IRRITABLE BOWEL SYNDROME

# Acupuncture treatment in irritable bowel syndrome

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**Background and aims:** Despite occasional positive reports on the efficacy of acupuncture (AC) on functions of the gastrointestinal tract, there is no conclusive evidence that AC is effective in the treatment of irritable bowel syndrome (IBS).

**Patients and methods:** Forty three patients with IBS according to the Rome II criteria were randomly assigned to receive either AC (n = 22) or sham acupuncture (SAC) (n = 21) using the so-called ''Streitberger needle''. Treatment duration was 10 sessions with an average of two AC sessions per week. The primary end point was improvement in quality of life (QOL) using the functional digestive diseases quality of life questionnaire (FDDQL) and a general quality of life questionnaire (SF-36), compared with baseline assessments. QOL measurements were repeated three months after treatment.

**Results:** Both the AC and SAC groups improved significantly in global QOL, as assessed by the FDDQL, at the end of treatment ($p = 0.022$), with no differences between the groups. SF-36 was insensitive to these changes (except for pain). This effect was partially reversed three months later. Post hoc comparison of responders and non-responders in both groups combined revealed a significant prediction of the placebo response by two subscales of the FDDQL (sleep, coping) ($F = 6.746$, $p = 0.003$) in a stepwise regression model.

**Conclusions:** Acupuncture in IBS is primarily a placebo response. Based on the small differences found between the AC and SAC groups, a study including 566 patients would be necessary to prove the efficacy of AC over SAC. The placebo response may be predicted by high coping capacity and low sleep quality in individual patients.

Complementary medical procedures are increasingly popular in the Western world,[1] and acupuncture (AC) in particular is frequently used, despite the fact that its efficacy has been demonstrated in only a few diseases.[2] The strongest evidence has been found with postoperative and other forms of nausea and vomiting,[2] and in the treatment of pain.[3] Studies have shown that AC modulates the endorphin system[4] via central pain processing pathways.[5]

AC has also been widely used in functional gastrointestinal disorders, such as irritable bowel syndrome (IBS).[6] This frequent disorder[7] still lacks an effective drug treatment for many patients in many parts of the world,[8] while alternative medicine offers treatment options for all suffering patients.[9]

Previous studies of AC in IBS have not provided conclusive evidence of its efficacy.[10] In a study by Chan and colleagues,[11] immediate improvement of symptoms was seen in seven patients but this pilot study did not include a control group. A randomised controlled study in 25 patients[12] did not find AC effective but employed atypical AC treatment with a single AC point. A data set published as an abstract only[13] reported symptomatic improvement in both AC and placebo AC groups to a similar degree, but randomisation, choice of AC points, and long term effects remained obscure. In addition to these clinical trials, AC has been found to affect a variety of intestinal functions[14–17] but also to produce high placebo responses.[13 18]

Placebo responses in IBS are known to be as high as 80% in single trials, with an average response rate of approximately 40%,[19] depending, among other things, on the amount of patient-doctor contact during the trial.[20] Predictors of a placebo response are currently not known[19] and require analysis of individual data[21] rather than the meta-analysis of published trials.[22]

The purpose of the present study was thus twofold: to test the efficacy of AC following the rules of traditional Chinese medicine (TCM) in comparison with sham AC (SAC = placebo acupuncture)[23] in patients with IBS, and to identify individual predictors of a placebo response in patients receiving SAC.

## METHODS

### Study design

The study was performed as a randomised placebo controlled trial. Block randomisation was done by a central telephone centre so that neither the patient nor the investigator (AS) knew whether the patient would receive AC or SAC. The randomisation result was told to the acupuncturist (SB, CW) directly after informed consent. Prior to treatment, immediately after its termination, and three months later patients were send a questionnaire requesting health related quality of life (QOL) information. The questionnaire evaluator (AS) was also blinded as to whether patients had received AC or SAC.

