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Neuroendocrinological effects of acupuncture treatment in patients with irritable bowel syndrome☆

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KEYWORDS
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Summary
Objectives: Quality of life (QoL) improvement in patients with irritable bowel syndrome (IBS) during acupuncture (AC) treatment seems to be due to a placebo effect. The aim was to explore if acupuncture has some specific influence on the neuroendocrinic and autonomic nervous system (ANS).
Design/setting: Patients with IBS were randomly assigned to receive either acupuncture (AC) or sham acupuncture (SAC) using the so-called ''Streitberger needle''. QoL was measured with the functional quality of life diseases quality of life questionnaire (FDDQL) and SF-36. The effect on ANS was evaluated by measuring salivary cortisol and by cardiovascular responses on a tilt table before and after 10 AC treatments. Complete data sets of tilt table and salivary morning cortisol were available for 9 patients in the AC and 12 in SAC group.
Results: QoL increased in both groups ($p = 0.001$) with no group differences. Salivary cortisol decreased in all groups ($F = 10.55$; $p = 0.006$). However, the decrease was more pronounced in the AC group ($F = 4.07$; $p = 0.033$) (ANOVA repeated measures model). Heart rate response decreased during orthostatic stress in the AC group while it increased in the SAC group ($F = 9.234$; $p = 0.005$), indicating an increased parasympathetic tone in the AC group. Improvement of pain was positively associated with increased parasympathetic tone in the AC group ($F = 10.1$; $p = 0.006$), but not in the SAC group.

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Conclusions: The acupuncture specific physiological effects are in contrast to the unspecific improvement of QoL in both AC and SAC groups. Thus, different mechanisms seem to be involved in placebo and real-acupuncture driven improvements. The specific mechanism of action of acupuncture on the ANS remains unclear and deserves further evaluation.

Introduction

Acupuncture is increasingly popular in patients with varying diseases.[1,2] It is used to treat chronic pain disorders such as low back pain or osteoarthritis as well as complex diseases such as asthma or somatoform disorders. Also patients with irritable bowel syndrome (IBS) are frequently using complementary medicine methods such as acupuncture.[3]

However, several recently published acupuncture studies show an improvement in patients' quality of life after acupuncture—regardless if traditional or sham acupuncture.[4–6] Also in patients with IBS, no significant group difference in quality of life improvement could be observed after treatment with verum or sham acupuncture.[7,8] This indicates high unspecific (placebo) effects of the acupuncture treatment.

These findings are in contrast to the results of experimental trials. For example, an inhibition of acid secretion mediated as well as effects on pressor reflex during gastric distension were observed in real acupuncture treatments.[9,10] Furthermore, a modulation of the autonomic nervous system by acupuncture has been seen in patients with advanced heart failure[11] and major depression.[12] Since modulation of the autonomic nervous system (ANS) may play a major role for pathophysiologic pathways of IBS,[13–16] we hypothesized that acupuncture effects in IBS patients would be mediated through the autonomic nervous system (ANS) and neuroendocrinic pathways.

Therefore, the effect of acupuncture on the ANS in patients with IBS was evaluated in the present study by measuring salivary cortisol and cardiovascular responses on a tilt table in regard to pain and health-related quality of life (QoL). This was a secondary analysis of a randomized, controlled study that has been reported previously.[8]

Methods

Study design

The study was performed as a randomized, placebo-controlled trial. The block randomization was done by a central telephone centre so that neither the patient nor the investigator (AS) could know previously, if the patient would receive real acupuncture (AC) or sham acupuncture (SAC). The randomization result was told to the acupuncturist (SB, CW) directly after informed consent. Prior to treatment, immediately after its termination, and 3 months later patients were send a questionnaire asking for health-related quality of life (QoL). The evaluator of these questionnaires (AS) was also blinded as to whether patients had received AC or SAC, as was the evaluator of the tilt table investigation.

Setting and patients

All participants met criteria for IBS according to the ROM II classification.[17] The details of the recruitment, diagnostic work-up and IBS classification are described elsewhere.[8] Patients were excluded if they had an insufficient diagnostic work-up, AC treatment within the last 3 months, concomitant medication with effects on the gut such as 5-HT3 antagonists and spasmolytics or were pregnant. All subjects gave their informed written consent and the study was approved by the Ethical Committee of the University of Heidelberg.

