Balneotherapy and Rheumatoid Arthritis: A Randomized Control Trial

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ABSTRACT: **Background:** The effects of balneotherapy on rheumatoid arthritis (RA) are still controversial partly due to poor methodology used in randomized controlled trials, as reported in the international medical literature.

Objectives: To determine whether spa therapy plus pharmacological treatment offers any benefit in the management of RA as compared to pharmacological treatment alone.

Methods: We conducted a prospective, controlled, unblinded randomly assigned study of patients with RA according to American College of Rheumatology criteria. Following the 2007 recommendations of AFRETH, the method designed for this study was "immediate treatment versus delayed treatment." All patients were followed at the Oporto Hospital Centre and each physician observed the same patients throughout the study. Patients continued with their usual medications and maintained their daily life activities at home, at leisure and/or in the workplace. The spa therapy group received spa treatments for 21 days at S. Jorge Spa-Santa Maria da Feira. The main outcome measure was the HAQ-DI; the moderated regression analysis, together with the Johnson-Neyman technique, was used for statistical analysis.

Results: HAQ-DI at the end of treatment (21 days) and at the 3 month follow-up was improved in the spa group (odds ratio 0.37, confidence interval 0.09–0.64, $P = 0.01$ at 21 days, and 0.44, 0.15–0.72, $P = 0.004$ at 3 months).

Conclusions: In individuals in whom pain (physical and psychological) predominates, any complementary gain in function is beneficial. The main goal is to enhance quality of life.

IMAJ 2016; 18: 474–478

KEY WORDS: rheumatoid arthritis (RA), balneotherapy, spa treatment, non-pharmacological treatment, quality of life

Rheumatoid arthritis (RA) [1] is a chronic systemic autoimmune disease characterized by persistent inflammation of synovial joints with pain, often leading to joint destruction and disability. Despite intensive research the cause of RA remains unknown [2]. New effective drug treatments in RA have led to less focus on non-pharmacological modalities such as therapeutic exercise and balneotherapy. A number of studies [3,4] underlined the concept that regular exercise programs are beneficial for RA patients without increasing radiographic damage. That is one of the reasons why we chose and emphasized underwater exercise for this study.

Balneotherapy has been used since ancient times; even today, it is recognized as a fundamental way to treat rheumatologic diseases, especially osteoarthritis. In Portugal, the diseases most frequently treated with sulphur mineral waters are respiratory and rheumatologic (mostly osteoarthritis). This type of mineral sulphur water is more common in the north of the country, and its source is natural springs. In Portugal, as in other European countries and the United States, the use of radon is controversial and in some regions prohibited [5]. Balneotherapy – also termed mineral baths or spa therapy – uses different mineral water compositions that include sulphur, radon, carbon dioxin, etc.

The role of balneotherapy is under debate. Sukenik and coworkers [6,7] wrote that the properties of sulphur mineral water are beneficial for patients with rheumatologic diseases, particularly in the active inflammatory phases of RA [6,7]. According to the recommendations of the "Haute Autorité de Santé" for rheumatoid arthritis published in 2007 and Forestier et al. [8], spa therapy provides an analgesic and functional benefit to patients with stable or long-established and non-progressive RA (grade C). It is not indicated when RA is active, based on professional agreement among members of the working group and peer reviewers [8]. Verhagen et al. [9] emphasized the need for randomized studies with high methodological quality to provide solid scientific evidence of the effectiveness of balneotherapy in RA.

While balneotherapy is mainly used for non-inflammatory osteo-articular conditions, its real benefits are established for RA. To enhance our understanding and to measure the effects of balneotherapy, we undertook a study to determine whether spa therapy plus the usual pharmacological treatment, as compared to pharmacological treatment alone, offers any benefit in the management of rheumatoid arthritis.

