



## Comparison of intra-articular hyaluronic acid injections and mud-pack therapy in the treatment of knee osteoarthritis

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**Objectives:** Conservative treatment should be tried prior to surgical treatment in knee osteoarthritis. This study was designed to evaluate the short-term effects of mud-pack therapy on pain relief and functional improvement in knee osteoarthritis in comparison with intra-articular hyaluronic acid injections.

**Methods:** The study included 23 patients who were diagnosed as having knee osteoarthritis according to the ACR (American College of Rheumatology) criteria, and had complaints lasting for more than three months. All the patients had stage 2 or 3 osteoarthritis radiographically according to the Kellgren-Lawrence criteria. Twelve patients (3 males, 9 females; mean age 54±6 years; range 46 to 67 years) received mud therapy bilaterally. Mud packs were heated to 45 °C and applied on both knees for 30 minutes daily for a total of 12 weekdays. Eleven patients (2 males, 9 females; mean age 53±9 years; range 40 to 66 years) received a total of three bilateral intra-articular hyaluronic acid injections, each interspersed by weekly intervals. The patients were evaluated before and after treatment in terms of pain and functionality using the pain subscale of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, Hospital for Special Surgery (HSS) score, and Knee Society clinical rating system (knee and function scores). The patients were followed-up for a mean of 5.9±6.3 months (range 4 to 8 months) after mud-pack therapy, and 5.8±0.8 months (range 5 to 7 months) after intra-articular hyaluronic acid injections.

**Results:** No significant differences were found between the two groups with respect to pre- and posttreatment WOMAC, HSS, and knee and function scores ( $p>0.05$ ). The scores of all instruments showed significant improvements following treatment in both groups ( $p<0.001$ ). Posttreatment changes in relation to baseline scores did not differ significantly between the two groups ( $p>0.05$ ).

**Conclusion:** Treatment of knee osteoarthritis with intra-articular hyaluronic acid injections or mud-pack therapy yielded similar results in the short-term in terms of functional improvement and pain relief. Mud-pack therapy is a noninvasive, complication-free, and cost-effective alternative modality for the conservative treatment of knee osteoarthritis.

**Key words:** Hyaluronic acid/therapeutic use; injections, intra-articular; mud therapy; osteoarthritis, knee/therapy; pain measurement; patient satisfaction; questionnaires.

Osteoarthritis is one of the most frequently seen musculoskeletal system diseases. Even though surgical treatment of knee osteoarthritis is increasingly used, conservative treatment modalities should be

applied in appropriate indications, including patient education, modification of activities, shoe modification, braces, analgesic and anti-inflammatory drugs, physical therapy, and intra-articular hyaluronic acid

injections.<sup>[1,2]</sup> Many studies showed beneficial effects of intra-articular hyaluronic acid injections on pain and activity.<sup>[3-7]</sup> Modern balneotherapy, which has long been used as a conventional and empirical remedy, is an effective discipline of medicine used for the prevention, treatment, and rehabilitation of chronic diseases. Balneotherapy has a significant role among commonly used complementary methods in the treatment of musculoskeletal diseases in many European countries and Turkey. Balneotherapy is a stimulation and regulation therapy where several natural healing substances such as thermomineral waters, mud (peloids), and gases are used with predetermined methods and doses, in the form of baths, packages, drinking, or inhalation, and with regular intervals.<sup>[8]</sup> It has been reported that balneotherapy has an efficacious use in the alleviation of osteoarthritic pain, improvement in functions, and decreased analgesic use.<sup>[9-12]</sup>

Our literature search did not show any study comparing the efficacies of mud-pack therapy, one of the modalities of balneotherapy, and intra-articular hyaluronic acid injection in the treatment of knee osteoarthritis. This study was designed to evaluate and compare the short-term effects of mud-pack therapy and intra-articular hyaluronic acid injections on pain and functional improvement in knee osteoarthritis.

