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Effectiveness of Leech Therapy in Chronic Lateral Epicondylitis

A Randomized Controlled Trial

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Objectives: Leech therapy has been found to be effective in osteoarthritis of the knee and hand in previous trials. Chronic epicondylitis is a prevalent pain syndrome with limited treatment options. In this study, we tested whether leech therapy would be beneficial in the symptomatic treatment of chronic lateral epicondylitis.

Methods: Forty patients with manifestation of epicondylitis of at least 1-month duration were randomized to a single treatment with 2 to 4 locally applied leeches or a 30-day course with topical diclofenac. The primary outcome was change of pain sum score on day 7 calculated from 3 visual analog scales for pain during motion, grip, and rest. Secondary outcomes included disability (Disability of the Arm, Shoulder, Hand questionnaire), physical quality of life (Short Form-36), and grip strength. Outcomes and safety were assessed on days −3, 0, 7, and 45.

Results: Leeches induced a significantly stronger decrease of the pain score (143.7 ± 36.9 to 95.3 ± 45.1) compared with topical diclofenac (131.6 ± 29.6 to 134.7 ± 70.7; mean difference −49.0; 95% confidence interval,−82.9—15.1; $P = 0.0075$) after 7 days. On day 45, this group difference was reduced (−27.5; confidence interval, −60.8-5.8; $P = 0.110$) due to delayed pain relief with diclofenac. Functional disability showed a stronger decrease in the leech group, which was most prominent after 45 days ($P = 0.0007$). Quality of life increased nonsignificantly in the leech group. Results were not affected by outcome expectation.

Discussion: A single course of leech therapy was effective in relieving pain in the short-term and improved disability in intermediate-term. Leeches might be considered as an additional option in the therapeutic approach to lateral epicondylitis.

Key Words: complementary medicine, epicondylitis, leech therapy, chronic pain, randomized trial

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Lateral epicondylitis of the elbow, commonly known as "tennis elbow," is one of the most prevalent diseases of the upper extremity, affecting approximately 1% to 3% of the population.[1] The condition is characterized by pain on the radial side of the elbow that usually occurs gradually in the course of repetitive strain or due to sudden injury.[2] Activities such as gripping, lifting, and carrying are painfully affected often leading to considerable impairment and absenteeism from work. The economical impact of this disease is large with costs of about 6500 US dollars per patient for lateral epicondylitis, as recently calculated for a North American community.[3]

A variety of therapeutic approaches including physiotherapy,[4] acupuncture,[5] devices,[6] shock wave therapy,[7] nonsteroidal anti-inflammatory drugs (NSAIDs),[8] corticosteroid injections,[9] and surgery,[10] are used for the treatment of tennis elbow; but except for acupuncture,[5,11] the evidence for short-term effects is limited and there is no clear evidence for long-term effects.[12,13]

Medicinal leeches has been used widely in ancient times for the relief of musculoskeletal pain.[14,15] In randomized controlled trials, we and other researchers have found that a single topical application of leeches effectively relieves pain and improves joint function in osteoarthritis of the knee and hand.[16–19] As in leech saliva, a variety of potent anti-inflammatory and analgesic substances have been identified[20–22] and empirical observations have found effectiveness of leech therapy in other chronic pain syndromes, we hypothesized that leeches might also be an effective treatment for pain relief in chronic epicondylitis.

MATERIALS AND METHODS

Our hypothesis was tested in a single-center randomized controlled open trial. The study design was approved by the Ethics Committee of the University Hospital Essen and by the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). The trial was registered at the European Clinical Trial Database (EUDRACT) at the European Medicines Agency, EMEA (EUDRA-CT number: 2005-000893-27). Written informed consents were obtained from all patients according to the Declaration of Helsinki.

