One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial

A. Fioravanti · G. Bacaro · C. Giannitti · S. Tenti · S. Cheleschi · G. M. Gui\delli · N. A. Pascarelli · M. Galeazzi

Accepted: 25 November 2014

Abstract The objective of this prospective parallel randomized single-blind study was to assess that a cycle of mud-bath therapy (MBT) provides any benefits over usual treatment in patients with bilateral knee osteoarthritis (OA). Patients with symptomatic primary bilateral knee OA, according to ACR criteria, were included in the study and randomized to one of two groups: one group received a cycle of MBT at spa center of Chianciano Terme (Italy) in addition to the usual treatment, and one group continued their regular care routine alone. Clinical assessments were performed 7 days before enrollment (screening visit), at the time of enrollment (basal time), after 2 weeks, and after 3, 6, 9, and 12 months after the beginning of the study. All assessments were conducted by two researchers blinded to treatment allocation. The primary efficacy outcomes were the global pain score evaluated by Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscore for physical function (W-TPFS). Of the 235 patients screened, 103 met the inclusion criteria: 53 patients were included in the MBT group and 50 in the control group. In the group of patients treated with MBT, we observed a statistically significant ($p<0.001$) reduction of VAS and W-TPFS score at the end of the treatment; this improvement was significant ($p<0.05$) also at 3 months of follow-up. The control group did not show significant differences between baseline time and all other times. The differences between one group were significant for both primary parameters already from the 15th day and persisted up to the 9th month. This beneficial effect was confirmed by the significant reduction of symptomatic drug consumption. Tolerability of MBT seemed to be good, with light and transitory side effects. Our results confirm that a cycle of MBT added to usual treatment provides a beneficial effect on the painful symptoms and functional capacities in patients with knee OA that lasts over time. Mud-bath therapy can represent a useful backup to pharmacologic treatment of knee OA or a valid alternative for patients who do not tolerate pharmacological treatments.

Keywords Osteoarthritis · Knee · Mud-bath therapy · Randomized clinical trial

A. Fioravanti (✉) · C. Giannitti · S. Tenti · S. Cheleschi · G. M. Gui\delli · N. A. Pascarelli · M. Galeazzi
Rheumatology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Policlinico "Le Scotte," Viale Bracci 1, 53100 Siena, Italy
e-mail: fioravanti7@virgilio.it

G. Bacaro
CNR-IRPI, Istituto di Ricerca per la Protezione Idrogeologica, Via Madonna Alta 126, 06128 Perugia, Italy

G. Bacaro
BIOCONNET, Biodiversity and Conservation Network, Department of Life Sciences, University of Siena, Via PA Mattioli 4, 53100 Siena, Italy

Introduction

Osteoarthritis (OA) is a chronic, degenerative disease caused by deteriorating cartilage and leads to joint damage, pain, and stiffness. It continues to be one of the leading causes of years lived with disability worldwide, representing a great risk to the quality of life (QoL) of the individual, given the consequent loss of autonomy that can be precipitated by its effect on lower extremity-based activities (such as walking up and down stairs, climbing, and squatting) (Woolf and Pfleger 2003; Arden and Nevitt 2006). Knee OA is the most common type of OA, with an incidence of 6 % people older than 30 years and increases to 40 % in people aged 70 years or older (WHO 1997). With this as basis, knee OA is destined to become an ever more important healthcare problem (Fautrel et al. 2007).

The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater than that due to another medical disorder in the elderly (Guccione et al. 1994). To date, no intervention for knee OA has been unequivocally demonstrated to prove effective in slowing disease progression or delaying time to joint replacement surgery. Current management of knee OA includes non-pharmacological (education, exercise, and lifestyle changes) and pharmacological (paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and topical drugs) treatments (Jordan et al. 2003; Hochberg et al. 2012).

Spa therapy is one of the most commonly used non-pharmacological approaches for OA in many European and Middle Eastern countries. It comprises a broad spectrum of therapeutic modalities, including hydrotherapy, balneotherapy, mud-pack therapy, physiotherapy, and exercise (Verhagen et al. 2007). Spa treatment usually consists of a health holiday lasting some 2–3 weeks and creates a special therapeutic "atmosphere" of its own that can lead to the placebo effect. This condition plays an important role in reducing pain and improving the patient's general well-being (Bender et al. 2005). Although various systematic reviews, meta-analyses, and clinical trials on balneotherapy for rheumatic diseases have been published, its role in modern medicine is still subject of debate (Verhagen et al. 2007). In the recent OARSI Guidelines for the nonsurgical management of knee OA (McAlindon et al. 2014), balneotherapy was considered appropriate only for the sub-phenotype with multiple joint OA and co-morbidities, because of paucity of treatment alternatives for that group. Although systematic reviews and randomized controlled clinical trial (RCTs) demonstrated the benefit of balneotherapy for pain when compared with controls, OARSI and EULAR positions about balneotherapy remain doubtful because of the lack and the poor methodologic quality of trials; thus, additional large and well-designed RCTs are needed.

The objective of our prospective randomized single-blind controlled study was to assess the therapeutic efficacy of a cycle of mud-bath therapy (MBT) in patients with knee OA. Specifically, the study was aimed to examine the differences in pain, function, and QoL, between a group of patients received a cycle of mud-bath therapy (MBT group) in addition to the usual treatment and a group of patients who received usual treatments alone (control group).

Methods

Trial design

This was a prospective randomized, single-blind (assessor) controlled trial. The study protocol followed the Principles of the Declaration of Helsinki 1964 and later amendments and was approved by the Ethics Committee of Siena University Hospital (decision no. 340, 12th August 2010) and was registered on http://www.clinicaltrials.gov (NCT01538043).

