Effects of mud pack therapy on patients with knee osteoarthritis. A randomized controlled clinical trial

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Abstract

Objective: To analyse the effects of mud-pack therapy on perceived pain, functional capacity, severity of the condition and consumption of drugs in people diagnosed with knee osteoarthritis against a control group that continues its daily pharmacological treatment.

Methods: Simple-blinded randomized controlled clinical trial. The sample (n=121) was divided randomly in an intervention group with 61 subjects (69.13±5.60 years) and a control group with 60 subjects (73.08 ± 8.90 years). The intervention group received 11 consecutive sessions of mud-pack therapy on the affected knees during 47 minutes according to the therapeutic treatment described. The control group did not receive any therapy and continued with its daily medication. The sample was assessed before and after with manual goniometry (Lafayette®,USA), digital spring scale (MICROFET 3®), perceived pain was measured through a Visual Analogue Scale (*VAS*), functional capacity through the *WOMAC* questionnaire and finally, the consumption of drugs was registered, establishing a signification level of $p \leq 0.05$. The data was analysed using the SPSS 19.0.

Results: There are statistically significant differences ($p \leq 0.05$) between the pre and post test in all the parameters. Pain which was assessed by the two scales (*VAS, WOMAC*) along with joint stiffness and functional capacity obtained a superior effect size than the rest.

Conclusion: Mud-pack therapy can be considered as an alternative therapy in the improvement of pain and functionality in patients with knee osteoarthritis, reducing the consumption of drugs.

Key words: Knee Osteoarthritis, Arthralgia, Rheumatic Diseases, Mud Therapy, Randomized Clinical Trial

Efectos de la Peloterapia en pacientes con osteoartritis de rodilla. Un ensayo clínico aleatorio controlado

Resumen
Objective: Analizar los efectos de la peloterapia en la percepción del dolor, la capacidad funcional, la gravedad de la enfermedad y el consumo de medicamentos en personas con diagnóstico de osteoartritis de la rodilla contra un grupo de control que continúa con su tratamiento farmacológico diario.
Métodos: Simple ciego, ensayo clínico aleatorizado controlado. La muestra (n = 121) se dividió al azar en un grupo de intervención con 61 sujetos (69,13 ± 5,60 años) y un grupo control de 60 sujetos (73,08 ± 8,90 años). El grupo de intervención recibió 11 sesiones consecutivas de peloterapia en las rodillas afectadas durante 47 minutos de acuerdo con el tratamiento terapéutico descrito. El grupo control no recibió ningún tratamiento y continuó con su medicación diaria. La muestra se evaluó antes y después de goniometría manual (Lafayette ®, EE.UU.), balanza digital primavera (MICROFET 3 ®), la percepción del dolor se midió mediante la Escala Visual Analógica (*EVA*), la capacidad funcional a través del cuestionario *WOMAC* y, por último, se ha registrado el consumo de medicamento. Se ha establecido un nivel de significación de $p \leq 0,05$. Los datos fueron analizados mediante el SPSS 19,0 software.
Resultados: Existen diferencias estadísticamente significativas ($p \leq 0,05$) entre el pre y post test en todos los parámetros. El dolor que fue evaluado por las dos escalas (*EVA, WOMAC*), junto con rigidez en las articulaciones y la capacidad funcional obteniendo una magnitud del efecto superior que el resto.
Conclusión: La peloterapia puede ser considerada como una terapia alternativa en la mejoría del dolor y funcionalidad en los pacientes con osteoartritis de la rodilla, reduciendo el consumo de medicamentos.

Palabras clave: Artrosis de Rodilla, Artralgias, Enfermedades Reumáticas, Fangoterapia, Ensayo Clínico Aleatorizado

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INTRODUCTION

Mud-pack therapy is defined as a therapeutic application of natural products containing a mix of mineral or mineral-medicinal water (including seawater or salt water from lakes) with organic or inorganic compounds resulting from geological, biological or even both processes, used in the form of a wrap or a bath[1]. Mud-pack

therapy has been widely used since ancient times as an effective therapy in diverse rheumatic illnesses[2-10] such as neuralgias or skin problems like acne, seborrhea or psoriasis[11].