Patients

Patients were recruited through a press release and referrals from healthcare professionals. Screening for eligibility was carried out by a semistandardized telephonic

interview. Patients were eligible if they were 18 to 70 years old and fulfilled the following diagnostic criteria for epicondylitis: (1) typical history of lateral elbow pain for at least 3 months and presence of pain during ≥ 50% of the last 30 days, characteristically aggravated by gripping or by exertion of the arm, especially by active extension of the wrist and alleviated by rest; (2) pressure pain on the radial epicondyle of the humerus; (3) aggravation of pain during extension of the wrist against resistance, and (4) a positive middle finger test. We excluded patients if they showed signs, such as dorsal elbow pain and cervical radiculopathy, which were not primarily attributable to lateral epicondylitis. Patients were not included if they had any systemic rheumatic disease, fibromyalgia, or acute psychotic disorder. Patients were excluded if they had local injections at the elbow within the preceding 3 weeks. Further criteria for exclusion were anticoagulation or hemophilia, diabetes mellitus, anemia, polyneuropathy, systemic medication with corticosteroids and immune suppressants, or coexisting serious illnesses. Patients regularly taking NSAIDs were not excluded if the mean weekly dosage and type of administration was stable during the preceding 3 months. NSAIDs were allowed as rescue medication during the trial and the intake was monitored in a diary held by the patients.

Study Procedures

Patients were examined 4 times by a physician at the study center at the Department of Internal and Integrative Medicine before therapy (days −3 and 0) and on days 7 and 45 after treatment. On day −3, a targeted physical examination and pain ratings were performed. If patients had not had any radiographs during the preceding 3 months, they were taken at this study visit. Enrolled patients were invited for a second study visit (day 0) during which they completed baseline questionnaires and underwent testing of grip strength. Thereafter, the patients were randomly assigned to either leech or topical diclofenac therapy and the allocated treatment was applied (day 0). At the subsequent study visits on days 7 and 45, all outcomes were assessed. Each patient was asked to keep a medical diary recording the intake of rescue medication, application of diclofenac gel, and appearance of adverse effects. All participants were asked not to apply other treatments during the study.

Randomization

Patients were randomly allocated to the treatments by a nonstratified block randomization with varying block lengths. The independent biometrician draws random numbers from the "ranuni" random number generator of the SAS software (release 9.1.3, SAS Institute, Cary, NC). On this basis, the biometrician prepared sealed and sequentially numbered opaque envelopes containing the treatment assignments. When a patient fulfilled all the enrollment criteria, the study physician opened the lowest numbered envelope to show that patient's assignment.

Interventions

Leeches were applied as previously described in detail for osteoarthritis of the knee and hand.[23] Two to 4 medicinal leeches (Hirudo medicinalis, Fa. Zaug, Biebertal, Germany) were applied once to the radial insertion of the extensor muscles of the wrist (mainly extensor carpi radialis brevis) with preference to maximum pain points during examination and palpation. Leeches were left in place until they detached by themselves, after a mean of approximately 45 minutes. The leeched area was then bandaged. Patients were asked to remove the bandage the next day and returned 7 days later for the first follow-up. Controls were given 2 tubes of 300 g of diclofenac gel (Diclofenac–Natrium 10 mg/1g gel, Pharmacia, Erlangen, Germany) and their proper use was shown. Patients were instructed to apply the gel at least twice daily throughout days 0 to 30 and to discontinue application thereafter. Compliance with diclofenac gel treatment was assessed from the diaries and by interviewing the patients.

Outcome Measures

The primary outcome measure was the change in the total pain score from days 0 to 7 as derived from the sum of 3 single 100 mm visual analog scale (VAS) pain scores (pain at rest, in motion, and during grip). Functional impairment was defined as a secondary endpoint measured by the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire that was developed by the Upper Extremity Collaborative Group.[24] Further secondary endpoints were physical quality of life assessed by the Medical Outcomes Study 36-Item Short-Form (SF-36).[25] Grip strength (resisted extension of the wrist while the arm is extended and pronated) was tested with a specially designed device (Laboratory for Electronic Devices, Hannover Medical School, Hannover, Germany). The maximum peak strength of 3 consecutive grip efforts was recorded. Adverse effects and the use of oral rescue medication were monitored by means of the patients' diaries from days 0 to 45, and by interviews on days 7 and 45.

