CLINICAL EFFECTIVENESS OF CERTAIN PHYSIOTHERAPIES IN MUSCULOSKELETAL DISORDERS

PhD thesis

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Szeged, 2019

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PhD programme titled
Clinical and Experimental Research in Reactivating and Organ-Saving Surgery.
Evidence based physiotherapy

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Szeged, 2019

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor, Professor Tamás Bender for his unstinting, continued support, professional guidance and great encouragement in my research work, not to mention his gentle humour and ever-positive attitude.

I also wish to thank Ferenc Szanyó for his invaluable institutional support and encouragement.

My thanks also go to my previous superiors, Péter Temesvári, László Hodinka and Judit Ortutay, for providing me with edification and their exemplariness.

I am very much obliged to Katalin Hodosi for her expert help with the statistical calculations.

I am also grateful to my colleague Péter Bálint for his professional support in our joint work.

Many thanks to my close colleagues, especially Edina Gömöri and Eszter Kővári for their collaboration, cooperation and professional help.

My special thanks go to the head assistant of the Department of Physiotherapy at the Petz Aladár County Teaching Hospital, Ildikó Horváth Geyerné and also to our physiotherapists, Edit Ravai Raufiné, Katalin Kovacsics Siposné, Mihályné Szalay and Ágnes Péntek Tóthné for their unwavering support in performing physiotherapy.

I am immensely thankful to my dear colleague and friend, Ildikó Katalin Tefner for the invaluable professional and human support she has given me throughout my PhD project.

I am extremely grateful to my parents, grandparents for giving me guidance and for their help and simply for loving me during my studies and work. I would also like to thank my brother for his love and support.

Many thanks to my late husband, who never ceased to encourage me and always placed great trust in me.

I also thank my dear son, Zoli for his love, patience and endurance while he was forced to spend less time with his mother all along my doctoral studies.

LIST OF PAPERS
included in the dissertation

I.
Kiraly M, Varga Zs, Szanyó F, Kiss R, Hodosi K, Bender T: Effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis - a randomized controlled trial. Brazilian Journal of Physical Therapy 2017;21(3):199-205, **IF:1,69**

II.
Kiraly M, Bender T, Hodosi K.: Comparative study of shock wave therapy and low level laser therapy effects in patients with myofascial pain syndrome of the trapezius. Rheumatol Int. 2018 Nov;38(11):2045-2052. doi: 10.1007/s00296-018-4134-x. Epub 2018 Aug 31. **IF:1,952**

III.
Király M, Kővári E, Hodosi K, Bálint P.V, Bender T: The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study. Int J Biometeorol. 2019 Aug 3. doi: 10.1007/s00484-019-01764-4. [Epub ahead of print] **IF: 2,377**

IV.
Király M, Gömöri E, Kiss R, Nógrádi N, Nusser N, Hodosi K, Bender T: Effects of Various Types of Ultrasound Therapy in Hip Osteoarthritis - a Double-blinded, Randomized, Controlled, Follow-up Study – publication in process

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CONTENTS

LITERARY OVERVIEW

Definitions

Physiotherapy is the most ancient medical discipline. It uses physical energy aimed at prevention, treatment and rehabilitation; although its effects are still left unexplored.

With the development of science, the causal treatment with chemicals has come to the front and empirical-based symptomatic treatment has become less significant. Nevertheless, physiotherapy still has an important role in everyday medicine, since with the development of civilisation, the emergence of chronic disorders that are more and more often affecting the active age-group limit the pharmacological treatments primarily used in western medicine due their side effects (especially gastrointestinal, caused by NSAIDs) [1].

The emergence of evidence-based medicine (EBM) enabled us to evaluate and verify the biological effects and modes of action of physiotherapy. It is now common knowledge that prevention and research are just as important elements of physiotherapy as symptomatic and specific treatments.

Physiotherapy has primarily become widespread in the treatment of musculoskeletal disorders; the efficiency of certain physiotherapeutic methods has been proved mainly in this particular area.

Assumed mechanism of action of certain physiotherapies and peloid therapy

Shockwave therapy has been applied since the 1980s in musculoskeletal diseases. The principle of high-intensity shockwave therapy is the production of mechanical energy by high-pressure air. This energy is propagated in the tissues as a longitudinal wave. It assists in revascularization, and by causing micro-functional and micro-structural changes leads to tissue regeneration. Its effective mechanisms still remain a mystery; pain and inflammation relief are attributed to modulatory effects on nitrogen monoxide (NO) and vascular growth factor (VEGF). Shockwave therapy can be used to stimulate angiogenetic factors and microvascular regeneration, such as microcapillary dilatation, which enables increased perfusion in ischemic tissues. Tissue regeneration could be further improved by the increased

prostaglandin production. Its positive effects were confirmed primarily in soft tissue diseases (fasciitis, tendinitis). ESWT has been shown to be effective in promoting the healing of fractures. In 2002 Wang et al. applying ESWT to the left femur of rats 10 mm above the knee at 0.16 mJ/mm^2 in a range of between 250 and 2000 impulses, found, that optimal treatment with ESWT could enhance rat bone-marrow stromal growth and differentiation towards osteoprogenitors presumably by induction of TGF-beta1 [2].

Low Level Laser Therapy (LLLT) or Photobiomodulation is a low intensity light therapy, which uses low-frequency continuous laser of typically 600 to 1000 nm wavelength for pain reduction and healing stimulation. The effect is photochemical not thermal [3]. In 1967 Mester E. et al. demonstrated the phenomenon of “laser bio stimulation” [4]. It enhances tissue regeneration, cell metabolism and preserves homeostasis. In the case of laser therapy pain relief, supposedly due to stimulation of endogenous opioid release, an increase in pain threshold and changes in bradykinin and histamine release are noted [5]. Animal studies have shown that soft laser therapy in myofascial syndrome decreases intramuscular levels of COX-2 and TNF-alpha, while beta-endorphin levels are increased in the serum, muscle, and spinal dorsal root ganglion [6]. Based on other animal models, LLLT is able to reduce the COX-2 mRNA expression in the central nervous system (CNS), which may be a possible explanation for its hyperalgesia decreasing effect [7].

Ultrasound (US) therapy has been used for medical purposes for more than 70 years. Its biological effects are still not exactly known. During ultrasound therapy electrical energy is converted into mechanical energy and heat. It has physical, chemical and biologic effects. Its physical effects are the thermal effect and micro-massage caused by tissue vibration generated by an acoustic wave. Its chemical effects involve oxidizing effect, acceleration of diffusion processes, and tissue pH increase. Its local biological effects include vasodilation, hyperemia, muscle spasm release and enhancing fibroblast activity. The effectiveness of ultrasonic therapy is influenced by its application parameters such as intensity, frequency, continuous or pulsed current, time of irradiation, and type of coupling agent. As air reflects almost 100% of the ultrasonic beam on the transducer/air interface, a suitable coupling medium has to be utilized to allow an effective transmission [8; 9]. Casarotto et al. [10] investigating the transmission properties of four coupling agents (gel, degassed water, mineral oil and petrolatum) found, that gel and water had the highest transmission coefficient and the lowest

reflection. Water as a coupling agent is preferable when irregular body parts and bony prominences with little soft tissue coverage are treated, such as small joints of the hand. Compared to contact mode of treatment, underwater US should be used at a higher intensity to achieve the same tissue temperature [11].

Balneotherapy deals with the effects and medical use of natural mineral waters, gases and peloids on preventive, therapeutic and rehabilitative purposes [12]. Pelotherapy is a considerable part of balneotherapy. Peloids are muddy suspensions with healing properties [13]. Peloids are a mixture of fine-grained materials of natural (geologic and/or biologic) origins, mineral water or sea water, and commonly organic compounds from a biological metabolic activity. Maturation could take place either in natural or in arteficial (e.g. in a tank) environments. During maturation, the growth of microorganisms originates several metabolic products. Medical muds/peloids have a high heat retention and low heat conduction capacity; therefore, they can provoke endogen heat formation (cooling time is rather long; they do not cause skin burn). Some peloids may also contain estrogen, which could be responsible for their analgesic effect. In Hungary, 6 types of medical peloids are used: peloids from Makó, Kolop, Héviz, Hajdúszoboszló, Alsópáhok (Georgikon), and peloid from Austria, Neydharting, which is a shallow peat. Judgement of medical utilisation of mineral waters or peloids is very strict in Hungary, clinical study is needed to gain the curative qualification.

Based on the results of an Italian study, mud bath therapy can decrease the serum level of adiponectin and resistin that may play a protective role in the course of knee osteoarthritis (14). As to chondroprotective effects of mud therapy, it was demonstrated in 2 different studies, that mud compress reduces the urine levels of C telopeptide fragment of collagen type II (uCTX-II) and increases the serum levels of C-terminal crosslinked telopeptide type II collagen (CTX-II), perhaps due to an increase in cartilage turnover induced by thermal stress [15; 16].

Musculoskeletal disorders relevant form physiotherapeutical perspective and the dissertation

In the treatment of musculoskeletal disorders physiotherapy has been used empirically for ages.

Neck pain is a very frequent musculoskeletal disorder with an estimated prevalence between 5.9 and 38.7% in the public [17; 18]. The pain is most frequently due to myofascial pain syndrome (MPS). MPS is caused by direct traumatic events (repeated micro-traumas and repetitive strains), and indirect factors (conditions that cause muscle weaknesses, nutrition disorders, sleep disturbances, endocrine metabolic pathologies, emotional stress). Factors released from damaged muscle fibers and from extracellular fluids are the causes of the pain. Myofascial pain syndrome is frequently found in the background of musculoskeletal disorders; also known as regional pain syndrome, it is mostly localized to the regions of the neck, lumbar spine, and shoulders. MPS is associated with intense and deep pain of muscle fasciae, with one or more myofascial trigger points (MTP), palpable muscle knots (contraction of the taut band), and, consequently, a restricted range of motion [19]. Theres is no specific therapy, so the aims are generally to inactivate painful trigger points, to release muscle tension, and to break the vicious cycle of pain-muscle spasms-ischaemia-pain. Literature data research proves that local injection therapy and various kinds of physiotherapy, such as shockwave therapy, acupuncture, exercise therapies (especially stretching), local heat applications, kinesio taping, and laser therapy are all efficient [20].

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease affecting multiple joints (mainly the wrists and small joints of the hand) with a prevalence of about 0.5-1.0%. The incidence is higher in women than in men, the sex ratio is 2-3:1 [21]. RA is most common in middle-aged people [22]. The disease has a multifactorial origin with genetic and environmental factors. RA affects not only the musculoskeletal system, but also has extraarticular manifestations, which worsen prognosis. Without adequate treatment and care, RA may lead to joint damage and disability.

Therapeutic recommendations for the treatment of rheumatoid arthritis have been made by both EULAR and ACR; guidelines are renewed in every 3 years. Non-pharmacological treatment options such as physical therapy and surgical intervention along with chemical and biological disease modifying anti-rheumatic drugs (DMARDs) can be used to preserve

physical function and improve quality of life in addition to reducing pain and inflammation. Among physical therapy ACR recommend aerobic exercise, especially flexibility and muscle conditioning exercises [23]. Application of cold can relieve joint pain and inflammation (ice packs, topical sprays, ice water), while heat is preferable in case if stiffness and in preparation for exercise (e.g. paraffin, mud packs, ultrasound, electrotherapy, balneotherapy). Based on a meta-analysis by Verhagen et al. in 2015, evidence is insufficient to show the effectiveness of balneotherapy in rheumatoid arthritis because of high risk of bias in most studies and absence of an adequate statistical analysis [24].

Osteoarthritis (OA) is the most prevalent musculoskeletal disease, which burdens not only the patients but also the society. Etiology of this multifactorial disease is still unknown, that is why therapeutical strategies for ease of pain are limited. Incidence rate of symptomatic knee OA in the United States in 2007 was 240 per 100 000 person-years, for hand OA 100 per 100 000 person-years, and for hip OA 88 per 100 000 person-years. [25]. Pathophysiologic processes lead to anatomical damage and functional insufficiency of the joint that may cause limitation of self-care and quality of life [26; 27; 28; 29]. The most frequently affected sites are the hands, knees, hips, and spine [30]. The main symptoms of osteoarthritis include persistent pain, morning stiffness, crepitus, bony enlargement and the decreased mobility of the joint [31].

Kellgren-Lawrence grading scheme is the most-widely used and accepted standard for diagnosis of radiographic OA. It has 5 grade - grade 0: no radiographic features of OA are present; grade 1: doubtful joint space narrowing and possible osteophytic lipping; grade 2: definite osteophytes and possible joint space narrowing; grade 3: multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity; grade 4: large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity [32].

The primary goal of the treatment is to relieve pain at rest and under load, prevent or reduce mobility limitations, and protect the affected joints as much as possible. In the last 20 years, several organizations have made therapeutic recommendations for the treatment of osteoarthritis (EULAR, OARSI, ACR, AAOS, NICE, ESCEO), which have been updated periodically. The recommendations include both drug and non-drug therapies: 1) reducing risk factors, 2) modifying physical activity, 3) using aids, 4) analgesic (non-steroidal anti-inflammatory drugs, acetaminophen, tramadol), 5) intraarticular steroid, 6) physiotherapy, 7)

arthroplasty, 8) hip-conserving surgery, 9) arthrodesis [33]. Among physiotherapies, exercise is ranked number one, however, there is also evidence of manualtherapy, TENS, laser and ultrasound therapies being effective combined with exercise [34; 35; 36; 37]. Based on best-available evidence, the new OARSI (Osteoarthritis Research Society International) guideline, updated in 2014, recommends balneotherapy besides intra-articular corticosteroids and oral non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of multiple-joint osteoarthritis with relevant comorbidities [38].

In the treatment of musculoskeletal disorders pharmacologic and non-pharmacologic therapies both have important roles but also have their own limitations. Choosing treatment modalities, we have to consider not only the disorder itself, but also co-morbidities, financial factors and possible adverse effects.

Evidences on the effects of physiotherapy on musculoskeletal disorders

The efficiencies of soft laser therapy in acute and chronic musculoskeletal pain are reported in medical literature to various extents. The analgesic effect and safety have been proven in temporomandibular disorders and in different joint areas [39; 40]. Based on a current review, many studies have demonstrated analgesic and anti-inflammatory effects provided by photobiomodulation in clinical, as well as in experimental trials. Authors concluded, that LLLT can be a complementary strategy used in symptom management for patients suffering from OA and chronic pain. [41]. The effectiveness of laser therapy in neck pain was studied alone in placebo-controlled trial, in comparison with exercise therapy and acupuncture, and also with combination with other therapeutic modalities [42]. In women suffering from fibromyalgia, photobiostimulation combined with exercise therapy improved qualitiy of life and the pain threshold [40]. In a work by Turkish authors, high-intensity laser therapy was more effective than the placebo in MPS [43].

Pain relieving effects of ESWT have been described in plantar fasciitis, calcifying tendinitis, as well as myofascial pain syndrome. High-energy ESWT was more effective in improving Neck Disability Index (NDI) and neck flexion range of motion, indicating its superiority in functional improvement [44], compared to low-energy ESWT. Shockwave therapy not only decreases pain in myofascial pain syndrome, but also improves motion and

increases pain tolerance. Fang et al. found in their randomized study, that combined electroacupuncture and shock wave therapy directly on trigger points and the surrounding area improved local metabolism, alleviated inflammatory reaction and accelerated the healing of tissue in MPS [45]. Jeon et al. investigating the effects of ESWT against trigger point injection (TPI) combined with TENS in MPS concluded, that ESWT (1500 impulses with low energy flux densitiy of 0.10 mJ/mm^2 per minute) was as effective as TPI and TENS for pain relief and improving cervical range of motion [46]. ESWT also proved to be efficacious treating chronic low back pain. In a Korean study shock wave therapy (1000 shock waves at low energy flux densities of 0.01–0.16 mJ/mm^2) was compared to conservative physical therapy (hot packs, ultrasound and TENS) in chronic low back pain patients. ESWT resulted in better improvement of pain, disability, and depression, than conservative physical therapy [47].

Previous research results have already confirmed the effects of US therapy on pain and function in a range of musculoskeletal disorders [48; 49; 50; 51]. For example Ucar M. et al. [48] observed benefits in patients with temporomandibular joint disorder. Similarly, Boyaci et al. found positive results in patients with knee osteoarthritis [49] by using ultrasound therapy. At the same time, in the majority of the studies, no significant differences were found in outcomes between humans treated with ultrasound or placebo US [52]. Beneficial effects of underwater US in RA has been confirmed. The Ottawa Methods Group found level ‘‘A’’ evidence for pain relief, and level ‘‘C’’ evidence for the decrease in joint swelling and morning joint stiffness [53]. Hawkes et al. compared three treatment groups, all including 10 patients: exercises and wax baths, exercises with ultrasound, and exercises with ultrasound and faradic hand baths. The 3 MHz continuous ultrasound with an intensity of 0.250 W/cm^2 was applied in water to the palmar aspect of the hand for 3 minutes, five times a week, for 3 weeks. These authors did not find significant differences between the three groups with regard to pain, grip strength, proximal interphalangeal joint circumference, articular index, range of motion or level of activity [54]. In the study by Konrád, the effects of underwater US therapy (0.5 W/cm^2 continuously, for ten minutes on alternate days for 3 weeks) were compared to placebo treatment in 50 RA patients. Significant improvement in the number of tender and swollen joints, joint stiffness, and dorsiflexion of wrists were reported in patients receiving ultrasound therapy, as compared to sham treatment [55].

The effectiveness of ultrasound therapy in OA has low evidence. It is hard to compare the numerous study designs and their conclusions due to the non-uniform treatment techniques and parameters (intensity, frequency, dose) [56]. Its beneficial effect on pain relief and movement function has been confirmed in knee osteoarthritis [57].]. In 2019, a meta-analysis that had processed the data of 15 RCTs, recommends ultrasound therapy combined with other physiotherapy in knee osteoarthritis, since studies have not confirmed the superiority of ultrasound therapy. Unfortunately, there is no study so far that would confirm the effectiveness of ultrasound therapy in hip OA as monotherapy [58]. In a study from 2010, ultrasound in combination with conventional physiotherapy reduced pain, and improved function and quality of life in hip OA more than physiotherapy alone [59]. Muftic et al. demonstrated that in case of chronic musculoskeletal pain, the continuous ultrasound therapy reduced pain regardless of the dose and intensity (one group received therapy at the intensity of 0.8 W/cm^2 for 4 minutes, another group received therapy at the intensity of 0.4 W/cm^2 for 8 minutes). For those patients receiving therapy at lower intensity, the degree of pain reduction correlated negatively with BMI (Body Mass Index), while age, sex and the location of pain showed no association with pain reduction [60].

The effectiveness of balneotherapy is supported by the most evidence in respect of the management of patients with osteoarthrosis (knee OA in particular). Randomized, controlled studies have shown that balneotherapy, in the long term, reduces the pain caused by knee osteoarthritis and improves the function [61]. A Hungarian working group has found that balneotherapy compared to tap water has more favorable effects in knee OA (pain, movement function, quality of life) [62]. A French multicentre, randomised, prospective clinical study showed that balneotherapy combined with exercise and conventional medical treatment improved function in knee osteoarthritis more significantly than exercise and pharmacological treatment alone [63]. The combination of sulfur bath and exercise showed similar results among patients with hip osteoarthritis: pain and movement function improved significantly compared to those who did exercise only [64].

Pelotherapy plays an important role in the local treatment of knee osteoarthritis [65]. In 2008, Turkish authors compared direct mud pack and nylon-covered mud pack on knee OA and revealed a better outcome in the directly applied mud group [66]. Similar results are published by Hungarian authors investigating the effects of Héviz mud on patients with hand

osteoarthritis. The treatment group received mud applied directly to both hands, whereas the control group received mud to both hands with a nylon layer that separated the skin from the mud. Both groups showed improvement at the end of treatment and after 16 weeks. However, the patients directly treated with mud, showed a significantly better improvement in some VAS scale parameters compared with the control group [67]. In another Hungarian double-blind RCT, the effects of Neydharting mud pack therapy were evaluated compared with hot-pack with similar physical properties (viscosity, plasticity, adherence to skin, water-binding capacity and colour) to that of the Neydharting mud. The clinical outcome parameters improved in both groups, which can be explained by the similar physical properties. There were no significant differences between the 2 groups, but the improvement in the treated group was greater than in the control group. The need for analgesics and NSAIDs decreased in the control group, while a significant change was observed in the mud-treated group by the follow-up visit. This might indicate a special chemical effect of the mud [68]. A quantitative meta-analysis of 7 studies (410 patients) in 2013 also confirmed the favourable effect of mud therapy on pain relief in patients with knee OA [69]. Fioravanti et al. published notable data about the long-term (12 months) effect of mud bath therapy added to usual treatment in patients with knee osteoarthritis (70). Besides the clinical effects, cost effectiveness of mud therapy is also important (71). In the recent meta-analysis of 12 RCTs, spa therapy and mud therapy are discussed together, and found to be effective in the treatment and in the secondary prevention of knee OA (72).

Assessment of the effects of physiotherapy and the tools of health assessment

Assessment of health status of patients suffering from musculoskeletal diseases include not only past medical history, physical and diagnostic examinations, but also the assessment of pain and quality of life. Validated disease-specific and general health questionnaires can be used to evaluate physical function and quality of life. Pain and disability can be measured by visual analogue scale (VAS). Patient reported outcome (PRO) methods such as questionnaires are the measurements come directly from the patient about their own health, quality of life, or functional status.

The Minimal Clinically Important Improvement (MCII) is the smallest change in measures that signifies an important improvement in a patient's symptom.

Neck Disability Index (NDI)

The questionnaire measures a patient's self-reported neck pain and disability. It includes 10 parts: pain intensity, personal care, lifting objects, reading, headache, concentration, work, driving, sleeping and entertainments. There are six presumptions; the first is given 0 (no disability) and the last presumption has the score of 5. The total maximum score is 50, that represents 100% disability. The lower score represents better outcome. NDI is the most widely used and translated questionnaire for neck pain. It has also been shown to be valid when comparing it to other pain and disability measures [73].

Knee injury and Osteoarthritis Outcome Score (KOOS)

This questionnaire is a self-administered instrument that was developed as an extension of the WOMAC Osteoarthritis Index. Knee injury most often includes damage to the ligaments, the menisci, or the cartilage. These injuries are frequently combined, and often result in the later development of OA. KOOS can be used for short-term and long-term follow-up of knee osteoarthritis. Its validations have been carried out in different populations with varying diseases and durations and at varying ages and activity levels. The KOOS is composed of five separately scored subscales: pain, various symptoms (swelling, restricted range of motion, mechanical symptoms), activities of daily living (ADL), function in sport and knee-related quality of life (QOL). A Likert scale is used and all items have five possible answer options scored from 0 (No Problems) to 4 (Extreme Problems) and each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0-100 scale, with zero representing extreme knee problems and 100 representing no knee problems. Scores between 0 and 100 represent the percentage of total possible score achieved [74].

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The WOMAC is a specific self-administered survey used in hip and knee osteoarthritis. It evaluates functional impairment in three dimensions (5 items for pain, 2 for stiffness, and 17 items for physical function). Items can be rated on a five-level Likert scale (no difficulty to

extremely difficult) or using a 0-100 mm visual analogue scale (VAS) or an 11-point numerical rating scale (NRS from 0 to 10). It is valid, reliable and sensitive to detect clinically-important changes in health status following a variety of interventions (e.g. pharmacologic, physiotherapy, surgical). In our study we prefered visual analogue scale format (WOMAC VA 3.0). The total score is calculated by summating the scores for each dimension. The range of possible subscale scores for the three dimensions is as follows: pain=0-500, stiffness=0-200, physical function=0-1700. The higher the score, the greater is the functional impairment. Based on the report of Tubach et al. relative MCII for knee and hip osteoarthritis are between: -26% and -21,1% for WOMAC function subscale score [75]. The WOMAC is validated in Hungarian [76].

Lequesne Algofunctional Index

Is is a disease-specific questionnaire. It includes three sections with a total of 11 questions; five questions pertaining to pain or discomfort, 2 questions about maximum walking distance with or without walking aids, and 4 questions about function in daily living. Each section has a score ranging from 0 to 8, resulting in a total score between 0 and 24. The sum of all questions is the overall Lequesne OA index score. Higher scores indicate a worse health condition. A sum between 1 and 4 represents a small disability, 5-7 intermediate, 8-10 serious, 11-13 very serious and greater than or equal to 14 extremely serious.

