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ORIGINAL ARTICLE

A pilot study of acupuncture as adjunctive treatment of rheumatoid arthritis

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Abstract We evaluated the efficacy of acupuncture as a useful adjuvant treatment in the management of rheumatoid arthritis (RA). A pilot, randomized, double-blind, and controlled clinical trial was conducted. Forty RA patients with active disease despite stable therapy for at least the preceding 1 month were randomized to receive a standard protocol of acupuncture (AC) or superficial acupuncture at non-acupuncture points (controlAC) for 9 weeks. The primary outcome was achievement of 20% improvement according to the American College of Rheumatology (ACR) 20 criteria after five and ten treatment sessions and after 1 month of follow-up. Secondary measures included Disease Assessment Scale (DAS), tender and swollen joint count, morning stiffness, Health Assessment Questionnaire (HAQ), visual analogue scale (VAS) of pain, physician global assessment of activity disease, physician and patient global assessment of treatment, and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). There was not significant difference between the groups regarding the number of patients that reached ACR20 at the end of the treatment (p=0.479). However, after 1 month of follow-up, there was a trend in favor of the AC group, with p=0,068. Compared with the controlAC, the AC group also demonstrated significant improvement in the patient and physician global assessment of treatment and physician global assessment of disease activity, but there was no difference on other clinical and laboratorial measures. On the other hand, only the AC patients had within group improvement on the variables DAS, HAQ, morning stiffness, patient and physician global assessment of treatment, and physician global assessment of disease activity in comparison to baseline visit. Despite the improvement of some studied variables, there was no significant difference in the proportion of patients that reached ACR20 between the AC and controlAC groups. This negative result can be related to the small sample size, selection of patients, type of acupuncture protocol applied, and difficulties in establishing an innocuous and trustworthy placebo group to studies involving acupuncture.

Keywords Acupuncture · Adjunctive treatment · Pilot study · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune inflammatory disease that affects the joints in a symmetrical way, which can additionally present with variable, but many times remarkable, extra-articular in-

volvement and functional loss. It is a progressive disease associated with severe morbidity, functional impairment, permanent disability, increased mortality [1, 2], and rapid disease progression in the early phases [3]. In the last decades, there has been a significant progress in the RA treatment with the disease modifying anti-rheumatic drugs (DMARDs) [4]. However, in a significant number of RA patients, the DMARDs do not control the disease in a satisfactory way or cause toxicity that requires its suspension. Additionally, the impact of these therapies on the long term is largely unknown [5].

Acupuncture (AC) is a therapeutic modality that has been used for at least 2,500 years and is currently a component of the Chinese health system [6]. In recent years, there has been an increased interest in research on AC in an attempt to reinterpret its traditional notions according to Western scientific concepts. Currently, it is known that acupuncture modulates pain transmission through: (a) stimulation of the Aδ e C afferent fibers on the skin and II and III afferent fibers on the muscle [7]; (b) release of endogenous opioid peptides (EOPs), such as β-endorphins, encephalins, and dynorphins, [8–12]; and (c) release of several anti-inflammatory substances [13], and other neurotransmitters involved in pain suppression [14]. Besides the liberation of analgesic substances, the counter-irritant effect to the needle insertion, sometimes described as painful and called "*teh Qi*," can also cause analgesia [15].

There is little scientific evidence in the literature supporting its use in RA and other pain conditions. There are only two well-controlled clinical trials studying the efficacy of AC in this disease [16, 17]; however, both studies used a very short protocol and duration, which could be considered insufficient for a systemic and chronic disease such as RA. Moreover, Ezzo at al [18], after an extensive review, concluded that there are limited evidence that acupuncture is more effective than no treatment for chronic pain and inconclusive evidence that acupuncture is more effective than placebo, sham acupuncture, or standard care.

Nevertheless, other randomized controlled clinical trials provide evidence of the efficacy of acupuncture in some conditions. The AC proved to be superior when compared to placebo in the shoulder pain [19], chronic neck pain [20, 21], and knee osteoarthritis [22].

Based on these observations, AC could have a potential benefit in the treatment of RA.

We now report a pilot randomized controlled clinical trial comparing the efficacy of AC with control acupuncture as adjunctive therapy for patients with active rheumatoid arthritis. This differs from the previous studies; an AC protocol with longer duration and larger number of acupuncture points was utilized.