Blinded treatment of leeching is difficult to achieve due to the specific nature of the treatment. A recent trial using a proposed sham leech intervention failed to show successful blinding of the intervention. To control for some of the nonspecific treatment effects, outcome expectation was rated by all patients on a 5-point Likert scale ranging from 4 (expecting considerable pain relief) to 0 (expecting no pain relief) immediately after they had been informed of their assigned treatment, and results were also adjusted for this outcome expectation. Workload ("Do you inevitably have to perform movements with your arm in your job or during daily living that augment your elbow pain: Yes or No?") and the level of chronification, as determined by a multidimensional German pain questionnaire,[26] were monitored as possible confounders. All self-reported data were collected by trained research staff, and data were monitored by research assistants who were unaware of study group assignments.

Sample Size Determination and Statistical Analysis

We conducted the study according to a group sequential design,[27] and implemented predefined stopping rules for an interim analysis after 40 patients: the trial had to be stopped if either the P value of a 1-sided t test exceeded $\alpha_1 = 0.5$ (early stopping with a negative result, ie, nonsuperiority of leech therapy) or was below $\alpha_1 = 0.0071$ (early stopping with a positive result, ie, superiority of leech therapy). In all other cases, the trial had to be continued for another 20 patients, confirming the superiority of leeches when the P value of a 1-sided t test was below $\alpha_2 = 0.02261$, or rejecting this hypothesis otherwise. This procedure maintained an overall 1-sided significance level of 2.5%

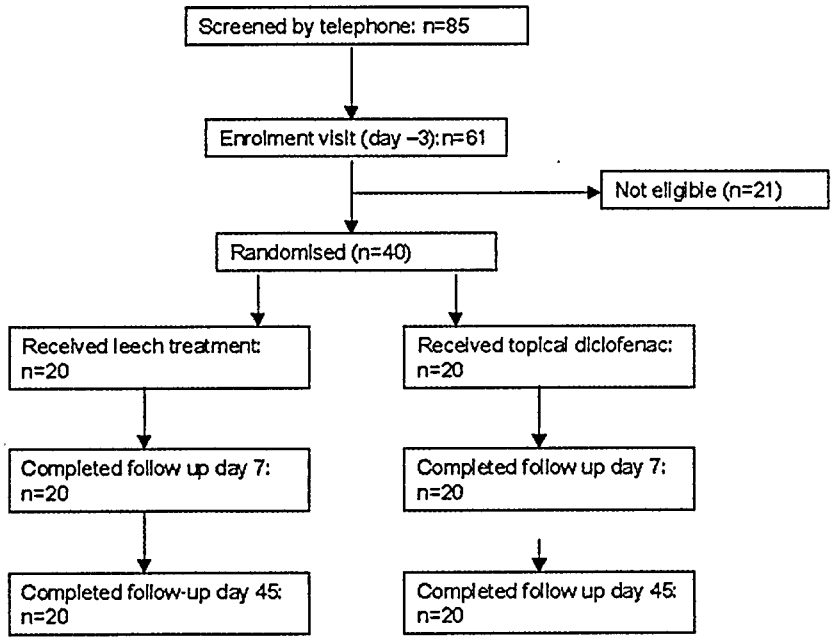

FIGURE 1. Trial profile.

(equals 5% two-sided). Sample size calculations were made with the ADDPLAN software.[28] We assumed that the overall pain would decrease by 24 mm from baseline to day 7 in the leech therapy group and by 10 mm in the diclofenac group with standard deviations of 18 mm each. This yields an overall statistical power of 80.9%.

All outcome criteria were analyzed with repeated measurement analyses of covariance (ANCOVA), in which time was the within-subject factor, group was a between-subject factor, and the respective baseline value was a linear covariate. All randomized patients entered this analysis irrespective of whether they dropped out or failed to adhere to the protocol (intention-to-treat analysis). Missing data were multiply imputed following the suggestions of Little and Rubin.[29] In detail, we used the Monte Carlo Marco Chain Method of the MIANALYZE procedure of the SAS/STAT software,[30] imputed missing values for each treatment group separately, created 20 different sets of data, analyzed them separately with the above-described ANCOVA models, and combined the results with the SAS MIANALYZE procedure. Subsequent analyses of the overall pain score were carried out to adjust for the effects of possible confounding variables, namely outcome expectation and prior treatments. Here, we added these variables as covariates to the ANCOVA models and estimated the group differences in presence of these covariates. At the interim analysis, we found a 1-sided P value of $P = 0.003$, which was substantially smaller than $\alpha_1 = 0.00710$; therefore, the study was stopped earlier having achieved a positive result after 40 patients.