Participants

Patients of both sexes with primary bilateral knee OA, who fulfilled the American College of Rheumatology (ACR) criteria (Altman et al. 1986) and were aged between 40 and 80 years, were included in the study. Patients were recruited by the general practitioners in the rural area within a 30-km radius of the "Chianciano Spa" Resort (Siena, Italy) and resided in the area near the spa, allowing them to continue to live at home and carry out their daily routines during the study period. After the recruitment by the general practitioners, the patients were examined at the Rheumatology Unit of Siena Hospital to verify the inclusion and exclusion criteria. The physician who performed the screening visit (G.M.G.) did not participate in the randomization process. Patients with pain in both knees during the previous 3 months or longer and rated >30 mm on a Visual Analog Scale (VAS; 0 to 100 mm) (Jensen et al. 1986; Kersten et al. 2010) will be selected for the trial. Radiological staging was carried out using the Kellgren method (Kellgren and Lawrence 1957); the radiographs were obtained within 6 months of enrollment. Patients with a radiological score of I–III were included in the study. Exclusion criteria were severe comorbidity of the heart, lung, liver, cerebrum, or kidney, acute illness, type 1 diabetes, varices, systemic blood disease, neoplasm, a BMI >30 kg/m^2 pregnancy, or nursing. Patients treated with intra-articular corticosteroids during the past 3 months, as well as all patients who had been treated with Symptomatic Slow Acting Drugs for OA (SYSADOA) agents or received intra-articular hyaluronic acid less than 3 months before the study were excluded. Furthermore, the patients who had a spa treatment in the 3 months previous to enrollment were not included.

At the screening visit, blood samples were taken for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), electrolyte, creatinine, aspartate and alanine aminotransferases, and complete blood count analysis; urinalysis was also performed to verify the absence of exclusion criteria. Written informed consent was obtained for all patients.

Interventions

Patients fulfilling the inclusion criteria were randomized to receive a cycle of MBT in addition to the usual treatment (MBT group) or to continue their care routine alone (control group). Patients allocated to the control group were offered a cycle of MBT at the end of the study to prevent withdrawal from the study and for ethical reasons. The MBT group was treated with a combination of daily local mud-packs prepared with water from the Sillene Spring (Chianciano Terme, Italy) and baths in the same water. The Sillene water is characterized by high sulfate, bicarbonate, calcium, and magnesium contents (Table 1). The mud used consisted of a solid argillaceous component, predominantly inorganic, which had "matured" for 6 months in mineral water from the Sillene Spring. After the 6-month maturation period, the physical and chemical properties of the mud are stable (Fraioli et al. 2011). Mud-packs were applied on both knees for 20 min at an initial temperature of 42 °C and with Sillene water at 37 °C for 15 min in a bathtub for a total of 12 applications carried out over a period of 2 weeks. The control group continued their regular care routine alone (exercise, acetaminophen, NSAIDs, SYSADOA, intra-articular hyaluronic acid, as explained below).

Patients in both groups were advised to continue their established pharmacological and non-pharmacological treatments. Washout of concomitant acetaminophen or NSAIDs was required for an entire week before randomization and 24 h before every assessment. However, the treatment with any of these drugs was recorded in a daily diary (see below). Furthermore, we asked the patients of both groups not to begin treatment with the new SYSADOA. Drugs prescribed for a disorder other than OA were included in the case report form at each clinic visit throughout the trial. Acetylsalicylic acid at dosage of 100 mg/day was permitted for the prevention of cardiovascular events. Further spa treatments were not permitted during the follow-up period.

Outcomes

In accordance with the European Agency for the Evaluation of Medicinal Products (EMEA 2005), recommendations on clinical investigation of medicinal products used in the treatment of OA (Committee for Proprietary Medicinal Products 1998), pain relief, and improvement of physical function were decided before the study began and considered as the primary efficacy criteria in this study. For this purpose, we evaluated either global pain using a Visual Analog Scale (VAS) and physical function by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscore (W-TPFS) (Bellamy et al. 1998). Global pain experienced during the last 24 h prior to assessment was rated on a 100-mm VAS (0="no pain"; 100="the worst pain possible") (Jensen et al. 1986; Kersten et al. 2010). The WOMAC is a widely used, reliable, valid, and responsive measure of treatment outcomes in patients with OA of the hip or knee (Bellamy et al. 1998; Salaffi et al. 2003). The WOMAC index consists of 24 questions (5 related to the amount of pain, 2 to stiffness, and 17 to physical function) and takes less than 5 min to complete (Bellamy 2009). For WOMAC, we used a 5-point Likert scale; the Likert scale may be more favorable over the VAS version (McConnell et al. 2001). The Likert version of the WOMAC rates each question on an ordinal scale of 0 to 4, with lower scores indicating lower levels of symptoms or physical disability (McConnell et al. 2001). The primary outcome measures were the comparisons between the MBT and control groups of the means of VAS and W-TPFS along the study.

Secondary efficacy endpoints included WOMAC total pain score (W-TPS), WOMAC total stiffness score (W-TSS), physical component summary (PCS), and mental component summary (MCS) of SF-12 (ranges 0–100 where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health) (Ware et al. 1996; Apolone and Mosconi 1998), European Quality-of-Life Questionnaire-5 Dimensions (EQ-5D; range between −0.594 and 1 (full health)) and EuroQol-VAS (range between 0 and 100 where 0 score indicates the worst imaginable health state and 100 the best imaginable health state) (Hurst et al. 1994); consumption of acetaminophen and NSAIDs reported in a daily diary given to each patient and handed to us at follow-up visits.

Clinical assessments of the patients were performed 7 days before enrollment (screening visit), at the time of enrollment (basal time), after 2 weeks, and after 3, 6, 9, and 12 months after the beginning of the study.

Safety parameters

All adverse events, whether reported spontaneously by the patients or observed by the physician, were reported in a diary, noting the severity and any possible correlations with the treatment. Serious adverse events were to be reported immediately to the University of Siena's Rheumatology Unit and resulted in the patient's exclusion from the treatment.

Table 1 Chemical and physical characteristics of the Sillene mineral water (Chianciano Spa, Italy)

Properties	Unit of measure	
pH	–	6.2
Conductivity	μS/cm	3050
Fixed residue at 180 °C	mg/l	3025
Carbon dioxide (CO_2)	mg/l	610
Sulfate (SO_4^{--})	mg/l	1584
Calcium (Ca^{++})	mg/l	657
Magnesium (Mg^{--})	mg/l	176
Bicarbonate (HCO_3^-)	mg/l	749
Sodium (Na^+)	mg/l	21
Potassium (K^+)	mg/l	6.0
Silica (SiO_2)	mg/l	22
Chlorides (Cl^-)	mg/l	17
Ammonium (NH_4^+)	mg/l	0.03
Strontium (Sr^{++})	mg/l	0.2
Lithium (Li^+)	mg/l	0.05

Randomization and blinding

Following confirmation that the patients fulfilled the screening criteria as defined above and having obtained written informed consent, the patients were randomized 1:1 and allocated to one of two groups using a computer-generated table of random numbers.

