

Efficacy of mud plus bath therapy as compared to bath therapy in osteoarthritis of hands and knees: a pilot single-blinded randomized controlled trial

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SUMMARY

The primary objective of this study was to assess the efficacy of mud plus bath therapy in comparison to bath therapy alone in hand and knee osteoarthritis (HOA and KOA).

We conducted a single-blinded randomized controlled trial (RCT). Patients were randomly assigned to either mud plus bath therapy (group 1) or balneotherapy (group 2). The primary outcome was a change in AUSCAN questionnaire for HOA and in WOMAC for KOA at month 12. Evaluations were performed at baseline (B), immediately after the interventions (week 2, W2) and after 3 (M3), 6 (M6), 9 (M9) and 12 (M12) months.

37 patients with KOA and 52 with HOA were randomized in the study. In HOA patients, AUSCAN pain improved more in group 1 compared to group 2 at M3, M6 and M12 ($p < 0.001$, $p = 0.001$ and $p = 0.038$, respectively). AUSCAN stiffness improved more in group 1 at M3 ($p = 0.001$). AUSCAN function improved more at M3, M6, M9 and M12 ($p = 0.001$, $p = 0.001$, $p = 0.014$ and $p = 0.018$, respectively). Regarding, KOA, WOMAC function decreased more prominently in group 1 compared to group 2 at M9 ($p = 0.007$). The absolute values of WOMAC function at M6 and M9 were lower in group 1 compared to group 2 ($p = 0.029$ and $p = 0.001$, respectively). WOMAC pain absolute values were lower in group 1 at W2 ($p = 0.044$) and at M9 ($p = 0.08$).

We conducted a RCT on the efficacy of mud plus balneotherapy over balneotherapy alone in HOA and KOA. We found that mud plus balneotherapy was more effective than balneotherapy alone on clinical outcomes of HOA. Differences in clinical outcomes of KOA were not significant, yet numerically higher.

Key words: Knee osteoarthritis, hand osteoarthritis, mud therapy, bath therapy.

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INTRODUCTION

Osteoarthritis (OA) is a chronic disease of the joints characterized by cartilage degradation, thickening of subchondral bone, osteophyte formation, variable degrees of synovial inflammation and degeneration of ligaments (1). OA leads to joint damage, pain, and stiffness and is one of the leading causes for disability worldwide and for the worsening of individual quality of life (QoL). OA can eventually conduct to loss of autonomy, which is commonly precipitated by the detrimental effects on lower extremity (2, 3). Knee and hand OA (KOA and HOA) are the most common

types of OA, with an incidence of about 240/100,000 and 100/100,000 person-years, respectively (4), and both negatively affect QoL (5, 6). Unfortunately, treatment options are limited, and no intervention has been unequivocally demonstrated to slower disease progression. The current recommended treatments of HOA include non-pharmacological and pharmacological interventions (7-9). In particular, physical exercise (yoga, Thai-chi, or specific movements for the hands), thermotherapy, acupuncture, orthosis, local and systemic anti-inflammatory medications, infiltrative therapy and chondroitin sulphate are currently largely recommended for OA treatment.

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For KOA, the standard of care includes physical, psychosocial, and mind-body approaches. The main interventions are physical exercise, weight loss, crenobalneotherapy, acupuncture and braces. Pharmacological therapies comprise topical and oral nonsteroidal anti-inflammatory drugs, topical capsaicin, acetaminophen, duloxetine tramadol and intra-articular injections of both steroids and hyaluronic acid.

Crenobalneotherapy is among the most common non-pharmacological treatment prescribed for OA in European and Middle Eastern countries. Crenobalneotherapy has been used in both inflammatory and non-inflammatory musculoskeletal diseases (10). It encompasses a broad spectrum of therapeutic interventions, including hydrotherapy, balneotherapy, mud-pack therapy, physiotherapy, and exercise (11, 12). However, health resort therapy is not currently recommended by international societies in spite of increasing evidence of its efficacy, especially for KOA. This lack of endorsement is mainly driven by the large heterogeneity of the studies and the small number of patients involved.