PATIENTS AND METHODS

The database of Oporto Hospital Centre included 450 RA patients who were followed in the Immunology Unit. They were enrolled

in the study if they lived not more than 30 km from the hospital to ensure that they could undergo the treatment and continue their daily activities. A letter was sent to these 120 patients inviting them to attend a lecture on spa therapy at the hospital. The inclusion criteria were: a definitive diagnosis of RA according to ACR criteria, age at least 18 years, disease evolution of at least 1 year, and functional status I-III (classification ACR, Steinbrocker et al. [10]). The exclusion criteria were: functional status grade IV, cognitive abnormalities (psychoses or senile dementia), active infection, and receiving other complementary treatment. Relative contraindications of spa therapy were venous insufficiency, phobia of swimming pools, and heat intolerance. Temporary contraindications included hyperalgesia, or exacerbation of clinical states, infectious skin diseases, phlebitis, or recent surgery. Absolute contraindications were serious organ insufficiencies (cardiac, pulmonary, cerebral, renal), recent or not clinically stabilized cancer, and significant immune suppression. A total of 44 patients were eligible, and after a code attribution were stratified by age to ensure a better balance between groups. The patients were randomly assigned to immediate thermal treatment or deferred thermal treatment. All patients signed an informed consent.

INTERVENTIONS

The hydromineral spring at the spa thermal center (S. Jorge Spa, 30 km from Porto) is chloride-rich sulphur water, whose composition includes the sodium cation. Most patients in the thermal group were transported to the spa thermal center in a dedicated minibus, leaving the hospital at 8 a.m. and returning to Porto at around 10.30 a.m. The trip took about 20 minutes. Some patients preferred to take their own cars. All patients, including those who worked, continued their usual pharmacological treatment and maintained their daily activities. The team at the spa center comprised a medical hydrologist, a physiotherapist, and two aquatic technicians. The medical hydrologist was present throughout the thermal treatment session, adjusting treatments individually if necessary.

For a period of 21 days the thermal group received daily sulphur bath treatments. There were two types of treatment given on alternate days, namely:

- Sulphur bath of 30 minutes at 34ºC in a water pool, complemented with underwater exercises supervised by an experienced physiotherapist. The medical hydrologist's prescription was specific for each clinical condition, namely the type of exercises for different body parts (paying attention to patients' limitations but emphasizing function and respiratory control) followed by 10 minutes of relaxation, including electronically controlled water jets directed at the most painful body areas while maintaining the jet at a safe distance.

- Sulphur bath for 20 minutes at 37ºC in individual tubs, plus underwater jets for 10 minutes at 38ºC directed at the most painful joints, and finally global steam for 5 minutes at 38ºC. The latter two treatments were also adjusted by two experienced aquatic technicians, trained to be aware of symptoms and signs for alarm. The medical hydrologist's prescription (jet force, temperature, body site) was targeted toward each patient's characteristics and disease course. Body massage was not given because of the subjectivity of each therapist.

The patients in the control group maintained their usual pharmacological treatment and daily activities. The evaluation was made simultaneously for both groups (thermal and control) at day 0 baseline, day 21 marking the end of the thermal treatment, and after 3 months, following a pre-established protocol. This comprised: HAQ-DI (Health Assessment Questionnaire-Disability Index), VAS (Visual Analogue Scale), reported by the patient, for pain, fatigue, and patient assessment of quality of life, and DAS28 (Disease Activity Score). An appreciation of Global Health Assessment (VAS) was also made by a physician who had no experience in the field of spa therapy, joint ultrasound of the hand (same joints in the same patient by the same experienced radiologist), and laboratory tests.

Additional information was collected from the patients regarding daily medications as well as complications during the study.

OUTCOMES

The main outcome of this study was the HAQ-DI, and its minimal clinical important difference was 0.22 [11]. Secondary outcomes were VAS, reported by the patient, regarding pain, fatigue and quality of life, physician VAS Global Health Assessment, and DAS28.

RANDOMIZATION

We used a blocked randomization stratified by age. For allocation of the participants to one of the two groups, a computer-generated list of random numbers was used. These procedures were executed by the administrative staff of the Immunology Unit.

BLINDING

Given the characteristics of sulphur water with its particular smell, the blinding of patients and therapists was not feasible. As for the physicians who made the evaluations, although they were not involved directly with the study or with spa therapy methods, we cannot ensure that patients did not relay any information during outpatient visits.

