SULPHUR BATH IN THE TREATMENT OF MUSCULOSCELETAL DISORDERS

PhD Thesis

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II.

Kovács C, Bozsik Á, Pecze M, Borbély I, Fogarasi A, Kovács L, Tefner IK, Bender T. Effects of sulfur bath on hip osteoarthritis: a randomized, controlled, single-blind, follow-up trial: a pilot study. Int J Biometeorol 2016 Jun 21. [Epub ahead of print] **IF: 2,309**

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LITERARY OVERVIEW

Definitions

Mineral waters contain at least 1000 mg/L of minerals or some of the important trace elements are present in the water in an increased concentration (e.g. sulfide or iodide ion >1 mg/l, bromide ion >5 mg/l, radon >1 millicurie/l). The classification of mineral waters in Hungary based on the Szilárd Papp system. Considering their composition, the mineral waters are classified as: carbonized, alkaline, calcium-magnesium-bicarbonated, chloridated (saline), ironic (ferrous), sulphuric, sulphated, iodated-bromidated, radioactive waters [1,2].

Balneotherapy is the therapeutic use of natural mineral waters, mud/peloids, and natural gases (carbon dioxide, hydrogen sulphide, radon). Balneotherapy is traditionally used for the treatment of musculoskeletal disorders in many countries rich in medicinal waters [3].

Thermal water, i.e. water the temperature of which is above 30°C can be found under nearly four-fifths of the territory of Hungary.

The use of plain water (tap water) for therapy is called hydrotherapy.

Hydrotherapy is used in most countries of the world for the purpose of treatment.

In case of this form of treatment, only the physical effects of the water prevail.

Medicinal water is natural mineral water that has documented medicinal effect. In Hungary, medicinal effect must be proven by way of clinical studies.

In sulfurous waters, the sulfur can be found in a variety of forms.

Sulfurous waters are mineral waters that contain hydrogen sulfide (H_2S), hydrogen sulfide ions (HS^-), sulfide ions (S^{2-}) and thiosulfate ions ($S_2O_3^{2-}$) in such quantities that the total quantity of the sulfur that can be titrated with iodine exceeds 1 mg per litre [4].

Mechanical and thermal effects of hydro- and balneotherapy

It is documented that thermal waters and sulfurous waters were used in bathing and drinking cures as early as in the Antiquity.

Vitruvius established different categories of waters and also identified what illnesses each is recommended for. He wrote the following about sulfurous water:

"For sulphur spring refresh muscular weakness by heating and burning poisonous humours from the body"[5].

The exact mechanism of action of balneotherapy is not fully understood. In addition to the mechanical and heat effect of water, absorption of minerals may also play a therapeutic role [6,7].

The physical effects of balneotherapy and hydrotherapy are based on three factors: hydrostatic pressure, buoyant force and temperature [8].

When the body is immersed in a vertical position to substernal height, the central venous pressure increases, the stroke volume cardiac output intensifies, and the peripheral vascular resistance decreases.

In terms of renal effects, diuresis and natriuresis increases [9,10,11].

As the result of the buoyant force, the loads on the muscular system decreases, since it is easier for the muscles to move the body in the water.

Hyperthermic water has a muscle-relaxing effect, and increases the stretchability of the structures of the connective tissues [12].

On the basis of the gate control theory, the temperature and the hydrostatic pressure of the water reduces pain through the thermoreceptors and mechanoreceptors of the skin [13].

As an effect of the heat, the beta-endorphin level of the body increases, which also has an analgetic effect [14].

Thermal stress shows a marked influence on secretion of "stress" hormones, but does not influence the circadian rhythm of plasma concentration of these compounds.

Heat also increased serum cortisol levels, which may have anti-inflammatory effect [15].

The chemistry of H_2S in aqueous solution

H_2S is a colorless, flammable gas with characteristic odor of rotten eggs.

Different sulphurous thermal waters have different physicochemical properties depending on their different compositions and amounts of ions and salts, but the common denominator is the presence of the sulfide species: hydrogen sulfide, hydrosulfide ion and sulfide ion.

The H_2S in solution is in dynamic equilibrium at the air-water interface with gaseous H_2S in the air. Characterizing the H_2S reaction intermediates in water and air is very complex, and the chemistry of H_2S is not completely understood [16].

Hydrogen sulfide dissociates in aqueous solution into hydrogen cation (H^+) and hydrosulfide anion (HS^-), which in a further step breaks down to H^+ and sulfide ion (S^{2-}) only at high pH values [17].

The air oxidation of H_2S in aqueous solution is a slow reaction at pH values below 6.

As the pH of the solution increases above pH 6, the concentration of the hydrogen sulfide ion (HS^-) increases. This species readily undergoes oxidation in air. The immediate product of oxidation of HS^- is sulphur, seen as a pale yellow or white precipitate in solutions of H_2S.

Further oxidation of sulfide leads to the formation of thiosulfate ($S_2O_3^{2-}$), tetrathionate ($S_4O_6^{2}$), sulfite (SO_3^{2-}) and finally sulfate (SO_4^{2-}) [18].

Special mention should be made of carbonyl sulfide (COS), discovered by Károly Than in 1868, while he was examining the mineral water of Harkány, which breaks up with water into carbon dioxide and hydrogen sulfide, and gradually replenishes the escaping hydrogen sulfide [19].

H_2S in the human body

H_2S has been proven to be produced endogenously in mammalian tissues and belongs to the gasotransmitter family like nitric oxide (NO) or carbon oxide (CO).

H_2S is also produced in the human body, acts as a neuromodulator in the central nervous system, provides protection from oxidative damage, and due to its vasodilator effect, it may even have a cardioprotective role [20].

H_2S displayed antinociceptive effects by activation of ATP-sensitive potassium channels.

In recent years the majority of studies proposed anti-inflammatory effects of H_2S caused by several key ways: supression of leukocyte adherence and migration, reduction of pro-inflammatory mediator expression, suppression of nuclear transcription factor kappa-B pathway activation as well as the promotion of vasodilatation and angiogenesis [21].

It is interesting to note that in certain rheumatological conditions, e.g. rheumatoid arthritis and reactive arthritis, a much higher H_2S level was observed in the synovia than in the blood, while in case of arthrosis there is no difference between the two levels. This indicates local production of H_2S, but its clinical significance is not yet known [22].