Bone health is known to play a role in the pathogenesis of OA. However, only one study (13) evaluated the possible effects of mud-therapy on bone metabolism, and showed a beneficial effect of prolonged balneotherapy on bone density.

The primary aim of this randomized controlled study (RCT) was to evaluate the efficacy on clinical outcomes of HOA and KOA of mud therapy plus balneotherapy and conventional treatment over balneotherapy alone and conventional treatment. Secondary outcomes included densitometric changes.

■ MATERIALS AND METHODS

Study design and randomization

This was a prospective randomized, single-blinded controlled trial. Inclusion criteria were: diagnosis of KOA or HOA according to the 1990 American College of Rheumatology classification criteria (14), age between 45 and 80 years, symptoms (stiffness and/or pain) for at least 6 months,

Kellgren score (15) of II or III (in at least 3 fingers for HOA) in a radiograph performed within the last 6 months, and Australian Canadian Osteoarthritis Hand Index (AUSCAN) (16) pain >4 and AUSCAN function ≥ 26 for HOA or Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (WOMAC) >46 for KOA (16, 17).

The exclusion criteria included: diagnosis of systemic inflammatory disease, active infections or cancer, dementia, active and severe psychiatric diseases, concurrent enrollment in other clinical trials, balneotherapy in the previous 6 months, intra-articular injection with hyaluronic acid in the previous 6 months or steroids in the past 3 months, treatment with systemic steroids or Symptomatic Slow Acting Drugs for OA (SYSADOA) in the previous 6 months and hand or knee surgery in the previous 6 months or scheduled before the end of the study.

All patients were enrolled at 'Terme di Pejo' and provided informed consent. Participants were randomly allocated with a 1:1 ratio through a Moses-Oakford algorithm to either mud treatment plus balneotherapy (group 1) or balneotherapy alone (group 2). All patients were allowed to continue treatment with NSAIDs or other analgesics other than steroids or SYSADOA. The Investigator was blinded to the treatment allocation. Outcomes were assessed immediately after the end of the intervention (W2) and 3, 6, 9 and 12 months after randomization (M3, M6, M9 and M12). The randomization list was stored at the Rheumatology Unit of Verona. The study was approved by the ethic committee of the Azienda Provinciale per i Servizi Sanitari di Trento, Italy (protocol n. 12299 of 07/08/2015).

Balneotherapy and mud treatments and other permitted drugs

Mud treatment consisted in a mud-pack prepared with the 'Nuova Fonte' water (Terme di Pejo, Peio, Trento, Italy) and argil that 'settled' for at least 6 months before use in order to have a stable compound. A mud-pack was applied on the affected joints at an initial temperature of

47-50°C for 15 minutes. Balneotherapy consisted in full body immersion in the 'Antica Fonte' water at a temperature of 35°C for 15 minutes. Table I summarizes the water characteristics. Both interventions were performed for 12 days with a break at day 6. Rescue therapy was allowed only with acetaminophen, diclofenac, piroxicam, naproxen, etoricoxib, celecoxib, ibuprofen. It was recorded in a daily diary reporting name of the drug, dose and frequency of administration.

Table I - Chemical-physical properties of the water used for preparation of mud-pack (Nuova Fonte) and in thermal bath (Antica Fonte).

	'Nuova Fonte' water	'Antica Fonte' water
pH	5.79	5.58
Free carbon dioxide (CO ₂) mg/L	1700	1500
Electrical conductivity µs/cm	1436	660
Fixed residue at 180°C mg/L	1100	440
Hardness °F	66	32
Alkalinity (HCO ₃) mg/L	1153	466
Ammonium (NH ₄) mg/L	1.29	0.76
Nitrites (NO ₂) mg/L	<0.002	<0.002
Phosphorus (P) mg/L	0.04	0.02
Fluorides (F) mg/L	0.4	0.3
Chlorides (Cl) mg/L	18	5.0
Sulfate (SO ₄) mg/L	3.5	12
Sulfides (H ₂ S) mg/L	<0.1	<0.1
Calcium (Ca) mg/L	164	76.2
Magnesium (Mg) mg/L	61.5	30.2
Sodium (Na) mg/L	142	36.3
Potassium (K) mg/L	17.9	8.27
Strontium (Sr) mg/L	0.77	0.36
Silica (SiO ₂) mg/L	73.6	50.2
Barium (Ba) mg/L	0.33	0.14
Boron (B) mg/L	1.3	0.1
Copper (Cu) mg/L	<0.1	<0.1
Manganese (Mn) mg/L	0.35	1.01
Selenium (Se) mg/L	<0.001	<0.001
Iron (Fe) µg/L	21300	23500
Lithium (Li) µg/L	849	215
Bromide (Br) µg/L	332	83
Iodine (I) µg/L	3.96	1.57

