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Original Research

Comparison of the pain-killing effects of leech therapy versus physiotherapy in patients with knee osteoarthritis: A double-blind randomized clinical trial

Seyed Saman Talebi[1], Ahmad Tahamoli Roudsari[1,*], Seyed Mohammad Zolhavarieh[2], Lobat Majidi[3], Hossein Ghiasi[4], Jalal Poorolajal[5], Seyed Alireza Vafaei[4]

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[1]*Department of Internal Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

[2]*Department of Anesthesiology, School of Medicine, Urology & Nephrology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran*

[3]*Department of Physical Medicine and Rehabilitation, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

[4]*Hamadan University of Medical Sciences, Hamadan, Iran*

[5]*Modeling of Noncommunicable Diseases Research Center, Hamadan University of Medical Sciences, Hamadan, Iran*

Correspondence

Ahmad Tahamoli Roudsari, Department of Internal Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

Email: ahmad.tahamoli@yahoo.com

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ABSTRACT

Background: Knee osteoarthritis is a debilitating disease that affects a large proportion of the elderly population. Treatments for this disease are mostly based on symptomatic management. The primary treatments are physiotherapy, which is associated with high costs, and nonsteroidal anti-inflammatory drugs (NSAIDs), which have serious side effects, including gastrointestinal bleeding, renal failure, and cardiovascular complications. This study aimed to assess the effects of leech therapy versus physiotherapy as a noninvasive method in the treatment of knee osteoarthritis. **Methods:** This double-blind randomized clinical trial was performed on 98 patients with osteoarthritis of the knee. The patients were randomly divided into two groups: leech therapy or physiotherapy. The analgesic effects and recovery of the patients were assessed using the KOOS questionnaire 90 days after the beginning of the study. Student's t-test, the Wilcoxon test, and the Mann–Whitney U test were used for comparisons between the two groups. **Results:** The mean age of the patients was 61.03 ± 10.99 years. The KOOS ADL and KOOS sport/recreational activities decreased significantly in the leech therapy group ($P < 0.05$). Additionally, the mean KOOS QOL after treatment was significantly lower than it was before treatment ($P < 0.001$). In the physiotherapy group, the KOOS pain score increased significantly after treatment (25.86 ± 18.77 *vs.* 31.60 ± 11.71; $P = 0.008$). The KOOS ADL score also showed a significant increase (24.59 ± 18.55 *vs.* 35.74 ± 15.83; $P < 0.001$). In addition, the median KOOS sport/recreational activities and KOOS QOL increased significantly in the physiotherapy group ($P < 0.05$). All of the factors in the physiotherapy group had significantly better prognoses than those in the leech salivary therapy group ($P < 0.05$). **Conclusion:** This study failed to identify any therapeutic or remedial effects of leech therapy on pain and symptoms in the symptomatic treatment of knee osteoarthritis. Future studies using more leeches and examining the therapeutic effects over a shorter period of time are recommended to more fully evaluate the effectiveness of leech therapy.

Key words: Clinical trial, Knee joint, Leech therapy, Osteoarthritis

INTRODUCTION

Osteoarthritis is a chronic, progressive, noninflammatory disease that destroys articular cartilage and forms marginal osteophytes in the bone beneath the cartilage[1]. Osteoarthritis is the most common joint disease in humans[2]; 80% of people over 79 years of age suffer from this disorder[3]. The development of society, along with an increase in obesity and an aging population, has increased the prevalence of this disease. Thus, the risk of developing osteoarthritsis is significantly higher after the age of 45[4]. In general, factors such as age, obesity, occupation, trauma, hereditary factors, and structural disorders in the lower extremities, such as meniscectomy, can predispose a patient to osteoarthritis[1]. Among these factors, age is the greatest risk factor[5,6]. Statistics in our country indicate that the prevalence of osteoarthritis is 26% in rural areas and 25% in urban areas[7].

The most common site of osteoarthritis is the small joints of the hand[8]. Other common areas are the large joints because they bear more body weight and are prone to mechanical damage[9]. The knee joint is particularly susceptible to mechanical damage and osteoarthritis compared to other joints. Thus, it can be considered a principal cause of disability in old age in developed countries[10–12]. The prevalence of knee osteoarthritis in Iran has been reported to range from 9.76% to 19.3%. These statistics confirm the high prevalence of osteoarthritis of the knee in Iran, which can be attributed to increasing average age, lifestyle changes, and bad habits[7].

