Original Article

The Effectiveness of Leech Therapy in Chronic Low Back Pain

A Randomized Controlled Trial

Christoph-Daniel Hohmann, Rainer Stange, Nico Steckhan, Sibylle Robens, Thomas Ostermann, Arion Paetow, Andreas Michalsen

Charité – University Medicine Berlin, corporate member of the Free University Berlin, Humboldt University of Berlin, and Berlin Institute of Health, Institute of Social Medicine, Epidemiology and Health Economics, Foundation Chair of Clinical Naturopathy: Christoph-Daniel Hohmann, Dr. Rainer Stange, Dr. Nico Steckhan, Prof. Andreas Michalsen

Department of Internal Medicine, Division of Naturopathy, Immanuel Hospital Berlin: Christoph-Daniel Hohmann, Dr. Rainer Stange, Dr. Nico Steckhan, Prof. Andreas Michalsen

Department of Psychology, Faculty of Health, Witten/Herdecke University: Dipl.-Stat. Sibylle Robens, Prof. Ostermann

KPW Garbsen, Center for Physiotherapy: Dr. Paetow

Summary

Background: Leech therapy has been found to be effective in the treatment of a number of chronic musculoskeletal pain syndromes. Leeches are also often used empirically to treat chronic low back pain, but data from clinical trials have been lacking to date. We therefore conducted the first randomized trial of leech therapy for chronic low back pain.

Methods: Patients with chronic low back pain were randomized to receive either a single session of local treatment with 4–7 leeches or four weekly sessions of exercise therapy (1 hour each) led by a physical therapist. The primary endpoint was a change in average back pain intensity, as measured using a 100-mm visual analog scale (VAS), after 28 days. Secondary endpoints included functional impairment (Roland–Morris Disability Questionnaire, Hannover Functional Ability Questionnaire), quality of life (Short-Form Health Questionnaire [SF 36]), pain perception (pain perception scale = Schmerzempfindungsskala [SES]), depressivity (Center for Epidemiological Studies Depression Scale [CES-D]), and analgesic consumption (questionnaire/diary). Trial visits took place before treatment and on days 28 ± 3 and 56 ± 5 after the start of treatment; the overall duration of the trial was 56 ± 5 days.

Results: The mean low back pain score improved from 61.2 ± 15.6 before treatment to 33.1 ± 22.4 on day 28 in the leech therapy group (n = 25) and from 61.6 ± 14.8 to 59.8 ± 16.7 in the exercise therapy group (n = 19) (group difference −25.2; 95% confidence interval [−41.0; −9.45]; p = 0.0018). Significant benefits of leech therapy were also found at both time points with respect to physical impairment and function as well as physical quality of life. The patients' expectations from treatment were higher in the leech therapy group but did not significantly affect the findings.

Conclusion: A single session of leech therapy is more effective over the short term in lowering the intensity of pain over the short term and in improving physical function and quality of life over the intermediate term (4 weeks and 8 weeks, respectively). The limitations of this trial are the lack of blinding and the small number of patients. Leech therapy appears to be an effective treatment for chronic low back pain.

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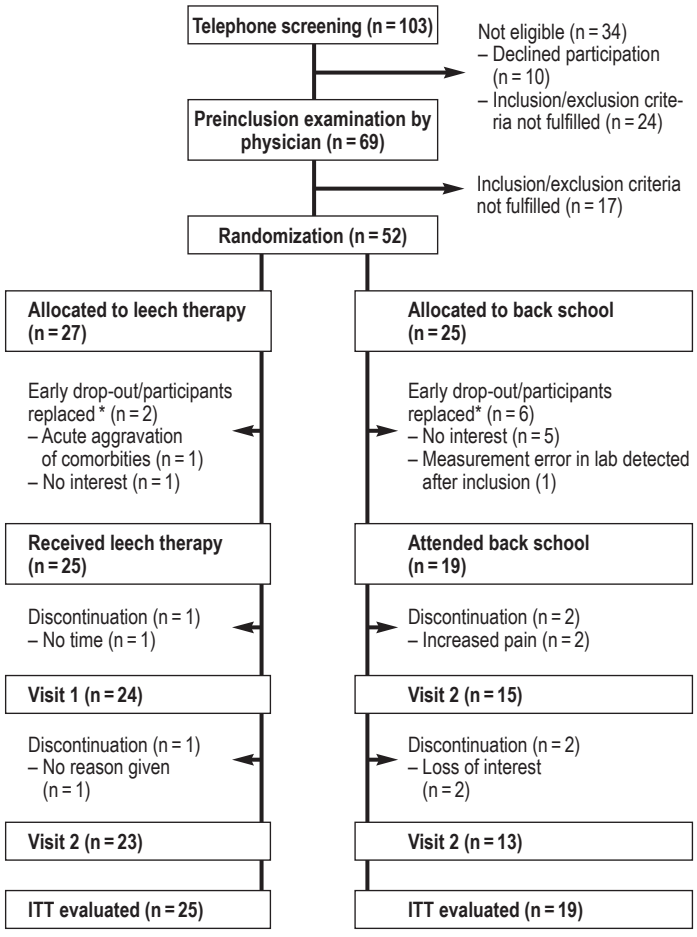
Chronic low back pain is a complex health problem of considerable epidemiological and therapeutic importance. It is one of the seven most commonly occurring diseases worldwide (1). In most cases the pain is caused by the interaction of several factors. Lack of exercise, overweight, overexertion, and a number of psychosomatic factors can all play a part and often reinforce each other in a vicious circle leading to chronification among the very large numbers of patients with acute low back pain (2–5). Despite advances in treatment—achieved largely by means of multimodal activation programs as recommended by current guidelines (6)—the success of treatment in individual cases leaves much to be desired, with increasing chronification and escalating therapy.

Leech therapy is a traditional medical procedure that is frequently employed for the treatment of chronic pain syndromes in European, Arabian, and Asian naturopathy. Historically, there is a long tradition of using leeches for clinical purposes, all the way from ancient Egypt and medieval Europe (7) to the recent renaissance in leech therapy (8). The leeches used in modern medical practice are mostly imported from Turkey and Bulgaria. Germany currently has one single leech breeding facility operating according to the standards of good manufacturing practice (GMP).

FIGURE 1



Flow chart (CONSORT) of study

* Participants replaced as early drop-outs were excluded before the first measurement of outcome parameters and were therefore not included in the ITT analysis.