■ OUTCOMES

Clinical outcome

According to the European Agency for the Evaluation of Medicinal Products (EMEA 2005) and recommendations on clinical trials on medicinal products for OA (Committee for Proprietary Medicinal Products 1998), the aim of the present study was to determine the efficacy in pain relief and improvement of physical function. The improvement in at least one of the sub-scores of WOMAC was considered as the primary outcome for KOA, while variations in AUSCAN (at least one among stiffness, pain and function scores) were used as primary outcome for HOA. WOMAC is a widely used, reliable, valid, and responsive measure of treatment outcomes in patients with OA of the knee (16, 17). For HOA we used the AUSCAN (18), since it has been used in clinical trials and reliable data on minimal clinically significant variation are available (19, 20). Secondary outcomes for HOA were the HAQ (21) and the Italian version of the functional index for hand osteoarthritis (FIHOA) (22). Regarding KOA, the secondary outcome was VAS pain after walking for 15 meters. For both KOA and HOA we collected data on VAS pain at rest, Short Form Health Survey (SF-36) (23) and intake of allowed pharmacological rescue medications. All adverse events were collected as reported by the patients and were further revised by the investigator for the possible causative relation with the treatment.

Densitometric outcome

Bone mineral density was evaluated with Dual-energy X-ray Absorptiometry (DXA) (GE Lunar iDXA). The DXA was performed at the baseline and at M12.

Statistical analysis

For the power analysis we hypothesized an improvement in primary outcomes of 30% for group 2 (balneotherapy alone) and 45% for group 1 (mud treatment plus balneotherapy). This assumption was based on previous reports on the efficacy of placebo, which has been proved to ameliorate OA outcomes of about 15% (24). We therefore determined a sample size of 30 patients per