Health Assessment Questionnaire (HAQ)

The HAQ disability index (HAQ-DI) was developed in 1978 for the measurement of outcome in patients with various rheumatic diseases (e.g. rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, lupus, scleroderma, fibromyalgia) [77]. It has eight categories: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. Discomfort is determined by the presence of pain and its severity. Each section has 2 or 3 questions and each question is scored from 0 (without any difficulty) to 3 (unable to do). The section receives the worst score within the section. If an aid or device is used or the patient requires help from another individual, then the minimum score for that section is 2. If the section score is already 2 or more, then no modification is made. Scores between 0-1 represent mild to moderate difficulty, between 1-2 represent

moderate to severe disability, and between 2-3 indicate severe to very severe disability [78]. The HAQ-DI is validated in Hungarian [79].

The EuroQoL five dimensions questionnaire (EQ-5D)

EQ-5D is a standardised measure of health status. There are three versions of the instrument: EQ-5D-5L, EQ-5D-3L, EQ-5D-Y. For over 25 years, they have been widely used in clinical trials, population studies and real-world clinical settings. EQ-5D-3L on the one hand has a descriptive system questionnaire with five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), where patients are asked to rate their health problems on 3 levels (no problems, some problems, extreme problems). On the other hand it contains a selfrating of health status using a visual analogue scale (EQ VAS) ranging from 0 to 100 (where 0 means the worst and 100 means the best health status). 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 may be converted into a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population of a country/region. This index value is obtained from a time trade-off (TTO) valuation technique [80].

Short Form (36) Health Survey quality of life questionnaires (SF-36)

It is a general, self-administered survey on the quality of life. It consists of 8 domains (physical functioning, role physical, role emotional, vitality, mental health, social functioning, bodily pain, and general health), the values of which are transformed into a scale from 0 to 100. The lower the value, the greater the impairment.

The questionnaire has been found to be reliable, valid, and responsive for a variety of medical diagnoses. It has been demonstrated to be more sensitive to clinical change in the lower extremities compared with the upper extremities [81; 82]. In SF-36 Version 2.0 the two role functioning scales have been changed from dichotomous scales to five point response categories thereby increasing score precision without increasing respondent burden [83]. The SF-36 is validated in Hungarian [84].

AIMS OF THE THESIS

I. To evaluate the effects of mechanotherapy and phototherapy in musculoskeletal disorders, especially in regional pain syndrome.

I./1. To evaluate and compare the effects of extracorporeal shock wave therapy and low level laser therapy in myofascial pain syndrome of the trapezius.

II. To evaluate the effects of thermotherapy in musculoskeletal disorders

II./1. To evaluate the effects of underwater ultrasound therapy in patients with rheumatoid arthritis compared to placebo treatment.

II./2. To evaluate the effects of various types of ultrasound on osteoarthrits of the hip compared to placebo treatment.

II./3. To evaluate and compare the effects of Tiszasüly and Kolop mud pack therapy on osteoarthritis of the knee.

COMPARATIVE STUDY OF SHOCK WAVE THERAPY AND LOW LEVEL LASER THERAPY EFFECTS IN PATIENTS WITH MYOFASCIAL PAIN SYNDROME OF THE TRAPEZIUS.

Objectives

The efficiencies of soft laser therapy and shockwave therapy in myofascial pain syndrome on pain and function are reported in medical literature to various extents. Both therapies were investigated compared to other physiotherapies but only one literature report, published by Taheri et al. is known to compare shockwave therapy and laser therapy in neck myofascial pain syndrome (however in that study, both groups also practised stretching exercises) [85].

Our aim was to compare the effects of shockwave therapy and laser therapy on pain tolerances, neck functionality, and quality of life in patients suffering from myofascial pain syndrome of the trapezius.

Protocol and study parameters

Design

In this randomized, assessor-blinded, follow-up study we evaluated the effects of soft laser therapy and shockwave therapy on myofascial pain syndrome of the neck.

Participants

The study was conducted at the Physiotherapy Devision of Petz Aladár County Teaching Hospital's Rheumatology Outpatient Clinic.

Patients with the following conditions were enrolled to the study: patients over 18-years of age diagnosed with myofascial pain syndrome according to Simon's Diagnostic Criteria (5 major, 1; regional pain, 2; referred pain, 3; a taut band, 4; a tender point in the taut band, 5; restricted range of motion, and one of minors, 1; pain complaints reproduced by pressure on the tender spot, 2; a local twitch response, 3; and relief of pain with injection, or by stretching) with persistent neck and/or shoulder regional pain, for at least 8-weeks

preceeding inclusion (chronic pain). Patients were not allowed to receive physical therapy, or any local trigger point injection for 3-months prior to starting the study [86].

Exclusion criteria were: pain persisting for less than 8-weeks in the neck or shoulder (acute or subacute pain), physiotherapy, or local trigger point injections of the involved regions within 3-months' time, blood parameter discrepancies (blood counts or erythrocyte sedimentation rates), infection, febrile states, symptoms of cervical radiculopathy, untreated hypertension, anticoagulant therapy or coagulation disorders, any cervical spine surgery in the medical history, metal devices, and implantations.

Participants were patients under regular outpatient care recruited by the rheumatologist of the Rheumatology Outpatient Clinic of Petz Aladár County Teaching Hospital. The study was conducted between February 2016 and September 2017.

Study participants received written information and signed the Informed Consent Form before the initiation of the study. The study was approved by the Regional Research Ethics Committee of Petz Aladár County Teaching Hospital (approval number:76-1-23/2015), and is registered in ClinicalTrials.gov (NCT03436459).

Intervention

Soft laser treatment (Group 1) was administered once daily, altogether 15 times (on 15 work days) on the trapezius muscle and on trigger point (PR999 4W scanning laser; Medical Italia; regions around the trigger point were treated with 2000 Hz (800 mW), 3 J/cm^2 for 2 min; the palpable trigger point was treated with 5000 Hz (2000 mW), 9 J/cm^2, for 2 min). In the shockwave arm (Group 2), patients received therapy once weekly, altogether three times to the trigger point and its vicinities (BTL-6000 SWT Topline Power; 1000 impulses in the region of the trigger point, 1.5 bar, 10 Hz, energy density: 0.25 mJ/mm^2, 15 mm treating head diameter, followed by 1000 impulses, 2 bar, 10 Hz, energy density: 0.25 mJ/mm^2, using a 15 mm treating head diameter to the trigger point).

Outcomes

Outcome measures were recorded by a rheumatologist before therapy (Week 0), after the last treatment session (Week 3), and at the end of the follow-up period, at Week 15. During each visit, we applied a 100 mm visual analogue scale to assess rest/spontaneous pain

level, we measured the functional impairment (Neck Disability Index - NDI), quality of life using SF-36, and the need for painkiller medication. At the start of the study, we applied a dolorimeter [BASELINE (Fabrication Enterprises, Inc.)] to determine pain tolerance in the upper parts of both trapezius muscles [pressure value in kg/cm^2, whereby a maximal (VAS:100 mm) pain is signalled by the patient]. In subsequent visits, by applying the same standarized pressure as at the baseline visit, we asked the patients to indicate their pain on 100 mm VAS. At Week 3 and Week 15 visits patients also evaluated their status/subjective well-being in a 4-grade Likert scale (1: significantly improved; 2: improved; 3: unchanged; 4: worsened). Patients were not to receive any other physiotherapy during the 3 months follow-up period.

Randomization and blinding

A concealed allocation random assignment of the enrolled patients to the treatment groups was performed by an independent study technician (using a computer software) who did not meet any of the patients and did not participate in the course of the study either. Neither the testing rheumatologist who examined the patients and measured the outcome parameters, nor the statistician was aware of the treatment assignments, nor the randomization process of the patients from start to end of the study.

Statistical analysis

The statistical analysis was processed with IBM SPSS 24 software. The data are expressed as the mean ± SD. Data distribution was investigated with the Kolmogorov-Smirnov test. We found a normal distribution for age and NDI; here we used the independent patterned t test and paired t test. Other data were calculated by Mann-Whitney and Wilcoxon test. The measurements of differences between groups were carried out by either an independent t test or Mann-Whitney test. The difference between the groups was expressed using mean differences, with a 95% confidence interval (95% CI). Chi-squared test and Fisher's exact test were used for categorical data. Missing data were imputed using the last observation carried forward (LOCF) method. P values < 0.05 were considered significant. We did not use an intention to treat analysis (ITT) approach.

Results

Altogether, 70 patients were included and 61 patients were randomized. Six patients did not meet inclusion criteria, and three patients revoked their consent. Following randomization, 61 patients were grouped to treatment with soft laser (n=31, mean age: 62.62 ± 9.62-years; male/female: 4/27) or shockwave (n=30, mean age 57.26 ± 14.31-years, male/female: 3/27) (**Figure 1**). There were no significant differences among the two groups in age or gender proportions.

During the follow-up one patient in Group 1 was lost due to lack of complience. Her data were handled using the last observation carried forward method.

Both groups demonstrated similar changes during the study in all parameters.

Resting pain significantly decreased in both groups after therapy and at a 15 weeks follow-up; immediately after therapy patients in Group 2 and at 3 months post-therapy patients in Group 1 demonstrated significantly better improvement compared to each other.

Pressure pain (a.k.a. pain tolerance) also significantly improved in both trapezius muscles in all treatment groups, as recorded during the visits, but here improvement was significantly higher in the shockwave therapy group at the 3rd week and at the 15th week. Comparing results on the right and left side of the musculature, shockwave therapy group patients demonstrated a higher improvement in the pressure pain on the left side, while no such difference was observed in the laser group.

Neck functionality impairment significantly improved in both the laser and the shockwave group for the Week 3 and Week 15 visits, and the amplitude of change was significantly higher in the shockwave group.

The SF-36 QoL questionnaire domains of physical function, energy, and pain showed significant improvements in both groups immediately after therapy and at Week 15. Shockwave therapy patients improved significantly in all eight parameters in all visits, while patients in the laser group only had five improved domains out of eight in total: physical function, physical role functioning, vitality, social role functioning, and bodily pain. When comparing changes between the two groups, both at Week 3 and Week 15, improvement in the shockwave therapy group was significantly higher, except for emotional wellbeing on week 3 and physical health at week 15 (**Table 1**).

Patients reported the improvement of their own status (a.k.a. subjective well-being) in both groups using the 4-grade Likert scale; in both groups 86.6% of patients improved, while 13.3% of them reported no changes after the therapy and at Week 15 (**Table 2**).

During the follow-up, it was noted that myelogelous knots had disappeared in approximately half of all patients in both groups.

In both groups, less than 25% of patients needed medication (analgesics, antirheumatics, or muscle relaxants) during the study. The majority of medicated patients took the medication for less than 1 week's time (**Table 3**).

No adverse events were noted or recorded during this study.

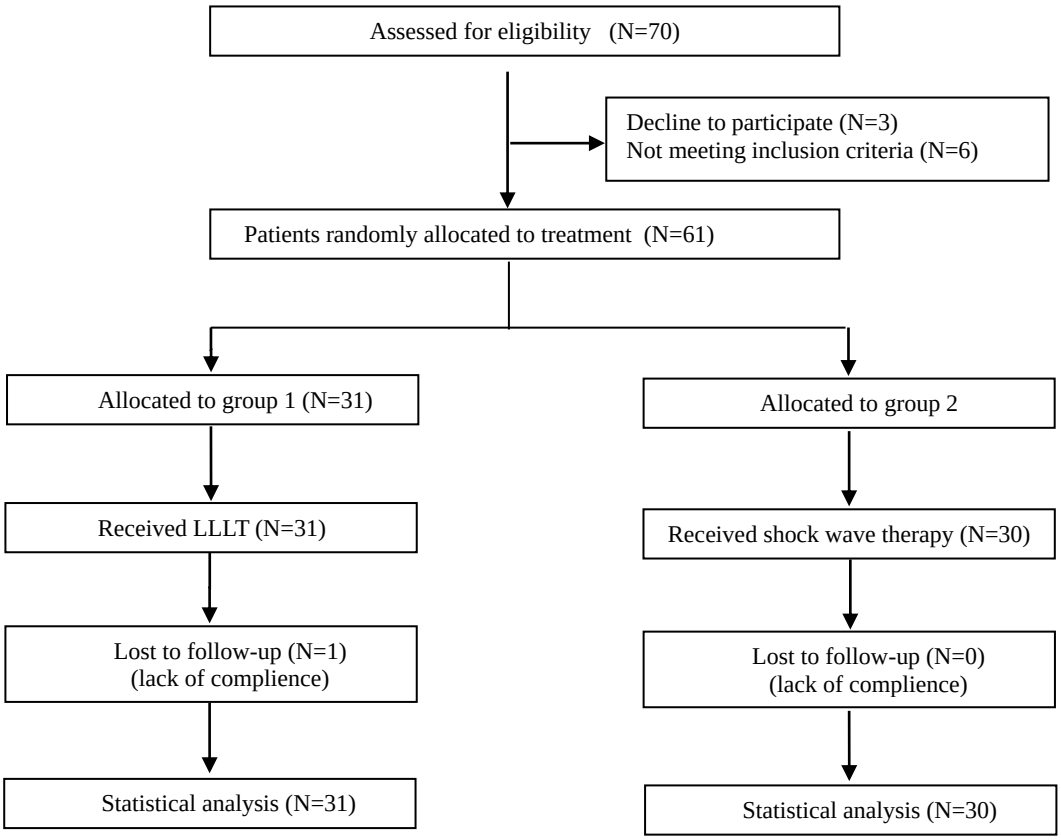

Figure 1 Participant flow to show the effects of LLLT and ESWT on pain, function and quality of life in patients with myofascial pain syndrome

Discussion

According to the results of our study both low level laser therapy and shockwave therapy have a beneficial effect on the clinical parameters and quality of life of patients with myofascial pain syndrome of the trapezius.

A 2013 meta-analysis reports that moderate evidence suggests that LLLT in chronic neck pain has improving effects on pain, vital function, and quality of life for short term (3 months) and also in mid-term (6 months) [42]. In our study, LLLT significantly improved resting and pressure pain, pain tolerance, neck function, and quality of life.

According to our results, patients receiving shockwave therapy demonstrated significantly better changes in all outcome measurements. It has been affirmed, that shockwave therapy not only decreases pain in myofascial pain syndrome, but also improves motion and increases pain tolerance as detailed in Literary overview [45; 46]. In a Korean study (with low patient numbers) patients received four shockwave therapies in 2 weeks in the upper trapezius muscle (0.056 mJ/mm^2, 1000 impulses) with good therapeutic effect [87].

We cannot currently find an exact reason for the higher analgesic effect using shockwave therapy, but we can postulate that the painful effects of therapy could have a role in that. Pressure pain was sensed differently in the left and right trapezius muscles in patients of the shockwave therapy, which we attribute to random variation or the small patient number. Physical functioning, vitality, social role functioning, and bodily pain improved the most among QoL domains in both groups in our study. This can be attributed to pain relief and trigger point inactivation effects of laser and shockwave therapies.

In our study, less than 25% of patients were taking medication for analgesia and muscle relaxation. As the constitution of patients taking medication, there was a difference in each follow-up visit, and the duration of pharmacotherapy was short. We cannot declare a relationship between changes in patient numbers, and the efficiency of therapy.

Our study is the second in the literature that compares shockwave therapy and laser therapy in neck myofascial pain syndrome. In the study by Taheri et al. during laser therapy, a Ga–AL–As laser was applied (6 J/cm^2 energy, mean power of 100 mW), while shockwave therapy was performed with 1000 impulses, 3 J/m^2 energy density, and 10 Hz of frequency. Both groups demonstrated improvement, but in their cases, laser therapy patients improved

significantly better, which is contrary to our findings [85]. In our study, higher laser power and higher energy density shockwaves were applied.

Limitation of the study

Patient number is one of the limitation of our study; increasing the number of study participants would be desirable in further studies.

The starting values were not homogeneous and the tests filled out by the patients were subjective (e.g. they may judge the same pain differently). There was also a high SD in age, which could have been narrowed by the inclusion criteria; but in that case the number of patients would have been low.

Literature reports are ambiguous as to the frequency and duration of therapy sessions; although a three times ESWT was efficient, increasing frequency could increase the clinical efficiency even further. In laser therapy, one parameter (power) was taken into account, while a power increase and multi-local irradiation of trigger points could also increase the effect. In our study the follow-up period was only 15 weeks, so the mid-term and long-term effects could not be demonstrated.

This chapter was published during my PhD work.

Kiraly M, Bender T, Hodosi K.: Comparative study of shock wave therapy and low level laser therapy effects in patients with myofascial pain syndrome of the trapezius. Rheumatol Int. 2018 Nov;38(11):2045-2052.

Measured clinical variables	Visit 0 (Week 0) mean±SD	Visit 1 (Week 3) mean±SD	Visit 2 (Week 15) mean±SD	Between group differences at visit 1-0 (95% CI)	p	Between group differences at visit 2-0 (95% CI)	p
VAS pain at rest							
Group 1	46.06±18.02	25.16±18.63	22.42±21.39	1.030 (-8.116-10.176)	0.822	-1.345 (-14.600-11.910)	0.840
Group 2	47.70±20.75	25.7±25.56	25.40±22.67				
VAS pressure pain right							
Group 1	100	60.65±21.60	56.16±21.17	4.078 (-7.135-15.292)	0.470	9.561 (-3.056-22.179)	0.135
Group 2	100	56.57±22.17	46.60±27.74				
VAS pressure pain left							
Group 1	100	61.65±24.70	59.29±21.65	14.911 (2.641-27.182)	0.018	17.190 (4.326-30.055)	0.010
Group 2	100	46.73±23.14	42.10±28.23				
NDI							
Group 1	15.55±6.09	10.51±7.28	10.01±6.91	0.660 (-1.933-3.253)	0.612	1.072 (-2.110-4.254)	0.503
Group 2	16.08±7.58	10.38±6.90	9.47±5.65				
Physical functioning (SF-36)							
Group 1	62.26±16.47	69.03±18.86	69.84±18.46	-2.059 (-9.044-4.926)	0.558	-2.419 (-11.104-6.265)	0.579
Group 2	67.83±20.12	76.67±18.30	77.89±19.19				
Role functioning/physical (SF-36)							
Group 1	45.16±36.18	59.68±41.67	56.45±41.32	-13.817 (-31.549-3.915)	0.124	-19.543 (-37.894--1.192)	0.037
Group 2	40.00±35.72	68.33±37.68	70.83±37.18				
Role functioning/emotional (SF-36)							
Group 1	62.35±40.18	63.43±39.76	62.35±43.67	-12.259 (-32.903-8.345)	0.239	-17.779 (-40.180-4.622)	0.118
Group 2	59.99±41.43	73.32±36.52	77.77±37.48				
Energy/fatigue (SF-36)							
Group 1	60.19±18.95	66.29±16.53	68.87±17.50	-7.237 (-15.439-0.966)	0.083	-7.823 (-17.432-1.787)	0.109
Group 2	53.17±19.00	66.50±16.30	69.67±13.89				
Emotional well-being (SF-36)							
Group 1	72.90±19.18	74,84±19,38	74,84±20,11	-8.665 (-15.375—1.954)	0.012	-6.331 (-14.538-1.875)	0.128
Group 2	69.20±16.94	79.80±14.60	77.47±14.72				
Social functioning (SF-36)							
Group 1	73.39±20.61	81.05±17.93	79.44±20.04	-2.339 (-12.959-8.281)	0.662	-5.618 (-15.542-4.306)	0.262
Group 2	72.50±17.80	82.50±17.25	84.17±19.40				
Pain (SF-36)							
Group 1	50.64±15.07	62.82±19.93	69.11±17.94	-6.489 (-15.100-2.121)	0.137	-5.116 (-16.704-4.472)	0.252
Group 2	44.50±20.12	63.17±17.26	69.08±18.53				
General health (SF-36)							
Group 1	51.94±15.37	55.97±17.82	56.29±17.84	-1.058 (-7.649-5.513)	0.747	-2.078 (-9.398-5.241)	0.572
Group 2	52.23±20.83	57.33±20.96	57.46±19.10				

Table 1 Mean ± SD at baseline and at the end of Week 3 and Week 15 for the two study groups (Group 1: patients receiving low-level laser therapy and Group 2: patients receiving extracorporeal shockwave therapy) and between-group differences at the end of Week 3 and Week 15 show the effects of LLLT and ESWT on pain, function and quality of life in patients with myofascial pain syndrome

	Outcome measure 0		Outcome measure 1		Outcome measure 2		p^a 0-1	p^a 0-2	p^a 1-2
	mean±SD	p	mean±SD	p	mean±SD	p			
Patient impression (1-4)									
Group 1			2.00±0.52	0.078	1.73±0.69	0.283			0.059
Group 2			1.73±0.69		1.90±0.61				0.660

Table 2 Changes in degree of patients' improvement in the study groups show the effects of LLLT and ESWT on pain, function, and quality of life in patients with myofascial pain syndrome

	Outcome measure 0 (Week 0)		Outcome measure 1 (Week 3)		Outcome measure 2 (Week 15)	
	n (%)	p	n (%)	p	n (%)	p
Medicine						
Group 1 (n=31)	4 (13%)	0.508	4 (13%)	0.389	8 (26%)	0.384
Group 2 (n=30)	6 (20%)		7 (23%)		5 (17%)	
Medicine <1 week						
Group 1 (n=31)	4 (13%)	1.000	4 (13%)	1.00	7 (23%)	0.147
Group 2 (n=30)	4 (13%)		3 (10%)		2	
Medicine >1 week						
Group 1 (n=31)	0	-	0	-	1	0.354
Group 2 (n=30)	2		4 (13%)		3 (10%)	
Myogelosis						
Group 1 (n=30)	12 (40%)	0.186	8 (27%)	0.153	6 (20%)	0.587
Group 2 (n=26)	15 (58%)		12 (46%)		7 (27%)	

Table 3 Changes in the number of patients taking medicine, and the number of patients having myogelosis in both treatment groups show the effects of LLLT and ESWT on pain, function and quality of life in patients with myofascial pain syndrome.

EFFECTS OF UNDERWATER ULTRASOUND THERAPY ON PAIN, INFLAMMATION, HAND FUNCTION AND QUALITY OF LIFE IN PATIENTS WITH RHEUMATOID ARTHRITIS - A RANDOMIZED CONTROLLED TRIAL.

Objectives

Previous research results have already confirmed the effects of US therapy on pain and function in a range of musculoskeletal disorders [48; 49; 50; 51], but there has not been any evidence that ultrasound treatment can alter inflammation.

The aim of this randomized, double-blinded, controlled clinical trial was to determine the effects of underwater US therapy in patients with RA; analgesic and anti-inflammatory effects (primary endpoint), and effects on joint function and quality of life (secondary endpoint). In case of the controll group, the US device was not turned on.

Protocol and study parameters

Design

In this randomized, double-blinded, controlled, follow-up study we evaluated the effects of underwater ultrasound in patients with moderately active rheumatoid arthritis.

Participants

The study was conducted at the Physiotherapy Division of the Rheumatology Outpatient Clinic of Petz Aladár County Teaching Hospital in Hungary.

Patients with the following criteria were enrolled to the study: patients over 18 years of age, mild-to-moderate (DAS28 > 3.2 and <5.1) rheumatoid arthritis meeting the American College of Rheumatology (ACR) diagnostic criteria. Further inclusion criterion was a stable-dose pharmacotherapy (DMARDs therapy, NSAIDs, steroids) given for at least 2 months. Patients were not allowed to receive physical therapy treatments for 1 month prior to starting the study.

Exclusion criteria included other concomitant autoimmune diseases, stable-dose pharmacotherapy for less than 2 months, and conditions contraindicating US therapy (infection; fever; osteomyelitis).

Participants were patients under regular outpatient care recruited according to the study protocol by the rheumatologists of the Rheumatology Outpatient Clinic of Petz Aladár County Teaching Hospital. Underwater ultrasound therapy and sham ultrasound were performed at the local Physiotherapy Department.

Patients were informed verbally about the study procedures, read the Patient Information Sheet and asked to sign an Informed Consent Form. The study was approved by the Regional Research Ethics Committee, Győr, Hungary (approval number: 76-1-7/2013) and registered in ClinicalTrials.gov (registration number: NCT02706028).

Intervention

Patients in the ultrasound group received 10 applications (10 working days) of continuous underwater US therapy (35-36 Celsius degree tap water; with the transducer at a distance of 2 cm from the treated surface) intensity of 0.7 W/cm^2 SATA (spatial average - temporal average [continuous]), for 7 min to the palmar and dorsal aspects of each hand and wrist using a 830 kHz ULTRON home OE-302 device with treatment head size of 4.2 cm^2 (BNR: max.5:1, energy: 1234.8J, power: 2.94W). Each side of the hand and the wrist were treated in the same treatment period. The control group received sham treatment (the US device was not turned on) during the 10 sessions for 7 min per session.

The study was considered completed and data were analyzed, if the patient participated in at least 80% of the treatment sessions and attended the follow-up visits. During the 3-month follow-up period, patients were asked not to have any physical therapy treatment or to change their medication. (The analgesic or anti-inflammatory drugs were documented).