The block randomization list was kept by individuals who had no contact with the investigators who assigned patients to their randomized treatment and with the investigators who performed the patient assessment or conducted the statistical analysis.

All assessments were conducted by two researchers (C.G. and S.T.) blinded to treatment allocation.

Statistical analysis

Power analysis (α=0.05; β=0.80) determined that a sample size of 50 patients in each group was needed to demonstrate a 10-mm difference in improvement in the patient's assessment of pain (using a 0–100-mm VAS) between the two groups, with a standard deviation (SD) of 20 mm and a dropout rate of 15 %.

The main analysis for efficacy and safety was an intent-to-treat (ITT) analysis. Missing follow-up assessments were replaced using the last observation carried forward (LOCF) method.

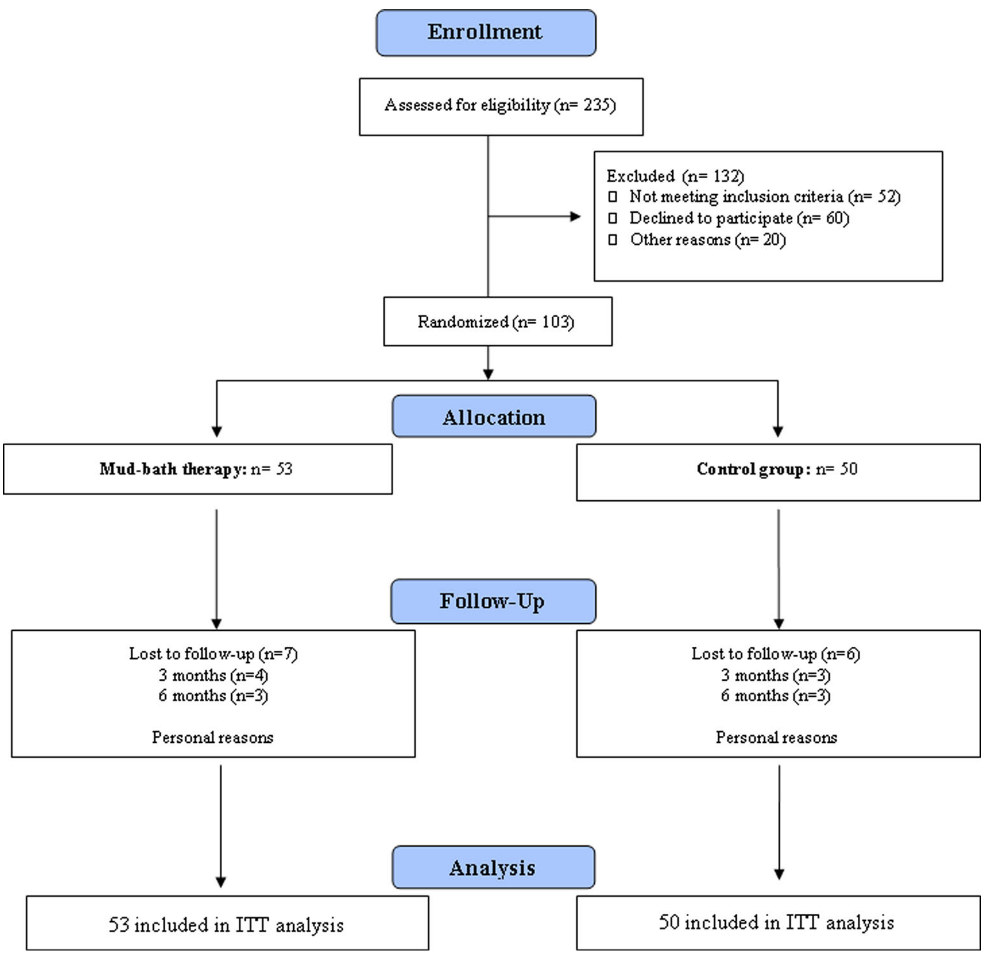
To analyze the effect over time of mud-bath therapy on pain, function and QoL in patients with knee OA, ANOVA with repeated measures in one factor was carried out on each parameter. Two-sided *t* tests were also used to assess inter- and intra-group statistical differences. Statistical significance was considered with α=0.025 considering the Bonferroni correction method. For W-TPS and W-TPFS, effect sizes were also calculated as the mean change in score from baseline to 12 months, divided by the SD of the baseline score.

The number of patients requiring acetaminophen and NSAIDs was compared by McNemar's test.

All the statistical analysis were performed using the R statistical software (Development Core Team 2013).

For missing data, the following rules of replacement were used: if the criterion was missing at one visit during the follow-up period (because of either missing values or invalidation of the given visit), the mean between values on the visit preceding and the visit following the missing visit was used.

Fig. 1 Flow of participants throughout the study



On the other side, if the last visit was missed, the value collected at 9 months has been carried forward.

Results

Between 1 December 2010 and 1 December 2011, 235 patients were screened, 103 met the inclusion criteria and were randomized. The visit at basal time in the full population showed some co-morbidities; in the MBT group, eight (15.09 %) presented arterial hypertension (well managed with antihypertensive drugs), four (7.5 %) had non-insulin-dependent diabetes (controlled with oral antidiabetic agents), two (3.77 %) had gastric ulcer, and two (3.77 %) had prostatic hypertrophy. In the control group, seven (14 %) patients presented arterial hypertension, four (8 %) had type 2 diabetes, and three (6 %) had hypothyroidism (data not showed). All patients in the MBT group received a cycle of mud-bath therapy. Seven patients (13.2 %) assigned to the MBT group and six (12 %) in the control group, were lost to follow-up for personal reasons; Fig. 1 provides the patient disposition throughout the study.

Baseline demographic and clinical characteristics of the ITT population are given in Table 2. Comparison of the two groups showed no statistically significant differences in demographic and clinical characteristics or in radiological features except for gender and W-TPS. Concerning pain measured by VAS in the MBT group, we observed a statistically significant ($p<0.001$) reduction at the end of treatment (15 days); this improvement was significant ($p<0.05$) also at 3 months of follow-up (Fig. 2). In the control group, there were no significant differences during the follow-up period. The differences between the two groups were already significant at day 15 and persisted until 12 months. The W-TPFS score in the MBT group showed a significant ($p<0.001$) decrease after 2 weeks and remain significant ($p<0.05$) until 3 months (Fig. 3). The control group showed no significant differences between the basal time and all other times. The difference between the two groups was significant at the end of the treatment and persisted up to the 9th period (Fig. 3).