Based on literature findings, a medium sized effect was expected.[11 12] Therefore, we intended to include 62 patients to detect a clinically relevant difference of 10 points on the functional digestive diseases quality of life questionnaire (FDDQL) scale with a power of 80%, based on a standard deviation of 14 and a type I error of 5%.

### Setting and patients

Patients were recruited at the outpatient clinic of the Department of Gastroenterology, University Medical Hospital, via gastroenterology specialists in private practice in the Heidelberg area, and via advertisements in local

**Abbreviations:** AC, acupuncture; BDQ, bowel disease questionnaire; FDDQL, functional digestive diseases quality of life questionnaire; IBS, irritable bowel syndrome; PHQ-D, patients' health questionnaire (German version); QOL, quality of life; SAC, sham acupuncture (= placebo acupuncture); SF-36, health related quality of life questionnaire; TCM, traditional Chinese medicine

**Table 1** Selection of acupuncture (AC) points; each patient was acupunctured at the same points. Sham AC was performed at locations in close proximity, 2 cm apart

| AC point | Anatomical location | Function according to TCM |
|---|---|---|
| Liver 3 | Proximal angle between os metatarsal I and II | ''Calms down the liver'' |
| Stomach 36 | 5 cm below patella, 2 cm lateral of the tibial rim | ''Strengthens spleen and stomach'' |
| Spleen 6 | 5 cm above the medial malleolus, dorsal tibial rim | |
| Conception 12 | Middle between navel and sternum | ''Removes stomach stagnation'' |
| Stomach 21 | 3 cm lateral of conception 12 | |
| Stomach 25 | 3 cm lateral of navel | |
| Heart 7 | In the angle between os pisiform and radial side of the tendon of m flexor carpi ulnaris | ''Calms down the mind'' |
| Du Mai 20 | On the midline of the head, approximately on the midpoint of the line connecting the apexes of the two auricles | |

TCM, traditional Chinese medicine.

newspapers. The recruitment period was from April 2003 to April 2004. Patients were at least 18 years of age and fulfilled the Rome II classification for IBS with symptoms present for at least 12 weeks out of the last 12 months. Diagnosis was confirmed by the presence of abdominal pain/discomfort with at least two of the following features: symptom relieve with defecation and/or symptoms associated with a change in frequency of stools, and/or associated with a change in form (appearance) of stools, in the absence of structural or metabolic abnormalities to explain the symptoms.[24]

A diagnosis of IBS had to exclude other causes of symptoms, such as inflammatory bowel diseases, carbohydrate malabsorption, and colon cancer. Colonoscopy had to have been performed within the last five years. Patients were excluded if they had an insufficient diagnostic workup, received AC treatment within the last three months, were receiving concomitant medication with effects on the gut, such as 5-$HT_3$ antagonists or spasmolytics, or were pregnant.

Compliance with the Rome II criteria was tested using the bowel disease questionnaire (BDQ)[25] and by assessing symptoms during history taking. Patients received a psychometric test (patients' health questionnaire (PHQ-D)) to verify the diagnosis on the subscales depression, somatisation, and anxiety.[26]

The local ethics committee approved the study protocol and patients had to give written informed consent prior to enrolment.

## Intervention

Each patient was scheduled for a total of 10 AC/SAC sessions, twice a week, over five weeks. AC treatment was performed as standardised AC according to TCM. From the point of view of TCM, the core problem of IBS is an ''affection of the spleen'', which could be explained by different so-called ''patterns''. For our study, the most important patterns, according to TCM, were ''weakness of the spleen caused by stagnation of liver qi'', ''weakness of the spleen qi'', and ''weakness of the spleen and kidney''. We tried to derive a global concept to include all of these patterns into therapy. According to Chinese textbooks, IBS could be defined as follows: ''suppressed emotions and concerns would induce a liver qi stagnation, which in turn would lead to an attack of the liver on the spleen and stomach. The resulting weakness of the spleen leads to digestion problems. Furthermore, liver qi stagnation would block qi flow in the meridians. This would induce abdominal pain''.[27 28]

Based on this concept, a fixed selection of AC points was used in all patients, comprising the most important points to treat the ''weakness of the spleen'' (basic pattern) and to strengthen digestion (table 1). The rules of TCM would have been best met if individual therapeutic schemes had been used. This was avoided to allow statistical comparison between groups and to keep the placebo effect as small as possible, as individualised treatment would amplify patient-doctor interactions.