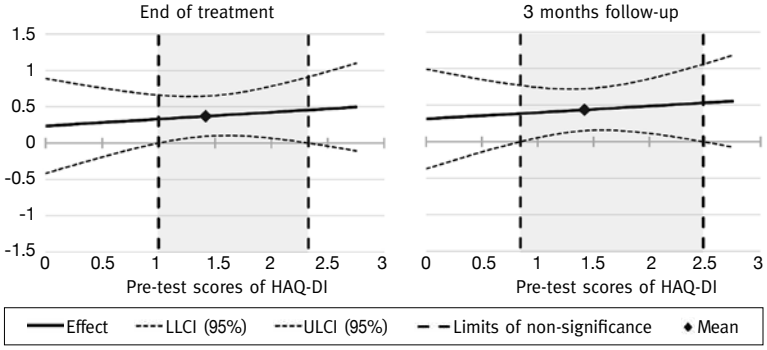
STATISTICAL ANALYSIS

Analysis was performed with the intention to treat. Since the assumption of homogeneity of regression slopes was violated with the ANCOVA model, we conducted a moderated regres-

Table 1. Baseline characteristics of the study population

Characteristics	Spa treatment group	Control group	Total
Female	20 (90.9%)	18 (81.8%)	38 (86.4%)
Age (mean ± SD), years	57.4 ± 11.6	59.4 ± 8.3	58.4 ± 10.0
Employment status			
Employed	7 (31.8%)	6 (27.35%)	13 (29.5%)
Sick leave	1 (4.5%)	1 (4.5%)	2 (4.5%)
Disabled	5 (22.7%)	6 (27.3%)	11 (25.0%)
Retired	8 (36.4%)	9 (40.9%)	17 (38.6%)
Duration of disease (mean ± SD), years	17.6 ± 10.5	14.9 ± 10.8	16.3 ± 10.6
Functional status			
I	2 (9.1%)	3 (13.6%)	5 (11.4%)
II	14 (63.6%)	14 (63.6%)	28 (63.6%)
III	6 (27.3%)	5 (22.7%)	11 (25.0%)
HAQ-DI, mean (SD)	1.50 ± 0.59	1.34 ± 0.83	1.42 ± 0.72
Pain intensity (mean ± SD), 100 mm VAS	45.91 ± 21.08	50.23 ± 31.34	48.07 ± 26.48
Fatigue intensity (mean ± SD), 100 mm VAS	55.45 ± 27.90	57.27 ± 30.11	56.36 ± 28.70
Quality of life (mean ± SD), 100 mm VAS	45.91 ± 19.92	48.18 ± 23.8)	47.05 ± 21.74
Global health (mean ± SD), 100 mm VAS	39.55 ± 16.47	45.91 ± 23.84	42.73 ± 20.50
DAS28 (mean ± SD)	4.92 ± 1.55	4.54 ± 1.53	4.73 ± 1.53

Figure 1. Difference between groups on HAQ-DI (95% confidence interval) at end of treatment (21 days) and at 3 months follow-up. Region of significance (Johnson-Neyman technique)



sion analysis, complemented with the Johnson-Neyman (J-N) technique. This is the best alternative to ANCOVA in experimental designs with pre- and post-test scores [12]. The model consists of testing whether the difference between groups (spa therapy and control), post-treatment or follow-up scores, is significant, moderated or influenced by the respective pre-treatment scores.

The main score difference between groups with 95% confidence interval (95%CI) are presented along with the *t* and *P* value. The Johnson-Neyman technique identifies the value or values within the measurement range of the pre-treatment scores, if they exist, where the conditional effect of a group changes between statistically significant and not, using an α level of 5%. These values identify the regions of significance illustrated in the respective graphs for each outcome. The statistical analyses were performed on the SPSS software version 22, and a computational tool for SPSS, named PROCESS [13].

RESULTS

When recruiting patients for this study we followed the modified CONSORT flow diagram for randomized controlled trials of non-pharmacological treatment [14]. At the beginning of the study (December 2010) the database system of the Immunology Unit in Porto included 450 patients with the diagnosis of rheumatoid arthritis.