RESULTS

Of the 85 patients who were screened by a telephonic interview, 61 were invited for further assessment. After a detailed examination, 40 patients fulfilled all the study criteria and underwent randomization after obtaining the informed consent. Twenty patients were assigned to the leech therapy and 20 to the topical diclofenac treatment. Compliance with diclofenac application was well documented in the patient diaries. The trial profile is summarized in Figure 1.

Treatment groups did not show any significant difference concerning demographic or illness-related variables (Table 1). All patients had elbow pain longer than 3 months. The higher mean duration of pain history in the diclofenac group was due to a single outlier, who had suffered from epicondylitis for 15 years. All except 4 patients had received previous conventional treatments. Baseline measures were constant from days −3 to 0.

TABLE 1. Baseline Characteristics of Study Patients

Characteristic	Leech Therapy (n = 20)	Topical Diclofenac (n = 20)	P
Sex, female	13	9	
Age, years	47.9 ± 9.5	50.2 ± 11.8	0.79
Mean duration of symptoms SD, months (range)	17.8 ± 18.4 (3-84)	30.9 ± 50.4 (3-180)	0.52
Mean Pain Sum Score, mm	143.7 ± 36.9	131.6 ± 29.6	0.65
Mean DASH sum score, pts	41.3 ± 15.9	35.9 ± 15.9	0.44
Physical Quality-of-life score, pts	39.5 ± 4.6	40.3 ± 5.2	0.28
Received previous conventional treatment, n	18	18	1.00

DASH indicates Disability of the Arms, Shoulder, Hand questionnaire; Pts, points; SD, standard deviation.

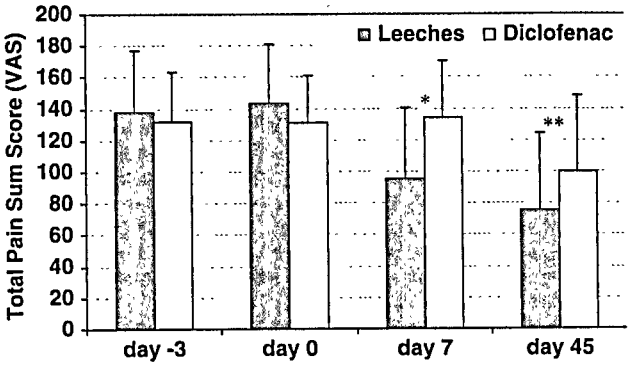

FIGURE 2. Mean ± SD of the pain sum score (mean of the sum of 3 single 100 mm VAS pain scores with pain at rest, in motion, and during grip) at run on day −3, at baseline (day 0), and on days 7 and 45 after treatment. *P=0.0075; **P=0.110.

Clinical Effect

All the patients received leech therapy as scheduled. Compliance with diclofenac application was excellent, as assessed by patients' diaries and by an interview at the final study visit. Leeches induced a significantly stronger decrease of the sum pain score (group difference: −49.0; 95% confidence interval (CI), −82.9—15.1, P = 0.0075), which decreased in the leech group from 143.7 (± 36.9) to 95.3 (± 45.1) and from 131.6 (± 29.6) to 134.7 (± 70.7) in the diclofenac group. This between-group difference diminished after 45 days and then was no more significant (group difference: −27.5, CI: −60.8-+5.8, P = 0.11) (Fig. 2). Leech therapy induced a stronger alleviation of disability in the DASH score, which was most prominent after 45 days with a decrease from 41.3 (± 15.9) to 21.4 (± 14.6) in the leech group and from 35.9 (± 13.8) to 31.9 (± 15.5) in the diclofenac group (Tables 2, 3). Quality of life and grip strength increased in both the groups during the course of treatment with no significant between-group difference (Table 3). Rescue medication was needed by 40% of the diclofenac group with a mean duration of 3.4 (± 7.8) days and in 35% of the leech group for 0.9 (± 1.3) days.

