Effectiveness of Leech Therapy in Osteoarthritis of the Knee
A Randomized, Controlled Trial

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Background: Leech therapy was commonly used in traditional medicine for treating localized pain. Clinically significant pain relief after leech therapy for osteoarthritis of the knee has been demonstrated by preliminary data.

Objective: To evaluate the effectiveness of leech therapy for symptomatic relief of osteoarthritis of the knee.

Design: Randomized, controlled trial.

Setting: Outpatient department for integrative medicine of an academic teaching hospital.

Patients: 51 patients with osteoarthritis of the knee (leech therapy: 24 patients, mean age [±SD], 62.5 ± 10.2 years; topical diclofenac therapy: 27 patients, mean age [±SD], 65.5 ± 6.7 years).

Intervention: A single treatment with 4 to 6 locally applied leeches (leech therapy group) or a 28-day topical diclofenac regimen (control group).

Measurements: Mean of the pain, function, and stiffness subscores of the Western Ontario and McMaster Universities Osteoarthritis Index and physical sum score of the Medical Outcomes Study 36-Item Short-Form Health Survey with group comparisons at days 3, 7, 28, and 91.

Results: The primary end point, pain at day 7, was reduced from a mean (±SD) of 53.5 ± 13.7 to 19.3 ± 12.2 after leech therapy compared with 51.5 ± 16.8 to 42.4 ± 19.7 with topical diclofenac (estimated group difference, −23.9 [95% CI, −32.8 to −15.1]; $P < 0.001$). Although the difference between group pain scores was no longer significant after day 7, differences for function, stiffness, and total symptoms remained significant in favor of leech therapy until the end of study and for quality of life until day 28. Results were not affected by outcome expectation.

Conclusions: Leech therapy helps relieve symptoms in patients with osteoarthritis of the knee. The potential of leech therapy for treating osteoarthritis and the pharmacologic properties of leech saliva remain to be clarified.

The application of medicinal leeches was widely practiced in ancient times (1, 2), but their use declined rapidly in Europe and America with the advent of modern surgery and pharmacology (3). In ancient medical practice, phlebitis and thrombotic states were 2 main indications for leech therapy (4). In more recent times, the polypeptide hirudin, one of several biologically active substances in leech saliva, was identified as the most potent known natural inhibitor of coagulation (5, 6). Natural leeches are currently used to treat postoperative local congestions after reconstructive and plastic surgery (7, 8).

Other traditional uses of leeching, such as treating localized inflammation and pain, are still part of many ethnomedical systems (9, 10). Besides hirudin, various anti-inflammatory substances and hyaluronidase have been found in leech saliva. In a nonrandomized pilot study, we found that a single treatment with 4 locally applied leeches rapidly relieved pain from osteoarthritis of the knee (11). Because of the lack of randomized, controlled trials of leech therapy, we designed this trial to assess the symptomatic short-term efficacy of leech therapy in osteoarthritis of the knee. Topically applied diclofenac was chosen as the control therapy to compare 2 types of local treatment. The effectiveness of topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) and diclofenac in treating osteoarthritis has been demonstrated (12, 31, 32); their use has

been recommended for symptomatic treatment of osteoarthritis of the knee (13).

METHODS
Protocol

The research protocol, reviewed and approved by our institutional ethics committee, included 6 study visits. Applicant patients were recruited by press announcements and first screened for eligibility by telephone. Those who fulfilled the initial enrollment criteria were invited for further assessment by detailed physical examination, blood analysis, and radiographs of the knee (first study visit, day −3). If patients had not had radiographs of the knee in the preceding 3 months, radiography was performed at day −3. All eligible patients who gave written informed consent were included in the study and asked to limit their osteoarthritis medications during the study to rescue medication. No patient took slow-acting substances against osteoarthritis. Baseline measurements were done at visit 2 (day 0), when the participant was randomly assigned to either leech or topical diclofenac therapy and the allocated treatment was started. During subsequent visits on study days 3, 7, 28, and 91, all outcomes were assessed except quality of life, which was assessed only on days 28 and 91. Each patient was asked to record intake of rescue medication, application of study gel, and appearance of adverse

effects in a medical diary. Patients were screened and re-cruited between January and June 2002. Patient treatments and follow-ups were completed by 1 November 2002.