CONSORT, Consolidated Standards of Reporting Trials; ITT, intention to treat

A number of randomized controlled trials have demonstrated the efficacy of leech therapy in alleviating pain and improving function for patients with osteoarthritis of the knee, osteoarthritis of the carpometacarpal joint of the thumb, and epicondylitis (9, 10). A meta-analysis has supported the effectiveness of leech therapy in osteoarthritis of the knee (11). Although back pain is by no means fully comparable with other musculoskeletal pain syndromes, on the basis of these findings it seems reasonable to investigate the efficacy of leech therapy for this indication.

The mechanism of action of leech therapy has not been fully elucidated. During the approximately 60 min of application the leeches release their saliva, containing more than 100 biologically active substances (12), into the wound. Recent biochemical studies have identified substances in the saliva that possess not only coagulation-inhibiting but also analgesic and anti-inflammatory properties (13). Furthermore, the leeches' saliva contains hyaluronidase, which increases the penetration depth of the other active substances. It is thought that the overall clinical effect is complemented by an antinociceptive action of the leech bite and by non-specific effects arising from the unusual nature of the treatment.

The aim of this clinical trial was to investigate the clinical effectiveness of leech therapy for chronic low back pain.

Methods

Study design

This proof-of-concept study was planned, approved, and conducted as a two-center, open, nonblinded, randomized controlled clinical trial. Formally a pharmaceutical trial, it was carried out according to the requirements of the German Medicines Act and the Ordinance on the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Use in Humans (GCP-V).

Eligible for inclusion were male and female patients between 18 and 70 years of age with confirmed, previously diagnosed chronic low back pain (chronic nonspecific lumbar spine syndrome). Patients were excluded on grounds of medicinal anticoagulation treatment, anemia, and for other reasons (see *eMethods* for details).

For the purposes of this trial four to seven leeches could be applied on one single occasion in an area 3 to 15 cm from the spinal column at the level of vertebrae L1 to S3. The control treatment comprised one 60-min session of exercise therapy each week for 4 weeks.

The outcome measures were determined at baseline, after 28 ± 3 days (visit 1; ± 3 corresponds to the tolerance set a priori for the time of measurement), and after 56 ± 5 days (visit 2). The primary outcome measure was the absolute change in average back pain intensity during the previous week (as measured using a 100-mm visual analog scale [VAS]) at the 28-day follow-up. The secondary outcome measures were, among others:

TABLE 1

Average intake of analgesic medications in % of maximal monthly dose (mean ± standard deviation) (maximal daily dose from product information multiplied by 28)

	Metamizole (novaminsulfon)	Diclofenac	Paracetamol	Ibuprofen	Acetylsalicylic acid	Naproxen	Average monthly analgesic consumption (as summed % of maximal monthly dose)
Leech therapy group							
Weeks –4 to 0 before study	0.36 ± 1.79	0.62 ± 2.20	0.00 ± 0	3.63 ± 6.20	0.00 ± 0	1.75 ± 8.57	6.40%
Weeks 1–4 during study*	0.71 ± 2.02	0.33 ± 1.44	0.00 ± 0	1.27 ± 5.43	0.05 ± 0.24	0.00 ± 0	2.35%
Weeks 5–8 during study*	0.43 ± 1.38	0.38 ± 1.90	0.00 ± 0	1.13 ± 3.11	0.00 ± 0	0.00 ± 0	1.94%
Exercise group							
Weeks –4 to 0 before study	0.20 ± 0.84	9.79 ± 28.08	0.12 ± 0.43	1.77 ± 5.65	0.00 ± 0	0.00 ± 0	11.88%
Weeks 1–4 during study*	0.19 ± 0.79	7.84 ± 24.95	0.00 ± 0	0.81 ± 2.15	0.00 ± 0	0.00 ± 0	8.83%
Weeks 5–8 during study*	0.00 ± 0	10.25 ± 29.95	0.00 ± 0	0.34 ± 0.772	0.04 ± 0.18	0.00 ± 0	10.63%

*According to patients' medication diaries
The monthly maximum dose was calculated from the daily maximal dose: metamizole 4000 mg x 28 = 112 000 mg; diclofenac 150 mg x 28 = 4200 mg; paracetamol 4000 mg x 28 = 112 000 mg; ibuprofen 2400 mg x 28 = 67 200 mg; acetylsalicylic acid 3000 mg x 28 = 84 000 mg; naproxen 1250 mg x 28 = 35 000 mg

- The intensity/frequency of analgesic medication, as recorded by the patient in a diary
- Limitations on daily functioning imposed by back pain (measured using the Roland–Morris Disability Questionnaire [RMDQ] and the Hannover Functional Ability Questionnaire for measuring back pain–related disability [*Funktionsfragebogen Hannover für Rückenschmerzen*, FFbH-R]) (14, 15)
- General quality of life (measured using the Short-Form Health Survey 36 [SF-36]) (16)
- Mood (using the Center for Epidemiological Studies Depression Scale [CES-D]) (17)
- Perception of pain (using the Pain Perception Scale [*Schmerzempfindungsskala*, SES]) (18).

Consumption of analgesics as medication on demand

To avoid any bias arising from changes of medication, no specific medication was stipulated for use in emergencies. To achieve approximate comparability for an important parameter in the treatment of chronic pain, the daily maximum dose as stated in the product information was multiplied by 28 to yield a monthly maximum dose. In the trial, the intakes of individual analgesics were summarized for the 4-week period immediately preceding baseline and the probands kept diaries to record consumption in the first (V1) and second (V2) 4-week periods after baseline. These intakes are presented here as percentages of the monthly maximum dose. The calculated monthly maximum doses for the drugs used were: metamizole (Novaminsulfon) 112 000 mg/month (4000 mg/day), diclofenac 4200 mg/month (150 mg/day), paracetamol 112 000 mg/month (4000 mg/day), ibuprofen 67 200 mg/month (2400 mg/day), acetylsalicylic acid 84 000 mg/month (3000 mg/day), naproxen 35 000 mg/month (1250 mg/day).

A detailed description of the methods employed can be found in the *eMethods*.

Results

A total of 103 participants were contacted. Thirty-four of them either did not meet the inclusion criteria or exhibited insufficient interest in the trial. The remaining 69 participants were examined by the study physician and 17 could not be included. Eight participants who left the trial after randomization but before the first data acquisition point were replaced *(Figure 1)*. Before the commencement of treatment, expectations were higher among the members of the leech therapy group than in the control group. However, ANCOVA (Analysis of Covariance) of the primary outcome measure revealed that the participants' expectations had no significant influence on the result (mean difference 3.11; 95% confidence interval [−12.1; 5.9]; p = 0.4969). This was also the case for all of the secondary outcome measures.

