Original Paper

Digestion

Digestion 2004;69:131–139
DOI: 10.1159/000078151

Received: September 3, 2003
Accepted: December 9, 2003
Published online: April 26, 2004

Acupuncture and Moxibustion in the Treatment of Active Crohn's Disease: A Randomized Controlled Study

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Key Words

Acupuncture · Complementary medicine · Crohn's disease · Activity index, Crohn's disease · Inflammatory bowel disease · Chinese medicine, traditional

Abstract

Background: Acupuncture has traditionally been used in the treatment of inflammatory bowel disease in China and is increasingly being applied in Western countries. The purpose of this study was to investigate the efficacy of acupuncture in the treatment of active Crohn's disease (CD). ***Methods:*** A prospective, randomized, controlled, single-blind clinical trial was carried out to analyze the change in the CD activity index (CDAI) after treatment as a main outcome measure, and the changes in quality of life and general well-being, serum markers of inflammation (α_1-acid glycoprotein, C-reactive protein) as secondary outcome measures. 51 patients with mild to moderately active CD were treated in a single center for complementary medicine by three trained acupuncturists and randomly assigned to receive either traditional acupuncture (TCM group, n = 27) or control treatment at non-acupuncture points (control group, n = 24). Patients were treated in 10 sessions over a period of 4 weeks and followed up for 12 weeks. ***Results:*** In the TCM group the CDAI decreased from 250 ± 51 to 163 ± 56 points as compared with a mean decrease from 220 ± 42 to 181 ± 46 points in the control group (TCM vs. control group: p = 0.003). In both groups these changes were associated with improvements in general well-being and quality of life. With regard to general well-being, traditional acupuncture was superior to control treatment (p = 0.045). α_1-acid glycoprotein concentration fell significantly only in the TCM group (p = 0.046). ***Conclusions:*** Apart from a marked placebo effect, traditional acupuncture offers an additional therapeutic benefit in patients with mild to moderately active CD.

Introduction

In the Western world an increasing number of patients, especially those with chronic diseases, are attracted by complementary healing methods [1, 2]. Recent epidemiological surveys confirm this trend also for patients with Crohn's disease (CD), particularly with regard to acu-

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0012–2823/04/0693–0131$21.00/0

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puncture [3, 4]. Chinese text books describe a condition called 'damp-hot diarrhea', which shares similar clinical symptoms with inflammatory bowel diseases [5]. For this condition traditional Chinese medicine (TCM) recommends acupuncture treatment tailored to a detailed clinical diagnosis, including the appearance of the tongue and the quality of the pulse [6]. However, no randomized controlled studies exist on the efficacy of acupuncture in the treatment of CD. Only some case reports suggest the possible effectiveness of acupuncture in patients with inflammatory bowel diseases [7–9].

We therefore performed a randomized controlled study in patients with active CD to investigate the efficacy of traditional acupuncture by assessing disease activity using an established scoring system and by evaluating quality of life, subjective well-being and serum markers of inflammation.

Patients and Methods

The study was performed from October 1998 through September 1999 in the Department of Complementary Medicine, Medicine I, University of Erlangen-Nuremberg, Germany. Ethics approval was obtained from the local ethics committee and the study was conducted under the principles of the Declaration of Helsinki. All patients gave written informed consent at the beginning of the trial and were free to withdraw from the study at any time.

Patients with CD were recruited through articles in the local newspapers and by informing general practitioners and gastroenterology specialists in the region. The diagnosis had to be confirmed by an endoscopic biopsy within the last 2 years. Patients with mild to moderate disease activity, as defined by a CD activity index (CDAI) score [10] between 150 and 350 at study entry were included. Further inclusion criteria were a minimum and maximum duration of disease of 1 and 20 years, respectively. Patients were allowed to enter the study if they received no pharmacological therapy or if they received aminosalicylates and/or prednisolone, the latter at a constant dose below 15 mg/day for at least 4 weeks before study entry. The main exclusion criteria were: treatment with other immunosuppressive drugs within the previous 3 months, or a prednisolone dose of >15 mg daily during the 4 weeks before study entry. Patients were asked to continue the same dosage of their regular medicine throughout the treatment period. If disease worsened during treatment, requiring an increase in prednisolone, patients were withdrawn from study. Dose adjustments of concomitant therapies during the follow-up period were permitted and had to be documented. In case the prednisolone dose exceeded 15 mg during follow-up, patients were withdrawn from the follow-up.

