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German Randomized Acupuncture Trial for chronic shoulder pain (GRASP) – A pragmatic, controlled, patient-blinded, multi-centre trial in an outpatient care environment ☆

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ABSTRACT

The German Randomized Acupuncture Trial for chronic shoulder pain (GRASP) comprised 424 outpatients with chronic shoulder pain (CSP) ⩾6 weeks and an average pain score of VAS ⩾50 mm, who were randomly assigned to receive Chinese acupuncture (verum), sham acupuncture (sham) or conventional conservative orthopaedic treatment (COT). The patients were blinded to the type of acupuncture and treated by 31 office-based orthopaedists trained in acupuncture; all received 15 treatments over 6 weeks. The 50% responder rate for pain was measured on a VAS 3 months after the end of treatment (primary endpoint) and directly after the end of the treatment (secondary endpoint). Results: In the ITT ($n = 424$) analysis, percentages of responders for the primary endpoint were verum 65% (95% CI 56–74%) ($n = 100$), sham 24% (95% CI 9–39%) ($n = 32$), and COT 37% (95% CI 24–50%) ($n = 50$); secondary endpoint: verum 68% (95% CI 58–77%) ($n = 92$), sham 40% (95% CI 27–53%) ($n = 53$), and COT 28% (95% CI 14–42%) ($n = 38$). The results are significant for verum over sham and verum over COT ($p < 0.01$) for both the primary and secondary endpoints. The PPP analysis of the primary ($n = 308$) and secondary endpoints ($n = 360$) yields similar responder results for verum over sham and verum over COT ($p < 0.01$). Descriptive statistics showed greater improvement of shoulder mobility (abduction and arm-above-head test) for the verum group versus the control group immediately after treatment and after 3 months. The trial indicates that Chinese acupuncture is an effective alternative to conventional orthopaedic treatment for CSP.

1. Introduction

Chronic shoulder pain (CSP) is a widespread condition. In Great Britain, about 17% of all chronic pain patients of general practitioners had suffered from shoulder pain in the previous 4 weeks and in the US about 7 billion dollars are spent annually on direct cost of treatment of disorders related to the shoulder joint [26,32]. The reported incidence of shoulder pain has increased 100% over the last 10 years, mainly because of changing work habits and sports activities, but also because of more sensitive diagnostic procedures. While in the 70s orthopaedic interest focused on the hip joint, emphasis shifted to the knee in the 80s and then to the shoulder in the 90s [13,33]. Pain and stiffness of the shoulder is commonly caused by rotator cuff disorders including tendonitis and bursitis, by adhesive capsulitis and by osteoarthrosis of the gleno-humeral joint [26]. The normal course of the disease consists of a gradual or sudden onset accompanied by night pain and pain on moving the affected joint. The mobility of the shoulder joint then becomes progressively more limited until in many cases a "frozen" or stiff shoulder is the result. The process, according to most of the literature, is generally "self-limiting", lasting for about 1–3 years. Nevertheless a significant number of patients suffer from a residual, clinically detectable restriction of movement beyond three years [3]. The common treatments for shoulder pain are NSAIDs, physiotherapy, cortisone injections and "wait and see" [43]. Unfortunately none of these treatments is clearly proven to be effective for CSP in the long run, calling for new treatment strategies to improve the situation of CSP sufferers [3,43].

In Chinese Medicine, CSP is considered one of the indications most amenable to treatment with acupuncture [12,15,36,37,46].

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A small number of clinical and methodologically diverse trials have been published recently which show little evidence to support or refute the use of acupuncture for shoulder pain and, as Green et al. concluded, there is a need for further well-designed clinical trials [5,17,22,38]. The German Randomized Acupuncture Trial for chronic shoulder pain (GRASP), a pragmatic, patient-blinded, three-armed, multi-centre trial, tested pain reduction of Chinese acupuncture 3 months and directly after treatment in comparison to sham acupuncture and conventional orthopaedic treatment in 31 orthopaedic centres for outpatient care in Germany. We used an outpatient care setting because it resembles the environment in which acupuncture is normally delivered. The multi-centre design gives the trial a high external validity and allowed us to include 424 patients, making GRASP one of the largest pragmatic RCTs to date to study acupuncture for chronic pain of the shoulder joint. GRASP was funded by the German Ministry of Education, Science and Research. Reference No. 01KT9411/9.

