

Department of Orthopedics, Faculty of Medicine,
University of Szeged, Clinical Medicine Doctoral School

EFFICACY OF BALNEOTHERAPY ON PAIN,
FUNCTION AND QUALITY OF LIFE IN PATIENTS
WITH CHRONIC LOW BACK PAIN,
AND HAND OR KNEE OSTEOARTHRITIS

Summary of Ph.D. Thesis

ÁGOTA KULISCH, M.D.

Supervisor:

Tamás Bender, M.D., Ph.D., D.Sc.

Szeged, 2016

Department of Orthopedics, Faculty of Medicine,
University of Szeged, Clinical Medicine Doctoral School

EFFICACY OF BALNEOTHERAPY ON PAIN,
FUNCTION AND QUALITY OF LIFE IN PATIENTS
WITH CHRONIC LOW BACK PAIN,
AND HAND OR KNEE OSTEOARTHRITIS

Summary of Ph.D. Thesis

ÁGOTA KULISCH, M.D.

Supervisor:

Tamás Bender, M.D., Ph.D., D.Sc.

Department of Orthopedics, Faculty of Medicine

University of Szeged, Hungary

Director of Doctoral School of Clinical Medicine:

Lajos Kemény, M.D., D.Sc.

PhD programme titled:

Clinical and Experimental Research in Reactivating and Organ-Saving Surgery.

Clinical and experimental investigations into solutions

based on evidence for sustaining and reactivating articular functions

Szeged, 2016

INTRODUCTION

Balneotherapy is a medical specialty using the beneficial effects of naturally found mineral waters, gases, and peloids. The most important modalities of use are bathing, drinking and inhalation. The mechanism of action of balneotherapy is not yet completely understood. The physical properties and chemical effects of thermal mineral waters may play a role in their mechanism of action, and the physical effects of buoyancy, hydrostatic pressure and water temperature may be highlighted. Balneotherapeutic procedures are mainly performed in the prevention, treatment, and rehabilitation of musculoskeletal diseases but their use has also been reported in various other indications such as in the treatment or rehabilitation of dermatological, gynaecological, chronic venous insufficiency, chronic occlusive arterial disease, or psychiatric conditions as well as in the rehabilitation of oncology patients. Balneotherapy is usually part of a complex physiotherapeutic treatment. The effectiveness of balneotherapy was long known only empirically. In the past decades, several clinical studies, reviews, and meta-analyses have evaluated the efficacy of balneotherapy mainly in the treatment of musculoskeletal disorders. Balneology is often not recognised as an independent medical specialty at a global international and domestic level, because of the lack of scientific evidence, and the fact that balneotherapy is not available in all countries.

Low back pain and osteoarthritis are prevalent diseases and their impact is pervasive. The prevalence of these conditions increases markedly with age and they are affected by lifestyle factors, such as obesity and lack of physical activity. They are a common cause of severe and chronic pain and physical disability, and they influence the quality of life of affected people. The need for high-quality care for a condition with major personal and societal impact is generally recognised and several guidelines for such care are available. International recommendations for management of musculoskeletal diseases are often divided into three main categories: non-pharmacological, pharmacological and surgical.

The efficacy of balneotherapy has been most clearly evidenced in gonarthrosis. Based on a systematic review and meta-analysis of randomized controlled trials, recommendations mention balneotherapy as a therapeutic option for knee osteoarthritis. In the recently published OARSI (Osteoarthritis Research Society International) Guidelines for Non-Surgical Management of Knee Osteoarthritis, balneotherapy was considered as an appropriate treatment for specific clinical subphenotypes with multiple joint osteoarthritis and comorbidities.

Balneotherapeutic procedures are widely used by physicians and preferred by patients for the treatment of chronic low back pain. Because of the limited scientific evidence balneotherapy is not included in the treatment guidelines for low back pain. The first meta-analysis available in English evaluated pooled data from only 5 studies. The first single-blind study was published concomitantly with the above meta-analysis.

Evaluating the effectiveness of balneotherapy presents specific methodological issues. In non-pharmacological treatments trials, it is often difficult to perform sham intervention, and blinding of participants is frequently impossible. Moreover, the success of balneotherapy often depends on environmental and other specific factors such as chemical and thermal characteristics, type of bath, nature, and combined intervention. The metaanalysis of completed trials in balneology is challenged by the diversity of their methods, therapies, and outcome parameters. Unlike for drug trials, the lack of adequate funding of balneology research makes it difficult to enroll sufficient numbers of patients in such trials.

Metaanalyses and review studies on the efficacy of balneotherapy evaluated the analyzed randomized, controlled trials as of inappropriate methodology. The authors emphasize the need for further additional, confirmatory studies which include an analysis of the person's physical function and their quality of life. Therefore, we aimed to design our studies with appropriate methodology, in accordance with the recommendations for study planning. These trials may provide data for a more precise evaluation of the role of balneotherapy in the management of each condition.