Evidences of the sulfur water effects

During bathing, sulfur enters the body via the skin and the respiratory tract.

The absorption of the sulfide ion from the skin depends on the sulfide ion concentration of the water, the skin surface immersed in the water, the blood supply of the skin, as well as the pH value of the water and the skin. Absorption is higher in case of lower pH values [23].

After passing through the outermost layer of the skin, sulfur with a valency of 2 is oxidised and transported; it is likely built into mucopolysaccharides, in the connective tissue mainly into chondroitin sulfate. Bathing in sulfurous water may cause the reddening of the skin, which is the consequence of the vasodilation.

Sulfur is known to have antiphlogistic, keratolytic, anti-bacterial, anti-fungal and anti-itching effects in the skin.

The reason for the keratolytic effect is that the sulfur atom loosens the disulfide bonds of the keratin, while the conversion of the sulfur into pentathionic acid ($H_2S_5O_6$) may explain the antibacterial effect [24].

Sulfur inhibits the Langerhans cells of the skin, which effect also depends on the concentration of water and sulfur [25].

In animal and human studies, Boros M. et al. observed somatostatin being released as a result of sulfurous water in dermatitis and psoriasis. It is assumed that the release of the somatostatin plays a role in the effect mechanism of sulfurous water [26].

Data exist about the immunologic effects of sulfur water.

In vitro study have demonstrated that suphurous waters have a dose-dependent inhibitory effect on the blast transformation and proliferation of T lymphocytes from peripheral blood in both healthy subjects and subjects affected by chronic upper respiratory disease and articular and periarticular disorders. It has been shown that sulfur water decreases IL2 and IFNγ production, and since these cytokines are produced by CD4+ lymphocytes, one of the targets of sulfur water is probably memory T cells [27].

It was observed in *in vitro* studies that hydrogen sulfide (H_2S) blocked the IL-1β-induced IL-6 and IL-8 expression in C-28/I2 human chondrocyte cell lines [28].

In their study, Sieghart et al. concluded that exogenous H_2S (NaHS) reduced the IL-1β-induced activation of fibroblast-like synoviocytes obtained from arthrosis patients, probably via the MAP-kinase and PI3K/Akt pathways [29].

The authors assume that this is also the effect in case of sulfur baths.

There is *in vitro* evidence for the antioxidant effect of sulfur water.

The incubation in sulphurous mineral water significantly reduces the release of reactive oxygen species (ROS) and the reactive nitrogen species (RNS) peroxynitrite by polymorphonucleate leukocytes (PMNs) stimulated by N-formyl-methionyl-leucyl-phenylalanine and phorbol-12myristate-13-acetate [16].

In patients with osteoarthritis treated with bathing in sulfur water, pain and oxidative stress biomarker levels and TNFα levels significantly decreased by the end of the treatment course.

The antioxidant profile (-SH level) of patients also consuming the water as a drinking course improved, the level of oxidative stress biomarkers (malondialdehyde, protein carbonyl) decreased, and the level of inflammatory and cartilage degradation markers (TNFα, COMP, MMP2) also decreased [30].

Ekmekcioglu et al. examined the changes of the antioxidant protection system and the lipid levels after 3 weeks of sulfurous baths (S^{2-} content: 11 mg/l), with the involvement of 38 arthrosis patients. The peroxide concentration decreased by 17.2%, and the superoxide dismutase activity also decreased. With respect to lipid levels, the LDL level showed a 5.9% decrease in case of those taking sulfur baths. There was no significant difference in the change of the triglyceride and HDL levels in comparison with the control group [31].

In case of patients with arthrosis it has been proved that sulfur bath treatments (S^{2-} content: 7.3 mg/l) significantly reduces the plasma homocysteine level, which is commonly known to be a risk factor for cardiovascular diseases. The other examined parameter, the level of 8-hydroxy-2'-deoxiguanosine (8-OHdG), however, did not change [32].

Sukenik et al. divided 40 patients with rheumatoid arthritis into four groups.

The first group took sulfur baths, while the second group received mud treatment for 2 weeks, the third group a combination of the two, while the fourth served as the control group.

A large part of the parameters examined (morning stiffness, number of active joints, circumference of proximal interphalangeal joints, hand grip, 15 metre walk time) improved in all three groups receiving treatment for 1 to 3 months [33].

Sherman et al. used sulfur bath treatment for one group of 44 patients with knee arthrosis, and the other group in jacuzzi (tap water) on 12 occasions over the course of 6 weeks. In case of the group receiving sulfurous water bath treatment, significant improvement was found in most clinical parameters examined even in case of the 6-month follow up examination [34].

30 patients with back pain received hydrotherapy in the sulfurous water of Kehidakustány for 15 days, while another 30 patients in tap water.

In case of patients receiving hydrotherapy in sulfurous water, significant improvements were found after the completion of the hydrotherapy treatment in the following parameters: pain, local sensitivity to pressure, antalgic posture, paravertebral spasm, spinal motion parameters. The improvement could be detected also after 3 months [35].

Tefner and Kovács et al examined, in the framework of a multicentral study, the effects of balneotherapy in case of chronic shoulder pain. The patients receiving balneotherapy bathed in sulfurous water. In this single-blind, randomized, follow-up study involving 46 patients with chronic shoulder pain, one group of patients received physiotherapy - exercise and transcutaneous electrical nerve stimulation - and the other group received balneotherapy in addition to physiotherapy for 4 weeks on 15 occasions. The following parameters were recorded before treatment (at week 0) and after treatment (at weeks 4, 7, and 13): Shoulder Pain and Disability Index (SPADI), the Short Form (36) Health Survey (SF-36) and EuroQuol-5D (EQ-5D) quality of life questionnaires, pain at rest and on movement on the visual analog scale (VAS), and active and passive range of motion. The SPADI pain, function, and total scores and the VAS scores at rest and on movement significantly improved in both groups after treatments. Agreater improvement was observed in the balneotherapygroup compared to the control group; regarding some parameters (VAS score on movement and SPADI function score at visit 2; VAS score at rest at visits 3 and 4), the difference between the groups was significant. The improvement of SF-36 and EQ-5D quality of life scores and the active range of motion was more pronounced in the balneotherapy group, the difference between the groups was not significant, except for EQ-5D at visit 2. Improvement of passive range of motion was not significant. Balneotherapy may have a beneficial effect on the clinical parameters and quality of life of patients with chronic shoulder pain [36].