Materials and methods

Design

The present study is a randomized, prospective, controlled clinical trial with two parallel groups.

Patients

RA patients were sequentially recruited at the Rheumatology outpatient clinic of the Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil) after fulfilling the inclusion criteria and signing the informed consent.

Inclusion criteria Patients had to be 18–75 years old and fulfill the American College of Rheumatology criteria for RA [23], with at least 6 months of evolution. Some degree of disease activity had to be present, and pharmacological treatment had to be stable for at least 1 month before the study, including analgesics, non-steroidal anti-inflammatory drugs, glucocorticoids (should be equal or less than 15 mg/day of prednisone or equivalent) and DMARDs. Active disease was considered the presence of signs and symptoms that, in the judgment of the assistant physician, would require change of therapy or progression to a more aggressive drug regimen. Patients also needed to be capable of answering the Health Assessment Questionnaire (HAQ) and patient global assessment of treatment and visual analogue scale of pain (VAS P).

Exclusion criteria Patients were excluded from this study if they had previous acupuncture treatments (to avoid unblinding of the therapeutic group), sensory disturbances, active infection, fear of needles, alcoholism or drug abuse, are pregnant or breastfeeding, on anticoagulation or other complementary treatment, presence of any concurrent disease that precluded the patient from attending the sessions, presence of any other rheumatologic or non-rheumatologic disease that could interfere in the evaluation of efficacy and safety and presence of severe complications of RA or a disease in very advanced phase (class IV).

During the study, patients maintained the previous drug therapy without adjustments, and they were allowed to use analgesics (Paracetamol) for pain. Intra-articular infiltrations or other therapeutic procedures, such as physiotherapy or corrective surgeries, were not allowed.

Recruited patients were randomized to a superficial acupuncture at non-acupuncture points group (controlAC) or an acupuncture group (AC) using computer-generated random numbers. Starting from that point, the patients received a total of ten sessions of AC or controlAC, twice a week for 5 consecutive weeks.

Four assessments were made, as follows:

Visit 1: baseline (before first session);
Visit 2: after 5th session:
Visit 3: after 10th (last) session
Visit 4: 1 month after last session

The first assessment included the following: patient identification, age, time of evolution of the disease, concomitant treatment used, completion of the HAQ validated to Portuguese [24] and VAS P by the patient, tender (maximum of 68)[25] and swollen joint count (maximum of 44), physician global assessment of disease activity [26], and morning stiffness. On this occasion, 100 tablets of Paracetamol (500 mg) were supplied to each patient. Subsequent assessments also included a patient and physician global assessment of treatment. The Disease Assessment Score (DAS), a scale that quantifies the activity of the RA [27], was calculated in all visits. Blood samples were obtained during visits 1, 3, and 4, and measurement of inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] was performed in the laboratory of the Clinical Pathology Service of the HCPA, according to documented routines and quality controls.

All clinical assessments were carried out at the rheumatology outpatient clinic by the same rheumatologist and trained medical student, who were blinded to the treatment allocation.

Treatments

The single acupuncturist stayed blind for the physical exam, laboratory test results, and efficacy assessments but was aware of the group allocation for each patient. During the procedures, she maintained minimal verbal contact with the patients.

Safety was monitored clinically at each visit and by standard laboratory test results. The occurrence of adverse events was documented in the patient's medical records.

According to guidelines for acupuncture studies [28, 29, 30], the details of the therapeutic protocol are presented below:

AC group We used a modification of the Stux protocol [31], with local and distal points to the articulations. Sterile needles with diameter of 0.25×40 mm were inserted and stimulated with production of the "*teh Qi*" sensation right after the beginning of the session. The treatment lasted 20 min with the patient in supine position and 20 min in ventral position. The following points were used: EX 1, PC6, IG4, EX 28, CV 12, CV 6, ST 36, SP 6, and LV 3, when the patients were positioned in supine position, and UB 20, UB 22, UB 23, GV 4, GV 14, UB 11, and UB60, when they were positioned in ventral position (Table 1).

ControlAC group For the control intervention, we opted for the model proposed by Vincent and Lewith [28], consisting of superficial acupuncture at non-acupuncture points, with minimal needle stimulation. Furthermore, we also opted for using fewer needles and shorter insertion duration. Needles of 15×0.25 mm size were inserted up to 2 mm, at non-acupuncture points. Patients remained in supine and ventral position for 10 min each one, receiving controlAC. No manual stimulation or triggering of the "*teh Qi*" sensation was produced.

