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ORIGINAL ARTICLE

The effect of balneotherapy on pain relief, stiffness, and physical function in patients with osteoarthritis of the knee: a meta-analysis

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Abstract This meta-analysis was performed to determine the effect of balneotherapy on relieving pain and stiffness and improving physical function, compared to controls, among patients with knee osteoarthritis. We searched electronic databases for eligible studies published from 2004 to December 31, 2016, with language restrictions of English or Japanese. We screened publications in Medline, Embase, Cochrane library, and the Japan Medical Abstracts Society Database using two approaches, MeSH terms and free words. Studies that examined the effect of balneotherapy for treating knee osteoarthritis of a ≥2-week duration were included. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were used as the outcome measure. A *total of* 102 publications were assessed according to the exclusion criteria of the study; eight clinical trial studies, which comprised a total of 359 cases and 375 controls, were included in this meta-analysis. The meta-analysis analyzed improvement in WOMAC score at the final follow-up visit, which varied from 2 to 12 months post-intervention. Our meta-analysis indicates that balneotherapy was clinically effective in relieving pain and stiffness, and improving function, as assessed by WOMAC score, compared to controls. However, there was high heterogeneity (88 to 93%). It is possible that balneotherapy may reduce pain and stiffness, and improve

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function, in individuals with knee osteoarthritis, although the quality of current publications contributes to the heterogeneity observed in this meta-analysis.

Keywords Balneotherapy · Meta-analysis · Osteoarthritis of the knee

Introduction

Osteoarthritis of the knee (knee OA) is characterized pathologically by both focal loss of articular cartilage and marginal and central new bone formation [1]. It is a major cause of functional disability among the elderly population and strongly associated with aging [2, 3]. In addition, the advancing severity of knee OA, represented by increasing OA grade, signifies more severe pain, stiffness, and loss of functional capacity that can lead to gait dysfunction. Gait dysfunction in these individuals, such as increased irregularity in step length, step width, and double-support time during walking [4], increases the risk of falling and further fractures [5, 6]. Patients with knee OA have been reported to experience an increase in the risk of fractures, and clinical diagnosis of knee OA in particular, compared to patients with knee pain alone, is associated with a greater risk of non-vertebral and hip fractures [6]. If these individuals sustain such a fracture, they may require nursing care which presents a health and economic burden. Thus, treating pain, stiffness, and functional limitation is key to improving locomotive function and may also be beneficial in reducing the risk of experiencing a fall and fracture in patients with knee OA.

Balneotherapy is a traditional approach to relieving pain and stiffness and improving physical function among the elderly experiencing musculoskeletal pain [7, 8]. It is defined as bathing in thermal mineral waters and comprises a broad spectrum of therapeutic modalities, including spa therapy, physiotherapy, and exercise [7]. Balneotherapy is recommended for patients with musculoskeletal disease, as bathing in thermal mineral waters has been shown to provide a range of benefits, including the reduction of pain. Previous meta-analyses and systematic reviews have shown its effectiveness in relieving symptoms for patients with musculoskeletal disease [9, 10]. The systematic review studies that evaluated the effectiveness of balneotherapy on pain relief showed inconclusive results regarding significant improvement in pain reduction among patients with rheumatoid arthritis; however, surprisingly, three studies found an improvement in handgrip strength up to 1 month after treatment [9]. Another study showed moderate-to-strong evidence for a small reduction in pain with regard to hydrotherapy for the management of fibromyalgia syndrome [10]. In addition, two meta-analyses, which studied the effect of balneotherapy on pain relief, showed improvement in pain control for patients with osteoarthritis, but were not able to analyze outcomes for patients with knee OA specifically [11, 12]. There is limited evidence for balneotherapy in the treatment of knee OA because of the small number of participants in existing studies and few studies evaluating balneotherapy in general [13]. The guidelines of the Osteoarthritis Research Society International indicate balneotherapy for OA generally, but do not specifically address its use for knee OA. In order to provide scientific evidence for the effectiveness of balneotherapy in patients with knee OA, further investigation of this therapy is needed with adequate data to power meaningful statistical analysis.

The current meta-analysis was therefore performed to determine the effect of balneotherapy on relieving pain and stiffness, and improving function, in patients with knee OA.