Currently, scientific studies have observed changes in the enzymatic and molecular action mechanisms after its application, like the reduction in TNF-α, IL-1β, IL-1, IL-6, PGE2 and LTB4 plasma[12-15], responsible for pain relief, improvement of inflammatory process and increase in the synthesis of noradrenalin, cortisol, betaendorphins and insulin growth factor due to the thermal stress provoked by mud therapy[16]. Other studies have shown as well stimulation in chondrocyte metabolism producing a protective effect on articular cartilage after a treatment cycle of mud-pack therapy[11-17]. Further studies affirm its influence on antioxidant reactions inhibiting free radicals[18-19].

Diverse studies have analysed the effectiveness of mud-packs on knee osteoarthritis (OA) showing improvements on perceived pain, functional capacity or quality of life[20-26].

An increase in an active ageing population[27] has led to a high prevalence in disability through osteoarticular conditions[28]. The knee joint is the most frequently affected, generating enormous expenditure on sources concentrated to attending the pathology[29]. In this way, numerous studies have analysed and compared the effectiveness of balneotherapeutic techniques against other programs and techniques of short and medium term intervention[8-30-31-32-33]. Among them, the mud-pack therapy was compared to pharmacological treatment[12-25-34] and other physical rehabilitation techniques[24-32-35], showing more effectiveness by the mud-pack therapy. Notwithstanding, the effects produced by this technique are usually hidden as it is frequently associated with other techniques within balneotherapeutic procedures[10].

Bearing in mind the need to know the clinical effects derived exclusively from the application of mud therapy, the main objective of this randomized controlled clinical trial and single-blind study was to know the effects derived from this treatment technique on perceived pain, joint functional capacity (range of movement and muscle strength) degree of severity of the condition and drugs consumption in people diagnosed with knee OA.

MATERIALS AND METHODS

Patient selection

A total of 136 patients with knee OA participated voluntarily in the study. Regarding the inclusion criteria established, the subjects had to be in a 65-80 age range and to be diagnosed with OA according to the criteria of the American College of Rheumatology[36]. Those patients who had partial or total knee prosthesis, those that received physiotherapy in the last two weeks or intraarticular injections in the last 6

months and those whose cognitive state made data collection difficult, were excluded.

The final sample was 121 people (80 women and 31 men). It was composed of patients who received treatment in the Raposo Spa (Extremadura, Spain) through the Social Thermalism Program offered by the "Instituto de mayores y servicios socials" or IMSERSO (Elderly and Social Services Institute) from the Spanish government and those diagnosed with knee OA from the Primary Health Care Centre 'La Mejostilla' (Cáceres, Spain) from the National Health System. The social demographic characteristics are shown in Table 1.

Table 1 - Sociodemographic characteristics of the sample.

	Group I (Intervention) (n=61)	Group II (Control) (n=60)
Male	17	14
Female	44	46
Age (years)[a]	69.13 (5.60)	73.08 (8.90)
Body mass (kg)[a]	78,01 (13,93)	74,03 (12,09)
Height[a]	160,18 (8,79)	163,12 (8,24)
BMI (Kg/cm^2)[a]	30,38 (4,59)	27,87 (4,41)
OA bilateral (%)	55,73	67,85
OA right (%)	19,67	17,85
OA left (%)	24,59	14,28
Consumed drugs		
Analgesics	12/30 (39,5%)	28/60 (46,6%)
NSAIDs	7/30 (22,47%)	4/60 (5,6%)
SYSADOA	7/30 (23,6%)	12/60 (20%)
Others	4/30 (14,43%)	16/60 (27,8%)

[a] Values are the mean (standard deviation); BMI: Body Mass Index; OA: Knee Osteoarthritis; Consumed drugs: individuals who take medications daily; NSAIDs: non steroidal-anti-inflammatory drugs; SYSADOA: symptomatic slow action drugs for osteoarthritis.

Intervention

The study was approved by the Bioethics committee from Extremadura University and informed consent was obtained from the participants.