The mean pain intensity was 61.2 ± 15.6 on the 100-mm VAS for the leech therapy group and 61.6 ± 14.7 for the exercise group. The average intake of analgesic medications, expressed as percentage of monthly maximum dose, was 6.40% versus 11.88% respectively *(Table 1)*. Before the beginning of the study, in addition to pain medication (100%), the participants' low back pain led to at least one session of physiotherapy in 100/91% of cases (intervention/control), massages in 82/73%, acupuncture in 53/91%, and rehabilitation measures in 53/45% *(Table 2)*.

TABLE 2

Baseline characteristics of the two groups (per-protocol analysis)

	Leech therapy (n = 25)	Exercise (n = 19)
Age (years ± SD)	59.29 ± 6.99	56.53 ± 7.8
Height (cm)	169.86 ± 9.92	168.53 ± 8.4
Weight (kg)	79.94 ± 15.9	72.52 ± 15.7
BMI	27.69 ± 5	25.53 ± 5.2
Proportion of women (%)	88 (n = 22/25)	95 (n = 18/19)
Duration of pain (years)	13.29 ± 14.01	11.18 ± 9.4
Expectations *1	4.00 ± 0.71	3.57 ± 1.06
MPSS stage I (n/%)	7/28	4/21
MPSS stage II (n/%)	13/52	11/57
MPSS stage III (n/%)	4/16	1/5
Physiotherapy (%) *2	100	91
Massage (%)	82	73
Acupuncture (%)	53	91
Rehabilitation (%)	53	45

BMI, body mass index; MPSS, Mainz Pain Staging System according to Gerbershagen, stages I–III as index for progress of pain; SD, standard deviation

*1 Related to the effect of the allocated treatment on a 5-point Likert scale

*2 Measures tried by the participants at least once during their history of pain before the commencement of the trial; percentages always for the given group

All members of the leech therapy group took part in the intervention. A median of seven leeches (min. five, max. seven) were used per treatment. The members of the back school group attended a median of four (min. three, max. four) of the four exercise sessions.

After inclusion of 44 participants the first intermediate evaluation was performed as foreseen by the sequential study design, and the trial was ended with a significant p value of 0.0018 for the primary outcome measure, a positive result *(Table 3)*.

Primary result

The leech therapy group showed a significantly greater reduction in VAS-rated pain at day 28 than the control group *(Figure 2, Table 3)*. At this time point, the VAS-assessed pain in the leech group had decreased by 25.2 mm more than that in the exercise group ([−41.0; −9.5]; p = 0.0018). Precise figures for all parameters, both in the per-protocol analysis without imputation of missing values and in the intention-to-treat evaluation with imputation can be found in *eTables 1 and 2*.

Secondary results

The VAS (for global impairment), the function inventories (RMDQ, FFbH-R), the SES, and the SF-36 all showed significant superiority of leech therapy on day 28 *(Table 1, Figure 3)*.

On day 56, leech therapy remained significantly superior for the function inventories RMDQ and FFbH-R and for physical quality of life. The difference between the two groups was no longer statistically significant for VAS-assessed pain (p = 0.056). The mean absolute pain reduction was still significantly improved in the leech group, but the values were scattered more widely.

The mood-related mental health scales of SF-36 and the SES showed improvement in both groups (study effect). The difference between the groups was not significant.

Safety and tolerability

Altogether, 20 adverse events were documented in 20 participants, none of them serious. Five of these events were classified as definitely connected with the leech therapy (prolonged continuation of bleeding up to 24 h [without anemia], n = 3; more intense itching on more than 3 days, n = 2). Six events (increased back pain) were classed as probably related to the treatment, five of them in the exercise group and one in the leech group. In this latter case there was a temporal association with heavy physical exertion on the day before the visit. Five events were rated as unlikely to be connected with the treatment, three in the leech group (influenza-like illness, cystitis, suspected biliary colic) and two in the back school group (migraine, influenza-like illness). Two members of the physiotherapy group dropped out because of worsening back pain.

Consumption of analgesics as medication on demand

The intake of analgesics decreased significantly in the leech therapy group, from 6.40% of the monthly maximum dose at baseline to 2.35% at V1 and 1.94% at V2. Analgesic consumption in the control group followed a U curve, from 11.88% at baseline to 8.83% at V1 and 10.63% at V2. The groups were heterogeneous, in that two members of the control group were taking very large amounts of analgesic medications at baseline.

Discussion

This randomized clinical trial was the first to evaluate the effectiveness of leech therapy in the management of nonspecific low back pain and compare it with a guideline-based standard treatment, i.e., kinesitherapy and back exercises. The reduction in pain at 28 days was significantly greater in the leech therapy group, and both functional improvement and enhancement of physical quality of life were more pronounced in the leech group at 28 days and 56 days. The outcome of exercise treatment was less positive than expected, possibly due to the fact that in many cases it was commenced at an early stage.

Both the almost 50% improvement in absolute pain and the absolute group difference of >20 mm on the VAS point to a clinically meaningful effect of leech therapy. The pain reduction achieved with leeches is quantitatively equivalent to the effects of conventional pharmacological treatments, e.g., nonsteroidal antirheumatic drugs. Hedges *g*, a measure of effect size, was −1.30 at V1 and −1.06 at V2. In other words,

TABLE 3

Means ± standard deviations for the outcome measures and mean group differences with 95% confidence intervals over the course of the study; p values of the ANCOVA model adjusted for baseline value and expectations (ITT analysis after imputation)

