Journal of Crohn's and Colitis (2014) 8, 945–955

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Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels

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Received 13 December 2013; received in revised form 6 January 2014; accepted 21 January 2014

KEYWORDS
Inflammatory bowel disease;
Irritable bowel syndrome;
Psychotherapy;
Mindfulness

Abstract

Background and Aims: Psychological interventions are used in patients with inflammatory bowel disease (IBD) but there is uncertainty about who the optimal target population is. Multi-convergent therapy (MCT) is a form of psychotherapy that combines mindfulness meditation with aspects of cognitive behavioural therapy and has been used in the management of irritable bowel syndrome (IBS). This study aimed to assess the feasibility and efficacy of MCT in the management of IBD patients with either functional abdominal symptoms or high perceived stress levels.

Methods: Sixty-six IBD patients in clinical remission with either IBS-type symptoms or high perceived stress levels were randomly allocated to a 16-week MCT course or waiting list control group. Patients were followed-up for one year with the Inflammatory Bowel Disease Questionnaire (IBDQ) as the primary outcome measurement.

Results: A higher mean IBDQ score was observed in the active group compared to controls at the 4-month assessment (167 vs. 156, p = 0.081), but this was not statistically significant nor did it reached the predefined clinically significant difference of 20. In patients with IBS-type symptoms at baseline there was a significantly higher mean IBDQ score in the active group compared to controls (161 vs. 145, p = 0.021). There was no difference between groups in relapse rate based on faecal calprotectin measurement.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BFI, Big Five Inventory; CAI, Clinical Activity Index; CD, Crohn's disease; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IBS-SSS, Irritable Bowel Syndrome Symptom Severity Scale; IBS, irritable bowel syndrome; ISEL, Interpersonal Support Evaluation List; ITT, intention-to-treat; MCT, multi-convergent therapy; MM, mindfulness meditation; NART, National Adult Reading Test; PSQ, Perceived Stress Questionnaire; RDHS, Revised Daily Hassle Scale; UC, ulcerative colitis; WCC, Ways of Coping Checklist.

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1873-9946/$ - see front matter
http://dx.doi.org/10.1016/j.crohns.2014.01.018

Conclusions: IBS-type symptoms in patients with IBD represent a potential therapeutic target to improve quality of life. This study suggests that MCT may be useful in the management of these symptoms but larger studies are required to confirm this.
Clinical Trial Registration Number: NCT01426568.

1. Introduction

A variety of psychotherapeutic interventions have been studied in patients with inflammatory bowel disease (IBD). These strategies include stress management, cognitive behavioural therapy, psychodynamic psychotherapy and hypnosis.[1–4] Meta-analysis of these trials has been limited due to diversity in the interventions used, patients included and outcomes analysed. Nevertheless, it appears that moderate improvements in mood disorders and quality of life (QOL) scores may occur whereas impact on disease activity seems minimal.[5–8] A Cochrane review of psychological interventions performed in unselected IBD patients concluded that psychotherapy should not be administered to all patients, but may be of benefit in specific circumstances and that further research should identify those sub-groups most likely to benefit.[9]

A recent meta-analysis of patients with IBD established that 25–46% of those in clinical remission have symptoms compatible with a diagnosis of irritable bowel syndrome (IBS).[10] These patients share similar characteristics to people diagnosed with IBS in the general population, and report a reduced QOL.[11–13] Psychological therapies have been shown to be an effective form of treatment in IBS and have been included in management guidelines.[14–17] It is feasible that IBD patients with IBS-type symptoms may represent a sub-group of patients that will benefit from psychotherapeutic intervention.

A second sub-group that could potentially benefit is those IBD patients with raised perceived stress levels. Several prospective studies have demonstrated that mood disorders and high perceived stress levels are associated with an increased risk of IBD relapse.[18–20] However these studies did not use objective markers of intestinal inflammation to define relapse and instead relied on Clinical Activity Index scores. These indices can be influenced by IBS-type symptoms, which occur more commonly in the presence of mood disorders, and so it is possible that disease activity and therefore relapse rate may have been over-estimated as a result.[21] Improving coping mechanisms and reducing perceived stress levels in this group may enhance outcomes by reducing the burden of functional symptoms.

Multi-convergent therapy (MCT) is a form of psychotherapy that combines mindfulness meditation together with aspects of cognitive behavioural therapy. Mindfulness is an awareness of the present moment experience, and emphasises attention on one's thoughts, bodily sensations and emotions. Through meditation, an ability to non-judgementally appreciate these aspects is developed with the aim of gaining a deeper perspective on one's own response to stress.[22] The clinical effectiveness of MCT has been demonstrated for the treatment of IBS, tinnitus, and chronic fatigue syndrome but its applicability and efficacy in an IBD population has not previously been assessed.[23–25]

IBD patients with IBS-type symptoms or high perceived stress levels represent two sub-groups that could potentially benefit from psychological therapy. The aim of this study is to assess the feasibility and efficacy of multi-convergent therapy in the management of these two groups of IBD patients.