Patients

Patients were eligible if they were older than 40 years of age, had definite osteoarthritis of the knee as defined by the American College of Rheumatology (14) without clin-ical evidence of rheumatoid arthritis and systemic joint disease, and had not undergone arthroscopy or surgery of the knee or had intra-articular injections in the previous 3 months. In addition, patients were required to have a pain rating greater than 40 on 1 of the 5 pain scales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analogue scales (15). Exclusion criteria were current anticoagulant treatment or hemo-philia, type 1 diabetes mellitus, anemia, polyneuropathy, severe articular inflammation on physical examination (ex-cluded also by an erythrocyte sedimentation rate > 40 mm/h and C-reactive protein level > 5 mg/L), or other serious illnesses. Patients regularly taking rescue medica-tion with NSAIDs or analgesics were not excluded if the mean weekly dosage and type of administration had not been altered during the preceding 3 months.

Randomization and Treatment Groups

Patients were randomly allocated to the treatment groups by a nonstratified block randomization with ran-domly varying block lengths. Sequentially numbered enve-lopes containing the treatment assignments were prepared. When a patient met the inclusion criteria and consented to participation, the study physician opened the lowest num-bered envelope, which determined the group of assign-ment.

Leech therapy was carried out as previously described and tested in our pilot study (11, 16). In summary, 4 to 6 medicinal leeches (*Hirudo medicinalis*, ZAUG GmbH, Biebertal, Germany) were applied once to the periarticular soft tissue of the affected knee, with preference to maxi-mally painful points during examination and palpation. Leeches were left in place until they detached by them-selves, after a mean of 70 minutes. The patient's knee was then bandaged, and the patient was cautioned not to be physically active for the next 12 hours. The patient re-turned the next day (study day 1) for a change of dressing and a repeated blood count. Control group patients were given 300 g of diclofenac gel (diclofenac–natrium 10 mg–1 g gel, Pharmacia, Erlangen, Germany), and the proper use was demonstrated. Patients were instructed to apply the gel at least twice daily for days 0 through 28 and to discontinue application thereafter. Adherence to diclofenac gel treatment was assessed from the diaries and cross-checked by counting used gel tubes and interviewing the patients.

Outcome Measures

The primary outcome measure was change in knee pain from day 0 to 7 as derived from the mean WOMAC

Context

Osteoarthritis causes pain and disability, but conventional therapies offer limited relief for many patients. Leech sa-liva contains anti-inflammatory substances, and leeches showed promise as an osteoarthritis therapy in a nonran-domized study.

Contribution

This randomized trial compared a single application of 4 to 6 leeches to the affected knee with 28 days of topical di-clofenac treatment. Patients with leech therapy had less pain through day 7 than those receiving diclofenac. The leech therapy group showed benefits in function, stiffness, and total arthritis symptoms through the 91 days of fol-low-up.

Cautions

Future studies should evaluate leeches and the substances in their saliva against various conventional therapies in blinded studies with long-term follow-up.

–The Editors

pain score. The WOMAC is a disease-specific question-naire addressing severity of joint pain (5 questions), limi-tation of physical function (17 questions), and stiffness (2 questions). Each question is assessed by a 100-mm visual analogue scale, and the aggregate WOMAC score is repre-sented by the sum of the 24-component item scores (15). Secondary end points consisted of all other WOMAC sub-scores and the WOMAC total score during the study and the physical sum score of quality of life assessed by the Medical Outcomes Study 36-Item Short-Form Survey (SF-36) (17) at days 28 and 91. The SF-36 scores were stan-dardized, taking the mean of the German population as 0 and its SD as 1. The prevalence of adverse effects and the use of oral rescue medication were monitored through the patients' diaries from days 0 to 28 and through interviews on days 28 and 91. To control for nonspecific treatment effects, outcome expectation was rated by all patients on a 5-point Likert scale ranging from 4 (expecting great pain relief) to 0 (expecting no pain relief) immediately after they had been informed of their assigned treatment. Current physical activity was evaluated by a standardized physical activity questionnaire and by calculating energy expendi-ture (kcal/wk) at baseline and days 28 and 91. Initially and at the end of the study, all participants completed a ques-tionnaire that included personal data, general medical in-formation, and queries about clinical status. Trained, un-blinded research assistants collected patient-reported data, and research personnel who were unaware of study group assignments performed data entry and monitoring.