Study Design and Outcome Measures

This study was conducted as a prospective, randomized, single-blind (patients) trial with 2 parallel treatment groups (TCM acupuncture, control acupuncture). Based on existing therapy studies [11, 12] the primary outcome measure was the change from baseline in the CDAI after 4 weeks of acupuncture treatment. Furthermore, the number of patients entering remission after acupuncture therapy was assessed. Remission was defined as a CDAI score of ≤150 points. For near remission the CDAI score had to be between 150 and 160 points. As secondary outcome measures changes from baseline in the quality of life, as assessed by the inflammatory bowel disease questionnaire (IBDQ) [13], and the general well-being, as assessed by a 10-cm visual analogue scale (VAS: 0 = excellent to 10 = poor), were used. The serum concentrations of C-reactive protein and α_1-acid glycoprotein served as laboratory markers reflecting disease activity.

During the first visit patients were informed about the concept of acupuncture and that two different forms of acupuncture were applied in the trial. Patients who met inclusion criteria and gave informed consent were diagnosed according to the principles of TCM [5, 6] based upon an interview including details of sleep, appetite, sweating, psychological state, etc. Furthermore the appearance of the tongue (color, form, fur) and the quality of the radial pulse were considered for the final TCM diagnosis. On the second visit, about 4 weeks after study entry but 3 days before the first acupuncture, and on the last 2 visits, 3 days after the last acupuncture and after the 12 week follow-up, respectively, serum was obtained and CDAI, IBDQ and VAS were determined. All assessments, Chinese diagnosing and acupuncture treatments were performed by one physician (S.J.) and two doctoral students (C.M. and N.M.). Due to organizational problems, clinical assessments of patients by independent blinded investigators were not possible, but it was ensured that each patient was assessed by another therapist than the treating one.

To assess the plausibility of both treatment arms, patients were asked how confident they felt about the efficacy of the treatment on a 5-point scale (1 = excellent to 5 = poor) after the first, the fifth and the last acupuncture (confidence in acupuncture). This question is part of the credibility of the treatment rating scale developed by Borkovec and Nau [14]. Furthermore, patients rated the response to treatment on a 5-point scale (1 = excellent to 5 = poor) after the fifth and the last acupuncture session (= patients' rating of response).

Acupuncture Protocol

All patients received 10 acupuncture sessions of 30 min each over a period of 4 weeks (weeks 1–2: 6 sessions; weeks 3–4: 4 sessions). Acupuncture was performed on a single blinded basis by one physician (S.J.) with certified training from an accredited German school of acupuncture and several years of practice. Two doctoral students studied TCM for half a year at Chengdu University, China (C.M.) and completed a course in acupuncture training at an accredited German acupuncture school (N.M.). Before start of the study, the mode of needling was compared and standardized. In both groups Seirin soft needles (Seirin GmbH, Germany) size No. 8, 0.30 × 30 mm, were used.

According to TCM [5, 6] five important syndromes can be differentiated in connection with chronic diarrhea: 'spleen-qi-deficiency', 'kidney-yang-deficiency', 'liver-qi-stagnation', 'retention of cold-dampness', and 'retention of damp-heat'. Since most patients with chronic diarrhea show signs of a 'deficiency' in the 'spleen-qi' (basic syndrome), all patients in the TCM group were treated at the same acupoints (basic points) [6] (table 1). Furthermore, after TCM diagnosing during the first visit, in 48 of the 51 patients we documented combinations with 'liver-qi-stagnation' (n = 18) or 'kidney-yang deficiency' (n = 22). Only 8 patients showed symptoms of 'damp-heat' and no patient had signs of 'cold-dampness'. In addition to the basic points the further acupoints and/or moxa were selected according to these Chinese syndromes (table 1). In case of other symptoms (sleep-

Table 1. Chinese syndromes and acupuncture points [5, 6]

Basic syndrome	Basic acupoints
Spleen-qi deficiency	BL 20, CV 12, ST 36, ST 25 in alternation SP 15
No combined syndrome	+ CV 6, BL 21, SP 6, moxa
Combined syndromes	**Additional acupoints**
+ Kidney-yang deficiency	+ CV 6, BL 23, GV 20, GV 4, moxa
+ Liver-qi stagnation	+ LIV 3, BL 18, GB 34 (moxa only in patients with cold symptoms).
+ Retention of damp-heat	+ LI 11, SP 10, ST 44.

BL = Bladder; ST = stomach; SP = spleen; LIV = liver; BG = gallbladder; LI = large intestine; CV = conceptional vessel; GV = governing vessel.

ing problems, acute colic pain, etc.) extra points were individually added.