2. Materials and methods

2.1. Patients

Patients with IBD were recruited from gastroenterology clinics at the University Hospital Llandough and the University Hospital of Wales, Cardiff, United Kingdom between February 2011 and May 2012. Diagnosis of ulcerative colitis (UC) and Crohn's disease (CD) was verified according to the European Crohn's and Colitis Organisation criteria [26,27] and disease extent was defined according to the Montreal classification.[28] The study was approved by the South East Wales research ethics committee. The trial was registered at ClinicalTrials.gov: trial identifier NCT01426568.

The inclusion criteria were (i) age 18–65 years, (ii) diagnosis of UC or CD that was in remission based on a clinical index score and a C-reactive protein level <10 mg/l, and (iii) the presence of IBS-type symptoms or a high perceived stress level. (Definitions of these criteria are provided below).

The exclusion criteria were (i) pregnancy, (ii) the presence of ileostomy or colostomy, (iii) previous colectomy, (iv) change in IBD medication (including use of steroids) within 3 months of study entry, (v) change in psychotropic medication within 3 months of study entry, (vi) diagnosis of cognitive impairment, and (vii) previous psychological therapy.

2.2. Intervention

Patients were randomly allocated to either the multi-convergent therapy course plus standard medical therapy (active group) or standard medical therapy alone (control group).

MCT employs a range of behavioural and cognitive techniques with mindfulness meditation as its central component. In this trial the therapeutic approach was standardised to follow the session plan summarised in Table 1. The MCT course consisted of six face-to-face sessions, each lasting for 40 min, and took place over a 16-week period. A single experienced therapist with qualifications in counselling and

Table 1 A summary of the session plan for the multi-convergent therapy course.

Session	Topic	Contents
1	Motivational interview	Explore biopsychosocial model + stress response Patient to keep diary of stressors/ behaviours/symptoms
2	Treatment rationale	Identify stressors + explore coping mechanisms Introduction to MM — written/audio material
3	Mindfulness meditation	Reflection on behaviour patterns Application of MM
4	Theme exploration	Teaching patient to become their own therapist Role of graded exercise and breathing exercises
5	Relapse prevention	Use of meditation to influence physiological responses Complement lifestyle to maintain and consolidate gains
6	Final review	Review of internal locus of control Reflect on techniques and patient preferences

MM = mindfulness meditation.

psychotherapy (MS) conducted the course, which was performed at the University Hospital of Wales, Cardiff.

2.3. Assessments and definitions

2.3.1. Rome III criteria

The presence of IBS-type symptoms was determined using the Rome III Criteria.[29] This symptom-based standard defines IBS as the presence of abdominal discomfort in at least 3 days per month, occurring in the last 3 months, and with onset at least 6 months ago. The abdominal discomfort must be associated with 2 or more of the following: improvement with defecation, onset associated with a change in frequency of stool and onset associated with a change in form of stool.

2.3.2. Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS)

The severity of IBS symptoms is assessed in 5 domains: frequency and severity of abdominal discomfort, severity of abdominal bloating, satisfaction with bowel habit, and impact of symptoms on life in general. Each domain is scored 0–100, and an overall score of 0–500 is obtained. A higher score is indicative of more severe symptoms.[30]

2.3.3. Revised Daily Hassle Scale (RDHS)

This measure of minor life stressors uses an ordinal scale of 0 to 3 grading the degree of hassle caused by each of 53 minor common events.[31] The cumulative score is calculated (range = 0–159).

2.3.4. Perceived Stress Questionnaire (PSQ)

Levels of perceived stress were evaluated using a questionnaire that has been based on observations of an IBD population.[32] An ordinal scale of 1 to 4 is applied to 30 questions regarding the level of perceived stress experienced in the previous month. A cumulative total is calculated. This total has 30 points subtracted, and then is divided by 90 (final score = 0.00–1.00). In a prospective study of patients with UC a PSQ score of >0.44 significantly increased the risk of an exacerbation in the following eight months.[19] Therefore the entry criteria cut-off for defining a high level of perceived stress was set at >0.44.

2.3.5. Ways of Coping Checklist (WCC)

Participants indicate how frequently they use certain behaviours and coping mechanisms in response to stressful scenarios.[33] The questions are split into 5 coping styles (wishful thinking, positive thinking, avoidance, seek advice, and self blame). A mean score for each coping style is calculated (range = 0–3) with a higher score representing more frequent use of that particular style.

2.3.6. Inflammatory Bowel Disease Questionnaire (IBDQ)

This is a validated QOL assessment tool specifically for patients with IBD.[34] An ordinal scale of 1 to 7 is used to respond to 32 questions concerning QOL (overall score 32–224). The questions are split into 4 domains (bowel, emotional, systemic, and social) and a mean score can be calculated for each domain.

2.3.7. National Adult Reading Test (NART)

This is a literacy assessment in which participants are tested on the pronunciation of 50 irregularly spelled words. The number of correct responses are counted (score = 0–50). It is a measure of crystallised intelligence.[35]

2.3.8. Big Five Inventory (BFI)

Using a self-rating scale participants answer 44 statements regarding their personality.[36] The responses are split into five domains: extraversion, agreeableness, conscientiousness, neuroticism and openness. A mean score (range = 1–5) is calculated for each domain with higher scores signifying a strong correlation with that particular type of personality.

