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## Disclosures:

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## ORIGINAL RESEARCH ARTICLE

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# Clinical Efficacy of Mudpack Therapy in Treating Knee Osteoarthritis

## A Meta-Analysis of Randomized Controlled Studies

### ABSTRACT

Xiang J, Wu D, Li J: Clinical efficacy of mudpack therapy in treating knee osteoarthritis: a meta-analysis of randomized controlled studies. *Am J Phys Med Rehabil* 2016;95:121–131.

**Objective:** The objective of this study was to evaluate the clinical efficacy of mudpack therapy for the treatment of knee osteoarthritis and identify the likely factors associated with the high heterogeneity of combined studies.

**Design:** The Medline, Embase, and Cochrane Library databases were systematically searched for randomized controlled trials in which mudpack therapy was used to treat knee osteoarthritis.

**Results:** Ten publications that reported the results from a total of 1010 subjects were included in this meta-analysis. Meta-analysis of improvement in joint function at the final follow-up visit suggested, given that the follow-up time was less than 4 mos, that the combined effect size of four studies was  $-0.30$  ( $-0.62$  to  $0.02$ ) and the difference did not reach the level of statistical significance. When the follow-up time reached 4 mos, the combined effect size was  $-1.10$  ( $-2.07$  to  $-0.14$ ) and the difference was significant. The  $I^2$  values of the two groups were 21.4% and 93.8%.

**Conclusion:** Functional improvement of the knee joint in patients treated with mudpack therapy was not significantly different from that of control subjects at the end of the 4-mo follow-up. The quality of current publications was a factor causing heterogeneity.

**Key Words:** Mudpack Therapy, Knee Osteoarthritis, Meta-analysis

**O**steoarthritis (OA) is one of the most common joint diseases seen by clinicians and mainly affects patients' knee and hip joints.<sup>1</sup> Clinical manifestations of OA include pain, stiffness, and dysfunction of diseased joints as well as joint space narrowing.<sup>2</sup> A variety of physiotherapies have been used as treatment of OA, with common approaches including mudpack therapy, balneotherapy, paraffin baths, and hot-pack application.

As a traditional treatment, mudpack therapy has a long history of use in Europe. The mud consists of refined granular organics and inorganics that are rich in minerals. The mud has therapeutic effects that are partially attributed to its thermal conductivity (transferring heat to the joints).<sup>3,4</sup> On the other hand, the organics contained in the mud are probably the type of factors that mediate the inflammatory response in the joints.<sup>5</sup> When the mud comes into contact with the human body, organic substances can be produced during the metabolic processes of microorganisms. Sulfide glycolipids can be produced by colonized microorganisms, which may be the effective anti-inflammatory substances involved in the therapy.<sup>6</sup>

The particular substances contained in the mud vary between regions. Although standards of classification of mudpack therapy have not been established, the efficacy of the therapy in treating OA has been reported frequently.<sup>7,8</sup> The local application of hot pack has been recommended by the European League Against Rheumatism to treat hand OA.<sup>9</sup> However, this proposition was based on expert opinion alone and the evidence level was reckoned as IV by the European League Against Rheumatism. Although local heat application is generally considered an effective and safe means of relieving pain, evaluating its efficacy is problematic in a blinded controlled design. Considering the larger contacting area, hot pack may exert a better outcome in treating knee OA than hand OA. Luckily, there were more clinical articles of heat pack for knee OA than hand OA. Differences in treatment approaches, duration of treatment, follow-up time, and quality of publication are probably responsible for the different results. Liu et al.<sup>10</sup> performed a meta-analysis and did not reach any definite conclusion because of the insufficiency of included literature and the high heterogeneity of combined studies.

So far, there are no published meta-analytic studies that draw a definite conclusion concerning the efficacy of mudpack therapy. This meta-analysis that included the latest randomized controlled trials systematically assessed the efficacy of mudpack therapy

in treating knee OA and analyzed possible reasons underlying the high heterogeneity of combined studies.