First all patients were treated in the sitting position at the back points for 10 min. After removing the back needles patients were treated at acupuncture points on the front for 20 min while lying on their backs. All needles were inserted between 0.5 and 3 cm and manipulated by hand at the beginning, in the middle and at the end of each treatment until the patient felt an aching, dull or tingling sensation, known as 'de-qi' in TCM. According to TCM the sensation of 'de-qi' indicates adequate access to the acupuncture point [5]. Additionally, depending on the Chinese diagnosis, patients of the TCM group (n = 21) were treated with moxa (Japanese term for *Artemisia vulgaris*) burned down in a wooden box (10 × 15 × 20 cm) positioned on the abdomen. All patients were reevaluated after 5 acupuncture sessions and, in case they presented with changes in symptoms, tongue or pulse, individual acupoints were exchanged.

In the control group so-called minimal acupuncture [15] was performed, meaning that needles were placed away from the classical or trigger points (non-acupoints) and inserted only 1–2 mm deep without manipulation. Nine points spread all over the body were chosen and their locations described anatomically. All control patients were treated on 7 of these points and were also reevaluated after 5 acupuncture sessions, with 2 points being modified thereafter. Control patients were not treated with moxa.

Statistical Methods

The available literature does not allow reliable prediction of the expected effect size between TCM and control acupuncture treatment. Therefore, sample size estimation was based on a 'strong' effect according to Cohen's [16] classification expecting an effect size (ES) of $\delta/\sigma = 0.8$ with respect to changes in the CDAI; with $\alpha = 0.05$ (two-sided), and $1\text{-}\beta = 80\%$, 26 patients per treatment group were required. All suitable patients were centrally randomized to the TCM or the control group by the Institute for Medical Research Management and Biometrics, Nuremberg, Germany. Using a minimization model, randomization was stratified with respect to the patient's age, duration of disease, CDAI score, usage of prednisolone and TCM therapist [17].

All data are presented as means ± standard deviation (SD) or as frequencies. Since in patients with premature discontinuation from treatment no post-baseline measurements were available, efficacy analyses were performed on a per-protocol basis including all randomized patients with a post-baseline measurement. Though intention-to-treat (ITT) analyses are considered the via regia of efficacy assessment, the PP analysis set promised a more conservative approach since more patients dropped out in the control group than in the TCM group. Additionally, however, ITT analyses were performed for sensitivity comparisons with the primary outcome measure CDAI, wherein missing data were substituted either by the mean or by the worst-case values of the non-missing data of the same treatment group. The values of dropouts during the follow-up period were substituted by the last observed values of the same patients (last-observation-carried-forward (LOCF) method). Remission rates were compared using Fisher's exact test. The changes in CDAI, IBDQ and VAS scores as well as the serum parameters were compared between the 2 treatment groups using an analysis of covariance model. Baseline values of the questionnaires were included as a covariate because of slightly different group means in the initial CDAI assessment. For within-group analyses of changes from baseline the Wilcoxon test for paired observations was used. To screen for the possible differential efficacy of both treatments, duration of disease, sex, concomitant steroid therapy, baseline CDAI and treating therapists were evaluated in subgroups. To assess the possible influence of different skill levels of the 3 acupuncturists, a 2 × 2 analysis of variance was calculated. Two-sided p values of <0.05 were regarded as statistically significant. Confirmatory testing was based on changes in the CDAI between baseline and week-4 assessment, all other statistical comparisons are interpreted in an exploratory way.

Results

Study Population

Of 78 screened patients, 24 could not be included due to CDAI score being too low (n = 14) or too high (n = 3), or for other reasons such as the duration of disease being too long or therapy with immunosuppressive drugs (n = 7). A total of 54 patients were randomly assigned to the TCM (n = 27) or the control group (n = 27) immediately after the screening visit. Three patients (all in the control group) had to be excluded during the 4-week period before the first acupuncture treatment because of acute lymph edema, CDAI score <150 on the second visit, or lost-to-follow-up prior to the first acupuncture session, resulting in 51 patients entering the treatment phase (fig. 1). Three control patients were withdrawn during the second half of the treatment period because of disease exacerbation requiring a prednisolone dose of >15 mg/day (exclusion criterion). Two more patients (1 TCM and 1 control) suffered from respiratory infection requiring discontinuation of acupuncture treatment during the first half of the treatment period. No post-baseline data were available in these 5 patients. Seven patients were withdrawn from the follow-up period: 6 because of an increased prednisolone dose of >15 mg/day (4 in the TCM and 2 in the control group)