## Patients and methods

In this retrospective study, patients treated with two diverse modalities for knee osteoarthritis were evaluated. Medical charts, routine knee scoring scales obtained before and after treatment were reviewed. Twenty-three patients were enrolled, who were diagnosed as having knee osteoarthritis according to the ACR (American College of Rheumatology) criteria,<sup>[13]</sup> and had complaints lasting for more than three months.

Exclusion criteria were defined as the presence of the following conditions: a history of orthopedic surgery, neuromuscular diseases of the lower extremities, acute lumbar pathologies, marked deformities or contractures of the lower extremities (flexion contracture  $>10^\circ$ , knee varus-valgus  $>7^\circ$ ), inflammatory diseases, posttraumatic arthrosis, use of anticoagulant drugs, use of oral or parenteral steroids within the past two months, and application of intra-articular hyaluronic acid injections within the past 12 months.

Knee osteoarthritis was classified radiographically according to the Kellgren-Lawrence criteria.<sup>[14]</sup> All the

patients had stage 2 or 3 osteoarthritis. The patients were evaluated before and after treatment in terms of pain and functionality using the pain subscale of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index (0-25 points,<sup>[15]</sup> Hospital for Special Surgery (HSS) score,<sup>[16]</sup> and Knee Society clinical rating system (knee and function scores).<sup>[17]</sup>

Eleven patients (2 males, 9 females; mean age  $53\pm 9$  years; range 40 to 66 years) received a total of three bilateral intra-articular hyaluronic acid injections (Orthovisc, Anika Therapeutics, Woburn, MA, USA), each interspersed by weekly intervals. In this group, 10 knees had stage 2, 12 knees had stage 3 osteoarthritis. The mean follow-up period was  $5.8\pm 0.8$  months (range 5 to 7 months).

The other group consisted of 12 patients (3 males, 9 females; mean age  $54\pm 6$  years; range 46 to 67 years) who received mud therapy bilaterally. There were 12 stage 2, 12 stage 3 knees. The mean follow-up period was  $5.9\pm 6.3$  months (range 4 to 8 months).

The constituents of medical mud (Spa Care, Denizli, Turkey) used in our patients have been reported as follows in the analysis report of the Ministry of Health of Turkish Republic: water 63%, mineral (of dry material) 86%, humic acid 3.94 g/l, bitumen 3.66 g/l, cellulose and hemicellulose 17.37 g/l, lignin and humin 75.57 g/l, pectin and carbohydrate 2.66 g/l, hydrogen sulfide 0.014 g/l, iodine 0.66 g/l; and total amounts of organic and inorganic materials being 102.20 g/l and 627 g/l, respectively.

Mud packs were heated to  $45^\circ\text{C}$  and applied on both knees for 30 minutes daily for a total of 12 weekdays. Three-centimeter thickness of mud was applied on the knees covering an area of 5 cm above and below the patella and, to increase efficacy, its surface was occluded with gelatine. The mud-pack therapy was designed in the light of applications of previous studies and with consideration of circumstances of our clinic and was carried out as a minimum cure program to be effective.<sup>[18-20]</sup>

## Statistical evaluation

Continuous variables used in the study demonstrated a normal distribution with the Kolmogorov-Smirnov test. Comparisons between the two groups were made using the two independent-sample t-test, and comparisons within the groups for pre- and posttreatment values were made using the two dependent-sample t-test.

**Table 1**

Pre- and posttreatment scores of the two groups

	Hyaluronic acid (22 knees)		Mud pack (24 knees)		$p^1$	$p^2$	$p^3$	$p^4$
	Before	After	Before	After				
HSS score	75.6±8.5	83.6±6.0	78.1±9.7	86.9±9.6	0.376	0.183	<0.001	0.719
Knee function score	64.7±13.5	73.8±11.5	63.9±19.3	80.5±13.6	0.873	0.096	<0.001	0.061
Knee score	74.3±11.1	88.3±6.1	74.9±14.9	86.4±11.4	0.882	0.503	<0.001	0.473
WOMAC pain score	11.9±2.9	6.5±2.2	11.8±1.9	6.1±1.6	0.940	0.644	<0.001	0.566

HSS: Hospital for Special Surgery; WOMAC: Western Ontario and McMaster Universities.  
 $p^1$ : Comparison of pre-treatment scores between the two groups;  $p^2$ : Comparison of posttreatment scores between the two groups;  $p^3$ : Comparisons within the groups for pre- and posttreatment scores;  $p^4$ : Comparison of posttreatment changes in relation to baseline values between the two groups.