In Table 3, we showed the analyses of secondary outcome parameters in the full population: as can be easily seen, much of these indices still remain significantly different between the control and MBT groups during the follow-up period, except for the W-TPS, MSC of SF-12, and the EQ-5D. On average, however, the differences between groups remain statistically different after 3 months from the treatments, with a decrease in significance after this time lag.

The effect sizes for VAS, W-TPS, W-TSS, and W-TPFS are shown in Table 4.

The number of patients in the MBT group requiring acetaminophen and NSAIDs showed a continuous downward trend after mud-bath therapy. In the control group, we observed only a slight decrease at 15 days' visit. The differences between the two groups were already significant at day 15 and persisted during the follow-up period for acetaminophen consumption (Table 5).

About tolerability, in the group treated with mud-bath therapy, 7.5 % of patients presented side effects because of treatment, but these were of light intensity and did not interrupt the therapy. Three patients presented an episode of mild hypotension, due to the treatment, while a patient suffered from an acute febrile episode. In the control group, 10 % of patients presented prevalently gastrointestinal side effects (i.e., 6 % complained of gastric pyrosis and 4 % presented epigastralgia),

Table 2 Patient demographic and baseline characteristics in the ITT population

	MBT group	Control group	*p* value
Number of pts	53	50	–
Men (no (% of group))	23 (43)	6 (12)	–***
Women (no (% of group))	30 (57)	44 (88)	–***
Age (years)	68.49±9.01	69.66±11.1	NS
BMI (kg/m^2)	28.58±4.01	28.01±4.18	NS
Disease duration (years)	7.10±5.90	7.01±6.53	NS
K-L grade (no (% of group))			
I	13 (24)	10 (20)	NS
II	23 (44)	13 (26)	NS
III	17 (32)	27 (54)	NS
VAS for pain (0–100)	51.54±20.02	57.1±24	NS
W-TPS	5.41±2.75	7.04±4.48	–**
W-TSS	2.47±1.44	3±2.07	NS
W-TPFS	18.73±10.7	23.60±14.85	NS
SF-12 PCS	28.66±15.48	27.63±14.62	NS
SF-12 MSC	47.70±10.36	43.83±8.40	NS
EQ-5D	0.46±0.31	0.37±0.36	NS
EQ-5D VAS	59.54±19.20	57.06±22.02	NS
Medication (at time of inclusion; no (% of group))			
Acetaminophen	17 (32.07)	14 (28)	NS
NSAIDs	40 (75.47)	38 (76)	NS
SYSADOA	15 (28.30)	19 (38)	NS
Hyaluronic acid	18 (33.96)	23 (46)	NS

Data are expressed as mean±SD

MBT mud-bath therapy, *pts* patients, *BMI* body mass index (body weight divided by the square of the height), *K-L grade* Kellgren Lawrence grade, *VAS* Visual Analog Scale, *W-TPS* WOMAC total pain score, *W-TSS* WOMAC total stiffness score, *W-TPFS* WOMAC total physical function score, *SF-12 PCS* physical component summary, *SF-12 MSC* mental component summary, *EQ-5D* European Quality of Life Questionnaire-5 Dimensions, *EQ-5D VAS* European Quality-of-Life Questionnaire-5 Dimensions Visual Analog Scale, *NSAIDs* non-steroidal anti-inflammatory drugs, *SYSADOA* symptomatic slow-acting drug for osteoarthritis

**$P<0.01$; ***$P<0.001$—significance between groups

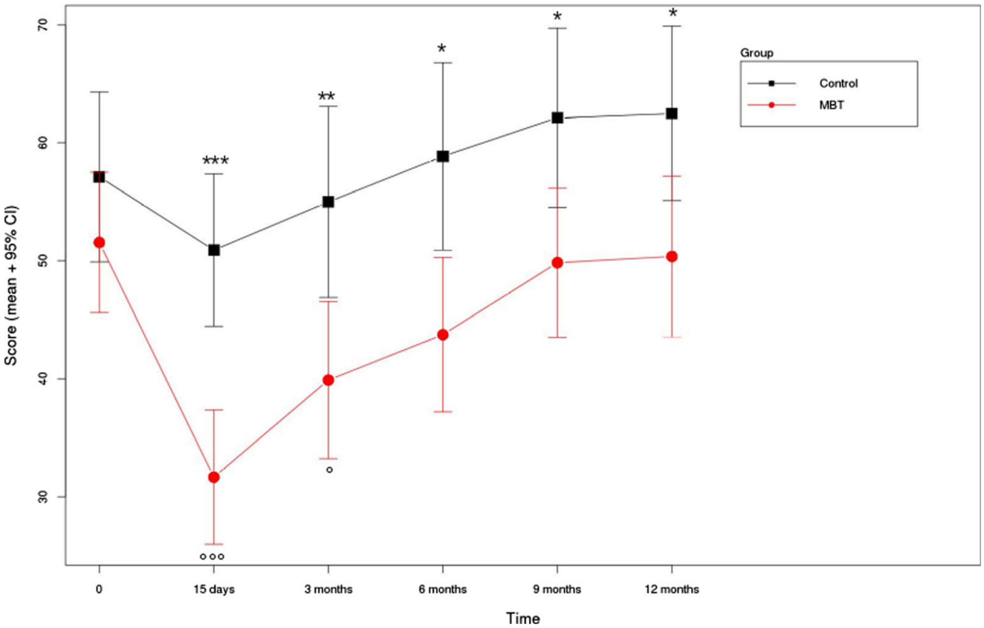


Fig. 2 Global pain on a 0–100-mm Visual Analog Scale (VAS), over time. $p<0.001$; $p<0.05$ vs basal time; ***$p<0.001$; **$p<0.01$; *$p<0.05$ MBT group vs control group

probably correlated with the higher recourse to symptomatic drugs compared with patients in the MBT group.