AIMS OF THE THESIS

I. Our aim was to evaluate the effectiveness of thermal mineral water compared with tap water and supplementary electrotherapy in patients with chronic low back pain first in the English literature in a double-blind trial. As primary endpoint, we aimed to monitor changes in low back pain, movement functions, and quality of life of the enrolled patients. Secondary end-points were to record changes in the dose requirements of analgesics and explore the safety profile of treatment.

II. There have been several publications about the use of balneotherapy in osteoarthritis of the knee. The effect of balneotherapy on hand osteoarthritis has not yet been studied. Our aim was to evaluate the efficacy of thermal mineral water, and supplementary magnetotherapy in patients with hand osteoarthritis. The primary endpoint was the effect of balneotherapy on hand pain, hand functions, and quality of life. As secondary endpoint, we assessed whether there is any clinically significant, evaluable difference in the effect of waters of different temperature.

III. Studies involving patients with knee osteoarthritis and systematic reviews confirmed the analgesic and knee function improving effect of balneotherapy. However, in most of the studies, bath therapy was combined with other therapies. Furthermore, only a limited number of previous studies covered the assessment of quality of life. Lake Hévíz is a biologically active, natural thermal lake, which deserves a special place within balneology. Therefore, the primary endpoint of the study was the evaluation and documenting of the pain-reducing effect of Lake Hévíz thermal mineral water on knee pain at rest or on exertion in patients with knee osteoarthritis as well as the assessment of the therapeutic effect compared to the control group treated with warmed tap water. The secondary endpoints included the evaluation of the effect of Lake Hévíz thermal mineral water on knee function and quality of life.

ETHICAL ASPECTS

These clinical studies were implemented in observance of the rules of good clinical practice. The study protocols were approved by the Regional Research Ethics Committee. All subjects were informed about the purpose, conditions and course of the study prior to inclusion. Patients were given oral and written explanation of the treatment prior to giving their written informed consent.

I. EFFECT OF THERMAL WATER AND ADJUNCTIVE ELECTROTHERAPY ON CHRONIC LOW BACK PAIN: A DOUBLE-BLIND, RANDOMIZED, CONTROLLED, FOLLOW-UP STUDY

Methods

In this randomized, controlled, double-blind, follow-up study, we evaluated the effects of thermal mineral water and adjunctive electrotherapy on chronic low back pain.

The study was conducted at the spa of Celldömök in Hungary. Male and female patients aged 25–70 years living in and around the town of Celldömök who presented with chronic lumbar pain of more than 12 weeks' duration were included in the study. Enrolled patients completed the balneotherapy treatment as outpatients, with no change in their daily routine or work attendance. Patients were randomized into either of the 2 treatment groups. One group was treated with thermal water, whereas the other group was treated with tap water. The water temperature was 34°C for both groups. Subjects underwent 20-min balneotherapy sessions daily for 3 weeks. Both treatment groups received additional electrotherapy under standardized conditions. Diadynamic current (long period current with waist electrodes of standard size, and discharge duration of 3 min) was applied 3 times per week, before the balneotherapy sessions. Outcome measures were visual analogue scale scores (VAS I: the severity of low back pain at rest, as rated by the patient, VAS II: the severity of low back pain upon exertion, as rated by the patient, VAS III: perceived status, as rated by the patient, VAS IV: the patient's progress, as rated by the investigator), Schober's sign, Domján's signs, Oswestry Disability Index (ODI) and Short Form (36) (SF-36) questionnaire. The study parameters were administered at baseline, immediately after treatment, and after 15 weeks.

The water source used was the well "Cell-4" at Vulcan Spa. This is a mild mineral water rich in solutes (sodium hydrogen carbonate and chloride), also containing fluoride and a substantial amount of iodides. Its total mineral content was 3350 mg/L. The appearance of the tap water was changed to resemble that of the thermal water; through the addition of extract of green walnut husks. The characteristic smell of the thermal water was simulated by using bathtubs located in the same hall as the treatments with thermal water were undertaken. Except for the bath attendants, neither the subjects, nor the investigators were aware of the randomly assigned treatment.

Data were entered into and analysed with MS Excel software. Statistical comparisons were made using single-sample (paired) and 2-sample *t*-tests. Intention-to-treat analysis was

performed. A separate analysis (a per protocol analysis) was carried out for patients who completed the full treatment course in compliance with study requirements. The level of significance was set at $p < 0.05$.