## **MATERIALS AND METHODS**

### **Systematic Literature Search**

The meta-analysis was performed according to the guidelines of the PRISMA statement.<sup>11</sup> Publications included in Medline (1945-), Embase (1980-), the Cochrane Central Register of Controlled Trials (1970-), and the Cochrane Database of Systematic Reviews and published before November 2014 were searched using two approaches (MeSH terms and free words). The English search words included *mud*, *peloid*, *pelotherapy*, *osteoarthritis*, *degenerative arthritis*, and *osteoarthrosis*. Only English publications were included in this study. The references in each article were used to extend the search range and to identify further relevant publications. Reports of systematic reviews and meta-analyses were searched using the same strategy.

### **Inclusion and Exclusion Criteria**

All randomized controlled trials that investigated the clinical efficacy of mudpack therapy in treating knee OA were included in this study. Any studies that investigated other treatments for OA but also contained a mudpack therapy group and a control group were also included. Measures for effects of included studies involved relief of knee pain and improvement of joint function. The results of the included studies should be presented as mean (SD) (Table 1). Studies that did not meet the inclusion criteria were excluded.

### **Data Extraction**

All related data were extracted and assessed independently by two investigators. The extracted information included the following: sample size of included studies, treatment approaches in therapeutic groups and control groups, treatment cycle, follow-up time, values of tests, quality of the publication, and whether the intention to treat was used in the studies. Inconsistent data were addressed by discussion.

### **Measures of Effects**

Measures for effects included relief of pain and improvement of the functions of the diseased knees in patients treated with mudpack therapy. To reduce reporting bias, the measures of pain listed in the highest rank of the Pain-Related Scale List were chosen.<sup>18</sup> Measures of pain included visual analog

**TABLE 1** Characteristics of included studies

Study	Year	Sample Size	ITT	Intervention Group	Control Group	Trial Duration, wks	Follow-up, mos	Outcome Extracted	BMI, <sup>a</sup> mean (SD), kg/m <sup>2</sup>	Age, mean (SD), yrs
Tefner et al. <sup>8</sup>	2013	53	Yes	Mudpack	Hot-pack therapy	2	12	WOMAC pain	NA	M/F: 63.42 (8.86)/63.55 (9.53)
Espejo Antúñez et al. <sup>7</sup>	2013	132	No	Mudpack	Routine drug therapy	2	0.5	WOMAC function VAS	I/C: 30.38 (4.59)/27.87 (4.41)	I/C: 69.13 (5.60)/73.08 (8.90)
Sarsan et al. <sup>12</sup>	2012	27	No	Mudpack	Hot-pack therapy	2	6	VAS WOMAC function	I/C: 31.8 (4.4)/32.9 (4.2)	I/C: 52.4 (5.2)/53.6 (8.0)
Güngen et al. <sup>13</sup>	2012	44	No	Mudpack	Hot-pack therapy	2	3	VAS WOMAC function	I/C: 27.95 (2.83)/27.60 (2.42)	I/C: 65.04 (7.11)/61.87 (6.73)
Forestier et al. <sup>14</sup>	2010	451	Yes	Mudpack plus spa	3-day wellness package	3	6	VAS WOMAC function	I/C: 30.7 (5.9)/29.0 (4.6)	I/C: 63.0 (9.1)/64.3 (10.4)
Fioravanti et al. <sup>15</sup>	2010	80	Yes	Mudpack plus spa	Routine drug therapy	2	9	WOMAC pain	I/C: 25.92 (4.17)/26.78 (4.11)	I/C: 69.06 (5.11)/71.3 (4.91)
Mahboob et al. <sup>16</sup>	2009	50	Yes	Mudpack	Placebo-control group	4	1	WOMAC function WOMAC pain	NA	44–79 (range)
Odabasi et al. <sup>17</sup>	2008	60	Yes	Mudpack	Placebo-control group	3	27	WOMAC function VAS WOMAC	NA	I/C: 69.2 (1.3)/69.0 (1.5)
Evcik et al. <sup>3</sup>	2007	55	No	Mudpack	Hot-pack therapy	2	3	VAS	I/C: 30.6 (4.1)/30.4 (4.9)	I/C: 57.4 (9)/59.6 (9.2)
Flusser et al. <sup>4</sup>	2002	58	No	Mudpack	Placebo-control group	3	3	VAS LI	I/C: 75.9 (10.9)/75.1 (11.2) (kg)	I/C: 64.7 (7.9)/64.8 (7.3)