Methods

Systematic literature search

This meta-analysis was performed according to the guidelines of the PRISMA statement [14]. We searched electronic databases for publications from 2004 to December 31, 2016, with language restrictions of English or Japanese. We screened publications in Medline, Embase, the Cochrane library, and the Japan Medical Abstracts Society Database using two approaches (MeSH terms and free words). The English and Japanese search keywords included "balneology," "balneotherapy," and "musculoskeletal disease." This study was registered with PROSPERO, the International Prospective Register of Systematic Reviews (registration number: CRD42016037000).

Inclusion and exclusion criteria

The clinical research studies identified included randomized clinical trials (RCTs), non-randomized trials, and comparative observational studies that investigated the clinical efficacy of balneotherapy. We included studies that examined the effect of balneotherapy alone or the combined effect of balneotherapy with other therapy for treating knee OA for a ≥2-week duration. If abstracts were unavailable or unclear, the full-text article was retrieved. Studies were excluded if the (i) study methods were not described, (ii) data on participants with knee OA could not be separated from other patient populations, and (iii) the study was a review article. Four independent reviewers examined titles and abstracts of the articles for inclusion or exclusion.

Data extraction

All related data were extracted and assessed independently by three investigators. Sample size of included studies, treatment approaches for the therapeutic groups and control groups, intervention period, follow-up period, values of assessments, and quality of the publication were assessed.

Measures of effects

The outcome measures evaluated to determine the effect of treatment with balneotherapy on patients with knee OA included relief of pain, stiffness, and physical dysfunction. The specific scores used as outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, stiffness score, and functional score [15].

Quality assessment of the publications

Risk of bias was assessed using the Cochrane risk of bias tool, according to the following parameters: randomized, concealment, blinding of participants and researcher, blinding of assessment, intention-to-treat (ITT) analysis, incomplete outcome data, selective outcome reporting, interruption, and check of other bias. The range of possible scores is 0 to −2; a lower score represents more bias. Two review authors independently assessed risk of bias of the included trials; any discrepancies between the investigators were resolved through discussion. For those studies with ITT analysis, the results were used in this meta-analysis.

Statistical analyses

Treatment effect size is reflected as the standardized mean difference, calculated by dividing the difference in changes from baseline (or difference between before and after treatment) between groups, by the pooled SD of outcomes among participants. Results for the comparative effect are presented by the standardized mean difference (SMD) estimates and 95% confidence intervals. We tested for heterogeneity with Cochran's Q test and measure of inconsistency I^2 statistics that represent the percentage of total variation across studies due to heterogeneity. I^2 is a value between 0 and 100%, with 25, 50, and 75% referring to low, moderate, and high heterogeneity, respectively. Publication bias was assessed using funnel plots. The funnel plot is based on the fact that precision in estimating the underlying treatment effect will increase as the sample size of component studies increases. In the absence of bias, the plot will show a symmetrical inverted funnel. On the contrary, if there is publication bias, funnel plots will often be skewed and asymmetrical. A p value <0.05 was used as the threshold for significance. All statistical analyses were performed using Review Manager 5.1.

Results

The process of literature screening and literature characteristics

Among 558 publications obtained by preliminary screening, 456 were excluded because they did not include the keywords "knee osteoarthritis" in the title or abstract. Therefore, a total of 102 publications were assessed according to the exclusion criteria of the study. Twenty-seven publications passed the initial screening based on the title and abstract and were further screened with a review of their full text. Among the 27 publications, three studies were excluded because of a lack of a control group [16–18]. There were seven studies that evaluated mud therapy or mudpack therapy [19–25]. Two of the studies did not have data available for the meta-analysis because the outcome results of these studies were reported as median (min–max) or the difference in pre- and post-intervention scores [26, 27]. Seven studies were excluded because they did not use the WOMAC or WOMAC subscores to measure outcomes [28–34]. Finally, eight studies remained for inclusion; the study populations comprised 359 balneotherapy cases and 375 control cases [8, 35–41] (Table 1). One study had two control groups, which we combined for the purposes of this meta-analysis [35]. The clinical trials included in the meta-analysis ranged in duration from 2 to 10 weeks. The shortest duration of time to last follow-up after intervention was 2 months, and the longest time to last follow-up was 12 months. Two studies used a methodology other than a randomized clinical trial and were ranked as low quality [39, 40] (Table 2).