The selected patients were assigned to the following groups: group I or intervention group and group II or control group. The intervention group received 11 consecutive sessions of mud-pack therapy following the therapeutic guidelines of the spa. This implies using brushes to apply the mud at a 30º temperature followed by a 30 min drying period in the solarium. Afterwards, the patients receive a mud bath with thermal water during 15 minutes with a 2 minute thermal jet to eliminate the mud. All the sessions were applied by the spa physiotherapists without knowledge of the study's objective. The total length of the intervention was 47 minutes. The mud from the Raposo spa in Spain is obtained directly from a natural spring. The mud obtains its chemical and thermophysical properties appropriate for its application after one month of maturity and at a temperature between 20-30º. It mainly contains calcite, silica, sodium feldspar (albite) and potassium feldspar (orthoclase), and therefore the most frequent inorganic compounds are SiO_2, LOI, Al_2O_3 y Ca O. Its mineral medicinal waters contain high levels of chloride, sodium, calcium and bicarbonate. The water is medium mineralized and emerges at 16,3º. It also contains chloride anions (87,3 mg/L) and bicarbonates (386,3 mg/L) and sodium cation (51,7 mg/L), calcium (133,2 mg/L).

Group II or control group did not receive any intervention as it was considered important to continue with its routine pharmacological treatment during the study.

All the patients were examined and assessed through independent researchers at the spa and the primary Health Centre therefore assuring the control of the study.

Assessments

Once the subjects been assigned and before the intervention started in group I, the main researcher assessed the knee flexion and extension range of movement with the manual goniometer (Lafayette®, USA) and the muscular strength through digital spring scales (MICROFET®) in all patients.

The intensity of perceived pain was measured through the visual analogue scale (VAS). This method assigns a score from 0 (no pain) to 10 (maximum pain)[29]. Functional capacity was measured through the *Western Ontario and McMaster Universities Arthritis Index* (WOMAC) questionnaire[37]. The WOMAC questionnaire contains 24 questions related to pain intensity[4], stiffness[2] and grade of disability[18] and the functionality index score ranges from 0 -96 points. Each question is answered with a Likert type scale of 5 levels which are coded in the following way: None = 0; little = 1; enough =2; much =3; very much =4.

Statistical analysis

A descriptive analysis was carried out on each of the variables, showing mean values and typical deviations. To determine if the sample followed a normal distribution, the Shapiro-Wilks test was used. After determining that the sample was

following a normal distribution, the obtained values for each variable were compared between a pre and post test through a t-student test on paired samples. To compare the obtained effects on the groups (intervention vs control group) after the intervention, an analysis on independent samples was done using the t-students and the Mann-Whitney U test (depending if the sample variances are considered equal or not). Moreover, the effect size was calculated in each intervention through Cohen's d coefficient. A value over 0.8 was considered high, around 0.5 moderate and less than 0.2 was considered low[38]. The level of statistical significance was established with the value of $p<0.05$. The analysis of the data was carried out using the statistics software SPSS version 19.

RESULTS

The mean values of the analysed variables (standard deviation) for the intervention and control groups in the baseline and final assessments are shown in Tables 2 and 3. The patients from the intervention group had statistically significant improvements between the baseline and final assessments ($p<0.05$) in all the analysed variables. In this group we highlight the main differences found between the pre and post-test on perceived pain and functional capacity variables measured with the WOMAC questionnaire.

In the control group, statistically significant improvements were not obtained in any of the variables analysed in the study ($p\geq 0.05$) (Table 2 and 3).

The t-student test showed that there were not statistically significant differences between the two groups before intervention. In the post-test the parametric t-student test and the non-parametric Mann-Whitney U test proved statistically significant differences between the groups ($p\leq 0.05$). All the variables showed differences between the intervention and the control groups except for right and left knee extension range of movement and the muscular strength in the right quadriceps (Table 2).

For the intervention group, the effect size was calculated through Cohen's coefficient, showing a mid-high effect in all the parameters, highlighting perceived pain in the two scales which analyse this aspect (VAS and WOMAC), joint stiffness and functional capacity (Table 3).

DISCUSSION

The main objective of this study was to find out the effects of natural mud-pack therapy from the Raposo Spa stream on perceived pain, joint functional capacity (range of movement and muscle strength), severity of the condition and drug use on people diagnosed with knee OA.

