



Research Article

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Rheumatoid Arthritis Disease Activity Influenced by Acupuncture

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To Cite This Article: Diana Seixas*, Fátima Farinha, Marcos Pacheco da Fonte, Manuel Laranjeira and Marília Rua. Rheumatoid Arthritis Disease Activity Influenced by Acupuncture. *Am J Biomed Sci & Res.* 2024 21(1) AJBSR.MS.ID.002796, DOI: [10.34297/AJBSR.2024.21.002796](https://doi.org/10.34297/AJBSR.2024.21.002796)

Received: 📅 October 18, 2023; **Published:** 📅 January 04, 2023

Abstract

Background: Evaluates the effect of acupuncture on Rheumatoid Arthritis (RA) disease activity, based on the principles of the treat-to-target strategy.

Methods: Experimental, randomized, prospective, controlled study. Research questions: Q1-What is the influence of acupuncture on the 28 joints count: tender (TJ) and swollen (SJ)? Q2-What are the analytical changes in C-reactive protein (CRP) produced by acupuncture? Q3-To what extent does acupuncture affect the patient's global perception of current health status (PGA)? Q4-How effective is acupuncture in the activity phase of RA?

Results: The results obtained are quite expressive, highlighting the decrease in the final score from "Moderate" to "Low" RA activity, in patients submitted to complementary treatment with acupuncture (tcA). Assuming a significance level 0.05, the TJ and SJ obtained $p < 0.01$, as well as the PGA analysis, showing the favorable influence of acupuncture on the count of the 28 joints and the perception of health from the patient's perspective. The CRP showed a slight improvement in analytical values after tcA, visible graphically.

Conclusions: Acupuncture proved to be effective in managing and controlling the progression of RA disease activity, with an impact on patient satisfaction and quality of life.

Keywords: Rheumatoid arthritis, Remission induction, Acupuncture

Introduction

Rheumatoid arthritis is an inflammatory, systemic, chronic polyarticular, multifactorial autoimmune disease of unknown etiology, prevalent in 0.5% to 1.0% of the world's population. Globally, the annual incidence in northern Europe and the USA is 0.15 to 0.60 per 1000 population and approximately 40 per 100,000 in women and about half in men. It affects mainly the joints, especially the hands and feet, causing pain, edema and stiffness, which lead to joint destruction and consequent functional limitation and disability in the long term, and extra-articular manifestations may also

occur [1-4]. Clinical evaluation, quantification of disease activity through composite indices recommended for its effect (analysis of acute phase molecular biomarkers -CRP or erythrocyte sedimentation rate and global assessment of disease activity provided by the patient and/or physician), as well as necessary therapeutic readjustments, are the tools for early diagnosis and treatment based on the T2T strategy. Although widely known and recognized for its benefits and feasibility, the T2T strategy is not yet implemented globally due to inherent barriers in clinical practice that have hin-



dered this process. According to EULAR (European League Against Rheumatism) recommendations, T2T is characterized by the management of “active” disease activity, aiming at a state of remission or at least low disease activity, which is an important factor for the decision of therapeutic escalation [5-8].

The pathophysiological mechanism of RA is complex and not yet fully understood-scientific evidence points to an association between genetic, hormonal and environmental factors that cause abnormal activation of the immune system and a joint inflammatory response [9,10].

The treatment of RA is preconized by addressing both short- and long-term complications of the disease, so that when treated early, remission is possible in more than 50% of patients and the reduction of RA activity can occur in 35% of patients [1]. Treatment is achieved through pharmacological and non-pharmacological means, using Disease-Modifying Antirheumatic Drugs (DMARDs) proven (by radiographic scores and functional disability) to inhibit or stop the progression of structural damage, suppressing inflammation and reducing signs and symptoms of the disease [11]. Thus, the sustained development of traditional drug therapy and medical advances in therapeutic strategies have made it possible to achieve significant results in improving the inflammatory process and the impact of RA. However, although the clinical status of patients has improved, some still show a limited response to new drugs that, at high doses and frequent administrations, cause undesirable side effects, as well as present disease activity values far from remission, reporting continued pain, edema, decreased functional capacity and also decreased quality of life.

In clinical practice, the parameters that guide the control of disease progression are mainly based on joint counts and analytical values of acute phase biomarkers, pain classification and global assessment of disease activity provided by patients’ reports-the latter two are considered health outcomes and express the patient’s clinical results and those reported by the patient (Patient-Reported Outcomes Measures-PROMs) [12-16]. The scientific advance resulting from the study of physicians and researchers is fundamental for positive changes in therapeutic strategies; however, although RA ancillary diagnostic and progression assessment tests are clinical indicators of the current status of the disease, they do not always reflect the patient’s experience [11, 17-19].

Nowadays, the management and treatment of RA require a multidisciplinary approach to achieve goals and standards of quality and satisfaction, opening doors to new requirements and new therapies. Acupuncture, as a form of Traditional Chinese Medicine (TCM), emerges as a complementary therapy to conventional treatments already in place, and is recommended by the World Health Organization (WHO) for its therapeutic effect.