Osteoarthritis of hand and hip

Osteoarthritis is a degenerative joint disease, occuring primarily in older persons, characterized by erosion of the articular cartilage, hypertrophy of bone at themargins (osteophytes), subchondral sclerosis, and a range of biochemical and morphologic alterations of the synovial membrane and joint capsule.

There are two classifications of osteoarthritis. In primary disease, although the exact cause remains unclear, onset of cartilage destruction appears to be associated with some element of abnormal joint biomechanics. In secondary disease, injury, infection, hereditary factors, developmental processes and metabolic or neurological disorders influence joint tissue metabolism and can initiate cartilage breakdown. Distinguishing between primary and secondary osteoarthritis may be difficult because the clinical presentation and symptoms are often so similar.

The pathogenesis of primary osteoarthritis is not completely understood and it was long time considered a non-inflammatory joint disease simply induced by wear and tear. Recent research revealed that osteoarthritis involves various elements of the inflammatory response including up-regulation of cytokines and chemokines driven by IL-1β and TNF-α increased levels of which were detected in the synovial fluid of osteoarthritis patients. Cytokines produced by the synovia and chondrocytes also play an important role in cartilage degradation. Matrix metaloprotease (MMP) family, collagenases (enzymes responsible for collagen degradation) and aggrecanases (enzymes responsible for aggrecan cleavage found in osteoarthritis synovial fluid) have been suggested to play major roles in the degradation of the extracellular matrix observed in osteoarthritis [37].

Symptomatic hand osteoarthritis is a common musculoskeletal disorder, its prevalence being 15.9% in women and 8.2% in men in a population aged 58.9 (± 9.9) [38]. This disease is characterized by pain, stiffness, and impairment in hand function, deterioration in handgrip strength, and the latter could decrease below the 60% of the normal value [39]. The disease typically affects the distal and proximal interphalangeal (DIP, PIP), and the first carpometacarpal (CMC) joints.

The course of the disease is less clear, but available data show that the whole joint is affected by osteoarthritis [40]. At present there do not exist such therapeutic methods that are able to modify the structure, and the studies related to symptomatic treatment are scarce [41,42].

Osteoarthritis of the hip is a chronic disease characterized by structural and functional impairment of the hip joint resulting in pain and disability as well as decreased quality of life [43]. The prevalence of hip osteoarthritis in adults is approximately 11% [44].

Treatment strategies for this condition include pharmacological, non-pharmacological and surgical therapies [45]. In practice, exercise therapy plays an important role in the treatment of hip osteoarthritis. Based on some studies and the 2014 Cochrane database, there is evidence that in hip osteoarthritis, exercise decreases joint pain and improves function [46,47,48]; however, in a recently published, placebo-controlled study, no difference in pain was found between exercise therapy and placebo [49].

It was the 2014 OARSI guidelines which first recommended balneotherapy along with biomechanical interventions, intra-articular corticosteroids, oral COX-2 inhibitors and antidepressants for the treatment of multi-joint osteoarthritis with comorbidities [50].

However, only limited data are available on the effects of balneotherapy in hip osteoarthritis.

Although the studies published so far suggest that balneotherapy might also be effective in this condition, these studies not only involved patients suffering from hip osteoarthritis but also patients with osteoarthritis of other joints [51,52,53,54].

Assesment of the effects of balneotherapy and the tools of health assessment

The Visual Analogue Scale (VAS)

The VAS for pain consists of a 10 cm line with two end-points representing ’no pain’ and ’pain as bad as it could possibly be’. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks [55].

The AUSCAN Hand Ostoarthritis Index

The AUSCAN Hand Ostoarthritis Index is tri-dimensional, disease-specific, self-administered, health status measure. It probes clinically-important, patient-relevant symptoms in the areas of pain, stiffness and physical function in patients with osteoarthritis of the hand joints.
The index consists of 15 questions: 5 pain, 1 stiffness, 9 physical function.
It is available in 5-point Likert scale (LK3.1), 100mm Visual Analogue and 11-point Numerical Rating Scale formats. We preferred the Likert format.
The AUSCAN LK3.1 allows patients to make their responses on 5-point adjectival scales (0=none, 1=mild, 2=moderate, 3=severe, 4= extreme). For each AUSCAN dimension, a subscale score is calculated by simple summation of the assiggned values scored on component items. Thus, the range of possible subscale scores for the three dimensions is as follows: pain: 0-20, stiffness=0-4, physical function= 0-36.
A higher score indicates greater impairment. The AUSCAN can be used only with license.
The index has been linguistically validated [56,57].

The WOMAC Osteoarthritis Index

The WOMAC Osteoarthritis Index is a tri-dimensional, disease-specific, self-administered, health status measure.

It probes clinically-important, patient-relevant symptoms in the areas of pain, stiffness and physical function in patients with osteoarthritis of the knee and/or hip.

The index consists of 24 questions (5 pain, 2 stiffness, 17 physical function) and can be completed in less than 5 minutes. It is avaible in Likert, Visual Analogue and Numerical Rating scaling formats. In our studies we preferred the Likert format. For Likert numerical values are assigned to each of the five response categories (0=none, 1=mild, 2=moderate, 3=severe, 4=extreme). For each WOMAC dimension, a subscale score is calculated by simple summation of the assigned values scored on component items. Thus, the range of possible subscale scores for the three dimensions is as follows: pain=0-20, stiffness=0-8, physical function=0-68. For convenience these scores can be normalised, and expressed on 0-10 or 0-100 scales, we preferred the last one [58,59].

The proposed absolute (and relative) Minimal Clinically Important Improvement (MCII) for knee and hip osteoarthritis are between others as follows: -19.9 mm (-40.8%) and -15.3mm (-32%) for VA pain, -9.1 (-26%) and -7.9 (-21%) for WOMAC function subscale score [60]. The questionnare is validated in Hungarian [61].

The EuroQoL five dimensions questionnaire (EQ-5D)

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: 1=no problems, 2=some problems, 3=extreme problems. A unique health state is defined by combining 1 level from each of the five dimensions. A total of 243 possible health states is defined in this way, each state is referred to in terms of a 5 digit code. EQ-5D health states, defined by the EQ-5D descriptive system, can be converted into a single summary index by applying a formula. The EQ VAS records the respondent's self-related health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state' [62,63].