Discussion

The present controlled randomized parallel single-blind trial demonstrated that a cycle of mud-bath therapy in addition to usual treatment provides any benefit over usual treatment alone in the management of patients with knee OA. The efficacy of MBT was significant in all the assessed parameters at examinations at the end of therapy. Furthermore, in patients treated with MBT, the values of VAS and W-TPS scores continued to be significantly better after 3 months of follow-up in comparison with basal values. In contrast, there were no significant modifications of the parameters measured throughout the follow-up period in the group treated with usual therapies alone. At the end of the 1-year follow-up, we observed a slight, but not significant increase in VAS score in control group, and in W-TPFS in both groups. These findings could be attributable to the natural history of OA. The effect

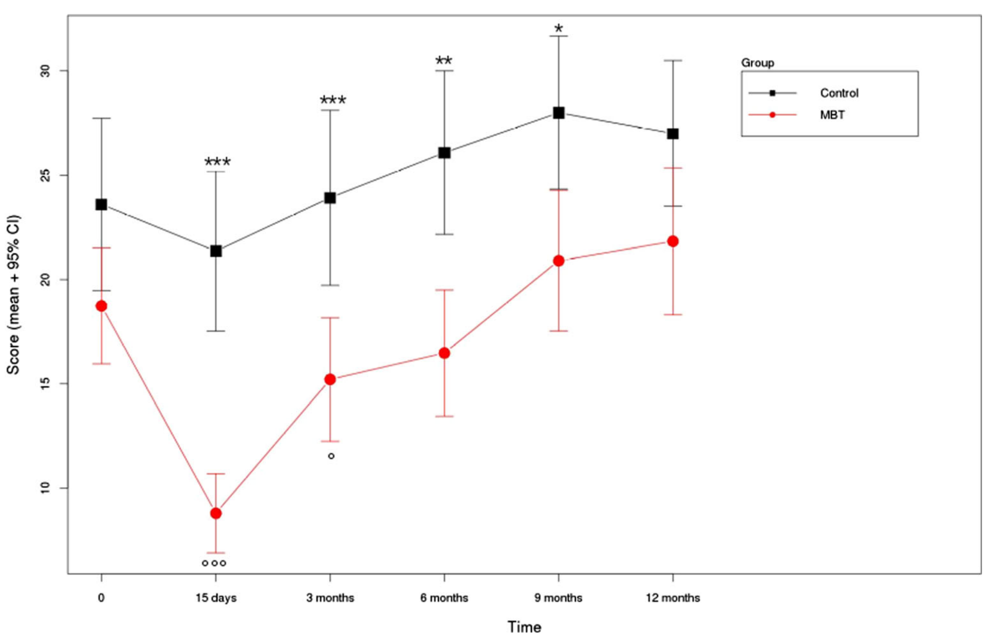


Fig. 3 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscore for physical function (W-TPFS) for knee OA over time. $p<0.001$; $p<0.05$ vs basal time; ***$p<0.001$; **$p<0.01$; *$p<0.05$ MBT group vs control group

Table 3 Results of pairwise comparisons between and within groups (p values are corrected using the Bonferroni method)

Parameters	Basal time	15 days	3 months	6 months	9 months	12 months
W-TPS						
MBT group	5.41	2.66$^{\#\#\#}$	3.88$^{\#\#}$	4.32$^{\#}$	5.73	6.26
Control group	7.04	5.82***	5.98**	6.64**	7.28	7.18
W-TSS						
MBT group	2.47	0.94$^{\#\#\#}$	1.79$^{\#\#}$	1.39$^{\#\#\#}$	1.98	2.22
Control group	3.00	2.42***	2.68**	2.94***	3.18***	3.06
SF-12 PCS						
MBT group	28.66	44.77$^{\#\#\#}$	41.27$^{\#\#\#}$	39.23$^{\#\#}$	36.08	33.98
Control group	27.63	31.09***	28.54***	26.77**	24.68*	22.13**
SF-12 MSC						
MBT group	47.70	55.17$^{\#\#\#}$	44.92	42.60	42.66	42.50
Control group	43.83	41.62***	46.18	44.52	44.38	45.21
EQ-5D						
MBT group	0.46	0.83$^{\#\#\#}$	0.71$^{\#\#\#}$	0.65$^{\#\#}$	0.56	0.47
Control group	0.37	0.55***$^{\#}$	0.49***	0.41**	0.44	0.37
EQ-5D VAS						
MBT group	59.54	71.09$^{\#}$	70.15$^{\#}$	69.67	72.56$^{\#}$	73.77$^{\#\#}$
Control group	57.06	59.32***	58.88**	55.32***	55.90***	51.68***

VAS Visual Analog Scale, *W-TPS* WOMAC total pain score, *W-TSS* WOMAC total stiffness score, *W-TPFS* WOMAC total physical function score, *SF-12 PCS* physical component summary, *SF-12 MSC* mental component summary, *EQ-5D* European Quality-of-Life Questionnaire-5 Dimensions, *EQ-5D VAS* European Quality-of-Life Questionnaire-5 Dimensions Visual Analog Scale

*p<0.05; **p<0.01; ***p<0.001—significance between groups; $^{\#}p$<0.05; $^{\#\#}p$<0.01; $^{\#\#\#}p$<0.001—significance within groups

sizes in the MBT group for VAS, W-TPS, W-TSS, and W-TPFS are similar to those for other treatments of knee OA, including hyaluronic acid, paracetamol, and NSAIDs (Arrich et al. 2005; Neame et al. 2004; Bjordal et al. 2004).

The results of our trial confirm those of studies previously reported in the literature on OA. In a large multicenter randomized prospective clinical trial in patients with knee OA, Forestier et al. (2010) reported that a 3-week course of spa therapy, together with home exercises and the usual pharmacological treatments, offer benefits after 6 months. Our previous trial Fioravanti et al. 2012) demonstrated that the beneficial effects of spa therapy in patients with knee OA last over time (3 months) with positive effects on the painful symptomatology, a significant improvement in functional capacities and QoL. Recently, Kulish et al. (Kulisch et al. 2014) in a randomized, tap water controlled, single-blind study, confirmed the efficacy of balneotherapy on pain, function, and QoL in patients with knee OA even 12 weeks after the treatment.