2.3.9. Interpersonal Support Evaluation List (ISEL)

This assesses the perceived availability of social resources.[37] It consists of 40 statements that are rated from 1 to 4 based on their applicability to the individual (overall score = 40–160).

2.3.10. Hospital Anxiety and Depression Scale (HADS)

A self-assessment scale consisting of 14 statements (7 regarding anxiety and 7 for depression) that are graded from 0 to 3 according to their relevance to the patient. A range of scores from 0 to 21 is provided for anxiety and depression respectively, with higher scores indicating a greater level anxiety or depression.[38]

2.4. Assessment of disease activity

Activity of IBD was determined using two respective definitions:

(i). Clinical indices: For UC patients, the Simple Clinical Colitis Activity Index was modified such that the 'general well being' score was excluded (it was considered that IBS-type symptoms and high perceived stress levels would disproportionately affect this element).[39] Remission was defined as a score <3. Similarly in CD a modified Harvey–Bradshaw index score was used with the 'general well being' score excluded, and remission was defined as <5 points.[40] The Simple Clinical Colitis Activity Index and the Harvey–Bradshaw Index are both validated symptom-based scores which do not require endoscopic or biochemical investigation.

(ii). Faecal calprotectin (FC): Faecal calprotectin levels were monitored to provide an objective marker of intestinal inflammation. They were not used as inclusion criteria for the study as samples were stored in batches before analysis and so results were not immediately available. Patients were asked to provide a stool sample within 1 week of their clinical assessment, and these were stored at $-20\ ^{\circ}C$. All samples were analysed within 1 month of collection using the CALPRO Calprotectin ELISA Test, a quantitative enzyme immunoassay. An FC level of $<150\ \mu g/g$ was used to define remission.

Changes in patients' medication during the follow-up period were also recorded. An escalation in IBD therapy included any initiation or increase in dosage of anti-inflammatory, steroid, immunosuppressant, or biological medication.

2.5. Trial protocol

Eligible patients were supplied with written and verbal information, and a consent form was signed prior to entering the study. A series of questionnaires were completed at baseline (time = 0) including Rome III Criteria, IBS-SSS, IBDQ, RDHS, PSQ, and WCC. Assessments of personality (BFI), social resources (ISEL), intelligence (NART), and mood disorder (HADS) were also performed at baseline in consideration of their potential to influence the outcome of therapy.

Patients in the active and control groups were assessed at 4, 8, and 12 months during the 1-year follow-up period using postal questionnaires. At each assessment their disease activity was assessed (together with providing a stool sample for FC level), and questionnaires were completed including Rome III Criteria, IBS-SSS, IBDQ, RDHS, PSQ, and WCC.

Patients in both groups continued to receive standard medical care for their IBD throughout the trial. They were asked to report any changes in medication at each 4-monthly assessment.

2.6. Randomisation

Patients were randomised to either an active or control group once the eligibility criteria had been fulfilled and consent had been obtained. A blocked randomisation process, using random permuted blocks of sizes 4 and 6 (selected at random), was generated by the South East Wales Trials Unit. The sequences were put into sequentially numbered sealed opaque envelopes for use in the clinic. Patients with IBS-type symptoms were stratified according to type of IBD (UC or CD) and severity of IBS (IBS-SSS$<$ or ≥ 300). Patients with high perceived stress levels who did not have IBS-type symptoms were stratified according to type of IBD. At the end of the study an audit of the randomisation record was completed.

2.7. Sample size

A power analysis was performed using $\alpha = 0.05$ and $\beta = 0.80$. The mean IBDQ score for patients in clinical remission has previously been reported as 183 with a standard deviation of 27.6.[41] A clinically significant improvement in QOL as measured by the IBDQ was taken to be 20.[42] This indicated that 30 patients would be needed in each trial arm. A 10% drop-out rate was predicted and so a recruitment target of 66 patients was set.

2.8. Outcome measures

The primary outcome measure in this study was IBDQ score at 4 months analysed in the complete case population. Secondary outcomes included descriptive analysis of the acceptability and feasibility of administering MCT to an IBD population, and the effect of MCT on disease activity, levels of perceived stress and coping mechanisms. Separate exploratory sub-group analyses were performed on those patients with FC $<150\ \mu g/g$ at baseline, those recruited with IBS-type symptoms at baseline, and those recruited with a high perceived stress level at baseline.

2.9. Study population definitions

2.9.1. Screening population
Patients approached to participate in the trial.

2.9.2. Intention-to-Treat Population (ITT)
Patients randomised into the trial.

2.9.3. Complete-case population
Those patients from the intention-to-treat population that completed the follow-up assessments.