Health Assessment Questionnaire (HAQ)

The HAQ is based on five patient centered dimensions: disability, pain, medication effects, costs of care, and mortality. Typically, one of two HAQ versions is used: the Full HAQ, which assesses all five dimensions, and the Short or 2-page HAQ, which contains only the HAQ disability index (HAQ-DI) and the HAQ's patient global and pain visual analog scales (VAS).

The HAQ-DI includes items that assess fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities.

Standard scoring takes into account the use of aids and devices or assistance from another person. There are 20 items in eight categories that represent a comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. For each item, there is a four-level response set that is scored from 0 to 3, with higher scores indicating more disability (0= without any difficulty; 1=with some difficulty; 2=unable to do). To calculate the HAQ-DI the highest subcategory score determines the value for each category. The category scores are then averaged into an overall HAQ-DI from zero to three. Scores of 0 to 1 generally represent mild to moderate difficulty, 1 to 2 represent moderate to severe disability, and 2 to 3 indicate severe to very severe disability [64,65]. The HAQ-DI is validated in Hungarian [66].

AIMS OF THE THESIS

I.

The aim of our study was to determine the effects of bathing in sulfurous water on pain, the morning stiffness of the joints and on manual functions among patients suffering from arthrosis in the joints of their hands. As a secondary objective, we also aimed to survey changes in the quality of the patients' lives. When designing our investigation, we have not found a similar clinical study in the medical literature.

II.

Limited data is available on the effects of balneotherapy in the arthrosis of the hip joint, which is the reason why we initiated our study of this question. The primary purpose of the clinical investigation was to determine if balneotherapy (immersion in sulfurous mineral water) applied in addition to corrective gymnastic therapy performed at home among patients with arthrosis of the hip has a more expressed, or perhaps more permanent effect than the corrective gymnastic therapy alone. The primary considerations were joint pain, stiffness and function. An additional objective was the assessment of the change in quality of life.

THE EFFECT OF SULPHUROUS WATER IN PATIENTS WITH OSTEOARTHRITIS OF HAND. DOUBLE-BLIND, RANDOMIZED, CONTROLLED, FOLLOW-UP STUDY.

OBJECTIVES

The aim of the study was to demonstrate the effectiveness of sulphurous water in patients with osteoarthritis of the hand. Primary endpoint is that the pain decrease, and hand functions increase at the end of treatment, and 3 and 6 months later. Secondary endpoint is to improve quality of life.

METHODS

Patiens

The outpatients of Mezőkövesd Musculoskeletal Rehabilitation Centre were enrolled into the study.

Twenty-four patients (male/female: 1/23) had bath in sulphurous water (balneotherapy group), while 21 patients (male/female: 2/19) had bath in tap water (control group). The assessments took place on four occasions: at the beginning and at the end of study, and three and six months after the therapy. Neither the patients nor the investigators knew the distribution of the two groups.

Osteoarthritis of the hand was diagnosed according to the 1990 criteria of the American College of Rheumatology [67]. Inclusion criteria included Kellgren-Lawrence radiographic grade ≥ 2 in at least two joints and ≥ 30 mm hand pain as assessed by the Visual Analog Pain Scale [68].

Patients younger than 45 years of age and older than 75 years were excluded from the study.

Further exclusion criteria were: erosive or secondary hand osteoarthritis, inflammatory rheumatic disorders, psoriasis, gout, carpal tunnel syndrome, trigger finger, tendovaginitis, fibromyalgia. The patients could not receive balneotherapy in the last 9 months, they could not get steroid injection into the small joints of hands in the last 3 months, or injection of a hyaluronate in the last 6 months, and they could not take symptomatic slow acting drogs (SYSADOA) in the last 3 months either. During the study period the patients did not get any other therapy for hand pain than balneotherapy, they did not take non-steroid drugs. For other pain occurring eventually they were allowed to take paracetamol or metamisole.

The permission necessary to carry out the study was received from the Regional Ethics Committee (license number: 01-03-2009).

Treatment

Both the balneotherapy group (n = 24) and the control group (n = 21) spent 20 minutes per occasion in the bath-tub, in all 15 times during a period of 3 weeks. The temperature of the spa water and that of the tap water was 37 C °.
The period of balneotherapy was measured and certified by the physiotherapy assistant.
During the study period, the patients did not receive any other physiotherapy on their hands.

Composition of the thermal water

The spa water of Mezőkövesd belongs to the group of sulphurous spa waters, its content of sulfide ion (13.2 mg / L) is the highest in Hungary. In addition, this spa water contains a significant amount of calcium, magnesium, bicarbonate and sodium chloride as well.
(Table 1)

Table 1 The composition of thermal water

Kation	mg/L	Anion	mg/L
Na^+	250	NO_3^-	< 1.0
K^+	69	NO_2^-	< 0.02
Li^+	1,68	Cl^-	254
NH_4^+	5,6	Br^-	1.08
Ca^{2+}	280	I^-	0.17
Mg^{2+}	48,2	F^-	2.9
Fe^{2+}	0,54	SO_4^{2-}	< 10
Mn^{2+}	0,41	HCO_3^-	1420
		PO_4^{3-}	0.15
		S^{2-}	13.2
Total concentration: 2347 mg/L			

Study parameters

The parameters studied were as follows:

Hand pain measured by visual analogue scale (0-100), morning joint stiffness (MJS) based on the self-report of patients (minutes), the grip strength of hands, measured by Dyna-9 dynamometer (Newton). The grip strength of both hands was measured three times, the final result was the average of three measurements [69].

In addition, completion of the following questionnaires took place:

Health Assessment Questionnaire Disability Index (HAQ-DI), Australian/Canadian Osteoarthritis Hand Index Likert-scaled Format (AUSCAN LK3.1) and EuroQol (EQ-5D / EQ VAS), quality of life questionnaire. The Health Assessment Questionnaire (HAQ) is the functional index of rheumatoid arthritis, however, it is usable in hand osteoarthritis, as well [64-66].