Intervention

Each patient was scheduled for a total of 10 AC/SAC sessions, twice a week over 5 weeks. The AC treatment was performed at 15 acupuncture points according to TCM (see Table 1).[8,18,19] Individual therapeutic schemes were avoided to allow statistical comparison between groups.

AC was performed by an experienced female acupuncturist (SB) and by a trained female research assistant (CW). A stainless steel needle (0.32 mm × 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 dump 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 (''Streitberger needle'', Asia Med, Munich, Germany) that simulates an AC procedure without penetrating the

Table 1 Selection of acupuncture points; each patients was acupunctured at the same points, sham acupuncture was performed at locations in close proximity, 2 cm apart

ACU point	Anatomical location	Function according to TCM
Liver 3	Proximal angle between Os metatasare I and II	Calms down the liver
Stomach 36 Spleen 6	5 cm below patella, 2 cm lateral of the tibial rim 5 cm above the medial malleolus, dorsal tibial rim	Strengthens spleen and stomach
Conception 12 Stomach 21 Stomach 25	Middle between navel and sternum 3 cm lateral of conception 12 3 cm lateral of navel	Removes stomach stagnation
Heart 7	In the angle between os pisiforme 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	

skin.[20] 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 since fixation of the plaster is not possible on the hairy head.

Assessment of quality of life

Patients had to complete two QoL questionnaires that were used to assess any effects of symptomatic improvement by AC on their overall QoL: (a) the Functional Digestive Diseases Quality of Life Questionnaire FDDQL[21] assesses the disease-related impact of bowel symptoms on quality of life, measured with 43 items on 8 subscales: daily activity disease-related anxiety, diet, sleep, discomfort, health perception, coping with disease, and impact of stress. Scores of subscales are added to a global QoL scale ranging between 0 (worst) and 100 (best). The FDDQL has an internal consistency of 0.94 (Crohnbach's alpha). (b) The SF-36[22] 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.[23] It uses 36 items to assess 8 scales (bodily function, bodily role, bodily pain, general health, vitality, social function, emotional role, and physical well-being). After transformation the range of each scale is from 0 (worst) to 100 (best). Both instruments were given prior to treatment (t1), immediately afterwards (t2), and 3 months later (t3). Improvement in global bowel symptom-related quality of life was the primary endpoint of the study.[8] The analysis for the actual explorative study will focus only on patients with complete tilt table data at t1 and t2.

Measurement of salivary cortisol

Immediately before and within 3 days after the 10 acupuncture treatments, the patients used 4 tubes (salivettes) containing a piece of cotton wool to absorb saliva (Sarstedt Salivettes®) at 4 time points (7:00 a.m., 12:00 a.m., 5:00 p.m., and 10:00 p.m.). They were instructed by a leaflet how to collect the saliva: by chewing on the piece of cotton wool or positioning it under the tongue for 30—45 s. The patients were instructed to store the salivettes in the refrigerator until the next appointment. The salivettes were centrifuged and frozen deeply after receipt until processing in the laboratory by radioimmune assay. The normal value of the morning salivary cortisol in our laboratory is in the range 3.0—24.8 nmol/l.

Assessment of autonomic function

Autonomic function was assessed before and after the 10th sessions of acupuncture treatment and was in accordance with earlier studies by our group.[24,25] All participants were asked to avoid smoking, eating and drinking alcoholic or caffeine containing beverages for 2 h preceding each examination. Participants were placed on a conventional tilt table device.