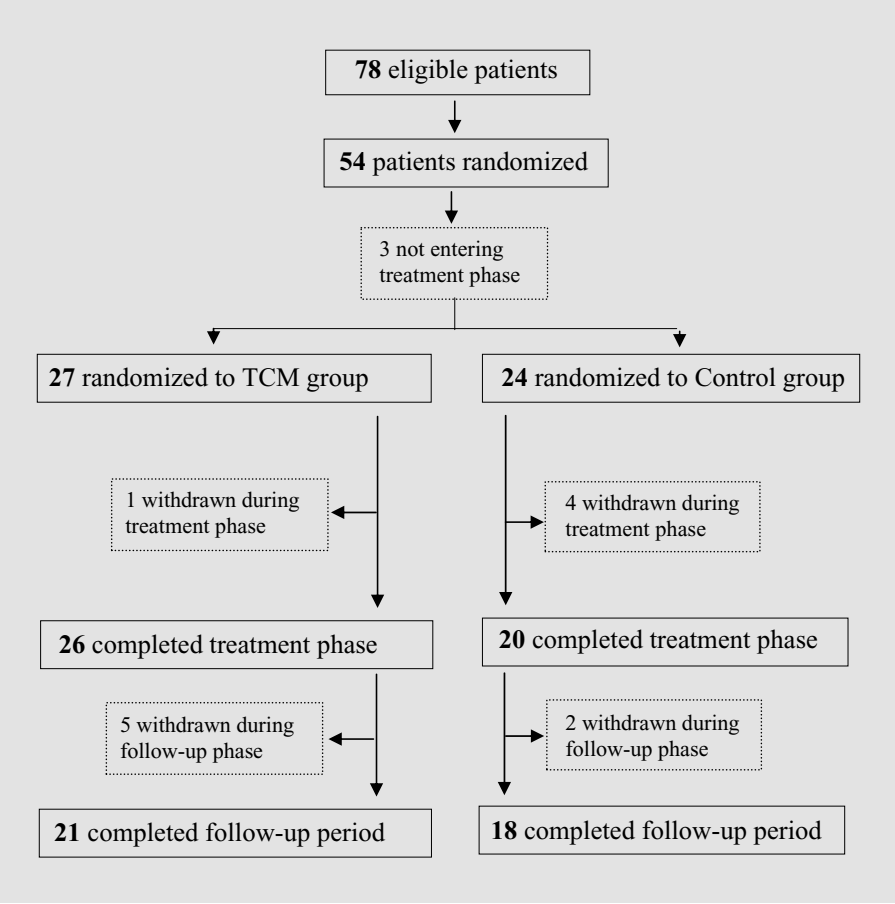

Fig. 1. Trial profile.

and 1 (TCM group) because of an elective segmental colonic resection due to stenosis.

The baseline characteristics of the 51 patients entering the treatment phase did not differ significantly among the groups, though the control group was slightly more favorable regarding the duration of disease, disease activity, frequency of prior resection and the serum α_1-acid glycoprotein concentration. Also, there were slight differences in the CDAI baseline score ($p = 0.051$) of the PP population with lower scores in the control group which were due to the influence of dropouts during screening (table 2). No differences were found in the baseline of the other efficacy measures.

Efficacy

In the patient group receiving acupuncture according to TCM principles, there was a significant fall in mean CDAI after treatment, which remained fairly stable in the follow-up period. This is evident both in the PP and the ITT analyses, substituting missing data by the mean or

Table 2. Patient characteristics before treatment

Characteristics	TCM group	Control group
Sex, f/m	19/8	17/7
Age, years	39.9 ± 7.7	36.2 ± 8.8
Weight, kg	70 ± 12.2	64 ± 9.6
Duration of disease, years	10.0 ± 5.3	7.9 ± 6.0
Prior resection	18	9
Prior acupuncture treatment	4	2
Concomitant medication	21	14
Corticosteroids	8	11
Aminosalicylates	19	12
CDAI at screening		
ITT population (n = 51)	239 ± 50	244 ± 53
PP population (n = 46)	241 ± 49	234 ± 53

Unless stated otherwise, values are means ± SD for the intention-to-treat (ITT) population (n = 51). The differences between the groups were not significant ($p > 0.05$).