Meta-analysis of the effects of balneotherapy on WOMAC in knee patients with knee OA

There were eight clinical trial studies [8, 35–41], including 326 cases and 339 controls, that measured WOMAC pain score as an outcome (Fig. 1). The results of our meta-analysis indicate that balneotherapy, on average, reduced the pain score by −92% when compared with controls (SMD= −0.92; 95% CI −1.08 to −0.75; $p < 0.00001$). There was a higher degree of statistical late heterogeneity across studies (I^2 = 88%; $p = 0.00001$). Among the eight articles, there were seven clinical trial studies [8, 35–38, 40, 41], including 301 cases and 314 controls, that measured WOMAC stiffness score as the outcome (Fig. 2). The results of our meta-analysis indicate that balneotherapy, on average, improved the clinical effective rate of relieving stiffness by −48% when compared with controls (SMD= −0.48; 95% CI −0.65 to −0.31; $p < 0.0001$). There was a higher degree of statistical late heterogeneity across studies ($I^2 = 90\%$; $p = 0.00001$). These same seven trials also measured the WOMAC function score [8, 35–38, 40, 41] and included 301 cases and 318 controls for whom functional scores were

Table 1 The characteristics of studies included in meta-analysis to examine the effects of balneotherapy on patients with knee osteoarthritis

Study	Regimen	Number of patients[a]	Intervention	Properties and ingredients of the spa water	Age (years)[a]	Men/women[a]	Duration of therapy	Last follow-up
M. Branco et al. 2016	Experimental group	47	· Individual thermal baths at temperatures ranging from 37 to 39 °C for 20 min	pH of 9.66 and contained hydrogen sulfide, sulfate, carbonate, fluoride, and sodium	65.47 ± 10.2	14/33	10 weeks	2 months
	Control group	93 (total)						
		43	· No treatment		65.28 ± 7.0	4/39	10 weeks	
		50	· Non-sulfurous water bath		63.69 ± 8.89	7/43		
A. Fazaa et al. 2014	Experimental group	119	· Individual thermal baths at temperatures ranging from 37 to 39 °C	Sodium sulfate, calcium, and magnesium	59.5 ± 8.0	30/89	20 days	12 months
	Control group	121	No treatment tap water thermal baths		60.9 ± 9.0	31/90		
A. Fioravanti et al. 2010	Experimental group	40	· Combination of mud packs applied on both knees for 20 min at an initial temperature of 45 °C · Bicarbonate-sulfate mineral bath water at 38 °C for 15 min	Hydrosulfide degree, carbon dioxide, bicarbonate, sulfate, calcium, magnesium, silica, chlorides, sodium, potassium, total iron, fluorides, ammonium, strontium, and lithium	69.06 ± 5.11	12/28	2 weeks	9 months
	Control group	40	· Continued regular routine ambulatory care (exercise, NSAIDs, and/or analgesics)		71.3 ± 4.91	8/32		
G. Sherman et al. 2009	Experimental group	24	· Bathed in a covered mineral waterpool (sulfur pool) heated to 35–36 °C twice weekly for 20 min	Not described	65.0 ± 5.7	6/19	6 weeks	6 months
	Control group	20	· Bathed in a covered Jacuzzi pool filled with tap water heated to 35–36 °C for 20 min		67.8 ± ?	3/17		
D. Evcik et al. 2007	Experimental group	25	· Bathed in mineral water pools at 36 °C	Sodium, bicarbonate, sulfate, calcium, magnesium, iron-aluminum cations, chlorine, and metasilicate anions	55.0 ± 8.7	2/23	2 weeks	3 months
	Control group	25	· Hot pack application		59.6 ± 9.2	1/24		
G.P Bálint et al. 2007	Experimental group	27	· Bathed in mineral water at 34 °C	Na^+, Cl^-, K^+, Br^-, $NH4^+$, J^-, Ca^{++}, F^-, Mg^{++}, HCO_3, Fe^{+++}, NO_2, Mn^{++}, NO_3, Li^+, and free CO_2	No date	10/17	4 weeks	3 months
	Control group	25	· Tap water		No date	9/16		
M. Yurtkuran et al. 2006	Experimental group	29	· Treated with 37 °C spa water in small therapeutic pools · A home-based standardized exercise program	Ca, CO_3, Ca^{2-}, Mg^{2-}, NH_4, NO_3, NO_2, Fe^{2+}, orthophosphate, SO, soluble solid substance, Na^-, K^-, Mn, free CO_2, Li, and S^{-2}	52.8 ± 6.7	1/28	2 weeks	3 months
	Control group	27	· Treated with 37 °C tap water in small therapeutic pools · A home-based standardized exercise program		55.4 ± 6.2	2/25		
M. Tishler et al. 2004	Experimental group	48	· Bathed in mineral water pools at 37 °C for 30 min (15 min each time with 1 h for the rest between bathing)	Sodium, chloride, bicarbonate, calcium, H_2S, bromide, magnesium, potassium, and sulfate	65.2 ± 10.1	10/34 (4 patients dropped out)	6 weeks	10 weeks
	Control group	24	· No intervention		63.1 ± 10.1	5/19		