2.9.4. Per-protocol population
Patients that fully complied with the protocol and completed the follow-up assessments.

2.10. Statistical analysis

Mean and standard deviation levels are shown for all normally distributed data, and comparisons were made using analysis of variance (ANOVA). Values of median and range are provided for non-normally distributed data, with comparisons performed using Kruskal–Wallis test. Categorical data is presented with percentages and absolute numbers, and was analysed using Chi-square tests. Assessment of IBDQ was performed for the complete-case-population and the per-protocol-population

using analysis of covariance (ANCOVA) with baseline IBDQ as covariate. ANCOVA was also used to compare stress scores, coping mechanisms, and in the sub-group analysis of IBS-SSS scores. Regression analysis was used to evaluate factors associated with failure to complete the MCT course, and also characteristics associated with an improvement in IBDQ after the MCT course. For questionnaires that had <50% of a domain completed the missing data was replaced with the mean result for that domain, otherwise they were regarded as missing data. All analysis was performed using PASW Statistics 18.0 (IBM Corporation, Armonk, NY, USA).

3. Results

A total of 66 patients were randomised into the trial. The demographic details and clinical characteristics of these patients are outlined in Table 2. Treatment and control patients did not differ significantly on any of the characteristics at baseline.

Of the 33 patients in the active arm, 8 did not attend the intervention and 6 dropped out during the course. The follow-up assessment at 4 months was completed by 27 patients. In the control group only 1 patient was lost to follow-up during the initial phase and so 32 patients completed the 4-month assessment. The progression of patients through the trial and the reasons for drop-out are shown in Fig. 1.

Overall, the only significant disparity between patients lost to follow-up and the complete-case-population was a younger age (respective mean age of 33 years vs. 47 years, p = 0.04). In the treatment group, logistic regression analysis did not identify any patient characteristics that were significantly associated with failure to complete the MCT course.

3.1. Primary Outcome

Analysis of the complete-case-population found that the mean IBDQ score at 4 months had improved to 167 in those patients randomised to the MCT course, whereas it remained unchanged at 156 for those in the control group. However the difference between the groups was not statistically significant (df = 58, F = 3.165, p = 0.081).

The improvement in IBDQ observed in the active group appeared to be of a global nature with increased scores in all four domains of the assessment (Table 3). The progression of IBDQ score over the 1 year follow-up period is illustrated for active and control groups in Fig. 2. There was no significant difference on repeated measure analysis over time, F(1,46) = 1.77, p = 0.190.

When the per-protocol population was analysed the IBDQ score at 4 months was significantly higher in the active trial group compared to controls (176 vs. 156, df = 49, F = 4.547, p = 0.038) reaching the pre-specified clinically significant difference of 20. However the difference became non-significant at 8 and 12-month assessments.

3.2. Secondary Outcomes

Using clinical indices to define relapse the active intervention group appears to have a lower rate of relapse at 8 and 12 months compared to the control group, although the difference is not statistically significant (Table 4). However when FC levels were used to determine flare-ups the rate of relapse appeared to be very similar in both groups. The kappa statistic, assessing level of agreement between relapse measures, was 0.13 when comparing clinical activity indices to FC, indicating only a slight level of agreement.[43] Patients in the active intervention arm also appeared to require less frequent escalations in IBD medication during the follow-up period (25% vs. 41%, p = 0.210).

Table 2 Demographic details and clinical characteristics of the ITT population at baseline.

	Active (n = 33)	Control (n = 33)
Age, years	44.4 (11.7)	45.4 (10.6)
Gender:		
Male	24% (8)	21% (7)
Female	76% (25)	79% (26)
Diagnosis:		
Ulcerative colitis	73% (24)	64% (21)
Proctitis	25% (6)	24% (5)
Left-sided	58% (14)	67% (14)
Pan-colitis	17% (4)	10% (2)
Crohn's disease	27% (9)	36% (12)
Ileal	22% (2)	33% (4)
Ileo-colonic	33% (3)	33% (4)
Colonic	44% (4)	33% (4)
IBD flare in the last year	52% (17)	55% (18)
IBD medication:		
5-ASA	70% (23)	67% (22)
Immunosuppressants	24% (8)	39% (13)
Biologics	9% (3)	0% (0)
Current smoker	9% (3)	6% (2)
Current antidepressant use	18% (6)	12% (4)
National Adult Reading Test score	33 (13–45)	37 (10–47)
ISEL score	82 (19)	85 (13)
Personality:		
Extraversion	3.1 (0.8)	3.1 (0.8)
Agreeableness	4.0 (0.6)	4.0 (0.8)
Conscientiousness	4.0 (0.6)	3.9 (0.7)
Neuroticism	3.5 (0.7)	3.5 (0.8)
Openness	3.4 (0.6)	3.6 (0.7)
HADS		
Anxiety score:	10.0 (3.5)	11.6 (4.4)
Depression score:	6.2 (2.9)	6.9 (3.4)
IBS-type symptoms present (meeting Rome III Criteria)	58% (19)	58% (19)
Severity of IBS-type symptoms (IBS-SSS)	237 (101)	221 (83)
Inflammatory Bowel Disease Questionnaire score	152 (33)	156 (20)
Faecal calprotectin level (μg/g)	105 (0–1019)	85.5 (0–1089)
Faecal calprotectin <150 μg/g	72% (21)	67% (20)

ISEL = Interpersonal Support Evaluation List; HADS = Hospital Anxiety + Depression Scale; IBS-SSS = Irritable Bowel Syndrome Symptom Severity score.