Outcomes

The outcome parameters were recorded by 1 blinded rheumatologist before the initiation of treatment (at Week 0 – Visit 1), immediately after the 10 treatment sessions (at the end of Week 2 – Visit 2), and 3 months later (at Week 14 –Visit 3).

At inclusion, the age and gender of patients as well as duration of the disease and DMARD therapy (in years) were recorded. Inflammatory laboratory parameters (i.e. ESR, CRP - these are the most current used parameters for inflammation considering their costs), disease activity (measured using DAS28), quality of life (measured using HAQ), number

of painful and swollen joints, severity of pain at rest recorded on a 100 mm VAS, and duration of morning joint stiffness (in minutes) were assessed at each visit. Physical function was assessed by measuring range of motion in the wrists (in degrees), degree of fist making (based on nail tilting, 3 grades were used: 0: insufficient, 1: incomplete, 2: complete); and hand grip strength (in kg) was measured with a JAMAR dynamometer. At the end of treatment period and at the Month 3 follow-up visit, patients evaluated their own condition on a 4-grade scale (1: significantly improved, 2: improved, 3: unchanged, 4: worsened).

Randomization and blinding

A concealed allocation random assignment of the enrolled patients to the treatment groups was performed (using an Excel computer program) by an independent investigator who had never met the patients and was not otherwise involved in the study procedures. The study was double-blinded, as neither the study participants nor the testing investigator (a rheumatologist) knew the treatment assignments. The statistician was not involved in the randomization procedures.

Statistical analysis

Statistical analysis was performed by using the IBM SPSS 20 software. The statistical power was 60%. Normality was verified with the Kolmogorov-Smirnov test. The difference between the groups was expressed using mean differences and 95% confidence interval (95% CI). Chi-squared test was used for categorical data. Missing data was imputed using the Last Observation Carried Forward (LOCF) method. We did not use an intention to treat analysis (ITT) approach.

Results

Sixty patients were screened and 50 patients were enrolled into the trial. Eight patients did not meet inclusion criteria, and two patients refused to sign the Informed Consent Form. 50 patients were randomized to the US group and the control group. Two patients did not start treatment and were excluded from the analysis (i.e. an intention to treat analysis was not performed) (**Figure 2**). Forty-eight patients completed the study i.e. attended at least 80% of

the treatment sessions; 25 patients in the US group (mean age: 63.24±11.04 years) and 23 patients in the control group (mean age: 62.83±7.25 years). Regarding demographic data, disease duration, and background therapy duration, the groups were similar at baseline (**Table 4**).

Inflammatory parameters, including ESR and CRP decreased in the US group at each successive visit compared to baseline. In the ultrasound group, only CRP levels showed a significant improvement (i.e. a decrease) immediately after treatment (Week 2) and at the follow-up visit (Week 14) when compared to the control group (CRP: mean between-group difference visit 2-1 =−5.77, 95% CI =−10.86 to −0.68, mean between-group difference visit 3-1 =−5.07, 95% CI =−10.13 to −0.01). Disease activity index decreased in both groups at the end of treatment and at Week 14 compared to baseline, but the difference between the groups was not significant (DAS28: mean between-group difference visit 2-1 =−0.18, 95% CI =−0.61 to 0.25, mean between-group difference visit 3-1 =−0.37, 95% CI =−0.84 to 0.09).

Pain sensation decreased in both groups compared to baseline, and this decrease was significant in the US group at the end of Week 2 (VAS: mean between-group difference visit 2-1 =−8.35, 95% CI =−16.12 to −0.58).

No substantive changes were observed in the duration of morning joint stiffness, the number of tender and swollen joints in any of the groups at any visits, and no difference was found between the groups.

Quality of life measured using HAQ improved in the US group, but the difference between the two groups was not significant.

Extension and flexion of the wrists improved non-significantly from baseline in the US group and did not change in the control group. In the ultrasound group, only left wrist extension showed a significant improvement at Week 2 when compared to the control group (mean between-group difference visit 2-1 = 4.35, 95% CI = 1.09 to 7.60). The degree of fist making did not show any changes in any of the groups. Hand grip strength slightly increased in the US group, but the difference between the two groups was not statistically significant.

Patients of both the US group and the control group considered their own condition improved at the end of treatment and at the Week 14 follow-up visit. Changes in the studied parameters and statistical data are shown in **Tables 5 and 6**. No adverse events were observed during the study.

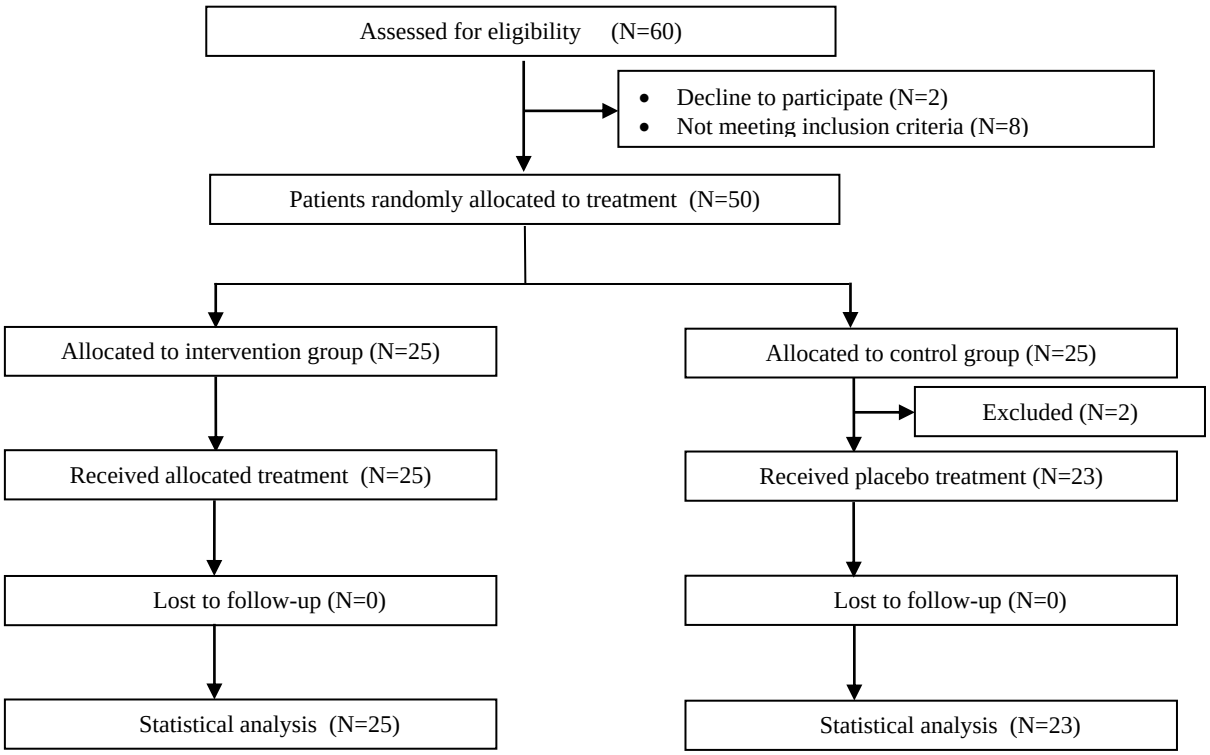

Figure 2 Participant flow to show the effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis.

Discussion

Our randomized, double-blinded, placebo-controlled study showed, that underwater ultrasound therapy has beneficial effect on the hand function and qualitiy of life of patients with rheumatoid arthritis. Not only the secondary endpoint parameters (HAQ and hand function), but also the primary endpoint parameters (i.e. pain and inflammation) showed significant improvement in the short term.

Pain measured on a VAS also decreased, although to a lesser extent, in the control group, which could be due to placebo effect [88]. The anti-inflammatory effect could be supposedly due to vasodilation caused by the thermal effect. Cruz et al. found, that 1 MHz continuous (0.4 W/cm^2 SATA), or pulsed (20% duty cycle, 0.08 W/cm^2 SATA) ultrasound therapy improved endothelial function in humans, which has an anti-inflammatory vascular effect.

They postulated a mechanical effect, which stimulated nitrogenmonoxid production resulting in vasodilation [89]. According to Watson, the overall influence of US in the inflammed tissue was pro-inflammatory, which enabled tissue repair [90]. This could explain the results of Hashish et al. testing the value of US for reducing postoperative inflammation. They described a placebo-mediated mechanism with maximum anti-inflammatory effect in the placebo group [91]. In the present study, the decrease of CRP in the control group could have been due to the normal tissue repair, which was enhanced by the therapy in the ultrasound group.

In case of underwater therapy, water is a coupling medium that allows ultrasound transmission to the biological tissue. Clinical studies have confirmed the beneficial effects of underwater US therapy in RA (see Literary overview). In our study we didn't find any significant difference between the two study groups in tender and swollen joint count, disease activity score or the duration of morning joint stiffness.

Wrist extension improved more than flexion, which is explained by the nature of the disease (i.e. impairment of extension is more pronounced during the course of the disease). Favorable changes in quality of life were only short-term. In 2002, based on data gathered from the Cochrane Database, Casmiro et al. found that in rheumatoid arthritis, US therapy increased hand grip strength, to a lesser degree decreased the tender and swollen joint counts, morning hand stiffness and improved wrist dorsal flexion. US therapy combined with other physical therapy methods was not better than US therapy alone [92]. In the present study, no significant changes in hand grip strength were found, which could be explained by the long (more than 10 years) disease duration.

Limitation of the study

The weakness of our study was the small sample size and lack of intention to treat analysis. Extention of our study (i.e. more patients) might increase the power of the study and could provide more precise results.

This chapter was published during my PhD work.

Kiraly M, Varga Zs, Szanyó F, Kiss R, Hodosi K, Bender T: Effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis - a randomized controlled trial. Brazilian Journal of Physical Therapy 2017;21(3):199-205.

Variable	**Ultrasound group (n=25)**	**Control group (n=23)**
Age (years)	63.24 (11.04)	62.83 (7.25)
Disease duration (years)	13.04 (9.30)	14.03 (13.49)
DMARD therapy duration (years)	10.67 (8.60)	12.35 (12.91)
Male	6 (24)	4 (17)
Female	19 (76)	19 (83)

Continuous data is expressed as mean (SD), categorical data is expressed as n (%)

Table 4 Demographic data, disease duration, and background therapy duration in the two study groups to show the effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis.

		Visit 1.	**Visit 2.**	**Visit 3.**	**Visit 1 p** (d)	**Visit 2 p** (d)	**Visit 3 p** (d)
Degree of fist making, right hand (3 grades)	Treated	5/11/9	3/12/10	5/10/10	0.638	0.280	0.506
	Control	7/10/6	7/8/8	8/7/8			
Degree of fist making, left hand	Treated	6/9/10	5/8/12	5/8/12	0.853	0.952	0.874
	Control	4/9/10	5/8/10	4/9/10			
Patient impression (1-4)	Treated		2,24±0,78	2,40±0,76		0,509	0,829
	Control		2,39±0,66	4/9/10			

d: Chi^2 test.

Table 5 Changes in degree of fist making and patients' impression in the study groups to show the effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis.

	Group	Visit 1 (Week 0) mean ± SD	Visit 2 (Week 2) mean ± SD	Visit 3 (Week 14) mean ± SD	Mean between group differences at visit 2-1 (95% CI)	Mean between group differences at visit 3-1 (95% CI)
ESR (mm/h)	Treated	23.64 ± 18.06	22.00 ± 18.07	19.16 ± 12.81	-4.59 (-11.44-2.26)	-5.05 (-11.15-1.06)
	Control	22.30 ± 12.20	25.26 ± 16.38	22.87 ± 12.50		
CRP (mg/l)	Treated	11.12 ± 9.38	7.49 ± 9.85	6.00 ± 8.35	**-5.77 (-10.86--0.68)**	**-5.07 (-10.13--0.01)**
	Control	6.17 ± 7.84	8.31 ± 8.97	6.12 ± 7.59		
DAS28	Treated	3.98 ± 0.67	3.35 ± 0.96	3.29 ± 1.09	-0.18 (-0.61-0.25)	-0.37 (-0.84-0.09)
	Control	4.10 ± 0.65	3.66 ± 0.70	3.78 ± 0.88		
HAQ	Treated	1.35 ± 0.80	1.26 ± 0.91	1.12 ± 0.85	-0.19 (-0.55-0.17)	-0.22 (-0.49-0.04)
	Control	1.36 ± 0.50	1.45 ± 0.56	1.35 ± 0.63		
Morning stiffness (min)	Treated	20.08 ± 29.10	17.48 ± 19.67	18.76 ± 27.46	-1.73 (-11.21-7.75)	1.11 (-18.52-20.75)
	Control	20.17 ± 37.60	19.30 ± 37.57	17.74 ± 28.16		
Tender joint count	Treated	3.32 ± 2.12	3.06 ± 2.70	2.68 ± 3.35	1.17 (-0.57-2.91)	0.01 (-1.80-1.83)
	Control	4.43 ± 3.51	3.00 ± 2.89	3.78 ± 3.41		
Number of swollen joints	Treated	1.32 ± 1.44	0.70 ± 1.13	0.68 ± 1.52	-0.10 (-0.81-0.61)	-0.47 (-1.53-0.60)
	Control	1.04 ± 1.40	0.52 ± 0.90	0.87 ± 1.52		
VAS	Treated	52.80 ± 20.26	38.80 ± 22.42	44.00 ± 26.85	**-8.35 (-16.12--0.58)**	-4.89 (-18.02-8.25)
	Control	48.91 ± 15.30	43.26 ± 16.21	45.00 ± 13.22		
Right wrist extension (degree)	Treated	57.40 ± 16.36	60.52 ± 17.47	59.08 ± 17.95	5.12 (-0.03-10.27)	2.38 (-3.60-8.35)
	Control	58.91 ± 22.41	56.91 ± 23.46	58.22 ± 24.33		
Right wrist flexion (degree)	Treated	46.84 ± 14.40	48.52 ± 12.12	49.16 ± 14.96	0.81 (-4.68-6.30)	1.75 (-4.73-8.24)
	Control	43.04 ± 22.47	43.91 ± 20.31	43.61 ± 20.31		
Left wrist extension (degree)	Treated	59.96 ± 18.95	63.96 ± 17.80	64.72 ± 16.87	**4.35 (1.09-7.60)**	5.93 (-0.05-11.92)
	Control	64.96 ± 22.66	64.61 ± 23.30	63.78 ± 24.96		
Left wrist flex. (degree)	Treated	46.96 ± 16.90	47.92 ± 17.50	49.96 ± 17.06	0.70 (-4.86-6.27)	2.96 (-2.35-8.27)
	Control	51.43 ± 18.07	51.70 ± 17.61	51.48 ± 15.79		
Hand grip strength, right (kg)	Treated	12.60 ± 7.19	14.13 ± 8.25	14.52 ± 9.03	1.87 (-0.47-4.20)	0.93 (-2.18-4.05)
	Control	13.30 ± 7.31	12.94 ± 6.59	14.28 ± 7.71		
Hand grip strength, left (kg)	Treated	13.55 ± 6.97	14.14 ± 7.86	14.81 ± 8.34	0.21 (-1.51-1.93)	0.52 (-2.16-3.19)
	Control	12.57 ± 6.80	12.94 ± 6.59	13.32 ± 6.91		

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale.

Table 6 Means±SD at baseline, at Week 2 and Week 14 for the two study groups (treated group: patients receiving underwater ultrasound and control group: receiving sham treatment) and between-group differences at Week 2 and Week 14.

EFFECTS OF VARIOUS TYPES OF ULTRASOUND THERAPY IN HIP OSTEOARTHRITIS - A DOUBLE-BLINDED, RANDOMIZED, CONTROLLED, FOLLOW-UP STUDY

Objectives

In the last 20 years, several organizations have made therapeutic recommendations with regard to the treatment of hip osteoarthritis; some of them also contain physiotherapy. Based on RCTs high evidence exists for the efficiency of exercise therapy and low evidence for the efficiency of ultrasound therapy in OA. There are two trials, that compared the continuous and pulsed modes in the treatment of OA, both have different results.

The aim of our study was to compare the effects of various types of ultrasound therapy on pain relief and quality of life in patients with moderate (Kellgren II-III stage) hip osteoarthritis.

Protocol and study parameters

Design

In this double-blinded, randomized, controlled, follow-up study we evaluated and compared the effects of various types of ultrasound therapy (continuous, pulsed, ultrasound combined with electrotherapy).

Participants

The study was conducted at the Department of Rheumatology in Petz Aladár County Teaching Hospital (H-9025 Győr, Híd u.2.) and at the Musculoskeletal Rehabilitation Department in Zsigmondy Vilmos Harkány Spa Hospital (H-7815 Harkány, Zsigmondy sétány 1.).

The study subjects were enrolled in the study if they met the following inclusion criteria: patients over 50 years of age with clinically and radiologically moderate hip osteoarthritis (Kellgren-Laurence II-III. stage), as defined by the ACR [93], having experienced chronic hip pain for at least 8 weeks. Their pain intensity at rest was ≥ 50mm on a VAS of 100mm; they had had no physiotherapy or local injection (steroid, viscosupplementation)

administered in the region of the hip joint or in the joint within 3 months before starting the study.

Patients were excluded from the study if they had hip pain (acute, subacute pain) for less than 8 weeks; they had received local injection or physiotherapy within 3 months before starting the study; their laboratory findings showed signs of inflammation / tumor (especially abnormality in blood test, abnormal ESR). Exclusion criteria included patients with infection, fever, osteomyelitis, severe osteoporosis, pregnancy, untreated hypertension, heart failure, malignancy, epilepsy, and pacemaker or intracardiac device.

Participants were recruited from patients of the Department of Rheumatology and Physiotherapy of Petz Aladár County Teaching Hospital and the Musculoskeletal Rehabilitation Department in Zsigmondy Vilmos Harkány Spa Hospital. The study was performed between June 2018 and May 2019.

The subjects had received verbal information about the study procedure, had read the package leaflet, and had signed the consent form. The study was conducted with the permission of the Regional Research Ethics Committee (number:76-1-9/2018) and has been registered on the ClinicalTrials.gov (NCT03952221) web page.

Intervention

The patients in each group received conventional treatment (exercise, massage, balneotherapy) every working day for two weeks, on a total of 10 occasions. The exercise included standardized hip exercises, Swedish massage techniques were used during the massage therapy, and the balneotherapy was performed in thermal water at 34 °C. In addition to the conventional therapy, patients in group 1 received continuous ultrasound therapy with moving head in three fields – inguinal, gluteal, trochanteric – for 3 minutes pro field, altogether 9 minutes every working day for two weeks, on a total of 10 occasions (calibrated BTL-4825S Premium device, head size of 5 cm, 3 MHz frequency, 1.5 W/cm^2 intensity); patients in group 2 received pulsed ultrasound therapy (1.5 W/cm^2 intensity, 3 MHz frequency, 50% duty cycle). Patients in group 3 received sonotens therapy for 10 minutes per day (US: 0.5 W/cm^2 intensity, 3 MHz carrier frequency; TENS: 100 Hz frequency, 100 μs impulse, constant frequency); patients in group 4 received sham ultrasound therapy (the device was switched off).

Patients were not allowed to receive other physiotherapy during the 3-month follow-up period.

Outcomes

The studied parameters were recorded by a rheumatologist before starting the treatment (Week 0), immediately after the treatment session in the second week (Week 2), and 3 months later (Week 14).

When including the patients in the study, their age, sex, weight, and Body Mass Index were recorded. In addition, the severity of hip pain at rest/spontaneous hip pain (on a 100mm VAS) was evaluated, the function was measured using the WOMAC VA 3.0 index and the 6-minute walking test, and the quality of life was documented (RAND 36-Item Health Survey (Version 1.0)) during each visit.

After the treatment (Week 2) and during the control examination in the third month (Week 14), the patients evaluated their own condition on a 4-point scale (1:extremely improved; 2:improved; 3:no change; 4:became worse). In accordance with the internationally accepted practice, the need of analgesic or anti-inflammatory medication during the treatment or the follow-up period was documented on the outpatient forms.

Randomization and blinding

A concealed allocation random assignment of the enrolled patients to the treatment groups (using a computer program) was done by an independent investigator, who did not meet the patients and was not involved in the study procedure. From the start of the study until its end, neither the investigator nor the patient knew which treatment group the patient had been assigned to by the assistant based on the randomization. The statistician was not involved in the randomization.

Statistical analysis

Statistical analysis was performed using the IBM SPSS 25 statistical software. The statistician was an independent person. Last observation carried forward (LOCF) method was used to handle missing data. As for the baseline values, normality was assessed by using the Kolmogorov-Smirnov test. Differences among the 4 groups were calculated by

Kruskal-Wallis test, while post-hoc test was performed by using Mann-Whitney test. The changes between endpoints and baseline data were compared by using Wilcoxon test.

Minimal Clinically Important Improvement (MCII) at Week 14 was defined as ≥21,1% relative improvement in a normalized WOMAC function score [75]. Improvement compared to the placebo group was measured by binary logistic regression and expressed with ODDS value. A p value <0.05 was considered significant for the statistical analysis.

Results

The study involved 80 patients, and 71 patients were randomized. 5 patients did not meet the inclusion criteria, 4 patients did not wish to participate in the study. Out of the 71 patients, 21 of them (mean age: 67.95 years; male/female:4/17) were randomized into group 1, 17 patients (mean age: 65.82 years, male/female:4/13) into group 2, 15 patients into group 3 (mean age: 65.93 years; male/female:2/13), and 18 patients into group 4 (mean age: 65.72 years; male/female:4/14). There were no differences among the groups in terms of age, sex ratio and Body Mass Index (BMI) (**Table 7**). Out of the 71 randomized patients, 1 only attended the baseline visit, and another 1 attended only the first two visits. (**Figure 3**).

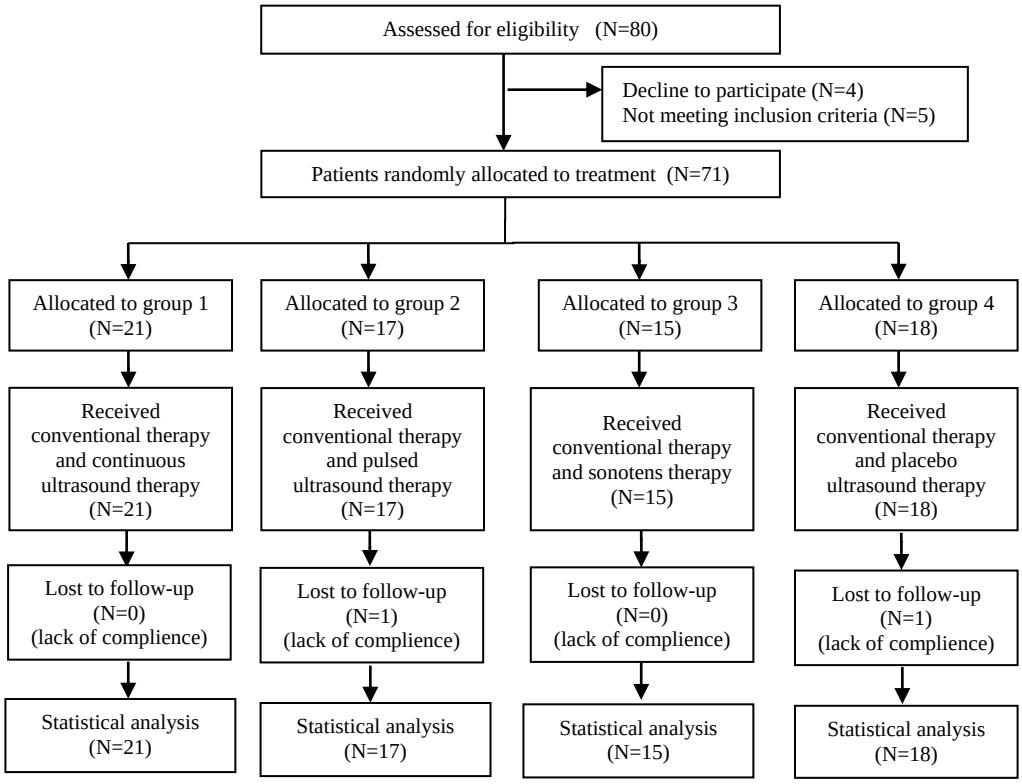

Figure 3. Participant flow to show the effects of continuous and pulsed ultrasound, sonotens and placebo therapy on pain, function and quality of life in patients with hip osteoarthritis.

The mean age of the patients involved was 65 years. Female dominance (m:f=1:4) was observed. Based on BMI, the patients were overweight or obese (**Table 7**).