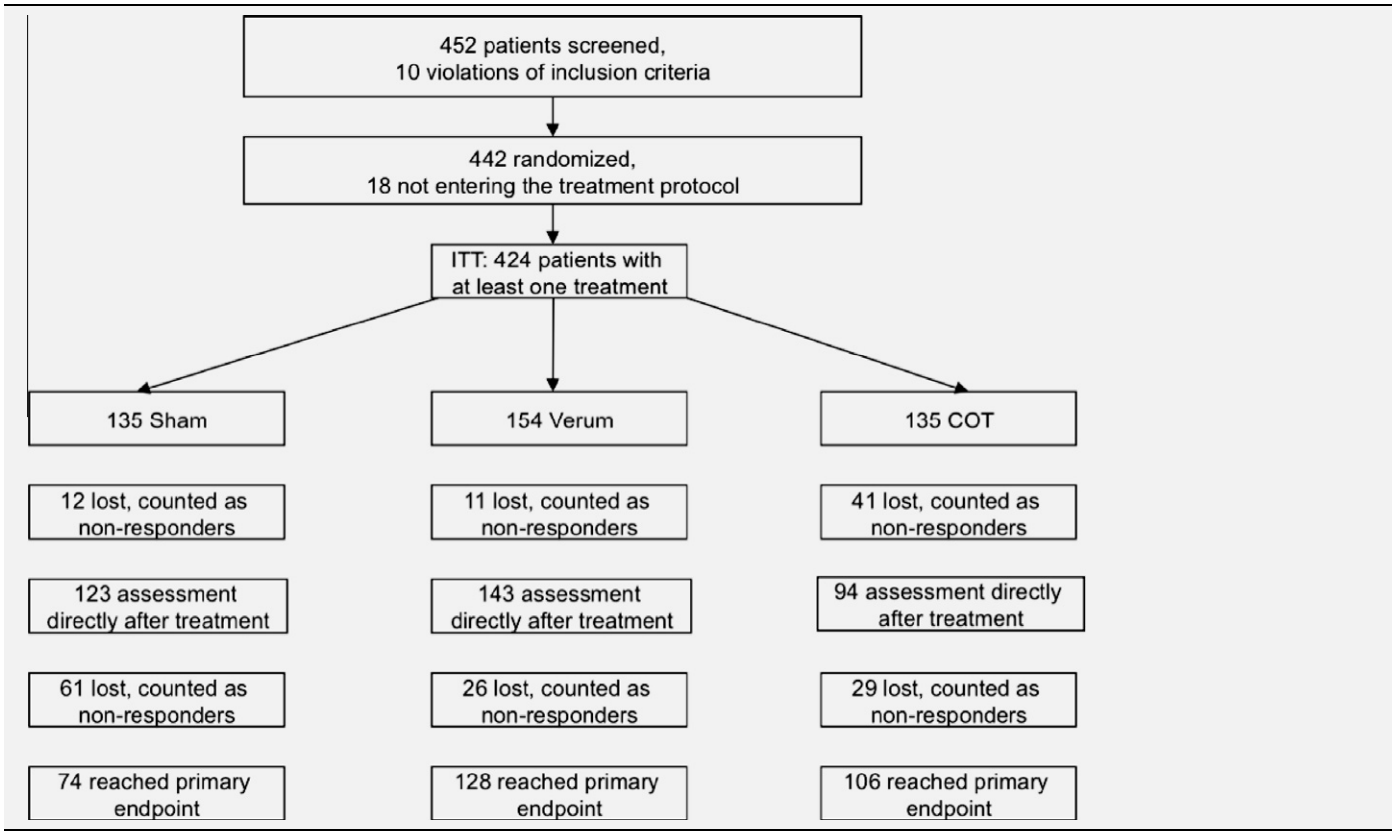
2. Materials and methods

2.1. Patients and randomisation

Acupuncture-naïve patients were recruited from office-based orthopaedic physicians between 1997 and 1999 (last patient out 8/99). Data from the medical examinations were sent via fax to the Department of Statistics in Medicine, Heinrich Heine University Düsseldorf, and assessed for eligibility according to the following criteria: one-sided shoulder pain for at least 6 weeks and up to two years; an average pain score of 50 mm or more on a 100-mm visual analogue scale (VAS) in the past week; age between 25 and 65 years; the ability to communicate in German; no neurological disorders causing shoulder pain; no referred pain from the cervical spine; no osteoarthritis of the gleno-humeral joint or systemic bone and joint disorder (e.g. rheumatoid arthritis); no history of shoulder surgery; no other current therapy involving analgesics; no overt psychiatric illness; no pregnancy; no incapacity for work longer than 3 months preceding the trial, and no pending compensation procedure (the latter to exclude a conflict of interest between the expected social benefit payments and possible positive treatment effects). All patients were informed about the trial and written consent was obtained. Care was taken that all patients received identical information about the trial (trial profile see Table 1). The study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical practice. The protocol was assessed and approved by the two ethics review boards of the participating regions.

Using central telephone randomisation (Department of Statistics in Medicine, Heinrich Heine University Düsseldorf), the patients were randomly allocated to treatment groups and informed via fax. The randomisation list was prepared with the SAS software package, version 6.12, and was concealed and recorded on a secure central database. Treatment assignment to one of verum acupuncture (verum), sham acupuncture (sham), or conventional orthopaedic conservative treatment (COT) was known to the acupuncturist. Randomisation was stratified in two balanced strata according to patient age: 25 to $\leqslant$45 years (stratum 1) and 46 to $\leqslant$65 years (stratum 2). The patients were blinded to whether they received verum or sham acupuncture, but were not blinded to COT. Therapy was administered by 31 office-based orthopaedists who all had passed nationally recognized acupuncture examinations with a minimum of 140 training hours, and additionally had attended a 1-day seminar explaining the specific modalities of the trial therapy.

Table 1
Flowchart of the trial.



2.1.1. Hypothesis and sample size

H_0: There is no significant difference in the responder rate for the acupuncture group (verum) compared to that of sham and of COT. H_N: There is a significant difference for the responder rate in the verum group compared to that of sham and of COT. The patients with a pain reduction of at least 50% compared to baseline were classified as responders. On the basis of pilot studies and reviews of published acupuncture trials, our trial was planned to detect a responder difference of verum over COT of at least 20%. To reach a test power of 90% to reject the H_0 hypothesis with a level of significance of $\alpha = 0.025$ for verum over sham and verum over COT, respectively, the calculated sample size was 459 valuable patients.

2.2. Intervention

2.2.1. Verum

The patients received 15 treatments of Chinese acupuncture, one to three per week, each lasting for 20 min. After a literature review of Chinese acupuncture textbooks [12,15,36,37,46] and a discussion by an expert panel (one author of a leading German acupuncture textbook, four experienced acupuncture practitioners and teachers) the following points were selected: one to three locus dolendi (Ahshi) points; local and distal points according to the channel and the individual location of the pain: ventral – Lung 1, 2; ventrolateral – Large Intestine 4, 11, 14, 15; lateral – Sanjiao 5, 13, 14; dorsal – Small Intestine 3, 9. Additionally distal points on the homolateral leg could be selected from Stomach 38, Gallbladder 34, Bladder 58; while needling these distal points a brief movement of the shoulder was allowed. Depending on the site and quality of the reported pain, 5–10 (average 8) needles (AsiaMed 0.3 mm) were inserted unilaterally to a depth of 1–2 cm. Needle manipulation was mild to strong, to achieve a feeling of heat and numbness around the acupuncture point (Deqi) (Fig. 1).

2.2.2. Sham

The patients received 15 treatments, one to three per week, each lasting for 20 min. Sham acupuncture was carried out by the same physicians as verum acupuncture and was standardized to 8 needles at defined non-acupuncture points, 4 needles above the medial part of the tibia bilaterally, with depth of needle insertion less than 5 mm (Fig. 1). Other than that, management of these patients and information provided to them was identical to that in the verum group.