Only few studies evaluated the efficacy of spa therapy on QoL (Verhagen et al. 2007). In this study, we used two different QoL scales, the SF-12, which is the most popular generic health status instrument, and EQ-5D. According to other authors (Tefner et al. 2013; Kulisch et al. 2014), a significant improvement in both QoL indexes was seen at the end of the therapy. This improvement persisted until the

Table 4 Effect size (95 % CI) for VAS and WOMAC subscales

Parameters	MBT group		Control group		p value
	Means (SD)	Effect size (95 % CI)	Means (SD)	Effect size (95 % CI)	
VAS	1.06 (24.03)	0.05 (0.05; −0.23)	5.59 (20.55)	0.27 (0.59; −0.02)	<0.05
W-TPS	1.30 (4.07)	0.32 (0.61; 0.03)	0.11 (4.79)	0.02 (0.32; −0.27)	<0.05
W-TSS	−0.10 (1.77)	−0.06 (0.23; −0.35)	0.06 (2.20)	0.03 (0.33; −0.26)	<0.05
W-TPFS	4.18 (10.66)	0.40 (0.68; 0.14)	3.60 (14.29)	0.25 (0.57; −0.04)	<0.05

VAS Visual Analog Scale, *W-TPS* WOMAC total pain score, *W-TSS* WOMAC total stiffness score, *W-TPFS* WOMAC total physical function score

Table 5 Number (%) of patients requires acetaminophen and NSAIDs in the ITT population during the study

Group	Basal time	15 days	3 months	6 months	9 months	12 months
MBT (53)						
Acetaminophen (*N* (%))	17 (32.07)	1 (2)###	0 (0)###	1 (2)###	2 (4)###	0 (0)°##
NSAIDs (*N* (%))	40 (75.47)	7 (13)###	21 (40)###	20 (38)###	20 (38)###	16 (30)###
Control (50)						
Acetaminophen (*N* (%))	14 (28)	10 (20)*	16 (32)***	13 (26)***	14 (28)***	14 (28)***
NSAIDs (*N* (%))	38 (76)	25 (50)###, ***	30 (60)#, *	32 (64)*	36 (72)*	33 (66)***

NSAIDs non-steroidal anti-inflammatory drugs

# $p<0.05$; ### $p<0.001$—significance between groups; *$P<0.05$; ***$P<0.001$—significance within groups

end of the follow-up for SF-12 PCS and until 6 months for EQ-5D.

The reduction in the consumption of symptomatic drugs (acetaminophen and NSAIDs) induced by MBT is particularly important, above all for the elderly, considering the toxicity of NSAIDs (Ofman et al. 2002; Huskisson et al. 1995; Bresalier et al. 2005; Kearney et al. 2006), as well as their cost, given that their use is often coupled with gastro-protective therapies. This evidence is in agreement with the results showed in the large multicentric study named "Naiade Italian Project" (Fioravanti et al. 2003) and with the results obtained by many other authors (Gaál et al. 2008; Fioravanti et al. 2012; Tefner et al. 2013).

The mechanisms by which the immersion in mineral or thermal water or the application of mud alleviates the main symptoms of OA and of other rheumatic diseases are not fully understood. The efficacy is probably the result of a combination of factors, among which mechanical, thermal, and chemical effects are most prominent (Sukenik et al. 1999; Fioravanti et al. 2011a, b). The beneficial effects of balneotherapy and application of mud-packs are, in part, ascribable to heat. Hot stimuli may influence muscle tone and pain intensity, helping to reduce muscle spasm and increase the pain threshold in the nerve endings. According to the "gate theory," pain relief may be due to the temperature and hydrostatic pressure of water on the skin (Melzack and Wall 1965; Schmidt 1995). Mud-bath therapy provokes a series of neuroendocrine reactions. In particular, the heat stimulates the release of adrenocorticotropic hormone (ACTH), cortisol, prolactin, and growth hormone (GH), although it does not alter the circadian rhythm of these hormones (Kuczera and Kokot 1996). Furthermore, various spa therapy techniques have been demonstrated to increase the plasma levels of beta-endorphin (Kubota et al. 1992). Interestingly, it has been found that application of mature thermal mud in healthy individuals brings about a rapid increase in plasma beta-endorphin, which returns to pretreatment levels within the period of the so-called thermal reaction (Cozzi et al. 1995). Recent data have demonstrated the possibility that normal keratinocytes can produce and secrete a precursor proopiomelanocortin (POMC) following various stimuli (e.g., ultraviolet rays, thermal stimuli), which is the common precursor of various endorphins (Ghersetich et al. 2000). This finding allows us to formulate the fascinating hypothesis that ultraviolet radiation or thermal stimuli could be used to condition the skin's production of opioid peptides, thus altering the personal emotional sphere or pain threshold. These mechanisms that relate to temperature of mud-bath therapy could explain the short-term clinical efficacy. Long-term effects on pain and functional status induced by mud-baths in OA as reported by us and other authors might be related to chemical composition of water or mud. However, one of the critical points is the controversial problem of the absorption of the minerals dissolved in waters or of the ingredients contained in mature mud. Unfortunately, experimental evidence available in this field is scarce. Shani et al. (1985) documented a significant increase in serum concentrations of bromine, rubidium, calcium, and zinc in patients with psoriatic arthritis who bathed in the Dead Sea. Furthermore, it has been reported that in patients with knee OA, the direct application of mud-pack has greater clinical effects than the application of nylon covered mud-pack (Odabasi et al. 2008) and mud-pack is more effective than hot pack especially over time (Güngen et al. 2012; Sarsan et al. 2012). It has recently been demonstrated that thermal mud-pack therapy induces a reduction in circulating levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), matrix metalloproteinases-3 (MMP-3), and adiponectin, which are important mediators of inflammation and cartilage degradation in OA (Bellometti and Galzigna 1998; Ardic et al. 2007; Bellometti et al. 2002; Bellometti et al. 2005; Fioravanti et al. 2011a).

Spa therapy has been found to cause an increase in insulin-like growth factor-1 (IGF-1) (Bellometti et al. 1997), which stimulates cartilage metabolism, and an increase in transforming growth factor-β (TGF-β), a very potent immunomodulating and anti-inflammatory cytokine (Shehata et al. 2006).