Results

Of the 71 patients (thermal water group $n=36$ male/female 23/13, age years mean (SD) 57.6 (7.9), control group $n=35$ male/female 23/13, age years mean (SD) 56.3 (7.5)) included in the study, 64 completed more than 80% of the therapy course. The 2 treatment groups were similar with regard to demographic data and baseline clinical characteristics. Seven patients discontinued the treatment period after 3 weeks (5 patients in the thermal group: $n=3$ lack of compliance, $n=1$ febrile infection, $n=1$ cataract surgery, and 2 patients in the tap water group: $n=1$ febrile infection, $n=1$ gynecological surgery). A further 13 patients because lack of compliance (2 from the thermal water group and 11 from the control group) did not return for the 15-week control visit.

ITT analysis at the end of 3 weeks treatment revealed a decrease in VAS scores for both groups. Within-group comparison to baseline showed significant improvement of pain at rest (VAS I $p < 0.01$), lumbar pain on exertion (VAS II $p < 0.01$), perceived status as rated by the subjects (VAS III $p < 0.01$), as well as the patient's general condition as rated by the investigator (VAS IV $p < 0.01$) for both treatment groups. The improvement remained significant for all 4 parameters after 15 weeks in the group treated with thermal water ($p < 0.01$). In the control group only 2 parameters, VAS II and VAS IV, scores remained significantly ($p < 0.05$) improved after 15 weeks.

Between-group analysis gave the following results. Within the 3-week study interval patients receiving thermal water therapy showed a significant therapeutic response, with a decrease in VAS IV scores compared with the control group ($p < 0.05$). After week 15, the changes in VAS III scores between baseline and the end of the study were significantly greater in the thermal water group ($p < 0.05$).

A similar trend was revealed by the results of the tests evaluating the range of motion of the lumbar spine (Schober's, Domján's R-L, ODI). While the improvement shown by these 4 tests was still statistically significant after 3 weeks in the thermal water group, only the Domján R and L tests remained significantly improved in the control group ($p < 0.05$). After week 15, however, only Domján L and ODI scores of the thermal water group were significantly superior compared with baseline values ($p < 0.05$). At the end of 3 weeks, there was no significant difference when comparing the test results between the thermal water and

the control group. Significant improvement was seen after week 15 in the Schober's index in the thermal water group compared with the control group ($p < 0.05$).

By the end of week 3 quality of life indicators, SF-36 items (PF: Physical Functioning, RP: Role Physical, BP: Bodily Pain, GH: General Health, V: Vitality, SF: Social Functioning, RE: Role Emotional, MH: Mental Health) improved significantly both in the thermal water and in the control group ($p < 0.01$) compared with baseline. The improvement in quality of life compared with baseline remained significant for both groups after 15 weeks. Although the improvement after week 15 was still significant compared with baseline, as shown by the PF, RP, BP, GH, V, RE items in the thermal water group ($p < 0.01$) and by the RP, V, RE items in the control group ($p < 0.05$), the outcome status of the 2 groups was not statistically different.

The 2 groups were also compared for patients who completed the full treatment course according to the study protocol. A total of 51 patients (29 in the thermal water and 22 in the control group) were analysed separately (per protocol analysis). The results were consistent with those of the ITT analysis, but between-group differences and the extent of the therapeutic response showed significantly greater improvement in the thermal water group. After 3 weeks, significant between-group differences were seen in the changes of VAS IV scores, in Schober's and ODI, as well as in SF-36 BP ($p < 0.05$). After week 15, however, the thermal water group proved significantly superior to controls with regards to the changes in VAS I scores, Schober's, and Domján's L indices compared with their baseline values ($p < 0.05$). After week 15, none of the SF-36 parameters indicated a significant change in the control group. Comparison of the 2 groups showed that the improvement of PF after week 15 was significantly greater in the thermal water group than in controls ($p < 0.05$). No adverse reactions were observed during treatment sessions or during the whole study period. Potential changes in the efficacy of analgesic therapy could not be monitored, due to the small number of subjects who took analgesics regularly; statistical analysis of this parameter therefore proved unfeasible.

II. EVALUATION OF THE EFFECT OF BALNEOTHERAPY IN PATIENTS WITH OSTEOARTHRITIS OF THE HANDS, A SINGLE-BLIND, RANDOMIZED, CONTROLLED, FOLLOW-UP STUDY

This trial was performed in co-operation and under shared lead authorship with Katalin Horváth M.D.

Methods

This was a randomized single-blind three-arm parallel-group controlled follow-up study. The study site was Gunaras bath, located 2 km from Dombóvár. Male and female patients between 50 and 70 years of age with moderate to mild osteoarthritis of the hands meeting the American College of Rheumatology classification criteria regarding hand osteoarthritis that has been confirmed by radiological assessments (comparative radiograph of the hands) and who have hand pain characteristic of osteoarthritis of the hands for at least three months were included in the study. The patients were examined by an independent rheumatologist. Enrolled patients completed the balneotherapy treatment as outpatients, with no change in their daily routine or work attendance. Patients were randomized into three treatment groups.