2.2.3. COT

The patients received conventional orthopaedic therapy with 50 mg diclofenac daily. Additionally 15 treatment sessions were individually selected from physiotherapy, physical exercise, heat or cold therapy, ultra-sonic treatment and TENS. Injections or cortisone applications of any kind were not allowed. Other than that management of these patients and information provided to them was identical to that in the other two groups.

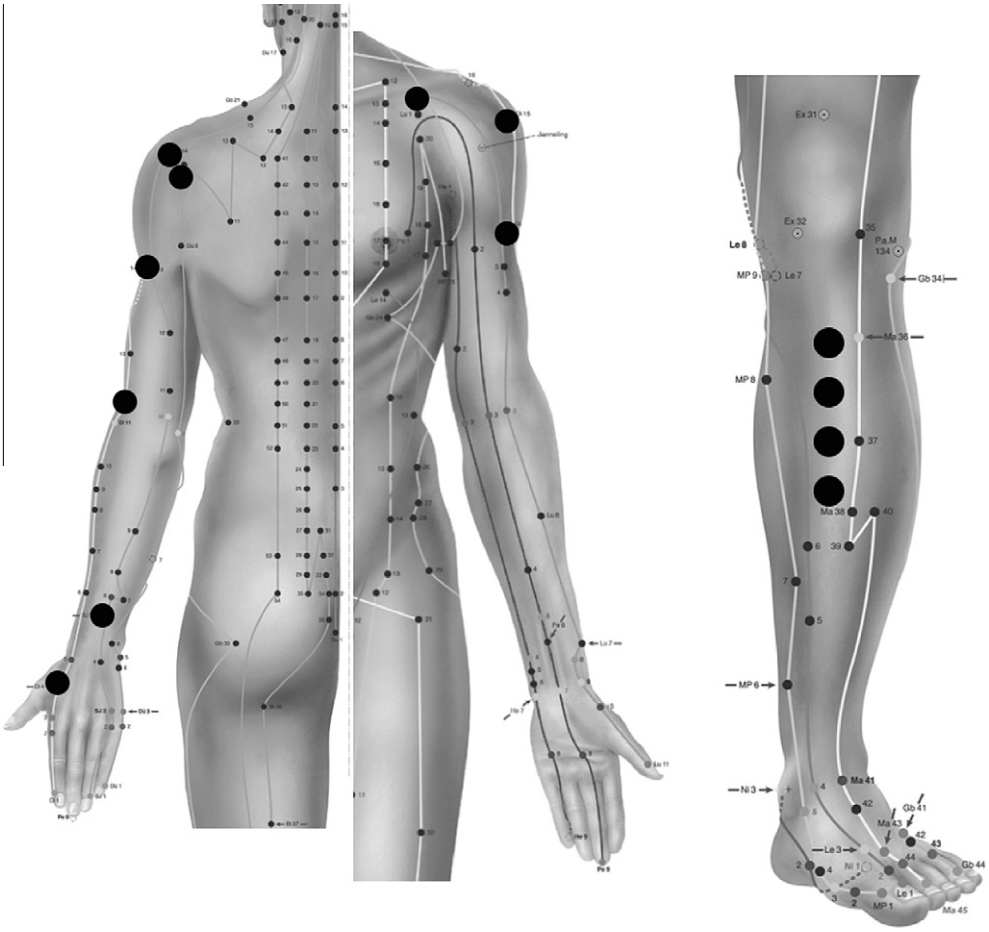


Fig. 1. Acupuncture points. Verum acupuncture: one to three locus dolendi (Ahshi) points; local and distal points according to the channel and the individual location of the pain: ventral – Lung 1, 2; ventrolateral – Large Intestine 4, 11, 14, 15; lateral – Sanjiao 5, 13, 14; dorsal – Small Intestine 3, 9, depth of needle insertion 1–2 cm. Sham acupuncture: 4 needles above the medial part of the left and right tibia, with depth of needle insertion less than 5 mm.

2.3. Data assessment

Personal data and details of the patient's medical history and present condition were obtained in the outpatient orthopaedic centres and included: localization and duration of CSP, impairment of work or sports activity, whether pain was worse at night, number of physicians consulted for shoulder pain, past treatments, and medical drug intake lasting more than 14 days.

Pain intensity was recorded on a 100-mm VAS by patients themselves, with 0 representing "no pain at all" and 100 mm representing "most intense pain imaginable".

The physical record of the shoulder included X-ray to detect osteoarthritis of the gleno-humeral joint or other bone pathology, results of the tests for diminished strength or atrophy of the muscle, and results of the tests of range of passive motion (abduction, adduction, rotation, and elevation). For diagnostic tests the Jobe test and the arm-above-head test were chosen. Data needed for correct Chinese acupuncture treatment were taken: precise pain localization and its relation to acupuncture channels, and pain quality (e.g. deep or superficial, of fixed or moving location, and influenced by cold or heat).

Three months after the end of the 6-week treatment protocol (primary endpoint) and directly after the end of the treatment protocol (secondary endpoint), the patients were asked to document the pain on the VAS (average pain level during the last 7 days) and shoulder mobility was assessed by the physician. In case of treatment protocol failures, the reasons were documented (e.g. need for surgery and worsening of the condition).

2.4. Primary and secondary endpoints

We chose pain as the primary and secondary endpoints for the following two reasons: (I) Acupuncture is considered to be primarily a treatment for pain, and (II) in an outpatient setting the treating physician also assesses the treatment outcome, therefore mobility assessment is more prone to be influenced by the physician's treatment beliefs than is a VAS score, self-reported by the patient. The patients with a reduction of at least 50% from the baseline VAS, with the VAS score referring to the average pain level during the last 7 days before measurement, were classified as responders. We chose this criterion because firstly it is well established for pain and acupuncture trials and secondly a pain reduction of at least 50% is considered to be clinically relevant [11,27]. The patients for whom no data were available for the primary or secondary endpoints were counted as treatment failures. From pilot data, clinical experience, and previous acupuncture trials [27] we observed that treatment outcome was better 3 months after the end of the treatment than directly after the end of the treatment. Therefore for the primary endpoint the responder rate was determined 3 months after the end of the treatment, and for the secondary endpoint it was determined directly after the end of the treatment protocol.