The knee is one of the most important joints in the body, and since it is the largest hinged synovial joint

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in the body, it plays a vital role in movement and weight bearing. Additionally, due to its sensitive position, knee dysfunction has a tremendous impact on a person's life. In addition, the position of the knee joint and its weight make it susceptible to trauma and various diseases. Environmental factors, lifestyle, and manner of use play roles in causing different diseases. Various factors, such as race, trauma, environment, and personal traits, are involved in predisposing a person to osteoarthristis of the knee. The goal of treatment in osteoarthritis is to alleviate pain, improve function, and preserve joint mobility [13,14]. Surgical treatments, including arthrodesis and arthroplasty, are expensive and are not used as primary interventions [15]. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as analgesics. However, long-term oral administration of NSAIDs has side effects, including gastrointestinal bleeding and related ulcers [16]. The only definitive treatment for this disease is joint replacement with implanted prostheses. However, this treatment is usually recommended in the late stages of the disease because it is invasive and expensive. In the early stages of knee osteoarthritis, patients usually undergo physiotherapy, which can include transcutaneous electrical nerve stimulation (TENS), as well as symptomatic therapies, such as NSAIDs, to reduce pain. However, physiotherapy imposes huge costs on the patient, and NSAIDs are associated with complications, such as gastrointestinal bleeding. For this reason, the current approach is to use conservative treatments and certain traditional remedies. In this regard, leech saliva therapy may have the potential to improve the symptoms of knee osteoarthritis [17]. The medicinal peptides in leech saliva contain analgesics, vasodilators, bacteriostatics, anti-inflammatories, anticoagulants, and antiedematous factors that contribute to healing [18,19].

Thus, this study was designed to compare the effects of leech therapy versus physiotherapy on the Knee Injury and Osteoarthritis Outcome Score (KOOS) in patients with knee osteoarthritis.

METHODS

This was a double-blind randomized clinical trial that was performed with 98 patients referred to the Rheumatology and General wards of Shahid Beheshti Hospital and Mobasher-e-Kashani Clinic in Hamedan City, Iran, from July 2017 to November 2018. The patients presented with unilateral or bilateral knee pain and were in grade 2 or higher according to the Kellgren-Lawrence (KL) osteoarthritis severity classification.

According to the American College of Rheumatology criteria, a patient with osteoarthritis of the knee should have at least three of the following six symptoms: 1) Age over 50 years; 2) Morning dryness less than 30 minutes; 3) Crepitus in active knee movements; 4) Bone sensitivity; 5) Bone enlargement; and 6) Lack of heat to the touch. The above criteria, along with pain, an erythrocyte sedimentation rate (ESR) below 40, and a negative rheumatoid factor, were necessary conditions for the patient to be enrolled in this study.

The radiologic criteria were classified as follows: Grade 0: no radiographic features of osteoarthritis; Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping; Grade 2: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph; Grade 3: multiple osteophytes, definite JSN, sclerosis, and possible bony deformity; and Grade 4: large osteophytes, marked JSN, severe sclerosis, and definite bony deformity.

The exclusion criteria were as follows: 1) Age less than 50 years; 2) Positive rheumatoid factor; 3) ESR above 40; 4) Previous history of intra-articular injections in the last six months; 5) Any hematological disorders including coagulopathy; 6) Injection phobia; 7) Morning dryness more than 30 minutes; 8) History of severe knee trauma; and 9) Severe knee deformity.

After entering the study and completing the informed consent form, the patients underwent conventional and standard oral treatment of knee osteoarthritis, which consisted of NSAIDs with an anti-inflammatory dose or prednisolone for two weeks plus Triple Flex or piascledine, along with general health recommendations (weight loss and proper sitting posture). Then, the patients were randomly divided into two groups: leech therapy or physiotherapy. The analgesic effects and recovery of patients over a short period of time (three months) were assessed using the KOOS questionnaire.

The KOOS questionnaire was developed to assess the short- and long-term outcomes of a knee injury. The questionnaire consists of 42 items in five areas: pain, symptoms, performance in daily activities, performance in sports and recreational activities, and quality of life related to knee function [20].