Outcome expectation was significantly higher in the leech group compared with the diclofenac group (P < 0.001). However, when adding expectation as a covariate to the ANCOVA model, the significance of group differences remained nearly unaffected. In addition, adjustment for workload and chronification had no impact on the observed between-group effects.

Conventional treatment might have an impact on the observed clinical benefits. In contrast to patients who received previous conventional therapy, none of the pretreated patients showed a better benefit from diclofenac compared with leech therapy (Fig. 3).

Safety

There were no serious adverse events in both the study groups. A frequent initial minor adverse effect of leech therapy was local mild-to-moderate itching and reddening of the skin, emerging 1 to 7 days after leech therapy in 10 of 20 patients, which lasted for a mean of 5 days and required no further treatment. Two patients experienced a moderate decrease of systolic blood pressure (20 and 15 mm Hg) with a mild sensation of dizziness for several minutes after application of the leeches requiring no further intervention. Mild bleeding at the site of leeching for some hours after treatment is an intended therapeutic effect, which was observed in 9 patients. A prolonged bleeding was not observed. Pain associated with the leeching procedure was rated as not severe by all patients. In the diclofenac group, 1 of 20 patients reported mild local skin reactions.

DISCUSSION

Leech therapy induced a significantly more pronounced decrease of pain after 1 week and improvement of disability after 6 weeks compared with topical diclofenac. The treatment was safe with only minor side effects, which was mainly due to local itching and mild bleeding at the treatment site.

In clinical practice, various treatment modalities are used for the therapy of lateral elbow pain. Few of them, however, are based on scientific evidence and none has been

TABLE 2. Group Differences in Treatment Effects for Change in Pain at Rest, in Motion, and During Grip

	Baseline (Day 0)	Day 7	Day 45
Pain at rest			
Leech therapy (mean+SD)	28.1 (± 17.5)	19.3 (± 14.6)	15.7 (± 14.3)
Diclofenac (mean+SD)	18.8 (± 13.5)	29.9 (± 24.9)	17.2 (± 12.8)
Group difference (mean, 95% CI, P value)		−13.0 (−23.2 to −2.7) P = 0.015	−3.9 (−14.1 to 6.4) P = 0.459
Pain at motion			
Leech therapy (mean+SD)	40.9 (± 13.7)	25.0 (± 14.9)	20.5 (± 20.1)
Diclofenac (mean+SD)	35.2 (± 15.6)	40.1 (± 26.2)	27.8 (± 19.0)
Group difference (mean, 95% CI, P value)		−17.9 (−29.9 to −5.9) P = 0.004	−10.1 (−22.1 to 1.9) P = 0.102
Grip pain			
Leech therapy (mean+SD)	74.8 (± 12.2)	51.0 (± 23.5)	39.2 (± 25.8)
Diclofenac (mean+SD)	77.6 (± 11.2)	64.8 (± 23.1)	54.8 (± 25.0)
Group difference (mean, 95% CI, P value)		−12.7 (−27.3 to 1.8) P = 0.091	−14.6 (−29.1 to 0.0) P = 0.054

Group differences, confidence intervals, and P values for ANCOVA with time as within-subject factor, group as a between-subject factor, and the respective baseline value as a linear covariate.

No significant baseline differences between groups.

SD indicates standard deviation.