AC was performed by an experienced female acupuncturist (SB) and by a trained female research assistant (CW). A stainless steel needle (0.32×30 mm; Asia Med, Munich, Germany) was inserted through a plaster over the respective AC points, under which a plastic ring was positioned. Care was taken that with needle insertion at each AC point, a dull needling sensation (called: de qi) occurred, that usually vanished during the course of a session.

In the control group, patients received SAC with a blunted telescopic placebo needle (Asia Med) that simulates an AC procedure without penetrating the skin.[23] The efficiency of this method has been shown in various studies.[29 30] Each SAC procedure was performed 2 cm adjacent to the real AC point to avoid acupressure effects. In the SAC group, the AC point LG 20 was not needled as fixation of the plaster is not possible on the head due to hair.

## Measurements

The BDQ[25] has been developed to validate symptom clusters in IBS in different nations. It was used here to confirm the diagnosis of IBS according to the Rome criteria in each patient prior to entry into the study. Psychological comorbidity was assessed at baseline by the subscales depression, anxiety, and somatisation of the PHQ-D, which diagnoses psychological disorders using the diagnostic criteria from the DSM-IV.[26]

Patients completed two QOL questionnaires that were used to assess any effects of symptomatic improvement by AC on their overall QOL: (a) FDDQL[31] assesses disease related impact of bowel symptoms on quality of life, measured with 43 items on eight subscales: daily activity disease related anxiety, diet, sleep, discomfort, health perception, coping with disease, and impact of stress. Scores for subscales are added to a global QOL scale ranging from 0 to 100. FDDQL has an internal consistency of 0.94 (Crohnbach's alpha); (b) the health related quality of life questionnaire (SF-36)[32] is a validated global measure of health related quality of life unrelated to specific diseases that has been widely used in a variety of diseases.[33] It uses 36 items to assess eight scales (bodily function, bodily role, bodily pain, general health, vitality, social function, emotional role, and physical well being).

Both questionnaires were given prior to treatment (t1), immediately after 10 AC treatments (t2 = five weeks after the first treatment), and three months after the last treatment (t3). Improvement in the global score of FDDQL immediately after the 10 treatments (t2) was the primary end point of the study. The other subscales of the FDDQL and the SF-36 were defined as secondary end points. Outcome measures at t3 were also defined as secondary end points. Baseline differences between the two cohorts were tested using the *t*