(1) After ECG-electrodes and blood pressure cuffs had been placed, subjects relaxed for 10 min in supine position. The arm with the adjusted finger cuffs was positioned such that the lower arm remained near the hydrostatic indifference point at any body posture. After the relaxing period, heart rate and blood pressure recordings were started during 5 min ''supine rest''.
(2) This was followed by 3 min of metronome controlled breathing to evaluate the respiratory sinus arrhythmia (RSA). The auditory cue indicated the beginning of inspiration and expiration and had a repeat cycle of 0.1 Hz (6 breaths/min), a rate which maximizes RSA and allows sensitive quantification. RSA is primarily

generated by cardiovagal function and serves as probe for parasympathetic function. For quantification the *E*/*I*-ratio as the most commonly used calculation was used: the ratio of the mean of the longest RR-intervals during expiration to the mean of the shortest RR intervals during inspiration of six respiratory cycles.[26]

(3) For the Valsalva maneuver, the patient was told to blow into a mouthpiece attached to a sphygmomanometer with a persistent pressure of 40 mmHg for 15 s. The system had a small leak to prevent participants to falsely maintain pressure by glottic closure of the airway or tongue closure of the mouthpiece. The Valsalva maneuver was repeated three times. During the Valsalva maneuver the RR-interval continuously decreases and after termination a parasympathetically mediated reflexive increase can be observed. The Valsalva ratio was calculated as the ratio of the longest RR interval during or shortly after the maneuver to the shortest RR interval within the first 3 s after the maneuver and averaged across the three trials.[26]

(4) After completion of the two cardiovagal tests, participants relaxed in supine position for another 5 min and breathed spontaneously. This baseline period was followed by head-up tilt testing, a passive orthostatic maneuver of 75° achieved with a motorized tilt table. The almost upright position was maintained for 10 min. For the evaluation of cardiovascular response to orthostatic stress, a steady period (3—10 min after tilting) was chosen (''orthostatic stress''). Blood pressure increase is primarily regulated by sympathetic adrenergic function and heart rate increase by parasympathetic cholinergic (cardiovagal) function. The smaller the difference of the RR intervals between orthostasis and rest, the higher is the influence of the parasympathetic tone.[26]

Cardiac autonomic assessment included the simultaneous recording of heart rate and blood pressure with a computer-based system (Task Force Monitor; CNSystems, Graz, Austria).[27] Blood pressure measurement was recorded non-invasively and continuously using a finger-cuff. The continuous blood pressure signal was equilibrated in intervals of 1 min by oscillometric blood pressure measurement of the contralateral upper-arm. The ECG and beat-to-beat blood pressure signals were sampled with a frequency of 1000 Hz. Time series of heart period data were visually displayed to control for outliers and technical artefacts and to determine computer assisted the autonomic parameters. ECG-sequences that showed premature beats and artefacts were excluded from the analysis.

Statistical analysis

Quality of life was evaluated with repeated measures 2×2 ANOVA model (AC/SAC; pre/post). The salivary cortisol was analyzed with a $2 \times 2 \times 4$ repeated measures ANOVA model (AC/SAC; pre/post; day time [7:00 a.m, 12:00 a.m, 5:00 p.m., and 10:00 p.m]). The longitudinal change of systolic and diastolic blood pressure, *E*/*I*-ratio and Valsalva ratio were analyzed with a 2×2 repeated measures ANOVA model (AC/SAC; pre/post). The autonomic response during the orthostatic maneuver was calculated as the differences between the resting condition (supine resting) and the orthostatic stress. The change was analyzed with a $2 \times 2 \times 2$ repeated measures ANOVA model (AC/SAC; rest/orthostasis; pre/post). For control purposes, quality of life changes (FDDQL[21]) that were reported previously[8] and that allowed classify patients as ''responders'' and ''non-responders'' were used as covariates. 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.[8] Associations between global FDDQL, pain score of SF-36, cortisol and autonomic functions were evaluated using regression analysis. All statistical testing was performed using the programs SPSS Version 11.0. As level of significance we choose $\alpha = 0.05$.

Results

Patients

A total of 43 patients were entered into the study. All patients were investigated by the tilt table. However, 9 patients were excluded as they had medications with a known influence on the autonomic nervous system ($5 \times \beta$-antagonists, $2\times$ anti-depressants, $2\times$ neuroleptics). Two patients dropped out in the course of the acupuncture therapy (Fig. 1). One was able to identify SAC as she received acupuncture in the past. She declined to participate in the study after the third treatment. Another female patient declined to participate after five treatments due to time constraints. Of these remaining 34 patients, 12 patients of the placebo group and 9 of the real AC group were able to deliver the salivary cortisol at morning time before and after acupuncture therapy; 9 patients of the placebo group and 8 of the real AC group