[a] Baseline characteristics of participants

Table 2 Quality assessment of included studies

Study	Design	Randomization	Concealment	Blinding (researcher and participants)	Blinding (assessment)	ITT	Incomplete outcome	Selective outcome	Interruption	Other bias
M. Branco et al. 2016	RCT	0	0	−2	0	0	0	0	0	−1
A. Fazaa et al. 2014	RCT	0	0	−2	−2	−2	−1	0	0	−1
A. Fioravanti et al. 2010	RCT	0	0	−1	0	0	0	0	0	0
G. Sherman et al. 2009	RCT	0	0	−2	0	−2	−1	0	0	−2
D. Evcik et al. 2007	Not RCT	−2	−2	−2	−2	−2	0	0	0	−2
G.P Bálint et al. 2007	Not RCT	0	−1	0	−2	−2	−1	0	0	−2
M. Yurtkuran et al. 2006	RCT	0	−1	0	0	−2	−1	0	0	−1
M. Tishler et al. 2004	RCT	0	−2	−1	−2	−2	−1	0	0	−2

RCT randomized clinical trials, *ITT* intention to treat

obtained (Fig. 3). The results from our meta-analysis indicate that balneotherapy, on average, improved the clinical effective rate of functional improvement by −55% when compared with controls (SMD= −0.55; 95% CI −0.72 to −0.38; $p = 0.00001$). There was a higher degree of statistical late heterogeneity across these studies ($I^2 = 93\%$; $p = 0.00001$). Funnel plots of WOMAC pain measures were shown to be slightly skewed. It is possible that publication bias contributed to this finding, as a symmetric funnel plot is often evidence of no publication bias (Fig. 4a–c).

Discussion

This meta-analysis included eight clinical trial studies showing the effect of balneotherapy on pain relief and functional improvement for patients with knee OA, as measured by WOMAC scores. Many previous studies have found that mud therapy, with or without balneotherapy, had a significant effect on pain relief. A recent meta-analysis on mud therapy for patients with knee OA showed that mudpack therapy, whether used alone or in combination with hydrotherapy, was not a factor significantly associated with high heterogeneity; the meta-analysis also highlighted the necessity of including combination therapy in evaluating such treatment [42]. In contrast, our study, which excluded mud therapy, showed positive effects of balneotherapy, in isolation, on pain relief and functional recovery. Thus, balneotherapy may be associated with superior positive effects compared to mud therapy in isolation.

A previous meta-analysis showed that balneotherapy with Hungarian thermal mineral waters was an effective remedy for lower back pain, as well as for knee and hand osteoarthritis [11]. This study indicated that there were four clinical trials conducted with Hungarian thermal mineral waters specifically evaluating the effect of balneotherapy on patients with knee OA. While these four clinical trials did not meet the criteria of the authors for inclusion in their meta-analysis, the nine clinical trials analyzed appear to confirm that Hungarian thermal mineral waters significantly reduced pain in patients with

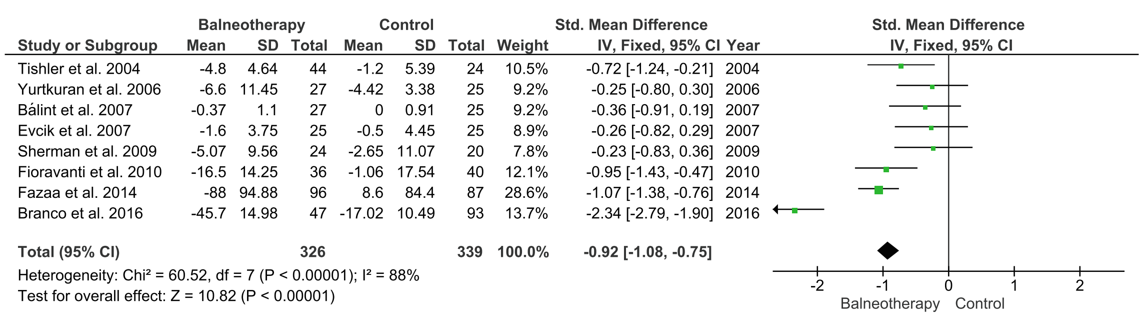

Fig. 1 Forest plot of the mean differences in WOMAC pain scores with 95% confidence intervals between the balneotherapy group versus control group, and the overall total for the eight studies included in the meta-analysis that were conducted to examine the effect of balneotherapy on pain relief in patients with knee osteoarthritis