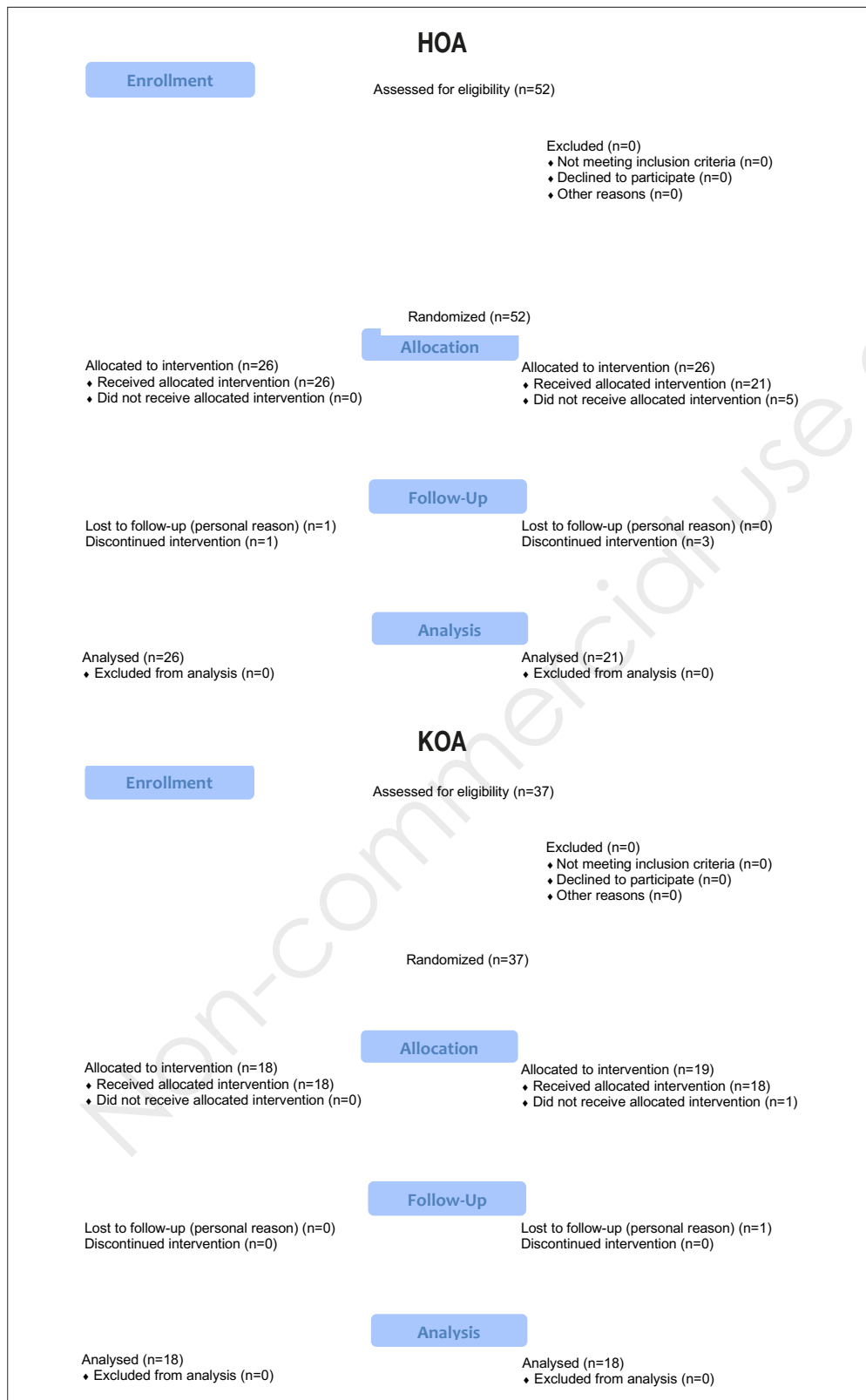


Figure 1 - Trial flow-chart.

arm for KOA and 30 per arm for HOA with an $\alpha=0.05$, a $\beta=0.80$ and anticipating a dropout rate of 30%.

Continuous variables are expressed as mean \pm standard deviation (SD), if they are normally distributed, and as median with interquartile range (IQR), if they are not normally distributed. Categorical variables are expressed as percentages. Comparisons between groups were performed using t-test, Mann-Whitey, Wilcoxon or Chi-square tests/Fisher's test, as appropriate. A p value of <0.05 was considered significant. We did not perform an ITT analysis given the low number of dropouts.

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

■ RESULTS

Hand osteoarthritis

A total of 52 patients were enrolled in the study and randomized. Of the 26 patients randomized in each group only 24 in group 1 and 21 in group 2 completed the study (Figure 1); all the dropouts occurred after randomization for personal problems not related to the interventions. Table II summarizes the main baseline cohort characteristics. No significant differences in the two groups were found at baseline. As regards group 1, AUSCAN pain significantly decreased in group 1 at M3 and M6 compared to baseline ($p<0.001$ for all comparisons). AUSCAN function decreased significantly

Table II - Main characteristics of patients with hand osteoarthritis at baseline.