	Leech therapy (n = 25)			Exercise (n = 19)			Mean difference [95% CI] Day 28 ± 3	p	Mean difference [95% CI] Day 56 ± 5	p
	Day 0	Day 28 ± 3	Day 56 ± 5	Day 0	Day 28 ± 3	Day 56 ± 5				
VAS: pain	61.2 ± 15.6	33.1 ± 22.4	33.2 ± 21.8	61.5 ± 14.7	59.7 ± 16.7	56.9 ± 21.9	−26.6 [−38.5; −14.7]	0.0018	−23.6 [−37.1; −10.2]	0.0568
VAS: global impairment	59.6 ± 18.0	31.7 ± 23.8	31.0 ± 27.8	54.4 ± 24.5	51.0 ± 17.6	58.4 ± 28.6	−19.3 [−31.9; −6.7]	0.0286	−27.4 [−44.9; −10.0]	0.0592
Roland-Morris Disability Questionnaire	12.6 ± 4.3	6.7 ± 4.7	5.6 ± 4.1	12.2 ± 5.4	11.6 ± 5.4	15.3 ± 8.1	−4.8 [−8.0; −1.7]	0.0045	−9.7 [−13.9; −5.6]	0.0011
FFbH-R	58.8 ± 16.8	74.7 ± 15.8	75.7 ± 13.9	56.1 ± 16.9	56.9 ± 19.0	51.9 ± 18.6	17.8 [6.9; 28.7]	0.0084	23.8 [13.5; 34.2]	0.0119
SF-36: physical health summary scale	33.1 ± 9.7	42.6 ± 8.7	43.3 ± 8.4	33.8 ± 7.1	36.1 ± 9.2	30.5 ± 11.7	6.5 [0.9; 12.0]	0.03	12.9 [6.4; 19.4]	0.0132
SF-36: mental health summary scale	46.5 ± 9.8	48.1 ± 10.0	50.3 ± 11.3	46.3 ± 12.3	47.9 ± 14.1	45.4 ± 18.6	0.2 [−7.6; 7.9]	0.7804	5.0 [−4.9; 14.9]	0.1373
CES-D	17.1 ± 8.8	13.1 ± 8.6	11.9 ± 10.7	17.6 ± 10.3	17.5 ± 10.9	19.4 ± 16.9	−4.4 [−10.6; 1.7]	0.0429	−7.5 [−16.6; 1.5]	0.1078
SES: affective pain perception	30.5 ± 9.6	22.0 ± 6.7	19.9 ± 5.3	28.6 ± 7.8	24.2 ± 4.9	23.7 ± 6.9	−2.3 [−5.8; 1.2]	0.1419	−3.9 [−7.7; 0.0]	0.1775
SES: sensory pain perception	17.1 ± 5.5	13.7 ± 4.2	12.9 ± 3.1	17.5 ± 4.5	17.1 ± 3.9	17.5 ± 5.9	−3.3 [−5.7; −0.8]	0.0135	−4.6 [−7.7; −1.5]	0.0865

CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; FFbH-R, Hannover Functional Ability Questionnaire for measuring back pain–related disability (*Funktionsfragebogen Hannover für Rückenschmerzen);* ITT, intention to treat; SES, Pain Perception Scale (*Schmerzempfindungsskala*); SF-36, Short-Form Health Survey 36; VAS, visual analog scale

the effect size was strong (>0.8) at both follow-up visits. The corresponding figures for RMDQ functional improvement were −0.95 at V1 and −1.56 at V2. (See *eTable 3* for a detailed presentation of these results.)

Other, nonmedicinal procedures recommended in current international guidelines (19), such as physiotherapy, acupuncture, the Alexander technique, or yoga, are less effective than documented for leech therapy in our trial (20). Leech therapy should therefore be considered a useful option for the nonmedicinal/noninvasive management of back pain.

Limitations

One major limitation of this trial is the lack of blinding to treatment. The characteristic leech therapy process, with application of living creatures to the skin, the initial bite, and the subsequent prolonged bleeding, makes effective blinding practically impossible. Indeed, the attempt at blinding in one of the knee osteoarthritis studies was unsuccessful, with most patients correctly identifying their treatment (21). The absence of blinding means that the size of the nonspecific (placebo) effect cannot be measured accurately. However, statistical allowance for the probands' expectations—an important factor for nonspecific treatment effects—also showed no essential influence on the results.

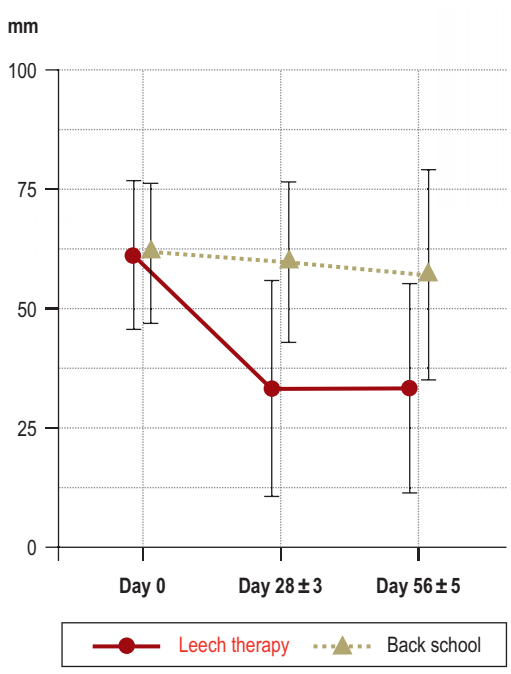
Nevertheless, it has to be assumed that the overall effect includes a considerable nonspecific component. Experimental clinical studies of nonpharmacological procedures in the treatment of pain show that the size of the treatment effect increases both with the invasiveness of the intervention and with the intensity of care (22). Leech therapy is characterized by a certain degree of invasiveness (leech bite, prolonged bleeding) and by a striking treatment setting (complex, unusual intervention involving living creatures). A strong nonspecific effect is thus likely due to the resulting neurocognitive processes.

The lack of a parameter based on objective assessment, e.g., the Physician's Global Assessment Scale, is another limiting factor. The fact that 91% of the members of the back school group had previously received comparable measures can also be viewed as a limitation. However, repeated use of physiotherapy is recommended in the guidelines.

A further limitation is the low number of cases in the trial. However, this was based on correct calculation and early attainment of the discontinuation criterion in the sequential design and was correspondingly determined by the high effect size of the leech therapy. The high drop-out rate in the control group, resulting in an imbalance of 25:19 evaluable participants on intention-to-treat criteria, must also be considered a limiting factor. However, a model calculation of the effect sizes for a hypothetical balanced distribution of 22:22 showed no meaningful alteration of the results, so we do not believe that the difference in group size essentially weakens the conclusions.

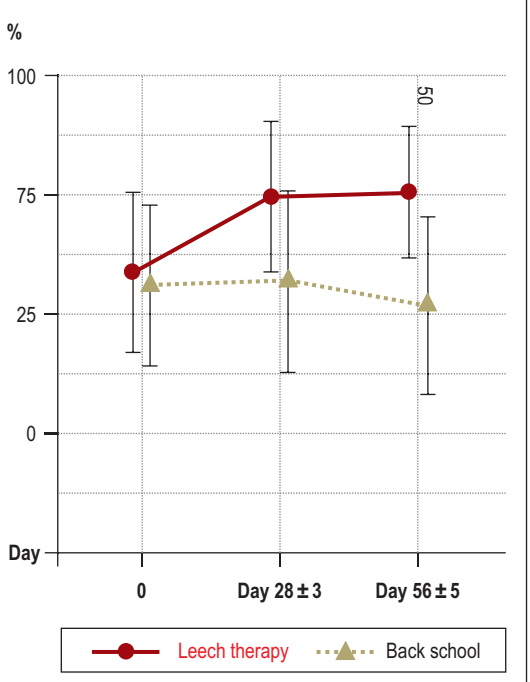
The groups differed with regard to analgesic intake at baseline. This may be viewed as showing a difference in perception of pain, particularly in view of the fact that analgesic consumption declined sharply in the treatment group. One last limitation is the possible selection bias, given that the participants were recruited in a tertiary study center.