Comparisons between the two groups with respect to posttreatment changes in relation to baseline values were analyzed using the two-way analysis of variance with repeated measures. All variables were expressed as mean ± standard deviation. A  $p$  value of less than 0.05 was considered statistically significant. Calculations were made using the SPSS statistical package program.

## Results

Pre- and posttreatment WOMAC, HSS, and knee and function scores obtained in the two groups are displayed in Table 1. No significant differences were found between the two groups with respect to pre- and posttreatment measurements ( $p>0.05$ ). The scores of all instruments showed significant improvements following treatment in both groups ( $p<0.001$ ). Posttreatment changes in relation to baseline values did not differ significantly between the two groups ( $p>0.05$ ).

## Discussion

The results of surgical treatment is favorable in knee osteoarthritis, which is one of the major causes of disability. However, surgical treatment may not be convenient for every stage of osteoarthritis, and risks of surgery must be considered when deciding on operative management. Besides, not all patients accept surgical treatment.<sup>[21]</sup> Thus, early diagnosis and conservative treatment modalities remain a top priority.<sup>[1,2]</sup> Among conservative treatment modalities, analgesics and anti-inflammatory drugs incur serious complications and financial burden due to associated gastrointestinal adverse effects.<sup>[22]</sup>

Intra-articular hyaluronic acid injections are widely used in the treatment of knee osteoarthritis.<sup>[3-7]</sup> Its mechanisms of action might involve increase in the

number of live chondrocytes, thickening and development (regeneration) of the amorphous surface layer of the cartilage, prevention of nitric oxide production in synovia and menisci, inhibition of chondrocyte apoptosis, and down-regulation of matrix metalloproteinase-3 and interleukin-1 beta in synovia.<sup>[23-26]</sup> Albeit rarely, some adverse effects of hyaluronic acid applications have been reported.<sup>[27,28]</sup> We did not observe any local and systemic side effects in our patients receiving hyaluronic acid injections. Following injections, all the patients exhibited significant improvements in the WOMAC pain subscale, HSS scores, and knee and function scores ( $p<0.001$ ).

Mud-pack therapy has been widely used in our country as in many other countries for the treatment of musculoskeletal diseases, with successful results. It is quite popular in France, Germany, Italy, and Eastern Europe due to provision of pain relief.<sup>[29]</sup> Contents of mud used in knee osteoarthritis may show regional variations. Despite these differences, it has been shown by many studies that mud-pack therapy provides significant improvements in pain, functions, and quality of life of patients with osteoarthritis.<sup>[18-20,29-31]</sup> Among reported mechanisms of action of mud-pack therapy are decrease in the levels of tumor necrosis factor-alpha (TNF- $\alpha$ ) resulting in decreased inflammatory reaction and cartilage damage, maintenance of cartilaginous hemostasis through decreasing serum levels of nitric oxide and myeloperoxidases, and decrease in serum concentrations of inflammatory mediators such as prostaglandin E2 (PGE2) and leukotriene B4 (LTB4).<sup>[32-34]</sup> There is a general assumption that thermal stimulation induces increases in serum levels of noradrenaline, cortisol, and beta-endorphins leading to anti-inflammatory and analge-

sic effects.<sup>[35,36]</sup> Increases in the levels of chondroprotective insulin-like growth factor 1 (IGF-1) have also been reported.<sup>[29]</sup>

Poensin et al.<sup>[37]</sup> demonstrated by laser-Doppler flowmetry that mud-pack therapy caused enhancement of skin blood circulation, which was possibly induced by local mechanisms, in particular transcutaneous ion transfer. Besides, some studies suggested that sulfur minerals absorbed by the skin might cause an analgesic effect.<sup>[35,36,38]</sup> Mazzulla et al.<sup>[39]</sup> proposed that sulfur in the mud induced the production of carotene, vitamins, and phytosterol in the skin matrix leading to an anti-inflammatory effect.