The AUSCAN is a three dimensional, self-administered questionnaire specific for the osteoarthrosis of the hand. A higher score indicates greater impairment [56,57]. The AUSCAN can be used only with license. We have received the authorization necessary to use the Hungarian version of the questionnaire. The EQ-5D quality of life questionnaire consists of two parts. The first part contains items referring to five dimensions of life quality, the second part is a Visual Analog Scale (EQVAS), by which patients self-report their actual health state [62,63].

Randomization

A computerized randomization took place, the patients got identification numbers when they were enrolled into the study. The randomization was made by an independent person. The result of the randomization was known exclusively by the physiotherapy assistant working in the bath who filled the bath-tubs with spa water or tap water. The bath-tubs could be filled both with spa water and with tap water, so balneotherapy could have happened in any bath-tubs. Patients sitting in the bath were holding only their heads out of the water while hands were kept in the water. The sulphurous smell that could be perceived everywhere in the bath was deceptive for the control group.

Statistical analysis

The statistical analyses were made using SPSS 15.0 software. Regarding the data gained at the beginning of the study, the Kolmogorov-Smirnov test was used as a normality test, and the Mann-Whitney test were used as homogeneity tests. The changes in state were assessed comparing the data to the baseline data or the data gained earlier (Wilcoxon test).
Comparison of data of the two groups was done by Mann-Whitney test. Taking into account the Bonferroni corrections, significant result, we appplied p-value <0,008 (5%/6=0.8%).

RESULTS

Patients were recruited by the family doctor in the Mezőkövesd rural area and sent to Mezőkövesd Muscolosceletal Rehabilitation Center, where the rheumatologist screened 60 patients for the study. The recruitment period was between May 2009 and May 2010. A total of 47 patients (male/female: 4/43) were randomised, of which two subjects dropped out during the treatment process for family reasons. Balneotherapy did not have to be interrupted because of side effects in any case.

During the whole period of the study adverse event was not reported.

The data of the two groups at the beginning of the study are indicated in Table 2. The baseline characteristics were similar between the two groups. The balneotherapy group showed significant improvement in every parameter under the scope of the study at the end of the treatment. The improvement was pronounced also regarding pain, MJS, the grip strength, the AUSCAN, the HAQ and the EQVAS ($p < 0.001$). After 3 months, the improvement remained significant with the exception of MJS and EQ5D. After 6 months, all the parameters still showed significant improvement in comparison with the baseline, except the MJS, the grip strength, the EuroQol.

The control group showed significant improvement in every parameter, except pain, HAQ, EuroQol (EQ5D+EQVAS), at the end of the treatment, however, this improvement was less expressed than in the balneotherapy group. After 3 and 6 months, no improvement could be detected in any parameter in the group that had bath in the tap water.

The difference between the two groups was significant after the bath in point of pain (VAS) and 3 months later both in point of pain (VAS) and of health state (EQVAS) but it was not significant in the point of MJS, grip strenght, HAQ-DI, AUSCAN and EQ5D. (Table 3)

The number needed to treat (NNT) is 5,6 patients [95% CI 2.28-10].

DISCUSSION

Our double-blind, randomized, controlled follow up study results suggest that balneotherapy is a succesful treatment in the osteoarthritis of the hand as well, since the pain in the hands of patients who had bath in spa water improved even during 3 months. No improvement could be detected in quality of life after 6 months. R. Forestier et al. [70], using the SF-36, came to the same conclusion regarding knee osteoarthritis. Mineral water has been used for ages for the alleviation of musculoskeletal pain. The beneficial effects of balneotherapy were studied and proven in a variety of rheumatological diseases in the past decades. In osteoarthritis of the knee, pain and musculoskeletal dysfunction improved in the short to medium term [70,71,72,73].

Unfortunately there're not so many studies that support conservative therapy interventions for osteoarthritis of hand, as for osteoarthritis of the hip and knee [74]. Low level laser therapy (LLLT) is no better than the placebo in improving subjects hand function or decreasing hand pain or morning stiffness [75]. Balneotherapy seems more efficient than LLLT treatment.

There are some modest evidence that the hot wrap and steam alleviate pain and increase the grip strength of the hand in hand osteoarthritis.

At the EULAR task force's recommendation, local application of heat is the beneficial treatment, but level of evidence is low [76].

This positive effect - which can be explained by the hot temperature and other physical effects of the water – was detected in the patients who had bath in tap water at the end of the treatment period. Longer-lasting improvement, however, could be detected in the patients that had bath in the sulphurous spa water, this refers to the positive role of the sulfur content in the water. The exact mechanism of action of balneotherapy is not known, but the minerals absorbed from the water can have a therapeutic role, in addition to the physical properties of the water [6,77].

It is difficult to analyse the effects of each component of spa waters seperately, probably a complex effect occurs. In the spa water used in the present study, the high sulfide ion (S^{2-}) content is dominant. The sulfur can get into the body through the skin and the airways. The hydrogen sulfide (H_2S) gas has a known antioxidant effect in the cells [20].

The results of Benedetti et al. [30] also demonstrated this antioxidant effect, as when the sulfurous mud baths were used in combination with the drinking of sulfurous water the quantity of the biomarkers of oxidative stress and that of biomarkers indicating inflammation and cartilage degradation decreased to a great degree in the blood.

It is assumed that this antioxidant effect of sulfurous mineral water protects against the oxidative damage of cartilage tissue in osteoarthritis [31,32]. In addition, the sulfide ion (S^{2-}) content is beneficial for the de novo proteoglycan synthesis in the cartilage tissue, counteracting the degradation of the cartilage. It is a remarkable fact that in 41% of patients with knee osteoarthritis, hand osteoarthritis was found as well, so it can be assumed that balneotherapy could be effective in the case of generalized osteoarthritis, too [78].

Limitation of the study

Sample size has not been calculated, so this may cause lack of statistical power.

The difference in colour between the mineral water and the tap water might have influenced the patient blinding.

The consumption of analgesics was not studied and patient global assessment was not estimated.