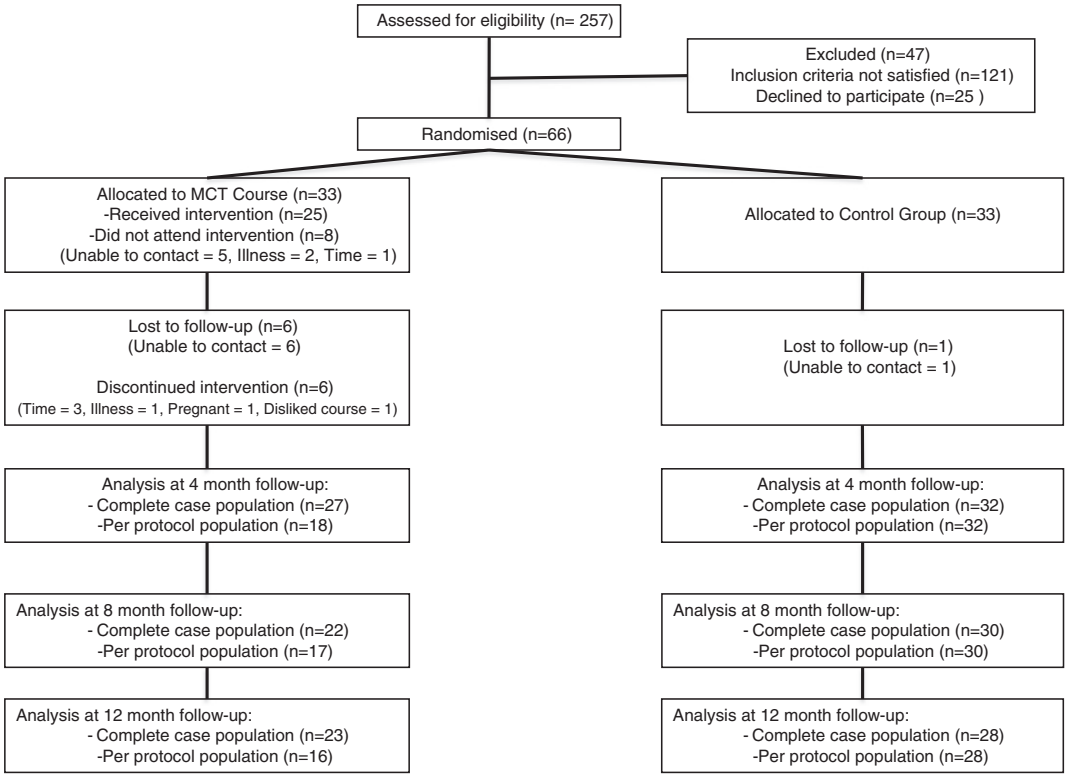

Figure 1 Patient flow through the study.

Levels of perceived stress reduced in both groups over the follow-up, with a marginally greater reduction observed in the active group (Table 5). A comparison of coping mechanisms at the end of follow-up showed a trend towards positive thinking (p = 0.102) and advice seeking behaviour (p = 0.009) in the active group that was not observed in the controls. The trends for using avoidance behaviour, wishful thinking and self blame were similar in both groups.

Table 3 Respective domains of the IBDQ at baseline and 4 months.

	Time = 0 months	Time = 4 months
Total IBDQ:		
Active (n = 27)	156 (32)	167 (30)
Control (n = 32)	156 (20)	156 (37)
Bowel IBDQ:		
Active (n = 27)	5.0 (1.1)	5.4 (1.1)
Control (n = 32)	5.3 (0.7)	5.2 (1.2)
Emotional IBDQ:		
Active (n = 27)	4.7 (1.1)	5.0 (1.0)
Control (n = 32)	4.5 (0.8)	4.5 (1.3)
Systemic IBDQ:		
Active (n = 27)	3.9 (1.1)	4.3 (1.0)
Control (n = 32)	4.1 (1.2)	4.2 (1.4)
Social IBDQ:		
Active (n = 27)	6.0 (1.3)	6.2 (0.9)
Control (n = 32)	6.0 (0.9)	5.7 (1.4)

IBDQ = Inflammatory Bowel Disease Questionnaire.

3.3. Sub-Group Analysis

Of the 59 patients that provided a stool sample at baseline, 41 (70%) had faecal calprotectin <150 μg/g indicating that they were in biochemical remission (as well as clinical remission) upon entering the trial. When only those patients with FC < 150 μg/g were analysed the mean IBDQ scores at 4 months remained similar to that of the complete-case population analysis for both active and control groups (166 vs. 155, p = 0.770).

A total of 38 patients from the ITT population had IBS-type symptoms at baseline. ANCOVA was used to analyse IBDQ score at 4 months in this sub-group and confirmed that it was significantly higher in the active group compared to the controls (161 vs. 145, p = 0.021) (Table 6 and Fig. 3). There was also a trend for IBS-type symptoms to occur less frequently and with less severity in the active group during the follow-up period, although these differences were not statistically significant (Fig. 4). When only those patients in this sub-group with FC < 150 μg/g at baseline were analysed (n = 20) the mean IBDQ score at 4 months was 21 points greater in the active group compared to the controls (163 vs. 142, p = 0.326).