**Table 2** Characteristics of the patients (bowel disease questionnaire)

| Characteristic | AC | SAC |
|---|---|---|
| No of subjects | 22 | 21 |
| Dropouts (n (%)) | 1 (4.5%) | 1 (4.5%) |
| Age (y) (mean (SD)) | 47.63 (14.71) | 47.14 (16.01) |
| Females (n (%)) | 17 (77.3%) | 17 (81.0%) |
| Did you suffer from intestinal pain/discomfort during the last year? (n (%)) | 22 (100%) | 20 (95.2%) |
| Did you consult a doctor for these complaints? (n (%)) | 14 (63.6%) | 13 (61.9%) |
| Does it happen frequently that you have to run for the bathroom? (n (%)) | 13 (59.1%) | 12 (57.1%) |
| Do you suffer from a bloated abdomen? (n (%)) | 20 (90.9%) | 20 (95.2%) |
| How would you describe your regular stool habits (n (%))? | | |
| Normal | 2 (9.1%) | 2 (9.5%) |
| Constipated | 3 (13.6%) | 2 (9.5%) |
| Diarrhoea | 8 (36.4%) | 9 (42.9%) |
| Constipation and diarrhoea alternating | 9 (40.9%) | 8 (38.1%) |
| How strong is your abdominal discomfort or pain? (n (%)) | | |
| Mild | 0 (0%) | 1 (4.5%) |
| Moderate | 7 (31.8%) | 5 (23.8%) |
| Strong | 12 (54.5%) | 11 (52.4%) |
| Very strong | 2 (9.1%) | 5 (23.8%) |
| On how many days during the last 12 months could you *not* perform your regular duties? (n (%)) | | |
| <3 days | 9 (40.9%) | 5 (23.8%) |
| 3–5 days | 5 (22.7%) | 4 (19.0%) |
| 6–10 days | 2 (9.1%) | 4 (19.0%) |
| >10 days | 5 (22.7%) | 8 (38.1%) |
| How long have you suffered from your intestinal complaints? (n (%)) | | |
| <2 y | 1 (4.5%) | 2 (9.5%) |
| 2–10 y | 8 (36.4%) | 6 (28.6%) |
| >10 y | 12 (54.5%) | 13 (61.9%) |

AC, acupuncture; SAC, sham acupuncture (=placebo acupuncture).

test and the $\chi^2$ test when appropriate. An ANOVA model adjusted for baseline scores was used to test group differences related to the primary end point (FDDQL) at week 5 and the secondary end point at week 12. In addition, a repeated measures ANOVA model with an unstructured covariance matrix was used to investigate the difference in the time pattern of the FDDQL and its subscales.

As trials with IBS patients usually report high placebo response rates,[19] it was intended to perform a post hoc analysis on potential predictors of a placebo response using stepwise (forward selection) multiple regression analysis of baseline psychometric and sociometric data to identify responders and non-responders of treatment. Responders were defined as patients in whom the change in the global FDDQL from baseline to week 5 was higher than the median change of the entire group.

All statistical testing was performed using the programs SPSS version 11.0 and SAS version 8.2 under Windows. The level of significance was set at 0.05 for all tests.

## RESULTS

### Patients

A total of 43 patients were entered into the study. Eleven (26%) patients were recruited from the outpatient clinic, one patient via a private practice, and 31 (72%) by advertisements. Patients were randomly assigned to either the AC or SAC group. Only one patient in the entire study population had received AC in the past. She was able to identify SAC and declined to participate in the study after the third treatment. Another female patient declined to participate after five treatments due to time constraints. Thus two patients dropped out during the course of the study. There were no differences in age or sex between the groups at entry (table 2). The intended number of 60 patients could not be obtained despite multiple advertisements in local newspapers. Therefore, we decided to stop the trial after one year and to conduct the final analysis. Discontinuation of the trial was not data driven.

### Symptoms at study entry

The BDQ illustrates the degree and severity of bowel symptoms among the patients (table 2): two thirds had consulted a doctor for their symptoms during the past year, one third had had more than 10 days in the past year during which they could not perform their regular work, and more than half of the patients had a history of illness for 10 years or more. No differences were seen between those who received AC or SAC after assessment.

### Quality of life with treatment

QOL, as measured by the FDDQL, improved with treatment and was significantly higher in comparison with baseline. Concerning the main outcome measurement immediately after 10 treatments (t2), the global FDDQL score increased significantly by 11% in the AC group and by 10% in the SAC group, and was moderately lower in both groups after three months of follow up (fig 1).

The global score revealed no difference between the groups immediately after 10 treatments (mean difference 1.98 (−3.59 to 7.38); $p = 0.489$, ANOVA with baseline adjustment) and three months later (mean difference 3.41 (−3.02 to 9.83); $p = 0.283$, ANOVA with baseline adjustment) (table 3). In both groups a significant time effect was seen ($p = 0.001$, ANOVA with repeated measures) (fig 1) but no interaction between time and treatment group ($p = 0.565$; not in fig 1). Therefore, the change over time did not seem to be affected by verum or placebo AC.