Acupuncture is one of the most widely used therapies in clinical practice, associated with the treatment of acute and chronic pain and neurodegenerative diseases [20], producing generalized pain relief, through the regulation of endogenous opiate levels, serotonin, norepinephrine and the inhibition of visceral nociceptors,

inflammatory cytokines and CNS activation [21]. This analgesic effect can be used alone or in combination with other conventional forms of therapy [22]. Acupuncture points include very dense and concentrated neural and neuro-active elements, producing a minimally invasive benign stimulation upon insertion and manipulation of the acupuncture needle. This stimulation causes changes in the local connective tissue and the secretion of several molecules and substances that act on several receptors of local nerve endings and transmit electrical and biochemical signals to the CNS, generating the therapeutic action of acupuncture [23]. These effects, produced by acupuncture stimulation, are physiologically inseparable and perceived differently in each individual, and may be both peripheral and central [23-25].

Acupuncture has been increasingly used by RA patients in order to control the disease and improve patients’ quality of life [26], reflecting the gradual integration of TCM in the complementary treatment of RA, associated with Western medicine [27]. This study presents the results obtained in the evaluation of DAS28-CRP, before and after acupuncture treatment, coadjuvant to the therapeutic plan already in course.

The study was designed to answer the following research questions: Q1-What is the influence of acupuncture on the 28 joints count: tender (TJ) and swollen (SJ)?; Q2-What are the analytical changes in C-reactive protein (CRP) produced by acupuncture?; Q3-To what extent does acupuncture affect the patient’s global perception of current health status (PGA)? and Q4-How effective is acupuncture in the activity phase of RA?

Materials and Methods

Sample and Study Design

Experimental, randomized, prospective and controlled study, carried out in two moments of evaluation, with an 8-week interval between each evaluation. The study population corresponds to patients with RA who used the external consultation of the Clinical Immunology Unit (UIC) of the University Hospital Center of Porto-Santo António Hospital (CHUP-HSA), between September 2018 and September 2019. Through the listing of these patients 301 telephone contacts were made, using the institutional telephone of the external consultation of the UIC of the CHUP-HSA, to present the program and request their participation in it. A convenience sampling was performed according to the defined selection criteria and 100 patients were considered eligible for the study: Inclusion criteria (age ≥ 18 years; diagnosed RA ≥ 12 months; stable therapeutic dose ≥ 3 months); Exclusion criteria (alteration of pharmacological treatment during the clinical protocol; initiation of another type of complementary treatment/therapy during the experimental trial; clinical analysis laboratory not being that of the CHUP-HSA).

The 100 patients eligible represent the study sample and are those with RA diagnosed within 12 months or more, according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [28,29] criteria, who attended the out-patient consultation of the UIC of the CHUP-HSA, between October

2019 and March 2020. The patients in the sample were equally distributed in Experimental Group (EG) and Control Group (CG), through a computer-generated randomization table.

All sample members, 50 EG patients and 50 CG patients, underwent a qualitative and quantitative evaluation in order to analyze the influence and effectiveness of acupuncture on the RA activity index. The evaluations occurs in 2 different moments, using the DAS28-CRP: 1st evaluation (corresponding to the first face-to-face contact with all the sample elements (CG and EG). Data was collected regarding the general characterization of each individual and the variables of the Disease Activity Score 28-CRP. The patients from the EG were subsequently submitted to the first acupuncture session out of eight total sessions); 2nd evaluation (performed 8 weeks after the 1st evaluation, to all the CG patients. The 2nd evaluation was done one week after the last acupuncture session, that is, at the 9th week of the experimental study. The DAS28-CRP was assessed again for the 100 patients in the sample).

The protocol of the experimental study, recommended as a complementary therapy to the treatment already established, comprised 8 consecutive acupuncture sessions, once a week, for 20 minutes (the insertion time of the needles in the acupoints), performed to the EG.

Data collection and assessments were performed in a multidisciplinary way: by the UIC clinical team, CHUP-HSA and the researcher.

Instruments

Disease activity was assessed by the Disease Activity Score, DAS28-CRP. Recognized as the most widely used tool for this purpose, it is a strong predictor of disability and radiological progression [30]. It consists of an algorithm resulting from the count of 28 joints with edema/tumefaction and/or painful/sensitive joints, the analytical value of the acute phase molecular marker (C-reactive protein-CRP mg/L) and the patient's Patient Global Assessment (PGA) against their current health status (through a visual analog scale (rated from 0 to 100mm) [31,32].

According to the DAS28-CRP, a score between: 0 and <2.6 indicates disease remission; 2.6 and ≤3.2 indicates low disease activity; 3.2 and ≤5.1 indicates moderate disease activity and ≥5.1 indicates

high disease activity [33-36]. The formula for calculating DAS28 CRP corresponds= $[0.56 \times \sqrt{(SJ)28}] + [0.28 \times \sqrt{(T)28}] + [0.36 \times \ln(CRP+1)] + [0.014 \times AGD\text{-patient (mm)}] + 0.96$ [37]. In the above formula, SJ28 represents the number of swollen joints and T28 represents the number of tender joints, out of the 28 analyzed. As far as the PGA is concerned, 0 corresponds to the best result and is representative of excellent activity of the patient and 100 corresponds to the worst result and, therefore, a patient without any activity [38].

Clinical and Epidemiological Analysis

The general characterization of the sample was performed by surveying the sociodemographic variables (gender, age, marital status and education) and clinical variables (time of RA diagnosis expressed in years, analytical value of RF, anti-CCP, SV and CRP, and therapy already instituted).