Forty-eight of the patients recruited had a PSQ > 0.44. The IBDQ score at 4 months was higher in those in the active group but the difference was not statistically significant (164 vs. 153, p = 0.095). At 4 months the PSQ score had reduced in both groups but they did not differ significantly (p = 0.417).

Linear regression was used to determine those characteristics of patients in the MCT group that were associated with an improvement in IBDQ score at 4 months. The factors

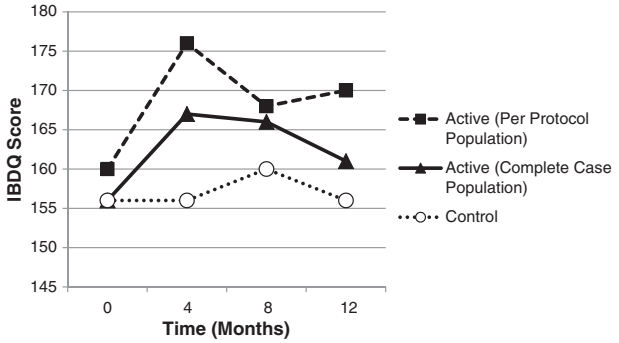

Figure 2 Progression of IBDQ score over the 1 year follow-up period.

analysed included age, gender, type of IBD, NART score, the presence of IBS-type symptoms, baseline LPSQ score, baseline FC level, and MCT course compliance (Table 7). The presence of IBS-type symptoms (p = 0.016) and baseline FC level (p = 0.022) were the only factors with a significant association. However when stepwise linear regression was used in the analysis the only significant association was found to be the presence of IBS-type symptoms (p = 0.038).

4. Discussion

This study assessed the feasibility of using a predominantly mindfulness-based therapy in an IBD population, and examined sub-groups of patients to identify those that may gain the most benefit. Whilst the increase in IBDQ score observed in the active arm of the ITT population was not statistically significant, the sub-group analysis identified that there was a significant improvement in quality of life in those IBD patients who were experiencing IBS-type symptoms. The improvement appeared to be due to a decline in the severity of symptoms. This study suggests that IBS-type symptoms in IBD patients represent a potential therapeutic target to improve QOL. Further studies are required to confirm the efficacy of mindfulness-based therapy in

Table 4 Cumulative rates of relapse and medication escalations over the 1-year follow-up period.

	Active	Control	p-Value
Cumulative relapse rate:			
Defined by CAI			
4 months	27% (7)	28% (9)	0.919
8 months	27% (7)	39% (12)	0.347
12 months	35% (9)	48% (15)	0.294
Cumulative relapse rate:			
Defined by FC			
4 months	25% (6)	37% (10)	0.355
8 months	48% (11)	46% (13)	0.921
12 months	65% (15)	62% (18)	0.815
Medication escalations			
4 months	12% (3)	19% (6)	0.495
8 months	16% (4)	29% (9)	0.251
12 months	25% (6)	41% (12)	0.210

CAI = Clinical Activity Index; FC = faecal calprotectin.

Table 5 Progression of hassle scores, perceived stress, and coping mechanisms over the follow-up period.

	Active	Control	p-Value
Hassle score			
0 months	38 (14)	42 (18)	N/A
4 months	35 (15)	35 (17)	0.579
8 months	33 (15)	37 (20)	0.509
12 months	36 (14)	40 (23)	0.421
Perceived Stress Questionnaire			
0 months	0.43 (0.14)	0.46 (0.16)	N/A
4 months	0.37 (0.14)	0.43 (0.17)	0.343
8 months	0.35 (0.10)	0.41 (0.17)	0.380
12 months	0.35 (0.11)	0.41 (0.17)	0.164
Coping mechanisms			
Wishful thinking			
0 months	1.31 (0.72)	1.44 (0.58)	N/A
4 months	1.13 (0.69)	1.35 (0.82)	0.392
8 months	0.95 (0.74)	1.27 (0.77)	0.364
12 months	1.21 (0.81)	1.24 (0.77)	0.914
Positive thinking			
0 months	1.47 (0.43)	1.37 (0.56)	N/A
4 months	1.55 (0.62)	1.36 (0.65)	0.689
8 months	1.56 (0.62)	1.39 (0.5)	0.685
12 months	1.60 (0.58)	1.30 (0.52)	0.102
Avoidance			
0 months	1.09 (0.53)	0.98 (0.49)	N/A
4 months	1.05 (0.62)	1.01 (0.61)	0.909
8 months	0.78 (0.52)	0.89 (0.54)	0.216
12 months	0.86 (0.56)	0.96 (0.67)	0.242
Seek advice			
0 months	1.32 (0.64)	1.33 (0.73)	N/A
4 months	1.36 (0.77)	1.23 (0.93)	0.658
8 months	1.44 (0.71)	1.12 (0.61)	0.078
12 months	1.44 (0.54)	1.05 (0.65)	0.009
Self blame			
0 months	1.19 (0.58)	1.38 (0.67)	N/A
4 months	1.04 (0.40)	1.08 (0.80)	0.616
8 months	0.79 (0.46)	1.13 (0.68)	0.147
12 months	0.98 (0.50)	1.18 (0.82)	0.369