With respect to secondary outcome measurements, some FDDQL subscales also showed a significant improvement in both groups immediately after 10 treatments (t2), such as daily activity index, which improved by approximately 7% and 16% (AC and SAC, respectively), diet (23% and 16%), discomfort (14% and 6% ), and disease coping (21% and 3%). These effects were stable for three months except for diet which decreased at follow up (t3) (fig 1). All of the other FDDQL subscales (anxiety, sleep, control of disease, and stress) did not respond significantly to treatment. Analysis (ANOVA with baseline adjustment) of all subscales showed

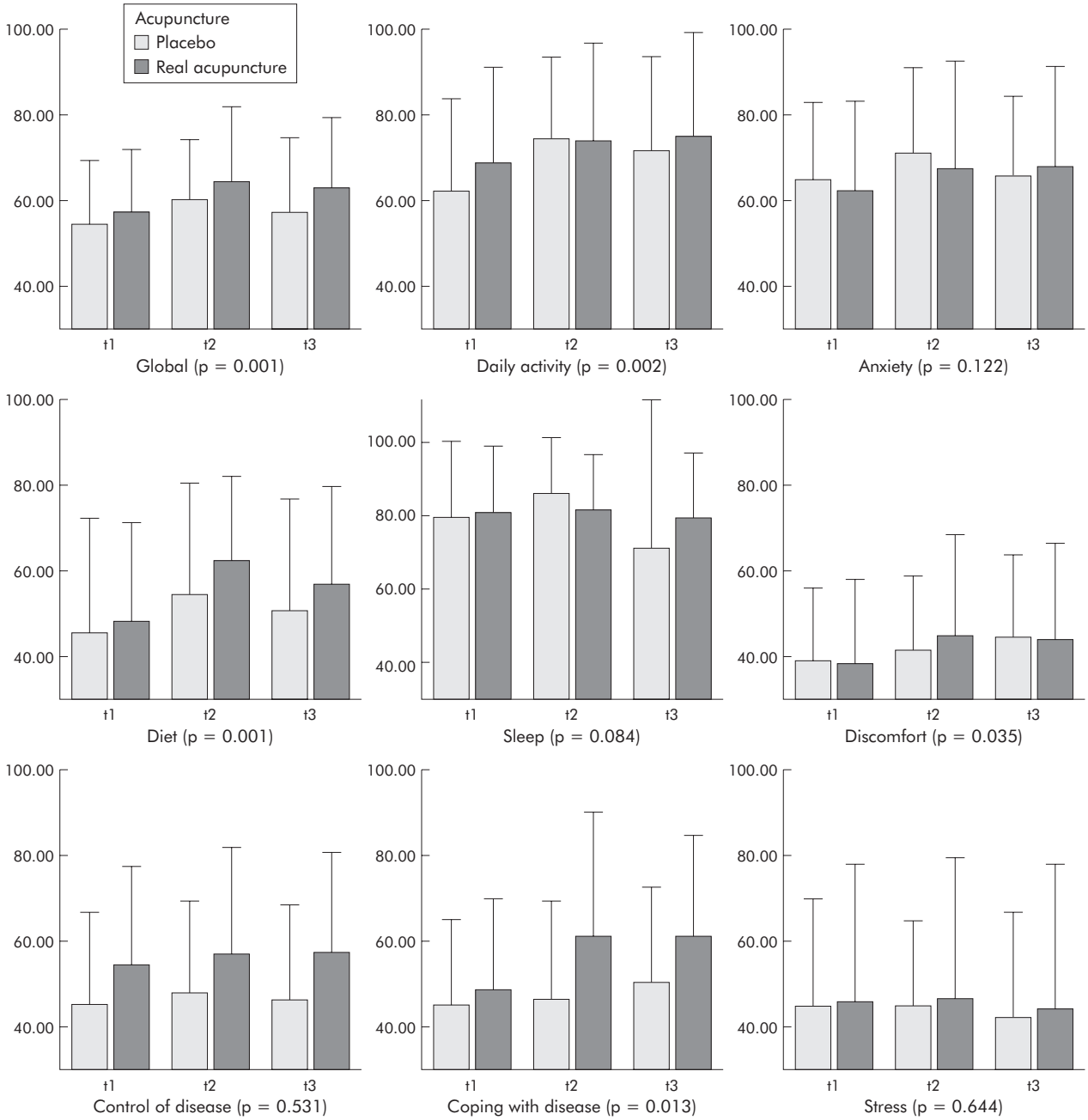


**Figure 1** Scales of the functional digestive disease quality of life questionnaire in the placebo and real acupuncture groups (p value for change over time, using ANOVA with repeated measures). t1 = Before treatment, t2 = immediately after treatment (five weeks after t1), and t3 = 12 weeks after t2. Values are mean (SEM).

no significant group differences between AC and SAC in improvement of quality of life (table 3).

Overall, no significant difference was found in treatment effects in relation to the acupuncturists who performed the AC/SAC.

SF-36 scales showed a similar trend as the FDDQL scales. However, only the bodily pain scale was significantly improved in both groups after treatment (12% in AC, 10% in SAC) but there was no difference between the AS and SAC groups (data not shown).

If the trial had been planned with one interim analysis after 40 patients, 526 (in addition to the 40) patients for the second stage should have been recruited to reach a conditional power of 80%. This number is based on the same primary end point after 10 treatments, a simple *t* test approach with an adaptive Pocock design,[34] and assuming the same effect size for the second stage. With an additional 20 patients a conditional power of only 5% could have been reached.