FIGURE 2



Course of primary outcome measure, pain intensity (100-mm VAS). (primary outcome measure day 28 ± 3; p = 0.0018; expressed as mean ± standard deviation)
VAS, visual analog scale

FIGURE 3



Course of secondary primary outcome measure daily functioning (Hannover Functional Ability Questionnaire for measuring back pain–related disability, FFbH-R; expressed as % of functional capacity ± standard deviation)

Possible mechanisms of action

Several different mechanisms of action may have contributed to the clinical amelioration of back pain by the leech therapy. In osteoarthritis, the effect has been attributed particularly to the analgesic/anti-inflammatory substances present in leech saliva. However, an anti-inflammatory action seems less likely to be relevant for chronic nonspecific back pain than for symptomatic osteoarthritis. A positive effect of leech therapy has also been described in other clinical contexts, even including an individual case of cancer pain relief (23). The leech bite, in analogy with other invasive procedures such as injections and acupuncture, can be expected to have an antinociceptive action. Regional blood and lymph loss with resulting decongestion and improvement of the microcirculation may have a relaxing effect on the musculature. Finally, the above-mentioned nonspecific (placebo-like) actions may contribute to the overall effect.

Safety

In this trial, as in earlier studies of the use of leech therapy for pain relief, there were no clinically meaningful adverse events. Cases of infection with the symbiont *Aeromonas hydrophila*, found in leech saliva, have been repeatedly reported from plastic and reconstructive surgery (24), but this has not yet been observed in pain therapy. However, patients should be informed about the high rate of occurrence of localized itching and the persistence of localized reddening of the skin for a period of up to several weeks, as observed in this study.

Duration of effect

Our data permit no conclusions as to the duration of effect of leech therapy in patients with nonspecific low back pain. For osteoarthritis, mean durations of effect of 4 to 8 months have been reported (25). In principle, leech therapy can be repeated when the effect wears off; in our experience, second and subsequent treatments are just as effective as the first. In individual cases, however, there is the risk of the patient becoming allergic to components of leech saliva, precluding long-term treatment.

Summary

This first randomized controlled trial demonstrates the effectiveness of leech therapy for chronic nonspecific low back pain. Larger randomized and observational studies are needed to investigate the reproducibility of the effects, the adverse effects, and acceptance among less selected cohorts of patients. Furthermore, the comparative effectiveness and the long-term effects should be evaluated in further clinical, preferably multicenter, trials. In the event that the results are positive, coverage of the costs of leech therapy not only by private

Key messages

- One treatment with four to seven leeches applied to the lower back achieved significant relief of chronic low back pain, as measured using a 100-mm visual analog scale 4 weeks after treatment, compared with the control treatment of 4 hours' physiotherapy.
- Leech therapy significantly ameliorated pain-related limitations, functionality, and physical quality of life during the 8-week study period.
- In the absence of blinding, the participants' expectations had no significant effect on the results.
- In both groups, only minor adverse effects were noted.
- Leech therapy has the potential to be used as a complementary measure in the management of chronic low back pain.

medical insurance, as at present in Germany, but also by statutory insurance should be discussed.

Following previous studies, this trial provides further clear evidence that leech therapy probably represents an effective means of ameliorating chronic regional pain syndromes in the musculoskeletal apparatus as a whole. It may be worthwhile to try combining the pronounced relief of symptoms achieved by leech therapy with activating treatments.

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Conflict of interest statement
Mr. Hohmann receives fees for regular lectures at leech therapy training courses in cooperation with Biebertal Leech Farm GmbH. He has received reimbursement of travel and accommodation costs in connection with the training of therapists in leech treatment techniques.

Prof. Michalsen has received study support (third-party funding) from the Biebertal Leech Farm. Biebertal Leech Farm GmbH supported the trial materially (provision of leeches) and by paying the official study fees, the costs of insuring the probands, and, in part, the personnel costs for a 2-month period (study physician).

The remaining authors declare that no conflict of interests exists.

Data sharing
The authors are willing to share the data arising from this study with others, for scientific purposes.

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Corresponding author
Prof. Dr. med. Andreas Michalsen
Klinik für Innere Medizin, Abteilung für Naturheilkunde
Immanuel Krankenhaus
Königstr. 63,
14109 Berlin, Germany
a.michalsen@immanuel.de

► **Supplementary material**

eMethods, eTables:
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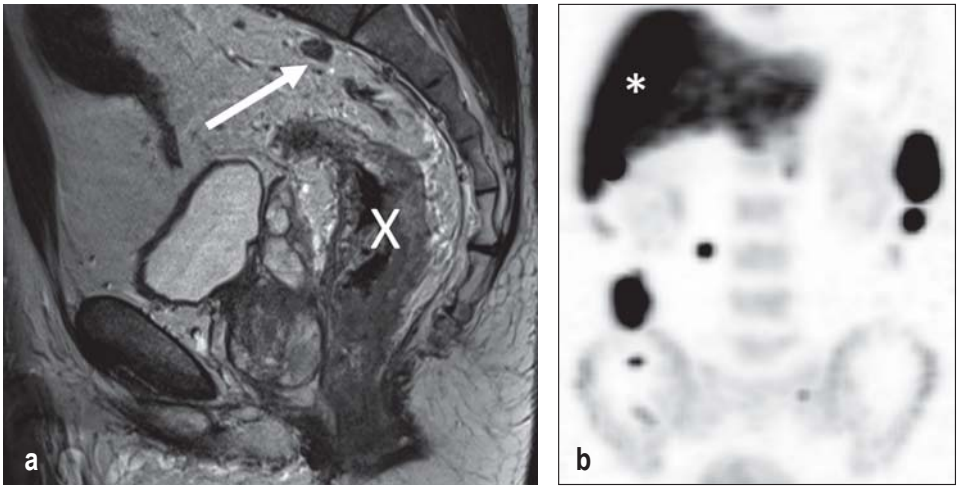
CLINICAL SNAPSHOT