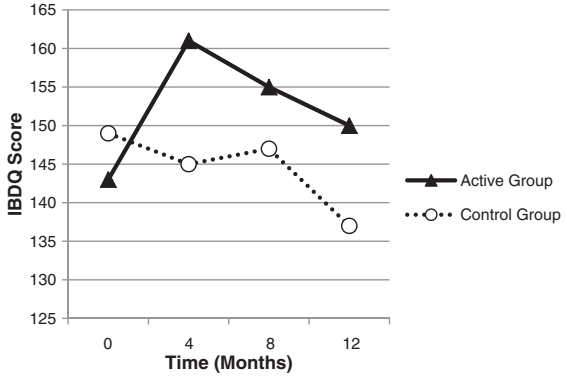

Figure 3 Sub-group analysis for patients with IBS-type symptoms at baseline: progression of IBDQ score during the follow-up period.

Table 6 Sub-group analysis of patients with IBS-type symptoms at baseline.

	Active	Control	p-Value
% with IBS-type symptoms			
0 months	100% (18)	100% (19)	N/A
4 months	69% (11)	89% (16)	0.214
8 months	62% (8)	82% (14)	0.242
12 months	85% (11)	81% (13)	1.000
IBS-SSS score			
0 months	237 (101)	221 (83)	N/A
4 months	160 (99)	206 (108)	0.219
8 months	166 (103)	221 (119)	0.213
12 months	187 (97)	224 (111)	0.234
IBDQ			
0 months	143 (32)	149 (99)	N/A
4 months	161 (35)	145 (39)	0.021
8 months	155 (32)	147 (38)	0.304
12 months	150 (41)	137 (38)	0.059

IBS-SSS = Irritable Bowel Syndrome Symptom Severity score; IBDQ = Inflammatory Bowel Disease Questionnaire.

treating these symptoms, and also to examine the use of alternative IBS therapies in this setting.

Analysis of mean IBDQ score at 4 months in the complete case population demonstrated an 11-point improvement in the active arm compared to no change in the controls. This difference was not statistically significant, and was below the pre-defined 20-point standard that represented a clinically relevant improvement in QOL. However when the per-protocol population was analysed, the IBDQ score was significantly greater in the active group with a mean difference of 20 points, suggesting that patients completing the course did initially gain a substantial benefit. Subsequently, at 8 and 12-month assessments the difference between groups became non-significant indicating that the effects of intervention may decline over time. However it is feasible that this decline in efficacy may be averted with the use of extra 'booster sessions' which are commonly employed in psychological interventions.

The high drop-out rate suggests that the intervention may not be acceptable to all patients. Eight patients randomised

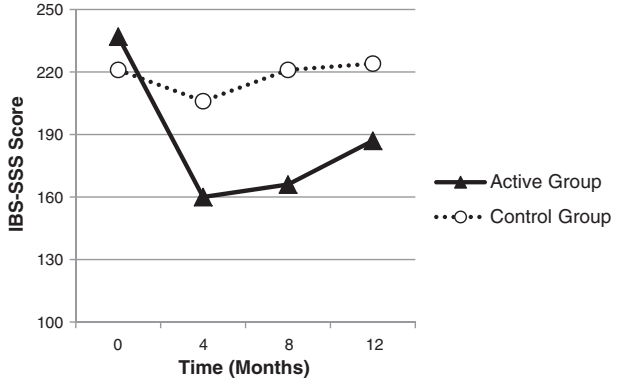

Figure 4 Sub-group analysis for patients with IBS-type symptoms at baseline: severity of IBS symptoms in active and control groups during the follow-up period.

Table 7 Linear regression of patient factors associated with a significant change in IBDQ at 4 months.

	B	Standard error	p-Value
(Constant)	−53.77	23.19	0.034
Age	0.43	0.32	0.198
Gender	9.36	8.18	0.269
Type of IBD	11.89	7.32	0.124
NART score	−0.14	0.34	0.689
IBS-type symptoms	17.88	6.61	0.016
Baseline PSQ score	29.69	20.94	0.175
Baseline FC level	0.027	0.011	0.022
MCT compliance	12.32	6.67	0.083

NART = National Adult Reading Test; PSQ = Perceived Stress Questionnaire; FC = faecal calprotectin; MCT = multi-convergent therapy.

to the active group did not attend a single appointment and six withdrew during the course. Five of the patients that failed to attend any appointment did not respond to a number of attempts at communication. It is possible that these individuals lacked motivation for attending the course and perhaps outside of the trial setting may have declined participation. Several participants had genuine medical reasons for non-attendance or withdrawal including illness and pregnancy (an exclusion criteria). Four patients reported that they were unable to attend due to time constraints related to work or family commitments. Detailed communication prior to starting therapy is clearly required to optimise attendance and efficacy. The MCT course will not be suitable for all patients and there is no problem in withdrawing if they are not gaining benefit.