Data analysis

The notation used in the study is the most usual in scientific and academic terms, namely in research articles in the area and in Applied Statistics courses. Regarding the programming language, the software used for the statistical analysis was RStudio, version 1.4.1103. The software has an associated error of $1,110223 \times 10^{(-16)}$. The data matrix considered for the statistical analysis had no missing values in the assessments of the observed individuals. To obtain the descriptive statistics necessary for the characterization of the variables, we considered the following functions: i. *table()*, to obtain absolute and relative frequencies, in the case of categorical variables; ii. *summary()*, for obtaining the statistics in the case of continuous variables. In applying the hypothesis tests, we considered a significance level of $\alpha = 0.05$, with the null hypothesis being the equality of statistics between groups in the 1st and 2nd evaluation. As we intended to compare the values of the variables relative to the same sample, but in two different moments, we chose the functions: i. *t.test()*, for the comparison of the means of the continuous variables; ii. *StuartMaxwellTest()* function, for the comparison of proportions in categorical variables. In the analysis of the sociodemographic and clinical characterization of the sample (Table 1), the χ^2 test was applied for comparison of proportions in the independent groups (control group and experimental group). The graphical representations of the boxplots were obtained by considering the *boxplot()* function.

Table 1: Sociodemographic and Clinical Characterization.

	Group			
	Sample	Control	Experimental	
n (%)	100 (100,0)	50 (50,0)	50 (50,0)	-
Gender	n (%)	n (%)	n (%)	Valor-p
Male	19 (19,0)	8 (8,0)	11 (11,0)	0.61
Female	81 (81,0)	42 (42,0)	39 (39,0)	
Age (years)	Média (SD)	Média (SD)	Média (SD)	Valor-p
	63.600 (10.262)	58.120 (10.720)	63.080 (9.236)	0.015
Marital Status	n (%)	n (%)	n (%)	Valor-p

Single	18 (18.0)	10 (10.0)	8 (8.0)	0.841
Married	73 (73.0)	36 (36.0)	37 (37.0)	
Widowed	9 (9.0)	4 (4.0)	5 (5.0)	
Education	n (%)	n (%)	n (%)	Valor-p
First cycle basic education	45 (45.0)	23 (23.0)	22 (22.0)	0.223
Upper secondary education	13 (13.0)	8 (8.0)	5 (5.0)	
Lower secondary education	11 (11.0)	2 (2.0)	9 (9.0)	
Secondary education	17 (17.0)	10 (10.0)	7 (7.0)	
University	14 (14.0)	7 (7.0)	7 (7.0)	
Disease diagnosis RA (years)	Média (SD)	Média (SD)	Média (SD)	Valor-p
	13.645 (9.801)	12.560 (9.214)	14.730 (10.334)	0.271
Rheumatoid Factor (UI/ml >14)	n (%)	n (%)	n (%)	Valor-p
Positive	76 (76.0)	36 (36.0)	40 (40.0)	0.482
Negative	24 (24.0)	14 (14.0)	10 (10.0)	
Anti-CCP (U/ml>20)	n (%)	n (%)	n (%)	Valor-p
Positive	60 (60.0)	30 (30.0)	30 (30.0)	1
Negative	40 (40.0)	20 (20.0)	20 (20.0)	
CRP (mg/dl >1)	Média (SD)	Média (SD)	Média (SD)	Valor-p
	5.421 (7.237)	5.420 (7.538)	5.423 (7.000)	0.999
SV (mm/h 0-19)	Média (SD)	Média (SD)	Média (SD)	Valor-p
	32.40 (21.256)	32.28 (21.526)	32.52 (21.201)	0.955
Treatment in course (drugs/medication)				
Analgesics	n (%)	n (%)	n (%)	Valor-p
Does not use	78 (78.0)	37 (37.0)	41 (41.0)	0.469
Uses	22 (22.0)	13 (13.0)	9 (9.0)	
NSAIDs	n (%)	n (%)	n (%)	Valor-p
Does not use	50 (50.0)	20 (20.0)	30 (30.0)	0.072
Uses	50 (50.0)	30 (30.0)	20 (20.0)	
Corticoids	n (%)	n (%)	n (%)	Valor-p
Does not use	54 (54.0)	29 (29.0)	25 (25.0)	0.547
Uses	46 (46.0)	21 (21.0)	25 (25.0)	
DMARDs	n (%)	n (%)	n (%)	Valor-p
Does not use	23 (23.0)	11 (11.0)	12 (12.0)	1
Uses	77 (77.0)	39 (39.0)	38 (38.0)	
bDMARDs	n (%)	n (%)	n (%)	Valor-p
Does not use	72 (72.0)	33 (33.0)	39 (39.0)	0.266
Uses	28 (28.0)	17 (17.0)	11 (11.0)	

Ethical Considerations

The research study was developed in accordance with the Helsinki Declaration 2013 and the Oviedo Convention 1997. Ethical approval was granted by the Department of Education, Training and Research: Hospital de Santo António (2019.143(114-DEFI/118-CE).