<sup>a</sup>Mean weight in kilograms is given if the mean BMI was not provided.

BMI, body mass index; C, control group; F, female; I, intervention group; ITT, intention to treat; LI, Lequesne Index; M, male; NA, not available; VAS, visual analog scale.

**TABLE 2** Methodology quality assessment of included studies by modified Jadad score

Study	Year	Score	Randomization	Allocation Concealment	Double Blinding	Withdrawals and Dropouts
Tefner et al. <sup>8</sup>	2013	6	2	1	2	1
Espejo Antúñez et al. <sup>7</sup>	2013	3	2	1	0	0
Sarsan et al. <sup>12</sup>	2012	3	2	1	0	0
Güngen et al. <sup>13</sup>	2012	4	2	1	0	1
Forestier et al. <sup>14</sup>	2010	7	2	2	2	1
Fioravanti et al. <sup>15</sup>	2010	4	2	1	0	1
Mahboob et al. <sup>16</sup>	2009	4	2	2	0	0
Odabasi et al. <sup>17</sup>	2008	4	2	1	0	1
Evcik et al. <sup>3</sup>	2007	1	1	0	0	0
Flusser et al. <sup>4</sup>	2002	1	1	0	0	0

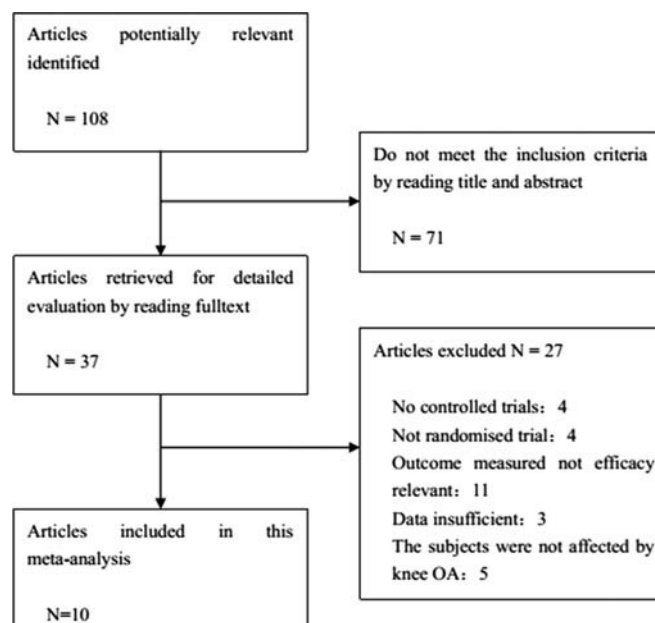
scale scores and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores.<sup>19</sup> Functional improvement was assessed using functional scores, including the Lequesne Index and functional scores of WOMAC (WOMAC function). For publications in which both WOMAC function and the Lequesne Index were reported, the WOMAC function was chosen because studies suggest that the score of WOMAC function is more sensitive than the Lequesne Index in monitoring the improvement of symptoms.<sup>20</sup>

### Quality Assessment of the Publications

The modified Jadad quality scale was used to assess the quality of included publications (Table 2).<sup>21</sup> Two investigators independently assessed each selected

report and inconsistent opinions were solved by discussion. Assessment included generation of random sequence, allocation concealment, application of blinding, and withdrawals and dropouts. Each study was scored on a scale of 1–7. A study was considered to be of a high quality if the score was 4–7 and low quality if the score was 1–3.