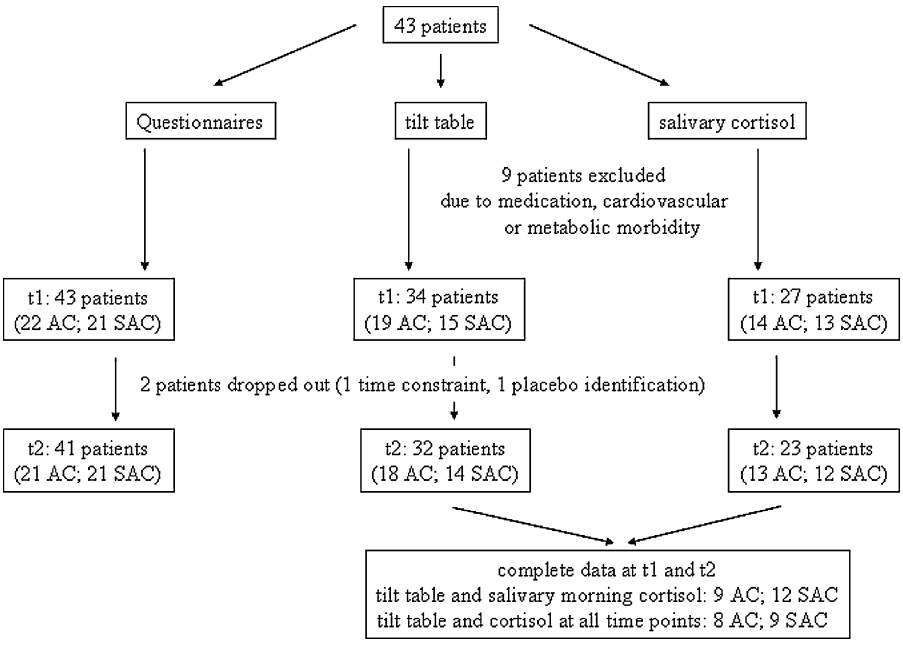

Figure 1 Flow chart of patients.

were able to deliver the salivary cortisol at all time points. The baseline characteristics are given in Table 2. There was no significant difference between the real and placebo acupuncture group (*t*-test and χ^2-test).

Quality of life

Quality of life improved in both groups without any group differences (Table 3). Concerning the SF-36, only the pain scale improved significantly. The global score of the FDDQL and the pain scale are given to show the representativeness for the whole study group.[8]

Salivary cortisol

The concentration of salivary cortisol decreased significantly at all time points (main effect of day time; $F = 15.90$; $p < 0.001$), and was significant lower post-treatment compared to pre-measures (main effect of treatment, $F = 10.55$; $p = 0.006$). In addition, a significant interaction between day time and type of treatment (AC/SAC) was found ($F = 4.07$;

Table 2 Characteristics of patients at baseline (t1, before treatment)

	Characteristics	AC	SAC
Patients	*N* (patients without distorting medication)	19	15
	Age [mean (S.D.)]	46.23 (15.00)	41.80 (14.51)
	Females [*n* (%)]	15 (78.9)	13 (86.6)
	Duration of illness (months) [mean (S.D.)]	67.32 (69.28)	75.20 (84.97)
Salivary cortisol	*N* (patients with cortisol at all time points)	8	9
	7:00 a.m. (nmol/l) [mean (S.D.)]	7.53 (4.78)	8.78 (3.54)
	12:00 a.m. (nmol/l) [mean (S.D.)]	3.30 (2.42)	3.31 (2.39)
	5:00 p.m. (nmol/l) [mean (S.D.)]	1.49 (1.41)	1.40 (1.18)
	10:00 p.m. (nmol/l) [mean (S.D.)]	1.47 (1.53)	0.29 (0.10)
Tilt table	*N* (patients without distorting medication)	18	14
	Systolic blood pressure (mmHG) [mean (S.D.)]	121.64 (12.77)	116.47 (8.94)
	Diastolic blood pressure (mmHG) [mean (S.D.)]	82.43 (10.10)	77.73 (7.67)
	RR-Interval (ms) [mean (S.D.)]	896 (133)	880 (123)
	E/I Ratio metronom [mean (S.D.)]	1.22 (0.13)	1.28 (0.14)
	E/I Ratio valsalva [mean (S.D.)]	1.69 (0.27)	1.78 (0.24)