Table 2 The baseline characteristics of patients

	Patients in spa water (n = 24)	**Patients in tap water (n = 21)**	**p**
Age (years)	58 (47-71)	61 (50-73)	0.356
BMI (kg/m²)	29.25±4.025	29.97±4.204	0.413
Pain (VAS)	59.96±16.643	52.57±11.378	0.158
MJS (min.)	16.75±18.536	10.62±8.698	0.435
Grip strength – right hand (N)	141.54±47.404	158.43±59.513	0.439
Grip strength – left hand (N)	121.58±41.740	144.27±49.319	0.130
HAQ DI	1.56±0.543	1.61±0.366	0.945
AUSCAN pain stiffness physical functions	36.75±9.336 12.62±2.961 2.75±0.676 21.38±6.639	36.57±6.376 12.38±1.962 2.90±0.768 21.29±5.051	0.649 0.407 0.429 0.820
EuroQol EQ5D EQVAS	 0.495±0.2061 48.92±15.929	 0.470±0.2080 49.71±13.488	 0.679 0.820

Table 3 Study parameters and the difference between groups

	Visit 1 (baseline)		Visit 2 (after bath)			Visit 3 (3 month later)			Visit 4 (6 month later)		
	Balneo-therapy group *n = 24*	Control *n = 21*	Balneo-therapy group *n = 24*	Control *n = 21*	Difference between groups	Balneo-therapy group *n = 24*	Control *n = 21*	Difference between groups	Balneo-therapy group *n = 24*	Control *n = 21*	Difference between groups
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	p	mean (SD)	mean (SD)	p	mean (SD)	mean (SD)	p
Pain (VAS) (mm)	59.96 ±16.643	52.57 ±11.378	24.29 ±17.53	42.10 ±15.757	0.002	33.75 ±16.294	49.40 ±18.048	0.006	42.75 ±17.855	54.45 ±16.214	0.055
MJS (min.)	16.75 ±18.536	10.62 ±8.698	7.17 ±11.768	6.93 ±10.847	0.722	10.88 ±10.999	13.75 ±19.194	0.617	11.42 ±13.270	11.95 ±13.375	0.601
Grip strength, right hand (N)	141.54 ±47.404	158.43 ±52.513	181.70 ±57.744	192.19 ±72.904	0.864	173.57 ±58.804	168.42 ±61.082	0.572	155.30 ±54.713	157.72 ±56.649	0.991
Grip strength, left hand (N)	121.58 ±41.740	144.27 ±49.319	153.49 ±57.648	173.52 ±58.511	0.237	154.65 ±62.580	160.34 ±55.119	0.671	133.37 ±50.527	153.50 ±58.266	0.352
HAQ-DI	1.56 ±0.543	1.61 ±0.366	1.11 ±0.600	1.42 ±0.423	0.110	1.24 ±0.502	1.60 ±0.440	0.037	1.34 ±0.468	1.71 ±0.374	0.012
AUSCAN	36.75 ±9.336	36.57 ±6.376	24.88 ±10.075	28.95 ±8.738	0.264	28.96 ±9.191	35.20 ±9.094	0.045	33.00 ±10.095	37.35 ±7.051	0.252
pain	12.62 ±2.961	12.38 ±1.962	8.92 ±3.387	9.48 ±2.892		10.33 ±2.632	12.15 ±3.514		11.71 ±3.043	12.50 ±2.395	
stiffness	2.75 ±0.676	2.90 ±0.788	1.92 ±0.776	2.00 ±0.837		2.25 ±0.532	2.45 ±1.050		2.58 ±0.584	2.65 ±0.745	
physical funcitons	21.38 ±6.639	21.50 ±5.084	14.04 ±7.111	16.90 ±6.308		16.38 ±6.826	20.60 ±5.688		18.29 ±7.190	22.35 ±4.760	
EuroQol											
EQ5D	0.481 ±0.206	0.470 ±0.208	0.570 ±0.226	0.475 ±0.201	0.129	0.510 ±0.181	0.429 ±0.193	0.108	0.495 ±0.168	0.418 ±0.192	0.212
EQVAS	48.92 ±15.929	49.71 ±13.488	64.417 ±16.96	55.29 ±13.131	0.038	61.21 ±13.164	45.35 ±11.807	0.001	52.12 ±16.716	43.15 ±16.468	0.054

EFFECTS OF SULFUR BATH ON HIP OSTEOARTHRITIS: A RANDOMIZED, CONTROLLED, SINGLE-BLIND, FOLLOW-UP TRIAL A PILOT STUDY

OBJECTIVES

The primary objective of our study was to evaluate whether combination of balneotherapy (immersion into thermal mineral water) and home exercise therapy has a more favorable and durable effect than home exercise therapy alone.

The main endpoint was achievement of Minimal Clinically Important Improvement (MCII) at 12 weeks, defined as ≥7.9 points in a normalized WOMAC function score [60].

The secondary objective was to assess changes in quality of life.

METHODS

Patients

Enrollment of outpatients and medical examinations were performed at the Musculoskeletal Rehabilitation Centre in Mezőkövesd, Hungary. Bath treatment was given at the Zsóry Thermal Bath and Spa in Mezőkövesd, Hungary.

Inclusion criteria included: osteoarthritis of the hip based on the ACR criteria [79], adults between 40 and 75 years of age, Kellgren-Lawrence radiological stage IIII in the joint investigated, at least mild (1 point on the Likert scale) hip pain for a minimum of 5 days a week for at least 3 months.

Exclusion criteria were: osteoarthritis of other joint(s) (knee, ankle) in the affected limb, lumbago and sciatica, total hip replacement surgery, any other surgery or previous fracture in the hip joint, subluxation, luxation, rheumatoid arthritis, algodystrophy, fibromyalgia, gout, balneotherapy within the past 6 months, intra-articular corticosteroid treatment of the affected hip joint within 3 months or any other joint within 1 month, hyaluronic acid injection within

6 months, initiation of symptomatic slow acting drugs for osteoarthritis (SYSADOA) within 3 months prior to screening, systemic corticosteroid treatment within 1 month prior to screening, physiotherapy within 1 month and balneotherapy within 6 months prior to screening.

Before starting treatment, participants read the Patient Information Sheet and signed the Consent Form. The study was approved by the Regional Research Ethics Committee (approval number: 1046294/2013).

Treatment

The patients were divided into two groups.

Both groups did exercise therapy daily at home for 3 weeks using a written guide with pictures.

In addition to these exercises, patients in the first (balneotherapy) group sat in sulfur mineral water for 20 minutes on 15 occasions. The second (control) group did home exercise therapy alone.