Statistical Analysis

We initially planned the trial as a sequential trial by using the triangular test with preset boundaries to permit

termination of the trial if the efficacy or inefficacy of leech therapy was established or if there was evidence of no difference in outcome between the 2 treatment groups (18). According to the test design with preplanned repeated data evaluations, the trial was designed to be terminated when the path of the t statistic, measuring imbalance between the outcome for the 2 randomized groups, crossed 1 of the preset termination boundaries (efficacy, inefficacy, or no difference in outcome) of the sequential design. In the triangular test, design blinding of the data evaluation is not feasible.

A between-group difference of 0.625 SD on the WOMAC pain scale was the anticipated effect size, and the minimum statistical power was fixed at 80%. With these assumptions, we expected to enroll approximately 60 patients to detect the above-mentioned difference with a 2-sided type I error of 5%. Data were evaluated weekly on the basis of a recruitment rate of 3 to 4 patients each week. Unexpectedly, the efficacy boundary of the sequential design was crossed early when 21 patients had been evaluated at day 7; thus, within the triangular study design, the primary study hypothesis that leeches are more efficacious than topical diclofenac was accepted ($P = 0.004$). The study review board stopped recruitment according to the protocol. At that time, 30 more patients were already included or on the waiting list for study inclusion. The study review board decided to follow these 30 patients to completion. Otherwise, the sample size would have been too small to detect any other group differences with the secondary end points.
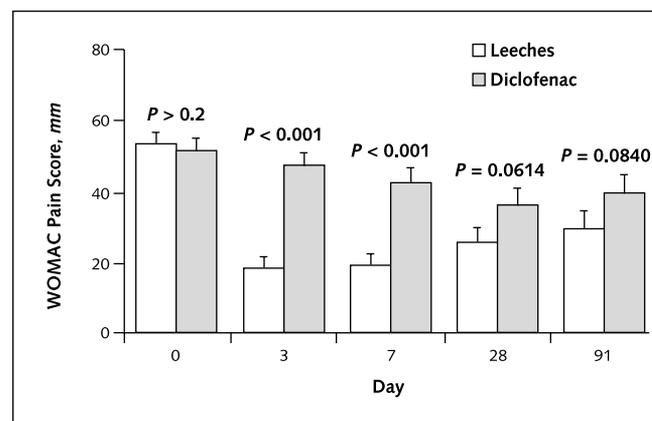
Thus, we were compelled to change our preplanned data analysis. Instead of applying a triangle test, we fitted general repeated-measurement analyses of variance to the WOMAC scores. In detail, we modeled a day-to-group interaction as an 8-level factor and assumed an exponential correlation function (19). Missing WOMAC scores were

Figure. **Western Ontario and McMaster Universities Osteoarthritis Index (*WOMAC*) pain score.**

Mean course of the WOMAC pain score in both groups in the study course (means [+SD] are based on raw [not imputed] data; *P* values were calculated from repeated-measurement analysis of variance). Complete WOMAC patient data in the leech therapy and topical diclofenac treatment group were available for 24 and 26 patients, respectively (day 7); 24 and 24 patients, respectively (day 28); and 23 and 23 patients, respectively (day 91).

multiply imputed following the suggestions of Rubin (20). In detail, we used the Monte Carlo Markov chain method of SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina), and imputed missing values for each treatment group separately. In total, we created 20 multiple imputed data sets and analyzed them with the SAS MIANALYZE procedure.