The baseline pain intensity at rest measured on the VAS was similar across all four groups, 62mm/100mm on average. By Week 2 and Week 14, the intensity of pain decreased significantly in all four groups; there was no significant difference among the groups during either visit.

The distance walked in the 6-minute walking test increased significantly after the treatment in all four groups, and it continued to increase until the control examination in the third month. The difference among the groups was not significant at either measurement time. The total score of the three dimensions (pain, stiffness, and physical function) of the WOMAC index increased significantly in each group after the treatment (Week 2), which was maintained until the third month in group 2, 3, and 4. In case of those patients who received conventional and continuous ultrasound therapy (group 1), the change in stiffness and physical function compared to the baseline was significant after the treatment, and non-significant by the third month; however, pain during movement was significantly less even during the first and the second visits than at baseline. The WOMAC values of the patients receiving conventional and pulsed ultrasound therapy (group 2) increased significantly in all three dimensions by both Week 2 and Week 14. Pain during movement and physical function of those patients who received conventional and sonotens therapy (group 3) improved significantly only by the third month, while stiffness and the total WOMAC score decreased significantly even in Week 2 and Week 14. For patients in the placebo group (group 4), stiffness, physical function, and the total WOMAC score improved significantly both after the treatment and in the third month, however, the decrease of pain during movement was not significant until Week 14. There was no significant difference in terms of the values of WOMAC dimensions among the groups during Visit 1 and Visit 2. The baseline pain during movement was significantly higher in patients of group 1 than group 4, but the baseline values for stiffness and physical function were not different in the four groups. The highest number of patients achieving Minimal Clinically Important Improvement (MCII) at Week 14 was in the sonotens group (73%), but the difference compared to the placebo group was not

significant. In Group 1 only 38% of patients showed MCII, which is less, than in the placebo group (**Table 10**).

Out of the eight domains of SF-36, 6 domains (role physical, vitality, mental health, social functioning, bodily pain, and general health) improved significantly in group 3; 4 domains (role emotional, vitality, bodily pain, and general health) in group 4; 3 domains (physical functioning, bodily pain, and general health) in group 2; and only 1 domain (bodily pain) in group 1 for a moderately long term, by the third month. All four groups showed significant improvement in the bodily pain domain, and the improvement in the general health domain was significant in three groups. (**Table 8, 9**)

More than 60% of patients in each group reported improvement in condition (measured on a 4-point Likert scale) immediately after the treatment. This tendency continued until Week 14, the majority of patients in each group reported improvement. By the third month, about 35% of patients in group 2 and about 22% of patients in the placebo group reported no improvement compared to their baseline condition. Deterioration was reported only by patients in group 1, group 2 and group 4 in the third month (approximately 20%, 5%, and 10% respectively) (**Table 11**).

Almost 2/3 of patients took non-steroidal anti-inflammatory or analgesic drugs at baseline. After the treatment, the proportion of those taking medicine slightly decreased (by about 20%), and by the third month the initial proportion was observed (**Table 12**).

At the start of the study, the majority of patients in all four groups did exercise only occasionally, but during the control examination in the third month, most of them reported doing exercise on a daily base (**Table 12**).

Discussion

According to the results of our double-blinded, randomized, controlled, follow-up study, conventional treatment (exercise, massage, balneotherapy) has positive effects on pain, function and quality of life in hip OA, and no significant difference was found among the effects of different modes of US.

The efficiency of exercise therapy (on land and under water) in OA is of high evidence. There is no specific recommendation regarding the type, the intensity or the frequency of exercise [94], [95]. Randomized, controlled studies have shown that balneotherapy in the long

term, reduces the pain caused by knee osteoarthritis and improves the function as mentioned in the Literary overview [61; 62; 63; 64]. In our study, patients in placebo group receiving only conventional therapy demonstrated improvement as regards pain, function and quality of life in the same way as those patients who received ultrasound therapy as well. The improvement of the studied parameters underpins the beneficial effect, supported by the previous studies mentioned above, of the combination of exercise, massage, and balneotherapy.

The effectiveness of ultrasound therapy in OA has low evidence. Two modes can be applied: 1) continuous (without pauses) and 2) pulsed (intermittent delivery of energy). The advantages of the pulsed mode are that higher intensity can be used and there is no thermal effect. Therefore, it could be beneficial in case of acute pain or inflammation. The continuous mode is more favorable in chronic musculoskeletal pathologies or treating decreased range of motion, due to its thermal effect. Two RCTs compared the continuous and pulsed modes; Tascioglu et al. found the pulsed mode to be more effective, while Yildiz et al. found no difference between the two modes. Unfortunately, there is no study so far that would confirm the effectiveness of ultrasound therapy in hip OA as monotherapy [58]. In our study, the degree of pain reduction was similar in all four groups. The functional impairment decreased in all ultrasound groups, however, only those patients receiving pulsed therapy showed improvement in all three dimensions of the WOMAC score both at Week 2 and Week 14. An intensity of 1.5 W/cm^2 was used in both the continuous and the pulsed modes, in accordance with the data of international studies. In pulsed mode, pulse rates of 1:4 or 1:5 are normally used, we used a pulse rate of 1:2 in accordance with the program of our equipment. We found no difference between the effectiveness of the two modes in relation to the study outcomes; however the proportion of patients achieving MCII was the lowest in case of continuous US and the highest in case of sonotens. We found in our study that pain both at rest and under load/during movement decreased in patients receiving sonotens and conventional treatment. As to functional impairment, in group 3 joint stiffness improved after the treatment session, while physical function improved significantly only by Week 14. These patients showed improvement in the most domains of SF-36, which can be explained by the fact that the effects of the two treatments were summed up. In the improvement of quality of life there was no statistically significant difference between the groups.

The treatments had no effect on the patients' analgesic drug need after 3 months. This may be explained by the fact that they suffer from a chronic disease, which flares up periodically, causing increasing pain in particular.

Doing exercise on a regular basis helps to improve movement function. The patients can maintain the achieved functional improvement and slow down the progression by changing their lifestyle and exercising regularly. This may be the reason why more patients did exercise on a daily basis 3 months after the treatment than at the start of the study.

Limitaion of the study

One of the limitation is the low patient number. Based on the power analysis, the ideal number of study patients would have been 20 patients in each group (80 patients altogether). We chose the transcutaneous electrical nerve stimulation in the group US combined with electrotherapy. However, comparison of ultrasound monotherapy with other combination therapy (ultrasound plus other impulse electrotherapy, e.g. interferential current) could be interesting as well.

This chapter in under publication process.

Márta Király, Edina Gömöri, Rita Kiss, Noémi Nógrádi, Nóra Nusser, Katalin Hodosi, Tamás Bender: Effects of Various Types of Ultrasound Therapy in Hip Osteoarthritis - a Double-blinded, Randomized, Controlled, Follow-up Study.

	Group		p
Age (years)	1 (n=21)	67.95±7.74	0.889
	2 (n=17)	65.82±10.45	
	3 (n=15)	65.93±9.12	
	4 (n=18)	65.72±8.77	
BMI	1	32.13±6.11	0.127
(Body Mass Index)	2	30.52±5.48	
	3	27.86±4.59	
	4	29.35±3.95	

Kruskal-Wallis test

Table 7. Demographic data and BMI of patients in th efour tretament groups (continuous, pulsed ultrasound, sonotens and placebo ultrasound)

Measured clinical variables	**Group**	**Visit 0 baseline)** mean ± SD	**Visit 1 (Week 2)** mean ± SD	**Visit 2 (Week 14)** mean ± SD	**p 0-1**	**p 0-2**	**p 1-2**
VAS pain (resting)	1	64.38±12.45	44.14±23.92	41.76±26.41	**<0.001**	**0.001**	0.823
	2	63.88±14.47	37.71±22.96	34.35±30.36	**0.001**	**0.002**	0.507
	3	61.33±17.78	43.07±21.19	31.13±22.26	**0.001**	**0.001**	0.099
	4	62.94±9.37	42.56±20.30	40.22±20.88	**<0.001**	**0.001**	0.422
6-minute walking test	1	281.95±115.92	299.57±125.74	309.67±111.23	**0.008**	**0.007**	0.104
	2	289.59±87.09	328.59±87.94	322.47±133.06	**0.003**	**0.011**	0.570
	3	306.13±85.99	338.47±87.02	355.40±88.78	**0.003**	**0.015**	0.348
	4	291.78±101.78	331.61±10.88	340.78±109.73	**0.001**	**0.025**	0.687
WOMAC pain (motional)	1	302.76±108.20	230.05±107.66	227.76±123.58	**0.001**	**0.021**	0.654
	2	280.65±105.18	187.65±123.34	185.94±137.50	**0.002**	**0.005**	0.733
	3	261.73±88.60	218.07±104.28	164.47±80.96	0.061	**0.003**	**0.047**
	4	249.33±67.75	215.00±83.88	203.33±84.82	0.145	**0.028**	0.266
WOMAC stiffness	1	112.86±40.10	87.05±50.48	99.48±55.97	**0.007**	0.167	0.116
	2	121.24±31.93	76.47±46.68	80.18±52.02	**0.002**	**0.011**	0.433
	3	126.33±79.55	84.13±45.01	66.00±28.41	**0.006**	**0.001**	0.125
	4	101.39±36.28	76.94±41.23	78.44±33.70	**0.045**	**0.031**	0.962
WOMAC phys. function	1	898.48±302.41	782.57±342.90	812.86±408.67	**0.007**	0.205	0.668
	2	970.12±252.43	693.41±351.64	656.29±423.22	**0.003**	**0.005**	0.820
	3	793.73±374.45	691.67±389.23	570.80±247.64	0.061	**0.020**	0.191
	4	861.17±255.92	685.39±269.09	657.06±236.82	**0.022**	**0.008**	0.686
WOMAC sum	1	1314.10±394.54	1099.67±486.40	1140.10±569.81	**0.001**	0.085	0.575
	2	1360.24±384.58	957.53±510.42	922.41±599.08	**0.003**	**0.007**	0.820
	3	1220.33±424.61	993.87±532.22	787.73±366.59	**0.023**	**0.001**	0.100
	4	1211.89±376.26	977.33±372.71	933.28±321.99	**0.022**	**0.002**	0.463
Physical functioning (SF-36)	1	32.14±21.54	38.81±23.29	38.33±24.20	0.122	0.469	0.979
	2	36.18±15.76	44.41±20.83	51.47±25.11	**0.030**	**0.003**	0.068
	3	42.33±20.69	42.33±19.81	50.67±29.27	0.671	0.346	0.271
	4	40.28±21.45	41.39±20.92	50.56±15.99	0.796	0.108	0.123
Role functioning/ physical (SF-36)	1	16.67±28.87	27.38±36.15	27.38±33.45	0.282	0.231	0.899
	2	19.12±25.81	26.47±31.21	38.24±41.57	0.493	0.111	0.071
	3	6.67±14.84	21.67±33.89	36.67±38.81	0.054	**0.008**	0.076
	4	26.39±32.62	27.78±31.96	27.78±31.96	0.739	0.858	0.972
Role functioning/ emotional (SF-36)	1	41.27±45.83	38.09±38.41	50.78±44.25	0.720	0.136	0.222
	2	60.77±41.22	64.69±39.92	62.79±48.43	0.671	0.677	0.916
	3	46.65±45.07	48.88±4.20	46.88±45.19	0.713	0.932	0.887
	4	37.02±37.72	53.69±42.99	62.94±35.96	**0.047**	**0.043**	0.580
Energy/ fatigue (SF-36)	1	50.48±17.53	48.57±17.69	57.14±21.01	0.390	0.055	0.052
	2	42.94±20.77	50.00±23.85	48.82±25.47	0.091	0.086	0.860
	3	42.33±17.51	55.00±21.55	65.53±20.09	**0.013**	**0.001**	**0.036**
	4	47.22±17.59	58.06±19.64	56.94±15.73	**0.003**	**0.014**	0.678
Emotional well-being (SF-36)	1	64.38±21.54	66.48±19.53	70.29±19.41	0.400	0.132	0.323
	2	63.76±28.30	71.29±26.54	71.06±27.84	0.181	0.157	1.000
	3	68.53±16.55	72.80±20.96	79.20±20.35	0.284	**0.020**	**0.044**
	4	65.11±18.09	73.33±16.69	72.44±15.82	0.139	0.092	0.833
Social functioning (SF-36)	1	62.50±27.10	66.07±25.96	69.05±26.99	0.403	0.193	0.749
	2	62.50±30.62	73.50±28.95	71.32±32.71	0.106	0.219	0.835
	3	69.17±19.40	67.50±16.90	80.98±19.36	0.794	**0.047**	**0.024**
	4	55.56±21.20	63.89±23.04	65.97±18.09	0.134	0.126	0.776
Pain (SF-36)	1	34.05±14.57	43.33±17.05	41.67±25.68	**0.019**	0.242	0.752
	2	32.65±17.75	42.21±17.07	51.91±25.73	**0.020**	**0.003**	0.084
	3	30.50±17.58	42.67±22.90	48.00±23.07	**0.009**	**0.005**	0.474
	4	35.56±170.5	44.44±21.58	4715±20.02	**0.012**	**0.014**	0.613

General health (SF-36)	1	38.81±16.42	43.81±20.97	41.43±17.40	0.106	0.204	0.451
	2	36.47±18.44	42.06±23.66	44.38±21.63	0.081	**0.018**	0.330
	3	36.33±18.27	45.67±15.68	51.63±18.20	**0.009**	**0.010**	0.395
	4	33.33±12.25	42.78±19.94	43.89±17.62	**0.013**	**0.004**	0.831
Patient impression	1		2.05±0.38	2.43±0.98			0.062
	2		1.94±0.57	2.06±0.85			0.564
	3		1.80±0.414	1.93±0.41			0.414
	4		2.22±0.548	2.33±0.57			0.569

Mann-Whitney test

Table 8. Means ± SD at baseline, at end of Week 2 and Week 14 for the four study groups (Group 1:patients receiving conventional and continuous ultrasound therapy, Group 2: patients receiving conventional and pulsed ultrasound therapy, Group 3: patients receiving conventional and sonotens therapy, Group 4: patients receiving conventional and placebo ultrasound therapy) and between-group differences at end of Week 2 and Week 14.
WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index

Measured clinical variables	**Group**	**p Visit 0 (Baseline)**	**p Visit 1 (Week 2)**	**p Visit 2 (Week 14)**
VAS pain (resting)	1-2-3-4	0.957	0.689	0.555
	1 vs. 4	0.922	0.749	0.835
	2 vs. 4	0.883	0.483	0.405
	3 vs. 4	0.708	0.708	0.215
6-minute walking test	1-2-3-4	0.719	0.653	0.606
	1 vs. 4	0.707	0.394	0.494
	2 vs. 4	0.636	0.832	0.807
	3 vs. 4	0.421	0.656	0.630
WOMAC pain (motional)	1-2-3-4	0.252	0.521	0.376
	1 vs. 4	**0.043**	0.512	0.587
	2 vs. 4	0.195	0.232	0.590
	3 vs. 4	0.735	0.789	0.202
WOMAC stiffness	1-2-3-4	0.656	0.851	0.272
	1 vs. 4	0.294	0.512	0.282
	2 vs. 4	0.245	0.987	0.883
	3 vs. 4	0.735	0.708	0.244
WOMAC phys. function	1-2-3-4	0.478	0.694	0.472
	1 vs. 4	0.606	0.223	0.379
	2 vs. 4	0.207	0.987	0.987
	3 vs. 4	0.509	0.986	0.421
WOMAC sum	1-2-3-4	0.605	0.707	0.337
	1 vs. 4	0.349	0.269	0.335
	2 vs. 4	0.232	0.782	0.909
	3 vs. 4	0.986	1.000	0.325
Physical functioning (SF-36)	1-2-3-4	0.445	0.841	0.223
	1 vs. 4	0.223	0.666	0.053
	2 vs. 4	0.568	0.636	0.961
	3 vs. 4	0.817	0.873	0.873
Role functioning/ physical (SF-36)	1-2-3-4	0.247	0.925	0.813
	1 vs. 4	0.349	0.945	0.922
	2 vs. 4	0.590	0.935	0.568
	3 vs. 4	0.093	0.605	0.556

Role functioning/ emotional (SF-36)	1-2-3-4	0.429	0.292	0.627
	1 vs. 4	0.900	0.308	0.443
	2 vs. 4	0.110	0.463	0.782
	3 vs. 4	0.630	0.789	0.325
Energy/ fatigue (SF-36)	1-2-3-4	0.595	0.497	0.286
	1 vs. 4	0.549	0.165	0.791
	2 vs. 4	0.732	0.443	0.443
	3 vs. 4	0.580	0.789	0.166
Emotional well-being (SF-36)	1-2-3-4	0.918	0.572	0.361
	1 vs. 4	0.989	0.321	0.900
	2 vs. 4	0.732	0.708	0.463
	3 vs. 4	0.442	0.873	0.190
Social functioning (SF-36)	1-2-3-4	0.444	0.609	0.252
	1 vs. 4	0.443	0.791	0.686
	2 vs. 4	0.424	0.207	0.232
	3 vs. 4	0.073	0.630	**0.027**
Pain (SF-36)	1-2-3-4	0.915	0.990	0.676
	1 vs. 4	0.791	0.813	0.512
	2 vs. 4	0.684	0.782	0.590
	3 vs. 4	0.509	0.986	0.817
General health (SF-36)	1-2-3-4	0.801	0.843	0.283
	1 vs. 4	0.364	0.791	0.900
	2 vs. 4	0.525	0.987	0.909
	3 vs. 4	0.509	0.381	0.126
Patient impression	1-2-3-4		0.092	0.422
	1 vs. 4		0.379	0.945
	2 vs. 4		0.237	0.506
	3 vs. 4		0.073	0.215

Kruskal-Wallis and Wilcoxon test

Table 9. Intergroup differences at end of Week 2 and Week 14 in the study groups (Group 1:patients receiving conventional and continuous ultrasound therapy, Group 2: patients receiving conventional and pulsed ultrasound therapy, Group 3: patients receiving conventional and sonotens therapy, Group 4: patients receiving conventional and placebo ultrasound therapy)

Group	After 2 weeks			After 14 weeks		
	Pts with MCII achievement	**p**	**ODDS (95% CI) vs. group 4**	**Pts with MCII achievement**	**p**	**ODDS (95% CI) vs. group 4**
1 (n=21)	7 (34%)	1.000	1.000 (0.263-3.802)	8 (38%)	0.688	0.769 (0.214-2.768)
2 (n=17)	10 (59%)	0.135	2.857 (0.722-11.311)	10 (59%)	0.397	1.786 (0.467-6.824)
3 (n=15)	8 (53%)	0.251	2.286 (0.558-9.366)	11 (73%)	0.101	3.437 (0.787-15.017)
4 (n=18)	6 (33%)			8 (44%)		

Table 10. Number of patients achieving MCII after 2 and 14 weeks in the four study groups

Group	Extremely improved (patient impression)		Improved (patient impression)		No change (patient impression)		Worse (patient impression)	
	Visit 1. (Week 2)	Visit 2. (Week 14)	Visit 1. (Week 2)	Visit 2. (Week 14)	Visit 1. (Week 2)	Visit 2. (Week 14)	Visit 1. (Week 2)	Visit 2. (Week 14)
1. (n=21)	4,76 %	9,52 %	85,71 %	66,67 %	9,52 %	4,76 %	0 %	19,04 %
2. (n=17)	17,64 %	29,41 %	64,7 %	29,41 %	11,76 %	35,29 %	5,88 %	5,88 %
3. (n=15)	20 %	13,34 %	80 %	80 %	0 %	6,67 %	0 %	0 %
4. (n=18)	5,55 %	11,11 %	66,67 %	55,55 %	27,78 %	22,22 %	0 %	11,11 %

Table 11. Percent of patients achieving extremely improvement, improvement, no change or worse condition in the four study groups at Week 2 and Week 14.

	Group	**Visit 0**	**Visit 1**	**Visit 2**
Antirheumatic medicine	1 (n=21)	15	10	11
	2 (n=17)	9	6	11
	3 (n=15)	11	9	10
	4 (n=18)	8	5	13
Doing exercise daily/occasionally/never	1 (n=21)	7/9/5	21/0/0	12/9/0
	2 (n=17)	7/5/5	17/0/0	8/9/0
	3 (n=15)	4/10/1	15/0/0	9/6/0
	4 (n=18)	7/9/2	17/1/0	11/7/0

Table 12. Number of patients taking antirheumatic medicine and doing exercises in the four study groups at baseline, at end of Week 2 and Week 14.

THE EFFECTS OF TISZASÜLY AND KOLOP MUD PACK THERAPY ON KNEE OSTEOARTHRITIS: A DOUBLE-BLIND, RANDOMISED, NON-INFERIORITY CONTROLLED STUDY

Objectives

Peloids have been used for the treatment of musculoskeletal diseases for a long time and several studies have confirmed their effectiveness in osteoarthritis [66; 67; 69]. The effects of Kolop peloid in knee osteoarthritis have been evaluated by Hungarian authors in a randomised, controlled, follow-up study [96].

Next to the production of Kolop peloid in Tiszasüly, another mud deposit was found. As the production of the two peloids is next to each other, thus their composition is similar; it is within a natural fluctuation (**Table 13**). In our non-inferiority study, we postulated that the clinical effectiveness of the two very similar peloids are alike.

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Protocol and study parameters

Design

In this randomized, double-blinded, controlled, non-inferiority study we evaluated and compared the effects of Tiszasüly and Kolop mud pack therapy on pain, function and quality of life in patients with knee osteoarthritis.

Participants

The study was conducted at the Physiotherapy Devision of Petz Aladár County Teaching Hospital's Rheumatology Outpatient Clinic.

We enrolled patients over 40 years of age, who are capable to answer questionnaires and have clinically and radiologically bilateral knee osteoarthritis according to EULAR recommendation (mechanical knee pain, morning stiffness < 30 min, reduced knee function, radiological signs: Kellgren-Laurence radiological grade 2–3; grade 2, osteophyte formation and possible joint space narrowing; grade 3, multiple osteophytes and definite

joint space narrowing, sclerosis and possible bone deformity) [97]. Patients must have had initial spontaneous knee pain ≥ 50 mm on visual analogue scale.

Exclusion criteria were infection, fever, ongoing malignant tumour, neuropathy of the lower extremities, skin changes of the treated area, high blood pressure, progrediating heart failure (NYHA Class II–IV), inflammatory rheumatic disease, prior arthroplasty of the knee, intraarticular steroid or viscosupplementation therapy within 3 months prior treatment, physiotherapy of the knee within 3 months prior treatment, and inflammatory knee osteoarthritis.

Participants were recruited from patients of the Department of Rheumatology and Physiotherapy of Petz Aladár County Teaching Hospital. The study was conducted between August 2016 and February 2018.

Study participants were informed verbally about the protocol, received written information and they signed the Informed Consent Form before the initiation of the study. The study was approved by the Regional Research Ethics Committee of Petz Aladár County Teaching Hospital (approval number: 76-1-9/2016) and registered in ClinicalTrials.gov (NCT03826511).

Intervention

Group 1 received Tiszasüly hot mud pack (42 °C), group 2 received Kolop hot mud pack (42 °C) on the painful knee once a day for 30 min on 10 occasions (2 weeks). The two mud packs had similar package and physical properties. The treatment was performed by an independent, blinded, qualified assistant. Patients were lying during the therapy and after 30 min the mud-pack was washed off by the assistant. The applied mud was discarded at the end of the treatment.

Outcomes

Outcome parameters were recorded by a blinded rheumatologist before the start of the therapy (Week 0), immediately after the therapy series (Week 2) and 3 months later (Week 12).

At the inclusion, patients' ages and genders were recorded. During each visit, we assessed range of motion, tenderness or swelling, applied a 100-mm visual analogue scale to assess

rest/spontaneous pain level. Functional impairment was measured by 3 different questionnaires: (1) the WOMAC VA 3.0, (2) the KOOS and (3) Lequesne Algofunctional Index. Quality of life was measured by EuroQoL-5D and EQ VAS questionnaires. EQ-5D was valued based on a standardised time trade-off (TTO) for the general population in the United Kingdom (UK).

Randomization and blinding

A concealed allocation random assignment of the enrolled patients to the treatment groups was performed by an independent study person (using Microsoft Excel software) who did not meet any of the patients and did not participate in the course of the study either. Neither the testing investigators and assistants nor the patients were aware of the treatment assignments both at the start and the end of the study. The statistician was not involved in the randomisation process either.