Statistical analysis

Due to the absence of previous studies in RA patients using an AC protocol similar to the one utilized in this study, it was not possible to precisely estimate the sample size and power of the study a priori. Therefore, we decided to carry out a pilot study with a sample of 20 patients in each group, a number that was intermediate in relation to the two previous randomized clinical trials [16, 17].

The primary outcome was the proportion of patients that reached clinical response of at least 20%, as defined by the ACR20 criteria [26]. These criteria require a 20% minimum improvement in the count of painful articulations and swollen joints and in three or more of the following variables: global evaluation of the treatment response by the physician and by the patient, pain intensity, HAQ, and ESR values. The secondary outcomes were the DAS [27]

Table 1 Acupuncture points at AC group

Acupuncture points	Chinese name
EX1	Yintang
EX27	Baxie
CV6	Qi hai
CV12	Zhong wan
LI4	He gu
GV 4	Ming men
GV 14	Feng fu
LV 3	Tai chong
PC6	Nei guan
SP 6	San yin jiao
ST 36	Zu san li
B 11	Da zhu
B 20	Pi shu
B 22	San jiao shu
B 23	Shen shu
B60	Kun lun

http://www.wpro.who.int/internet/files/pub/72/toc.pdf
Meridians of acupuncture: *EX* extra point, *CV* conception vessel, *LI* large intestine, *GV* governor vessel, *LV* liver, *PC* pericardium, *SP* spleen, *ST* stomach, *B* bladder

and the improvement from the baseline on each of the studied variables.

An intention-to-treat analysis of all patients was performed. The continuous parameters of efficacy were evaluated by *t* test or Wilcoxon test for two samples. The baseline differences, central effects, or other prognostic or discrepant factors were analyzed by analysis of variance (ANOVA) if necessary. The 95% confidence intervals for the differences between treatments were considered for each terminal point of the efficacy. Chi-square test was used for the differences in ACR20 improvement rates.

Ethical aspects

Ethical approval for the study was obtained from the Institutional Review Board of the Hospital de Clínicas de Porto Alegre.

Results

Sample characteristics

A total of 67 consecutive RA patients were evaluated for the study, and after application of the inclusion and exclusion criteria, 20 patients were randomized to the real acupuncture (AC) group and 20 patients to the control acupuncture (controlAC) group. Six controlAC patients and four AC patients withdrew from the study before its completion, and this difference was not statistically significant (Fig. 1).

Baseline characteristics

There were no significant differences in the baseline characteristics between the AC and controlAC groups. Table 2 summarizes the baseline information.