Diagnosis: Splenosis

In a 43-year-old man, rectal cancer (T3c on MRI criteria) with lymph-node metastases *(Figure a)* was confirmed by examination of endoscopically obtained biopsy samples. Further investigation (thoracic and abdominal computed tomography and magnetic resonance imaging of the pelvis minor) revealed numerous nodular foci throughout the abdomen. The patient reported abdominal trauma with rupture and resection of the spleen 27 years earlier. Splenic scintigraphy with 99mTc-marked heat-damaged red blood cells was performed to determine whether these nodules represented peritoneal carcinosis or splenosis *(Figure b)*. In the course of degeneration, heat-damaged red blood cells accumulate in splenic and hepatic tissue. The scintigraphy confirmed the suspicion of secondary splenosis. The rate of intra-abdominal autotransplantation of splenic tissue following rupture and post-traumatic resection of the spleen is reported in the literature as 65 to 80%. After neoadjuvant radiochemotherapy and restaging, surgical treatment of the patient's rectal cancer was planned.



a) MRI of the pelvis minor in the sagittal plane: X, rectal cancer; arrow, lymph-node metastasis
b) Maximum-intensity projection of splenic scintigraphy in the frontal plane: numerous abdominal "hotspots" with physiological appearance of the liver (*); in a fusion of the SPECT and MRI slices (not shown) the abdominal splenic foci showed up as hotspots.

Dr. med. Christoph Erxleben, Klinik und Hochschulambulanz für Radiologie, Charité – Universitätsmedizin Berlin, Campus Benjamin-Franklin, christoph.erxleben@charite.de

Dr. med. Roland Scherer, Zentrum für Darm- und Beckenbodenchirurgie, Krankenhaus Waldfriede, Berlin

PD Dr. med. Thomas Elgeti, Klinik und Hochschulambulanz für Radiologie, Charité – Universitätsmedizin Berlin Campus Benjamin-Franklin, Klinik für Nuklearmedizin, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum

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Supplementary material to:

The Effectiveness of Leech Therapy in Chronic Low Back Pain

A Randomized Controlled Trial

by Christoph-Daniel Hohmann, Rainer Stange, Nico Steckhan, Sibylle Robens, Thomas Ostermann, Arion Paetow, and Andreas Michalsen

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eMETHODS

Methods

Study design

This proof-of-concept study was planned and conducted as a two-center, open, nonblinded, randomized controlled clinical trial. Formally a pharmaceutical trial, it was carried out according to the requirements of the German Medicines Act (AMG) and the Ordinance on the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Use in Humans (GCP-V). Approval was obtained at federal level (Federal Institute for Drugs and Medical Devices, BfArM) and from the local ethics committee (State Office for Health and Social Affairs, Berlin [*Landesamt für Gesundheit und Soziales Berlin*]). The study was registered under the EudraCT number 2011–004393–28 (EudraCT, European Union Drug Regulatory Authorities Clinical Trials) and under number DRKS00004871 at the German Clinical Trials Registry.

Study participants

Participants for the study were recruited by placing advertisements and distributing information materials and flyers. Applicants were screened in telephone conversations with study center staff, and those who passed preselection (questioning about the inclusion and exclusion criteria using a predetermined protocol) were invited to attend the study center for examination by the study physician. Probands found to fulfill the criteria for inclusion were given written and oral information about the trial. All study participants signed a form to indicate their informed consent.

By consenting to participate in the study, the participants declared their willingness to continue all ongoing treatments and physical activities unchanged and not to start any new treatment interventions unless urgently required and after consultation with the study center.

Inclusion criteria

- Men and women in the age range 18 to 70 years
- Pre-existing diagnosis of chronic nonspecific lumbar spine syndrome (chronic low back pain), confirmed by a specialist physician (orthopedics, neurology, pain therapy), over a period >3 months
- Mean initial pain intensity ≥ 40 mm on a visual analog scale (VAS) of 0 to 100 mm and pain on at least 4 days of each week for the previous 3 months

Exclusion criteria

- Pre-existing anticoagulant medication
- Hemophilia
- Anemia or known erythropoietic disorder
- Erosive gastritis, gastrointestinal bleeding, or gastric ulcer in the previous 3 months
- Immune-suppressing medication, pronounced allergic diathesis
- Regular intake of opioid analgesics
- History of wound healing disorders or keloid formation
- Invasive spinal treatment within the previous 6 weeks or planned within the next 8 weeks
- Prolapsed disk within the previous 3 months
- Severe comorbidity
- Pregnancy, breastfeeding
- Known diagnosis of a somatoform pain disorder
- Rheumatoid arthritis, spondylarthropathy, or other inflammatory joint disease
- Previous leech therapy for back problems
- Ongoing application for early retirement owing to back problems

Randomization

The included participants were block-randomized (block size 11) in a ratio of 1:1 to a leech therapy group and an exercise group. The randomization list was produced by an independent biometrician with the aid of the random number generator "ranuni" (SAS®). Using this list, an assistant not involved in the study prepared sealed opaque envelopes that contained the allocation and featured the serial proband number. At the conclusion of the initial examinations, the envelopes were opened and the participants were assigned to their group.

Interventions

Leech therapy: The leech therapy comprised a single local application of four to seven leeches in an area 3 to 15 cm from the spinal column at the level of vertebrae L1 to S3. Following careful examination of each participant's back by the study physician, the leeches were preferentially applied at points of maximal pressure sensitivity and at zones of hardened and/or swollen connective tissue. No two leeches were placed closer than 5 cm to each other in any direction, and there were a maximum of four leeches per square decimeter. The number of leeches used depended on the area of the participant's lower back and on the extent of the zones classed as requiring treatment.

As stipulated by BfArM, all of the leeches used for this study were bred in Germany. The breeder adheres to GMP standards and the leeches are kept in species-appropriate conditions. After being used for treatment the leeches can be returned to the breeding facility, where they are again kept appropriately in a separate area ("pensioner's pond").

Back school/ exercise treatment: The control intervention was a 4-week course of exercise treatment with one 60-min session each week. The exercise consisted of aerobic training in the form of Nordic walking plus various back exercises in small groups under the supervision of a physiotherapist.

Both groups also received a brochure containing advice on how to behave in the presence of chronic low back pain ("back school"), produced by the health insurance provider *Techniker Krankenkasse*.