Statistical analysis

The statistical analysis was processed by the IBM SPSS 25 software. Data distribution was investigated with the Kolmogorov-Smirnov test. We found a non-normal distribution; the data were calculated by the Mann-Whitney and Wilcoxon test and are represented as the mean ± SD. The measurements of differences between groups were carried out by the Mann-Whitney test. We handled missing data using the last observation carried forward (LOCF) method. P values < 0.05 were considered significant. We did not use an intention to treat analysis approach. The power analysis done by the G power 3.1.9.2 programme was calculated from VAS pain values at week 2 using the Mann-Whitney nonparametric test. The power proved to be 84% in case of 29 and 31 sample sizes.

Results

Altogether, 75 patients were included and 60 patients were randomised into two groups. Eleven patients did not meet inclusion criteria, and four patients revoked their consent. The allocation and the type of mud pack in the groups were concealed by using sealed, opaque envelopes. Twenty-nine patients out of 60 (mean age, 65.03 ± 8.56 years; male/female, 10/19) were assigned to group 1 and 31 patients (mean age, 66.67 ± 7.62 years; male/female, 8/23) to

the Group 2 (**Figure 4**). There were no significant differences among the two groups in gender proportions, comorbidities, knee osteoarthritis duration, and radiological score distribution (**Table 14**). The most frequent co-morbidities in both treatment groups were cardiovascular diseases. The majority of the patients had grade 2 Kellgren-Laurence radiological score. Approximately twothirds of the patients did not have osteoarthritis besides the knees, and one-third had hip OA.

Both groups demonstrated similar changes during the study in all parameters. Spontaneous pain significantly decreased in both groups after therapy and at 12 weeks follow-up ($p0–1 < 0.001$, $p0–2 < 0.001$); however, the difference between Week 2 and Week 12 was not significant. Immediately after therapy, the Tiszasüly mud pack group (group 1) showed better improvement ($p = 0.009$) compared with group 2 (Kolop mud pack).

Knee function impairment significantly improved in both the Tiszasüly and the Kolop mud pack groups for the Week 2 and Week 12 visits measured by WOMAC and the Lequesne index (group 1, $p0–1 = 0.002$, $p0–2 = 0.001$, and $p0–1 = 0.001$, $p0–2 = 0.001$ respectively; group 2, $p0–1 < 0.001$, $p0–2 < 0.001$, and $p0–1< 0.001$, $p0–2 = 0.004$ respectively). The KOOS score showed decreasing impairment in both groups, but significant changes were demonstrated only in the Kolop mud pack group (group 2, $p0–1= 0.046$, $p0–2 = 0.039$; group 1, $p0–1 = 0.991$, $p0–2 = 0.905$).

As to quality of life of patients measured by EuroQoL-5D, we found significant improvement in both groups (group 1, $p0–1 = 0.039$, $p0–2 = 0.028$; group 2, $p0–1 < 0.001$, $p0–2 < 0.001$), there were no significant differences between the groups at each visit. EQ-5D VAS score increased so in group 1 as in group 2, and the changes were significant in both groups (group 1, $p0–1 = 0.024$, $p0–2 = 0.011$; group 2, $p0–1 < 0.001$, $p0–2 < 0.001$) (**Table 15**).

No adverse events were noted or recorded during this study.

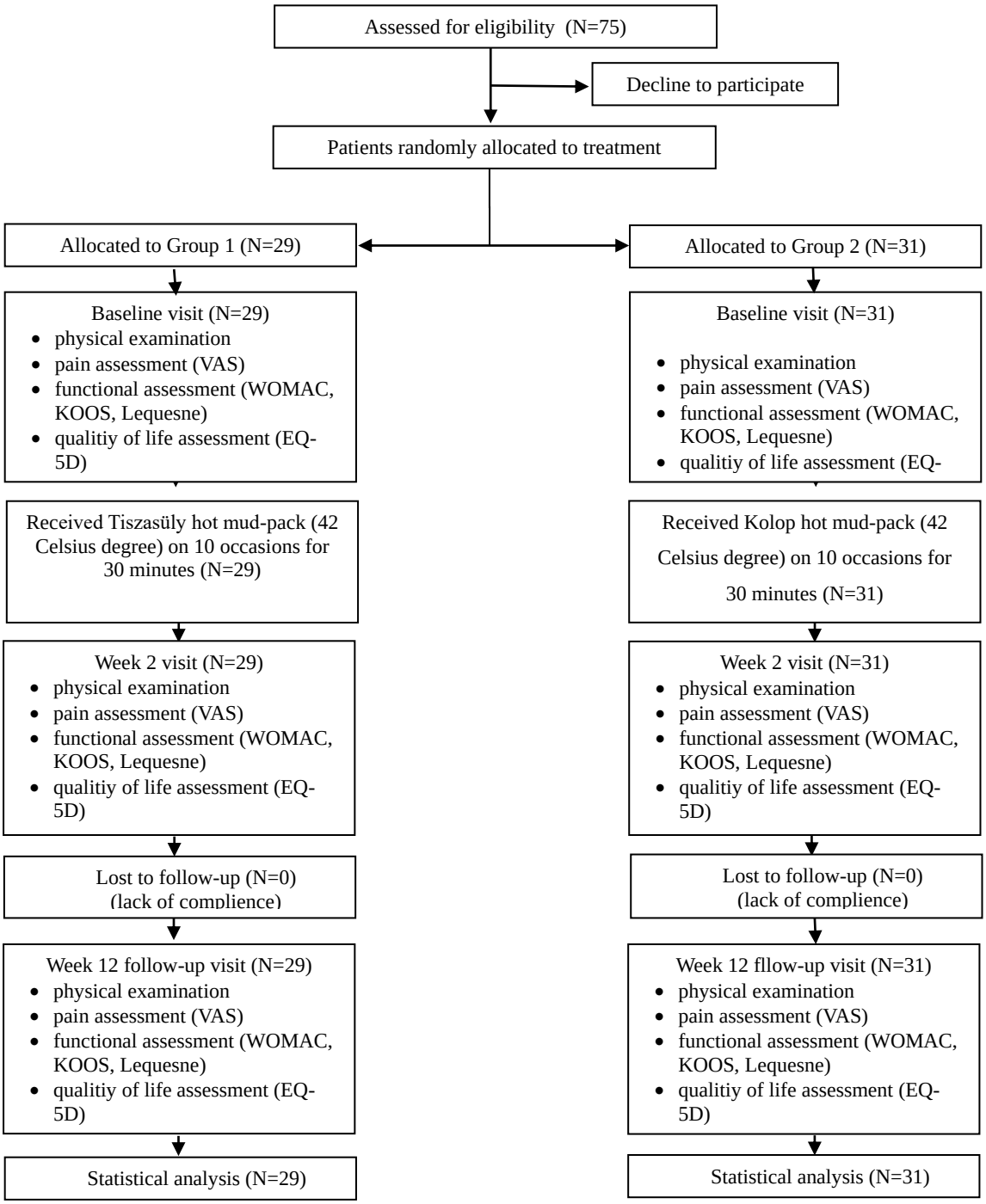

Figure 4. The disposition of patients

Discussion

In our randomized, double-blinded, controlled non-inferiority study we confirmed that the clinical effects of Tiszasüly and Kolop muds are basically the same, there was no significant

difference between them, though Tiszasüly mud-pack showed better improvement in one parameter right after treatment. This corresponds to the fact, that production of the 2 muds is located very close to each other and the physical and chemical parameters of both muds are the same.

Peloid therapy applied directly to the skin, alone, or as part of combined physio- and balneotherapy has proved to be effective on clinical parameters and quality of life in knee osteoarthritis. In the effect of mud terapy, not only thermal effect, but also chemical effect my play a role [68]. A recent metaanalysis verified the suspected effect of chemical components in balneotherapy [98]. In an experimental study, Hungarian authors investigated the anti-inflammatory and analgesic effects of Héviz thermal water and mud in monosodium iodoacetate-induced osteoarthritis and Complete Freund's adjuvant-induced rheumatoid arthritis murine models. The treatment group received Héviz thermal water and mud pack, the control group received tap water and sand. Balneotherapy did not influence mechanical hyperalgesia, weight bearing, or oedema formation in the rheumatoid arthritis models, but had antinociceptive and anti-inflammatory effects in osteoarthritis [99] and both treatment had positive effect on pain, function an quality of life in patients with knee osteoarthritis.

In a randomised, controlled, follow-up study, Hungarian authors evaluated the effects of Kolop peloid as part of combined physio- and balneotherapy treatment on knee osteoarthritis in the day hospital care setting. Peloid therapy combined with mineral water bathing, aquatic exercise and magnetotherapy significantly improved pain, function and quality of life compared with physio- and balneotherapy without peloid therapy [96].

All in all, based on our study and literature data, we can conclude, that mud therapy has been proved to be effective and safe in the treatment of knee osteoarthritis. It did not have any side effects in our patients with co-morbidities. It could be a good therapeutic choice not only in early osteoarthritis, but after several years disease duration. Despite the increasing evidence of the favourable effects of balneotherapy and mud therapy, they are traditionally used mainly in countries rich in thermal waters. This fact can interfere the appearance of mud therapy in guidelines of non-pharmacological treatment of osteoarthritis, although there are several excellent, welldesigned studies based on consort statement available.

Limitation of the study

Increasing the number of patients would power our study, though this number was enough to draw conclusions. We are planning to extend the follow-up period to 6 and 9 months.

This chapter was published during my PhD work.

Király M, Kővári E, Hodosi K, Bálint P.V, Bender T: The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study. Int J Biometeorol. 2019 Aug 3. doi: 10.1007/s00484-019-01764-4. [Epub ahead of print]

Mud	Kolop	Tiszasüly		Kolop	Tiszasüly
SiO_2	60,05%	69,1%	CaO	1,54%	2,53%
TiO_2	0,54%	-	MgO	2,10%	-
Al_2O_3	17,91%	17,58%	Na_2O	0,89%	-
Fe_2O_3	4,34%	-	K_2O	2,39%	2,73%
FeO	2,38%	-	CO_2	0,29%	-
MnO	0,05%	-	Cl^-	0,05%	-
P_2O_5	0,14%	-	SO_3	0,28%	-
Organic content	1,53%	1,475%			

Table 13. The chemical composition of the Kolop and Tiszasüly mud

	Group 1 (n=29)	Group 2 (n=31)	p

Age (years)	65,03±8,56	66,67±7,62	0,435
Male/Female	10/19	8/23	0,464
Comorbidities:			
Cardiovascular diseases	26 (89,6%)	28 (90,3%)	1,000
Endocrine diseases	8 (27,6%)	7 (22,6%)	0,881
Metabolic diseases	8 (27,6%)	13 (41,9%)	0,372
Gastrointestinal diseases	5 (17,2%)	3 (9,6%)	0,465
Benign prostate hyperplasia	3 (10,3%)	2 (6,4%)	0,666
Psychiatric diseases	3 (10,3%)	2 (6,4%)	0,666
Osteoporosis	4 (13,8%)	6 (19,3%)	0,732
Knee OA duration (years)	6,57±5,30	4,88±3,53	0,353
Radiological score distribution			
Kellgren-Laurence grade 2	19 (65,5%)	25 (80,6%)	0,302
Kellgren-Laurence grade 3	10 (34,5%)	6 (19,3%)	
Other OA			
Hip OA	11 (37,9%)	11 (35,5%)	0,844
Shoulder OA	2 (6,9%)	4 (12,9%)	0,672
Ankle OA	2 (6,9%)	1 (3,2%)	0,606

Table 14. Demographic characteristics of patients

Measured clinical variables	Treatment groups	Baseline visit		Week 2 visit		Week 12 visit		p 1-2 (significance level, difference between visits)	p 1-3 (significance level, difference between visits)	p 2-3 (significance level, difference between visits)
		Mean±SD	p (significance level, between group difference)	Mean±SD	p (significance level, between group difference)	Mean±SD	p (significance level, between group difference)			
WOMAC sum.	Tiszasüly (n=29)	888,62±354,47	0,188	651,10±382,90	0,126	608,17±445,19	0,201	**0,002**	**0,001**	0,399
	Kolop (n=31)	1048,74±05,61		808,77±389,09		773,35±491,16		**<0,001**	**<0,001**	0,445
Koos score	Tiszasüly (n=29)	52,15±9,46	0,083	50,98±21,68	0,790	50,57±21,63	0,717	0,991	0,905	0,762
	Kolop (n=31)	57,40±12,81		51,68±17,34		49,81±19,69		**0,046**	**0,039**	0,943
EQ5D score	Tiszasüly (n=29)	0,613±0,177	0,488	0,694±0,249	0,893	0,704±0,265	0,327	**0,039**	**0,028**	0,689
	Kolop (n=31)	0,490±0,307		0,734±0,146		0,652±0,255		**<0,001**	**<0,001**	0,193
EQ5D VAS score	Tiszasüly (n=29)	0,601±0,145	0,577	0,680±0,199	0,911	0,700±0,213	0,313	**0,024**	**0,011**	0,647
	Kolop (n=31)	0,534±0,192		0,708±0,150		0,655±0,187		**<0,001**	**<0,001**	0,214
VAS score for knee pain	Tiszasüly (n=29)	57,83±14,16	0,329	**24,10±21,93**	**0,009**	29,52±26,15	0,296	**<0,001**	**<0,001**	0,160
	Kolop (n=31)	61,39±14,56		**36,61±17,50**		35,16±25,02		**<0,001**	**<0,001**	0,509
Lequesne sum index	Tiszasüly (n=29)	10,45±2,65	0,784	8,21±3,93	0,953	7,72±4,17	0,267	**0,001**	**0,001**	0,354
	Kolop (n=31)	10,95±3,70		8,00±3,68		9,24±4,49		**<0,001**	**0,004**	0,046

Table 15. Means ± SD at baseline, at end of Week2 and Week12 for the two study groups (Group 1: patients receiving Tiszasüly hot mud-pack and Group 2: patients receiving Kolop hot mud-pack) and between-group differences at end of Week2 and Week12 show the effects of Tiszasüly and Kolop mud-packs on pain, function and quality of life in patients with knee osteoarthritis

CONCUSIONS, NEW RESULTS

I./1. According to the results of our study both low level laser therapy and shockwave therapy have a beneficial effect on the clinical parameters (pain, pain tolerance), physical function and quality of life of patients with myofascial pain syndrome of the trapezius. In our study the shockwave group improved significantly better. It is desirable that both therapies can decrease the analgesic and NSAID requirements. We can conclude, that both laser and shockwave therapy are possible therapeutic options in the treatment of myofascial pain syndrome of the upper trapezius.

II./1. Our randomized, double-blinded, placebo-controlled study showed, that underwater ultrasound therapy has beneficial effect on the hand function and qualitiy of life of patients with rheumatoid arthritis. All measured parameters showed significant improvement in the short term. There wasn't any statistically significant difference between the groups in tender and swollen joint count, DAS28 score and morning stiffness. Wrist extension improved more than flexion, which is explained by the nature of the disease. Based on our study, underwater ultrasound therapy is a possible therapeutic option treating the hands of rheumatoid arthritis patients.

II./2. According to our double-blinded, randomized, controlled, follow-up study, conventional treatment (exercise, massage, balneotherapy) has positive effects on pain, function and quality of life in hip OA. No significant differences were found among the effects of different modes of US (continuous, pulsed, combined with electrotherapy, placebo US). As in the placebo group significant improvement was noticed and there wasn't any inter-group difference, we can assume, that ultrasound does not increase the effects of conventional treatment. Based on our results, ultrasound therapy could be an adjunctive therapy in the treatment of hip OA beside other physiotherapy.

II./3. In our randomized, double-blinded, controlled non-inferiority study we confirmed that Kolop mud pack decreases pain, improves function and quality of life in knee OA. We

proved, that the clinical effects of Tiszasüly and Kolop muds are basically the same, there was no significant difference between them, though Tiszasüly mud-pack showed better improvement in one parameter right after treatment. We can conclude, that not only Kolop mud, but also Tiszasüly mud could be a therapeutic option in knee osteoarthritis.

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murine osteoarthritis and rheumatoid arthritis models. Evid Based Complement Alternat Med. 2018(4):1–15.

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LIST OF ABBREVATIONS

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
BNR	Beam Nonuniformity Ratio
CNS	Central nervous system
CRP	C-reactive protein
uCTX-II	C telopeptide fragment of collagen type II
CTX-II	C-terminal crosslinked telopeptide type II collagen
DAS28	Disease Activity Score in 28 Joints
DMARD	Disease modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
ESWT	Extracorporeal Shockwave Therapy
EULAR	European League Against Rheumatism
ITT	Intention-to-treat
LLLT	Low Level Laser Therapy
LOCF	Last Observation Carried Forward
MCII	Minimal clinically important improvement
MPS	Myofascial Pain Syndrome
MRI	Magnetic Resonance Imaging
MTP	Myofascial trigger points
NICE	National Institute for Health and Care Excellence
NO	Nitrogen monoxide
NRS	Numerical rating scale
NSAID	Non-steroidal Antiinflammatory Drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International

p	Value probability
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SATA	spatial average - temporal average
SF-36	Short Form (36) Health Survey quality of life questionnaires
TENS	Transcutaneous electrical nerve stimulation
TGF-beta1	Transforming growth factor-beta1
TNF-α	Tumor necrosis factor alpha
TPI	Trigger point injection
TTO	Time trade-off
US	Ultrasound
VAS	Visual analogue scale
VEGF	Vascular growth factor
WOMAC	Western Ontario and McMaster Universities Osteoarthritis

APPENDIX

I.
Effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis --- a randomized controlled trial

II.
Comparative study of shockwave therapy and low-level laser therapy effects in patients with myofascial pain syndrome of the trapezius

III.
The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study

I.

Brazilian Journal of Physical Therapy 2017;21(3):199–205

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Associação Brasileira de Pesquisa e Pós-Graduação em Fisioterapia

Brazilian Journal of Physical Therapy

https://www.journals.elsevier.com/brazilian-journal-of-physical-therapy

ORIGINAL RESEARCH

Effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis – a randomized controlled trial

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Received 13 January 2016; received in revised form 8 May 2016; accepted 13 July 2016
Available online 13 April 2017

KEYWORDS
Physical therapy;
Underwater ultrasound therapy;
Rheumatoid arthritis

Abstract
Objectives: To investigate the effects of underwater ultrasound (US) therapy in 48 patients with moderately active rheumatoid arthritis (disease activity score in 28 joints [DAS28] > 3.2 and < 5.1).
Methods: Patients randomly assigned to the ultrasound group ($n = 25$) received underwater continuous ultrasound therapy to both wrists and hands for 7 min per session with an intensity of 0.7 W/cm^2 for 10 sessions. The control group ($n = 23$) received sham treatment under the same conditions. At baseline, at the end of treatment (end of Week 2) and at the follow-up visit (Week 14), the following outcomes were evaluated: disease activity (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], tender and swollen joint counts, pain on a visual analog scale, DAS28, hand function (fist making, wrist extension and flexion, hand grip strength) and quality of life (Health Assessment Questionnaire [HAQ]).
Results: A significant decrease in C-reactive protein at the end of Week 2 and Week 14 compared to control group (mean between-group difference at 2 weeks = −5.77, 95% CI = −10.86 to −0.68, mean between-group difference at 14 weeks = −5.07, 95% CI = −10.13 to −0.01), and non-significant decrease in DAS28 was observed. By the end of treatments at the end of week 2, ultrasound alleviated pain significantly (mean between-group difference at two weeks = −8.35 95% CI = −16.12 to −0.58), as well as improved left wrist extension compared to the control group (mean between-group difference at 14 weeks = 4.35, 95% CI = 1.09–7.60).

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http://dx.doi.org/10.1016/j.bjpt.2017.04.002

Conclusion: Underwater ultrasound therapy was better than sham treatment at the end of 2 weeks of treatment, but not at long term (14 weeks) in patients with rheumatoid arthritis.

Clinical trial registration number: NCT02706028 (https://clinicaltrials.gov/ct2/show/NCT02706028)

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease affecting multiple joints (mainly the wrists and small joints of the hand) with a prevalence of about 0.5–1.0%.[1] RA is most common in middle-aged people.[2] Without adequate treatment and care, RA may lead to joint damage and disability. A decrease in the ability to make a closed fist and hand grip strength can occur in the hands; subluxation and limitation of flexion and extension may develop in to the wrists.

Non-pharmacological treatment options such as physical therapy along with chemical and biological disease modifying anti-rheumatic drugs (DMARDs) can be used to preserve physical function and improve quality of life in addition to reducing pain and inflammation.

Ultrasound (US) therapy has been used for medical purposes for more than 70 years. Its biological effects are still not exactly known. The effectiveness of ultrasonic therapy is influenced by its application parameters such as intensity, frequency, continuous or pulsed current, time of irradiation, and type of coupling agent.[3] As air reflects almost 100% of the ultrasonic beam on the transducer/air interface, a suitable coupling medium has to be utilized to allow an effective transmission.[4,5] Casarotto et al.[3] investigating the transmission properties of four coupling agents (gel, degassed water, mineral oil and petrolatum) found, that gel and water had the highest transmission coefficient and the lowest reflection. Water as a coupling agent is preferable when irregular body parts and bony prominences with little soft tissue coverage are treated, such as small joints of the hand. Compared to contact mode of treatment, in case of underwater US should be used at a higher intensity to achieve the same tissue temperature.[6] When calculating the intensity, the distance of the transducer from the treated surface should be taken into consideration.[7]

Previous research results have already confirmed the effects of US therapy on pain and function in a range of musculoskeletal disorders.[8–11] For example Mehmet et al.[8] observed benefits in patients with temporomandibular joint disorder. Similarly, Boyaci et al. found positive results in patients with knee osteoarthritis[9] by using ultrasound therapy. Unlike pain and physical function, there has not been any evidence that ultrasound treatment can alter inflammation.

The aim of this clinical trial was to determine the effects of underwater US therapy in patients with RA; analgesic and anti-inflammatory effects (primary endpoint), effects on joint function and quality of life (secondary endpoint). It was decided to treat the wrists and the small joints of the hands, since they are the most prevalent, but not equally affected joints during the disease.

Methods

This randomized, placebo-controlled, assessor- and patient-blinded trial was conducted in accordance with the ethical principles of the Helsinki Declaration and the guidelines of the International Conference on Harmonization of Good Clinical Practice. The study was approved by the Regional Research Ethics Committee, Győr, Hungary (approval number: 76-1-7/2013) and registered in ClinicalTrials.gov (registration number: NCT02706028). Patients were informed verbally about the study procedures, read the Patient Information Sheet and asked to sign an Informed Consent Form.

Patients

Inclusion criteria: Patients over 18 years of age (mean: 62.94 ± 9.27 years) with mild-to-moderate (DAS28 > 3.2 and <5.1) rheumatoid arthritis meeting the American College of Rheumatology (ACR) diagnostic criteria were enrolled into the study. Further inclusion criterion was a stable-dose pharmacotherapy (DMARDs therapy, Non-steroidal Antiinflammatory Drugs – NSAIDs, steroids) given for at least 2 months. Patients were not allowed to receive physical therapy treatments for 1 month prior to starting the study.

Exclusion criteria included other concomitant autoimmune diseases, stable-dose pharmacotherapy for less than 2 months, and conditions contraindicating US therapy (infection; fever; osteomyelitis).

Study procedures

The study was conducted at the Physiotherapy Division of the Rheumatology Outpatient Clinic of Petz Aladár County Teaching Hospital in Hungary.

Sixty patients were screened and 50 patients were enrolled into the trial. Eight patients did not meet inclusion criteria, and two patients refused to sign the Informed Consent Form. All 50 eligible patients were randomly allocated into two groups (ultrasound group and control group). The allocation was concealed by using seales, opaque envelopes.

Patients in the ultrasound group received 10 applications (10 working days) of continuous underwater US therapy (35–36 Celsius degree tap water; with the transducer at a distance of 2 cm from the treated surface) intensity of 0.7 W/cm^2 SATA (spatial average – temporal average

[continuous]), for 7 min to the palmar and dorsal aspects of each hand and wrist using a 830 kHz ULTRON home OE-302 device with treatment head size of 4.2 cm^2 (BNR: max.5:1, energy: 1234.8J, power: 2.94W). Each side of the hand and the wrist were treated in the same treatment period. The control group received sham treatment (the US device was not turned on) during the 10 sessions for 7 min per session.

The study was considered completed and data were analyzed, if the patient participated in at least 80% of the treatment sessions and attended the follow-up visits. During the 3-month follow-up period, patients were asked not to have any physical therapy treatment or to change their medication. (The analgesic or anti-inflammatory drugs were documented). The outcome parameters were recorded by 1 blinded rheumatologist before the initiation of treatment (at Week 0 – Outcomes Testing 1), immediately after the 10 treatment sessions (at the end of Week 2 – Outcomes Testing 2), and 3 months later (at Week 14 – Outcomes Testing 3).

Randomization and blinding

A concealed allocation random assignment of the enrolled patients to the treatment groups was performed (using an Excel computer program) by an independent investigator who had never met the patients and was not otherwise involved in the study procedures. The study was double-blinded, as neither the study participants nor the testing investigator (a rheumatologist) knew the treatment assignments. The statistician was not involved in the randomization procedures.

