Table 3). There were no significant differences between patients with moderate-to-severe and severe BAM (data not shown).

Safety

The rate of adverse events was higher in the colestyramine than in the hydroxypropyl cellulose group: eight adverse events (in six patients) (61.5%) vs. two adverse events (15.4%) ($P = 0.041$) (Table 4). However, only two adverse events had a probable causal relationship with colestyramine (abdominal distension and dyspepsia). No patients experienced serious adverse events.

DISCUSSION

This is the first controlled trial of the efficacy of colestyramine in patients with chronic watery diarrhoea and BAM. Though initially the trial was designed as a placebo-controlled RCT, we realised that hydroxypropyl cellulose may be an active drug in treating BAM. In fact, hydroxypropyl cellulose is a food additive that acts as a thickener and emulsifier, and conceivably might have some bulking effect. Moreover, it has been previously shown in a proof-of-concept study published only in

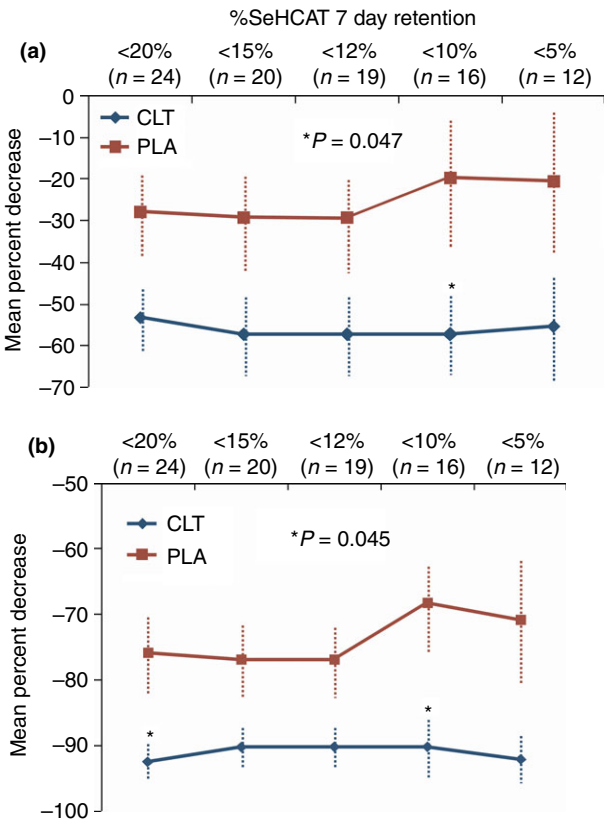

Figure 5 | Effect of study drugs on the daily stool number depending on the SeHCAT 7-day retention: (a) Daily total stool number; (b) Daily watery stool number.

Table 3 | Effect of study drugs on GIQLI scores in the PP population

	Colestyramine (n = 11)	Hydroxypropyl cellulose (n = 10)*
GIQLI		
Initial	119.7 ± 6.2	116.1 ± 8.9
Final	146.5 ± 4.9	135.9 ± 5.9
P value	<0.0005	0.014
Symptoms		
Initial	3.33 ± 0.16	3.27 ± 0.21
Final	4.10 ± 0.14	3.81 ± 0.12
P value	<0.0005	0.014
Physical		
Initial	2.84 ± 0.25	2.96 ± 0.39
Final	3.78 ± 0.18	3.42 ± 0.33
P value	<0.0005	0.07
Emotional		
Initial	3.64 ± 0.22	3.28 ± 0.21
Final	4.04 ± 0.19	3.73 ± 0.24
P value	0.011	0.076
Social		
Initial	3.66 ± 0.21	3.53 ± 0.32
Final	4.09 ± 0.22	4.13 ± 0.15
P value	0.068	0.015

* The final GIQLI questionnaires of three patients were not valid.

abstract form, to be effective in reducing symptoms in bile acid-induced watery diarrhoea.[7] Regrettably, we do not become aware of that study until finishing the present trial. This has to be taken into account when interpreting the results of the present trial.

The results showed that colestyramine was better than hydroxypropyl cellulose, but the differences only reached statistical significance for the secondary end-point reduction in liquid stools, and not for our primary end-point of remission rate. The remission rate after colestyramine observed in the PP population was similar to that reported in systematic reviews.[2, 3] However, we failed to note a statistically significant difference due to the previously unexpectedly high 'placebo' response rate. With the present response rates of 64% and 38.5% for the colestyramine and hydroxypropyl cellulose groups, respectively, a sample of 60 patients per group would be required to yield a statistically significant result with an alpha value of 5% and a statistical power of 80%. However, the present sample size is enough to find statistical differences between groups, with also an alpha value of 5% and a statistical power of 80%, if the sample size is calculated on the basis of a reduction on daily stool number, with a hypothesised difference between groups of 15% and the observed variance.