Results

Sample Characteristics

The sample under analysis, illustrated in Table 1, is composed

of 100 individuals equally distributed between the control group (50%) and the experimental group (50%). The individuals are mostly female, representing 81% of the sample, with ages ranging from 30 to 80 years old, with a mean age of 63.6 years and a standard deviation of 10.2, five years higher in the experimental group (63.0) than in the control group (58.1). With regard to academic qualifications, 45% of the subjects had completed the first cycle of basic education, and only 14% had attended higher education. As for marital status, 73% of the participants are married and 9% are widowed. On average, the diagnosis of RA occurred 13.6 years ago (SD9.80), with 76% of patients having positive rheumatoid factor

and 60% having positive analytical values for anti-cyclic citrullinated peptide antibody (anti-CCP). The acute phase reactants show higher than standardized values, where both CRP and SV are similar in the control group and in the experimental group, being in the total sample on average, 5.42 mg/dl and 32.4 mm/h, respectively. With respect to the therapeutic plan already in course, most patients are medicated with DMARDs and only 28 patients (28%) of the total sample are undergoing treatment with biological agents. Regarding SOS drugs, whose administration is managed by patients at home according to their complaints, 78% reported that the drugs they use the least are analgesics, followed by corticoids (54%) and NSAIDs (50%). When interpreting the p-values obtained through the application of a Student's t-test to assess the equality of means between the independent groups and assuming a significance level of 0.05, we can only reject the null hypothesis for the variable Age, accepting the alternative hypothesis that there are differences between the means of the independent groups for the remaining variables. As shown in Table 1, the variable Age is the only one where there is a statistically significant difference between the control group and the experimental group, indicating that for the remaining variables there are no statistically significant differences, so that in a sociodemographic and clinical context the two groups, control and experimental, can be considered homogeneous. Thus, all the statistical analysis of this study and the respective conclusions cannot be read or interpreted under the influence of the socio-demographic and clinical characteristics of each of the groups,

with the exception of the variable Age (Table 1).

DAS28 CRP Evaluation

The assessment of the RA activity index of the total sample comprised, the DAS28-CRP by counting the 28 joints (listing the painful and swollen ones), the laboratory results of CRP, and the patient's global assessment (PGA) regarding their current health status.

DAS28 CRP Score

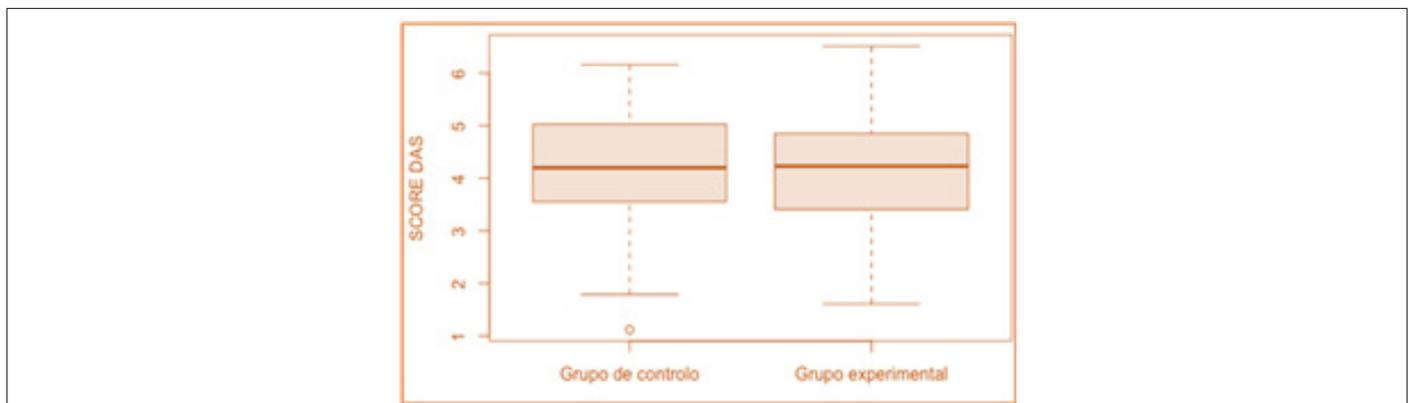
The mean DAS28-CRP value at the first evaluation (before tcA-complementary acupuncture treatment) was 4.19 in the sample, being higher than this value in the control group (4.24) and lower in the experimental group (4.13). As we can see in Table 2, the evaluation of the similarity between the means in the control and experimental groups, performed through the hypothesis test, "Student's t", obtained a p-value (p 0.62) that does not allow us to rule out the hypothesis of equality between the means, considering a significance level of 0.05. In the second evaluation (after the tcA), the mean value of DAS28-CRP in the sample evaluated dropped to 3.74, justified by the decrease in the mean value of the experimental group (2.95), since in the control group we found an increase in DAS28-CRP (4.54). For a significance level of 0.05, the hypothesis test applied allows us to rule out the similarity between the mean values of DAS28-CRP of the two groups after treatment, since the p-value is significantly less than 0.05 (p<0.01), which highlights the statistical significance of the results. Thus, we can state that tcA has an influence on the value of DAS28-CRP (Table 2).

Table 2: DAS28-CRP.