	Total	Mud + balneotherapy (n=26)	Balneotherapy (n=21)	p
Age	66.0 (8.1)	67.3 (6.8)	64.3 (9.4)	NS
Male sex	4 (8.5)	2 (7.7)	2 (9.5)	NS
Menopause age	49.8 (4.2)	50.6 (3.2)	48.5 (5.2)	NS
VAS pain*	45 (27)	46.5 (17.0)	45.0 (30.0)	NS
Kellegren score*	2 (1)	2 (1)	2 (1)	NS
AUSCAN pain*	25.2 (9.0)	24.5 (9.7)	25.3 (8.4)	NS
AUSCAN stiffness*	5.6 (3.0)	5.6 (4)	5.6 (3)	NS
AUSCAN function*	42.9 (14.1)	44.4 (12.7)	41.6 (10.6)	NS
FIHOA*	7 (7)	9 (9)	7 (5)	NS
SF-36 PSY*	52 (11)	53.5 (10.0)	50.0 (12.0)	NS
SF-36 PHIS*	45 (11)	45 (12)	45 (11)	NS
HAQ*	0.625 (0.625)	0.625 (0.625)	0.500 (0.440)	NS
NSAIDs therapy	14 (29.8)	8 (30.8)	6 (28.6)	NS
Acetaminophene therapy	2 (4.3)	2 (7.7)	0 (0.0)	NS
BMD lumbar	0.909 (0.170)	0.878 (0.177)	0.947 (0.158)	NS
T-score lumbar*	-1.4 (2.2)	-1.5 (2.5)	-1.0 (1.7)	NS
Z-score lumbar*	0.4 (2.0)	0.2 (2.0)	0.7 (2.0)	NS
BMD neck	0.783 (0.142)	0.706 (0.144)	0.756 (0.137)	NS
T-score neck*	-1.4 (1.4)	-1.5 (1.6)	-1.0 (1.7)	NS
Z-score neck*	0.3 (1.6)	0.0 (1.5)	0.3 (1.6)	NS
BMD hip total	0.844 (0.156)	0.832 (0.154)	0.859 (0.160)	NS
T-score hip total*	-1.0 (1.6)	-1.0 (1.7)	-1.0 (1.1)	NS
Z-score hip total*	0.3 (1.4)	0.4 (1.8)	0.2 (1.3)	NS

*Expressed as median (IQR). VAS, visual analog scale; AUSCAN, Australian Canadian Osteoarthritis Hand Index; FIHOA, functional index for hand osteoarthritis; SF-36 PSY, Short Form Health Survey psychological; SF-36 PHIS, Short Form Health Survey physical; HAQ, health assessment questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; BMD, bone mineral density.



Figure 2 - Variation in Australian Canadian Osteoarthritis Hand Index (AUSCAN) over time in patients with hand osteoarthritis (HOA). *If $p < 0.05$, **if $p < 0.001$.

at M3 and M6 ($p < 0.001$ for all comparisons). AUSCAN stiffness decreased at M3, M6, M9 and M12 compared to baseline ($p < 0.001$, $p < 0.001$, $p = 0.004$ and $p = 0.029$, respectively). In group 2 AUSCAN pain and stiffness improved only at M3 and M12 ($p < 0.001$ and $p = 0.027$ for pain and $p = 0.019$ and $p < 0.001$ for stiffness). AUSCAN function improved only at M12 ($p < 0.001$).

When comparing AUSCAN variations over time between groups (Figure 2), we found that AUSCAN pain improved significantly more in group 1 compared to group 2 at M3, M6 and M12 ($p < 0.001$, $p = 0.001$ and $p = 0.038$, respectively). AUSCAN stiffness improvement was greater in group 1 compared to group 2 only at M3 ($p = 0.001$). AUSCAN function improvement was greater in group 1 compared to group 2 at any time point (M3 $p = 0.001$, M6 $p = 0.001$, M9 $p = 0.014$ and M12 $p = 0.018$). In addition, a higher proportion of patients in group 1 compared to group 2 felt that the improvement after treatment was significant at M3 (100.0% vs 73.7%, $p = 0.001$), M6 (76.0% vs 10.5%, $p < 0.001$) and M9 (37.5% vs 0.0%, $p = 0.005$). No significant differences between groups were found in the number

Table III - Differences in visual analog scale pain, functional index for hand osteoarthritis, health assessment questionnaire between groups affected by hand osteoarthritis.