Study or Subgroup	Balneotherapy Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Tishler et al. 2004	-1.95	1.99	44	-0.8	3.43	24	11.0%	-0.44 [-0.94, 0.06]	2004
Yurtkuran et al. 2006	-0.2	1.68	27	-1.47	1.83	25	8.8%	0.71 [0.15, 1.28]	2006
Bálint et al. 2007	-0.11	0.84	27	0	1.08	25	9.4%	-0.11 [-0.66, 0.43]	2007
Sherman et al. 2009	-1.56	4.34	24	0.91	5.78	20	7.7%	-0.48 [-1.08, 0.12]	2009
Fioravanti et al. 2010	-18.85	20.1	36	-3.3	21.31	40	12.9%	-0.74 [-1.21, -0.28]	2010
Fazaa et al. 2014	-32.83	43.64	96	-24.2	44.97	87	33.0%	-0.19 [-0.48, 0.10]	2014
Branco et al. 2016	-44.7	14.72	47	-21.7	12.9	93	17.1%	-1.69 [-2.09, -1.29]	2016
Total (95% CI)			**301**			**314**	**100.0%**	**-0.48 [-0.65, -0.31]**	

Heterogeneity: Chi² = 58.43, df = 6 (P < 0.00001); I² = 90%
Test for overall effect: Z = 5.65 (P < 0.00001)

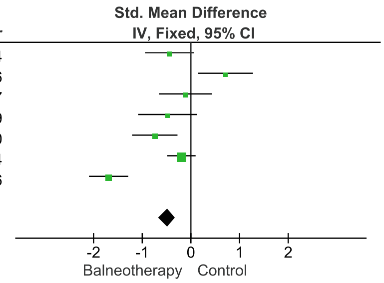

Fig. 2 Forest plot of the mean differences in WOMAC stiffness scores with 95% confidence intervals between the balneotherapy group versus control group, and the overall total, for the seven studies included in the meta-analysis conducted to examine the effect of balneotherapy on stiffness relief in patients with knee osteoarthritis

degenerative joint and spinal disease. A total of 1720 patients with rheumatological and other musculoskeletal diseases were evaluated in the meta-analysis [43]. Patients with rheumatological diseases and chronic low back pain showed greater reduction in pain with balneotherapy in comparison to the control group in most studies; in the other clinical trials evaluated, while pain improved in the balneotherapy treatment arm, the improvement was not statistically different from the comparator treatment arm(s). These previous studies could not definitively demonstrate the effects of balneotherapy for pain relief in patients with knee OA, although balneotherapy is recommended for the elderly who have musculoskeletal pain. Thus, this meta-analysis is the first study to investigate the effectiveness of balneotherapy for alleviating pain in the knee among patients with knee OA.

Eight clinical trial studies were included in this meta-analysis. There is high heterogeneity (88 to 93%). First, there is clinical heterogeneity due to different interventions, methods, and controls, as well as a difference in follow-up periods. Another relevant factor is the difference in the components of the mineral water used for balneotherapy; one study did not disclose the ingredients of the water [38]. The location of the hot spring and the district and county in which it resides may impact the content of the mineral water and may affect heterogeneity. In addition, the control group treatments varied by study and included no intervention, tap water, or hot packs. The follow-up time for evaluating the WOMAC score outcomes ranged from 2 to 12 months, although the period of treatment intervention was, on average, about 1 month. The time of last follow-up after the intervention is an important element in determining the continuing effectiveness of balneotherapy. Only one study did not show significant improvement in WOMAC stiffness and function scores; the control group cases in this study were treated with tap water therapy [41]. In addition, participants in this study were younger than the other studies included, and the ratio of female participants was higher; furthermore, physical therapy was provided after the balneotherapy. It is possible that heat therapy in general, as with tap water in this clinical trial, may improve knee OA symptoms. However, this meta-analysis shows that balneotherapy, which involves bathing in rich mineral water, is more effective than tap water therapy [38, 40, 41]. This study also has methodological heterogeneity due to the difference in quality of the publications and study designs. Two studies are not RCTs, and one of them was ranked as a low-quality assessment in blinding or randomization [39, 40]. We believe that these factors may be related to the resulting differences between the groups and impact the overall effects and heterogeneity of our study.