The mineral water used in this study is one of the mineral waters with the highest sulfide ion content (13.2 mg/L) in Hungary. It also contains a significant amount of calcium, magnesium, bicarbonate, and sodium chloride. Water temperature was 36°C (96.8°F).

A member of the bath staff supervised the patients' attendance in the treatment sessions and the duration of bathing.

Patients were evaluated at 3 visits: prior to the first treatment session (Visit 1), at the end of the 3week treatment course (Visit 2), and 12 weeks after the end of treatment (Visit 3).

Hip exercises were compiled by experienced hospital physiotherapists. In both groups, the first exercise therapy session was done in the presence of a physiotherapist.

Both groups performed the same active exercises.

Study parameters

The WOMAC Likert 3.1 index evaluating changes in pain, joint stiffness and function was completed as the primary endpoint, and the EQ5D quality of life questionnaire was completed as the secondary endpoint. Both questionnaires were completed during all three visits.
The WOMAC index is a hip and knee osteoarthritis-specific, self-administered questionnaire with three dimensions. The total score is the sum of the three dimensions. The higher scores indicate more severe impairment [58,59,61].
EuroQol5D is a self-administered quality of life questionnaire with two parts. The first part consists of questions about five quality of life dimensions (EQ5D index), and the second part is a Visual Analogue Scale (EQVAS) on which patients rate their current health-related quality of life state [62,63].

Randomization

Patients enrolled into the study were randomized by an independent person living in another city by using a computer program and receiving patient data via email.
After randomization, an independent person assigned the patients into the appropriate group.
Visits were also performed by an independent investigator. Patients were asked not to tell the investigator which treatment they receive.

Statistical analysis

Statistical analysis was performed by an independent person using the IBM SPSS 22 software.
As for the baseline values, normality was assessed by using the Kolmogorov-Smirnov test.
The main endpoint was tested using the Chi-square test.
The results of the two groups were compared by using the Mann-Whitney test and repeated measures ANOVA. The efficacy of treatment was proved by effect size (partial eta squared). A p-value < 0.05 was considered significant for the statistical analysis. Data were analyzed according to the intention-to-treat (ITT) principle.

RESULTS

The study was conducted between November 2013 and April 2015 with continuous enrollment of patients. By using the hospital database, 130 outpatients with hip osteoarthritis were screened.

During screening, 48 patients did not meet the specified criteria.

38 patients refused to participate due to their living distance from the bath and for other family reasons. 44 patients were randomized: 22 patients to the balneotherapy group and 22 patients to the control group. Three patients withdrew from participation after randomization prior to the first examination.

During the treatment sessions, no adverse effects were noted.

Patient demographics and measured baseline parameters of the two groups were balanced.

Mean age of the patients was 59.14±7.55 and 60.66±7.6 years in the balneotherapy and control group, respectively.

The difference in MCII at 12 weeks is statistically significant in favour of balneotherapy group (Table 4). Comparing the results of the two groups at the end of treatment, there was a significant difference in the WOMAC stiffness score only, whereas after 12 weeks, the WOMAC pain, stiffness, function, and total scores also showed a significant difference. After 12 weeks, significant improvement could be detected in quality of life (EQVAS) (Table 5).

DISCUSSION

The results of our study suggest that in hip osteoarthritis, the combination of balneotherapy and home exercise therapy improves joint function and decreases pain.

It appears that the two treatments together has a more sustained effect than exercise therapy alone, since after 12 weeks there was a significant difference between the two groups in all subscales of the WOMAC index as well as in the total score.

Significant difference was noted in quality of life between the two groups in our study.

Over the past decades, the beneficial effects of balneotherapy have been evaluated and proven in many rheumatic diseases, including osteoarthritis of the knee and hands, where pain and musculoskeletal functions improved both in the short and medium term [70,80,81].

However, controlled studies are not yet available in osteoarthritis limited to the hip.

The exact mechanism of action of balneotherapy is not fully understood. In addition to the mechanical and heat effect of water, absorption of minerals may also play a therapeutic role [6,7].

During bathing, sulfur enters the body via the skin and the respiratory tract. The medicinal water used in our study has an outstanding sulfide ion (S^{2-}) content. In sulfur waters, sulfur is present in multiple and variable forms. The dominant compound is hydrogen sulfide (H_2S). H_2S is also produced in the human body, acts as a neuromodulator in the central nervous system, provides protection from oxidative damage, and due to its vasodilator effect [20].

Sulfur presumably reaches the connective tissues and joints, but its direct incorporation is not yet supported with studies using exact measurements. Data exist about the immunologic effects of sulfur water. It has been shown that sulfur water decreases IL2 and IFNγ production, and since these cytokines are produced by CD4+ lymphocytes, one of the targets of sulfur water is probably memory T cells [27].

There is in vitro evidence for the antioxidant effect of sulfur water [16].

It appears that sulfur compounds affect the body through multiple pathways.

These compounds influence the inflammatory cascade, affect the immune system, provide protection from oxidative damage, and their analgesic and function-improving effects are also observed in the clinical practice.

In conclusion, although exercise therapy for hip osteoarthritis could have positive effects on pain and hip joint function when used alone, but these effects are even more pronounced and durable when balneotherapy is added to the treatment.

Limitations

Due to the single-blind nature of the study, all patients were aware of the treatment received. The lack of blinding of patients may overestimate the treatment effect. The drog consumption was not studied. The number of patients should be increased.

	Balneotherapy (n=21)	Control (n=20)	p	Odds (CI95%)
3 weeks	16 (76%)	8 (40%)	0.019	4.80 (1.25-18.42)
12 weeks	17 (81%)	6 (30%)	0.001	9.92 (2.33-42.25)

Table 4 Number of patients achieveing MCII 3 and 12 weeks.