A letter was sent to 120 patients who met the criterion of living not more than 30 km from the hospital, inviting them to attend a lecture on spa therapy, which yielded 44 eligible patients. Thus, two groups – study and control – comprised 22 patients each. The study was conducted between August and November 2011.

Adherence to spa treatment was continuously assessed and very good compliance of patients was achieved. There were only three cases of discontinued treatment for reasons not related to the study. Table 1 summarizes the baseline characteristics of the enrolled sample, and Table 2 presents the results of the statistical analysis for the primary and secondary outcomes. The primary outcome was HAQ-DI. The secondary outcomes were VAS reported by the patient for pain, fatigue, and quality of life; VAS reported by the physician for global health; and DAS-28. The analysis revealed a significant difference in the HAQ-DI score between groups at the end of treatment with a mean difference of 0.37, 95%CI (0.09–0.64), $t(40) = 2.712$, $P = 0.01$, considering the effect of each individual pre-test score. Using the J-N technique to identify the region of significance at α level of 5%, we found those limits to be between 1.00 and 2.33 of the pre-test scores, which covers 68% of all patients. Between these limits the standardized effect size, Cohen's *d*, is at least 0.61, which may be considered between moderate and large effect size.

At 3 months follow-up the results were similar, with a mean difference of 0.44, 95%CI (0.15–0.72), $t(40) = 3.069$, $P = 0.004$. The region of significance at α-level of 5% stands between 0.84 and 2.49 of the pre-test scores, which covers 72% of all patients. The effect size within these limits varies from 0.61 to 0.93.

Figure 1 shows the significant regions across the range of pre-test scores of HAQ-DI, illustrating the difference between groups throughout the range of the pre-test scores along with 95%CI. The vertical hatched lines denote the points at which the upper (ULCI) and/or lower (LLCI) confidence bands cross the zero line and also represent the boundary between the area where the differences are not significantly different from zero versus the area where they are. For the secondary outcomes the analysis was similarly performed, but we only found significant differences for VAS pain intensity, quality of life and global health assessment and not simultaneously at the end of

Table 2. Statistical analysis of the outcomes

Characteristics	Spa treatment group	Control group	Total Mean values	*t* (40)	*P* value	Limits of significance		
						LLCI (95%)	ULCI (95%)	Cases within limits (%)
HAQ-DI, mean (95%CI)								
Initial score, before treatment	1.50 (1.24, 1.76)	1.34 (0.97, 1.70)	1.42 (1.19, 1.64)					
Difference between groups, end of treatment, 21 days*	+0.37 (0.09, 0.64)			2.712	0.010‡	1.00	2.33	68.2%
Difference between groups, follow-up, 3 months*	+0.44 (0.15, 0.72)			3.069	0.004‡	0.84	2.49	72.7%
Pain intensity, mean (95%CI), 100 mm VAS								
Initial score, before treatment	45.91 (36.56, 55.26)	50.23 (36.33, 64.12)	48.07 (40.02, 56.12)					
Difference between groups, end of treatment, 21 days*	+10.19 (-3.47, 23.86)			1.507	0.140	Non-significant		
Difference between groups, follow-up, 3 months*	+12.77 (0.26, 25.28)			2.063	0.046‡	46.96	75.83	31.8%
Fatigue intensity, mean (95%CI), 100 mm VAS								
Initial score, before treatment	55.45 (43.08, 67.82)	57.27 (43.92,70.62)	56.36 (47.64, 65.09)					
Difference between groups, end of treatment, 21 days*	+2.89 (-13.48, 19.26)			0.357	0.723	Non-significant		
Difference between groups, follow-up, 3 months*	+11.81 (-1.69, 25.31)			1.768	0.085	Non-significant		
Quality of life, mean (95%CI), 100 mm VAS								
Initial score, before treatment	45.91 (37.08, 54.74)	48.18 (37.62, 58.75)	47.04 (40.44, 53.65)					
Difference between groups, end of treatment, 21 days*	+6.53 (-8.11, 21.18)			0.902	0.372	Non-significant		
Difference between groups, follow-up, 3 months*	+17.97 (3.21, 32.72)			2.461	0.018‡	16.86	55.27	70.5%
Global health, mean (95%CI), 100 mm VAS								
Initial score, before treatment	39.55 (32.24, 46.85)	45.91 (35.34, 56.48)	42.73 (36.49, 48.96)					
Difference between groups, end of treatment, 21 days*	+26.87 (16.87, 36.87)			5.430	< 0.001‡	0.10	55.60	68.2%
Difference between groups, follow-up, 3 months*	+10.71 (-2.18, 23.61)			1.679	0.101	Non-significant		
DAS28, mean (95%CI)								
Initial score, before treatment	4.92 (4.23, 5.60)	4.54 (3.86, 5.21)	4.73 (4.26, 5.19)					
Difference between groups, end of treatment, 21 days*	+0.21 (-0.26, 0.68)			0.911	0.368	Non-significant		
Difference between groups, follow-up, 3 months*	+0.48 (-0.03, 0.99)			1.917	0.062	Non-significant		