The subjects in the first two groups bathed in thermal mineral water of two different temperatures (36°C and 38°C) for three weeks five times a week for 20 minutes a day and received magnetotherapy to their hands three times weekly. The third group received only magnetotherapy. Outcome measures were visual analogue scale scores (VAS 1-100 mm, VAS I: the severity of pain in the small joints of the hands at rest, as rated by the patient, VAS II: the severity of pain in the small joints of the hands upon exertion, as rated by the patient, VAS III: patient's global assessment of hand status, VAS IV: physician's global assessment of hand status), handgrip strength, pinchgrip strength, the number of swollen and tender joints of the hand, the duration of morning joint stiffness, Health Assessment Questionnaire (HAQ), and SF-36 questionnaire. We presented from the SF-36 subscales the norm-based physical component summary (PCS) and mental component summary (MCS) scores. The study parameters were administered at baseline, immediately after treatment and after 13 weeks. The examiner was blinded regarding the received therapy.

The thermal mineral water is an alkaline sodium hydrogen carbonate containing soft water that contains significant amounts of fluoride. Its total mineral content was 2210 mg/L, its temperature was 36°C in one group and 38°C in the other group.

Data were entered into and analysed with MS Excel and SPSS software. Statistical comparisons were made using ANOVA and as post-hoc tests Scheffe' and Dunnett. Intention-to-treat analysis was performed. The level of significance was set at $p < 0.05$.

Results

Of the 63 patients (thermal water 36 °C $n=21$ male/female 4/17, age years mean (SD) 63.5 (4.7), thermal water 38 °C $n=21$ male/female 5/16, age years mean (SD) 62.3 (4.8), control group $n=21$ male/female 3/18, age years mean (SD) 63.8 (4.4)) included in the study, 59 completed more than 80% of the therapy course. The treatment groups were similar with regard to demographic data and baseline clinical characteristics. All study patients except two were right-handed. Four patients discontinued the treatment period after three weeks because lack of compliance (two patients in the thermal group I (36°C), and two patients in the control group).

Examination of the hands revealed an improvement in the subjective parameters measured by VAS scale in all study groups. After the three-week treatment, patients receiving 36°C thermal water therapy showed a significant therapeutic response compared with the control group, with a decrease in VAS I ($p < 0.05$) and VAS II ($p < 0.05$) scores. In patients treated with 38°C water, VAS IV score showed a similar statistical effect compared with the control group ($p < 0.01$). During the follow-up period, long-term improvement was seen in the VAS I ($p < 0.05$) and VAS IV ($p < 0.05$) parameters of the 36°C thermal water group and in the VAS III ($p < 0.05$) and VAS IV ($p < 0.01$) scores of the 38°C thermal water group compared with control.

Remarkable and long-term improvement was noted in the grip and pinch strengths of both hands in the thermal water groups at all study time points. By the end of week 3, the grip strength of the right hand significantly improved in patients treated with 36°C thermal water compared with the control group ($p < 0.05$). No significant difference was seen between the thermal water-treated and control groups at other study time points. In patients receiving 38°C thermal water therapy, pinch strength of the dominant right hand with the control group ($p < 0.05$). This significant improvement lasted even during the follow-up period ($p < 0.05$).

Improvement of the HAQ index was significant only in the 38°C thermal water-treated group both after treatment ($p < 0.01$) and during the follow-up period ($p < 0.01$) compared with the control group. Decrease of morning joint stiffness was detectable in all groups. However, no significant differences were found between the treated and control groups at any of the time points studied.

The number of swollen joints significantly decreased in the thermal water groups compared with the control group at both time points studied ($p < 0.01$). A substantial and

significant decrease was seen in the number of tender joints in the thermal water groups after treatment ($p<0.01$) and during follow up ($p<0.01$) compared with the control group.

The SF-36 health survey questionnaire documented a substantial and permanent improvement of physical component summary (PCS) scores in the thermal water-treated groups, right after the therapy and during the follow-up period. After the three-week treatment, this improvement was significantly better in the 38°C thermal water-treated group compared with control ($p<0.05$). Mental component summary (MCS) scores improved only in the thermal water groups. After week 3, this improvement was significantly higher in the 36°C thermal water-treated group compared with control ($p<0.05$). During follow-up, no significant improvements were noted in the PCS and MCS scores of the thermal water-treated groups compared with control.

Direct comparison of the effects of the 36°C and 38°C thermal waters revealed no significant differences in the treatment responses.