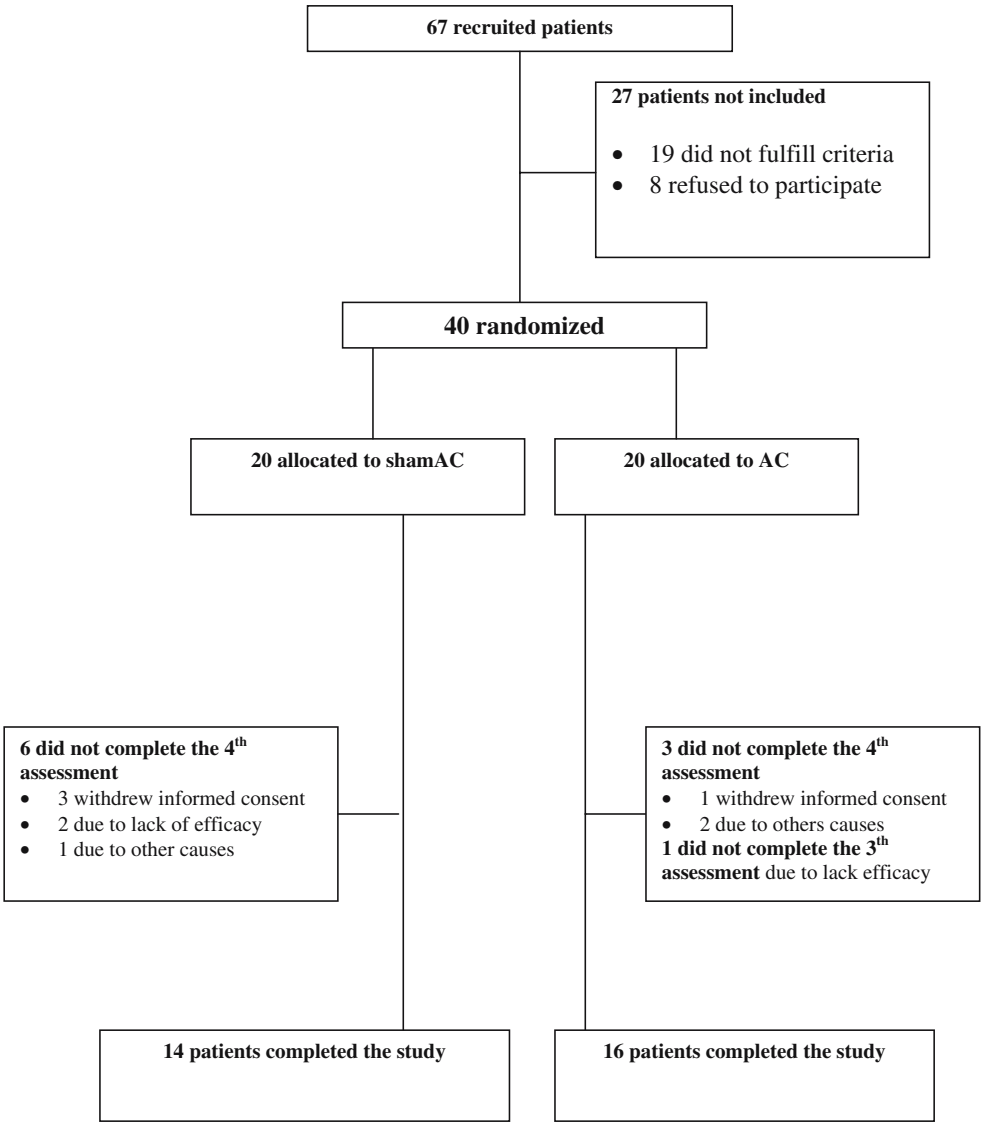

Fig. 1 Trial profile

Table 2 Baseline characteristics

	controlAC (n=20)	AC (n=20)	p value
Demography			
Age[a]	46.5 (9.9)	53.1 (12.44)	0.071
Women	20 (100%)	17 (85%)	0.231
Time of the disease (years ago)[b]	10 (7 a 15)	13 (8 a 16)	0.495
Drugs in use			
NSAID	15 (78.9%)	12 (60%)	0.350
Prednisone	10 (52.6%)	13 (65%)	0.646
DMARD	18 (94.7%)	17 (85%)	0.605
MTX	15 (75%)	17 (85%)	0.695
SSZ	2 (10%)	1 (5%)	1.000
Hydroxychloroquine	6 (30%)	6 (30%)	1.000
Leflunomide	2 (10%)	1 (5%)	1.000
Clinical characteristics			
DAS[a]	4.96 (1.35)	5.26 (1.54)	0.510
Tender joint count[a]	28.50 (18.07)	36.25 (21.83)	0.229
Swollen joint count[a]	13.55 (9.06)	12.6 (7.67)	0.722
HAQ[a]	1.46 (0.73)	1.42 (0.57)	0.835
VAS of pain[a]	6.62 (2.65)	6.38 (2.59)	0.774
Morning stiffness (minutes)[b]	60 (30 a 120)	60 (30 a143)	0.835
Physician global assessment of activity disease[b, c]	2 (1 a 3)	2 (2 a 3)	0.327
Inflammatory markers			
ESR[a]	34.63 (20.97)	42.20 (23.41)	0.295
CRP[b]	9.59 (2.26 a 17.92)	11.6 (1.5 a 25.98)	0.640

controlAC Control acupuncture group; *AC* acupuncture group; *NSAID* non-steroidal anti-inflammatory drugs; *DMARD* disease-modifying antirheumatic drugs; *MTX* methotrexate; *SSZ* sulphasalazine; *DAS* Disease Activity Score; *HAQ* Health Assessment Questionnaire; *VAS* Visual Analogue Scale; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *%* percentage of the variable into the each group; *p* statistical difference

[a] Mean (standard deviation; *t test*)

[b] Median (25–75 percentile; Mann–Whitney test)

[c] Likert scale with 5 points (0=very well, 1=well, 2=regular, 3=bad, 4=very bad)

Clinical efficacy

Primary outcome

ACR20 There was no significant difference between treatment groups regarding the number of patients that reached ACR20 improvement criteria in the assessments after the fifth and tenth sessions and 1 month after the end of the protocol. At this last visit (visit 4), there was a trend for better efficacy in the AC group, where 40% (eight patients) of the group achieved the ACR20 criteria vs 10% (two patients) in the control group (p=0.068, chi-square with Yate's correction; Fig. 2).