## Post hoc placebo analysis

As the AC group was not different from the SAC group, the post hoc analysis for potential predictors of the placebo response was performed on both groups together to increase the statistical power.

The average change in the global FDDQL scale was 5.02 (1.28) (mean (SEM); median: 4.46) and approximately followed a normal distribution, with a range between −15 and +25. According to the definition, 19 patients were identified as responders and 24 as non-responders.

**Table 3** Group differences in the functional digestive disease quality of life (FDDQL) subscales

| | Immediately after treatment (t2) | | 3 months after treatment (t3) | |
|---|---|---|---|---|
| FDDQL | Group difference | 95% CI | Group difference | 95% CI |
| Daily activity | −3.87 | −13.63 to 5.89 | −1.18 | −10.51 to 8.16 |
| Anxiety | −2.02 | −12.25 to 8.21 | 3.96 | −4.92 to 12.83 |
| Diet | 6.06 | −2.44 to 14.56 | 4.12 | −6.24 to 14.48 |
| Sleep | −3.78 | −9.72 to 2.16 | 8.36 | −10.39 to 27.12 |
| Discomfort | 4.68 | −2.27 to 11.63 | 0.71 | −7.37 to 8.79 |
| Control of disease | −0.70 | −7.33 to 5.94 | 2.22 | −5.76 to 10.19 |
| Coping with disease | 11.6 | −0.72 to 23.99 | 7.98 | −3.19 to 19.14 |
| Stress | −0.19 | −9.75 to 9.37 | 0.13 | −11.73 to 11.99 |
| Global | 1.98 | −3.59 to 7.38 | 3.41 | −3.01 to 9.83 |

Calculation based on ANOVA with baseline adjustment.
Positive values: AC better than SAC; negative values: SAC better than AC.
95% CI, 95% confidence interval.

Comparing all variables at entry between these two groups identified five potential predictors of the placebo response: the subscales sleep and coping of the FDDQL, and the PHQ-D subscales depression, anxiety, and somatisation. They were entered into a stepwise (forward) multiple regression model, together with the grouping variable (AC/sham AC). The variables sleep and coping remained significant factors predicting responsiveness to placebo ($t = -2.945$, $p = 0.005$ and $t = 2.672$, $p = 0.011$, respectively). A model with these two variables had a combined power of $F = 6.764$, $p = 0.003$ to explain responsiveness to AC/sham AC.