the worst values of the non-missing data of the same treatment group (table 3; fig. 2). Though a considerable improvement in disease activity according to CDAI could also be observed in the control group, TCM acupuncture was significantly superior. ESs were $\delta/\sigma = 1.08$ for week-4 assessments and ES = 0.75 for follow-up status indicating both a statistically and clinically strong difference between both treatments in the primary outcome measure of changes from baseline. The acupuncturists' level of skill had no influence on treatment outcome as found by 2×2 analysis of variance (end of treatment $p = 0.342$, follow-up $p = 0.592$ for the main effect of the therapists; PP population). Remission rates were not significantly different between both groups. Remission occurred in 11 patients of the TCM group (41%, ITT) and 8 patients of the control group (33%, ITT), whereas 4 other patients (15%, ITT) of the TCM group, but none of the control group had a CDAI score between 150 and 160 (remission and near remission, 56 vs. 33%; $p = 0.095$, Fisher's exact test).

Changes in the quality of life evaluation did not reach a significant difference ($p = 0.064$), since IBDQ score improved in both treatment groups (table 4). However, general well-being improved significantly more under TCM acupuncture than under control treatment by week 4, whereas no difference between both groups was found at

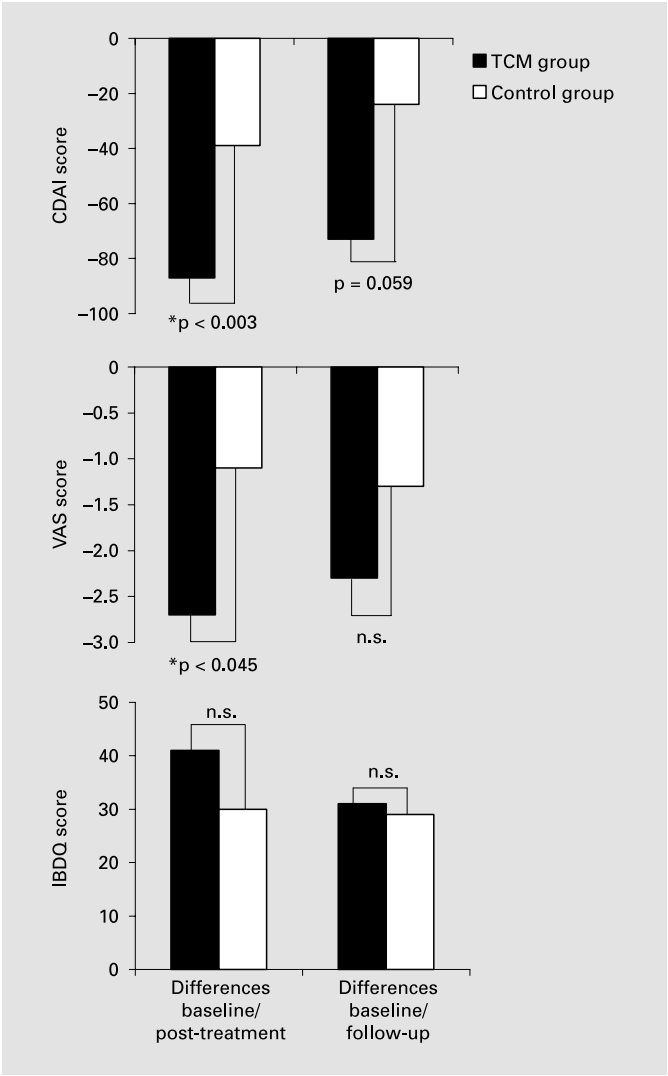

Fig. 2. Changes in Crohn's disease activity index (CDAI), general well-being (VAS) and quality of life (IBDQ). Per-control analysis with 46 patients. * $p < 0.05$; n.s. = not significant for the comparison between TCM and control group.

Table 3. Results of the main outcome measure CDAI (PP and ITT analysis)

Analysis set	Group	n	Baseline	Post-treatment	p value[1]	n	Follow-up	p value[1]
PP analysis	TCM	26	250 ± 51	–87 ± 43**	0.003	21	–73 ± 61**	0.059
	Control	20	220 ± 47	–39 ± 46**		18	–24 ± 72	
ITT analysis mean[2]	TCM	27	246 ± 43	–83 ± 46**	0.073	27	–76 ± 64**	n.s.
	Control	24	236 ± 57	–55 ± 53**		24	–42 ± 75	
ITT analysis worst case[3]	TCM	27	246 ± 43	–78 ± 61**	0.003	27	–44 ± 84	0.088
	Control	24	236 ± 57	–26 ± 53*		24	–3 ± 77	

Values are means ± SD.

* $p < 0.05$ for the within-group comparison; ** $p < 0.001$ for the within-group comparison.