Table 2 - Results of the statistical comparison between groups regarding the variables range of movement and muscle strenght after 11 days of intervention.

	Baseline	Final	Mean differences (95% CI)	*d*
ROM(°)				
Right knee flexion *				
Group I	108,62 (8,05)	112,18(7,24)[b,d]	0,04(0,01;0,06)	,52
Grupo II	103,26 (9,63)	103,22 (9,71)		
Left knee flexion †				
Group I	109,04 (8,20)	112,08 (8,46)[b,d]	0,03 (0,01;0,04)	,67
Group II	103,93 (10,04)	104,28(9,82)		
Right knee extension *				
Group I	5,58 (4,46)	4,42 (3,15)[a,e]	0,27 (1,24;1,79)	,56
Group II	4,93 (3,02)	4,69 (3,26)		
Left knee extension †				
Group I	5,91 (5,65)	4,67 (3,83)[a,e]	0,54 (1,26;2,34)	,51
Group II	5,41 (3,84)	5,21 (3,63)		
Muscular strength (N)				
Right quadriceps *				
Group I	58,79 (15,90)	58,79 (15,90)[b,e]	7,61 (2,70;17,90)	,77
Grupo II	62,39 (12,16)	62,29 (13,10)		
Left quadriceps †				
Group I	58,05 (13,07)	58,05 (13,07)[b,e]	11,96(2,84;21,08)	,90
Grupo II	61,17 (13,96)	61,45 (14,00)		
Right hamstring †				
Group I	210,22 (129,48)	210,22 (129,48)[b,d]	112,33(55,21;169,15)	,75
Group II	154,89 (73,31)	158,62 (73,25)		
Left hamstring †				
Group I	180,40 (110,15)	180,40 (110,15)[b,d]	84,47(36,79;132,16)	,62
Group II	147,49 (59,10)	149,24 (59,72)		

ROM: Range of movement, degree (°), min= minimum, max= maximum. WOMAC: Western Ontario and McMaster Universities Arthritis Index. The values showed are the initial and final mean values (standard deviation) obtainedbefore and after 11 days of intervention and the difference between groups as mean value (95% confidence interval), *d*: Cohen's *d* coefficient.

[a]: p≤0,05 grupo I vs basal

[b]: p≤0,001 grupo I vs basal

[c]: p≤0,05 entre grupos

[d]: p≤0,001 entre grupos

[e]: p≥0,05 entre grupos

* Test t-Student; † Test U de Mann-Whitney

The results showed statistically significant improvements in all the analysed variables in the intervention group, with a mid-high effect size on all the items valued.

Until recently, balneotherapy had been a procedure used in the management of rheumatic illnesses based on empiricism and intuitive reasoning[39]. Currently studies such as Pnevmatikatos et al[6], Cantarini et al[8], Fraioli et al[21] o Balint et al [22] analyse

the therapeutic effect of the mud-packs in different thermal centres. With the need to know whether its application is more effective than other treatment techniques, some studies have carried out comparisons between the effects of mud-pack treatment and other techniques, like pharmacological therapy[12-25-34] or magnetic fields[8-24]. Others, like this present study, compare an intervention group with a control group[13-21-40].

Table 3 - Results of the statistical comparison between groups regarding the questions analised of the WOMAC questionnaire and perceived pain after 11 days of intervention.

	Baseline	Final	Mean differences (95% CI)	*d*
WOMAC				
Pain *				
Group I	8,29(4,29)	4,49(3,48)[b,d]	0,53(0,36;0,70)	1,10
Group II	7,00 (4,55)	6,85 (4,42)		
Stiffness †				
Group I	2,81 (2,51)	1,36 (2,02)[b;c]	0,90 (0,02;1,83)	0,82
Group II	2,42 (2,22)	2,33(2,19)		
Functional Capacity *				
Group I	21,40(12,51)	17,08(12,63)[b;d]	10,90(4,60;17,19)	0,99
Group II	27,52 (16,85)	27,98 (16,19)		
Perceived Pain				
*VAS**				
Group I	4,53 (2,32)	2,55 (2,33)[b,d]	2,39 (1,34;3,46)	0,96
Group II	5,33 (2,48)	5,20 (2,24)		

The values showed are the initial and final mean values (standard deviation) obtained before and after 11 days of intervention and the diference between groups as mean value (95% confidence interval), *d*: Cohen's *d* coefficient.