No adverse reactions were observed during treatment sessions or during the whole study period.

III. EVALUATION OF THE EFFECT OF LAKE HÉVÍZ THERMAL MINERAL WATER IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE, A SINGLE-BLIND, RANDOMIZED, CONTROLLOED FOLLOW-UP STUDY

Methods

This was a randomized, single-blind, controlled, parallel-group, follow-up study. The study took place at Spa Hévíz and St. Andrew Hospital for Rheumatic Diseases. This study included male and female patients between 45 and 75 years of age with mild to moderate, bilateral primary osteoarthritis of the knee (meeting the American College of Rheumatology knee osteoarthritis classification criteria) diagnosed and documented with imaging techniques (comparative knee radiograph not older than 2 years). Patients had been suffering from knee pain characteristic for osteoarthritis for at least 3 months. The enrolled patients received the treatment in an outpatient setting and they were able to continue their daily activities and work. Patients were randomized into two groups.

In group I, subjects bathed in Lake Hévíz and in group II, patients were treated in a pool full of tap water. Water temperature was 34°C for both groups. Participants underwent 30-minute therapy sessions, five times a week for three weeks. Patients were

asked not to swim during bathing. Patients did not receive any other physiotherapy in addition to the bath therapy. Outcome measures were pain visual analogue scale scores (VAS 0-100 mm, VAS I: knee pain at rest, as rated by the patient, VAS II: knee pain on exertion, as rated by the patient, VAS III: condition of the knee, as rated by the patient, VAS IV: condition of the knee, as rated by the investigator), active flexion degree, knee circumference, stair-climb time, Western Ontario and MC Master Universities Arthritis Index (WOMAC) and EuroQoL five dimensions questionnaire (EQ-5D). Study parameters were recorded at baseline, immediately after treatment, and after 15 weeks. The thermal mineral water of Lake Hévíz is rich in dissolved and gas components, thereby it combines the favorable characteristics of carbonate, sulfur, calcium, magnesium, hydrogen carbonate and very light radon-containing waters. Its total mineral content was 754 mg/L.

Sample size calculation was based on power analysis ($\alpha=0.05$, $\beta=0.80$, effect size=0.65). Results were processed and evaluated in Microsoft Excel. For the statistical comparison of the samples, self-controlled and group-controlled methods: one-sample (paired) and two-sample t-tests were used. The analysis of the results was conducted by intention to treat. The level of significance was set at $p<0.05$.

Results

Of the 77 patients (thermal water $n=38$ male/female 8/30, age years mean (SD) 65.6 (6.4), control $n=39$ male/female 9/30, age years mean (SD) 65.5 (7.7)) included in the study, 75 completed more than 80% of the therapy sessions. Treatment groups were similar with regard to demographic data and baseline clinical characteristics. Two patients discontinued the treatment ($n=1$ patient in the thermal group knee joint inflammation, and $n=1$ patient in the control group erysipelas). Two patients in the control group did not attend the Visit 3 (lack of compliance).

Examination of the knee revealed an improvement in the pain parameters measured by VAS scale in both study groups. After the 3-week treatment, patients receiving thermal water therapy showed a significant therapeutic response compared to the control group, with a decrease in VAS I ($p<0.01$), VAS II ($p<0.01$), VAS III ($p<0.01$), and VAS IV ($p<0.01$) scores. During the follow-up period, long-term improvement was seen in all of the VAS scales: VAS I ($p<0.01$), VAS II ($p<0.01$), VAS III ($p<0.01$), and VAS IV ($p<0.01$).

In the thermal water-treated group, all three dimensions of the WOMAC index (pain, joint stiffness, function) showed significant improvement after the treatment and during the follow-up period. Comparing the changes in the study groups, all three parameters of the

WOMAC index showed significantly better improvement in the thermal water-treated group than in the control group: pain subscales ($p<0.05$), stiffness subscales ($p<0.01$), function subscales ($p<0.01$), and function score during follow-up ($p<0.05$).

Knee function and movement were characterized by changes in flexion angles. In response to treatment, knee flexion improved in both knee in both groups. Improvement of joint function was significantly better in the thermal water-treated group than in the control group: flexion changes were significant ($p<0.01$). Similar results were obtained during the follow-up period ($p<0.01$).

As a response to treatment, stair-climb time decreased in both groups; patients completed the unit distance in a shorter period of time. Stair-climb time was slightly more decreased in the thermal water-treated group than in the control group when compared to baseline. The difference between the two groups was not significant.

The utility index of the EQ-5D questionnaire showed permanent and significant improvement of general health-related quality of life in the thermal water-treated group compared to the control group after the treatment ($p<0.05$) and during the follow-up period ($p<0.05$). The responders' self-rated health measured on the EQ-5D VAS scale slightly improved, but the changes were not statistically significant between the two groups.