TABLE 3. Physical Quality of Life and Daily Life Disability (DASH Questionnaire) in Study Groups With Group Differences for Change With Treatment

	Baseline (Day 0)	Day 7	Day 45
DASH score			
Leech therapy (mean+SD)	41.3 (± 15.9)	31.2 (± 15.5)	21.4 (± 14.6)
Diclofenac (mean+SD)	35.9 (± 13.8)	34.2 (± 17.6)	31.9 (± 15.5)
Group difference (mean, 95% CI, *P* value)		−6.6 (−14.5 to 1.2) *P* = 0.101	−14.1 (−22.0 to −6.3) *P* = 0.001
Grip strength			
Leech therapy (mean+SD)	61.1 (± 53.9)	67.9 (± 57.2)	81.3 (± 68.6)
Diclofenac (mean+SD)	66.3 (± 56.5)	65.8 (± 59.3)	70.1 (± 63.3)
Group difference (mean, 95% CI, *P* value)		5.8 (13.5 to 25.1) *P* = 0.559	12.2 (−7.1 to 31.5) *P* = 0.219
Quality of life			
Leech therapy (mean+SD)	40.0 (± 8.4)	41.9 (± 8.0)	45.6 (± 9.2)
Diclofenac (mean+SD)	41.9 (± 7.0)	42.1 (± 6.9)	46.1 (± 5.4)
Group difference (mean, 95% CI, *P* value)		0.9 (−2.8 to 4.7) *P* = 0.627	0.8 (−3.0 to 4.6) *P* = 0.679

Group differences, confidence intervals and *P* values for ANCOVA with time as within-subject factor, group as a between-subject factor and the respective baseline value as a linear covariate; grip strength as measured by vigorimeter.

DASH indicates Disabilities of the Arm, Shoulder, Hand questionnaire; SD, standard deviation; SF-36, Short-form 36 health survey, physical health.

proven to be more effective than the others.[12] In this study, the effect size of pain reduction in leech therapy was stronger (d = 0.96 for main outcome measure) compared with commonly used conventional modalities, such as local steroid injections[9] or orthotic devices.[6] However, considering the more invasive character of leeching compared with topical diclofenac, the clinical relevance of this pain reduction might be limited, as between-group differences diminished after 6 weeks. The alleviation of disability by leech therapy, as found by a substantial decrease in the DASH score after 6 weeks, was remarkable. This result was comparable to the results obtained in an earlier randomized controlled trial in osteoarthritis of the knee.[18] Thus, the strength of leech therapy might not be only an immediate pain relief but also a prolonged improvement of disability.

The mechanisms of action of leeches are still not fully understood. A plausible explanation would be the improvement of local tissue function due to pharmacological active substances that have been found in the saliva of leeches. The saliva is injected by the leeches after biting to augment local blood flow and analgesia of the host.[14,15] In addition to hirudin, histamine-like vasodilators, kallikrein and tryptase inhibitors, a variety of other analgesics, and proteinase inhibitors have been found in leech saliva.[20–22,31] Furthermore, hyaluronidase has been identified,[32] which might allow these substances to reach deeper tissue zones leading to a sustained improvement of function. This has to be studied in further clinical and experimental studies.

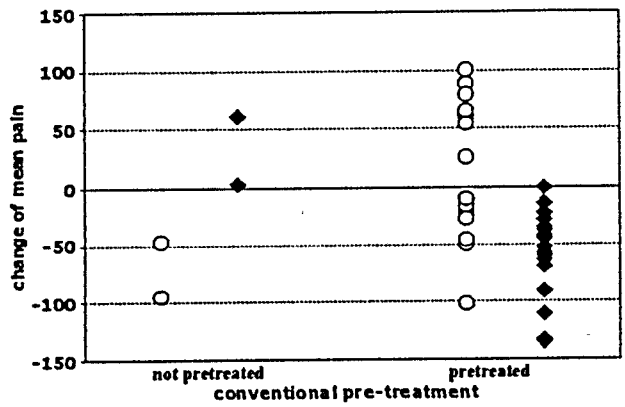

FIGURE 3. Change of mean pain (mean of 3 single 100 mm VAS pain scores with pain at rest, in motion, and during grip) from baseline to day 7 dependent on pretreatment. ♦, patients treated with leeches; O, patients treated with diclofenac.