2.5. Statistical analysis

The patients who received at least one study treatment constituted the safety population and the intention-to-treat (ITT) analysis, irrespective of their compliance or adherence to protocol specifications. An additional per-protocol analysis (PPP) was undertaken for patients without major protocol deviations who could be interviewed for the primary or secondary endpoints. The patients for whom no endpoint data were available were counted as treatment failures.

Statistical analysis was completed by statisticians who were blinded to treatment allocation (Department for Statistics in Medicine, Heinrich Heine University of Düsseldorf). To detect departures from homogeneity after randomization, the three treatment groups were compared with nonparametric tests: the Kruskal–Wallis for metrically scaled, continuously distributed variables (VAS, age, duration of chronic pain), and the chi-square contingency tables test for nominally and ordinally scaled variables (gender, frequencies of pain attacks, and intensity of night pain).

COT and sham were each compared to verum with a global level of significance of $\alpha = 0.05$ for the single primary endpoint (nominal level $\alpha = 0.025$. Frequencies were compared with an approximate chi-square or an exact Fisher test, as appropriate; for quantitative variables, the changes were compared between the treatment groups using the nonparametric Mann–Whitney–Wilcoxon rank test. Nominal confidence levels were adjusted for multiple testing according to the appropriate adjustments for tests of effects in each comparison. All calculations were carried out with the SAS software package, version 6.12, under the OS/2 operating system.

3. Results

3.1. Patients and randomisation

Thirty-one orthopaedists recruited 452 outpatients, of whom 442 could be successfully randomised after external screening. The most common reason for non-randomisation ($n = 10$) was violation of the inclusion criteria. Eighteen patients were randomised but did not enter the treatment protocol and no data were obtained. Four hundred and twenty-four patients constitute the safety population and the ITT analysis; 308 patients for the primary endpoint and 360 patients for the secondary endpoint had no major protocol violations and constituted the patient per-protocol analysis (Table 1). All baseline characteristics (gender, age, duration of disease, intensity of pain, radiographic and clinical diagnosis) were similar across the three treatment groups (Table 2). In the ITT population 62.3% of all trial patients were female. The patients were approximately 50.8 (SD 9.7) years old and reported of moderate to severe pain that had lasted on average 10.6 (SD 9.5) months. In 57.6% the pain was in the right shoulder. The shoulder pain interfered with most patients' ability to work (73.3%), engage in leisure activities (60.6)%, and sleep (70.4%). Most patients had consulted one to three medical doctors (78.5%). Prior to the trial 52% of patients had received oral drug treatment (NSAIDs and others), 45.9% had received injections in the shoulder joint, and 43% had received physical therapy (mobilisation, massage, infrared radiation, electrotherapy and others). In significant numbers of patients, radiographs revealed calcium deposits at the supraspinatus tendon (32.6%), osteoarthrosis of the acromioclavicular joint (10.9%), or lifting of the shoulder head (22.4%). Clinical diagnoses included bursitis subacromialis (40.0%), bursitis calcarea (29.4%), frozen shoulder (3.9%) and biceps tendonitis (2.5%). For shoulder mobility at baseline see Table 2.

3.1.1. Primary endpoint

In the ITT analysis, 65% (95% CI 56–74%) of patients in the verum group ($n = 100$), 24% (95% CI 9–39%) in the sham group ($n = 32$), and 37% (95% CI 24–50%) in the COT group ($n = 50$) reported of pain relief of at least 50% 3 months after the end of treatment and were classified as responders; the results are significant for verum versus sham ($p < 0.01$) and for verum versus COT ($p < 0.01$). These significant differences remain robust in the per-protocol analysis with a responder rate of 78% (95% CI 71–85%) in the verum group ($n = 100$), 43% (95% CI 32–54%) in the sham group ($n = 32$), and 47% (95% CI 37.5–56.5%) in the COT group ($n = 50$) (Table 3).

Table 2
Baseline characteristics. Verum = Chinese acupuncture; sham = sham acupuncture; COT = conventional orthopedic therapy; SD = standard deviation; * = chi-square test; ** = *F*-test. All baseline characteristics (gender, age, duration of disease, intensity of pain, and clinical diagnosis) were similar across the three treatment groups, no significant differences were detected.

Baseline characteristics	Sham	Verum	COT	*p*-Value
Sample sizes: number of patients	135	154	135	
Gender: male/female (%)	45/89 (33/66)	66/88 (43/57)	45/87 (33/64)	0.18*
Affected shoulder: right/left (%)	87/48 (64/36)	86/68 (56/44)	71/64 (53/47)	0.12*
Age: mean in years (SD)	51.3 (9.4)	50.3 (9.6)	50.8 (10.0)	0.68**
Duration of the disease: mean in months (SD)	11.6 (11.4)	10.7 (9.7)	9.6 (7.3)	0.23**
Pain intensity VAS: mean (SD)	66.0 (13.8)	66.3 (13.6)	66.2 (13.9)	0.98**
Shoulder mobility – abduction: mean in degrees (SD)	129 (41.6)	129 (36.3)	125 (39.4)	0.62**
Jobe test positive: *n* (%)	100 (74)	115 (75)	93 (69)	0.49*
Full elevation of the arm possible: *n* (%)	69 (51)	82 (53)	67 (50)	0.82*

3.1.2. Secondary endpoint

Directly after the end of the treatment protocol, pain relief of at least 50% was reported by 68% (95% CI 58–77%) in the verum group ($n = 92$), 40% (95% CI 27–53%) in the sham group ($n = 53$), and 28% (95% CI 14–42%) in the COT group ($n = 38$); verum versus sham ($p < 0.01$), verum versus COT ($p < 0.01$). The significant difference between the treatment groups did not change in the per-protocol analyses with 64% (95% CI 56–72%) in the verum group ($n = 92$), 43% (95% CI 34–52%) in the sham group ($n = 53$), and 40% (95% CI 30–50%) in the COT group ($n = 38$) (Table 4).