Secondary outcomes

Mean change from baseline Mean differences between the values at baseline and at the end of the treatment (visit 3, after the tenth session) for the studied variables are shown in Table 3. There was no difference in the change from baseline for the DAS, the number of painful and swollen joints, functional level (HAQ), pain quantification (VAS), duration of morning stiffness, VSG, and PCR between the intervention groups. There was a significant improvement in the physician assessment of disease activity in the AC group compared with the controlAC group (p<0,001) and a trend for better effect in the physician global assessment of the treatment response (p=0.072).

Evolution of secondary outcomes At visit 4 (1 month after the last treatment), there was statistical difference favoring the AC group for the global assessment of the treatment by the physician (p=0.012) and patient (p=0.003) and for the physician global assessment of disease activity (p= 0.011; Table 4).

Within group comparisons of secondary outcomes Within each group, some variables presented significant improvement between the baseline visit and after the tenth (last session) only in the AC group: DAS (p=0.032), HAQ (p= 0.002), VAS P (p=0.014), patient's global assessment of

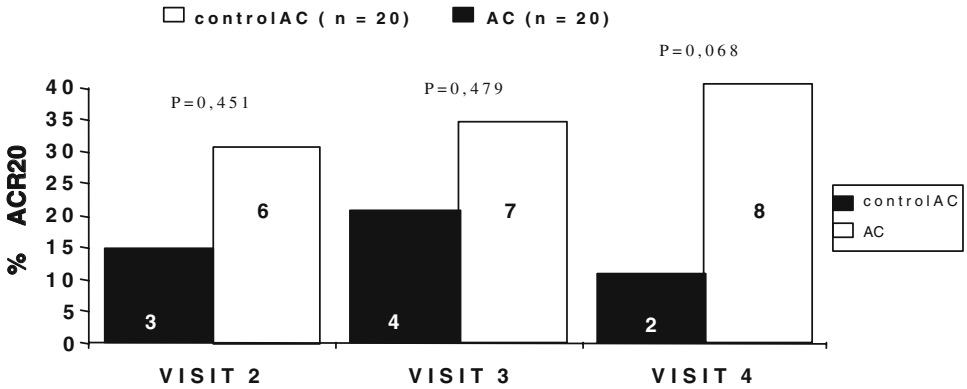

Fig. 2 Percentage of patients that reached ACR20; *controlAC* control acupuncture group; *AC* acupuncture group; *visit 2* after fifth treatment; *visit 3* after tenth and last treatment; *visit 4* 1 month after last treatment; *% ACR20* percentage of patients that reached 20% of improvement in the American College of Rheumatology criteria (ACR20); *numbers inside the block* numbers of patients that reached a 20% of improvement in the ACR20; *n* sample; *p* statistical difference

treatment (p=0.011), and physician (p<0.001) and patient's (p=0.002) global assessment of disease activity. Still in this group, 1 month after the end of the protocols (visit 4) in relation to the baseline, the count of painful joints (maximum of 68) tended to the reduce (p=0.077), and the duration of morning stiffness decreased significantly (p=0.003).

Safety

No serious adverse effects were reported in either intervention group. One patient in the AC group had a self-limited episode of low back pain.

Discussion

This randomized controlled clinical study was the first one to try to evaluate the use of acupuncture in the treatment of RA utilizing a more extensive therapeutic protocol, with longer duration, larger number of acupuncture points, and longer needle insertion times. Previous studies [16, 17] used more limited acupuncture protocols, with a maximum of three points, what could be considered insufficient to treat RA, taking into account the systemic and complex nature of this disease.