If intention-to-treat analysis was included in a study, the result of intention-to-treat analysis was used in this meta-analysis. For continuous variables, standardized mean difference of measures acted as the effect size (ES) to improve comparability among different results.<sup>22</sup> ES was assessed using the magnitude of the standardized mean difference put forward by Cohen.<sup>23</sup> Standardized mean difference values of 0.2, 0.5, and 0.8 were considered as small, medium, and large ESs of active

**FIGURE 1** Flowchart of the selection of studies.

therapy compared with placebo. According to the data provided in the included studies, the results at the end of the treatment and the last follow-up visit were chosen. Subgroup analysis was performed according to the types of treatment, follow-up time, treatment approaches, and quality of studies.  $I^2$  was calculated to evaluate the heterogeneity of combined ES estimates.<sup>24</sup>  $I^2$  is a value between 0% and 100%, with 25%, 50%, and 75% referring to low, moderate, and high heterogeneity, respectively. The Q statistic with significance set at  $P$  less than 0.05 was used as a second measure of heterogeneity. If heterogeneity was not detected among included studies, a fixed-effects model was used to perform the meta-analysis; otherwise, a random-effects model would be used.<sup>25</sup> Publication bias was evaluated using the Egger test.<sup>26</sup> All statistical analyses were performed using STATA version 11.0 (Stata Corp, College Station, TX).

## RESULTS

### The Process of Literature Screening and Literature Characteristics

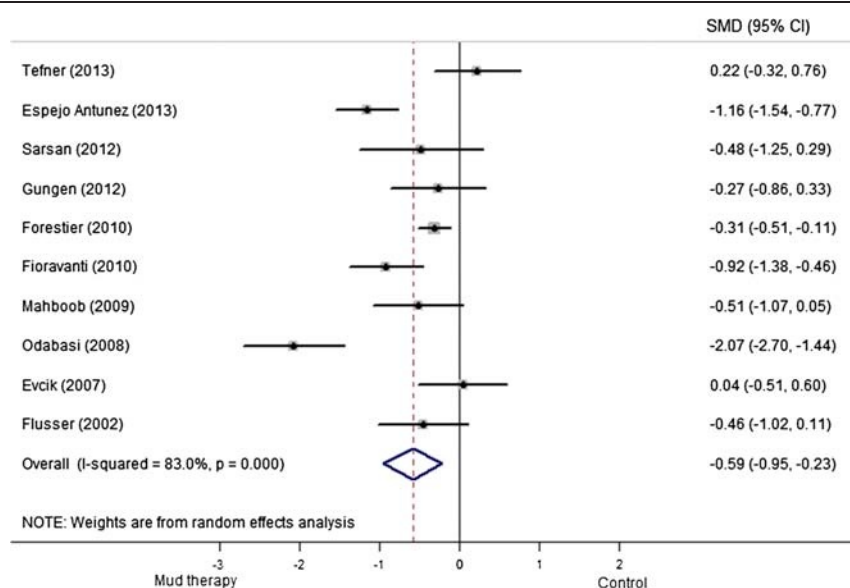
The process of literature screening is shown in Figure 1. Among 108 publications obtained by preliminary screening, 71 were excluded by looking through titles and abstracts of the articles including 59 non-English publications. The remaining 37 publications were screened by reading the full text of the articles. Among them, four studies were excluded because of lack of a placebo control group.<sup>27–30</sup> A further 11 studies that did not meet the inclusion criteria were excluded.<sup>31–41</sup> Four nonrandomized controlled trial

studies were excluded<sup>42–45</sup> and three studies were excluded because of insufficient data.<sup>46–48</sup> Five articles were excluded because the subjects were not affected by knee OA.<sup>49–53</sup>