Outcome measures

The outcome measures were documented at the beginning of the study (baseline), after 28 ± 3 days (visit 1, V1) and after 56 ± 5 days (visit 2, V2). The primary outcome measure was the absolute change in average intensity of back pain during the previous week (100-mm VAS) at 28 days after the intervention.

The secondary outcome measures at both visits were defined as follows:

- Average global impairment by back pain during the previous week (100-mm VAS)
- Intensity and frequency of regular and rescue analgesic medication (diary)
- Roland–Morris Disability Questionnaire (RMDQ) (14)
- Hannover Functional Ability Questionnaire for measuring back pain–related disability (*Funktionsfragebogen Hannover Rückenschmerz*, FFbH-R) (15)
- Short-Form Health Survey 36 (SF-36) to document general quality of life (16)
- Mood, depression (by means of Center for Epidemiological Studies Depression Scale, CES-D) (17)
- Affective and sensory pain perception, using the Pain Perception Scale (*Schmerzempfindungsskala*, SES) (18)
- Average back pain during the previous week (100-mm VAS) at V2.

The participants' expectations regarding the planned intervention were recorded on a 5-point Likert scale immediately after the beginning of the study. To assess tolerability and safety, the probands were asked to report any adverse events at each study visit. The RMDQ and the FFbH-R are considered the best patient survey inventories for objective recording of the restrictions in daily activities caused by back pain. The German National Disease Management Guidelines (*Nationale VersorgungsLeitlinien*, NVL) emphasize the importance of depressive cofactors. We therefore also documented these factors in order to determine whether there was any study/placebo effect on mood and therefore indirectly on pain intensity. The Mainz Pain Staging System (MPSS) according to Gerbershagen, stages I to III, was used to assess the degree of chronification. Tolerability and safety were documented on the basis of the adverse events reported at the study visits.

Sample calculation and statistical analysis

The group sequential study design according to O'Brien and Fleming (26, 27) was used with the software Addplan to determine the sample size with a planned interim analysis. The overall sample size needed to demonstrate an effect size ≥ 0.75 at a one-sided level of $\alpha = 2.5\%$ and power of 84% was 66 probands (33 in each group). An effect size of at leat 0.75 corresponded to the assumption that with a standard deviation (SD) of 18 mm, the VAS pain score would decrease by 24 mm in the leech therapy group and 10 mm in the control group. In the knee osteoarthritis study by Michalsen et al. (28), pain reduction of 10 mm (SD = 18) was seen in the control group, while in the leech therapy group the decrease was 34 mm (SD = 19). The assumption of pain reduction of 24 mm is thus rather conservative.

For the interim analysis after inclusion of 44 patients, the study process was defined as follows with the aid of the one-sided sequential procedure:

- If $p<0.0071$: termination of the study with a positive result.
- If $p \geq 0.5$: termination of the study with a negative result. It can be assumed that a successful result would also not be achieved with a larger study group.
- If $0.0071 \leq p<0.5$: continuation of the study with 66 participants and termination with a positive result, if $p<0.02261$.

This test observes the multiple one-sided level of $\leq 2.5\%$ and the two-sided level of $\leq 5\%$.

Analysis of the documented outcome measures ensued in the framework of the intention-to-treat method. Missing values were imputed with correlation models according to the Markov chain Monte Carlo method. No restrictions were imposed on the range of the imputed results. Via the procedure PROC Mi, 50 different complete data sets were created (29).

For the primary outcome measure of VAS pain reduction, a univariate covariance analysis model (ANCOVA) was used in the framework of the general linear model (SAS procedure PROC GLM) in which the outcome measure was modeled as a function of group membership (classified, fixed factor on two levels), the baseline value (linear, fixed covariate), and the participant's expectations (ordinal, fixed factor on five levels).

Evaluation of the secondary outcome measures was analogous to that of the primary outcome measure in the general linear model, taking the baseline value and the probands' expectations into account. Regression coefficients were calculated with their 95% confidence intervals and p values.

Official approval to conduct the study was granted on 12 July 2012. The first patient was recruited in May 2013, and the last follow-up visit took place in February 2016.

eTABLE 1

Descriptive parameters without imputation: number of probands without missing data (n), mean (M), and standard deviation (SD) at baseline (B), visit 1 (V1) and visit 2 (V2)

Variable	Visit	Leech therapy			Physiotherapy		
		n	M	SD	n	M	SD
Expectations	B	25	4.00	0.71	17	3.53	1.01
100-mm VAS: pain	B	25	61.23	15.60	19	61.55	14.76
	V1	24	33.74	22.71	17	60.44	17.52
	V2	23	31.62	21.52	15	53.47	23.19
100-mm-VAS: impairment	B	25	59.66	17.98	19	54.41	24.46
	V1	24	32.67	23.90	17	50.77	18.42
	V2	23	26.41	22.67	15	50.21	25.55
Roland–Morris Disability Score	B	25	12.60	4.28	19	12.16	4.39
	V1	24	6.83	4.74	17	11.59	4.80
	V2	23	5.09	3.76	15	12.60	5.12
FFbH-R: Functional capacity in %	B	25	58.83	16.77	19	56.14	16.92
	V1	24	74.20	15.90	17	56.37	19.04
	V2	23	76.05	14.46	15	53.33	18.31
SF-36: physical functioning	B	25	52.60	23.98	19	53.68	22.52
	V1	24	72.50	18.00	17	56.47	21.34
	V2	23	76.67	17.39	14	52.38	21.57
SF-36: physical role functioning	B	25	28.00	39.74	19	30.26	32.89
	V1	24	63.54	38.99	17	51.47	43.72
	V2	23	78.26	33.12	13	57.69	41.31
SF-36: emotional role functioning	B	22	54.55	45.48	19	59.65	42.42
	V1	24	70.83	37.19	17	72.55	39.50
	V2	23	81.16	37.37	14	78.57	38.36
SF-36: social role functioning	B	25	71.00	22.74	19	64.47	25.77
	V1	24	75.52	21.64	17	72.06	24.82
	V2	23	84.78	18.06	15	75.83	25.21
SF-36: mental health	B	25	60.64	17.46	19	63.16	18.45
	V1	24	72.83	14.78	17	67.76	21.28
	V2	23	75.30	14.65	15	69.87	20.78
SF-36: bodily pain	B	25	30.24	15.03	19	35.11	12.74
	V1	24	56.21	19.48	17	39.76	15.13
	V2	23	58.65	20.40	15	35.73	17.99
SF-36: vitality	B	25	41.80	18.65	19	41.58	16.50
	V1	24	52.50	21.32	17	44.71	17.81
	V2	23	57.39	15.58	15	49.67	17.97
SF-36: general health perceptions	B	25	52.40	20.71	19	54.37	20.63
	V1	24	59.00	18.99	17	54.88	21.21
	V2	23	59.51	14.91	15	54.72	23.27
SF-36: change in health (only for this SF-36 variable are lower values better)	B	25	3.24	0.78	19	3.32	0.89
	V1	24	2.79	0.93	17	3.00	0.61
	V2	22	2.50	0.91	14	3.14	0.77