## DISCUSSION

To date, this is the largest randomised controlled trial of AC treatment for IBS. We found that there was a significant improvement in global quality of life of up to 11% in both AC and SAC treated patients, which is similar to effect sizes achieved with psychotherapeutic interventions[35 36] and also with antidepressants.[35] In particular the scales ''coping with disease'' and ''diet'' increased by more than 20%, as well as the daily activity index and the discomfort experienced. This effect decreased moderately after three months. As no differences between the AC and SAC groups were found, these effects must be seen as placebo responses. This is in contrast with previous studies which have shown physiological effects of AC (for example, for pain treatment during colonoscopy[37] and gastroscopy).[38] Effects were also found for visceral reflex activity[15] and acid secretion in the stomach.[14]

Our new method was the performance of SAC, 2 cm adjacent to the AC points, thus excluding acupressure effects in the control group. In previous studies, this has often been a concern as acupressure may also induce physiological effects.[39 40] Despite being the largest AC trial in IBS, the critical issue is the small sample size. Nevertheless, calculation of conditional power showed that a very high additional sample, with 566 patients in total, would be needed to achieve significance. It may be speculated as to whether standardisation of AC instead of an individualised AC strategy in the present study may be the reason for the lack of efficacy.[41 42] On the other hand, the placebo effect due to intensive patient-doctor interaction during the diagnosis and treatment might be smaller within a standardised procedure. There is no evidence that an individual AC treatment has greater efficacy than a standardised concept. A recently published large randomised controlled trial of AC treatment of migraines does not strengthen the hypothesis that individual AC is superior.[43] In this study, the effectiveness of individualised AC was equal to SAC, but both were more effective than a waiting list control. One reason for the high placebo response could be the personal intensive attribution during the AC treatment, combined with the option for the patient to relax in unusually calm surroundings. Additionally, AC is known to establish a close doctor-patient relationship. This could be explained by the composition of an explicit ''handling'' as a treatment strategy and implicit signalling of an holistic understanding of the patient's problems. This might be due to the hypothesised unknown incidental effects in complex interventions such as AC treatment.[44] The importance of professional attention is underscored by the influence of psychological factors on the development and course of the disease.[45 46] Assuming that the increase in QOL in both groups is due to a strong placebo effect known to exist in functional bowel disorders[19 20 47] for any type of treatment, and similar to other medical conditions,[48 49] our post hoc data analysis provides the first clue as to what the potential determinants of these placebo responses may be: among the psychometric variables of QOL assessed prior to study entry, high disease coping capacities were linked positively to being a placebo responder, while poor sleep quality was associated with being a placebo non-responder. Other variables that may influence placebo responses are suggestions and expectations,[50] cognitions,[51] suggestibility,[51 52] and an external ''locus of control''[53] and other ''personality'' factors. Also, perception of bodily sensations seems to play some form of role[54] but this needs to be shown in a prospective way in future trials.

Identification of any predictor of the placebo response has not been shown in IBS patients to date, and meta-analyses of published treatment trials in IBS[20] as well as other diseases do not allow for such a conclusion, as published data sets normally do not include such variables. It has been claimed that for other conditions (for example, depression), more individualised data are necessary to identify reliable predictors of the placebo response.[21]

In summary, the effects of AC in IBS seem to be due to placebo effects when proper control of AC by a novel sham AC needle is used. Based on the small differences found between AC and SAC, a study using individual TCM patterns with 566 patients would be necessary to prove efficacy. The question is whether such a difference would be clinically relevant. The placebo response in both AC and SAC may be linked to individual psychological variables such as coping that can be assessed prior to treatment. The placebo responsiveness of an individual may thus become predictable in future trials.

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