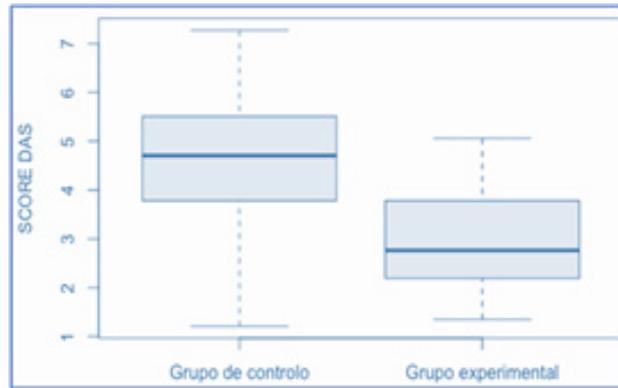
Variable	Group			Hypothesis test
	Sample	Control	Experimental	
DAS28-CRP	Mean (SD)	Mean (SD)	Mean (SD)	p-value
First Evaluation	4.192 (1.087)	4.245 (1.096)	4.139 (1.088)	0.629
Second Evaluation	3.747 (1.371)	4.541 (1.279)	2.953 (0.936)	< 0.01

The results shown in Table 2 are corroborated by Graphs 1 and 2 of the whiskers boxes, which depict the first and second evaluation, respectively, and which we show below:

tion, respectively, and which we show below:



Graph 1: DAS28-CRP 1st evaluation.



Graph 2: DAS28-CRP 2nd evaluation.

Tender and Swollen Joints

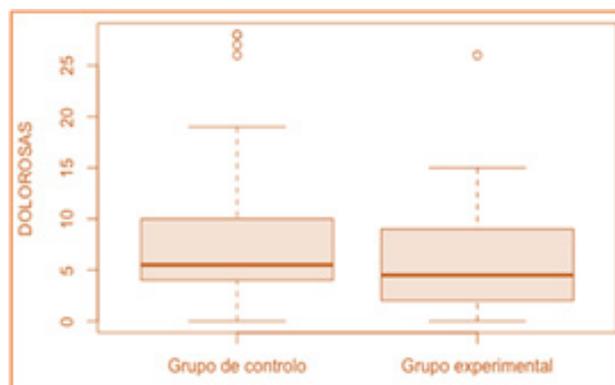
As we can see in Table 3, through the count of the 28 joints, we verified that the mean value of tender joints (TJ) showed an overall decrease from the first evaluation (6.81) to the second evaluation (5.52), as illustrated in Table 3. However, this decrease was mainly due to the decrease in the mean TJ value in the experimental group (from 6.04 to 2.38), since in the control group the mean TJ value increased (from 7.58 to 8.66). The counting of swollen joints (SJ) allows for identical conclusions, with a decrease in the mean values from the first evaluation (6.55) to the second evaluation (4.77). Since in the control group there was an increase from 6.60 to 7.72, the clear decrease in the number of SJ is justified above all by the mean values found in the elements of the experimental group,

which decreased from 6.50 to 1.82.

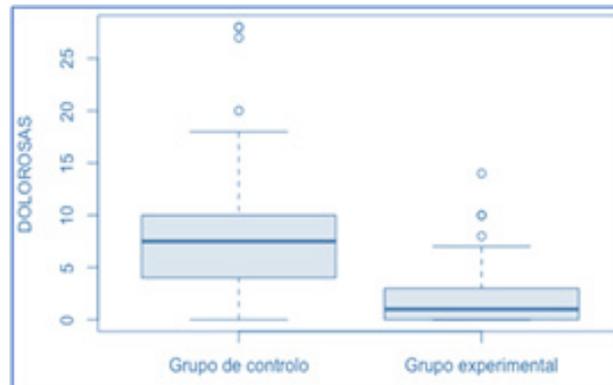
The results obtained for the p-values of the hypotheses tests allow us to conclude that in the first evaluation the control group and the experimental group were similar (p 0.22 and p 0.93)-that is, for a significance level of 0.05 it is not possible to reject the null hypothesis that the averages of the two groups were equal. For the means obtained in the 2nd evaluation and after the tcA, the p-value obtained (p<0.01) allows us to assume a difference between the means of the two groups, control and experimental. This result is relevant, given the statistically significant differences, which allow us to assume that there is a better condition in the Tender Joints and Swollen Joints after the tcA (Table 3).

Table 3: Count 28 Joints, Tender and Swollen.

Variable	Sample	Group		Hypothesis test
		Control	Experimental	
Joints TENDER (TJ)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
First Evaluation	6.810 (6.260)	7.580 (7.186)	6.040 (5.131)	0.221
Second Evaluation	5.520 (6.203)	8.660 (6.951)	2.380 (3.050)	< 0.01
Joints SWOLLEN (SJ)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
First Evaluation	6.550 (5.783)	6.600 (5.945)	6.500 (5.676)	0.932
Second Evaluation	4.770 (6.085)	7.720 (7.060)	1.820 (2.685)	< 0.01



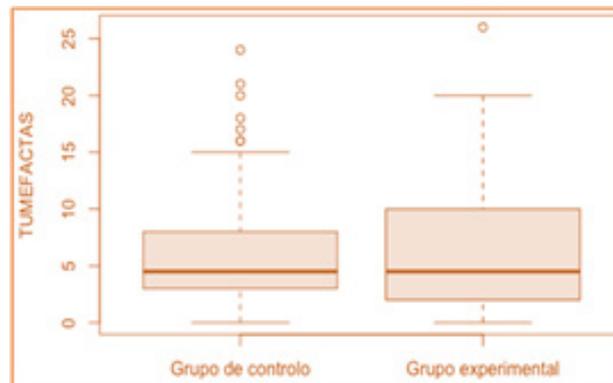
Graph 3: DAS28-CRP-Tender Joints 1st evaluation.