[a]: p≤0,05 group I vs basal

[b]: p≤0,001 group I vs basal

[c]: p≤0,05 among groups

[d]: p≤0,001 among groups

* Test t-Student; † Test U de Mann-Whitney

The intensity of perceived pain has been the most researched symptom after applying therapy through mud-packs on knee OA. The results obtained in the studies as well as in this present work are very positive. Previous studies showed an improvement after isolated application[3-12-21-31-32-40] and in combination with techniques like thermal baths[13-34] or physical exercise[35] showing its efficacy in the management of pain related to OA.

For the range of movement variable, a significant improvement was noted after the 11 daily sessions of mud-packs treatment, demonstrating differences in the flexion range of movement compared with the control group. We agree with recent studies such as Mika et al[35] o Fraioli et al[21], although in the latter the length of

treatment was extended to three cycles during a year. The results from quadriceps and hamstrings muscle strength showed statistically significant differences between the baseline and final assessments and between the intervention and the control group except for muscle strength in the right quadriceps. We did not find any study that analyses the influence of mud-packs on muscular strength, therefore this present study could be considered as the first.

The degree of severity of the pathology measured through the WOMAC has been previously analysed by other recent studies[17-25] in which, after applying the same frequency and number of sessions that in the present study, improvements very similar to our own were obtained. The results achieved showed significant differences between the baseline and final assessments as well as in comparison with the control group. The joint stiffness variable obtained the best results, being one symptom that responds well to mud-pack therapy treatment[41]. Studies with a methodological design similar to our own[25-40] also obtained improvements in the WOMAC questionnaire, such as others which use it to compare mud-pack therapy with other thermo therapeutic procedures[32].

In spite of the clinical and biochemical and molecular marker results along with the studies carried out, the effects of spas on rheumatic afflictions are still considered controversial[10]. Mainly due to the lack of consensus on some application parameters such as temperature and time ranging from 47º C during 20 minutes[21], 46º C during 15-20 minutes[24], 45º C during 30 minutes[40- 42] or 42º C during 15-20 minutes[31-32-35].

Other controversial aspects are the external factors in thermal centres, where nutritional habits and daily activities change, as they can decisively influence the evolution of the patient. In this sense, Flusser et al[3] show that therapy with mud-packs applied at the patients' home is as effective on perceived pain and on the values of degree of severity.

One of the limitations of this study was not being able to establish follow-up periods due to the difficulty to engage again the patients admitted to the study. We agree with Fioravanti et al.[17] on the need for future studies that establish follow-up periods with the end to identify an effective therapeutic approach to ensure a mid-long term improvement of the symptoms[8- 21].

Definitely, mud-pack therapy on patients diagnosed with knee OA obtains immediate effects on the symptomatic management of the illness, therefore constructing an alternative treatment to pharmacological treatment. Studies which establish homogeneous application criteria which allow for scientific evidence of this technique would be needed.