Additional post hoc analysis (ITT) revealed that the mean VAS scores changed (i) in the verum group from 66.31 at baseline to 25.46 directly after treatment and to 18.51 after 3 months; (ii) in the sham group from 65.96 at baseline to 35.37 directly after treatment and to 33.42 after 3 months; (iii) in the COT group from 66.20 at baseline to 40.29 directly after treatment and to 33.13 after 3 months ($p < 0.001$) (Table 5). The mobility of the shoulder – assessed by abduction and ability to raise the arm above the head – and the number of patients reporting of no pain on the Jobes test increased in all groups, but to a greater extent in the verum group ($p < 0.05$) (Table 5).

No serious adverse events or side effects were observed in any of the intervention groups.

4. Discussion

The GRASP trial shows that a course of 15 acupuncture treatments more effectively reduces pain and improves mobility in patients with chronic shoulder pain then does standard therapy using NSAIDs and physiotherapy. The therapeutic effect can be observed immediately after the end of the treatment and for a period of up to 3 months, with the difference between acupuncture and standard therapy increasing over this time. Our results suggest that verum acupuncture is superior to sham acupuncture. With 424 patients treated in 31 outpatient centres, the trial has a high external validity, and shows that acupuncture can be effectively integrated into the medical setting of an outpatient care environment. To our knowledge this is the largest pragmatic trial on acupuncture for CSP conducted to date.

4.1. Strength and limitations

Our results are applicable to the typical patient with CSP. The patients in this study had a mean VAS pain score of 66, an average age of 50.8 and an average duration of the disease of 10.6 months, and thus had typical items and characteristics found in other trial populations and surveys [3,16,38].

The acupuncture treatment designed for this study consisted of a set of obligatory points as well as points selected on an individual basis. Although there are many different forms of acupuncture, the Chinese acupuncture treatment used in this trial reflects a broad consensus in the literature and is based on a treatment strategy that is widely used in Germany.

The origin of shoulder pain is manifold and not always clear. Generally accepted guidelines for the conventional treatment of shoulder pain conditions do not exist [6,19,29]. Care was taken to exclude standard therapy procedures of unproven efficacy, such as injections of any kind, which might interfere with acupuncture needling, especially when coincidentally placed in acupuncture points [1–3,21,41,44]. In the absence of accepted guidelines, the standard therapy protocol was developed by consulting textbooks on orthopaedic treatment of shoulder pain, experienced clinicians

Table 3
Primary endpoint, ITT and PP analysis (3 months after treatment protocol). Responders: patients with a reduction of at least 50% from the baseline VAS, with the VAS score referring to the average pain level during the last 7 days before measurement. *n* = number of assessed patients, who had followed the treatment protocol, n.a. = number of patients not available. Percentage of assessed patients. Verum = Chinese acupuncture, sham = sham acupuncture, COT = conventional orthopedic therapy.

Characteristics	Sham		Verum		COT	Total
Sample size	135		154		135	424
Pain relief ⩾ 50%		Verum/sham		Verum/COT		
ITT analysis: primary endpoint (3 months after treatment protocol)						
Yes	32 (23.7%)		100 (64.9%)		50 (37.0%)	182
No	103 (76.3%)		54 (35.1%)		85 (63.0%)	242
p-Value		<0.001		<0.001		
Odds ratio (95% CI)		5.96 (3.45–10.35)		3.15 (1.90–5.23)		
PP analysis: primary endpoint (3 months after treatment protocol)						
Yes	32 (43.2%)		100 (78.1%)		50 (47.2%)	182
No	42 (56.8%)		28 (21.9%)		56 (52.8%)	126
n	74		128		106	308
n.a.	61		26		29	116
p-Value		<0.001		<0.001		
Odds ratio (95% CI)		4.69 (2.41–9.18)		4.00 (2.19–7.35)		

Table 4
Secondary endpoint, ITT and PP analysis (directly after treatment protocol). Responders: patients with a reduction of at least 50% from the baseline VAS, with the VAS score referring to the average pain level during the last 7 days before measurement. *n* = number of assessed patients, who had followed the treatment protocol, n.a. = number of patients not available. Percentage of assessed patients. Verum = Chinese acupuncture, sham = sham acupuncture, COT = conventional orthopedic therapy.

Characteristics	Sham		Verum		COT	Total
Sample sizes	135		154		135	424
Pain relief ⩾ 50%		Verum/sham		Verum/COT		
ITT analysis: secondary endpoint (directly after treatment protocol)						
Yes	53 (39.3%)		92 (68.1%)		38 (28.1%)	182
No	82 (60.7%)		62 (31.9%)		97 (71.9%)	242
p-Value		<0.001		<0.001		
Odds ratio (95% CI)		2.30 (1.40–3.78)		3.77 (2.24–6.41)		
PP analysis: secondary endpoint (directly after treatment protocol)						
Yes	53 (43.1%)		92 (64.3%)		38 (40.4%)	183
No	70 (56.9%)		51 (35.7%)		56 (59.6%)	177
n	123		143		94	360
n.a.	12		11		41	64
p-Value		<0.001		<0.001		
Odds ratio (95% CI)		2.38 (1.41–4.03)		2.65 (1.50–4.71)		

and an expert panel. The standard therapy protocol therefore reflects the usual clinical treatment of shoulder pain in Germany, with the exception that neither injections of any kind nor cortisone therapy were allowed.

In view of the outpatient care setting of the trial, we chose endpoints that are generally accepted for shoulder pain, and that can easily be assessed by the patients themselves. Since acupuncture is primarily regarded as a pain treatment, the outcome criteria refer to shoulder pain. The CONSTANT score deliberately was not used, because only 15% of it refers to pain and the remaining 85% to shoulder function [8]. In accordance with Collins et al., who showed in a meta-analysis that simple outcome scales correlate highly with very complex tools of pain or functional measurements, we argue that the VAS scale is a very satisfactory replacement for the CONSTANT score, especially in an outpatient environment [7].