The randomized placebo-controlled clinical study by Man and Baragar [16] compared electro-acupuncture

Table 3 Mean change from baseline (at visit 3)

	controlAC	AC	*p* value
Clinical characteristics			
DAS[a]	−0.24 (0.63)	−0.61 (0.86)	0.129
Tender joint count[a]	−2.45 (9.63)	−8.35 (14.88)	0.145
Swollen joint count[a]	−1.4 (5.42)	−2.65 (6.45)	0.511
HAQ[a]	−0.28 (0.48)	−0.44 (0.56)	0.317
VAS of pain[a]	−1.46 (2.40)	−2.24 (3.72)	0.421
Morning stiffness (minutes)[b]	0 (−30–0)	−30 (−57.5–0)	0.149
Global assessment of treatment			
Physician[b]	0 (0–1)	1 (0–2)	0.072
Patient[b]	0 (−0.75–0.75)	0.5 (0–1)	0.102
Physician's global assessment of disease activity[b]	0 (0–0)	−1 (2–1)	<0.001
Inflammatory markers			
ESR[b]	3 (−8–10)	0 (−5.75–2)	0.206
CRP[b]	0 (−6.19–3.34)	−2.58 (−5.53–0.6)	0.714

Mean change from baseline Mean differences between the baseline and the tenth session; *controlAC* control acupuncture group; *AC* acupuncture group; *DAS* Disease Activity Score; *HAQ* Health Assessment Questionnaire; *VAS* Visual Analogue Scale; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *%* percentage of the variable into the each group; *p* statistical difference

[a] Mean (standard deviation; *t test*)

[b] Median (*IQR* interquartile range; Mann-Whitney test)

[c] Likert scale with 5 points (0=very well, 1=well, 2=regular, 3=bad, 4=very bad)

Table 4 Secondary outcomes at visit 4

	controlAC	AC	*p* value
Clinical characteristics			
DAS[a]	4,72 (1.46)	4.66 (1.17)	0.875
Tender joint count[a]	26 (18)	27 (21)	0.767
Swollen joint count[a]	12 (8)	10 (6)	0.363
HAQ[a]	1.19 (0.74)	0.98 (0.56)	0.312
VAS of pain[a]	5.19 (2.76)	4.14 (2.99)	0.259
Morning stiffness (minutes)[b]	60 (15–120)	25 (0–120)	0.258
Global assessment of treatment			
Physician[b, c]	2 (1–2)	3 (1–3)	0.012
Patient[b, c]	2 (1–3)	3 (2–3)	0.003
Physician global assessment of activity Disease[b, d]	2 (1–2)	1 (0–1)	0.011
Inflammatory markers			
ESR[a]	37.95 (23.19)	39.30 (24.11)	0.858
CRP[b]	8.11 (1.5–15.55)	8.84 (3.93–20.88)	0.445

Visit 4 Assessment 1 month after the last treatment; *controlAC* control acupuncture group; *AC* acupuncture group; *DAS* Disease Activity Score; *HAQ* Health Assessment Questionnaire; *VAS* Visual Analogue Scale for pain; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *%* percentage of the variable into the each group; *p* statistical difference

[a] Mean (standard deviation; *t* test)

[b] Median (25–75 percentile; Mann–Whitney test)

[c] Likert scale with 5 points (0=none, 1=poor, 2=regular, 3=good, 4=very good)

[d] Likert scale with 5 points (0=very well, 1=well, 2=regular, 3=bad, 4=very bad)

(EAC) with control electro-acupuncture (controlEAC) in 20 seropositive RA patients with predominant activity in both knees. In the EAC group, there was a 90% improvement in pain up to the third month of treatment, while in the controlEAC group only 10% referred improvement in this variable. There was no significant difference on inflammatory signs between the groups. However, the interpretation of the results of this study is limited by the small sample size, the fact that the treatment was localized and for just one therapeutic session, there was a concomitant use of intra-articular hydrocortisone on the contra lateral knee, which has a potential for systemic absorption and could be a confounding factor, and because of the lack of description of the baseline characteristics, such as the presence of other joint with inflammatory signs and other concomitant therapies.

In 1999, David et al. [17] randomized 56 RA patients in a double-blind and cross-over study to evaluate the effect of the acupuncture as adjunct treatment. There was no significant difference among the groups in any one of the variables. Although this study was developed with appropriate assessment methodology [26], the use of a only one acupuncture point and the needle permanence in situ for 4 min could be insufficient to expect a good therapeutic response in a systemic disease. In chronic conditions such as RA, an increase of the analgesic effect can be reached with the permanence of needles for 30–60 min, with the possibility of use more needles than the usual [28, 32, 33].