[1] p values for the comparison between the TCM and control groups (ANCOVA with baseline measures as covariates). n.s. = Not significant.

[2] Substitution of missing data by the mean of the non-missing values of the same treatment group.

[3] Substitution of missing data by the worst of non-missing values of the same treatment group.

follow-up (table 4; fig. 2). Under TCM acupuncture serum concentrations of α_1-glycoprotein decreased after 4 weeks ($p = 0.046$; table 4). However, no statistically relevant difference in changes from baseline could be shown between both treatment groups, mainly because of a large variation in this marker. There were no relevant changes in C-reactive protein serum concentrations in both groups (table 4).

Both groups expressed comparable confidence in acupuncture at the beginning and at the end of treatment (table 5). After the 5th acupuncture, confidence in acupuncture as well as patients' rating of response was significantly more favorable in the TCM group (table 4). Both parameters were significantly correlated at the 5th and 10th treatment ($r = 0.53$, $p < 0.05$ for confidence, and $r = 0.62$, $p < 0.05$ for response).

Subgroup Analysis

The clinical outcome, as assessed by the CDAI, was tested for possible differential treatment effects (table 6) in subgroups of patients. TCM effects were homogeneous in both genders, while male patients did not respond to

Table 4. Results of the secondary outcome measures

	Before treatment (baseline)	Changes from baseline to post-treatment measurements	p value[1]	Changes from baseline to follow-up measurements	p value[1]
IBDQ					
TCM group	137 ± 18	+41 ± 19**	n.s.	+31 ± 14**	n.s.
Control group	150 ± 17	+30 ± 22**		+29 ± 28**	
VAS					
TCM group	4.9 ± 1.8	−2.7 ± 2.0**	0.045	−2.3 ± 1.7*	n.s.
Control group	4.0 ± 1.9	−1.1 ± 1.8**		−1.3 ± 2.0*	
α_1-GP, mg/dl					
TCM group	132.4 ± 42.0	−7.7 ± 19.5*	n.s.		n.s.
Control group	116.7 ± 36.1	−3.8 ± 20.5		–	
CRP, mg/dl					
TCM group	1.8 ± 2.2	+0.3 ± 1.4	n.s.	–	n.s.
Control group	1.3 ± 1.6	−0.2 ± 0.6		–	

Per-protocol analysis with 46 patients. Values are means ± SD.

* $p < 0.05$ for the within-group comparison; ** $p < 0.001$ for the within-group comparison.

[1] p values for the comparison between TCM and control group. n.s. = Not significant.

Table 5. Patients' confidence in acupuncture and rating of response

Group	After 1st acupuncture		After 5th acupuncture		After 10th acupuncture	
	confidence in acupuncture	patients' rating of response	confidence in acupuncture	patients' rating of response	confidence in acupuncture	patients' rating of response
TCM	1.7 ± 0.9	–	1.4 ± 0.6 *	1.6 ± 0.6	1.2 ± 0.4 **	1.3 ± 0.5 *
Control	2.0 ± 1.1	–	1.8 ± 0.7	2.2 ± 0.7	1.5 ± 0.7 *	1.6 ± 0.5 **
p value[1]	0.278	–	0.010	0.005	0.064	0.083

Per-protocol analysis with 46 patients. Values are means ± SD on a 5-point scale (0 = excellent; 5 = poor).

* $p < 0.05$ and ** $p < 0.01$ for the within-group comparisons (baseline to 5th acupuncture and baseline to 10th acupuncture, respectively).

[1] p values for the comparison between TCM and control groups.

Table 6. Baseline to post-treatment changes in CDAI in subgroups

Subgroups (TCM patients/ control patients)	TCM group	Control group	p value[1]
Sex			
Female (18/15)	−81 ± 39	−52 ± 44	0.049
Male (8/5)	−99 ± 52	−1 ± 32	0.003
Duration of disease, years			
1–5 (6/9)	−110 ± 29	−20 ± 45	<0.001
6–10 (7/5)	−82 ± 43	−36 ± 47	n.s.
11–15 (9/3)	−84 ± 52	−90 ± 39	n.s.
16–20 (4/3)	−67 ± 39	−50 ± 22	n.s.
Treatment with corticosteroids			
Yes (8/8)	−77 ± 41	−24 ± 45	0.028
No (18/12)	−91 ± 44	−49 ± 46	0.019
CDAI at baseline			
<250 (12/16)	−75 ± 43	−48 ± 44	n.s.
≥250 (14/4)	−97 ± 42	−3 ± 43	0.001
Therapists			
Therapist 1 (S.J.) (7/8)	−107 ± 42	−51 ± 49	0.036
Therapist 2 (N.M.) (9/5)	−77 ± 44	−33 ± 61	0.151
Therapist 3 (C.M.) (10/7)	−82 ± 42	−29 ± 35	0.016