REFERENCES

1. Societé Internacionale d'Hydrologie Médicale. Decisions prises au cours de la Session 1949. Proceedings of the IV e Conférence Scientifique Internationale de Dax; 1949 Oct 13-16; Dax, France. Imp. Larrat, 1949.156-7.
2. Van Tubergen A, Landewe R, van der Heijde D, Hidding A, Wolter N, Asscher M et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum.2001, 45:430-38.
3. Flusser, D., Abu-Shakra, M., Friger, M., Codish, S., Sukenik, S. Therapy with mud compresses for knee osteoarthritis: Comparison of natural mud preparations with mineral-depleted mud. J Clin Rheumatol. 2002; 8(4):197-203.
4. Kovacs I, Bender T. The therapeutic effects of Cserkeszölö thermal water in osteoarthritis of the knee: a double blind, controlled, follow-up study. Rheumatol Int. 2002; 21:218–21.
5. Balogh Z, Ordogh J, Gász A, Német L, Bender T. Effectiveness of balneotherapy in chronic low back pain-A randomized single-blind controlled follow-up study. Forschende Komplementarmedizin und Klassische Naturheilkunde. 2005; 12(4):196-201.
6. Pnevmatikatos S, Tzougrana C, Papadas T, Kintziou H. The efficacy of sea mud compresses from missolonghi lagoon as a treatment for osteoarthritis symptoms on neck, shoulder, arm, lower back, hip and knee joints. Epitheorese Klinikes Farmakologias kai Farmakokinetikes.2011; 29 (2):159-68.
7. Codish S, Abu-Shakra M, Flusser D, Friger M, Sukenik S. Mud compress therapy for the hands of patients with rheumatoid arthritis. Rheumatol Int. 2005; 25:49-54.
8. Cantarini L, Leo G, Giannitti C, Cevenini G, Barberini P, Fioravanti A. Therapeutic effect of spa therapy and short wave therapy in knee osteoarthritis: a randomized, single blind, controlled trial. Rheumatol Int. 2007; 27:523–9.
9. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Knipschild PG. Balneotherapy for rheumatoid arthritis and osteoarthritis. Cochrane Database of Syst Rev 2000; (2):CD000518.
10. Fioravanti A, Perpignano G, Tirri G, Cardinale G, Gianniti C, Lanza CA et al. Effects of mud-bath treatment on fibromyalgia patients: a randomized clinical trial. Rheumatol Int. 2007; 27:1157-61.
11. Bellometti S, Giannini S, Sartori L, Crepaldi G. Cytocine levels in osteoarthritis patients undergoing mud bath therapy. Int J Clin Pharm Res; 1997; XVII (4):149–53.
12. Bostan B, Sen U, Günes T, Sahín SA, Sen C, Erdem M et al. Comparison of intra-articular hyaluronic acid injections and mud-pack therapy in the treatment of knee osteoarthritis. Acta Orthop Traumatol Turc. 2010; 44 (1):42-7.

13. Benedetti S, Canino C, Tonti G, Medda V, Calcaterra P, Nappi G et al. Biomarkers of oxidation, inflammation and cartilage degradation in osteoarthritis patients undergoing sulfur-based spa therapies. Clin Biochem. 2010; 43: 973-78.
14. Bellometti S, Galzigna L, Richelmi P, Gregotti C, Berté F. Both serum receptors of tumor necrosis factor are influenced by mud pack treatment in osteoarthrotic patients. Int J Tissue React.2002; 24:57–64.
15. Bellometti S, Galzigna L. Serum levels of a prostaglandin and a leukotriene after thermal mud pack therapy. J Investig Med.1998; 46:140–5.
16. Cozzi F, Lazzarin P, Todesco S, Cima L. Hypothalamic-pituitary-adrenal axis dysregulation in healthy subjects undergoing mud-baths applications. Arthritis Rheum. 1995;38(5):724-6.
17. Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M. Mechanisms of action of spa therapies in rheumatic disease what scientific evidence is there? Rheumatol Int.2011; 31:1-8.
18. Bellometti S, Cecchettin M, Lalli A, Galzigna L. Mud pack treatment increases serum antioxidant defenses in osteoarthrosic patients. Biomed Pharmacother 1996; 50:37.
19. Bellometti S, Richelmi P, Tassoni T, Berte F. Production of matrix metalloproteinases and their inhibitors in osteoarthritic patients undergoing mud bath therapy. Int J Clin Pharmacol Res 2005; 25 (2):77-94.
20. Espejo Antúnez L. Estudio comparativo de dos tratamientos balnearios, hidrocinesiterapia versus peloides aplicados en pacientes diagnosticados de artrosis de rodilla. [Doctoral Thesis]. Badajoz. University of Extremadura; 2012.
21. Fraioli A, Serio A, Mennuni G, Ceccarelli F, Petraccia L, Fontana M et al. A study on the efficacy of treatment with mud packs and bathswith Sillene mineral water (Chianciano Spa Italy) in patients suffering from knee osteoarthritis. Rheumatol Int.2011; 31(10):1333-40.
22. Bálint GP, Buchanan WW, Ádám A, Ratkó I, Poór L, Bálint PV et al. The effect of the termal mineral wáter of Nagybaracska on patients with knee joint osteoarthritis- a double blind study. Clin Rheumatol. 2007; 26: 890-4.
23. Ceccarelli F, Perricone C, Alessandri C, Modesti M, Iagnocco A, Croia C et al. Exploratory data analysis on the effects of non pharmacological treatment for knee osteoarthritis. Clin Exp Rheumatol. 2010; 28(2):250-3.
24. Fioravanti A, Bisogno S, Nerucci F, Cicero MR, Locunsolo S, Marcolongo R. Evaluation of the efficacy and tolerance of radioactive fangotherapy in gonarthrosis. Comparative study versus short wave therapy. Minerva Med. 2000; 91(11-12):291-8.
25. Fioravanti A, Iacoponi F, Bellisai B, Cantarini L, Galeazzi M. Short- and long-term effects of spa therapy in knee osteoarthritis. Am J Phys Med Rehabil. 2010; 89(2):125-32.