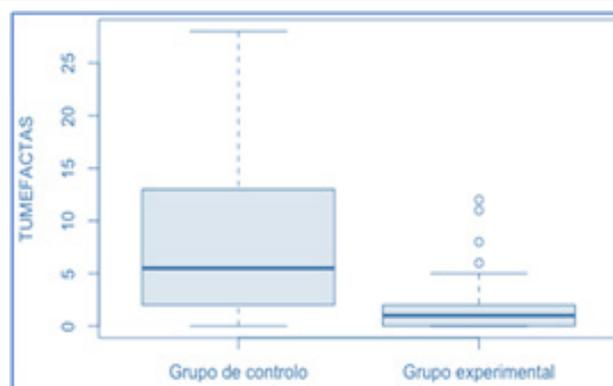
Graph 4: DAS28-CRP-Tender Joints 2nd evaluation.

Graphs 3 and 4 of the boxplot we present below, corroborate the results of Table 3, corresponding to the first and second assessment of the tender joint count. The results of Table 3, relative to the

first evaluation and the second evaluation of the swollen joint count are evidenced by Graph 5 and Graph 6 of the whiskers boxes, which we illustrate below:



Graph 5: DAS28-CRP-Swollen Joints 1st evaluation.



Graph 6: DAS28-CRP-Swollen Joints 2nd evaluation.

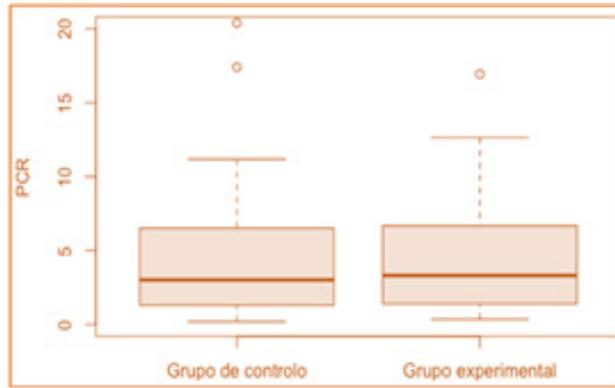
C-Reactive Protein

In the first evaluation, the average CRP value was 5.42 in the total sample. This value was slightly lower in the control group (5.42) and slightly higher in the experimental group (5.42). This similarity is corroborated by the result of the p-value obtained through the hypothesis test applied "Student's t", very close to 1 ($p = 0.99$), revealing no statistically significant differences.

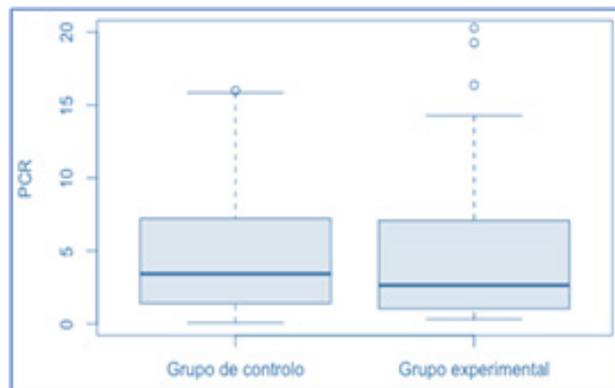
In the second evaluation, the average value of CRP in the evaluated sample rose to 5.98, and the average values of the two groups (control and experimental) also increased. In the control group, the average value rose to 5.68, and in the experimental group it rose to 6.29. However, the p-value ($p = 0.70$) obtained does not allow us to exclude the similarity between the average CRP values of the two groups. We can observe these results in (Table 4).

Table 4: Analytical values CRP (mg/dl >1).

Variable	Group			Hypothesis test
	Sample	Control	Experimental	
CRP (mg/dl >1)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
First Evaluation	5.421 (7.237)	5.420 (7.538)	5.423 (7.000)	0.999
Second Evaluation	5.989 (7.924)	5.684 (6.652)	6.295 (9.080)	0.702



Graph 7: Analytical values CRP 1st evaluation.



Graph 8: Analytical values CRP 2nd evaluation.

Graphs 7 and 8 of the whiskers box presented below, attest to the results of Table 4 against the CRP analytical values in the first and second evaluation.

Global Assessment of Patient: Current Health Status

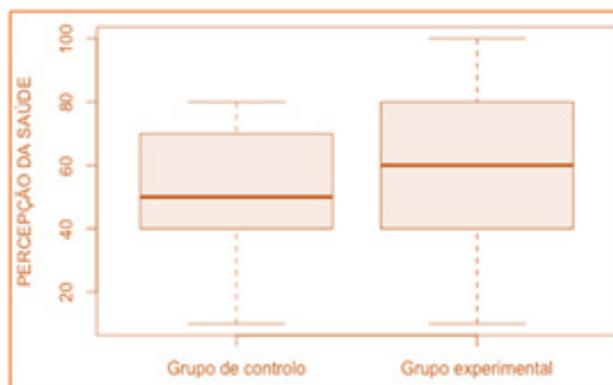
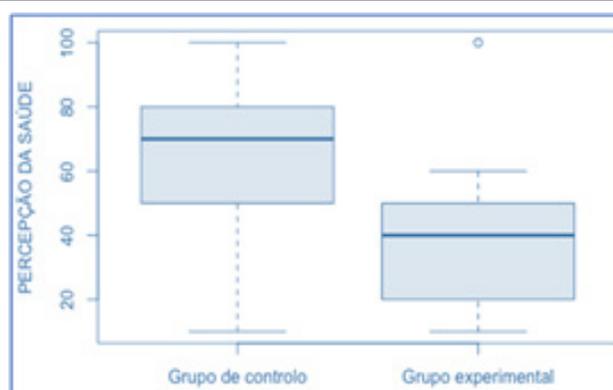
The patient’s global assessment of their current health status (PGA), illustrated in Table 5, shows a mean value of 54.7 in the first assessment in the total sample, being higher than this value in the experimental group (56.4) and lower in the control group (53.0). The p-value obtained (p 0.40) in the hypothesis test applied to evaluate the similarity between the means in the control and experimental groups, with a significance level of 0.05, does not allow us to reject the hypothesis of equality between the means. In the second evaluation, the mean PGA value in the evaluated sample decreased