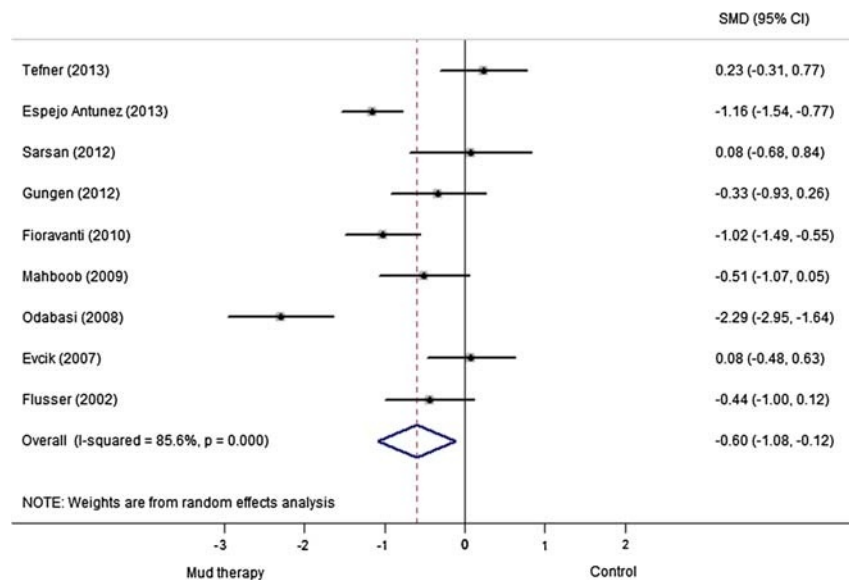
After screening, 10 studies were included in this meta-analysis, which consisted of 1010 subjects in total.<sup>3,4,7,8,12–17</sup> The year of publication was from 2002 to 2013. The smallest sample size was 27 and the largest was 451. Among the included clinical trials, the shortest duration was 2 wks and the longest was 4 wks. The shortest follow-up time was 2 wks and the longest was 27 mos. There were eight studies in which the treatment approach in the therapeutic group was mudpack therapy alone, and in two studies, the approach was mudpack therapy in combination with hydrotherapy. Four publications were ranked as low quality on the modified Jadad quality scale and another six publications were ranked as high quality.

### Meta-Analysis of the Effects of Mudpack Therapy on the Relief of Joint Pain in Knee OA Patients

The effects of mudpack therapy in relieving the joint pain of knee OA were assessed at the final follow-up visits in these studies. As shown in Figure 2, the  $I^2$  value from heterogeneity testing of included studies was 83.0% ( $Q = 52.80, P < 0.001$ ), implying the presence of heterogeneity among these studies. Therefore, a random-effects model was applied. The high heterogeneity of the included studies might affect the estimate of ES. Nine studies reported the results of pain relief at the end of the trials (Fig. 3). However, no definite conclusion could be reached



**FIGURE 2** The effects of mudpack therapy in relieving the joint pain of knee OA at the final follow-up visits.



**FIGURE 3** The effects of mudpack therapy in relieving the joint pain of knee OA at the end of the trials.

because of the high heterogeneity of the included studies ( $I^2 = 85.6\%$ ,  $Q = 55.41$ ,  $P < 0.001$ ).

The authors attempted to perform subgroup analyses to identify the factors associated with heterogeneity. To evaluate the effects of mudpack therapy in relieving joint pain at the final follow-up visit, subgroup analyses were performed in which the grouping factors were follow-up time ( $\geq 4$  mos or  $< 4$  mos), treatment approach, and the quality of publications. All of the  $I^2$  values were more than 50% (Table 3) in subgroup analyses, which suggested that no definite conclusion could be reached based on combined ES. To evaluate the effects of mudpack therapy in relieving joint pain at the end of the clinical trials, subgroup analyses grouping factors were the duration of the trial ( $\geq 2$  wks or  $< 2$  wks), treatment approach, and the quality of publications (Table 4). The  $I^2$  values were still high, which suggested that combining ES was inappropriate based on the included studies.