Outcome parameters

At inclusion, the age and gender of patients as well as duration of the disease and DMARD therapy (in years) were recorded. Inflammatory laboratory parameters (i.e. erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] – these are the most current used parameters for inflammation considering their costs), disease activity (measured using Disease Activity Score in 28 Joints [DAS28]), quality of life (measured using Health Assessment Questionnaire [HAQ]), number of painful and swollen joints, severity of pain at rest recorded on a 100 mm visual analog scale for pain (VASp), and duration of morning joint stiffness (in minutes) were assessed at each of the 3 Outcomes Measure Testing sessions (Week 0 [before treatment}, 2 [after last treatment session], and 3 months later). Physical function was assessed by measuring range of motion in the wrists (in degrees), degree of fist making (based on nail tilting, 3 grades were used: 0: insufficient, 1: incomplete, 2: complete); and hand grip strength (in kg) was measured with a JAMAR dynamometer. At the end of treatment period (Outcome Measure 2) and at the Month 3 follow-up visit (Outcome Measure 3), patients evaluated their own condition on a 4-grade scale (1: significantly improved, 2: improved, 3: unchanged, 4: worsened).

Statistical analysis

Statistical analysis was performed by using the IBM SPSS 20 software. The statistical power was 60%. Normality was verified with the Kolmogorov–Smirnov test. The difference between the groups was expressed using mean differences and 95% confidence interval (95% CI). Chi-squared test was used for categorical data. Missing data was imputed using the Last Observation Carried Forward (LOCF) method. We did not use an intention to treat analysis approach.

Results

Fifty rheumatoid arthritis patients receiving care at the Rheumatology Outpatient Clinic were involved in the study, which was conducted between 2013 and 2014. Forty-eight patients completed the study i.e. attended at least 80% of the treatment sessions. Two patients did not start treatment and were excluded from the analysis (i.e. an intention to treat analysis was not performed – Fig. 1).

The US group and the control group included 25 and 23 patients, respectively. Regarding demographic data, disease duration, and background therapy duration, the groups were similar at baseline (Table 1).

Inflammatory parameters, including ESR and CRP decreased in the US group at each successive outcomes measure testing session compared to baseline. In the ultrasound group, only CRP levels showed a significant improvement (i,e. a decrease) immediately after treatment (Outcome Measure 2) and at the follow-up visit (Outcome Measure 3) when compared to the control group (CRP: mean between-group difference visit 2–1 = −5.77, 95% CI = −10.86 to −0.68, mean between-group difference visit 3–1 = −5.07, 95% CI = −10.13 to −0.01). Disease activity index decreased in both groups at the end of treatment (Outcome Measure 2) and at Month 3 (Outcome Measure 3) compared to baseline, but the difference between the groups was not significant (DAS28: mean between-group difference visit 2–1 = −0.18, 95% CI = −0.61 to 0.25, mean between-group difference visit 3–1 = −0.37, 95% CI = −0.84 to 0.09). Pain sensation decreased in both groups compared to baseline, and this decrease was significant in the US group at the end of Week 2 (Outcome Measure 2) (VAS: mean between-group difference visit 2–1 = −8.35, 95% CI = −16.12 to −0.58). No substantive changes were observed in the duration of morning joint stiffness, the number of tender and swollen joints in any of the groups at any outcome test session, and no difference was

Table 1 Demographic data, disease duration, and background therapy duration in the two study groups to show the effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis.

Variable	Ultrasound group ($n = 25$)	Control group ($n = 23$)
Age (years)	63.24 (11.04)	62.83 (7.25)
Disease duration (years)	13.04 (9.30)	14.03 (13.49)
DMARD therapy duration (years)	10.67 (8.60)	12.35 (12.91)
Male	6 (24)	4 (17)
Female	19 (76)	19 (83)

Continuous data is expressed as mean (SD), categorical data is expressed as *n* (%).

Table 2 Means ± SD at baseline, at end of Week 2 and Week 14 for the two study groups (treated group: patients receiving underwater ultrasound and control group: receiving sham treatment) and between-group differences at end of Week 2 and Week 14 to show the effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis.

	Group	Outcome Measure 1 (Week 0)	Outcome Measure 2 (end of Week 2)	Outcome Measure 3 (Week 14)	Mean between group differences at visit 2–1 (95% CI)	Mean between group differences at visit 3–1 (95% CI)
		mean ± SD	mean ± SD	mean ± SD		
ESR (mm/h)	Treated	23.64 ± 18.06	22.00 ± 18.07	19.16 ± 12.81	−4.59 (−11.44 to 2.26)	−5.05 (−11.15 to 1.06)
	Control	22.30 ± 12.20	25.26 ± 16.38	22.87 ± 12.50		
CRP (mg/l)	Treated	11.12 ± 9.38	7.49 ± 9.85	6.00 ± 8.35	**−5.77 (−10.86 to 0.68)**	**−5.07 (−10.13 to 0.01)**
	Control	6.17 ± 7.84	8.31 ± 8.97	6.12 ± 7.59		
DAS28	Treated	3.98 ± 0.67	3.35 ± 0.96	3.29 ± 1.09	−0.18 (−0.61 to 0.25)	−0.37 (−0.84 to 0.09)
	Control	4.10 ± 0.65	3.66 ± 0.70	3.78 ± 0.88		
HAQ	Treated	1.35 ± 0.80	1.26 ± 0.91	1.12 ± 0.85	−0.19 (−0.55 to 0.17)	−0.22 (−0.49 to 0.04)
	Control	1.36 ± 0.50	1.45 ± 0.56	1.35 ± 0.63		
Morning stiffness (min)	Treated	20.08 ± 29.10	17.48 ± 19.67	18.76 ± 27.46	−1.73 (−11.21 to 7.75)	1.11 (−18.52 to 20.75)
	Control	20.17 ± 37.60	19.30 ± 37.57	17.74 ± 28.16		
Tender joint count	Treated	3.32 ± 2.12	3.06 ± 2.70	2.68 ± 3.35	1.17 (−0.57 to 2.91)	0.01 (−1.80 to 1.83)
	Control	4.43 ± 3.51	3.00 ± 2.89	3.78 ± 3.41		
Number of swollen joints	Treated	1.32 ± 1.44	0.70 ± 1.13	0.68 ± 1.52	−0.10 (−0.81 to 0.61)	−0.47 (−1.53 to 0.60)
	Control	1.04 ± 1.40	0.52 ± 0.90	0.87 ± 1.52		
VAS	Treated	52.80 ± 20.26	38.80 ± 22.42	44.00 ± 26.85	**−8.35 (−16.12 to 0.58)**	−4.89 (−18.02 to 8.25)
	Control	48.91 ± 15.30	43.26 ± 16.21	45.00 ± 13.22		
Right wrist extension (degree)	Treated	57.40 ± 16.36	60.52 ± 17.47	59.08 ± 17.95	5.12 (−0.03 to 10.27)	2.38 (−3.60 to 8.35)
	Control	58.91 ± 22.41	56.91 ± 23.46	58.22 ± 24.33		
Right wrist flexion (degree)	Treated	46.84 ± 14.40	48.52 ± 12.12	49.16 ± 14.96	0.81 (−4.68 to 6.30)	1.75 (−4.73 to 8.24)
	Control	43.04 ± 22.47	43.91 ± 20.31	43.61 ± 20.31		
Left wrist extension (degree)	Treated	59.96 ± 18.95	63.96 ± 17.80	64.72 ± 16.87	**4.35 (1.09 to 7.60)**	5.93 (−0.05 to 11.92)
	Control	64.96 ± 22.66	64.61 ± 23.30	63.78 ± 24.96		
Left wrist flex. (degree)	Treated	46.96 ± 16.90	47.92 ± 17.50	49.96 ± 17.06	0.70 (−4.86 to 6.27)	2.96 (−2.35 to 8.27)
	Control	51.43 ± 18.07	51.70 ± 17.61	51.48 ± 15.79		
Hand grip strength, right (kg)	Treated	12.60 ± 7.19	14.13 ± 8.25	14.52 ± 9.03	1.87 (−0.47 to 4.20)	0.93 (−2.18 to 4.05)
	Control	13.30 ± 7.31	12.94 ± 6.59	14.28 ± 7.71		
Hand grip strength, left (kg)	Treated	13.55 ± 6.97	14.14 ± 7.86	14.81 ± 8.34	0.21 (−1.51 to 1.93)	0.52 (−2.16 to 3.19)
	Control	12.57 ± 6.80	12.94 ± 6.59	13.32 ± 6.91		

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; HAQ, Health Assessment Questionnaire; VASp, visual analog scale – pain.
Where confidence intervals of different parameters do not contain 0 (zero), there are statistically significant differences between groups.

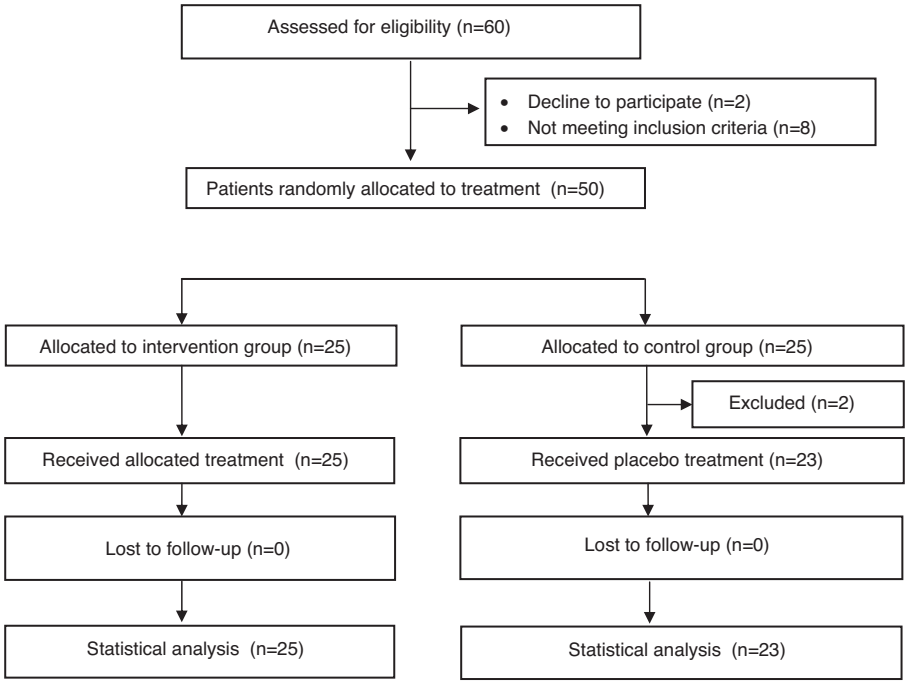

Figure 1 Participant flow to show the effects of underwater ultrasound therapy on pain, inflammation. Hand function and quality of life in patients with rheumatoid arthritis.

found between the groups. Quality of life measured using HAQs improved in the US group, but the difference between the two groups was not significant. Extension and flexion of the wrists improved non-significantly from baseline in the US group and did not change in the control group. In the ultrasound group, only left wrist extension showed a significant improvement at Week 2 (Outcome Measure 2) when compared to the control group (mean between-group difference Outcome Measure 2−1 = 4.35, 95% CI = 1.09–7.60). The degree of fist making did not show any changes in any of the groups. Hand grip strength slightly increased in the US group, but the difference between the two groups was not statistically significant. Patients of both the US group and the control group considered their own condition improved at the end of treatment (Outcome Measure 2) and at the Month 3 follow-up visit (Outcome Measure 3). Changes in the studied parameters and statistical data are shown in Tables 2 and 3. No adverse events were observed during the study.

Discussion

In this randomized, double-blinded, placebo-controlled trial both the primary endpoint parameters (i.e. pain and inflammation) and the secondary endpoint parameters (HAQ and hand function) showed significant improvement in the short term in patients with RA treated with ultrasound. Pain measured on a VAS also decreased, although to a lesser extent, in the control group, which could be due to placebo effect.[12] The anti-inflammatory effect could be supposedly due to vasodilation caused by the thermal effect. Cruz et al. found, that 1 MHz continuous (0.4 W/cm^2 SATA), or pulsed (20% duty cycle, 0.08 W/cm^2 SATA) ultrasound

Table 3 Changes in degree of fist making and patients' impression in the study groups to show the effects of underwater ultrasound therapy on pain, inflammation, hand function and quality of life in patients with rheumatoid arthritis.

		Outcome Measure 1	Outcome Measure 2	Outcome Measure 3	Outcome Measure 1 p[a]	Outcome Measure 2 p[a]	Outcome Measure 3 p[a]
Degree of fist making, right hand (3 grades)	Treated Control	5/11/9 7/10/6	3/12/10 7/8/8	5/10/10 8/7/8	0.64	0.28	0.51
Degree of fist making, left hand	Treated Control	6/9/10 4/9/10	5/8/12 5/8/10	5/8/12 4/9/10	0.85	0.95	0.87
Patient impression (1–4)	Treated Control		2.24 ± 0.78 2.39 ± 0.66	2.40 ± 0.76 2.39 ± 0.66		0.51	0.83

[a] Chi^2 test.

therapy improved endothelial function in humans, which has an anti-inflammatory vascular effect. They postulated that a mechanical effect, which stimulated nitrogen-monoxid production resulting in vasodilation.[13] According to Watson, the overall influence of US in the inflammed tissue was pro-inflammatory, which enablesd tissue repair.[4] This could explain the results of Hashish et al.[14] testing the value of US for reducing postoperative inflammation. They described a placebo-mediated mechanism with maximum anti-inflammatory effect in the placebo group.[14] In the present study, the decrease of CRP in the control group could have been due to the normal tissue repair, which was enhanced by the therapy in the ultrasound group. Based on the meta analysis of Robertson and Baker[15] in 2001, the randomized controlled trials evaluating US therapy are heterogenous in terms of the investigated parameters and the dosage of US. In the majority of the studies, no significant differences were found in outcomes between humans treated with ultrasound or placebo US.[15] In case of underwater therapy, water is a coupling medium that allows ultrasound transmission to the biological tissue. Underwater treatment has the advantage of enabling the treatment of small joints of the hand simultaneously and effectively. Clinical studies have confirmed the beneficial effects of underwater US therapy in RA. The Ottawa Methods Group found level ''A'' evidence for pain relief, and level ''C'' evidence for the decrease in joint swelling and morning joint stiffness.[16] Hawkes et al.[17] compared three treatment groups, all including 10 patients: exercises and wax baths, exercises with ultrasound, and exercises with ultrasound and faradic hand baths. The 3 MHz continuous ultrasound with an intensity of 0.250 W/cm^2 was applied in water to the palmar aspect of the hand for 3 minutes, five times a week, for 3 weeks. These authors did not find significant differences between the three groups with regard to pain, grip strength, proximal interphalangeal joint circumference, articular index, range of motion or level of activity.[17] In the study by Konrád,[18] the effects of underwater US therapy were compared to placebo treatment in 50 RA patients. US was applied to the dorsal and palmar aspects of the hand, at 0.5 W/cm^2 continuously, for ten minutes on alternate days for 3 weeks. Significant improvement in the number of tender and swollen joints, joint stiffness, and dorsiflexion of wrists were reported in patients receiving ultrasound therapy, as compared to sham treatment.[18]

Considering secondary endpoint parameters, a significant change in wrist extension and quality of life was observed in the US group when compared to the control group. Wrist extension improved more than flexion, which is explained by the nature of the disease (i.e. impairment of extension is more pronounced during the course of the disease). Favorable changes in quality of life were only short-term. In 2002, based on data gathered from the Cochrane Database, Casmiro et al.[19] found that in rheumatoid arthritis, US therapy increased hand grip strength, to a lesser degree decreased the tender and swollen joint counts, morning hand stiffness and improved wrist dorsal flexion. US therapy combined with other physical therapy methods was not better than US therapy alone.[19] In the present study, no significant changes in hand grip strength were found, which could be explained by the long (more than 10 years) disease duration. Krawczyk-Wasielewska et al. have confirmed that in cases of longer RA disease duration, the primary effect of physical therapy was pain relief, while range of motion of the joints improved to a lesser extent.[20] In rheumatoid arthritis, a decrease in pain and improvement in function both have a beneficial effect on quality of life in the long term.

Limitations of the study

The weakness of our study was the small sample size and lack of intention to treat analysis. We are planning to extend our study and involve more patients even in a multicenter setting, which may increase the power of the study and provide more precise results.

Conclusion

Similar to previous results, our randomized trial has shown favorable short-term effects of underwater US therapy on pain, quality of life, and joint function in patients with rheumatoid arthritis but in the long-term it was not superior to sham treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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Rheumatology International
https://doi.org/10.1007/s00296-018-4134-x

Rheumatology
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CLINICAL TRIALS

Comparative study of shockwave therapy and low-level laser therapy effects in patients with myofascial pain syndrome of the trapezius

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Received: 2 July 2018 / Accepted: 14 August 2018

Abstract

The objective of the study was to compare the effects of shockwave therapy and laser therapy on pain, neck functionality, and quality of life in patients with myofascial pain syndrome of the trapezius. 61 patients (> 18 years) were randomly allocated to two treatment groups: (1) 31 patients received soft laser therapy once daily in a 3-week period for a total of 15 sessions, (2) 30 patients received shockwave therapy once in a week for 3 weeks, totalling 3 treatments. Resting pain and pain tolerance were assessed by a 100 mm visual analogue scale; functional status and quality of life were measured by specific questionnaires (Neck Disability Index, SF-36) before and after the 3-week therapy and at the 15th week follow-up visit. All measured parameters improved significantly in both groups at week 3 and week 15. Comparing the two groups, patients receiving shockwave therapy demonstrated significantly better changes in pain tolerance (mean between-group differences at visit 1–0 = 14.911, 95% CI = 2.641–27.182, mean between-group differences at visit 2–0 = 17.190, 95% CI = 4.326–30.055 in the left trapezius), neck functionality (mean between-group differences at visit 1–0 = 0.660, 95% CI = − 1.933 to 3.253, mean between-group differences at visit 2–0 = 1.072, 95% CI = − 2.110 to 4.254), and in all domains using SF-36 QoL questionnaire. The only parameter in which the laser group showed significantly higher benefits was at week 15 for resting pain (mean between-group differences at visit 2–0 = − 1.345, 95% CI = − 14.600 to 11.910). The results of our study point to a conclusion that both laser and shockwave therapy are effective in myofascial pain syndrome, though we found shockwave therapy to be somewhat more beneficial.
Clinical trial registration number NCT03436459 (https://clinicaltrials.gov/ct2/show/NCT03436459).

Keywords ESWT · Laser therapy · MPS

Introduction

Neck pain is a very frequent musculoskeletal disorder with an estimated prevalence between 5.9 and 38.7% in the public [1, 2]. The pain is most frequently due to myofascial pain syndrome (MPS). MPS is caused by direct traumatic events, which are repeated micro-traumas and repetitive strains, and indirect factors, which are conditions that cause muscle weaknesses, such as nutrition disorders, sleep disturbances, endocrine metabolic pathologies, and emotional stress. Factors released from damaged muscle fibers and from extracellular fluids are the causes of the pain. Myofascial pain syndrome is frequently found in the background of musculoskeletal disorders; also known as regional pain syndrome, it is mostly localized to the regions of the neck, lumbar spine, and shoulders.

MPS is associated with intense and deep pain of muscle fasciae, with one or more myofascial trigger points (MTP), palpable muscle knots (contraction of the taut band), and, consequently, a restricted range of motion [3]. Theres is no specific therapy, so the aims are generally to inactivate painful trigger points, to release muscle tension, and to break the vicious cycle of pain-muscle, and spasms–ischaemia–pain. Literature data research proves that local injection therapy and various kinds of physiotherapy, such as shockwave therapy, acupuncture, exercise therapies (especially stretching), local heat applications, kinesio taping, and laser therapy are

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Published online: 31 August 2018

all efficient. Masticatory muscle pain LLLT decreases the pain better than pharmacotherapy [4].

Low-level intensity laser therapy—LLLT—induces photochemical effects. Penetrating through the tissue, it provides biostimulation; by supplying energy to the cell it increases cellular metabolism. This can help muscle regeneration. In parallell, LLLT activates intradermal somatosensory receptors, which decreases local pain and efficiently relaxes musculature [5, 6].

The principle of high-intensity shockwave therapy is the production of mechanical energy by high-pressure air. This energy is propagated in the tissues as a longitudinal wave. It assists in revascularization, and by causing micro-functional and micro-structural changes leads to tissue regeneration. Its pain relieving effects have been described in plantar fasciitis, calcifying tendinitis, as well as myofascial pain syndrome. High-energy ESWT was more effective in improving Neck Disability Index (NDI) and neck flexion range of motion, indicating its superiority in functional improvement [7], compared to low-energy ESWT.

Due to the pain relieving and muscle relaxation effects of these two therapies, patients are expected to see improvements in both motion and quality of life of myofascial pain syndrome, too.

Aim of the study

Our aim was to compare the effects of shockwave therapy and laser therapy on pain tolerances, neck functionality, and quality of life in patients suffering from myofascial pain syndrome of the trapezius.

Patients and methods

Our study protocol followed the principles of the Helsinki Declaration. Study participants received written information and signed the Informed Consent Form before the initiation of the study. This randomized, controlled, assessor-blinded trial was approved by the Regional Research Ethics Committee of Petz Aladár County Teaching Hospital (approval number: 76-1-23/2015), and is registered in ClinicalTrials.gov (NCT03436459). Participants were recruited from patients from the Department of Rheumatology and Physiotherapy of Petz Aladár County Teaching Hospital`s Rheumatology Outpatient Clinic. The study was conducted between February 2016 and September 2017.

Inclusion criteria

The study included patients over 18 years of age diagnosed with myofascial pain syndrome according to Simon's Diagnostic Criteria (5 major, 1; regional pain, 2; referred pain, 3; a taut band, 4; a tender point in the taut band, 5; restricted range of motion, and one of minors, 1; pain complaints reproduced by pressure on the tender spot, 2; a local twitch response, 3; and relief of pain with injection, or by stretching) with persistent neck and/or shoulder regional pain, for at least 8 weeks preceeding inclusion (chronic pain). Patients were not allowed to receive physical therapy, or any local trigger point injection for 3 months prior to starting the study [8].

Exclusion criteria

Exclusion criteria were: pain persisting for less than 8 weeks in the neck or shoulder (acute or subacute pain), physiotherapy, or local trigger point injections of the involved regions within 3 months' time, blood parameter discrepancies (blood counts or erythrocyte sedimentation rates), infection, febrile states, symptoms of cervical radiculopathy, untreated hypertension, anticoagulant therapy or coagulation disorders, any cervical spine surgery in the medical history, metal devices, and implantations.

Randomization

A concealed allocation random assignment of the enrolled patients to the treatment groups was performed by an independent study technician (using a computer software) who did not meet any of the patients and did not participate in the course of the study either.

Blinding method

Neither the testing investigator nor the statistician was aware of the treatment assignments, nor the randomization process of the patients from start to end of the study.

Altogether, 70 patients were included and 61 patients were randomized. Six patients did not meet inclusion criteria, and three patients revoked their consent. Following randomization, 61 patients were grouped into two arms: the laser (Group 1) and shockwave (Group 2). The allocation was concealed by using sealed, opaque envelopes. 31 patients out of 61 (mean age: 62.62 ± 9.62 years; male/female: 4/27) were assigned to the laser group and 30 patients (mean age 57.26 ± 14.31 years, male/female: 3/27) to the shockwave group (Fig. 1). There were no significant differences among the two groups in age or gender proportions.