DISCUSSION, CONCLUSIONS AND NEW RESULTS

I. Our randomized, tap water-controlled, follow-up study is the first double-blind investigation in the English literature evaluating the efficacy of balneotherapy in patients with chronic low back pain.

Overall, study parameters indicated a tendency for positive physiological changes in both groups. In the group treated with thermal water, improvement occurred earlier, lasted longer, and was statistically significant in more patients, both in within-group and in between-group comparisons. Compared with controls, however, the statistically significant difference (VAS III, IV scores and Schober's sign) between the groups was smaller than the (more substantial) improvement expected on theoretical grounds. While the analgesic effect of thermal water is well known, the short-term relief seen among controls emphasizes the beneficial, relaxing effect of hydrotherapy with hot water. In contrast to the intention to treat analysis, the per protocol analysis demonstrated the advantage of the thermal water group over controls, as reflected by the improvement in a greater number of study parameters (VAS

IV, Schober's sign, ODI, SF-36 Bodily Pain on week 3, and VAS I, Schober's sign, Domján L, SF-36 Physical Function on week 15). Evidently, the statistical power of per protocol analysis is weaker in a double-blind placebo-controlled trial; however, presenting the results of patients who have completed the study in compliance with the protocol was deemed important, to demonstrate the statistical significance of differences in addition to the statistical trend revealed. No adverse reactions were observed during treatment sessions or during the whole study period. Potential changes in the efficacy of analgesic therapy could not be monitored, due to the small number of subjects who took analgesics regularly; statistical analysis of this parameter therefore proved unfeasible.

Our results suggest that treatment with thermal mineral waters is an effective treatment modality for the management of chronic lumbar pain, besides improves the function and quality of life. In view of the differences between the groups treated with thermal versus tap water, balneotherapy with the former may be regarded as a more effective basic treatment modality, as well as an efficient adjunct to pharmaco- and physical therapy, owing to the addition and enhancement of positive effects.

II. Our randomized, controlled, single-blind, follow-up study is the first trial in the English literature evaluating the effect of balneotherapy in hand osteoarthritis.

The study was planned and conducted in accordance with the guidelines of the Osteoarthritis Research Society International regarding hand osteoarthritis.

Based on the results 36°C and 38°C thermal water treatment was more effective, clinically significant improvement was recorded in pain reduction, the number of swollen and tender joints, hand function and quality of life compared with the control magnetotherapy group after treatment, these benefits were maintained at 13 weeks.

The small improvements in pain reduction in the control group confirm the inconclusive effect of magnetotherapy.

Although direct comparison of the effects of the 36°C and 38°C thermal waters revealed no significant differences in the treatment responses. It can be postulated that the thermal water at 38°C is more effective than that at 36°C, since the 38°C water treatment significantly improved the pinch strength of the right hand and the HAQ parameters, even in the long term, whereas no significant changes were noted in the same parameters in the 36°C thermal water-treated group compared with control. The treatment was well tolerated and adverse reactions were not reported.

Based on our results, we can conclude that the balneotherapy is a possible and safe therapeutic option in the treatment of hand osteoarthritis.

A larger number of patients would have increased the power of the study. Furthermore patients were not blinded to the received therapy. Since no specific, validated Hungarian hand function tests are available, HAQ was used for the assessment of functional status of the hands.

III. In this randomized, tap water controlled, single-blind, follow-up study we evaluated the effectiveness of thermal mineral water on pain, function and quality of life in patients with knee osteoarthritis.

The primary endpoint parameters indicating pain at rest and on exertion measured on a visual analogue scale and the secondary endpoint parameters such as the physical function parameter of the WOMAC index, angle of knee flexion, and index values of the EQ-5D global health-associated quality of life questionnaire showed greater improvement and were statistically and clinically significant and more durative in the thermal water-treated group compared to the control group. The difference in the above mentioned parameters were significant between the two groups at the end of treatment and during the follow-up period. The results of our study demonstrated explicitly the effects of thermal mineral water, in the short and long term, compared to the control group who were treated with the tap water. Positive changes were also documented with tap water treatment, but the effect and durability of these changes were less compared to thermal mineral water treatment. Our study has some limitations. First, those patients, who bathed in the covered part of the lake, were not allowed to swim, due to the deepness of the water, they had a better opportunity to move around. This might have influenced the improvement in function. Further studies should include larger sample. Bathing in the lake did not make the application of the double-blind method possible.

Our study confirmed the findings of previous studies on the efficacy of balneotherapy in the treatment of patients with knee osteoarthritis. With regard to the common side effects of continuous pharmacological, NSAID therapy, balneotherapy can be a useful therapeutic tool or adjunctive therapy in the treatment of knee osteoarthritis.