It is very likely that leeches exert a strong unspecific (placebo-like) effect. As recently shown in clinical trials and by functional brain mapping, the more impressive a treatment is, the bigger the unspecific effects are.[33–35] Thus, the magnitude of placebo effects seems to depend on the aspects and behaviors embedded in medical rituals. Leech therapy is undoubtedly more impressive for a western European than the application of diclofenac gel; thus, a certain part of the treatment effect may be explained by the ritual embedded in leeching. Hence, a limitation of the study is the lack of blinding. Currently, there is no available "leech placebo." A recent randomized trial on leech therapy in knee osteoarthritis did not succeed in blinding leech therapy properly.[16] To have some estimation of the impact of nonspecific treatment effects, we analyzed the outcome expectation. As expected, patients in the leech group showed a significantly higher healing expectation than those in the diclofenac group. Yet, when adjusting statistical analysis for this baseline difference (modeling expectancy as covariate in ANCOVA), group differences for the main outcome measure and for the DASH score remained largely unaffected and significant. Therefore, it seems unlikely that the observed treatment effects are predominantly unspecific.

Patients who were treated conventionally before, showed a better therapeutic response to leeches than those who were treated with leeches as their "first-line" approach. Keeping in mind that the value of this observation is limited, as only 4 patients did not receive an earlier conventional treatment, leeches might be especially helpful as a second-line treatment in patients who have been pretreated without success. Further studies should investigate this subgroup of patients.

A limitation of our study is related to the selected control treatment. In this study, a 4-week topical NSAID treatment was used as control intervention. We preferred topical diclofenac to oral administration to compare 2 modalities of local treatment. In a recent systematic review, topical NSAIDs have been found to be effective in the treatment of acute and chronic musculoskeletal pain.[36,37] In this study, there was no initial pain-relieving effect of topical diclofenac, but a late symptomatic effect was seen. The group difference of pain scores on day 45 was still in favor of the leech therapy, but it was not statistically significant due to the small sample size. Thus, future trials should compare the effectiveness of leech therapy with other conventional treatment options, and should have larger sample sizes when assessing the mid-term and long-term effects of leech therapy. Such trials should also try to develop suitable sham procedures for leeching. Then, double-dummy study designs could be used and would help to differentiate the role of specific and nonspecific treatment effects. As leech therapy has so far shown intriguing pain-relieving effects in chronic pain syndromes, clarification of the underlying mechanisms seems important.

In conclusion, a single course of leech therapy was effective and safe in relieving pain in short term and improving disability in intermediate term in patients with chronic lateral epicondylitis. Mechanisms of action for leeches are widely unknown and warrant further research. The effectiveness of leech therapy in chronic epicondylitis and other related musculoskeletal pain syndromes should be further evaluated in long-term randomized controlled trials.