Mud-packs and thermal baths also have been shown to exert positive effects on the oxidant/antioxidant system, resulting in a reduced release of reactive oxygen (ROS) and nitrogen (RNS) (Ekmekcioglu et al. 2002; Bender et al. 2007; Braga et al. 2008; Benedetti et al. 2010).

Many other non-specific factors may also contribute to the effects observed after mud-baths therapy, including changes in the environment, the pleasant scenery, and the absence of work duties (Sukenik et al. 1999; Fioravanti et al. 2011a, b). In our study, however, in order to temper these factors, all the patients selected lived in the area surrounding the spa, continued working, and did not modify their lifestyles. Another aspect that often contributes to amplifying the effects of spa therapy is its frequent association with physio-kinesiotherapy. These treatments were excluded from the protocol of this study if they had not already begun and were not already established.

Finally, the tolerability of spa therapy seemed to be good, with light and transitory side effects even in the patients who presented co-morbidities with knee OA.

Some limitations of our study need to be discussed. The main limitation of this study is the lack of a double-blind-placebo design. However, the persistence of a positive clinical effect over time after the treatment suggests that an additional benefit over placebo was obtained. On the other hand, patients randomized into the control group were offered a cycle of MBT at the end of the study. This could have overestimated the treatment effect. The small number of patients and the lack of patients with more severe symptoms (pain and function) of knee OA could be another limitation. Furthermore, being all self-reported questionnaires, the assessor was the patient and blinding of assessor not possible and the influence of the placebo effect could be increased. Another limitation could be represented by the lack of blinding of therapist that may overestimate the treatment effect. Finally, we should consider that continuous outcomes can lead to a significant placebo effect.

In conclusion, our results, in keeping with other studies in the literature, confirm the beneficial effects of spa therapy in patients with knee OA. A cycle of mud-bath therapy added to usual treatment provides a beneficial effect on the painful symptoms, functional capacities, and on QoL that lasts over time. Mud-bath therapy can represent a useful backup to pharmacologic treatment of knee OA or a valid alternative for patients who do not tolerate pharmacological treatments.

Conflict of interest None.

Funding This study was funded by Regione Toscana. This study sponsors did not participate in the study design, in the collection, analysis, or the interpretation of data.

References

Altman R, Asch E, Bloch D et al (1986) Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee diagnostic and therapeutic criteria committee of the american rheumatism association. Arthritis Rheum 29:1039–1049

Apolone G, Mosconi P (1998) The Italian SF-36 health survey: translation, validation and norming. J Clin Epidemiol 51:1025–1036

Arden N, Nevitt MC (2006) Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol 20:3–25

Ardic F, Ozgen M, Aybek H, Rota S, Cubukçu D, Gökgöz A (2007) Effects of balneotherapy on serum IL-1, PGE2 and LTB4 levels in fibromyalgia patients. Rheumatol Int 27:441–446

Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Müllner M (2005) Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ 172:1039–1043

Bellamy N (2009) WOMAC Osteoarthritis Index: user guide IX. Queensland: WOMAC

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW (1998) Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15:1833–1840

Bellometti S, Galzigna L (1998) Serum levels of a prostaglandin and a leukotriene after thermal mud pack therapy. J Investig Med 46:140–145

Bellometti S, Giannini S, Sartori L, Crepaldi G (1997) Cytokine levels in osteoarthrosis patients undergoing mud bath therapy. Int J Clin Pharmacol Res 17:149–153

Bellometti S, Galzigna L, Richelmi P, Gregotti C, Bertè F (2002) Both serum receptors of tumor necrosis factor are influenced by mud pack treatment in osteoarthrotic patients. Int J Tissue React 24:57–64

Bellometti S, Richelmi P, Tassoni T, Bertè F (2005) Production of matrix metalloproteinases and their inhibitors in osteoarthritic patients undergoing mud bath therapy. Int J Clin Pharmacol Res 25:77–94

Bender T, Karagülle Z, Bálint GP, Gutenbrunner C, Bálint PV, Sukenik S (2005) Hydrotherapy, balneotherapy, and spa treatment in pain management. Rheumatol Int 25:220–224

Bender T, Bariska J, Vághy R, Gomez R, Kovács I (2007) Effect of balneotherapy on the antioxidant system—a controlled pilot study. Arch Med Res 38:86–89

Benedetti S, Canino C, Tonti G et al (2010) Biomarkers of oxidation, inflammation and cartilage degradation in osteoarthritis patients undergoing sulfur-based spa therapies. Clin Biochem 43:973–978

Bjordal JM, Ljunggren AE, Klovning A, Slørdal L (2004) Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 329:1317

Braga PC, Sambataro G, Dal Sasso M, Culici M, Alfieri M, Nappi G (2008) Antioxidant effect of sulphurous thermal water on human neutrophil bursts: chemiluminescence evaluation. Respiration 75:193–201

Bresalier RS, Sandler RS, Quan H et al (2005) Adenomatous polyp prevention on Vioxx (APPROVe) trial investigators. N Engl J Med 352:1092–1102

Committee for Proprietary Medicinal Products (1998) Points to consider on clinical investigation of medicinal products used in the treatment of osteoarthritis. European Agency for the Evaluation of medicinal products (London 23 July 1998). CPMP/EWP/784/97

Cozzi F, Lazzarin P, Todesco S, Cima L (1995) Hypothalamic-pituitary-adrenal axis dysregulation in healthy subjects undergoing mud-bath applications. Arthritis Rheum 38:724–726

Ekmekcioglu C, Strauss-Blasche G, Holzer F, Marktl W (2002) Effect of sulfur baths on antioxidative defense systems, peroxide concentrations and lipid levels in patients with degenerative osteoarthritis. Forsch Komplementarmed Klass Naturheilkd 9:216–220

EMEA. Committee for medicinal products for human use (CHMP).Guideline on the choice of the non-inferiority margin. Doc. Ref. EMEA/CPMP/EWP/ 2158/99, issued London July, 27 2005

Fautrel B, Hilliquin P, Rozenberg S et al (2007) Impact of osteoarthritis: results of a nationwide survey of 10,000 patients consulting for OA. Joint Bone Spine 72:235–240

Fioravanti A, Valenti M, Altobelli E et al (2003) Clinical efficacy and cost-effectiveness evidence of spa therapy in osteoarthritis. The results of "Naiade" Italian Project. Panminerva Med 45:211–217

Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M (2011a) Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there. Rheumatol Int 31:1–8. doi:10.1007/s00296-010-1628-6