Per-protocol analysis with 46 patients. Values are means ± SD.
[1] p values for the comparison between TCM and control groups.

the control treatment on average. TCM acupuncture seemed to be most efficacious in patients with a disease duration of <5 years. Concomitant treatment with steroids did not modify the differences between acupuncture and control treatment, and patients with high CDAI scores at baseline possibly derive greater benefit from TCM than from the control treatment. Moreover, no significant differences in the clinical outcome were seen with regard to the three different acupuncturists (table 6).

Further statistical analysis revealed no significant differences in CDAI scores as well as in 'confidence in acupuncture' scores after treatment comparing TCM patients with (n = 21) and without moxa (n = 5; CDAI difference −84 ± 43 vs. −97 ± 46; 'confidence in acupuncture' 1.19 ± 0.40 vs. 1.20 ± 0.45).

It must be noted that the sample sizes of several subgroups were low and limit global conclusions. Furthermore, due to a higher dropout rate among controls, patient distribution in both treatment groups is partly skewed. This is evident especially in the distribution of the patients' baseline CDAI (table 6).

Safety

No serious adverse effects of the acupuncture treatments were observed. Two control patients reported mild headache after the end of one single session. One TCM patient with a known history of kidney stones reported colic pain in the lumbar region for a few hours following acupuncture on one occasion. Two patients (1 TCM, 1 control) withdrew from the trial because of a respiratory infection. However, an association with the acupuncture treatment seems improbable in all 3 TCM patients.

Discussion

In this first randomized controlled study of acupuncture and moxibustion in active CD we demonstrated a clear benefit for patients receiving acupuncture treatment according to the principles of TCM compared to superficial needling at non-acupoints. Confirmatory analysis of change in disease activity, as assessed by CDAI, showed a statistically and clinically (effect size about 1.0) relevant improvement. This result remained fairly stable throughout the 12-week follow-up (effect size about 0.75).

Despite a difference of more than 20% in patients with remission or being near to remission in favor of the TCM group (56%) vs. the control group (33%), statistical significance was not reached in this trial. However, the decrease in disease activity was associated with a significantly improved general well-being compared to the control group. Though also quality of life improved, no differences could be found between both groups. Interestingly, α_1-acid glycoprotein a specific laboratory marker of intestinal inflammation decreased significantly only under TCM acupuncture, but not under control treatment (table 4). Again, differences between both treatment groups were not large enough to reach the level of statistical significance. Exploratory subgroup analyses revealed that acupuncture might be comparably active in both genders as well as in patients with or without concomitant steroid therapy. In addition, higher CD activity grades or disease duration of less than 5 years but not more than 10 years seem to predict the efficacy of acupuncture therapy. Importantly, no significant differences were seen when the outcome (CDAI) of the 3 acupuncturists were compared. Nonetheless, a trend in favor of the more experienced therapists was found (table 6). The findings of the follow-up assessment support stability of the treatment differences; however, further long-term studies with even longer exposition to therapy and longer follow-up periods are required to demonstrate the maintaining treatment effect of acupuncture.

No clinically relevant treatment-related adverse reactions were observed when acupuncture was administered by well-trained therapists. Insufficient efficacy was a major reason for discontinuation only in the control but not in the TCM group. From an outcome perspective, the distribution of treatment-related dropouts supports the assumption that TCM is an efficient treatment strategy in moderately active CD.

A small sample size was chosen in our study mainly for ethical reasons since we wanted to prevent exposing a large number of ill patients to two possibly inefficient treatments. Unequal distributions of patients in both treatment groups arose from the rather high dropout rate in the control group. Since randomization was performed at the first visit, which was about 4 weeks prior to the start of treatment, 3 patients in the control group could not be treated and 3 more patients of this group discontinued the study prematurely because of clinically relevant disease exacerbation. The slightly different initial values in the CDAI scores at baseline in favor of the active treatment group in the PP population are not considered as a major regression-to-the-mean factor for the treatment differences when taking the large effect size into account; the observed differences are not to be expected from the natural course of the disease in a randomized clinical trial. Furthermore, different substitution strategies of missing endpoints in ITT analyses revealed that the efficacy of TCM remained stable against the influence of dropouts. Nevertheless, further large-scale studies are required to confirm our findings, which by taking advantage of our rigorous methodological approach should use an improved design in terms of time of randomization and blinding procedures.