		Mud + balneotherapy	Balneotherapy	p
VAS pain	Baseline*	46.5 (17.0)	45.0 (30.0)	-
	W2	-69.8 (81.9)	-37.5 (34.0)	0.028
	M3	-67.3 (75.9)	-36.4 (32.9)	0.001
	M6	-31.3 (49.2)	-18.5 (31.7)	NS
	M9	-11.8 (39.5)	-16.5 (44.5)	NS
	M12	-10.6 (26.6)	-3.9 (45.6)	NS
FIHOA	Baseline*	9 (9)	7 (5)	-
	W2	-28.6 (50.0)	-15.5 (23.8)	NS
	M3	-35.0 (75.0)	0.0 (36.5)	0.002
	M6	-12.5 (62.1)	14.3 (25.0)	0.003
	M9	7.7 (53.5)	26.8 (17.0)	0.010
	M12	6.9 (52.2)	28.6 (22.0)	0.001
HAQ	Baseline*	0.625 (0.625)	0.500 (0.440)	-
	W2	-33.3 (67.6)	-23.1 (33.3)	NS
	M3	-50.0 (68.5)	0.0 (21.3)	<0.001
	M6	-33.3 (72.4)	0.0 (40.0)	0.020
	M9	-1.6 (75.2)	14.6 (44.8)	NS
	M12	0.0 (57.1)	20.0 (47.1)	0.040

VAS, visual analog scale; FIHOA, functional index for hand osteoarthritis; HAQ, health assessment questionnaire; *Absolute values expressed as median (IQR).

of days on pharmacologic treatment at any point. At W2 a trend for lower consumption of analgesics was found for group 1 compared to group 2 (0 ± 0 vs 0 ± 2 , $p=0.058$). A significant decrease of medication intake was found in both groups from baseline and W2, M3 and M6 ($p=0.008$, $p=0.020$, $p=0.034$ for group 1 and $p=0.025$, $p=0.014$, $p=0.046$ for group 2).

Table III shows the differences between groups for VAS pain, FIHOA and HAQ. No differences were found for SF-36. No adverse events were reported.

We found no difference in bone mineral density at the distal radius.

Knee osteoarthritis

37 patients were screened, 18 were allocated to the treatment group (group 1) and

19 to the control group (group 2); 18 subjects in each arm completed the study (Figure 1). Table IV summarizes the main baseline cohort characteristics. During the follow up, WOMAC significantly decreased in group 1 at W2, M3, M6, M9 and M12 compared to baseline for pain ($p<0.001$, $p>0.001$, $p<0.001$, $p=0.001$ and $p=0.003$ respectively) and function ($p<0.001$ for all comparisons except M12 $p=0.006$). In group 2 WOMAC pain improved at W2, M3, M6 and M12 ($p<0.001$, $p<0.001$, $p=0.002$, $p=0.019$ and $p=0.033$, respectively) for pain, while WOMAC function improved only at W2, M3 and M6 ($p<0.001$, $p=0.003$ and $p<0.001$, respectively).

When comparing WOMAC variations between groups we observed a significant improvement in group 1 compared to group 2

Table IV - Main characteristics of patients with KOA at baseline.

	Total	Mud + balneotherapy (n=18)	Balneotherapy (n=18)	p
Age	61.8 (7.2)	60.3 (5.9)	63.3 (8.1)	NS
Male sex	17 (47.2)	7 (38.9)	10 (55.6)	NS
Menopause age	50.0 (4.1)	49.7 (3.7)	50.4 (4.9)	NS
VAS pain*	46 (18)	47.5 (18.0)	44.0 (18.0)	NS
VAS pain after 15 m walking*	47.5 (22.0)	47 (18)	48 (23)	NS
Kellegren score*	2 (0)	2 (0)	2 (0)	NS
WOMAC pain*	48.5 (8.0)	48.5 (9)	48.5 (7)	NS
WOMAC function*	49 (3)	48.5 (5.0)	49.0 (2.0)	NS
SF-36 PSY*	55.0 (13.0)	55.0 (11.0)	54.5 (25.0)	NS
SF-36 PHIS*	40.0 (11.0)	41 (12)	40 (11)	NS
NSAIDs therapy	16 (44.4)	9 (50.0)	7 (38.9)	NS
Acetaminophen therapy	4 (11.1)	1 (5.6)	3 (16.7)	NS
BMD lumbar	0.980 (0.168)	0.972 (0.178)	0.988 (0.161)	NS
T-score lumbar*	-1.0 (2.2)	-1.0 (2.6)	-0.9 (2.0)	NS
Z-score lumbar*	0.1 (2.1)	0.1 (2.7)	0.3 (1.8)	NS
BMD neck	0.800 (0.105)	0.823 (0.111)	0.779 (0.096)	NS
T-score neck*	-0.9 (1.1)	-0.7 (1.8)	-0.9 (0.7)	NS
Z-score neck*	0.3 (0.9)	0.3 (1.6)	0.2 (0.8)	NS
BMD hip total	0.928 (0.120)	0.950 (0.123)	0.907 (0.117)	NS
T-score hip total*	-0.4 (1.0)	-0.2 (1.0)	-0.4 (1.0)	NS
Z-score hip total*	0.4 (1.4)	0.8 (1.0)	0.4 (1.2)	NS