to 51.6. This reduction was due to the decline in the mean value in the experimental group (37.6), since in the control group there was an increase in the PGA (65.6). For a significance level of 0.05, the hypothesis test-“Student’s t” applied, allows us to exclude the similarity between the average values of PGA of the two groups after treatment, since the p-value (p < 0.01) is significantly less than 0.05. Therefore, based on the statistically significant results of the second evaluation, we can conclude that complementary treatment with acupuncture has an influence on the value of Health Perception from the patient’s perspective (Table 5).

Through Graph 9 and Graph 10, represented by the box plot, it is possible to verify the results of Table 5, referring to the global assessment of the patient in the first and second evaluation of the two groups, control and experimental, respectively.

Table 5: Global Assessment of Patient.

Variable	Group			Hypothesis test
	Sample	Control	Experimental	
PGA (0 - 100mm)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
First Evaluation	54.7 (20.423)	53.0 (17.985)	56.4 (22.656)	0.408
Second Evaluation	51.6 (24.852)	65.6 (21.586)	37.6 (19.542)	< 0.001

**Graph 9:** Global Assessment of Patient 1st evaluation.**Graph 10:** Global Assessment of Patient 2nd evaluation.

Discussion

The sociodemographic and clinical characterization of this sample, as shown in Table 1, allows us to assume that the 100 members of the control and experimental groups are representative of the population. Among the typical characteristics of RA patients, as described by numerous authors, 81% are female and the mean age is 63 years, as attested by data from the Portuguese Society of Rheumatology and Kerola, et al., [39,40], in relation to the incidence of RA.

Concerning the educational level of the total population, 45% have completed the first cycle of basic education, with the rest equally distributed among the other study cycles (2nd and 3rd cycles of basic education, secondary education and higher education). Education is known to be directly related to literacy and represents a cross-cutting issue and a crucial tool in health, from health promotion and protection to disease prevention [41]. Nowadays, RA

treatment guidelines recommend the sharing of decisions between patients and the multidisciplinary clinical team, where the low literacy levels of these patients are associated with poor communication in sharing these decisions [42].

It is also possible to verify that 77% of patients are on DMARDs, although we verified that only 28% are on biological DMARDs. This evidence is corroborated by Radu and Bungau, who highlight the use of DMARDs as one of the medical advances in the diagnosis and treatment of the disease, allowing the improvement of the clinical status of patients with RA [43]. The results obtained in Table 1 also reflect the diagnosis of RA based on the ACR Guidelines [44], revealing an average of 13 years of diagnosis of the disease, where more than half of the total population has positive rheumatoid factor and anti-CCP, as well as showing analytical values for inflammatory biomarkers, CRP and SV higher than the standard ones. For this reason, we reinforced one of the inclusion criteria in this study, which required patients with RA to be diagnosed for more than 12 months.

The DAS28-CRP analysis focused on the total score results, which are shown in Table 2 and Graphs 1 and 2, but also on the 3 categories evaluated by the score: the count of 28 joints (shoulders, elbows, wrists, metacarpophalangeal and interphalangeal joints, and knees) that were tender and/or swollen, the analytical value of the CRP, and the patient's overall perception of health, illustrated in Tables 3, 4 and 5 and Graphs 3 and 4, 5 and 6, 7 and 8, 9 and 10, respectively. The isolated study of the categories that make up the DAS28-CRP was intended to evaluate the influence of acupuncture individually. We found that overall the DAS28-CRP score is positively influenced by acupuncture, in opposition to an article published in 2018 that reports the unlikely or even null impact of acupuncture on the DAS28-CRP score [45], but in line with data from a 2022 study, which reveal that acupuncture combined with the use of DMARDs is the best therapeutic association to obtain a better DAS28 score [46]. In the present clinical study, we confirmed that the results of the experimental group, at the second moment of evaluation, showed a decrease in disease activity, compared to the control group, where values increased slightly, although the RA activity index remained the same. Objectively, we found that the experimental group after tcA decreased the total score from "Moderate RA activity" to "Low RA activity" (4,139 at the 1st evaluation, to "2,953 score at the 2nd evaluation). In contrast, in the control group after tcA there was no change in the disease activity index, (total score= 4.245, 1st evaluation and 4.541, 2nd evaluation) and therefore the patients maintained a "Moderate RA Activity".