All statistical analyses were based on all randomly assigned patients, including patients who dropped out for nonadherence to the treatment or withdrew for other reasons (intention-to-treat sample). All tests were 2-sided, and *P* values less than 0.05 were considered to be statistically significant.

Subsequent analyses on the WOMAC pain score were done to adjust for the effects of possibly confounding variables: outcome expectation, use of rescue medication, and WOMAC scores at baseline. We included these variables as covariates in the analyses of variance and estimated the group differences in the presence of these factors.

Role of the Funding Source

The funding source had a role in the design and conduct of the study but not in the interpretation of data or in the decision to submit the manuscript for publication.

RESULTS

Of 112 patients screened by telephone interview, 61 patients were invited for further assessment. After detailed examination, 51 patients fulfilled all study criteria, agreed to study participation, and underwent randomization. Twenty-four patients were assigned to leech therapy, and 27 patients were assigned to topical diclofenac treatment. One patient (receiving diclofenac) declined to return for

Table 1. **Baseline Characteristics of Study Patients***

Characteristic	Leech Therapy (*n* = 24)	Topical Diclofenac (*n* = 27)
Age, y	62.5 ± 10.2	65.5 ± 6.7
Sex, *n*		
Men	9	9
Women	15	18
Previous regular NSAID intake, *n* (%)	19 (79)	23 (85)
Duration of knee osteoarthritis, y	10.1 ± 8.9	10.3 ± 8.4
Previous arthroscopy, *n* (%)	15 (63)	15 (56)
Body mass index, *kg/m²*	27.6 ± 3.7	27.1 ± 3.7
Weight, *kg*	80.7 ± 13.6	79.8 ± 13.2
WOMAC pain score	53.0 ± 13.7	51.5 ± 16.8
WOMAC function score	58.7 ± 14.2	51.9 ± 15.4
WOMAC stiffness score	63.3 ± 19.0	48.6 ± 22.2
WOMAC total score	57.5 ± 12.5	51.9 ± 14.9
SF-36 physical quality-of-life score	282 ± 88.0	311 ± 88.0

* Values with plus/minus signs are expressed as means ± SD. NSAID = nonsteroidal anti-inflammatory drug; SF-36 = Medical Outcomes Study 36-Item Short-Form Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Group Differences for Change in Western Ontario and McMaster Universities Osteoarthritis Index Scores Compared with Baseline*

End Point	Leech Therapy	Topical Diclofenac	Estimated Difference (95% CI)	P Value
WOMAC stiffness score				
Day 3	−37.9 ± 20.9	−4.7 ± 22.9	−31.0 (−40.5 to −21.6)	<0.001
Day 7	−39.9 ± 21.6	−7.5 ± 25.6	−28.3 (−38.9 to −17.7)	<0.001
Day 28	−36.5 ± 22.4	−5.3 ± 25.0	−25.9 (−36.8 to −14.9)	<0.001
Day 91	−29.1 ± 26.1	−9.3 ± 24.3	−15.4 (−27.1 to −3.7)	0.0099
WOMAC function score				
Day 3	−33.8 ± 19.4	−4.6 ± 14.2	−28.7 (−34.9 to −22.4)	<0.001
Day 7	−35.2 ± 19.7	−10.4 ± 16.6	−24.1 (−32.5 to −15.7)	<0.001
Day 28	−30.8 ± 22.0	−14.4 ± 19.2	−15.1 (−25.7 to −4.5)	0.0053
Day 91	−28.5 ± 22.8	−13.4 ± 21.8	−11.5 (−22.9 to −0.2)	0.0460
WOMAC total score				
Day 3	−35.0 ± 16.8	−4.7 ± 14.2	−30.0 (−36.0 to −24.0)	<0.001
Day 7	−35.7 ± 17.6	−9.7 ± 17.4	−25.6 (−33.5 to −17.6)	<0.001
Day 28	−30.8 ± 19.4	−14.3 ± 19.9	−15.4 (−25.3 to −5.6)	0.0022
Day 91	−27.2 ± 21.7	−13.9 ± 20.9	−11.7 (−22.3 to −1.0)	0.0317

* Values are means ± SD. Means indicate mean changes from baseline based on raw data; because of multiple imputations of missing values, the estimated difference is not equal to the difference of means. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

further visits to the study center and withdrew from the study immediately at day 1. Two more patients in the diclofenac group withdrew from the study after day 7 because of persisting symptoms. One patient in each group dropped out before the last study visit (day 91) because they received unallowed co-interventions after day 28.