### Meta-Analysis of the Effects of Mudpack Therapy in Improving Joint Functions of Knee OA Patients

Data on the improvement of joint function at the final follow-up visit were provided in eight studies (Fig. 4). The  $I^2$  value of 87.3% ( $Q = 55.15$ ,  $P < 0.001$ ), which suggested a high heterogeneity among included studies, supported application of the random-effects model. Data on the improvement of joint function at the end of the treatment period were provided in seven studies (Fig. 5). However, high heterogeneity ( $I^2 = 75.0\%$ ,  $Q = 23.98$ ,

$P = 0.001$ ) suggested that it was inappropriate to combine ES.

The process of subgroup analyses was described above. The follow-up time of four studies was less than 4 mos and the combined ES of these four studies was  $-0.30$  ( $-0.62$  to  $0.02$ ) (Table 3). A statistically significant difference and low heterogeneity ( $I^2 = 21.4\%$ ,  $Q = 3.81$ ,  $P = 0.282$ ) suggested that mudpack therapy produced no significant improvement of joint function in knee OA patients within the 4-mo follow-up period. The combined ES of two low-quality studies was  $-0.03$  ( $-0.48$  to  $0.42$ ) (Table 3). Heterogeneity was not detected in these two studies. The result indicated that mudpack therapy produced no significant improvement of joint function in knee OA at the final follow-up visit. The high heterogeneities in other subgroup analyses implied that no definite conclusion could be drawn based on the combined ES (Table 4).

No publication bias was detected by the Egger test.

### DISCUSSION

This meta-analysis investigated the beneficial effects of mudpack therapy on relieving joint pain and improving joint functions of knee OA patients. Ten studies were included in this meta-analysis. High heterogeneity among the included studies suggested that calculating combined ES based on these 10 studies was inappropriate. Therefore, subgroup analyses were performed to find the likely reasons that lead to high heterogeneity. Mudpack therapy is generally used in combination with hydrotherapy. However, hydrotherapy is not necessarily

**TABLE 3** Subgroup analyses of mudpack therapy in relieving the symptoms of knee OA at the final follow-up visits

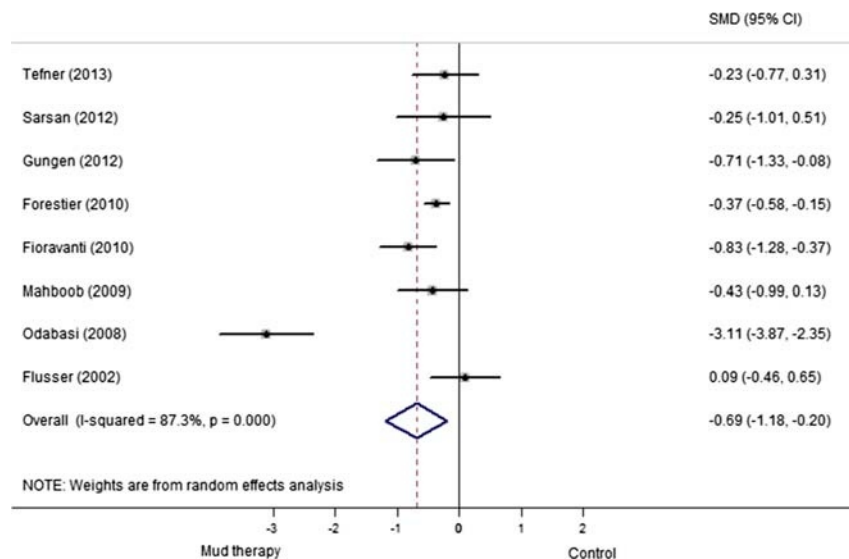
	Pain				Function					
	Trials	ES (95% CI)	I <sup>2</sup> , %	Q	P	Trials	ES (95% CI)	I <sup>2</sup> , %	Q	P
Follow-up time										
>4 mos	4	-0.93 (-1.66 to -0.19)	90.1	30.28	<0.001	4	-1.10 (-2.07 to -0.14)	93.8	48.48	<0.001
<4 mos	6	-0.37 (-0.83 to 0.08)	77.6	22.32	<0.001	4	-0.30 (-0.62 to 0.02)	21.4	3.81	0.282
Intervention group										
Mudpack only	8	-0.59 (-1.08 to -0.09)	84.3	44.63	<0.001	6	-0.75 (-1.56 to 0.06)	90.2	51.03	<0.001
Mudpack plus spa	2	-0.58 (-1.17 to 0.02)	82.3	5.65	0.017	2	-0.55 (-0.99 to -0.11)	69.1	3.23	0.072
Study quality										
High	6	-0.62 (-1.13 to -0.11)	86.7	37.61	<0.001	6	-0.89 (-1.50 to -0.29)	90.0	49.78	<0.001
Low	4	-0.54 (-1.12 to 0.04)	77.4	13.29	0.004	2	-0.03 (-0.48 to 0.42)	0.0	0.51	0.475