Colestyramine was significantly superior to hydroxypropyl cellulose in reducing the daily stool number, mainly the watery stool number. This parameter is probably more accurate than stool frequency alone to differentiate between active intervention and placebo in patients with chronic watery diarrhoea, similar to what occurred in a recent trial in patients with collagenous colitis.[5] In microscopic colitis, watery stools are a major determinant of quality of life.[8] Likewise, the improvement in both GIQLI and symptom scale in the present study was more marked after colestyramine than placebo.

SeHCAT 7-day retention is a continuous variable, and the debate has been whether the cut-offs of 10% or 15% (or even 20%) should be used in the prediction of response to bile acid sequestrants.[2, 3, 9] All patients included in the present trial had low SeHCAT values (≤20%), lower than those previously described in healthy controls (30–40% 7-day retention).[10, 11] However, it has

Table 4 | Adverse events for each group

Adverse event	Colestyramine (n = 13)	Hydroxypropyl cellulose (n = 13)
Total	8 (61.5%)	2 (15.4%)*
Causal relationship with study drug	2 (15.4%)	0
Headache	3	0
Muscle pain	0	1
Acute gastroenteritis	1	0
Nasopharyngitis	1	1
Abdominal distension	1	0
Dyspepsia (heartburn)	1	0
Nausea/vomiting†	1	0

* P = 0.041.

† After withdrawal from the study, this patient tolerated colestyramine well in an open-label form, and thus this adverse event was considered to be unrelated to the drug.

been suggested that diarrhoea *per se* might induce malabsorption of orally ingested (exogenous) radiolabelled bile acid (^{14}C-taurocholate) through less efficient ileal absorption.[12] In this sense, diarrhoea induced in healthy subjects by intake of a polyethylene glycol-containing electrolyte solution produced a decrease in 7-day SeHCAT retention.[10] Thus, BAM may be a secondary effect of accelerated transit by diarrhoea itself rather than the cause of diarrhoea in many instances. Although BAM is a known cause of diarrhoea, only aqueous concentrations of dihydroxy bile acids in the colon greater than 3 mM can induce it.[13] Several mechanisms including water and sodium secretion, and increases of both epithelial permeability and intestinal motility have been involved.[14, 15] Measurement of faecal bile acid concentrations requires, unfortunately, expensive analytical techniques and considerable expertise, which limits its use. Thus, it has been stated that the contribution of BAM to diarrhoea in a given patient would be determined by a therapeutic trial of colestyramine.[16] In the present trial, colestyramine induced diarrhoea cessation in 64% of patients who tolerate it, but its efficacy was similar in those patients with SeHCAT 7-day retention cut-offs of 5% or 10% than in the whole series. These data are in agreement with a systematic review and with a recent study evaluating the effect of colestipol in bile acid-induced diarrhoea both suggesting that response rate to bile acid sequestrants is not dependent on the severity of BAM.[2, 9] Thus, the effect of colestyramine in improving diarrhoea could be by another mechanism other than by binding malabsorbed bile acids. In this sense, colestyramine has been shown to preferentially bind dihydroxy bile acids and reduce the secondary bile acid pool, but in addition, it elevates the ratio of glycine- vs. taurine-conjugated bile acids in bile. Because glycine conjugates are more subject to passive absorption, this may also contribute to reduce malabsorption.[17] Besides, colestyramine is a strong anion-exchange resin which can bind other compounds in the colon lumen, like bacterial toxins and mycotoxins.[18–21]

Our study confirms the safety of short-term colestyramine treatment, with only minor adverse events with a causal relationship with the study drug. Reported side effects in the literature included abdominal bloating and pain, dyspepsia, nausea and vomiting, flatulence, borborygmi, abdominal distension, constipation and diarrhoea increasing in severity.[2] The present study reveals that minor adverse events associated with colestyramine use appeared in only 15% of patients.

In summary, our study confirms that colestyramine is effective and safe for short-term treatment of patients with functional watery chronic diarrhoea. Besides, the high rate of response to hydroxypropyl cellulose suggests that this compound is also active in bile acid diarrhoea.

AUTHORSHIP

Guarantor of the article: Fernández-Bañares, Esteve.

Author contributions: Fernández-Bañares, Esteve: study concept and design. Fernández-Bañares, Rosinach, Piqueras, Ruiz-Cerulla, Modolell, Zabana, Guardiola, Esteve: acquisition of data. Fernández-Bañares, Esteve: analysis and interpretation of data. Fernández-Bañares, Esteve: drafting of the manuscript. Fernández-Bañares, Rosinach, Piqueras, Ruiz-Cerulla, Modolell, Zabana, Guardiola, Esteve: critical revision of the manuscript for important intellectual content. Fernández-Bañares: statistical analysis. Fernández-Bañares: study supervision. All authors have approved the final version of the manuscript.

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