*Expressed as median (IQR). VAS, visual analog scale; AUSCAN, Australian Canadian Osteoarthritis Hand Index; FIHOA, functional index for hand osteoarthritis; SF-36 PSY, Short Form Health Survey psychological; SF-36 PHIS, Short Form Health Survey physical; HAQ, health assessment questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; BMD, bone mineral density.

only at M9 as regards WOMAC function ($p=0.007$). Nevertheless, the absolute value of WOMAC pain at M9 (40 ± 10 vs 45 ± 13 , $p=0.08$) and at W2 (31 ± 13 vs 37 ± 9 , $p=0.044$) was numerically lower in group 1 compared to group 2. In addition, WOMAC function was lower in group 1 compared to group 2 at M6 and M9 (38 ± 10 vs 43 ± 13 , $p=0.029$ and 41 ± 10 vs 46 ± 8 , $p=0.001$, respectively). A higher proportion of patients in group 1 reported symptom improvement at M3 (100.0% vs 72.2%, $p=0.045$), M6 (100.0% vs 27.8%, $p<0.001$) and M9 (50.0% vs 0.0%, $p=0.001$) compared to group 2. Finally, VAS pain at rest decreased more prominently in group 1 as compared to group 2 at M3 ($47.5\pm 25.2\%$ vs $22.4\pm 29.3\%$, $p=0.024$) and at M6 ($35.1\pm 31.1\%$ vs $15.6\pm 32.3\%$, $p=0.022$). However, no differences were found in the number of days with rescue pharmacological treatment nor for SF-36.

We found no difference in densitometric examinations performed at baseline and at M12. No adverse events were reported.

■ DISCUSSION AND CONCLUSIONS

Herein we presented a RCT aimed to evaluate the efficacy of mud plus balneotherapy over balneotherapy alone in patients with HOA and KOA. Overall, we found that mud plus balneotherapy is an effective and safe option for the treatment of HOA and KOA. The addition of mud therapy to balneotherapy was more effective on clinical outcomes of HOA and KOA than balneotherapy alone.

Despite the lack of truly effective pharmacological options for HOA, to date only a few studies evaluated the effect of mud and/or balneotherapy in this setting. Nevertheless, many reviews (25, 26), published over the last few years confirmed a rising interest in this therapeutic option and an interesting debate over its efficacy.

One study (27) showed that bath plus magnetotherapy was superior to magnetotherapy alone in terms of symptoms and grip strength in HOA. Later, Kovacs et al. (28) compared the effects of bath with 'sham

bath', confirming what was previously found by Horvath et al., regarding symptoms (27). It is worth noting that both studies had a short follow up, lasting approximately 3 months.

The only study on mud therapy was published by Fioravanti et al. (29), in which patients were randomized to either mud plus balneotherapy or routine outpatient care. The authors found a significant improvement in symptoms at 6 months after the end of treatment (total follow up 12 months). Similarly, we evaluated the effects of mud therapy in HOA and confirmed its efficacy in controlling symptoms long after the end of treatment. In our opinion, this long-term effect cannot be explained by the 'health holiday effect' alone, but rather by a truly effective therapeutic and analgesic mechanism of mud. This hypothesis was also proposed by Fioravanti et al. (29), who studied a population that continued their regular activities of daily living even during balneotherapy. In addition, our study, unlike the previous one (29), compared mud therapy with balneotherapy, lowering the confounding effect of the health holiday: the control group received a treatment which resulted also effective for HOA (27, 28).