‡Conditional effect of group on outcome scores at the mean value of the pre-test scores

*$P < 0.05$

LLCI(95%) = lower limit of the 95%CI

ULCI(95%) = upper limit of the 95%CI

treatment and follow-up, as evident in Table 2. For all other scores, including synovitis [Table 2], there were no significant differences between groups regardless of the tendency for a median positive difference.

Patients did not mention in their diary – in which they noted their medications and comments – any complications during the study, such as infectious diseases.

DISCUSSION

The main outcome of this study was the significant improvement in HAQ-DI scores in the spa group compared to the control group, establishing that balneotherapy can markedly improve functioning and participation in society, as seen in the new guidelines of the World Health Organization and the ICF (International Classification of Functioning) (http://www.who.int/classifications/icf) [15].

This study was limited by the absence of blinding, which was not feasible with sulphur water. It is recognized, however, that blinding in non-pharmacological trials is much more complex [16]. Other limitations were the small sample size, subjective outcomes, and the fact that some of the outcome questions did not always correspond to the major concerns of patients, as they commented during the evaluations. The same concerns about standardized or individualized measures were raised in some articles [17,18]. We must also stress that the patients lived in the 'real world' and not in the spa hotel facilities.

Patients with rheumatoid arthritis have much to say about their own experience during the course of their disease. For instance, patients highlighted fatigue as a major concern,

sometimes more important than pain, but this is often disregarded by clinicians [19]. Fatigue is documented as a temporary adverse effect of spa therapy; nevertheless, our results did not show any significant difference between groups.

Although we acknowledge that age could have confounding effects, we stratified patients by age to achieve the best possible homogeneity of the two groups.

In our study we included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the DAS28 [20], and we observed a non-significant improvement in the thermal group, indicating that these patients had a mean or moderate disease activity at baseline.

EULAR recommendations state that ultrasound may be used to detect damage at an earlier time point (especially in early RA). Furthermore, Dougados et al. [21] claimed that the presence of synovitis could predict structural damage in RA. In 2010, Smolen and colleagues [22] also highlighted the importance of synovitis detection in daily practice. In our study, the same specialist in skeletal ultrasonography performed all the evaluations (diagnosis and monitoring) and did not find any significant difference with regard to synovitis.

Some published studies emphasize the mechanisms of action of mineral water-inclusive sulphur baths [23]. Other studies focused on genetic, bone, synovial and cartilage markers and other autoantibody/inflammatory markers [24,25].

CONCLUSIONS

In a population where pain (physic and psychological) predominates, any gain contributing to enhanced quality of life (better functional disability beyond wellbeing) is a benefit. That is what balneotherapy appears to have achieved in the patients in this study. In addition to comparing between different patients and/or mean values, it is far more important to highlight wellbeing felt by the same patient over time, according to environmental and personal factors.

Further studies, particularly multicenter randomized controlled trials, should be carried out to validate non-drug interventions considered to have only a marginal benefit. These interventions have never been well assessed, especially those for rheumatoid arthritis. It is time to restore an ancient, natural, geological and less costly therapy – one that has long been discarded. Once its safety is confirmed according to proper indications, spa therapy could supplement other therapeutic modalities.

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