Interventions

Laser arm (Group 1) patients received soft laser treatment once daily, altogether 15 times (on 15 work days) (PR999 4W scanning laser; Medical Italia; regions around the trigger point were treated with 2000 Hz (800 mW), 3 J/cm^2 for

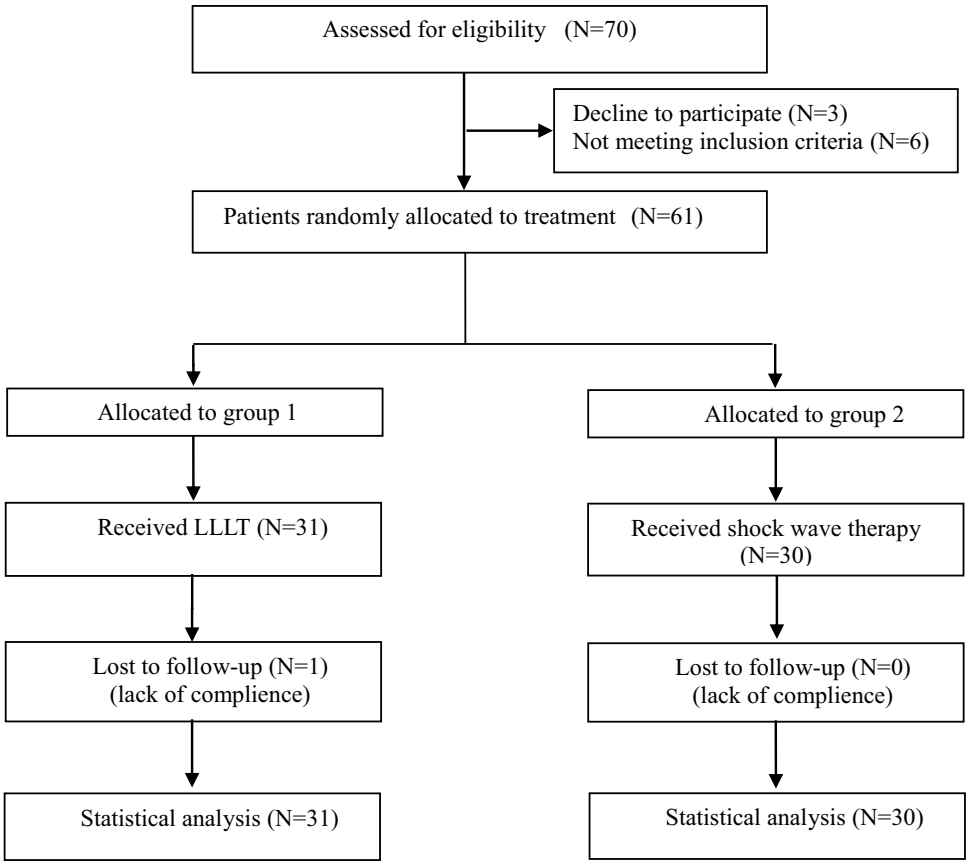

Fig. 1 Participant flow to show the effects of LLLT and ESWT on pain, function and quality of life in patients with myofascial pain syndrome

2 min; the palpable trigger point was treated with 5000 Hz (2000 mW), 9 J/cm^2, for 2 min) on the trapezius muscle and on trigger point. In the shockwave arm (Group 2), patients received therapy once weekly, altogether three times (BTL-6000 SWT Topline Power; 1000 impulses in the region of the trigger point, 1.5 bar, 10 Hz, energy density: 0.25 mJ/mm^2, 15 mm treating head diameter, followed by 1000 impulses, 2 bar, 10 Hz, energy density: 0.25 mJ/mm^2, using a 15 mm treating head diameter to the trigger point) to the trigger point and its vicinities. Patients were considered to have completed the study if they participated in at least 80% of the therapies and presented themselves on follow-up visits. Patients were not to receive any other physiotherapy during the 3 months follow-up period. According to internationally accepted practice, patients were asked to sign if they needed any analgesic or anti-inflammatory medication, which we recorded in their ambulant files. Before the start of therapy (week 0), the outcome parameters were recorded by a rheumatologist, as well as immediately after the therapy series (week 3) and 3 months later (week 15).

Outcome parameters

At the inclusion, patients' ages and genders were recorded. During each visit, we applied a 100 mm visual analogue scale (VAS) to assess rest/spontaneous pain level, and we measured the functional impairment (Neck Disability Index—NDI), quality of life (SF-36), and the need for painkiller medication. At the start of the study, we applied a dolorimeter [BASELINE (Fabrication Enterprises, Inc.)] to determine pain tolerance in the upper parts of both trapezius muscles [pressure value in kg/cm^2, whereby a maximal (VAS:100 mm) pain is signalled by the patient]. In subsequent visits, by applying the same standarized pressure as at the baseline visit, we asked the patients to indicate their pain on 100 mm VAS. Immediately following 3 weeks of therapy, and during the control visit at week 15, patients also evaluated their status/subjective well-being in a 4-grade Likert scale (1, significantly improved; 2, improved; 3, unchanged; 4, worsened).

The same study technician recorded the outcome measures before therapy, after the last treatment session, and at the end of the follow-up period, at week 15.

Statistical analysis

The statistical analysis was processed with IBM SPSS 24 software. The data are expressed as the mean ± SD. Data distribution was investigated with the Kolmogorov–Smirnov test. We found a normal distribution for age and NDI; here we used the independent patterned *t* test and paired *t* test. Other data were calculated by Mann–Whitney and Wilcoxon test. The measurements of differences between groups were carried out by either an independent *t* test or Mann–Whitney test. The difference between the groups was expressed using mean differences, with a 95% confidence interval (95% CI). Chi-squared test and Fisher's exact test were used for categorical data. Missing data were imputed using the last observation carried forward (LOCF) method. *P* values < 0.05 were considered significant. We did not use an intention to treat analysis approach.

Results

Both groups demonstrated similar changes during the study in all parameters.

Resting pain significantly decreased in both groups after therapy and at a 15 weeks follow-up; immediately after therapy patients in Group 2 and at 3 months post-therapy patients in Group 1 demonstrated significantly better improvement compared to each other.

Pressure pain (a.k.a. pain tolerance) also significantly improved in both trapezius muscles in all treatment groups, as recorded during the visits, but here improvement was significantly higher in the shockwave therapy group at the 3rd week and in the 15th week. Comparing results on the right and left side of the musculature, shockwave therapy group patients demonstrated a higher improvement in the pressure pain on the left side, while no such difference was observed in the laser group.

Neck functionality impairment significantly improved in both the laser and the shockwave group for the week 3 and week 15 visits, and the amplitude of change was significantly higher in the shockwave group.

The SF-36 QoL questionnaire domains of physical function, energy, and pain significantly showed improvements in both groups immediately after therapy and at week 15. Shockwave therapy patients showed significant improvements in all eight parameters (1, physical functioning; 2, physical role functioning; 3, emotional role functioning; 4, vitality; 5, mental health; 6, social role functioning; 7, bodily pain; 8, general health perceptions) in all visits, while patients in the laser group only had five improved domains out of eight in total: physical function, physical role functioning, vitality, social role functioning, and bodily pain.

When comparing changes between the two groups, both at week 3 and week 15, improvement in the shockwave therapy group was significantly higher, except for emotional well-being on week 3 and physical health at week 15 (Table 1).

Patients reported the improvement of their own status (a.k.a. subjective well-being) in both groups using the 4-grade Likert scale; in both groups 86.6% of patients improved, while 13.3% of them reported no changes after the therapy and at week 15 (Table 2).

During the follow-up, it was noted that myelogelous knots had disappeared in approximately half of all patients in both groups.

In both groups, less than 25% of patients needed medication (analgesics, antirheumatics, or muscle relaxants) during the study. The majority of medicated patients took the medication for less than 1 week's time. No adverse events were noted or recorded during this study (Table 3).

Discussion

In our study, all measured parameters improved significantly in both groups at the end of treatment and the follow-up period. Analysing the results, patients receiving shockwave therapy demonstrated significantly better changes in all outcome measurements.

In the case of laser therapy pain relief, supposedly due to stimulation of endogenous opioid release, an increase in pain threshold and changes in bradykinin and histamine release are noted [9]. Animal studies have shown that soft laser therapy in myofascial syndrome decreases intramuscular levels of COX-2 and TNF-alpha, while beta-endorphin levels are increased in the serum, muscle, and spinal dorsal root ganglion [10]. Based on other animal models, LLLT is able to reduce the COX-2 mRNA expression in the central nervous system (CNS), which may be a possible explanation for its hyperalgesia decreasing effect [11]. In a model of induced hyperalgesia, LLLT decreased Fos expression and the mRNA levels of IL-6, TNF-α, and B1 and B2 kinin receptors leading to pain relief [12].

The efficiencies of soft laser therapy in acute and chronic musculoskeletal pain are reported in medical literature to various extents. The analgesic effect and safety have been proven in temporomandibular disorders and in different joint areas [13–15]. Based on a current review, many studies have demonstrated analgesic and anti-inflammatory effects provided by photobiomodulation in clinical, as well as in experimental trials [16]. The effectiveness of laser therapy was studied alone in a placebo-controlled trial in comparison with exercise therapy and acupuncture, along with combination with other therapeutic modalities.

A 2013 meta-analysis reports that moderate evidence suggests that LLLT in chronic neck pain has improving effects

Table 1 Mean ± SD at baseline and at the end of week 3 and week 15 for the two study groups (Group 1: patients receiving low-level laser therapy and Group 2: patients receiving extracorporeal shockwave therapy) and between-group differences at the end of week 3 and week 15 show the effects of LLLT and ESWT on pain, function and quality of life in patients with myofascial pain syndrome

Measured clinical variables	Outcome measure 0 (week 0) mean ± SD	Outcome measure 1 (week 3) mean ± SD	Outcome measure 2 (week 15) mean ± SD	Between-group differences at visit 1–0 (95% CI)	*p*	Between-group differences at visit 2–0 (95% CI)	*p*
VAS pain at rest							
Group 1	46.06 ± 18.02	25.16 ± 18.63	22.42 ± 21.39	1.030 (− 8.116 to 10.176)	0.822	− 1.345 (− 14.600 to 11.910)	0.840
Group 2	47.70 ± 20.75	25.7 ± 25.56	25.40 ± 22.67				
VAS pressure pain right							
Group 1	100	60.65 ± 21.60	56.16 ± 21.17	4.078 (− 7.135 to 15.292)	0.470	9.561 (− 3.056 to 22.179)	0.135
Group 2	100	56.57 ± 22.17	46.60 ± 27.74				
VAS pressure pain left							
Group 1	100	61.65 ± 24.70	59.29 ± 21.65	14.911 (2.641 to 27.182)	0.018	17.190 (4.326 to 30.055)	0.010
Csoport 2	100	46.73 ± 23.14	42.10 ± 28.23				
NDI							
Group 1	15.55 ± 6.09	10.51 ± 7.28	10.01 ± 6.91	0.660 (− 1.933 to 3.253)	0.612	1.072 (− 2.110 to 4.254)	0.503
Group 2	16.08 ± 7.58	10.38 ± 6.90	9.47 ± 5.65				
Physical functioning (SF-36)							
Group 1	62.26 ± 16.47	69.03 ± 18.86	69.84 ± 18.46	− 2.059 (− 9.044 to 4.926)	0.558	− 2.419 (− 11.104 to 6.265)	0.579
Csoport 2	67.83 ± 20.12	76.67 ± 18.30	77.89 ± 19.19				
Role functioning/physical (SF-36)							
Group 1	45.16 ± 36.18	59.68 ± 41.67	56.45 ± 41.32	− 13.817 (− 31.549 to 3.915)	0.124	− 19.543 (− 37.894 to 1.192)	0.037
Group 2	40.00 ± 35.72	68.33 ± 37.68	70.83 ± 37.18				
Role functioning/emotional (SF-36)							
Group 1	62.35 ± 40.18	63.43 ± 39.76	62.35 ± 43.67	− 12.259 (− 32.903 to 8.345)	0.239	− 17.779 (− 40.180 to 4.622)	0.118
Group 2	59.99 ± 41.43	73.32 ± 36.52	77.77 ± 37.48				
Energy/fatigue (SF-36)							
Group 1	60.19 ± 18.95	66.29 ± 16.53	68.87 ± 17.50	− 7.237 (− 15.439 to 0.966)	0.083	− 7.823 (− 17.432 to 1.787)	0.109
Group 2	53.17 ± 19.00	66.50 ± 16.30	69.67 ± 13.89				
Emotional well-being (SF-36)							
Group 1	72.90 ± 19.18	74.84 ± 19.38	74.84 ± 20.11	− 8.665 (− 15.375 to 1.954)	0.012	− 6.331 (− 14.538 to 1.875)	0.128
Group 2	69.20 ± 16.94	79.80 ± 14.60	77.47 ± 14.72				
Social functioning (SF-36)							
Group 1	73.39 ± 20.61	81.05 ± 17.93	79.44 ± 20.04	− 2.339 (− 12.959 to 8.281)	0.662	− 5.618 (− 15.542 to 4.306)	0.262
Group 2	72.50 ± 17.80	82.50 ± 17.25	84.17 ± 19.40				
Pain (SF-36)							
Group 1	50.64 ± 15.07	62.82 ± 19.93	69.11 ± 17.94	− 6.489 (− 15.100 to 2.121)	0.137	− 5.116 (− 16.704 to 4.472)	0.252
Group 2	44.50 ± 20.12	63.17 ± 17.26	69.08 ± 18.53				
General health (SF-36)							
Group 1	51.94 ± 15.37	55.97 ± 17.82	56.29 ± 17.84	− 1.058 (− 7.649 to 5.513)	0.747	− 2.078 (− 9.398 to 5.241)	0.572
Group 2	52.23 ± 20.83	57.33 ± 20.96	57.46 ± 19.10				

NDI Neck Disability Index

Table 2 Changes in degree of patients' improvement in the study groups show the effects of LLLT and ESWT on pain, function, and quality of life in patients with myofascial pain syndrome

	Outcome measure 0		Outcome measure 1		Outcome measure 2		p^a 0–1	p^a 0–2	p^a 1–2
	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*			
Patient impression (1–4)									
Group 1			2.00 ± 0.52	0.078	1.73 ± 0.69	0.283			0.059
Group 2			1.73 ± 0.69		1.90 ± 0.61				0.660

[a]Chi^2 test

Table 3 Changes in the number of patients taking medicine and the number of patients having myogelosis in both treatment groups show the effects of LLLT and ESWT on pain, function, and quality of life in patients with myofascial pain syndrome

	Outcome measure 0 (week 0)		Outcome measure 1 (week 3)		Outcome measure 2 (week 15)	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Medicine						
Group 1 ($n=31$)	4 (13%)	0.508	4 (13%)	0.389	8 (26%)	0.384
Group 2 ($n=30$)	6 (20%)		7 (23%)		5 (17%)	
Medicine < 1 week						
Group 1 ($n=31$)	4 (13%)	1.000	4 (13%)	1.00	7 (23%)	0.147
Group 2 ($n=30$)	4 (13%)		3 (10%)		2	
Medicine > 1 week						
Group 1 ($n=31$)	0	–	0	–	1	0.354
Group 2 ($n=30$)	2		4 (13%)		3 (10%)	
Myogelosis						
Group 1 ($n=30$)	12 (40%)	0.186	8 (27%)	0.153	6 (20%)	0.587
Group 2 ($n=26$)	15 (58%)		12 (46%)		7 (27%)	

on pain, vital function, and quality of life for short term (3 months) and also in mid-term (6 months) [5]. In women suffering from fibromyalgia, photobiostimulation combined with exercise therapy improved qualitiy of life and the pain threshold [17]. In our study, LLLT significantly improved resting and pressure pain, pain tolerance, neck function, and quality of life.

Considering the contraindication of LLLT, we did not use it during advanced pregnancy or over the thyroid gland. There is no data, that ESWL is safe in patients suffering from malignant tumours, or in patients having survived carcinoma. It can be harmful to the eyes, a problem that can be avoided by using tinted glasses. Side effects are hardly reported in medical literature, and in our study we did not find any side effects.

Shockwave therapy has been applied since the 1980s in musculoskeletal diseases. Its effective mechanisms still remain a mystery; pain and inflammation relief are attributed to modulatory effects on nitrogen monoxide (NO) and vascular growth factor (VEGF). Shockwave therapy can be used to stimulate angiogenetic factors and microvascular regeneration, such as microcapillary dilatation. Tissue regeneration could be further improved by the increased prostaglandin production. Its positive effects were confirmed primarily in soft tissue diseases (fasciitis, tendinitis). Shockwave therapy not only decreases pain in myofascial pain syndrome, but also improves motion and increases pain tolerance [18, 19]. In our study, patients receiving shockwave therapy demonstrated significant improvement in pain, pain tolerance, neck functionality, and quality of life.

Shockwave therapy can be painful; minor skin bruising, reddening, and swelling around the treated area can occur, but these side effects often disappear after a short period of time. Our patients did not report any side effects.

Up to now, one literature report, published by Taheri et al., is known to compare shockwave therapy and laser therapy in neck myofascial pain syndrome (however in that study, both groups also practised stretching exercises). During laser therapy, a Ga–AL–As laser was applied (6 J/cm^2 energy, mean power of 100 mW), while shockwave therapy was performed with 1000 impulses, 3 J/m^2 energy density, and 10 Hz of frequency. Both groups demonstrated improvement, but in their cases, laser therapy patients improved significantly better, which is contrary to our findings [20]. In a Korean study (with low patient numbers) patients received four shockwave therapies in 2 weeks in the upper trapezius muscle (0.056 mJ/mm^2, 1000 impulses) with good therapeutic effect [21]. In another work by Turkish authors, high-intensity laser therapy was more effective than the placebo in MPS [6]. In our study, higher laser power and higher energy density shockwaves were applied.

Patients in the shockwave therapy group had a better improvement in resting pain after the treatment sessions, in pain tolerance, neck function throughout the follow-ups, and they demonstrated significantly better improvement in all domains of SF-36. We cannot currently find an exact reason for the higher analgesic effect using shockwave therapy, but we can postulate that the painful effects of therapy could have a role in that. Pressure pain was sensed differently in the left and right trapezius muscles in patients of the shockwave therapy, which we attribute to random variation or the small patient number.

In nonpharmacologic physiotherapies, shockwave has also been widespread in the past years, along with dry needling acupuncture, different stretching exercises, and laser therapy for the treatment of MPS trigger points. Similarly, results reported in medical literature confirmed the results of our studies that showed an improvement of neck function

and QoL due to both therapy regimens. Physical functioning, vitality, social role functioning, and bodily pain improved the most among QoL domains in both groups in our study. This can be attributed to pain relief and trigger point inactivation effects of laser and shockwave therapies.

In our study, less than 25% of patients were taking medication for analgesia and muscle relaxation. As the constitution of patients taking medication, there was a difference in each follow-up visit, and the duration of pharmacotherapy was short. We cannot declare a relationship between changes in patient numbers, and the efficiency of therapy.

We consider that the two examined therapies do have a role in decreasing pain and the increase of QoL in patients with myofascial pain syndrome. Comparative studies of different therapy modalities can assist practising physicians to make the best choices of therapy.

Limitation of the study

The outcome measures show a high standard deviation (SD) and big differences between the changes. That is why we chose to use mean differences, with a 95% confidence interval (95% CI) instead of parametric test. The starting values were not homogeneous and the tests filled out by the patients were subjective (e.g. they may judge the same pain differently). There is also a high SD in age, which could have been narrowed by the inclusion criteria; but in that case the number of patients would have been low. Otherwise, there were no divergent values, the data of the two groups showed similar SD and so the results are not so distorted.

In further studies, we recognize that increased patient numbers is desirable. Literature reports are ambiguous as to the frequency and duration of therapy sessions; although a three times ESWT was efficient, increasing frequency could increase the clinical efficiency even further. In laser therapy, one parameter (power) was taken into account, while a power increase and multi-local irradiation of trigger points could also increase the effect. In our study the follow-up period was only 15 weeks, so the mid-term and long-term effects could not be demonstrated.

The inclusion criteria regarding the duration of the symptoms was at least 8 weeks, which might be short. However, most of the study patients reported more than 12 weeks duration of neck or shoulder pain.

Conclusion

In our study, carried among middle-aged patients suffering from myofascial pain syndrome of the trapezius mucle, both laser and shockwave therapy have proven to effectively improve pain tolerance, neck functionality, and quality of life, but the clinical effectiveness of shockwave therapy was found to be higher. In the future, we will need more studies with larger sample sizes to test a variety of additional parameters.

Funding None.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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III.

The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study

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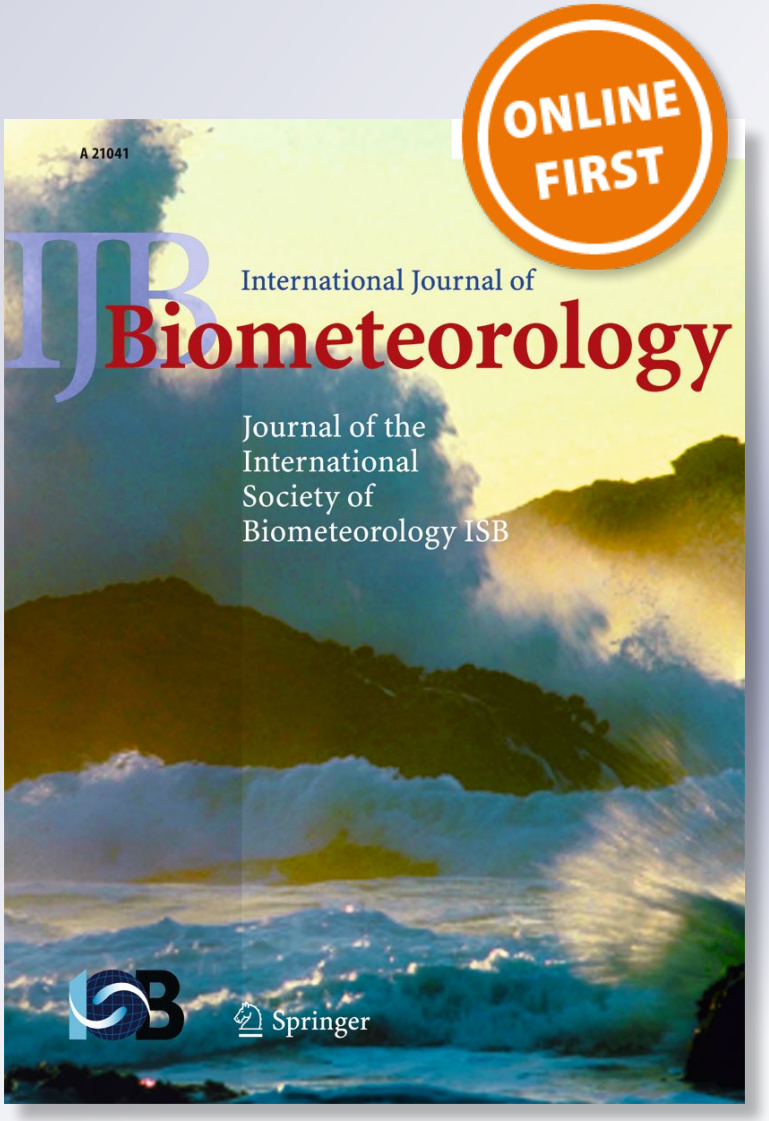
International Journal of Biometeorology

ISSN 0020-7128

Int J Biometeorol
DOI 10.1007/s00484-019-01764-4



Springer

International Journal of Biometeorology
https://doi.org/10.1007/s00484-019-01764-4

SPECIAL ISSUE: BALNEOLOGY

The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study

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Received: 2 April 2019 / Revised: 29 June 2019 / Accepted: 12 July 2019

Abstract

The aim of this non-inferiority study was to evaluate and compare the effects of Tiszasüly and Kolop mud pack therapy on pain, function and quality of life in patients with knee osteoarthritis. In this double-blind, randomised, follow-up study, 60 patients with knee osteoarthritis were treated with either Tiszasüly hot mud pack (group 1) or with Kolop hot mud pack (group 2) on 10 occasions for 2 weeks (10 working days). One hundred millimetre visual analogue scale (VAS) for knee pain, the Western Ontario and McMaster Universities Arthritis Index (WOMAC), the Knee injury and Osteoarthritis Outcome Score (KOOS), the Lequesne Index for physical function and EuroQoL-5D for quality-of-life measurements were recorded at baseline, at the end of treatment (week 2) and 3 months later (week 12). In both groups, all measured parameters improved significantly from the baseline until the end of treatment and during the follow-up period ($p < 0.05$). There were no significant differences between the groups in terms of the WOMAC, KOOS, EQ-5D and Lequesne Index at any visits. Knee pain improved in both groups at week 2 and week 12; the only significant difference visible between the groups was at the end of the treatment in favour of the Tiszasüly mud pack group ($p = 0.009$). Tiszasüly and Kolop mud packs both have a favourable effect on knee pain, physical function and quality of life in patients with knee osteoarthritis. Our results proved non-inferiority of Tiszasüly mud pack.

Keywords Mud pack therapy · Osteoarthritis of the knee · Hot-pack therapy · Non-inferiority study

Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disease, which burdens not only the patients but also the society. Etiology of this multifactorial disease is still unknown, that is why therapeutical strategies for ease of pain are limited. Pathophysiologic processes lead to anatomical damage and functional insufficiency of the joint that may cause limitation of self-care and quality of life (Helmick et al. 2008; Lawrence et al. 2008; Bijlsma et al. 2011). Various factors may play a role in the development of OA like age, sex, occupation, weight, recreation, and diet, but also genetic and environmental factors and mechanical stress are thought to be in the background of the disease. Based on European surveys, in treating degenerative musculoskeletal diseases, we can intensely count not only on direct (medical treatment), but also on indirect costs (e.g. working disability, expenses due to disabled self-care) (Rabenda et al. 2006).