CI, confidence interval.

**TABLE 4** Subgroup analyses of mudpack therapy in relieving the symptoms of knee OA at the end of the trials

	Pain				Function					
	Trials	ES (95% CI)	I <sup>2</sup> , %	Q	P	Trials	ES (95% CI)	I <sup>2</sup> , %	Q	P
Treatment duration										
>2 wks	3	-1.07 (-2.19 to 0.05)	90.7	21.60	<0.001	3	-0.79 (-1.62 to 0.04)	84.4	12.79	0.002
≤2 wks	6	-0.38 (-0.91 to 0.14)	83.1	29.54	<0.001	4	-0.65 (-1.22 to -0.09)	72.6	10.94	0.012
Intervention group										
Mudpack only	8	-0.55 (-1.09 to 0.00)	86.7	52.72	<0.001	6	-0.64 (-1.13 to -0.14)	75.4	20.34	0.001
Mudpack plus spa	1	NA	NA	NA	NA	1	NA	NA	NA	NA
Study quality										
High	5	-0.78 (-1.54 to -0.01)	89.4	37.71	<0.001	5	-0.74 (-1.31 to -0.17)	81.1	21.11	<0.001
Low	4	-0.40 (-1.05 to 0.26)	82.5	17.19	0.001	2	-0.61 (-1.35 to 0.12)	55.7	2.26	0.133

CI, confidence interval; NA, not applicable.