The effect of balneotherapy is often attributed to the effect of environmental changes. In order to eliminate this possibility, balneotherapy was applied as outpatient treatment.

Further studies should include larger sample maybe as a multicenter study. Finally, in a future study it would be useful to associate it with a study into its cost-effectiveness.

LIST OF PUBLICATIONS included in the dissertation

I. **Kulisch Á**, Bender T, Németh A, Szekeres L. Effect of thermal water and adjunctive electrotherapy on chronic low back pain: a double-blind, randomized, follow-up study.

J Rehabil Med 2009; 41: 73-9. **IF: 1.882**

II. Horváth K*, **Kulisch Á***, Németh A, Bender T. Evaluation of the effect of balneotherapy in patients with osteoarthritis of the hands: a randomized controlled single-blind follow-up study. Clin Rehabil 2012; 26: 431–441. **IF: 2.191**

(* Katalin Horváth and Ágota Kulisch contributed equally to this work.)

III. **Kulisch Á**, Benkő Á, Bergmann A, Gyarmati N, Horváth J, Kráncz Á, Mándó Zs, Matán Á, Németh A, Szakál E, Szántó D, Szekeres L, Bender T.: Evaluation of the effect of Lake Hévíz thermal mineral water in patients with osteoarthritis of the knee: a randomized, controlled, single-blind, follow-up study. Eur J Phys Rehabil Med. 2014; 50(4): 373-81.

IF: 2.060

LIST OF PUBLICATIONS related to the subject of the dissertation

Gyarmati N., **Kulisch Á.**: History and description of Hévíz spa with special emphasis on weight-bath. Press. Therm. Climat. 2008; 145: 233-242.

Bender T., **Kulisch Á.**, Kovács Cs., Horváth K., Gyarmati N., Tefner I., K.. A balneoterápia jelentősége az osteológiában. Lege Artis Med. 2012; 22: 655-60.

Kulisch Á., Horváth K., Németh A., Bender T. A balneoterápia és kiegészítő elektroterápia hatásának vizsgálata térdarthrosisban szenvedő betegekre. Balneológia, Gyógyfürdőügy, Gyógyidegenforgalom, XXXIII. Évfolyam 1. szám, Budapest, 2014.

LIST OF PUBLICATIONS non related to the subject of the dissertation

Kulisch Á., Fekete S., Osváth P. Öngyilkosságot elkövetők búcsúleveleinek grafológiai elemzése. Psychiatria Hungarica, 2000, 15 (2): 575-582.

Kulisch Á., Lengyel Zs., Battyáni Z., Szekeres Gy. Sejtproliferáció és apoptózis immunmorfológiai vizsgálata melanóma malignumban. Bőrgyógyászati és Venerológiai Szemle 2001. 77. évf. 6. 255 - 258.

BOOK CHAPTERS

Kulisch Ágota, Horváth Katalin, Kovács Csaba. Hidroterápia és hidroterápiás eljárások
In: Bender T, szerk. Balneoterápia és hidroterápia. Budapest, Medicina Könyvkiadó Zrt;
2014: 153-177.

Gyarmati Noémi, **Kulisch Ágota**, Mándó Zsuzsanna. A balneológia helye az
egészségturizmusban. In: Lőke Zs., szerk. Desztinációmenedzsment az egészségturizmusban.
Keszthely, Pannon Egyetem Georgikon Kar, Keszthely 2014: 77-107.

PRESENTATIONS related to the subject of the dissertation

Ágota Kulisch, Alice Dalmadi, Magdolna Mózes, Sándor Kertai, György Végh, László
Haraszti, Agnes Vathy, Agnes Czibalmos. The therapeutics effects of Hévíz thermal water
in osteoporosis and LBP. (oral presentation) 35 th World Congress of ISMH 2006, Istanbul

Kulisch Ágota, Dalmadi Alice, Mózes Magdolna, Kertai Sándor, Végh György, Haraszti
László, Vathy Ágnes, Czibalmos Ágnes. A hévizi termálvíz hatásának vizsgálata
osteoporosisban és krónikus LBP-ben szenvedő betegeken. Magyar Balneológiai Nagygyűlés,
2006, Debrecen

Kulisch Ágota, Németh András, Szekeres László, Bender Tamás. The therapeutic effects of
Celldömölk thermal water in low back pain. V. Hungarian-Turkish Balneological Symposium
2007, Hévíz

Kulisch Ágota, Németh András, Szekeres László, Bender Tamás. A celldömölki ásványvíz
gyógyhatásának vizsgálata LBP-ben szenvedő betegeken. Kettős vak, randomizált, placebo
kontrollált vizsgálat. Magyar Reumatológusok Egyesülete Ifjúsági Fórum 2007, Noszvaj