	Group	Visit 1 (baseline)		Visit 2		Visit 3		Effect size (partial eta squared)	p^2 (visit x group)
		Mean±SD	p^1	Mean±SD	p^1	Mean±SD	p^1		
WOMAC pain score	Balneotherapy (n=21)	10,57±3,31	0,372	6,38±3,44	0,313	6,62±3,23	0,041	0.152	0.002
	Control (n=20)	9.65±3,17		7,45±3,61		8,75±3,48			
WOMAC stiffness score	Balneotherapy (n=21)	4,19±1,54	0,524	2,61±1,50	0,013	2,57±1,54	0,001	0.121	0.007
	Controll (n=20)	4,50±1,15		3,95±1,70		4,20±1,40			
WOMAC functional limitation score	Balneotherapy (n=21)	38,05±11,34	0,425	25,05±12,38	0,171	25,29±12,01	0,030	0.168	0.001
	Control (n=20)	36,20±10,03		30,45±13,02		32,70±11,38			
WOMAC total score	Balneotherapy (n=21)	52,81±15,52	0,396	34,05±16,89	0,137	34,48±16,33	0,018	0.176	0.001
	Control (n=20)	50,35±13,35		41,85±17,69		45,65±15,39			
EQ-5D index	Balneotherapy (n=21)	0,483±0,218	0,948	0,645±0,206	0,430	0,637±0,196	0,087	0.073	0.051
	Control (n=20)	0,483±0,219		0,595±0,215		0,514±0,216			
VAS score	Balneotherapy (n=21)	54,62±20,69	0,886	67,86±18,50	0,191	69,05±20,87	0,026	0.090	0.034
	Control (n=20)	57,60±12,84		60,50±13,98		58,35±12,94			

Table 5 Study parameters and the difference between groups

CONCLUSION AND NEW RESULTS

I. On the basis of the double-blind, controlled, randomised study with follow-up conducted among patients suffering from the arthrosis of small joints of the hand, it appears that balneotherapy with immersion in sulfurous mineral water is an effective therapy in the treatment of the arthrosis of the small joints of the hand. The positive impact was primarily observed in terms of improvements for 3 months concerning pain and quality of life experienced by the patients.

We explain the relative improvement of the patients bathing in mineral water in comparison with the control group primarily with the chemical effect of the mineral water, i.e. its sulfur content, since the physical and thermal effects were the same in the two groups.

The limitation of the study was the low number of patients involved in it.

II. The results of our investigation suggest that balneotherapy with immersion in sulfurous water applied in addition to corrective gymnastic therapy performed at home reduces pain and improves the joint functions.

According to some studies, as well as the review of the Cochrane database for 2014, it appears to be proven that gymnastic exercises reduce pain in the joints and improve the motoric functions in case of the arthrosis of the hip joint. We have no similar data for balneotherapy in case of patients suffering from this illness.

By the end of the treatments, significant improvements were found in the results of both groups, and in terms of stiffness, we found significantly better results in case of those who received the balneotherapy treatment.

It appears that the application of the two types of treatment together has a longer-lasting effect than the corrective gymnastic therapy alone, since after 12 weeks, those who received balneotherapy treatment had significantly better results in terms of pain in the joints, stiffness and functions, as well as in their quality of life.

In summary, it can be concluded that corrective gymnastic therapy has a positive effect on pain and hip joint functions also when applied in itself for the treatment of the arthrosis of the hip joint, but more effective and more permanent results can be achieved if this treatment is combined with balneotherapy with immersion in sulfurous water.

The limitation of our investigation was the low number of patients, as well as the use of the single blind method, namely that the patients were aware of what kind of treatment they received.

SUMMARY

Sulfur bath treatments have been used for therapeutic purposes for a long time.

Unfortunately, evidence from clinical studies are scarce, and therefore, we are still not familiar with the exact effect mechanism of sulfur baths, but the clinical studies aimed at exploring and mapping these effects are under way also today.

It is assumed that after dermal absorption the sulfide also gets into the connective tissues and the joints, but no studies supported with accurate measurements are available yet concerning their direct incorporation.

On the basis of existing studies, it appears that sulfur baths effect the body in various ways, and have immune modulating, anti-inflammatory and anti-oxidant effects as well. In the clinical practice, their functions of relieving pain and improving joint functions have also been observed, which is why they have been used to this day for the treatment of locomotor diseases. Unfortunately, there are few evidence-based clinical studies available, and a limitation of most studies is the low number of patients involved.

A major step forward is that 2014 OARSI Guideline mentions balneotherapy for the first time on the same level in the treatment of knee joint arthrosis with biomechanical interventions, intra-articular steroids, oral COX-2 inhibitors and antidepressants in the treatment of generalised arthrosis involving comorbidities.

However, very limited data is available on the efficacy of balneotherapy in the treatment of arthrosis of the small joints of the hand and hip joint arthrosis, and therefore, we conducted our studies with respect to these locomotor diseases.

Indications for sulfur bath treatment today are primarily based on the experiences of many years.

It is recommended mainly in case of degenerative diseases of the locomotor system (e.g. arthrosis), extra-articular rheumatism, and the non-acute stage of rheumatoid arthritis, as well as for the post-treatment of injuries, rehabilitation after orthopaedic surgery and neurosurgical operations, as well as in case of skin diseases such as psoriasis. On the basis of our studies it appears that sulfur baths can be an effective treatment for hand and hip arthrosis. To confirm this, however, additional studies with the involvement of a larger number of patients would be necessary. Sulfurous water still has many hidden secrets, which is why it is worth continuing to study its chemical effects.

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Table 5 Study parameters and the difference between groups

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ANOVA	analysis of variance
ATP	adenosine triphosphate
CI	confidence interval
CMC	carpometacarpal joint
COX-2	cyclooxygenase-2
DIP	distal interphalangeal joint
EQ-5D	EuroQoL five dimensions questionnaire
EQ VAS	EuroQoL visual analogue scale
EULAR	European League Against Rheumatism
g	gram
HAQ	Health Assessment Questionnaire
HDL	high-density lipoproteins
H_2S	hydrogen sulfide
IL	interleukin
L	liter
LDL	low-density lipoprotein
LLLT	low level laser therapy
MCII	minimal clinically important improvement
mg	milligram
MJS	morning joint stiffness
mm	millimetre
MMP	matrix metalloproteinase
NNT	number needed to treat
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
PIP	proximal interphalangeal joint
p value	probability value
RCT	randomized controlled trial
SD	standard deviation
SF-36	Short Form (36) Health Survey quality of life questionnaires
SMD	standardized mean difference
SPADI	Shoulder Pain and Disability Index
SYSADOA	Symptomatic Slow Acting Drugs in Osteoarthritis
TNF-α	tumor necrosis factor alpha
VAS	visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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