Ice applications after acute phases of degenerative joint diseases increase pain threshold through decreasing Na-K pump activity in nerve endings, repolarization, and excitability, decrease nerve conduction velocity, and help relieve pain through gate-control mechanisms. In contrast, local hot applications induce vasodilatation, which in turn increases blood flow, metabolism, and viscoelasticity of connective tissue, resulting in resolution of muscle spasm and pain relief.<sup>[40,41]</sup>

Despite the lack of a meta-analysis to evaluate the use of mud therapy in knee osteoarthritis, several studies exist in the literature reporting favorable results following mud therapy. Cutović et al.<sup>[42]</sup> compared the effectiveness of spa alone or combined with mud therapy in the treatment of knee osteoarthritis and found that combination therapy was more effective in alleviating pain and improving articular functions. Another study reported similar improvements in balneotherapy and mud-pack therapy groups.<sup>[19]</sup> Odabaşı et al.<sup>[20]</sup> reported that direct mud application to the skin was more effective than indirect application in knee osteoarthritis. Flusser et al.<sup>[43]</sup> concluded that mud-pack therapy could be used as a complementary method to conventional therapies in knee osteoarthritis. Besides knee osteoarthritis, mud-pack therapy is also used in the treatment of lumbar spondylosis. It was found to be effective in alleviation of pain in lumbar spondylosis.<sup>[10,44]</sup> Significant improvements compared to baseline were seen at the last control visits of all the patients treated with mud-pack therapy in the WOMAC pain subscale, HSS scores, and Knee Society knee and function scores.

The two most frequently used conservative treatment options in osteoarthritis are analgesics and anti-

inflammatory drugs and intra-articular hyaluronic acid injections. The use of analgesics and anti-inflammatory drugs is associated with common gastrointestinal side effects. Hyaluronic acid injections, on the other hand, may rarely cause local and systemic adverse effects and require access to intra-articular compartments. These disadvantages may make mud-pack therapy a more preferable method because it is free of any adverse effect, does not require any intervention, and is easily reproducible. There are also significant differences between the costs of these therapies. The overall cost of mud-pack therapy is about 20 dollars per patient and intra-articular hyaluronic acid injections cost about 150 dollars per patient. Moreover, in our country, the cost of mud-pack therapy is completely covered by the social security system, whereas the cost of hyaluronic acid injections is paid by the patient as it is not included in the reimbursement system. Thus, mud-pack treatment is considerably cost-effective for both patients and social security systems.

No complications have been reported regarding the use of mud-pack therapy in knee osteoarthritis.<sup>[8-20]</sup> In our study, we did not observe any adverse effect associated with mud-pack therapy and intra-articular hyaluronic acid injections. However, there are sporadic case reports on local and systemic side effects seen with hyaluronic acid injections.<sup>[27,28]</sup>

One of the limitations of our study is the absence of randomization. The patients were enrolled from the population of two different clinics that had already been using one of the two treatment modalities. Other shortcomings include its retrospective design, small sample sizes, and the relatively short follow-up period. Nonetheless, both the number of patients and follow-up period were comparable with those of relevant studies, and suggest that our data were adequate to derive conclusions.

We suggest that both treatment methods are non-invasive, may be helpful in prolonging time to surgical treatment, and are convenient for patients who do not have an indication for surgery, have poor general health status that does not allow surgery, and for patients who refuse surgical treatment. As there is no previous study comparing these two methods, we believe that our study would provoke subsequent studies

In conclusion, similar clinical results obtained from the two treatment groups, potential complica-

tions and risks and high cost of intra-articular hyaluronic acid injections make medical mud therapy an effective conservative treatment alternative for stage 2-3 osteoarthritis, with no complication risk and a low cost profile. However, comparative, prospective, and randomized studies of both treatment modalities are required with larger patient numbers and mid- and long-term results.

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