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

Table 3 Quality of life and pain (t1, before treatment; t2, immediately after 10 treatments (5 weeks after t1)

	AC ($n = 18$)	SAC ($n = 14$)	p (All)	p (Group difference)
FDDQL global score				
t1 [mean (S.D.)]	57.7 (14.5)	55.3 (14.0)		
t2 [mean (S.D.)]	64.6 (17.4)	60.6 (14.9)	0.001	0.327
SF-36 pain scale				
t1 [mean (S.D.)]	48.2 (22.7)	39.6 (16.0)		
t2 [mean (S.D.)]	55.8 (25.7)	48.6 (14.9)	0.007	0.992

FDDQL, functional digestive diseases quality of life questionnaire; AC, acupuncture; SAC, sham acupuncture (placebo).

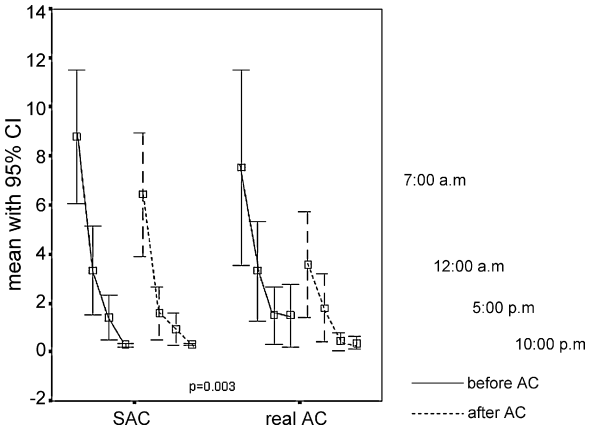

Figure 2 Salivary cortisol before and after treatment ($n_{\text{real AC}} = 8$; $n_{\text{placebo}} = 9$). Calculation based on ANOVA with repeated measures with 'being reponder/non-responder' as a covariate.

$p = 0.033$) (Fig. 2). As can bee seen in Fig. 2, AC treatment resulted in significantly lower cortisol concentrations at all four assessment points, while in SAC this decrease was much less pronounced. Being a responder or non-responder with quality of life had no effects on these results. There was no significant relation between changing in salivary cortisol and changing in global score of FDDQL. There was also no significant relation between the pain scale of SF36 and salivary cortisol.

Autonomic nervous system

If both groups are compared before acupuncture (t1) the blood pressure appears to be higher in the AC group (Table 2). However, this difference was not significant ($p = 0.193$, t-test). The other autonomic parameters of the tilt table also showed no significant group difference at t1. Concerning the longitudinal analysis, there was a significant change with group difference in the orthostatic maneuver. As is shown in Table 4, there was a parasympathetically driven decrease of the heart rate response in the AC group during orthostasis at t2 (counteracting the orthostasis-induced increase of the heart rate). This effect could not be seen in the SAC group. The ANOVA with repeated measures revealed a significant interaction between the factors AC/SAC and rest/orthostasis with responder/non-responder as a covariate ($F = 9.234$; $p = 0.005$). No effects of AC/SAC were seen on the E/I-ratio and on the Valsalva ratio; no effects were seen on systolic and diastolic blood pressure when being a 'responder' or 'non-responder' was introduced as covariate (results not in table). The regression analysis showed no significant relation between changing in heart rate response and changing in global score of FDDQL. However, the regression analysis revealed a significant relation between decrease of heart rate response (which indicated an

Table 4 Orthostatic stress (t1, before treatment; t2, immediately after 10 treatments (5 weeks after t1)

	AC ($n = 18$)	SAC ($n = 14$)	p
RR-interval (ms)			
t1			
At rest [mean (S.D.)]	869 (133)	880 (123)	
Orthostase [mean (S.D.)]	771 (114)	757 (101)	
Heart rate response t1 (Δ [mean (S.D.)])	135 (64)	123 (91)	
t2			
At rest [mean (S.D.)]	894 (116)	900 (108)	
Orthostase [mean (S.D.)]	784 (103)	745 (90)	
Heart rate response t2 (Δ [mean (S.D.)])	109 (60)	184 (106)	
Change (Δ (mean t2) − Δ (mean t1))	−26	+61	0.005

Calculation based on ANOVA with repeated measures with 'being responder/non-responder' as a covariate.