In our study, we observed a trend for improvement in several of the studied variables and a significant improvement in physician global assessment of the disease activity and in physician and patient assessment of the effect of treatment in the AC group. More patients in the AC group achieved ACR20 improvement criteria, the primary outcome of this study, but this difference did not reach statistical significance. This could be explained by the sample size, the selection of patients, the choice of the control intervention, and the acupuncture protocol applied.

The sample size, with 20 patients in each group, established as an intermediate number in relation to the two randomized clinical studies described in the literature, probably limited the power of the study to demonstrate a clinical effect of AC [16, 17].

Moreover, each group presented withdrawals during the study (four in the AC and fix6 in the controlAC). When comparisons between the groups are done without an intention-to-treat analysis, the AC group reached statistical difference in most of the studied variables.

The selection of patients was carried out based on the clinical assessment of the attending rheumatologist, which identified the need for adjustments in the therapy. Therefore, it was not based on the presence of pre-defined objective criteria for disease activity. By this way, although probably being more representative of the patients from everyday rheumatology practice, our sample presented with a high heterogeneity of clinical conditions. As a matter of fact, after the standardized assessment, we observed that several patients included in both groups presented with disease of low activity, what might have further diminished the power of the study in detecting an intervention effect.

There is great controversy regarding the best control intervention for studies evaluating the efficacy of acupuncture. The use of sham acupuncture as described by Vincent and Lewith [28], through very superficial needle insertion (1 to 2 mm) and done in non-classical points, was chosen because of its availability, its similarity to true acupuncture, and because it promotes more patient credibility. Besides that, we reduced the number of needles and its time of insertion to restrict the action of this procedure on the modulator pain system. The model of placebo needle of Streitberger and Kleinhenz [34], whose plastic device fastens the needle and prevents its penetration in the skin, seemed interesting to us, but it has not been proved yet as the most appropriate control technique for studies with AC [35]. Although not formally tested, the investigators feel that blinding was well maintained throughout the study.

Even with the caution of a superficial needle insertion, without stimuli that produced the sensation "teh Qi," and the shorter permanence than the recommended, the diffuse noxious inhibitory control pathway [15, 36] could have been triggered and induced an analgesic effect in the controlAC group, as reported in other clinical studies involving acupuncture and pain [37, 38].

Although we believe that the acupuncture protocol applied in our study was more adequate than those of previous clinical trial, the use of needles with manual stimulation limited to the beginning of the procedure could be insufficient in RA. There are evidences that electro-acupuncture presents a greater efficacy effect when compared to acupuncture without continuous stimulation [39]. It is possible that in RA, being a systemic disease, the use of this form of acupuncture could have achieved more favorable results.

Our study presented significant improvement in the ACgroup, when compared to the controlAC group, in the patient and physician assessment of activity of the disease, and effect of the treatment. The intra-group assessment demonstrated significant difference in several outcomes, which make us suppose that acupuncture could have a beneficial clinical effect on RA patients. On the other hand, there was no difference or improvement trend in the swollen joint count and in the inflammatory markers (ESR and CRP). This observation suggests that acupuncture might not have an important anti-inflammatory effect on RA and that its clinical effect could be restricted to an analgesic action. This is in agreement with the results of Man and David described above. Further studies in RA are needed to better address this issue.

Conclusion

There was no difference between the acupuncture and the sham acupuncture groups in the number of patients that reached the ACR20 improvement criteria in any moment of the study.

In the acupuncture group, there was a significant improvement in the physician global assessment of disease activity and in the patient and physician global assessment of treatment. Moreover, in visit 3 (end of the tenth treatment assessment), this group demonstrated favorable results in most of the variables (HAQ, VAS for pain, morning stiffness, patient and physician global assessment of treatment, and physician global assessment of disease activity) in relation to the baseline characteristics. There was no detectable effect of AC on swollen joint count and inflammatory serum markers.

Our interpretation of these findings is that the absence of significant improvement in the primary outcome between the interventions could be related mainly to the small sample size. Based on the observations of this study, we can now estimate that a sample size of 40 patients in each group would be required for an 85% power to detect a difference in the ACR20 outcome. Considering the current limitations in the treatment of RA, especially the long term toxicity of the disease-modifying therapies and frequency of incomplete response, we believe that further studies on the use of AC as adjunctive therapy in this disease are needed.

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