SF-36: physical summary scale	B	22	33.80	9.70	19	33.83	7.08
	V1	24	42.47	8.81	17	35.94	9.68
	V2	23	44.29	8.06	13	33.97	8.59
SF-36: mental summary scale (larger = better)	B	22	45.97	10.29	19	46.27	12.26
	V1	24	48.90	9.21	17	49.23	13.04
	V2	23	51.53	9.16	13	51.41	12.77
CES-D: depression summary score (smaller = better)	B	25	17.08	8.81	19	17.58	10.26
	V1	24	12.29	7.78	17	16.59	10.14
	V2	23	10.83	8.38	15	12.87	7.63
SES: affective pain perception (larger = worse)	B	25	30.50	9.58	19	28.58	7.78
	V1	23	21.98	6.93	17	24.02	4.88
	V2	23	19.50	5.17	15	24.19	6.86
SES: sensory pain perception (larger = worse)	B	24	17.09	5.56	18	17.56	4.6
	V1	23	13.48	4.24	17	16.53	3.59
	V2	23	12.45	2.76	15	16.05	5.43

CES-D, Center for Epidemiological Studies Depression Scale; FFbH-R, Hannover Functional Ability Questionnaire for measuring back pain–related disability (*Funktionsfragebogen Hannover Rückenschmerz*); SES, Pain Perception Scale (*Schmerzempfindungsskala*); SF-36, Short Form Health Survey 36; VAS, visual analog scale

eTABLE 2

Descriptive parameters after imputation: mean (M) and standard deviation (SD) at baseline visit (B), visit 1 (V1), and visit 2 (V2)

Variable		Leech therapy (n = 25)		Physiotherapy (n = 19)	
		M	SD	M	SD
Expectations	B	4.00	0.71	3.57	1.06
100-mm VAS: pain	B	61.23	15.60	61.55	14.76
	V1	33.14	22.43	59.75	16.66
	V2	33.21	21.79	56.85	21.85
100-mm-VAS: impairment	B	59.66	17.98	54.41	24.46
	V1	31.75	23.84	51.04	17.63
	V2	30.98	27.81	58.42	28.62
Roland–Morris Disability Score	B	12.60	4.28	12.16	4.39
	V1	6.72	4.68	11.56	5.44
	V2	5.58	4.09	15.30	8.05
FFbH-R: Functional capacity	B	58.83	16.77	56.14	16.92
	V1	74.72	15.79	56.92	18.96
	V2	75.71	13.94	51.88	18.58
SF-36: physical functioning	B	52.60	23.98	53.68	22.52
	V1	72.32	17.64	56.15	20.31
	V2	75.03	17.60	44.21	25.58
SF-36: physical role functioning	B	28.00	39.74	30.26	32.89
	V1	62.18	38.78	48.86	46.72
	V2	71.52	41.36	4.70	112.34
SF-36: emotional role functioning	B	56.84	45.69	59.65	42.42
	V1	68.60	38.07	68.69	43.19
	V2	75.63	43.79	39.29	84.92
SF-36: social role functioning	B	71.00	22.74	64.47	25.77
	V1	74.62	21.66	69.81	28.65
	V2	83.46	19.31	72.99	31.15
SF-36: mental health	B	60.64	17.46	63.16	18.45
	V1	71.25	16.50	65.52	22.57
	V2	73.29	18.00	61.91	30.42
SF-36: bodily pain	B	30.24	15.03	35.11	12.74
	V1	56.31	19.07	39.68	15.07
	V2	56.76	20.92	29.91	28.85
SF-36: vitality	B	41.80	18.65	41.58	16.50
	V1	51.74	21.21	43.99	17.23
	V2	55.40	16.57	43.94	22.80
SF-36: general health perceptions	B	52.40	20.71	54.37	20.63
	V1	58.95	18.60	55.41	20.09
	V2	57.12	16.56	55.41	28.37
SF-36: change in health (only for this SF-36 variable are lower values better)	B	3.24	0.78	3.32	0.89
	V1	2.80	0.91	3.03	0.62
	V2	2.60	0.92	3.72	1.41
SF-36: physical summary scale	B	33.04	9.65	33.83	7.08
	V1	42.62	8.66	36.17	9.25
	V2	43.34	8.42	30.46	11.71
SF-36: mental summary scale (larger = better)	B	46.50	9.84	46.27	12.26
	V1	48.05	9.97	47.89	14.06
	V2	50.36	11.29	45.36	18.61
CES-D: depression summary score	B	17.08	8.81	17.58	10.26

CES-D, Center for Epidemiological Studies Depression Scale; FFbH-R, Hannover Functional Ability Questionnaire for measuring back pain–related disability (*Funktionsfragebogen Hannover Rückenschmerz*); SF-36, Short Form Health Survey 36; VAS, visual analog scale

eTABLE 3

Effect sizes (Hedges g)

	Visit 1 (day 28 ± 3)		Visit 2 (day 56 ± 5)	
	Mean difference leech therapy vs exercise	Effect size n1 = 25 n2 = 19	Mean difference leech therapy vs exercise	Effect size n1 = 25 n2 = 19
100-mm VAS: pain	–26.61	–1.30	–23.65	–1.06
100-mm-VAS: global impairment	–19.29	–0.89	–27.44	–0.96
Roland–Morris Disability Questionnaire	–4.83	–0.95	–9.73	–1.56
FFbH-R	17.80	1.02	23.83	1.45
SF-36: physical summary scale	6.45	0.71	12.89	1.27
SF-36: mental summary scale	0.16	0.01	4.99	0.33
CES-D	–4.44	–0.45	–7.52	–0.54
SES: affective pain perception	–2.26	–0.37	–3.87	–0.63
SES: sensory pain perception	–3.29	–0.80	–4.62	–1.00

CES-D, Center for Epidemiological Studies Depression Scale; FFbH-R, Hannover Functional Ability Questionnaire for measuring back pain–related disability (*Funktionsfragebogen Hannover Rückenschmerz*); SES, Pain Perception Scale (*Schmerzempfindungsskala*); SF-36, Short Form Health Survey 36; VAS, visual analog scale