At the beginning of treatment both groups displayed no significant difference with regard to confidence in acupuncture. The observed difference after the 5th acupuncture correlated with the patients' rating of response and may therefore reflect the greater clinical benefit that the patients receiving TCM acupuncture were deriving. The onset of action of acupuncture is supposed to represent an important prerequisite for acceptance of such treatment by patients.

The management of CD is often complicated by the lack of sustained clinical response to corticosteroid treatment and by disease recurrence on tapering of the drug [11, 12]. Since prolonged use of steroids causes serious side effects, a combination with acupuncture may allow lowering of steroid doses or accelerated steroid withdrawal. In our study we did not observe that concomitant steroid therapy or increased steroid requirement during the follow-up period compromised the efficacy of acupuncture treatment. Therefore, it remains to be shown whether even patients with a steroid-dependent or refractory course of disease could benefit from adjunctive acupuncture treatment.

In this trial, acupuncture was planned according to the principles of TCM. This has to include moxibustion, because acupuncture and moxibustion have been paired therapies for hundreds of years. The word 'acupuncture' represents an incomplete translation of the Chinese phrase 'zhen-jiu' which means 'to prick and to burn', if translated correctly. While acupuncture represents the mechanical stimulation at special points on the body surface, moxibustion represents an additional but solely thermic stimulation. Traditionally, *Artemisia vulgaris* (Japanese word = moxa) is used to generate heat, because it burns very steadily. Omitting moxibustion would invalidate the traditional as well as the currently practiced acupuncture treatment. Therefore, an additional placebo effect could be generated by using moxa. Such an effect would be difficult to assess, since control procedures for thermic stimulation are impractical. However, because statistical analysis comparing TCM patients with and without moxa revealed no significant differences in the evolution of CDAI and in the 'confidence in acupuncture' scores, moxibustion does not appear to play a major role for treatment outcome. Generally, in clinical acupuncture studies appropriate control treatment remains an important research problem, since no control procedure is physiologically inert and at the same time also credible for the patients [18]. Also, the newly developed placebo needle [19], which does not penetrate the skin, certainly induces a physiological response because of its acupressure-like mode of action. Although there is no scientific evidence for the possible specific effects of the different acupuncture control procedures, we have to suppose that minimal acupuncture might also have some specific and probably therapeutic effect [15].

Furthermore factors such as the time spent with patients or the manual contact during the treatment are known to be essential determinants of the placebo response [20]. Placebo effects seem to be more frequent and greater when the effect is assessed as a change in subjective sensation [20]. Prior studies in CD patients revealed that the quality of life, particularly emotional and social aspects, is influenced rather by psychological, disease-independent therapeutic factors than by changes in disease activity [21]. These unspecific therapeutic factors may explain the improvement in the self-rating scales of the control group whilst laboratory parameters remained unchanged.

Despite our demonstration of significant clinical effects of acupuncture the molecular mechanisms remain unknown. A modulation of the immune system is a possible explanation. Accordingly, in allergic asthma and in cancer patients significant changes in lymphocyte subpopulations as well as in circulating cytokines were found after acupuncture treatment [22, 23]. The autonomic nervous system may play a key role in mediating these suspected effects, since immunomodulation by acupuncture could be inhibited by β-blockers [24]. In addition, acupuncture stimulates the release of hormones like ACTH, β-endorphin, substance P and somatostatin [25, 26]. Future efforts should therefore be aimed at measuring those parameters, which are implicated as important immunomodulators in CD, during acupuncture [27, 28].

In summary, an improvement of nearly 90 points in the CDAI score that persisted nearly unchanged throughout the 12-week follow-up period suggests that acupuncture is an interesting adjunctive treatment for patients with moderately active CD. Additional advantages of acupuncture appear to be the absence of clinically relevant side effects, the high patient compliance and the cost-effectiveness of the therapy. These are noteworthy advantages compared to other currently investigated therapeutic strategies [29, 30].

Acknowledgments

This study was supported by a grant from the Rut and Klaus Bahlsen Foundation, Hannover, Germany, and the German Medical Acupuncture Association (DÄGFA e.V.), Munich, Germany. S.J. was supported by a graduation scholarship from the University of Erlangen-Nuremberg, Germany. We thank SEIRIN International Inc., Fort Lauderdale, Fla., USA, for supplying acupuncture needles.

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