26. Fioravanti A., Giannitti, C., Bellisai, B., Iacoponi, F., Galeazzi, M. Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. Int J Biometeorol. 2012; 56(4):583-90.
27. White Paper on Active Ageing. Ministry of Health and Social Policy. IMSERSO. Madrid. 2010.
28. National Health Survey (NHS 2006). National Institute of Statistics. Ministry of Health and Social Policy.
29. Cimmino MA, Sarzi-Puttini P, Scarpa R, Caporali R, Parazzini F, Zaninelli A et al. Clinical presentation of osteoarthritis in general practice: determinants of pain in Italian patients in the AMICA study. Semin Arthritis Rheum. 2005; 35 (1 Suppl 1):17-23.
30. Karagülle MZ, Karagülle M. Balneotherapy and spa therapy of rheumatic disease in Turkey: a systematic review. Forch Komplementarmed Klass Naturheilkd. 2004;1:33-41.
31. Vath M, Birkenfeldt R, Ubner M. An evaluation of the effect of differing lengths of spa therapy upon patients with osteoarthritis (OA).Complement Ther Clin Pract. 2008; 14:60-4.
32. Evcik D, Kavuncu V, Yeter A, Yigit I. The efficacy of balneotherapy and mud-pack therapy in patients with knee osteoarthritis. Joint Bone Spine 2007; 74: 60-5.
33. Yilmaz B, Goktepe AS, Alaca R, Mohur H, Kayar AH. Comparison of a generic and a disease specific quality of life scale to assess a comprehensive spa therapy program for knee osteoarthritis. Joint Bone Spine. 2004; 71(6):563-6.
34. Forestier R, Desfour H, Tessier JM, Françon A, Foote AM, Genty C et al. Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis. 2010; 69(14):660–65.
35. Mika A, Dabal E, Mika L. The efficacy of mud pack treatment on ailments related to gonarthrosis. Rehabilitacja Medyczna. 2006; 10(1): 49-54.
36. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheumatism 1986; 29:1039-49.
37. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J. Validation study of WOMAC: a health status instrument for measuring clinically-important patient-relevant outcomes following total hip or Knee arthroplasty in osteoarthritis. J Orthop Rheumatol. 1988;1:95-108.
38. Cohen, J. Statistical power analysis for the behavioral science (2nd ed).1998. Hillsdale, NJ: Lawrence Erlbaum Associates.
39. Bagnato G, De Filippis LG, Morgante S, Morgante ML, Farina G, Caliri A et al. Clinical improvement and serum amino acid levels after mud-bath therapy. Int J Clin Pharmacol Res. 2004; 24(2-3):39-47.

40. Odabasi E, Turan M, Erdem H, Pay S, Gulec M, Karagülle MZ.The Effect of Mud Pack Treatment in Knee Osteoarthritis. Turk J Rheumatol. 2009; 24:72-6.
41. Sukenik S, Flusser D, Codish S, Abu-Shakra M. Balneotherapy at the Dead Sea area for Knee osteoarthritis. Isr Med Assoc J. 1999; 1:83-85.
42. Bender T, Karagülle Z, Bálint GP, Gutenbrunner C, Bálint PV, Sukenik S. Hidrotherapy, balneotherapy and spa treatment in pain management. Rheumatol Int .2005; 25:220-24.