Fioravanti A, Cantarini L, Bacarelli MR, de Lalla A, Ceccatelli L, Blardi P (2011b) Effects of spa therapy on serum leptin and adiponectin levels in patients with knee osteoarthritis. Rheumatol Int 31:879–882. doi:10.1007/s00296-010-1401-x

Fioravanti A, Giannitti C, Bellisai B, Iacoponi F, Galeazzi M (2012) Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. Int J Biometeorol 56:583–590. doi:10.1007/s00484-011-0447-0

Forestier R, Desfour H, Tessier JM et al (2010) Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis 69:660–665

Fraioli A, Serio A, Mennuni G et al (2011) A study on the efficacy of treatment with mud packs and baths with Sillene mineral water (Chianciano Spa Italy) in patients suffering from knee osteoarthritis. Rheumatol Int 31:1333–1340. doi:10.1007/s00296-010-1475-5

Gaál J, Varga J, Szekanecz Z, Kurkó J, Ficzere A, Bodolay E, Bender T (2008) Balneotherapy in elderly patients: effect on pain from degenerative knee and spine conditions and on quality of life. Isr Med Assoc J 10:365–369

Ghersetich I, Freedman D, Lotti T (2000) Balneology today. J Eur Acad Dermatol Venereol 14:346–348

Guccione AA, Felson DT, Anderson JJ et al (1994) The effects of specific medical conditions on the functional limitations of elders in the Framingham study. Am J Publ Health 84:351–358

Güngen G, Ardic F, Fındıkoğlu G, Rota S (2012) The effect of mud pack therapy on serum YKL-40 and hsCRP levels in patients with knee osteoarthritis. Rheumatol Int 32:1235–1244

Hochberg MC, Altman RD, April KT et al (2012) American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 64:465–474

Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H (1994) Validity of Euroqol—a generic health status instrument—in patients with rheumatoid arthritis. Economic and health outcomes research group. Br J Rheumatol 33:655–662

Huskisson EC, Berry H, Gishen P, Jubb RW, Whitehead J (1995) Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. LINK Study Group Longitudinal investigation of nonsteroidal antiinflammatory drugs in knee osteoarthritis. J Rheumatol 22:1941–1946

Jensen MP, Karoly P, Braver S (1986) The measurement of clinical pain intensity: a comparison of six methods. Pain 27:117–126

Jordan KM, Arden NK, Doherty M et al (2003) Standing committee for international clinical studies including therapeutic trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). Ann Rheum Dis 62:1145–1155

Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C (2006) Do selective cyclo-oxygenase-2 inhibitors and traditional nonsteroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 332:1302–1308

Kellgren JH, Lawrence JS (1957) Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494–502

Kersten P, White PJ, Tennant A (2010) The visual analogue WOMAC 3.0 scale-internal validity and responsiveness of the VAS version. BMC Musculoskelet Disord 11:80

Kubota K, Kurabayashi H, Tamura K, Kawada E, Tamura J, Shirakura T (1992) A transient rise in plasma beta-endorphin after a traditional 47 degrees C hot-spring bath in Kusatsu-spa, Japan. Life Sci 51:1877–1880

Kuczera M, Kokot F (1996) Effect of spa therapy on the endocrine system. I. Stress reaction hormones. Pol Arch Med Wewn 95:11–20

Kulisch A, Benkö A, Bergmann A et al (2014) 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 50:373–381

McAlindon TE, Bannuru RR, Sullivan MC et al (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartil 22:363–388

McConnell S, Kolopack P, Davis AM (2001) The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 45:453–461

Melzack R, Wall PD (1965) Pain mechanism: a new theory. Science 150:971–979

Neame R, Zhang W, Doherty M (2004) A historic issue of the annals: three papers examine paracetamol in osteoarthritis. Ann Rheum Dis 63:897–900

Odabasi E, Turan M, Erdem H, Tekbas F (2008) Does mud pack treatment have any chemical effect? A randomized controlled clinical study. J Altern Complement Med 14:559–565. doi:10.1089/acm.2008.0003

Ofman JJ, MacLean CH, Straus WL et al (2002) A metaanalysis of severe upper gastrointestinal complications of nonsteroidal anti-inflammatory drugs. J Rheumatol 29:804–812

R Development Core Team (2013). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN: 3-900051-07-0, http://www.R-project.org/

Salaffi F, Leardini G, Canesi B et al (2003) Reliability and validity of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index in Italian patients with osteoarthritis of the knee. Osteoarthr Cartil 11:551–560

Sarsan A, Akkaya N, Ozgen M, Yildiz N, Atalay NS, Ardic F (2012) Comparing the efficacy of mature mud pack and hot pack treatments for knee osteoarthritis. J Back Musculoskelet Rehabil 25:193–199. doi:10.3233/BMR-2012-0327

Schmidt KL (1995) Scientific basis of spa treatment in rheumatic diseases. Rheumatol Eur 24:136–140

Shani J, Barak S, Levi D et al (1985) Skin penetration of minerals in psoriatics and guinea-pigs bathing in hypertonic salt solutions. Pharmacol Res Commun 17:501–512

Shehata M, Schwarzmeier JD, Hilgarth M et al (2006) Effect of combined spa-exercise therapy on circulating TGF-beta1 levels in patients with ankylosing spondylitis. Wien Klin Wochenschr 118:266–272

Sukenik S, Flusser D, Abu-Shakra M (1999) The role of spa therapy in various rheumatic diseases. Rheum Dis Clin North Am 25:883–897

Tefner IK, Gaál R, Koroknai A et al (2013) The effect of Neydharting mud-pack therapy on knee osteoarthritis: a randomized, controlled, double-blind follow-up pilot study. Rheumatol Int 33:2569–2576. doi:10.1007/s00296-013-2776-2

Verhagen AP, Bierma-Zeinstra SM, Boers M et al (2007) Balneotherapy for osteoarthritis. Cochrane Database Syst Rev 17, CD006864

Ware J Jr, Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34:220–233

WHO (1997). The world health report: 50 facts. Geneva: World Health Organization. Available from http://www.who.int/whr/1997/media_centre/50facts/en/. Accessed on February 18, 2014

Woolf AD, Pfleger B (2003) Burden of major musculoskeletal conditions. Bull World Health Organ 81:646–656