REFERENCES

1. Allander E. Prevalence, incidence, and remission rates of some common rheumatic diseases or syndromes. *Scand J Rheumatol.* 1974;3:145–153.
2. Reid DC. *Elbow Region. Sports Injury Assessment and Rehabilitation.* New York: Churchill Livingstone; 1992.
3. Silverstein B, Welp E, Nelson N, et al. Claims incidence of work-related disorders of the upper extremities: Washington state, 1987 through 1995. *Am J Public Health.* 1998;88:1827–1833.
4. Smidt N, Assendelft WJ, Arola H, et al. Effectiveness of physiotherapy for lateral epicondylitis: a systematic review. *Ann Med.* 2003;35:51–62.
5. Trinh KV, Phillips SD, Ho E, et al. Acupuncture for the alleviation of lateral epicondyle pain: a systematic review. *Rheumatology (Oxford).* 2004;43:1085–1090.
6. Struijs PA, Smidt N, Arola H, et al. Orthotic devices for the treatment of tennis elbow. *Cochrane Database Syst Rev.* 2002;CD001821.
7. Buchbinder R, Green SE, Youd JM, et al. Shock wave therapy for lateral elbow pain. *Cochrane Database Syst Rev.* 2005;CD003524.
8. Green SE, Barnsley L, Hall S, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database Syst Rev.* 2002;CD003686.
9. Smidt N, Assendelft WJ, van der Windt DA, et al. Corticosteroid injections for lateral epicondylitis: a systematic review. *Pain.* 2002;96:23–40.
10. Buchbinder R, Green S, Bell S, et al. Surgery for lateral elbow pain. *Cochrane Database Syst Rev.* 2002;CD003525.
11. Fink M, Wolkenstein E, Karst M, et al. Acupuncture in chronic epicondylitis: a randomized controlled trial. *Rheumatology (Oxford).* 2002;41:205–209.
12. Hong QN DM, Loisel P. Treatment of lateral epicondylitis: where is the evidence? *Joint Bone Spine.* 2004;71:369–373.
13. Theis C, Herber S, Meurer A, et al. Evidence-based evaluation of present guidelines for the treatment of tennis elbow-a review. *Zentralbl Chir.* 2004;129:252–260.
14. Adams SL. The medicinal leech. A page from the annelids of internal medicine. *Ann Internal Med.* 1988;109:399–405.
15. Fields WS. The history of leeching and hirudin. *Haemostasis.* 1991;21(suppl 1):3–10.
16. Andereya S, Stanzel S, Maus U, et al. Assessment of leech therapy for knee osteoarthritis: a randomized study. *Acta Orthop.* 2008;79:235–243.
17. Michalsen A, Deuse U, Esch T, et al. Effect of leeches therapy (Hirudo medicinalis) in painful osteoarthritis of the knee: a pilot study. *Ann Rheum Dis.* 2001;60:986.
18. Michalsen A, Klotz S, Ludtke R, et al. Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med.* 2003;139:724–730.
19. Michalsen A, Ludtke R, Cesur O, et al. Effectiveness of leech therapy in women with symptomatic arthrosis of the first carpometacarpal joint: a randomized controlled trial. *Pain.* 2008;137:452–459.
20. Baskova IP, Aguejouf OM, Azougagh-Oualane F, et al. Arterial antithrombotic effect of piyavit, the novel pharmacological preparation from the medicinal leech, and of its components, prostanoids and enzyme destabilase. *Thromb Res.* 1995;77:483–492.
21. Rigbi M, Levy HZ, Eldor A, et al. The saliva of the medicinal leech Hirudo medicinalis- II. Inhibition of platelet aggregation and of leucocyte activity and examination of reputed anaesthetic effects. *Comp Biochem Physiol.* 1987;88:95–98.
22. Rigbi M, Levy HZ, Iraqi F, et al. The saliva of the medicinal leech Hirudo medicinalis-I. Biochemical characterisation of the high molecular weight fraction. *Comp Biochem Physiol.* 1987;87:567–573.
23. Michalsen A, Moebus S, Spahn G, et al. Leech therapy for symptomatic treatment of knee osteoarthritis: results and implications of a pilot study. *Altern Ther Health Med.* 2002;8: 84–88.
24. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) (corrected). The Upper Extremity Collaborative Group (UECG). *Am J Ind Med.* 1996;29: 602–608.
25. Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473–481.
26. Nagel B, Gerbershagen HU, Lindena G, et al. Development and evaluation of the multidimensional German pain questionnaire. *Schmerz.* 2002;16:263–270.
27. O'Brien P, Fleming T. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35:549–556.
28. Wassmer G, Eisebitt R. *ADDPLAN Adaptive Designs and Analyses 3.1.1.* Köln: ClinSearch GmbH; 2005.
29. Little R, Rubin D. *Statistical Analysis with Missing Data.* New York: J. Wiley and Sons; 1987.
30. SAS/STAT® Software OnlineDoc® 9.1.3. Cary, NC: SAS Institute Inc; 2004.
31. Sawyer RT. *Leech Biology and Behaviour.* Oxford: Oxford University Press; 1986.
32. Claude A. Spreading properties and mucolytic activity of leech extracts. *Proc Soc Exp Biol Med.* 1940;43:684.
33. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? *Ann Intern Med.* 2002;136:817–825.
34. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ.* 2006;332:391–397.
35. Kong J, Gollub RL, Rosman IS, et al. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. *J Neurosci.* 2006; 26:381–388.
36. Mason L, Moore RA, Edwards JE, et al. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2004;5:28.
37. Mason L, Moore RA, Edwards JE, et al. Topical NSAIDs for acute pain: a meta-analysis. *BMC Fam Pract.* 2004;5:10.