Kulisch Ágota, Németh András, Szekeres László, Bender Tamás. A celldömölki ásványvíz
gyógyhatásának vizsgálata LBP-ben szenvedő betegeken. Kettős vak, randomizált, placebo
kontrollált vizsgálat. Magyar Balneológiai Nagygyűlés 2007, Esztergom

Horváth Katalin, **Kulisch Ágota**, Németh András, Szekeres László, Bender Tamás. A
gunarasi termál-ásványvíz gyógyhatásának vizsgálata primér kézarthrosisban szenvedő
betegeken. (oral presentation) 37th World Congress of ISMH 2010, Paris

Kulisch Ágota Balneotherapy in Hévíz Conference on „Rehabilitation and wellness services in Hungary”. 2010, Vilnius

Kulisch Ágota, Horváth Katalin, Németh András, Szekeres László, Bender Tamás. A gunarasi termál-ásványvíz gyógyhatásának vizsgálata primér kézarthrosisban szenvedő betegeken. Magyar Balneológiai Nagygyűlés 2010, Gyula

Kulisch Ágota, Benkő Ágota, Bergmann Annamária, Gyarmati Noémi, Horváth József, Kránicz Ágota, Mándó Zsuzsanna, Matán Ágnes, Németh András, Szakál Erika, Szántó Dóra, Szekeres László, Bender Tamás. A Hévízi-tó termál-ásványvizének vizsgálata primér térdarthrosisban szenvedő betegekre (randomizált, kontrollált, egyszeresen vak, utánkövetéses vizsgálat). Magyar Balneológiai Nagygyűlés 2012, Hajdúszoboszló

Kulisch Ágota, Benkő Ágota, Bergmann Annamária, Gyarmati Noémi, Horváth József, Kránicz Ágota, Mándó Zsuzsanna, Matán Ágnes, Németh András, Szakál Erika, Szántó Dóra, Szekeres László, Bender Tamás. Evaluation of the effect of Hévíz thermal water in patients with, osteoarthritis of the knee (a randomized, controlled, single-blind, follow-up study). (poster presentation) Controversies in Rheumatology and Autoimmunity, 2013, Budapest

Kulisch Ágota, Benkő Ágota, Bergmann Annamária, Gyarmati Noémi, Horváth József, Kránicz Ágota, Mándó Zsuzsanna, Matán Ágnes, Németh András, Szakál Erika, Szántó Dóra, Szekeres László, Bender Tamás. A Hévízi-tó termál-ásványvizének vizsgálata primér térdarthrosisban szenvedő betegekre. "Az egészségturizmus orvosi és turisztikai szemmel". 2013, Hévíz

Kulisch Ágota, Benkő Ágota, Bergmann Annamária, Gyarmati Noémi, Horváth József, Kránicz Ágota, Mándó Zsuzsanna, Matán Ágnes, Németh András, Szakál Erika, Szántó Dóra, Szekeres László, Bender Tamás. A Hévízi-tó termál-ásványvizének vizsgálata primér térdarthrosisban szenvedő betegekre (randomizált, kontrollált, egyszeresen vak, utánkövetéses vizsgálat). Orvosi Rehabilitáció és Fizikális Medicina Magyarországi Társasága XXXII. Vándorgyűlése 2013, Miskolc

ACKNOWLEDGEMENTS

I owe a debt of gratitude to my doctoral advisor, Tamás Bender, M.D., Ph.D., D.Sc., for his continuing and magnanimous support from the beginning of our acquaintance through my years in the Doctoral School.

My sincere thanks also goes to László Szekeres, M.D., who fundamentally oriented and helped me to become a rheumatologist as well as encouraged my interest in balneology.

Special thanks to András Németh, MD., for his outstanding knowledge in statistics and his dedicated work in preparation of the manuscripts.

My sincerest thanks to László Czirják, M.D., Ph.D., D.Sc. and colleagues of Department of Rheumatology and Immunology, University of Pécs for their teachings.

I am also grateful to Alice Dalmadi, M.D., for our first balneological examination.

I am also thankful to Katalin Horváth, M.D., for the good atmosphere for our common work.

I would like to thank Kránicz Ágota, M.D., for extending her support and professional assistance in our everyday work.

Thank you to the management of the St. András Hospital, Hévíz and to Zsuzsanna Mándó, M.D., for supporting and helping my work.

My special thanks go to the staff of the „G” and „D” Department for our daily common work.

With much fondness I thank my mother for her encouragement and background work that she does till date so she can support me. To my husband, my children, my family members, a special thank you for your patience, love and endurance, which made it possible for me to carry out my work.