All investigators were counselled and trained to give equal information, time and care to all patients, regardless of treatment group. Because of the setting of the trial in outpatient treatment centres, the trial is patient blinded but not observer blinded for verum and sham acupuncture and not blinded for standard therapy. We did not formally examine the success of blinding nor patients' expectations since the trial was designed and carried out before the testing of these confounders became well-accepted methodological procedures for acupuncture trials [31]. However, the equal drop-out rates of 11 patients in the verum group and 12 patients in the sham group during the expanded treatment protocol of 6 weeks strongly suggest that patient blinding was successful and that both verum and sham treatments were equally convincing.

At the point of the 3-month follow-up, the trial was compromised by the loss of about 27% of trial patients. However, this is not unusual for trials in an ambulatory environment and the PPP analysis shows the robustness of the data [10].

In acupuncture trials practitioners cannot be blinded and thus the practitioners' belief might introduce a bias in favour of acupuncture in the assessment of the patient (e.g. mobility of the shoulder). One cannot fully rule out this effect in a pragmatic trial located in an outpatient setting but we took care to minimize it by choosing pain, reported by patients themselves on the VA scale, as the primary outcome metric. Although we did not observe any serious adverse events (SAEs), it cannot be excluded that this is due to an underreporting by centres not being experienced in reporting SAEs.

Table 5
Additional results (post hoc analyses): mean pain intensity on VAS and shoulder mobility. Verum = Chinese acupuncture, sham = sham acupuncture, COT = conventional orthopedic therapy. SD = standard deviation. Post hoc analysis of *p*-values:* = chi-square test; ** = *F*-test. For all VAS measurements patients were asked to evaluate the average pain intensity during the last week.

	Sham 135	Verum 154	COT 135	Verum/sham mean of difference (95% CI)	*p*-Value	Verum/COT mean of difference (95% CI)	*p*-Value
Mean pain intensity on VAS: mean (SD)							
Baseline	66.0/13.8	66.3/13.6	66.2/13.9				
Immediately after treatment protocol	35/26.9	25/24.0	40/26.7	10 (4.12–15.89)	<0.001**	15 (9.13–20.87)	<0.001**
Three-month follow-up	33/29.6	19/23.3	33/26.6	14 (7.87–20.13)	<0.001**	14 (8.22–19.78)	<0.001**
Shoulder mobility: positive Jobe test n (%)							
Baseline	100 (74)	115 (75)	93 (69)				
Immediately after treatment protocol	66 (49)	48 (31)	79 (58)	2.11 (1.27–3.51)	0.002*	3.11 (1.87–5.21)	<0.001*
Three-month follow-up	87 (64)	48 (31)	57 (42)	4.00 (2.38–6.74)	<0.001*	1.61 (0.97–2.69)	0.051*
Shoulder mobility: abduction, degree (SD)							
Baseline	129 (41.6)	129 (36.3)	125 (39.4)				
Immediately after treatment protocol	141 (38.0)	153 (31.5)	136 (38.5)	12 (3.95–20.05)	0.004**	17 (8.89–25.12)	<0.001**
Three-month follow-up	143 (36.2)	154 (32.2)	145 (32.0)	11 (3.08–18.92)	0.007**	9 (1.55–16.45)	0.018
Full elevation of arm possible n (%)							
Baseline	69 (51)	82 (53)	67 (50)				
Immediately after treatment protocol	79 (64)	117 (82)	58 (62)	2.24 (1.31–3.83)	0.001*	4.20 (2.46–7.17)	<0.001*
Three-month follow-up	53 (72)	110 (86)	76 (72)	3.87 (2.30–6.52)	<0.001*	1.94 (1.16–3.26)	0.007*

4.2. Comparison to other studies

Our results are supported by the outcomes of other, smaller trials testing acupuncture for shoulder pain alone or as an adjunct treatment to physiotherapy [4,22,38] as well as by one larger trial recently published. Vas et al. showed that single-point acupuncture in association with physiotherapy improves shoulder function and alleviates pain, compared with mock TENS and physiotherapy [42]. For locomotive disorders, superiority of acupuncture over standard therapy has also been documented by other large-scale multi-centre trials. The German Acupuncture trials (GERAC) (gonarthrosis, low back pain) and two independent RCTs on acupuncture for low back pain, one by one of the authors (AM et al.), the other by Thomas et al. in an outpatient environment in Great Britain, showed acupuncture to be superior to standard therapy [18,34,40]. All of these large-scale, rigorous RCTs revealed the pattern that, as in our trial, the difference between standard therapy and acupuncture increases over time. Furthermore in the GRASP trial we discovered a substantial difference between verum and sham acupuncture. For shoulder pain Vas et al. also detected this difference between verum acupuncture and mock TENS. Still, a significant difference between verum and sham acupuncture is not a common finding in rigorous RCTs. One explanation for our findings might be the fact that in the GRASP trial, the sham acupuncture points were located on the leg, far away from the verum Chinese acupuncture points at the shoulder joint. This also can be observed in the large-scale acupuncture trials in Germany (ART, osteoarthrosis and GERAC, headache trials): the further away sham points were located from verum points, the greater the observed difference between verum and sham treatment [9,11,45].

Patients' expectation and placebo responses have been shown to contribute substantially to the effect of acupuncture. This has been widely discussed in the literature [20,24,25,35]. However, the time pattern of sustained and increasing effect as shown in the GRASP trial as well as in some other recently published RCTs on acupuncture might not be sufficiently explained by those factors only. Nor does the well-established mechanism of acupuncture-stimulating endorphins explain a long-term therapeutic effect lasting more than 3 months [36]. We therefore suggest that other as yet unidentified mechanisms need to be investigated, such as stimulation of anti-inflammatory cytokines and growth factors by destruction and stimulation of cell tissues resulting from the insertion and manual stimulation of the acupuncture needle. This has been recently supported by experimental evidence. Langevin has shown that rotation of a needle inserted in the skin (rat model) activates fibroblasts and induces active growth of cell shape [23]. It has also been shown that electroacupuncture (EA) upregulates platelet-derived growth factors (PDGFs) in the dorsal root ganglion in cats [39], EA upregulates the endogenous insulin-like growth factor 1 (IGF-1) expression following cerebral ischemia after middle cerebral artery occlusion in monkeys [14], EA inhibits interleukin 6 (IL-6) secretion, reduces NF-κB DNA-binding activity in anaphylactic and inflammatory reactions [28], and EA for 11 days in rats with retinitis pigmentosa causes an increase of retinal nerve growth factor (NGF) and enhanced vascularization [30]. We therefore hypothesize that especially the long-term effect of acupuncture as shown in this and the other recent large-scale RCTs speaks in favour of a multicausal theory for the effect of acupuncture. Besides the role of endorphins, placebo and expectation factors, such a theory should also include direct mechanically induced effects on cell hormones.