In the leech treatment group, the patients began by completing the KOOS questionnaire. Five leeches for each patient of the *Medicinalis* breed that were completely germ-free were purchased from the Faculty of Traditional Medicine of Tehran University of Medical Sciences by a person who was unaware of the severity of the disease. The leeches were placed

in a container until they started working. The treatment area was thoroughly washed with water first and slightly stimulated to become red and bloody. The leeches were applied for 30 minutes and then separated from the blood collection site by pouring a solution of NaCl. The leeches were removed and discarded, and the treatment area was washed and bandaged. New leeches were used for each patient in each session.

The patients in the physiotherapy treatment group completed the KOOS questionnaire and then underwent 10 sessions of conventional osteoarthritis physiotherapy. Each physiotherapy session lasted 75 minutes.

The patients in both groups were trained in knee strengthening exercises after their respective interventions. They were asked to perform the exercises at home three times daily for 10 minutes each session until the end of the study. All of the patients were also trained and encouraged to lose weight and change their lifestyles. Three months after the intervention, the patients were called to the Rheumatology Clinic of Shahid Beheshti Hospital for a revisit. During this visit, the KOOS questionnaire was completed by the patients for a second time.

Clinical symptoms, pain, and stiffness of the knee joint impact a patient's daily performance, ability to play sports, and entertainment activities. The leech therapist, physiotherapist, and patients were unaware of the severity of the knee osteoarthritis. Finally, the quality of life of each patient at the beginning (before physiotherapy and leech therapy) and three months after the intervention was reviewed and compared based on the KOOS standard questionnaire.

Statistical analysis

For statistical analysis, the results are presented as mean ± standard deviation (SD) for quantitative variables and summarized by frequency (percentage) for categorical variables. Continuous variables were compared using Student's t-test or the Wilcoxon test whenever the data did not appear to have a normal distribution or when the assumption of equal variances was violated across the study groups. Additionally, changes before and after treatment in the physiotherapy and leech therapy groups were compared using the Mann–Whitney U test. P-values of ≤ 0.05 were considered statistically significant. IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis.

Ethical considerations

The patients were informed of their rights as well as the risks and benefits of participating in this clinical trial. Signed informed consent was obtained from each participant. They were informed about the random allocation procedure, and they were aware that they would be assigned to an experiment or control group. Ethical approval was obtained from the institutional review board of Hamadan University of Medical Sciences (UMSHA), and the study was conducted in accordance with the Declaration of Helsinki. Ethics committee reference number: IR.UMSHA.REC.1395.597. Approval date: 2017-03-04. IRCT ID: IRCT201703239014N153.

RESULTS

One hundred and eighteen patients with knee osteoarthritis were evaluated for this study. Of these, 11 patients did not meet the inclusion criteria, and seven did not want to participate in the study. Thus, 100 patients were included in the treatment phase of the study. The patients were randomly assigned to two groups (50 patients in the intervention group and 50 patients in the control group). One patient was lost to follow-up in each group, so 49 patients from each group were ultimately entered into the final analysis (**Figure 1**).

The mean age of the patients was 61.03 ± 10.99 years (61.44 ± 8.97 years in the leech therapy group and 60.61 ± 12.77 years in the physiotherapy group, P = 0.71). Only four (4%) patients were male, while the rest were female.

As shown in **Table 1**, in the leech therapy group, the decreases in KOOS pain and KOOS symptoms after the intervention were not statistically significant (21.04 ± 12.43 *vs.* 20.78 ± 10.16, P = 0.7 and 25.44 ± 10.74 *vs.* 24.82 ± 9.78, P = 0.73, respectively). KOOS activities of daily living (ADL) decreased significantly (23.11 ± 12.79 *vs.* 21.14 ± 10.62; P = 0.03). The median KOOS sport/recreational activities also decreased significantly. Additionally, the mean KOOS quality of life (QOL) after the treatment was significantly lower than it was before treatment (P < 0.001). In the physiotherapy group, KOOS pain increased significantly after treatment (25.86 ± 18.77 vs. 31.60 ± 11.71; P = 0.008). KOOS ADL showed a significant increase (24.59 ± 18.55 vs. 35.74 ± 15.83; P < 0.001). In addition, the median KOOS sport/recreational activities and KOOS QOL increased significantly (P < 0.05). The results of comparing the changes in the studied factors between the physiotherapy and leech therapy groups demonstrated that all of the factors in the physiotherapy group were significantly higher than those in the leech therapy group (P < 0.05).