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Published online: 03 August 2019

Balneotherapy deals with the effects and medical use of natural mineral waters, gases and peloids on preventive, therapeutic and rehabilitative purposes (Gutenbrunner et al. 2010). Pelotherapy is a considerable part of balneotherapy, which plays an important role in the local treatment of knee osteoarthritis (Meng and Huang 2018). Peloids are muddy suspensions with healing properties (Gomes et al. 2013). International nomenclature and classification of mud or peloid are still not uniform. Peloids are a mixture of fine-grained materials of natural (geologic and/or biologic) origins, mineral water or sea water, and commonly organic compounds from a biological metabolic activity. Maturation could take place either in natural or in artificial (e.g. in a tank) environments. During maturation, the growth of microorganisms originates several metabolic products. Medical muds/peloids have a high heat retention and low heat conduction capacity; therefore, they can provoke endogen heat formation (cooling time is rather long; they do not cause skin burn). Some peloids may also contain estrogen, which could be responsible for their analgesic effect. In Hungary, 6 types of medical peloids are used: peloids from Makó, Kolop, Héviz, Hajdúszoboszló, Alsópáhok (Georgikon), and peloid from Austria, Neydharting, which is a shallow peat. These peloids can be classified in three groups based on their origin: (1) the Makó, Kolop and Hajdúszoboszló peloids are inorganic, because of their notable mineral content, and very little organic component; (2) the Héviz peloid represents the mixed peloids, which are rich in volcanic minerals and contain 20–25% Sphagnum peat; and (3) the Georgikon' peat belongs to the organic peloids containing a large amount of organic components and humins. Mud/peloid therapy can be used as an active or passive treatment. In case of an active therapy, patients are able to move in the mud (mud bath, mud lake), whereas passive treatment means topical use like mud pack or mud wrap.

Kolop peloid has been used in most of the spas in Budapest since the early twentieth century. Kolop is located in Jász-Nagykun-Szolnok county (Hungary) under the municipality of Tiszasüly. Production of Tiszasüly and Kolop peloid is next to each other, thus their composition is similar; it is within a natural fluctuation (Table 1). In our non-inferiority study, we postulated that the clinical effectiveness of the two very similar peloids are alike. As judgement of medical utilisation of mineral waters or peloids is very strict in Hungary, we needed to conduct this clinical study to gain the curative qualification of Tiszasüly peloid.

Table 1 The chemical composition of the Kolop and Tiszasüly mud

Mud	Kolop	Tiszasüly		Kolop	Tiszasüly
SiO_2	60.05%	69.1%	CaO	1.54%	2.53%
TiO_2	0.54%	–	MgO	2.10%	–
Al_2O_3	17.91%	17.58%	Na_2O	0.89%	–
Fe_2O_3	4.34%	–	K_2O	2.39%	2.73%
FeO	2.38%	–	CO_2	0.29%	–
MnO	0.05%	–	Cl^-	0.05%	–
P_2O_5	0.14%	–	SO_3	0.28%	–
Organic content	1.53%	1.475%			

Physical properties of Kolop peloid, such as particle size, rheological properties, its radium content, and heat storage capacity makes it appropriate for balneotherapy, in particular for musculoskeletal disorders. The particle size and distribution of the peloid is more than 90% in the ideal range (0.02–0.002 mm). Its radium (^{226}Ra) content (4.18 mg radium/10 tons) may have an important role in therapy. The chemical composition is summarised in Table 1. Hungarian experimental studies performed by comet assay on Eisenia coelomocytes have ruled out the potential genotoxic effects of Kolop peloid and proved that it inhibits the reproductive capacity of Eisenia and also root elongation (Gerencsér et al. 2015; Varga 2012).

Aim of the study

The aim of our non-inferiority study was to evaluate and compare the effects of Tiszasüly and Kolop mud pack therapy on pain, function and quality of life in patients with knee osteoarthritis.

Patients and methods

Our study protocol met the principles of the Helsinki declaration. Study participants were informed verbally about the protocol, received written information and they signed the Informed Consent Form before the initiation of the study. This randomised, controlled, assessor-blinded trial was approved by the Regional Research Ethics Committee, Petz Aladár County Teaching Hospital (approval number: 76-1-9/2016) and registered in ClinicalTrials.gov (NCT03826511). Participants were recruited from patients of the Department of Rheumatology and Physiotherapy of Petz Aladár County Teaching Hospital. The study was conducted between August 2016 and February 2018.

Inclusion criteria

We enrolled patients over 40 years of age, who are capable to answer questionnaires and have clinically and radiologically bilateral knee osteoarthritis according to EULAR recommendation (mechanical knee pain, morning stiffness < 30 min, reduced knee function, radiological signs: Kellgren-Laurence radiological grade 2–3; grade 2, osteophyte formation and possible joint space narrowing; grade 3, multiple osteophytes and definite joint space narrowing, sclerosis and possible bone deformity) (Zhang et al. 2009). Patients must

have had initial spontaneous knee pain ≥ 50 mm on Visual Analogue Scale.

Exclusion criteria

Exclusion criteria were infection, fever, ongoing malignant tumour, neuropathy of the lower extremities, skin changes of the treated area, high blood pressure, progrediating heart failure (NYHA Class II–IV), inflammatory rheumatic disease, prior arthroplasty of the knee, intraarticular steroid or viscosupplementation therapy within 3 months prior treatment, physiotherapy of the knee within 3 months prior treatment, and inflammatory knee osteoarthritis.

Randomisation

A concealed allocation random assignment of the enrolled patients to the treatment groups was performed by an independent study person (using Microsoft Excel software) who did not meet any of the patients and did not participate in the course of the study either.

Blinding method

Neither the testing investigators and assistants nor the patients were aware of the treatment assignments both at the start and the end of the study. The statistician was not involved in the randomisation process either.

Recruitment of the patients

Altogether, 75 patients were included and 60 patients were randomised. Eleven patients did not meet inclusion criteria, and four patients revoked their consent. Following randomisation, 60 patients were grouped into 2 arms: the group 1 and group 2. The allocation and the type of mud pack in the groups were concealed by using sealed, opaque envelopes. Twenty-nine patients out of 60 (mean age, 65.03 ± 8.56 years; male/female, 10/19) were assigned to group 1 and 31 patients (mean age, 66.67 ± 7.62 years; male/female, 8/23) to the Group 2 (Fig. 1).

There were no significant differences among the two groups in gender proportions, comorbidities, knee osteoarthritis duration, and radiological score distribution (Table 2). The most frequent co-morbidities in both treatment groups were cardiovascular diseases. About one-third of the patients had metabolic diseases like hyperlipidaemia and endocrine diseases like diabetes. The mean duration of the knee osteoarthritis was 5–6 years. The majority of the patients had grade 2 Kellgren-Laurence radiological score. Approximately two-thirds of the patients did not have osteoarthritis besides the knees, and one-third had hip OA.

Interventions

Group 1 received Tiszasüly hot mud pack (42 °C), group 2 received Kolop hot mud pack (42 °C) on the painful knee once a day for 30 min on 10 occasions (2 weeks). The two mud packs had similar package and physical properties. The treatment was performed by an independent, blinded, qualified assistant. Patients were lying during the therapy and after 30 min the mud-pack was washed off by the assistant. The applied mud was discarded at the end of the treatment.

Outcome parameters

At the inclusion, patients' ages and genders were recorded. During each visit, we examined the patient to assess range of motion, tenderness or swelling. We also applied a 100-mm visual analogue scale (VAS) to assess rest/spontaneous pain level. Functional impairment was measured by 3 different questionnaires: (1) the Western Ontario and McMaster Universities Arthritis Index (WOMAC) has 24 questions to evaluate pain (5 questions), physical function (17 questions) and stiffness (2 questions). (2) The Knee injury and Osteoarthritis Outcome Score (KOOS) is a self-administered instrument that was developed as an extension of the WOMAC Osteoarthritis Index. It can be used for short-term and long-term follow-up of knee osteoarthritis. The KOOS is composed of five separately scored subscales: pain, various symptoms, activities of daily living (ADL), function in sport and knee-related quality of life (QOL) (Roos and Lohmander 2003). (3) Lequesne Algofunctional Index has 10 questions; it has five questions pertaining to pain or discomfort, 1 question about maximum walking distance, and 4 questions about function in daily living. The total score is between 0 and 24. Lower scores mean less functional impairment. Quality of life was measured by EuroQoL-5D (EQ-5D) questionnaire. It has five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), where patients are asked to rate their health problems on 5 levels (no problems, slight, moderate, severe or extreme problems). It also contains a self-rating of health status using a visual analogue scale (EQ VAS) ranging from 0 to 100 (where 0 means the worst and 100 means the best health status). EQ-5D was valued based on a standardised time trade-off (TTO) for the general population in the United Kingdom (UK).

Outcome parameters were recorded by a blinded rheumatologist before the start of the therapy (week 0), immediately after the therapy series (week 2) and 3 months later (week 12).

Statistical analysis

The statistical analysis was processed by the IBM SPSS 25 software. Data distribution was investigated with the Kolmogorov–Smirnov test. We found a non-normal distribution; the data were calculated by the Mann–Whitney and

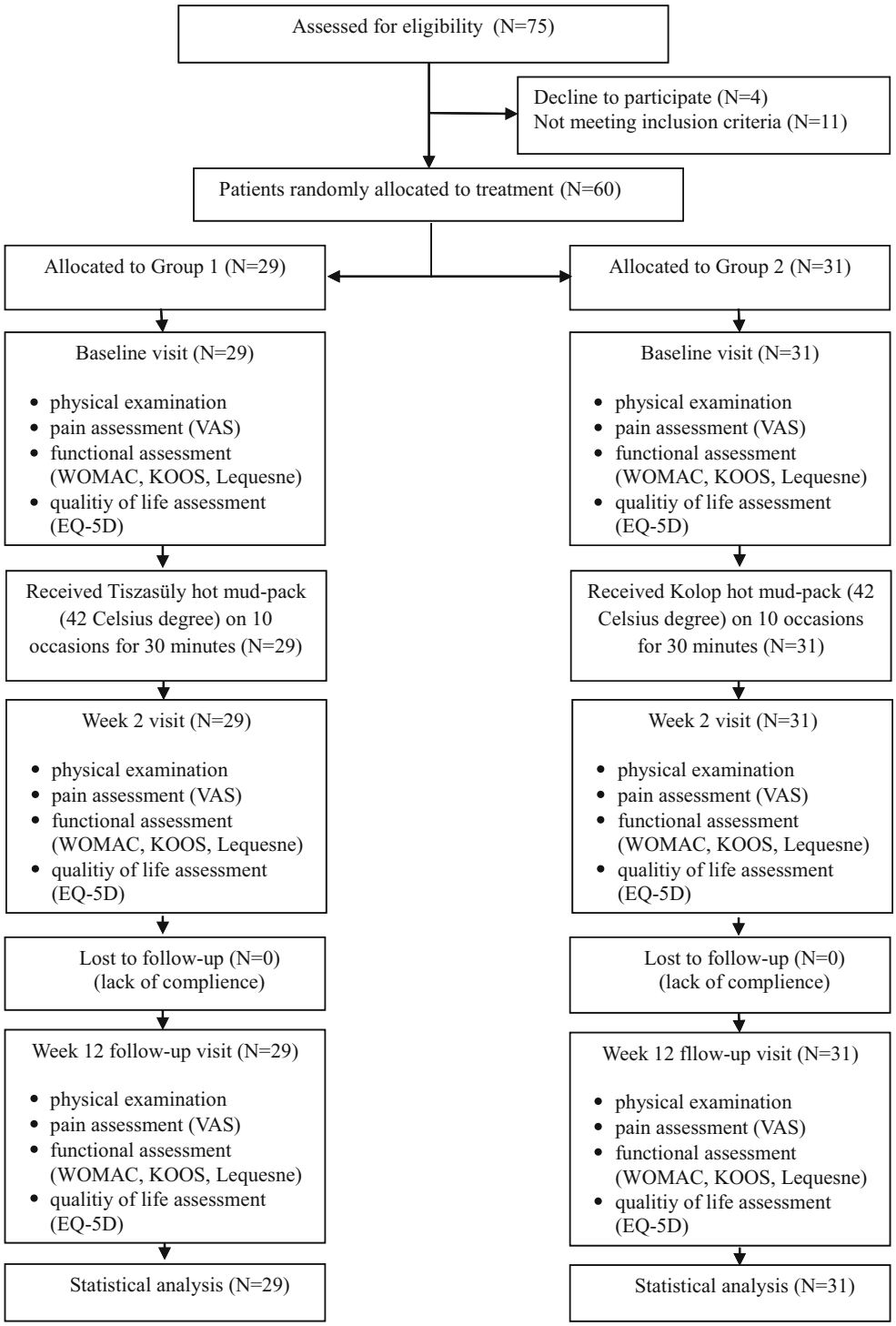

Fig. 1 The disposition of patients

Wilcoxon test and are represented as the mean ± SD. The measurements of differences between groups were carried out by the Mann–Whitney test. We handled missing data using the last observation carried forward (LOCF) method. p values < 0.05 were considered significant. We did not use an intention to treat analysis approach. The power analysis done by the G power 3.1.9.2 programme was calculated from VAS pain values at week 2 using the Mann–Whitney non-parametric test. The power proved to be 84% in case of 29 and 31 sample sizes.

Results

Both groups demonstrated similar changes during the study in all parameters.

Table 2 Demographic characteristics of patients

	Group 1 ($n = 29$)	Group 2 ($n = 31$)	p
Age (years)	65.03 ± 8.56	66.67 ± 7.62	0.435
Male/Female	10/19	8/23	0.464
Comorbidities:			
Cardiovascular diseases	26 (89.6%)	28 (90.3%)	1.000
Endocrine diseases	8 (27.6%)	7 (22.6%)	0.881
Metabolic diseases	8 (27.6%)	13 (41.9%)	0.372
Gastrointestinal diseases	5 (17.2%)	3 (9.6%)	0.465
Benign prostate hyperplasia	3 (10.3%)	2 (6.4%)	0.666
Psychiatric diseases	3 (10.3%)	2 (6.4%)	0.666
Osteoporosis	4 (13.8%)	6 (19.3%)	0.732
Knee OA duration (years)	6.57 ± 5.30	4.88 ± 3.53	0.353
Radiological score distribution			
Kellgren-Laurence grade 2	19 (65.5%)	25 (80.6%)	0.302
Kellgren-Laurence grade 3	10 (34.5%)	6 (19.3%)	
Other OA			
Hip OA	11 (37.9%)	11 (35.5%)	0.844
Shoulder OA	2 (6.9%)	4 (12.9%)	0.672
Ankle OA	2 (6.9%)	1 (3.2%)	0.606

Spontaneous pain significantly decreased in both groups after therapy and at 12 weeks follow-up ($p0–1 < 0.001$, $p0–2 < 0.001$); however, the difference between week 2 and week 12 was not significant. Immediately after therapy, the Tiszasüly mud pack group (group 1) showed better improvement ($p = 0.009$) compared with group 2 (Kolop mud pack).

Knee function impairment significantly improved in both the Tiszasüly and the Kolop mud pack groups for the week 2 and week 12 visits measured by WOMAC and the Lequesne index (group 1, $p0–1 = 0.002$, $p0–2 = 0.001$, and $p0–1 = 0.001$, $p0–2 = 0.001$ respectively; group 2, $p0–1 < 0.001$, $p0–2 < 0.001$, and $p0–1 < 0.001$, $p0–2 = 0.004$ respectively). The KOOS score showed decreasing impairment in both groups, but significant changes were demonstrated only in the Kolop mud pack group (group 2, $p0–1 = 0.046$, $p0–2 = 0.039$; group 1, $p0–1 = 0.991$, $p0–2 = 0.905$).

As to quality of life of patients measured by EuroQoL-5D, we found significant improvement in both groups (group 1, $p0–1 = 0.039$, $p0–2 = 0.028$; group 2, $p0–1 < 0.001$, $p0–2 < 0.001$), there were no significant differences between the groups at each visit. EQ-5D VAS score increased so in group 1 as in group 2, and the changes were significant in both groups (group 1, $p0–1 = 0.024$, $p0–2 = 0.011$; group 2, $p0–1 < 0.001$, $p0–2 < 0.001$) (Table 3).

No adverse events were noted or recorded during this study.

Discussion

Balneotherapy is a conventional treatment of osteoarthritis (Forestier et al. 2016; Kulisch et al. 2014; Fioravanti et al. 2017; Karagülle et al. 2007). Based on best-available evidence, the new OARSI (Osteoarthritis Research Society International) guideline, updated in 2014, recommends balneotherapy besides intra-articular corticosteroids and oral non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of multiple-joint osteoarthritis with relevant comorbidities (McAlindon et al. 2014). Peloids have been used for the treatment of musculoskeletal diseases for a long time and several studies have confirmed their effectiveness in osteoarthritis. In 2008, Turkish authors compared direct mud pack and nylon-covered mud pack on knee OA and revealed a better outcome in the directly applied mud group (Odabasi et al. 2008). Similar results are published by Hungarian authors investigating the effects of Héviz mud on patients with hand osteoarthritis. The treatment group received mud applied directly to both hands, whereas the control group received mud to both hands with a nylon layer that separated the skin from the mud. Both groups showed improvement at the end of treatment and after 16 weeks. However, the patients directly treated with mud, showed a significantly better improvement in some VAS scale parameters compared with the control group (Gyarmati et al. 2017). A quantitative meta-analysis of 7 studies (410 patients) in 2013 also confirmed the favourable effect of mud therapy on pain relief in patients with knee OA (Liu et al. 2013). In our study, we confirmed that the clinical effects of the 2 muds (Tiszasüly and Kolop) are basically the same, there was no significant difference between them, though Tiszasüly mud-pack showed better improvement in one parameter right after treatment. This corresponds to the fact, that production of the 2 muds is located very close

Table 3 Means ± SD at baseline, at end of week 2 and week 12 for the two study groups (Group 1, patients receiving Tiszasüly hot mud pack; and group 2, patients receiving Kolop hot mud pack) and between-group differences at end of week 2 and week 12 show the effects of Tiszasüly and Kolop mud packs on pain, function, and quality of life in patients with knee osteoarthritis

Measured clinical variables	Treatment groups	Baseline visit		Week 2 visit		Week 12 visit		*p* 1–2 (significance level, difference between visits)	*p* 1–3 (significance level, difference between visits)	*p* 2–3 (significance level, difference between visits)
		Mean ± SD	*p* (significance level, between group difference)	Mean ± SD	*p* (significance level, between group difference)	Mean ± SD	*p* (significance level, between group difference)			
WOMAC sum.	Tiszasüly ($n = 29$)	888.62 ± 354.47	0.188	651.10 ± 382.90	0.126	608.17 ± 445.19	0.201	**0.002**	**0.001**	0.399
	Kolop ($n = 31$)	1048.74 ± 405.61		808.77 ± 389.09		773.35 ± 491.16		**< 0.001**	**< 0.001**	0.445
Koos score	Tiszasüly ($n = 29$)	52.15 ± 9.46	0.083	50.98 ± 21.68	0.790	50.57 ± 21.63	0.717	0.991	0.905	0.762
	Kolop ($n = 31$)	57.40 ± 12.81		51.68 ± 17.34		49.81 ± 19.69		**0.046**	**0.039**	0.943
EQ5D score	Tiszasüly ($n = 29$)	0.613 ± 0.177	0.488	0.694 ± 0.249	0.893	0.704 ± 0.265	0.327	**0.039**	**0.028**	0.689
	Kolop ($n = 31$)	0.490 ± 0.307		0.734 ± 0.146		0.652 ± 0.255		**< 0.001**	**< 0.001**	0.193
EQ5D VAS score	Tiszasüly ($n = 29$)	0.601 ± 0.145	0.577	0.680 ± 0.199	0.911	0.700 ± 0.213	0.313	**0.024**	**0.011**	0.647
	Kolop ($n = 31$)	0.534 ± 0.192		0.708 ± 0.150		0.655 ± 0.187		**< 0.001**	**< 0.001**	0.214
VAS score of knee pain	Tiszasüly ($n = 29$)	57.83 ± 14.16	0.329	24.10 ± 21.93	**0.009**	29.52 ± 26.15	0.296	**< 0.001**	**< 0.001**	0.160
	Kolop ($n = 31$)	61.39 ± 14.56		36.61 ± 17.50		35.16 ± 25.02		**< 0.001**	**< 0.001**	0.509
Lequesne sum index	Tiszasüly ($n = 29$)	10.45 ± 2.65	0.784	8.21 ± 3.93	0.953	7.72 ± 4.17	0.267	**0.001**	**0.001**	0.354
	Kolop ($n = 31$)	10.95 ± 3.70		8.00 ± 3.68		9.24 ± 4.49		**< 0.001**	**0.004**	0.046

to each other and the physical and chemical parameters of both muds are the same (Table 1). In a randomised, controlled, follow-up study, Hungarian authors evaluated the effects of Kolop peloid as part of combined physio- and balneotherapy treatment on knee osteoarthritis in the day hospital care setting. Peloid therapy combined with mineral water bathing, aquatic exercise and magnetotherapy significantly improved pain, function and quality of life compared with physio- and balneotherapy without peloid therapy (Horváth et al. 2013).

In another Hungarian double-blind RCT, the effects of Neydharting mud pack therapy were evaluated compared with hot-pack with similar physical properties (viscosity, plasticity, adherence to skin, water-binding capacity and colour) to that of the Neydharting mud. The clinical outcome parameters improved in both groups, which can be explained by the similar physical properties. There were no significant differences between the 2 groups, but the improvement in the treated group was greater than in the control group. The need for analgesics and NSAIDs decreased in the control group, while a significant change was observed in the mud-treated group by the follow-up visit. This might indicate a special chemical effect of the mud (Tefner et al. 2013). A recent meta-analysis verified the suspected effect of chemical components in balneotherapy (Morer et al. 2017). Based on the results of an Italian study, mud bath therapy can decrease the serum level of adiponectin and resistin that may play a protective role in the course of knee osteoarthritis (Fioravanti et al. 2015b). As to chondroprotective effects of mud therapy, it was demonstrated in 2 different studies, that mud compress reduces the urine levels of C telopeptide fragment of collagen type II (uCTX-II) and increases the serum levels of C-terminal crosslinked telopeptide type II collagen (CTX-II), perhaps due to an increase in cartilage turnover induced by thermal stress (Gungen et al. 2016; Pascarelli et al. 2016). In an experimental study, Hungarian authors investigated the anti-inflammatory and analgesic effects of Héviz thermal water and mud in monosodium iodoacetate-induced osteoarthritis and Complete Freund's adjuvant-induced rheumatoid arthritis murine models. The treatment group received Héviz thermal water and mud pack, the control group received tap water and sand. Balneotherapy did not influence mechanical hyperalgesia, weight bearing, or oedema formation in the rheumatoid arthritis models, but had antinociceptive and anti-inflammatory effects in osteoarthritis (Tékus et al. 2018).

Fioravanti et al. published notable data about the long-term (12 months) effect of mud bath therapy added to usual treatment in patients with knee osteoarthritis (Fioravanti et al. 2015a). Besides the clinical effects, cost effectiveness of mud therapy is also important (Ciani et al. 2017). In the recent meta-analysis of 12 RCTs, spa therapy and mud therapy are discussed together, and found to be effective in the treatment and in the secondary prevention of knee OA (Fraioli et al. 2018).

All in all, based on our study and literature data, we can conclude, that mud therapy has been proved to be effective and safe in the treatment of knee osteoarthritis. It did not have any side effects in our patients with co-morbidities. It could be a good therapeutic choice not only in early osteoarthritis, but after several years disease duration. Despite the increasing evidence of the favourable effects of balneotherapy and mud therapy, they are traditionally used mainly in countries rich in thermal waters. This fact can interfere the appearance of mud therapy in guidelines of non-pharmacological treatment of osteoarthritis, although there are several excellent, well-designed studies based on consort statement available.

Limitation of the study

Increasing the number of patients would power our study, though this number was enough to draw conclusions. We are planning to extend the follow-up period to 6 and 9 months.

Conclusion

Based on our double-blind, controlled pilot study, we can conclude, that both Tiszasüly and Kolop mud packs have a favourable effect on knee pain, physical function and quality of life in patients with knee osteoarthritis. We could not find any significant difference in the clinical effects of the 2 muds, so our results proved the non-inferiority of Tiszasüly mud pack.

Funding Information Open access funding provided by Polyclinic of Hospitaller Brothers of St. John of God in Budapest (BIR BIK).

Compliance with ethical standards

Conflict of interest Regarding material costs, this study was sponsored by Triberg Kft. (9200 Mosonmagyaróvár, Alkotmány u. 32., Hungary).

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