Unlike in previous papers, we did not find any differences in pharmacologic rescue therapy between treatment arms. Nevertheless, in both groups, patients took fewer NSAIDs or acetaminophen at W2, M3 and M6, compared to baseline, further corroborating the efficacy of bath treatments in HOA. The lack of statistically significant differences between groups might be due to small sample size and, potentially to the small number of analgesics used by the study population overall.

In 2017 Gyrmati et al. (30) studied the efficacy of the application of mud with or without wearing nylon gloves. Despite the latter study did not test mud therapy against a different treatment, the authors demonstrated a significant reduction in VAS, HAQ, swollen and tender joints in all patients under study, further supporting a possible role of mud therapy in HOA.

Several studies investigated the role of

health resort therapy in KOA (29, 31-34) showing a good efficacy in different clinical outcomes, including the WOMAC. As an example, mud therapy has been tested in association with balneotherapy or short-wave therapy in 3 studies (32-34) and alone in two other studies (35, 36), demonstrating an acceptable benefit/risk profile.

In line with the aforementioned studies, we found that balneotherapy was associated with a significant improvement of clinical outcomes of KOA over time. We also found that the addition of mud to balneotherapy resulted in a significant improvement of WOMAC compared to balneotherapy alone. In particular, significant differences were found in absolute values of WOMAC pain and WOMAC function, as well as VAS pain at rest.

We found no difference in bone mineral density over time. Interestingly, Loi et al. (13) previously found that patients undergoing regular full-body mud and balneotherapy for at least 3 years had a lower prevalence of osteoporosis and osteopenia compared to a control group. Zivna et al. (37) tested mud-therapy in a murine model of arthritis showing a positive effect on bone metabolism, probably driven by reduced inflammation and pain eventually leading to improved mobility. Given these previous, positive, studies, our null result might be explained by the short follow up, which made the improvement in bone density undetectable. In addition, the treatment was applied locally and for a relatively short time, hence the decrease in pain may not be enough to increase mobility which mechanically stresses the bone. Nevertheless, it is reasonable to think that balneotherapy and mud therapy have no effects at all on bone health. Unfortunately, to our knowledge, no other data on this topic is available in the literature for a proper evaluation.

Our study confirmed that mud and balneotherapy are safe since no adverse event has occurred. This represents a major strength of such treatment, since KOA and HOA mainly affect the elderly who commonly have many comorbidities that may limit the chronic use of drugs.

Our study should be interpreted in the light of some limitations. The main limitation might be the small number of patients, especially for KOA. However, we provided a sample size calculation that was based on the available data from the literature. In addition, albeit the AUSCAN is a widely used questionnaire for the assessment of HOA, it has not been validated in Italian, thus limiting the validity of our results. However, the FIHOA, which was developed and validated in Italy, confirmed the results of AUSCAN. It is worth noticing that the control group was treated with an effective treatment, namely balneotherapy, and this is both a limit, since we needed an adequate sample size to have a good statistical power, and a strength of the study. Indeed, we did find a statistically significant difference between groups in terms of clinical outcomes in HOA. Another strength of this study was the use of widely validated scores as primary outcomes and the collection of several other variables and scores.

In conclusion, we showed that balneotherapy might be effective in reducing symptoms of HOA. We conducted a single blinded RCT that demonstrated that mud plus balneotherapy is superior to balneotherapy alone on clinical outcomes of HOA. Despite the encouraging results on KOA, further studies enrolling larger populations are needed to clarify the effects of mud plus balneotherapy on this condition.

Conflict of interests

MR received grants from Terme di Pejo, GR received grants from Provincia autonoma di Trento and Comune di Pejo. No other conflict of interests relevant to the present study to declare.

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Ethics approval

The study was approved by the ethic committee of Azienda provinciale per i servizi sanitari of Trento, Italy (protocol n. 12299 of 07/08/2015).

Consent to participate

The consent was signed after the investigator had explained the nature of the study to the participant and answered all questions regarding the study. A copy of the ICF(s) has been provided to the participant or the participant's legally authorized representative.

Availability of data and material

Data are available by direct request to the corresponding author.

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