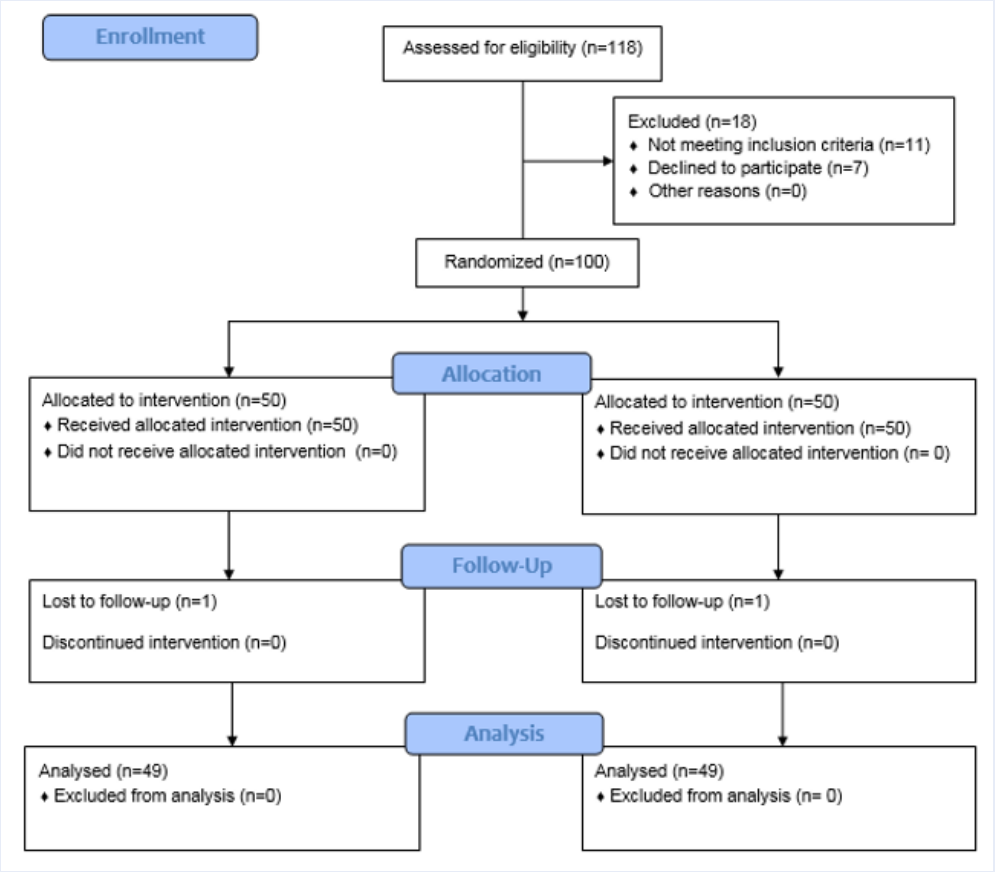

Figure 1: **Flowchart on the allocation of patients to the studied groups.**

DISCUSSION

The results of this study indicate that there was a significant improvement in all factors of the KOOS questionnaire, including KOOS pain, KOOS symptoms, KOOS ADL, KOOS sport/recreational activities, and KOOS QOL, in the physiotherapy group. Thus, physiotherapy seemed to improve pain, symptoms, quality of life, and recreational activities. Conversely, leech therapy had a slight but nonsignificant reduction in KOOS pain and KOOS symptoms. Additionally, the regressive course of KOOS ADL, KOOS sport/recreational activities, and KOOS QOL in the leech therapy group continued significantly. It appeared that leech therapy for one session of 30 minutes could partially delay the worsening of a patient's pain and symptoms. However, the deteriorating course of the patient's quality of life and performance continued in these patients.

Shiffa *et al.* examined the effect of leech therapy in knee osteoarthritis patients on improving symptoms, function, and quality of life according to the KOOS questionnaire. Their results after four and eight weeks showed a significant improvement over both time periods for all factors related to KOOS. In other words, the pain, quality of life, and performance of patients improved significantly. The visual analog scale (VAS) pain scores also improved significantly after four and eight weeks. However, the significant advantage of leech therapy compared to the control group was only observed four weeks after the intervention. It seems that leech therapy may have healing effects only in the short term [21].