Several factors that might play a role in the mechanism of action of balneotherapy include thermal action, the effect of mineral content, and other physiologic and endocrine effects [44]. An increase in blood circulation is a well-known physiological response to heat application, as would occur with balneotherapy, and application of heat to inflamed tissue brings in a supply of fresh blood to remove the nociceptive elements; repair of the inflamed tissue is enhanced by the fresh oxygen brought in after removal of the free oxygen radicals

Study or Subgroup	Balneotherapy Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Tishler et al. 2004	-16.8	11.28	44	-3.8	12.74	24	10.1%	-1.09 [-1.62, -0.56]	2004
Yurtkuran et al. 2006	-6.45	14.49	27	-12.68	10.91	25	9.3%	0.48 [-0.08, 1.03]	2006
Bálint et al. 2007	-0.48	2.12	27	1	2.76	25	9.2%	-0.60 [-1.15, -0.04]	2007
Sherman et al. 2009	-13.28	33.12	24	-13.52	35.38	24	8.9%	0.01 [-0.56, 0.57]	2009
Fioravanti et al. 2010	-18.19	17.71	36	-5.06	20.73	40	13.2%	-0.67 [-1.13, -0.21]	2010
Fazaa et al. 2014	-237	326.13	96	-215.9	363.43	87	33.8%	-0.06 [-0.35, 0.23]	2014
Branco et al. 2016	-41.7	13.34	47	-16.8	11.29	93	15.5%	-2.06 [-2.49, -1.63]	2016
Total (95% CI)			**301**			**318**	**100.0%**	**-0.55 [-0.72, -0.38]**	

Heterogeneity: Chi² = 80.06, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.38 (P < 0.00001)

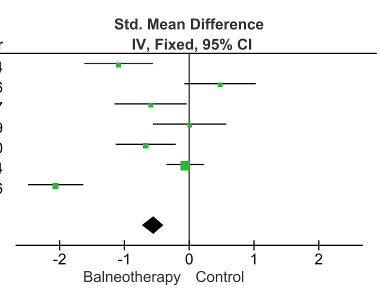

Fig. 3 Forest plot of the mean differences in WOMAC function scores with 95% confidence intervals between the balneotherapy group versus control group, and the overall total, for the seven studies included in the meta-analysis conducted to examine the effect of balneotherapy on improvement of physical function in patients with knee osteoarthritis