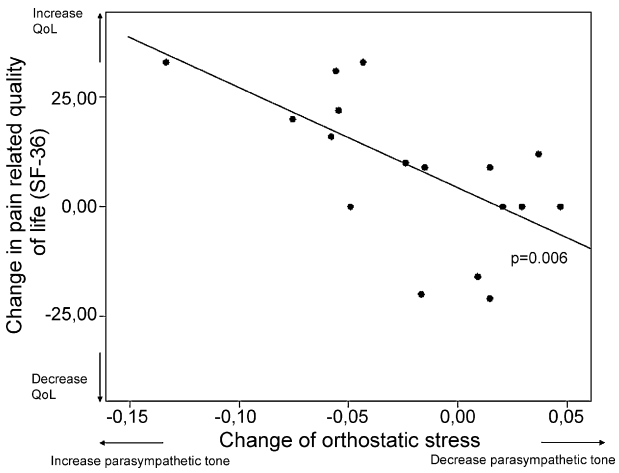

Figure 3 Correlation between change in parasympathetic tone and change in pain related quality of life (AC group; $n = 17$).

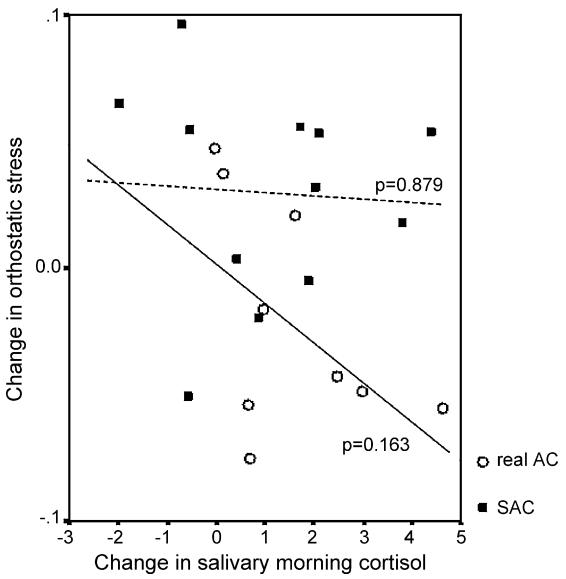

Figure 4 Correlation between change in orthostatic stress reaction and change in morning salivary cortisol ($n_{\text{real AC}} = 9$; $n_{\text{placebo}} = 12$).

increase of the parasympathetic tone) and increase of pain related QoL (SF-36) in the acupuncture group ($F = 10.1$; $p = 0.006$; $r^2 = 0.40$) (Fig. 3). There was no significant association of these parameters in the SAC group.

Correlation between cortisol and autonomic functions

When the maximal change in saliva cortisol (7:00 a.m. value pre- and post-therapy) was correlated to the change in RR interval (supine minus orthostasis) prior and post-therapy, it became evident, that in AC this correlation was negative, while in SAC no such association could be found. However, this effect was not significant which might be due to the small sample sizes (Fig. 4).

Discussion

This is the first study evaluating the effects of acupuncture on parameters of the neuroendocrinological system in patients with IBS within a RCT design. We could show that salivary cortisol decreased after acupuncture treatment in both groups but significantly more in the real AC group. The real AC group showed an increase of the parasympathetic tone whereas the sham AC group remained constantly. The increase of the parasympathetic tone correlated with pain improvement in the AC group. These effects are surprising as they are in contrast to the results concerning the general clinical improvement (evaluated as health-related quality of life) where we could not demonstrate group differences after treatment.