5. Conclusion

The pragmatic GRASP trial showed that Chinese acupuncture is an effective alternative to conventional standard therapy in chronic shoulder pain. Fifteen Chinese acupuncture treatments over 6 weeks are more effective than conventional standard therapy with NSAIDs and physiotherapy. After the end of treatment, the therapeutic effect of acupuncture lasts for 3 months. The pragmatic trial shows that verum acupuncture is more effective than sham acupuncture at non-verum points located far away from the verum acupuncture points.

Conflict of interest

The study was approved by the ethical board for clinical studies of the North Rhine Medical Association (Ärztekammer Nordrhein), No. 10238, dated October 16, 1996, with the medical associations of Berlin, Hamburg, Niedersachsen and Westfalen Lippe assenting.

A.M. has received fees for speaking, organising education and funds for research on the subject. T.S., H.G. and A.D. declare that the answer to the questions on your competing interest form http://www.bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare.

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Appendix A. Consort statement

Paper section and topic	Item	Descriptor	Reported in Section no.
TITLE and ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned")	
INTRODUCTION Background	2	Scientific background and explanation of rationale	1
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	2.1
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	2.2
Objectives	5	Specific objectives and hypotheses	2.1.1
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable,	2.4

Appendix A (*continued*)

Paper section and topic	Item	Descriptor	Reported in Section no.
		any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors)	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	2.1.1
Randomization – Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)	2.1
Randomization – Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned	2.1
Randomization – Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	2.1
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated	2.1
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses	2.5
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons	2.1, Table 1
Recruitment	14	Dates defining the periods of recruitment and follow-up	2.1
Baseline data	15	Baseline demographic and clinical characteristics of each group	3.1, Table 2
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%)	3, Tables 3–5
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval)	3, Tables 3–5
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory	Not applicable
Adverse events	19	All important adverse events or side effects in each intervention group	3.1.2
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes	4.1
Generalizability	21	Generalizability (external validity) of the trial findings	4
Overall evidence	22	General interpretation of the results in the context of current evidence	4.1

References

[1] Bernstein RM. Injections and surgical therapy in chronic pain. Clin J Pain 2001;17:S94–S104.

[2] Berry H, Fernandes L, Bloom B, Clark RJ, Hamilton EB. Clinical study comparing acupuncture, physiotherapy, injection and oral anti-inflammatory therapy in shoulder-cuff lesions. Curr Med Res Opin 1980;7:121–6.

[3] Buchbinder R, Hoving JL, Green S, Hall S, Forbes A, Nash P. Short course prednisolone for adhesive capsulitis (frozen shoulder or stiff painful shoulder): a randomised, double blind, placebo controlled trial. Ann Rheum Dis 2004;63:1460–9.

[4] Ceccheerelli F, Bordin M, Gagliardi G, Caravello M. Comparison between superficial and deep acupuncture in the treatment of the shoulder's myofascial pain: a randomized and controlled study. Acupunct Electrother Res 2001;26:229–38.

[5] Ceccherelli F, Gagliardi G, Ruzzante L, Giron G. Acupuncture modulation of capsaicin-induced inflammation: effect of intraperitoneal and local administration of naloxone in rats. A blinded controlled study. J Altern Complement Med 2002;8:341–9.

[6] Cofield RH. Rotator cuff disease of the shoulder. J Bone Joint Surg Am 1985;67:974–9.

[7] Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough? Pain 2001;91:189–94.

[8] Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. Clin Orthop 1987:160–4.

[9] Diener HC, Kronfeld K, Boewing G, Lungenhausen M, Maier C, Molsberger A, Tegenthoff M, Trampisch HJ, Zenz M, Meinert R. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. Lancet Neurol 2006;5:310–6.

[10] EMEA. EMEA the European agency for the evaluation of medicinal products. Evaluation of medicines for human use. Points to consider missing data; 2001.

[11] Endres HG, Bowing G, Diener HC, Lange S, Maier C, Molsberger A, Zenz M, Vickers AJ, Tegenthoff M. Acupuncture for tension-type headache: a multicentre, sham-controlled, patient- and observer-blinded, randomised trial. J Headache Pain 2007;8:306–14.

[12] Focks C, Hillenbrand N. Leitfaden traditionelle chinesische medizin, schwerpunkt akupunktur. Ulm, Stuttgart, München: Gustav Fischer; 2000.

[13] Fu FH, Harner CD, Klein AH. Shoulder impingement syndrome. A critical review. Clin Orthop 1991:162–73.

[14] Gao H, Guo J, Zhao P, Cheng J. Influences of electroacupuncture on the expression of insulin-like growth factor-1 following, focal cerebral ischemia in monkeys. Acupunct Electrother Res 2006;31:259–72.

[15] Geng Su. Practical TCM – acupuncture and moxibustion. Peking: New World Press; 1991.

[16] Gerdesmeyer L, Wagenpfeil S, Haake M, Maier M, Loew M, Wortler K, Lampe R, Seil R, Handle G, Gassel S, Rompe JD. Extracorporeal shock wave therapy for the treatment of chronic calcifying tendonitis of the rotator cuff: a randomized controlled trial. JAMA 2003;290:2573–80.

[17] Green S, Buchbinder R, Hetrick S. Acupuncture for shoulder pain. Cochrane Database Syst Rev 2005:CD005319.