Table 1 shows the baseline demographic and clinical characteristics of the study patients. Treatment groups were similar with the exception of a higher mean stiffness score in the leech therapy group than in the topical diclofenac group ($P = 0.017$). All patients had radiographically confirmed stage II to III osteoarthritis of the knee according to the classification of Kellgren and Lawrence (21). Forty-two (82%) of all study patients had received regular NSAID or acetaminophen therapy in the last 3 years. Fifteen patients (63%) in the leech group and 19 patients (70%) in the topical diclofenac group were currently having physiotherapy or were exercising quadriceps strengthening on a regular basis. Adherence to diclofenac application was good, with regular application in 24 of the 26 patients analyzed at day 7. One patient did not use diclofenac after the fifth day because of an ongoing local skin reaction.

Outcome Measures

Leech therapy provided a greater benefit than topical diclofenac in the primary outcome measure, change in knee pain after 1 week. The mean WOMAC pain score (±SD) was reduced from 53.5 ± 13.7 ($n = 24$) to 19.3 ± 12.2 ($n = 24$) at 7 days in the leech therapy group and from 51.5 ± 16.8 ($n = 27$) to 42.4 ± 19.7 ($n = 26$) in the diclofenac group. After multiple imputing of missing values, there was a highly significant estimated between-group difference (−23.9 [CI, −32.8 to −15.1]; $P < 0.001$, repeated-measurement analysis of variance). The estimated group difference for pain relief in favor of leech therapy was most pronounced at day 3 (−29.5 [CI, −36.3 to −22.6]; $P < 0.001$) and diminished over time,

with a nonsignificant group difference of −9.9 (CI, −20.3 to 0.5; $P = 0.061$) at day 28 and −9.4 (CI, −20.0 to 1.3; $P = 0.084$) at day 91 (**Figure**).

In addition, joint function improved and stiffness decreased rapidly and statistically significantly with leech therapy. These effects were maintained until day 91 and resulted in significant group differences favoring leech therapy, including the WOMAC total score (**Table 2**). The physical dimension of quality of life improved only for the leech therapy group on day 28 (group difference, 0.49 [CI, 0.07 to 0.91]; $P = 0.023$); at day 91, these group differences were no longer detectable (difference, 0.13 [CI, −0.31 to 0.56]; $P > 0.2$). Calculated physical activity increased nonsignificantly in the leech therapy group compared with the diclofenac group.

No study patient was receiving stable therapy with NSAIDs or analgesics during the study course. **Table 3** shows the type and frequency of rescue medication use in each treatment group. In the first 7 days (that is, before the primary outcome was evaluated), 8 patients in the diclofe-

Table 3. Rescue Medication Use from Days 0 to 28 and Days 29 to 91 in the Treatment Groups*

Medication	Days 0 to 28		Days 29 to 91	
	Leech Therapy	Topical Diclofenac	Leech Therapy	Topical Diclofenac
	←————— n/d —————→			
Diclofenac	4/47	5/48	4/71	5/103
Aspirin	0/0	2/4	0/0	2/16
Ibuprofen	2/32	3/30	2/93	3/74
Acetaminophen	1/5	0/0	1/18	0/0
Meloxicam	2/16	1/2	2/31	1/3
Piroxicam	0/0	0/0	1/12	0/0
Celecoxib	0/0	1/6	0/0	1/10
Rofecoxib	0/0	1/18	0/0	1/38
Total	9/100	13/108	10/225	13/244

* Data are number of patients/medication days.