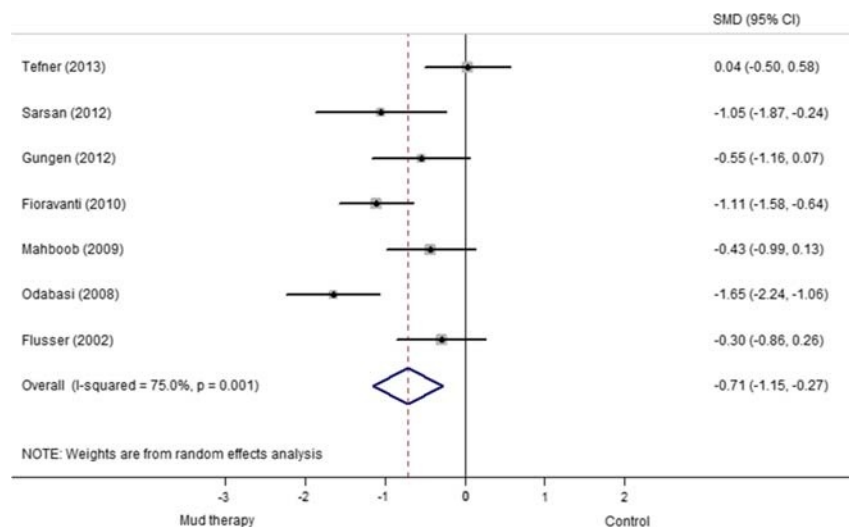


**FIGURE 4** The effects of mudpack therapy in improving joint functions of knee OA at the final follow-up visits.

combined with mudpack therapy. There were two included studies in which mudpack therapy was combined with hydrotherapy. A subgroup analysis was performed between mudpack therapy alone and mudpack therapy combined with hydrotherapy. However, the heterogeneity did not change significantly. This indicated that whether mudpack therapy was used alone or in combination with hydrotherapy was not a significant factor associated with the high heterogeneity and highlighted the necessity of including combination therapy.

The duration of follow-up varied between 2 wks and 27 mos and the duration of treatment was between 2 wks and 4 wks. This relatively long time span was one possible reason for the high heterogeneity. Subgroup analysis was based on the duration of follow-up. The combined ES of four studies

in which the duration of follow-up was less than 4 mos was  $-0.30$  ( $-0.62$  to  $0.02$ ) and was not significantly different from that of the control group. The low heterogeneity ( $I^2 = 21.4\%$ ) among four studies supported the reliability of the combined ES. Based on the above data, within a 4-mo follow-up period, there was no significant difference in the improvement of joint functions of knee OA patients between those who received mudpack therapy and control subjects. Although the combined ES of four studies in which the duration of follow-up was 4 mos or more was  $-1.10$  ( $-2.07$  to  $-0.14$ ), the high heterogeneity ( $I^2 = 93.8\%$ ) might impair the reliability of the combined ES. High heterogeneity still existed in other subgroup analyses; thus, no conclusions could be drawn based on the combined ES. Group results were attempted according to other time



**FIGURE 5** The effects of mudpack therapy in improving joint functions of knee OA at the end of the trials.



spans but heterogeneity could not be avoided (data not shown).

Among the 10 studies included in this meta-analysis, only 2 applied the double-blind design correctly. A study has shown that low-quality publications often overestimate the efficacy of therapies.<sup>54</sup> The modified Jadad quality scale was used to assess the quality of included publications. A meta-analysis conducted by Liu et al.<sup>10</sup> showed that mudpack therapy was superior to placebo. Although the same methodological quality scale as Liu et al.'s research was used, there were some discrepancies in assessing the identical included articles. Liu was attempted to be contacted but there was no reply. Considering the discrepancies with Liu et al.'s research, the quality of included articles was assessed repeatedly and has resulted to these outcomes. The authors then performed a subgroup analysis according to the quality of the publications. The combined ES of two low-quality publications was  $-0.03$  ( $-0.48$  to  $0.42$ ) and no heterogeneity was detected. This suggested that quality of study is one of the factors that can cause heterogeneity.

There are some limitations to this meta-analysis. First, mudpack therapy is extensively used for treating OA in Europe. However, a number of non-English language publications were not included in this meta-analysis, which is likely to cause bias. Second, the standards for evaluating pain and joint function in the original publications were inconsistent, which is a possible reason for heterogeneity. The authors improved the comparability among the various studies by using the standardized mean difference method. Third, 10 publications were included in this meta-analysis, and more studies will be needed to perform subgroup analyses to identify the factors causing heterogeneity.

## CONCLUSION

There was no significant difference in the improvement of joint function over the 4-mo follow-up period between the knee OA patients treated with mudpack therapy and control subjects. The quality of current publications may be one cause of heterogeneity.

## Supplementary Checklist

PRISMA Checklist: <http://links.lww.com/PHM/A149>;  
PRISMA Flow Diagram: <http://links.lww.com/PHM/A150>

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