[18] Haake M, Muller HH, Schade-Brittinger C, Basler HD, Schafer H, Maier C, Endres HG, Trampisch HJ, Molsberger A. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. Arch Intern Med 2007;167:1892–8.
[19] Harmon PH. Methods and results in the treatment of 2580 painful shoulders, with special reference to calcific tendinitis and the frozen shoulder. Am J Surg 1958;95:527–44.
[20] Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med 2002;136: 817–25.
[21] Kennedy JC, Willis RB. The effects of local steroid injections on tendons: a biomechanical and microscopic correlative study. Am J Sports Med 1976;4: 11–21.
[22] Kleinhenz J, Streitberger K, Windeler J, Gussbacher A, Mavridis G, Martin E. Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. Pain 1999;83:235–41.
[23] Langevin HM, Bouffard NA, Badger GJ, Churchill DL, Howe AK. Subcutaneous tissue fibroblast cytoskeletal remodeling induced by acupuncture: evidence for a mechanotransduction-based mechanism. J Cell Physiol 2006;207: 767–74.
[24] Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B, Willich SN, Melchart D. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain 2007;128:264–71.
[25] Manheimer E, Linde K, Lao L, Bouter LM, Berman BM. Meta-analysis: acupuncture for osteoarthritis of the knee. Ann Intern Med 2007;146:868–77.
[26] Meislin RJ, Sperling JW, Stitik TP. Persistent shoulder pain: epidemiology, pathophysiology, and diagnosis. Am J Orthop 2005;34:5–9.
[27] Molsberger AF, Mau J, Pawelec DB, Winkler J. Does acupuncture improve the orthopedic management of chronic low back pain – a randomized, blinded, controlled trial with 3 months follow up. Pain 2002;99:579–87.
[28] Moon PD, Jeong HJ, Kim SJ, An HJ, Lee HJ, Yang WM, Park SK, Hong SH, Kim HM, Um JY. Use of electroacupuncture at ST36 to inhibit anaphylactic and inflammatory reaction in mice. Neuroimmunomodulation 2007;14:24–31.
[29] Morrison DS, Frogameni AD, Woodworth P. Non-operative treatment of subacromial impingement syndrome. J Bone Joint Surg Am 1997;79:732–7.
[30] Pagani L, Manni L, Aloe L. Effects of electroacupuncture on retinal nerve growth factor and brain-derived neurotrophic factor expression in a rat model of retinitis pigmentosa. Brain Res 2006;1092:198–206.
[31] Park J, Bang H, Canette I. Blinding in clinical trials, time to do it better. Complement Ther Med 2008;16:121–3.
[32] Parsons S, Breen A, Foster NE, Letley L, Pincus T, Vogel S, Underwood M. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. Fam Pract 2007;24:308–16.
[33] Rocks JA. Intrinsic shoulder pain syndrome: rationale for heating and cooling in treatment. Phys Ther 1979;59:153–9.
[34] Scharf HP, Mansmann U, Streitberger K, Witte S, Kramer J, Maier C, Trampisch HJ, Victor N. Addition of acupuncture or sham acupuncture to conservative therapy with physiotherapy and as-needed anti-inflammatory drugs for knee osteoarthritis: a randomized controlled trial. Arch Intern Med 2007;167: 1892–8.
[35] Streitberger K, Vickers A. Placebo in acupuncture trials. Pain 2004;109:195.
[36] Stux G, Berman B, Pomeranz B, Kofen P. Basics of acupuncture. Berlin, Heidelberg, New York, Hongkong, London, Mailand, Paris: Springer; 2003.
[37] Stux G, Stiller N, Berman B, Pomeranz B. Akupunktur, lehrbuch und atlas. Berlin, Heidelberg, New York, Hongkong, London, Mailand, Paris: Springer; 2003.
[38] Sun KO, Chan KC, Lo SL, Fong DY. Acupuncture for frozen shoulder. Hong Kong Med J 2001;7:381–91.
[39] Sun WW, Zhao W, Wang TH. Effects of electro-acupuncture on PDGF expression in spared dorsal root ganglion and associated dorsal horn subjected to partial dorsal root ganglionectomy in cats. Neurochem Res 2008;33:437–43.
[40] Thomas KJ, MacPherson H, Thorpe L, Brazier J, Fitter M, Campbell MJ, Roman M, Walters SJ, Nicholl J. Randomised controlled trial of a short course of traditional acupuncture compared with usual care for persistent non-specific low back pain. BMJ 2006;333:623.
[41] Valtonen EJ. Double acting betamethasone (Celestone Chronodose) in the treatment of supraspinatus tendinitis: a comparison of subacromial and gluteal single injections with placebo. J Int Med Res 1978;6:463–7.
[42] Vas J, Ortega C, Olmo V, Perez-Fernandez F, Hernandez L, Medina I, Seminario JM, Herrera A, Luna F, Perea-Milla E, Mendez C, Madrazo F, Jimenez C, Ruiz MA, Aguilar I. Single-point acupuncture and physiotherapy for the treatment of painful shoulder: a multicentre randomized controlled trial. Rheumatology (Oxford) 2008;47:887–93.
[43] Vas J, Perea-Milla E, Mendez C, Galante AH, Madrazo F, Medina I, Ortega C, Olmo V, Fernandez FP, Hernandez L, Seminario JM, Brioso M, Luna F, Gordo I, Godoy AM, Jimenez C, Ruiz MA, Montes J, Hidalgo A, Gonzalez-Quevedo R, Bosch P, Vazquez A, Lozano JV. Acupuncture and rehabilitation of the painful shoulder: study protocol of an ongoing multicentre randomised controlled clinical trial [ISRCTN28687220]. BMC Complement Altern Med 2005;5:19.
[44] Withrington RH, Girgis FL, Seifert MH. A placebo-controlled trial of steroid injections in the treatment of supraspinatus tendonitis. Scand J Rheumatol 1985;14:76–8.
[45] Witt C, Brinkhaus B, Jena S, Linde K, Streng A, Wagenpfeil S, Hummelsberger J, Walther HU, Melchart D, Willich SN. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. Lancet 2005;366:136–43.
[46] Xinnong C. Chinese acupuncture and moxibustion. Beijing China: Foreign Languages Press; 1987.