Table 4. Adverse Events

Adverse Event	Leech Therapy	Topical Diclofenac
	n	
Patients exposed to treatment	24	26
Local itching	17	0
Local skin reaction	1	1
Dizziness	1	0
Abdominal pain	0	1
Prolonged oozing	1	0
Local burning sensation	2	1
Prickling	0	2

nac group and 6 patients in the leech therapy group took a rescue medication. On average, patients needed rescue medication on less than 1 of every 5 days throughout the study; differences between groups were not statistically significant.

Outcome expectation was slightly higher in the leech therapy group (mean [±SD], 2.4 ± 0.8 vs. 1.9 ± 0.6; $P = 0.008$). Yet after adjustment for outcome expectation, medication use, and other predefined variables, including all WOMAC baseline scores, the group difference between the pain score of the 2 treatment groups remained significant; the trend favored leech therapy at day 7 ($P < 0.001$), and pain was still nonsignificantly reduced at day 28 (-9.9 [CI, -20.3 to 0.6]; $P = 0.064$) and day 91 (-9.3 [CI, -20.0 to 1.4]; $P = 0.087$).

Table 4 summarizes the adverse events in the study treatment groups. Neither group experienced serious adverse effects. A common minor adverse effect of leech therapy was mild to moderate itching at the leech bite sites, which lasted for a mean of 4 days. All patients in that group rated pain associated with the leeching procedure as not severe. Twenty-four hours after leeching, the mean hemoglobin level (±SD) decreased from 8.9 ± 0.7 mmol/L to 8.5 ± 0.4 mmol/L ($P < 0.001$), but in no patient did it decrease below 6.8 mmol/L. At the end of the study period, 21 of 23 patients in the leech therapy group stated that they would like to undergo repeated therapy in case of renewed severe joint pain.

DISCUSSION

Since long-term therapy for osteoarthritis of the knee has limited options and treatment carries substantial risk for serious adverse effects (22), new therapeutic approaches should be considered. Leech therapy, although extensively used for treating pain throughout medical history (9, 23), has never been evaluated in a modern scientific context.

In this randomized, controlled trial, patients with osteoarthritis of the knee who were treated with leech therapy experienced clinically significant improvements in self-perceptions of pain for a limited period. Moreover, a single application of leeches improved functional ability and joint stiffness for at least 3 months.

The observed improvements confirm the results of our pilot study and are most likely attributable to the therapeutic intervention. Slightly higher symptom scores of the patients in the leech therapy group at the outset could have biased the results. Yet, baseline differences were not statistically significant for pain and functional ability, and statistical adjustment for baseline WOMAC scores did not change the overall results.

Different mechanisms may explain the observed effects. First, various pharmacologically active substances besides the thrombin-inhibitor hirudin have been found in leech saliva, such as histamin-like vasodilators, kallikrein and tryptase inhibitors, various other proteinase inhibitors, and anesthetics (24–27). Through the concomitant activity of a further leech saliva component, hyaluronidase (28), these substances might reach deeper tissue zones and possibly the joint space. However, it is not clear whether pain-relieving therapy in osteoarthritis needs to affect the cartilage and subchondral bone directly. The various bioactive substances in leech saliva may also be as pharmacologically potent as hirudin and thus exert substantial effects in periarticular tissue and adjacent structures.

Second, nociceptive activation contributes to chronic pain (29). Leech therapy could induce pain relief through antinociceptive effects and counterirritation. However, it is not known to what extent leech bites may induce such mechanisms, and it seems unlikely that reduction of nociceptive input on a single occasion would result in the observed lasting effect, such as improved joint function.

Third, placebo effects might be responsible for the symptomatic benefit. The principal limitation of this study is that the placebo-like effects of this invasive and uncommon treatment cannot be precisely assessed. All invasive treatments of osteoarthritis of the knee are subject to relevant placebo-like effects; for example, in a recent trial, sham arthroscopy was not inferior to arthroscopic debridement and lavage (30). Currently, a sham leech treatment is not available and treatment blinding is not feasible. We assessed outcome expectation to approximate the placebo-like effects, but despite higher scores in the leech therapy group, adjustment for the confounding effect of outcome expectation did not change the overall results. Future trials should include treatment groups with other invasive procedures or use genetically modified leeches.