IBS-type symptoms are common in IBD patients who appear to be in remission and are associated with a reduced QOL. Yet so far they have been the target of very few therapeutic trials. In this study the presence of IBS-type symptoms at baseline was associated with an improvement in IBDQ score following the MCT course. In the active group the percentage of patients with IBS-type symptoms initially decreased but at the end of follow-up the number was similar to that in the control group. However the main impact seemed to be on the severity of IBS symptoms, which remained lower in the active group throughout the study. We speculate that MCT may reduce the severity of IBS-type symptoms in IBD patients and in this way improve their QOL.

This improvement in functional abdominal symptoms may explain the discrepancy in results for relapse rates. The trend for lower relapse rates in the active group based on clinical indices was not apparent when faecal calprotectin was used to define relapse. A recent study has demonstrated that functional symptoms can mimic active inflammation when clinical indices alone are used to assess disease activity,[21] and so it is possible that the more severe IBS-type symptoms in the control group may account for the higher relapse rates observed based on clinical indices. The FC levels represent objective markers of intestinal inflammation and it does not appear that the MCT course had any effect on this. Interestingly, there was also a trend for fewer medication escalations in the active group. Therapeutic clinical decisions are frequently guided by patients' symptoms and so a further consequence of a

reduction in functional symptoms may be to lower use of medication.

Faecal calprotectin levels were not used as an inclusion criterion to define remission as specimens were analysed in batches with results unavailable for up to a month following collection. Remission was defined using clinical indices together with a normal CRP level, however Table 1 suggests that a considerable number of patients had ongoing inflammation with approximately 30% having FC > 150 μg/g. The proportion of patients with raised FC was similar in both active and control groups. Sub-clinical inflammation may play a role in causing IBS-type symptoms in IBD and for this reason a separate sub-group analysis was performed including only those patients with IBS-type symptoms and FC < 150 μg/g. The active group had a 21-point greater IBDQ score compared to the controls at 4 months, and although the difference was not statistically significant this may reflect the smaller number of participants involved in the analysis. In clinical practise, FC analysis should help to determine those patients with active inflammation who are likely to benefit from an escalation in medical therapy before considering management of potential functional symptoms.

Three aspects of stress and its management were assessed during the follow-up period, but the study was not directly powered to detect statistically significant differences in these secondary outcomes and so only trends could be observed. Both groups reported similar amounts of daily hassles throughout the follow-up period. Levels of perceived stress appeared to reduce in both groups but a slightly greater reduction was observed in the active group. However MCT's principal effect appeared to be on coping mechanisms for which a trend towards greater use of positive thinking and advice seeking behaviour was observed. These changes would generally be regarded to represent a healthier style of coping, leading to a reduction in perceived stress in the longer-term.

This trial has several limitations that need to be considered when interpreting the results. Participants were not blinded as to their allocation following randomisation and there was no placebo therapy used in the control group. As a result, we are unable to determine the placebo effects of an expectation to improve and contact attention. This is particularly relevant in the setting of IBS in which the mean placebo response is reported to be 47% with a range from 0 to 84%.[44,45]

The intervention arm experienced a high drop-out rate, with 24% of those randomised into the MCT course failing to attend even a single appointment, and in the majority of cases they were also lost to follow-up. An extra 10% of patients were recruited in view of potential drop-outs, however this underestimated the actual numbers, and as a result the power of the study has been reduced. High drop-out rates are a recognised phenomenon in trials of psychological intervention, and recent trials of mindfulness-based therapy for IBS have experienced drop-out rates of 23–26%.[46–48] There is clearly a demand for psychological interventions in IBD populations with some centres reporting nearly a third of patients expressing interest, however careful patient selection remains essential.[49]

The generalisation of the results of this study is also limited by the fact that a single therapist administered the MCT course. In this type of intervention the relationship between the patient and therapist is vital in determining outcome, and so further studies with multiple therapists and recruiting across several sites would be required to evaluate the effects of MCT more thoroughly.

In the general population psychological therapy is only used for the management of IBS in a minority of cases, typically after other forms of intervention such as dietary modification, antidepressant medication, and serotonin receptor agonists have failed to provide adequate symptom relief. Further trials are needed to examine the role of these treatments in managing IBS-type symptoms in patients with IBD. A pilot study of dietary modification in which patients reduced their intake of short-chain carbohydrates has already demonstrated an improvement in abdominal symptoms in this setting.[50]

IBS-type symptoms in inflammatory bowel disease can have a variety of causes. Sub-clinical inflammation, bile salt malabsorption, and small bowel bacterial overgrowth need to be identified and managed appropriately. By excluding these pathologies the efficacy of interventions directed towards improving 'true IBS symptoms' should be improved. This study suggests that IBD patients with IBS-type symptoms may benefit from a psychotherapeutic intervention. However, a multi-centre trial with adequate provision of placebo in the control arm is needed to confirm this.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

Declaration of funding interests:

The South East Wales Trials Unit is funded by the National Institute for Social Care and Health Research (NISCHR).

Specific author contributions:

JB, MS, KH and JG were involved with the study concept and design; JB performed the data collection; MS conducted the multi-convergent course; JB and KH analysed and interpreted the data; and JB, MS, KH and JG drafted the manuscript.

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