Contrary to the results of this study, Michalsen et al. demonstrated that leech therapy can improve joint function, joint dryness, and quality of life. The overall conclusion of their study was that leech therapy seems to be an effective symptomatic treatment for knee osteoarthritis [22]. Additionally, Andereya *et al.* observed an improvement in KOOS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in patients undergoing leech therapy; only the rate of dryness did not show a significant improvement [23]. Furthermore, the benefits of

Table 1: Comparison of KOOS domains in Leech therapy and physiotherapy groups

KOOS domain		Before intervention	After intervention	P-Value
KOOS pain	Leech therapy	21.04 ± 12.43	20.78 ± 10.16	0.79*
	Physiotherapy	25.86 ± 18.77	37.5 ± 15.95	0.004*
P Value***		0.14	< 0.001	-
KOOS symptoms	Leech therapy	25.44 ± 10.74	24.82 ± 9.78	0.43*
	Physiotherapy	26.34 ± 13.04	31.6 ± 11.71	0.008*
P Value***		0.71	0.002	-
KOOS ADL	Leech therapy	23.11 ± 12.79	21.14 ± 10.62	0.029*
	Physiotherapy	24.59 ± 18.55	35.74 ± 15.83	< 0.001*
P Value***		0.65	< 0.001	-
KOOS sports/recreational activities	Leech therapy	-10 (-25, 0)	-15 (-25, 0)	0.001**
	Physiotherapy	-25 (-25, -5)	-15 (-25, 0)	0.002**
P Value***		0.35	0.002	-
KOOS QOL	Leech therapy	-6 (-19, 0)	-25 (-25, -13)	< 0.001**
	Physiotherapy	-13 (-25, 0)	0 (-13, 13)	< 0.001**
P Value***		0.11	< 0.001	-

*t-test, ** Wilcoxon test, *** Mann-Whitney test

leech therapy on knee osteoarthritis symptoms were also observed in studies by Zaidi *et al.* and Stange *et al.*[24,25]. Differences in the study sample sizes and questionnaires used may partially explain this discrepancy with our findings.

Isik *et al.* (2017) examined leech therapy compared with TENS in the treatment of 90 patients with knee osteoarthritis. On day 21, both groups reported significant improvements in VAS scores. Additionally, the comparison of WOMAC scores similarly decreased in the two groups, but the differences were not significant. They concluded that leech therapy relieves symptoms in knee osteoarthritis patients and has a similar effect to TENS[26].

In the case of leech therapy, it is important to recognize the effects of leech saliva. The active ingredients in leech saliva are the reasons for its analgesic and anti-inflammatory effects. Shakouri *et al.* (2018) examined the effectiveness of leech saliva gel on the symptomatic treatment of knee osteoarthritis. In their study, nanoliposomes were used to deliver the leech saliva, and the VAS and Lequesne index were used to evaluate the effectiveness of the 30-day gel treatment. The results showed that after one month of using the gel, the patients' pain levels decreased by almost 50%. Additionally, due to the reduction in inflammation and joint dryness, their range of motion increased, and their quality of life improved significantly[27].

This study has some limitations. First, five leeches were used simultaneously to treat the knee osteoarthritis, which is moderate compared to the other studies discussed; perhaps increasing the number of leeches could have greater effects. Second, it would be better to study the effects of leech therapy in combination with another treatment. Third, the KOOS questionnaire was the only instrument used to evaluate the effects of treatment. Finally, the results were evaluated only at the end of 90 days of the study.

CONCLUSION

This study failed to identify any therapeutic or remedial effects of leech therapy on pain and symptoms in the treatment of knee osteoarthritis. It seems that future studies using more leeches and examining the therapeutic effects over a shorter period of time are needed to further evaluate the effects of leech therapy on knee osteoarthritis.

ABBREVIATIONS

ADL: Activities of daily living, **JSN**: joint space narrowing, **KOOS**: Knee Injury and Osteoarthritis Outcome Score, **NSAIDs**: Nonsteroidal anti-inflammatory drugs, **QOL**: quality of life, **SD**: standard deviation, **TENS**: Transcutaneous electrical

nerve stimulation

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AUTHOR'S CONTRIBUTIONS

SST, ATR, LM and SMZ developed the original idea and the protocol, abstracted, and prepared the manuscript. JP and HG participated in the study design and analyzed the data. LM, ATR, SAV and SST contributed to the data gathering. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of the study are available from the corresponding author in SPSS form upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional review board approval was obtained from the ethics committees of Hamadan University of Medical Sciences. Ethics committee reference number: IR.UMSHA.REC.1395.597, Approval date: 2017-03-04.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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