Further study limitations are due to nature of the control treatment. In the present study, leech therapy was compared with 4-week topical diclofenac treatment. Randomized, controlled trials showed the pain-relieving effect of topical diclofenac in knee osteoarthritis (31, 32). Topical NSAIDs in general have been evaluated as an effective but secondary treatment in osteoarthritis (12). In our current study, topical diclofenac was preferred over oral NSAIDs to compare 2 types of local treatment. The mechanisms of topical diclofenac include local accumulation in synovial fluid and periarticular tissue, as well as systemic distribution (33, 34). Compared with leech therapy, the

observed improvement with topical diclofenac in our study was modest, but the 20% to 25% reduction in pain and disability corresponds to treatment effects seen in previous trials with topical NSAIDs (31, 35). However, leech therapy might be less effective if compared with standard therapies for osteoarthritis pain, such as intra-articular steroids or oral NSAIDs, and its superiority compared with these treatments remains to be evaluated.

We do not know whether our findings may be generalized to all patients with knee osteoarthritis. Age and sex ratio of the study sample are typical for patients with knee osteoarthritis. A selection bias might be introduced by the fact that patients who agree to participate in a leech therapy study may have had high treatment expectations and thus be more susceptible to a placebo effect than the general patient population with osteoarthritis of the knee.

Finally, this study may not have been long or large enough to exactly assess the clinical value and long-term effect of leech therapy. Pain reduction diminished within 4 weeks, but the beneficial effects on joint function and stiffness persisted until the end of the 3-month study period. Because of the sequential design of the study and the clear effect of leech therapy on the primary outcome, the resulting study groups were rather small for the analysis of secondary outcomes. Day-to-day symptom variation may be considerable in patients with osteoarthritis, pointing also to the need for larger study groups in future trials. In our pilot study, the pain-relieving effect of leech therapy was more pronounced after 4 weeks than after 1 week. Nonrandomization could have biased the results of the pilot study in favor of leech therapy, but these patients were also treated actively with physiotherapy. This possibly supported the treatment effect (11).

Our present data suggest that re-treatments will be necessary for leech therapy to become clinically valuable in the long-term management of osteoarthritis of the knee. According to empirical reports, re-treatments are well tolerated and effective (9). From our experiences, costs may be estimated at $70 per treatment; however, the cost–benefit ratio must be precisely assessed in long-term trials.

Leech therapy, as applied in this study, was safe and well tolerated. As expected, a slight but clinically nonrelevant decrease in hemoglobin level was seen after leeching. In 1 patient, the wound oozed for 12 hours, but this did not result in relevant blood loss as controlled by blood count. Yet, the safety of leech therapy with regard to the blood-letting effects has to be further evaluated. A common minor side effect with leech therapy was local itching in more than 70% of treated participants; patients should be informed about this frequent adverse effect. Theoretically, leech therapy carries an infection risk because of the physiologic colonization of *Hirudo medicinalis* with the bacterium *Aeromonas hydrophila* (36). Cases of infection and septicemia with *A. hydrophila* have been reported when leeches were applied in severely ill patients or to malperfused tissue in reconstructive and plastic surgery (8, 37, 38). So far, there are no reported cases of *Aeromonas* infection when leeches were applied for treating osteoarthritis or local pain syndromes.

In summary, traditional leech therapy seems to be an effective symptomatic treatment for osteoarthritis of the knee. However, because only subjective, patient-reported end points were evaluated and the patients were not blinded to the intervention, we emphasize the preliminary nature of this study. The effectiveness and safety of this treatment, especially when applied repeatedly, should be further evaluated in larger randomized studies. In addition, the active compounds in leech saliva and their local release (that is, in the synovial fluid) deserve further study. Currently, no pharmacologic agent has similar lasting effects after a single local administration. Further research into the anti-inflammatory compounds of leech saliva could lead to the development of new effective substances for treating osteoarthritis.

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