The deconstruction of the DAS28-CRP score initially leads us to the counting of the 28 Joints, listing the Tender Joints (TJ) and the Swollen Joints (SJ). Acupuncture treatment is known to be associated with a decrease in TJ, compared to control groups [47]. In fact, the results presented in this study reveal weakly positive values before and after tcA, also highlighting the differences between the group submitted to the treatment itself (experimental group) and the control group, without acupuncture intervention. Analogously, the results were interpreted in the same way as those considered by the DAS28-CRP score, with the experimental group showing "High RA Activity" in the first evaluation, and a considerable drop in values for the state of "Disease remission" in the second evaluation. Compared to the control group, both in the TJ and SJ counts, the "Disease Activity" index remains "High" in both evaluations, with a slight increase in the final values. One of the most used mechanisms to prove the efficacy of acupuncture in RA is the anti-inflammatory effect associated with acute phase molecular biomarkers, such as CRP [48]. In this study, a minor improvement is graphically observed after tcA in the experimental group. However, this improvement is not confirmed by the analytical values obtained, since it is such a small change that it is not significant. That is, statistically, through the comparison of the results, we realize that the p-value obtained does not allow us to affirm the distinction between the experimental group and the control group, under the influence of the tcA, although graphically we can see a little change in the values between the 1st and 2nd evaluation. This evidence becomes even more expressive when comparing the results between the CRP and the other two categories assessed by the DAS28-CRP: the TJ and the

SJ, as well as the PGA. The studies published on the subject indicate that acupuncture as a complementary therapy may be related to the decrease of acute phase molecular biomarkers, such as CRP and the anti-inflammatory effect in RA [48]. Finally, regarding the evaluation of DAS28-CRP, we analyzed the category corresponding to the PGA that exposes a satisfactory effect of acupuncture, from the 1st to the 2nd evaluation. The meaning of the PGA is subject to patient interpretation, which may affect the validity and reliability of clinical evaluations, but it plays an important role in the evaluation of disease activity [49], which motivated us to investigate it individually. Considering that a value of 0 represents the best outcome and excellent patient activity and a value of 100 the worst outcome and low or no patient activity, we concluded that PGA is considerably better after tcA in patients undergoing the treatment itself. Compared to the control group, the results also show the positive influence of tcA, since in the experimental group the values decreased by about 33%, reflecting a better activity of the patient, unlike the control group, where the PGA increases from the 1st to the 2nd evaluation by about 23%, indicating a worsening of the patient's activity evaluated by the PGA. Although the investigation of this scale is included in DAS28-CRP, we highlight the importance of the results obtained by the relevant role of PGA as Patient Reported Outcome (PRO) [50], where the total population indicates how they feel on the day of the assessment regarding RA and how the disease affects them.

Conclusions

Rheumatoid Arthritis, a chronic and systemic pathology, is nowadays the target of a multiplicity of therapies aimed at treating not only the disease but also the patient. Significant advances in the treatment of RA have allowed a better understanding of the imbalances that are involved in this disease, both from the perspective of Western Medicine and Traditional Chinese Medicine. In general, the therapeutic course is designed to achieve an absolute objective, where remission of the disease, or at least a significant decrease in its activity, is the major target. Acupuncture, approved by the WHO for the treatment of various pathologies, has been the subject of much research by Western Medicine, and has been growing in clinical practice in numerous health institutions, combined with other forms of therapy. The results are surprisingly objective about the influence of acupuncture on RA activity, with a decrease in DAS28-CRP from "Moderate disease activity" to "Low disease activity" in patients in the experimental group who underwent tcA. Also, through these results we concluded that regarding the count of the 28 joints, the mean value of the joints considered painful by the patient decreased more than 60% and more than 70%, in the case of swollen joints, after tcA. With regard to the global perception of health reported by the patient, the values presented prove the beneficial action of the complementary acupuncture treatment in this score, which obtained statistical significance in all the variables related to its analysis, reflecting the effect on the RA activity. The analytical values of CRP, although with little significance, showed positive results, since after the tcA the experimental group presented lower CRP values, graphically illustrated, although statistically this

evidence is not expressive. However, more strong evidence on the positive tendency of acupuncture effect on this molecular biomarker could emerge if the number of patients in the study were larger.

The present study contributes to the increase of knowledge about the influence of acupuncture as a complementary therapy and when associated with the treatments recommended by Western medicine. We emphasize the association of the methodology and principles of both medicines (Western and Eastern) to achieve better results and not the abandonment of one intervention or therapeutic strategy in favor of another. We admit that the different ways of establishing the diagnosis of RA and the respective inherent interventions produce the right synergy to better treat the disease and care for the patient. The results presented also provide a range of scientific information highlighting the importance of acupuncture in the treatment of RA and the real and effective effects produced and reported by patients. However, although the scientific literature is constantly growing, more studies are needed to assess the notoriety of the effectiveness of this therapy in patients with RA.

Author Contributions

Conceptualization, D.S. and M.R.; methodology, D.S., F.F., and M.R.; software, D.S.; validation, M.F., M.L., and M.R.; formal analysis, D.S.; investigation, D.S.; resources, D.S.; data curation, D.S. and M.R.; writing—original draft preparation, D.S.; writing—review and editing, D.S.; visualization, D.S.; supervision, D.S. and M.R.; project administration, D.S.; funding acquisition, D.S. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the by the Department of Education, Training and Research: Hospital de Santo António (2019.143(114-DEFI/118-CE).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. All patients who agreed to participate in the study had the ability to read and interpret the applied questionnaires. Written informed consent was signed prior to the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Acknowledgments

In this section, you can acknowledge any support given which is not covered by the author's contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest

The authors declare no conflict of interest.

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