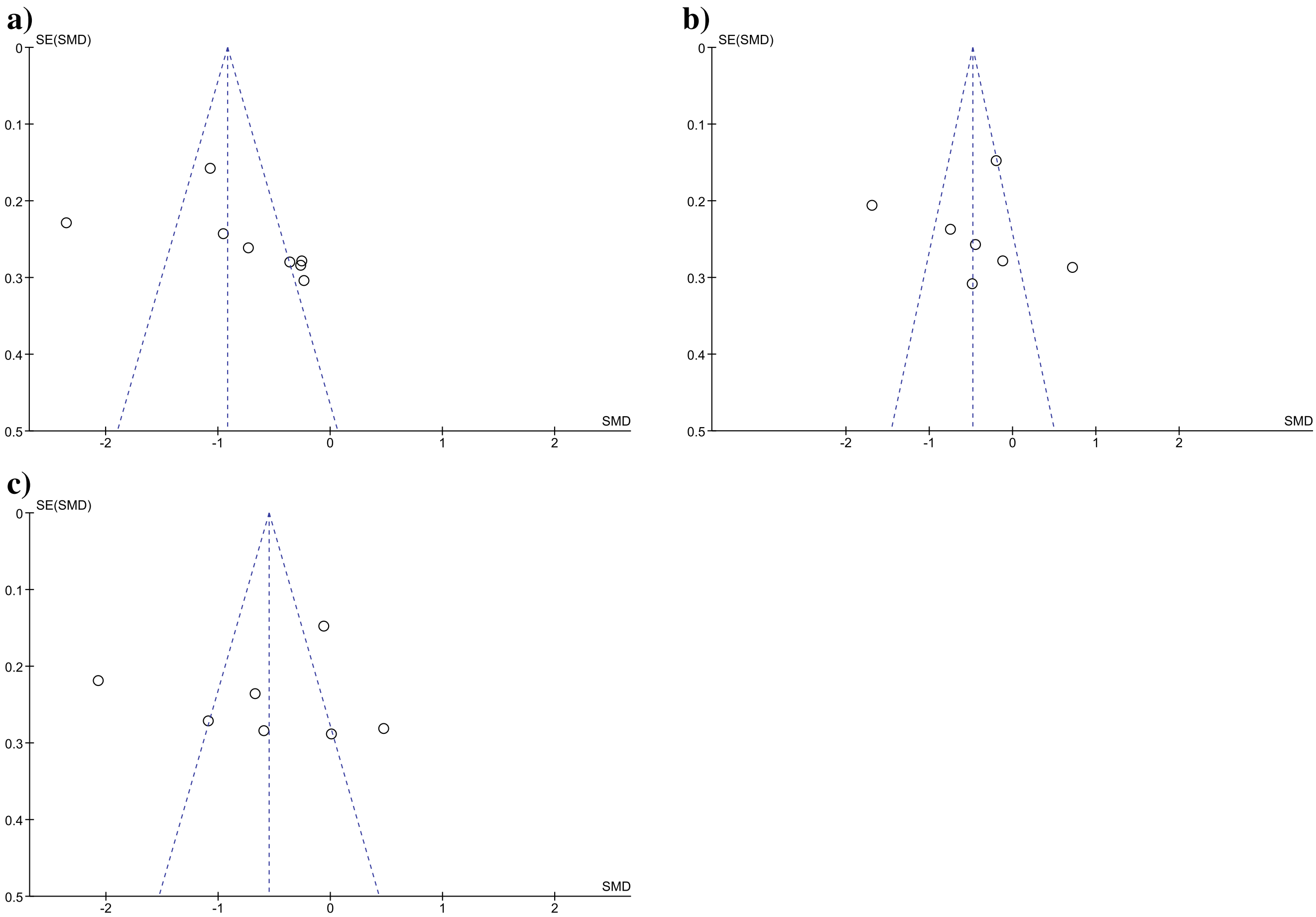

Fig. 4 Funnel plot of the WOMAC scores from the studies conducted to examine the effect of balneotherapy on pain and stiffness relief, and improvement of function, in patients with knee osteoarthritis included in the meta-analysis. **a** WOMAC pain score. **b** WOMAC stiffness score. **c** WOMAC function score

[45]. Another mechanism to reduce pain is to alter perception of the severity of pain by increasing the pain threshold of an individual through affecting sensory and muscle nerve endings. Beta-endorphin release and the washing out of pain mediators by peripheral vasodilatation also play a role in producing analgesia and sedation diuresis [46]. Our findings indicate that balneotherapy may be a cost-effective treatment for knee pain and function in individuals with knee OA. Furthermore, in addition to direct pain relief, a decrease in use of additional treatments, such as physical and pharmacological therapies, was found [47].

There are limitations to this meta-analysis. First, this study was not limited exclusively to RCTs because of the small number of studies using the same outcome measurement, i.e., WOMAC. Second, eight publications were included in this meta-analysis, and additional studies would be needed to perform subgroup analyses to identify the factors causing heterogeneity. Third, each study had a different protocol for the balneotherapy treatment, and spas were located in different areas. Existing study findings do not show a consensus on the differential effect of mineral water type on reducing pain among patients with knee OA. Finally, it is possible that publication bias exists among the studies on this subject, which was indicated in our assessment of publication bias; additional valid studies with positive and negative findings would be needed to address the impact of publication bias on our findings. It is recommended that future studies identify and evaluate objective physiologic indicators and biomarkers, such as inflammatory cytokines, to further investigate the effectiveness of balneotherapy.

In conclusion, our meta-analysis appears to confirm that existing clinical trials that evaluated balneotherapy found it is significantly associated with a reduction in pain and stiffness, and improvement in function, in patients with knee OA. It is possible that balneotherapy may improve functional ability in individuals with knee OA, although this finding is limited by the low quality of current publications, which contributes to the heterogeneity observed in this meta-analysis.

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Compliance with ethical standards

Disclosures None.

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