In patients with heart failure,[11] major depression,[12] in healthy subjects[28] and athletes[29] modulation of the ANS by acupuncture has been shown. However, only Middlekauff et al.[11] and Haker et al.[28] evaluated the effectiveness in a placebo-controlled setting and found real AC superior to SAC, similar to the results described here. In our trial, the increase of the parasympathetic tone in response to orthostatic stress in the AC group is accompanied by a significantly more pronounced decrease of salivary cortisol and decrease of pain. This fits into the picture of an overactivity of the hypothalamic—pituitary—adrenal (HPA) axis in patients with IBS, which was shown by experimental studies.[16,30] Therefore, the decrease of cortisol could explain the improvement of pain symptoms in our patients.

This raises the question why the acupuncture-specific response of the ANS does not result in a parallel improvement in quality of life exclusively in patients with true acupuncture. Instead, the health-related QoL improved in both the acupuncture and the placebo-acupuncture group without significant group differences. It appears from the data of our current study and the previously reported clinical results[8] that placebo acupuncture treatment has such a great power that it generates similar effects than the specific acupuncture-driven physiological effects reported here. Several studies have shown the power of placebo acupuncture. Kaptchuk et al. demonstrated that placebo acupuncture had greater effects than placebo pills on self-reported pain and severity of symptoms

in patients with persistent arm pain.[31] Kong et al. could show that sham acupuncture with the ''Streitberger-needle'' activates pain-suppressing brain regions.[32] This is in line with the experiment of Pariente et al. who showed that patients' expectation and belief seem to modulate brain activity of the reward system during sham acupuncture with that needle.[33] Also effects on the immune system were observed during placebo acupuncture treatment.[34] Similar observations have been made with placebo-controlled medication indeed. In depression treatment for instance, placebo responders usually are undistinguishable from medication responders in terms of clinical benefit (e.g. on the Hamilton Depression Anxiety Scale). However, when both were compared with respect to biological markers of the response, e.g. brain activation by means of EEG, PET, or fMRI[35,36] it became evident that different mechanisms were involved in placebo- and medication-driven improvement of symptoms. While the placebo response usually involves strong prefrontal cortex activation, medication response at least in depression is generated by predominant subcortical inhibition—these ''top down'' and ''bottom up'' processes results in similar clinical efficacy.[36] Similar mechanisms could be postulated for placebo versus real acupuncture treatment.

Since our study is of explorative nature, some limitations must be noted. To allow conclusions about the autonomic nervous system response, we had to select patients with complete data. However, tilt table assessments could not be analyzed in all patients because of confounding variables such as medication; and it was not possible to obtain tilt table data and salivary cortisol at all time points from all patients. Indeed the results regarding the parameters of the autonomic nervous system of the tilt table were concordant with results of other IBS studies.[15,37] Another limitation is that parameters of the autonomic nervous system show great individual variability that restricts the validity of conclusions especially in trials with small sample sizes. However, tilt table testing is regarded as one of the most reliable and valid technique to assess the autonomic nervous function, as it is less dependent on the cooperation of the participant. To our knowledge, this is the first RCT investigating autonomic response after 10 sessions of acupuncture, in particular in IBS patients. Therefore further research with larger sample sizes is needed to proof these preliminary findings and to determine if there is a long-term impact on the course of disease.

To conclude, in patients with IBS unspecific (placebo) effects accompanying acupuncture[7,8,38] as well as in many other types of treatment[39] may play a major role. One reason might be found in the suggestibility of these patients.[40] Also the increased frequency of medical encounter and active treatment strategy might contribute to this phenomenon.[41] However, this does not imply that there is no specific physiological effect of acupuncture treatment as we found an acupuncture specific increased parasympathetic tone accompanied by an increase of pain related quality of life. The placebo-effects may be due to explicit ''handling'' as a treatment strategy and signalling holistic understanding.[8] This effect may also occur in other methods of alternative medicine,[42] where specifics of the doctor-patient interaction could cause characteristic and incidental effects.[43] The mechanism of action of acupuncture on the ANS and the HPA axis remains unclear. Thus, further studies are needed to shed light on this phenomenon and — if possible — to use this effect in the management of IBS treatment in the future.

Conflict of interest statement

A.S., S.J., and K.S. are teachers and members of the scientific centre of the German Medical Acupuncture Association (DÄGfA). The other authors had no conflicts of interest.

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