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Effectiveness of leech therapy in women with symptomatic arthrosis of the first carpometacarpal joint: A randomized controlled trial

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Abstract

Leech therapy has been shown to be effective for symptomatic treatment of osteoarthritis of the knee. We aimed to investigate the effectiveness of leech therapy in another type of osteoarthritis, osteoarthritis of the first carpometacarpal joint (thumb saddle joint). Thirty-two women with symptomatic painful osteoarthritis of the first carpometacarpal joint and who scored > 40 mm on a 100 mm VAS pain scale were randomized to a single treatment with 2–3 locally applied leeches (leech group) or a 30-day course with topical diclofenac twice a day. Primary outcome measure was change of overall pain (mean of VAS for pain at rest, in motion, during grip) from baseline to day 7. Secondary outcomes were functional disability (DASH-questionnaire), quality of life (QoL, SF-36) and grip strength. Patients were examined baseline and at days 7, 30 and 60 after treatment. Overall pain score at day 7 was reduced from 59.6 ± 13.8 to 27.1 ± 20.6 in the leech group ($n = 16$) and from 50.6 ± 13.3 to 46.9 ± 18.5 with diclofenac ($n = 16$) (group difference -26.5, 95%CI -40.3; -12.7; $p = 0.0003$). Group differences for pain relief favoring the leech treatment increased at days 30 and 60. Significant treatment effects were also observed for the DASH score, QoL and grip. Results were not affected by outcome expectation or consumption of analgetics. A single course of leech therapy is effective in relieving pain, improving disability and QoL for at least 2 months. The potential of leech therapy for treatment of arthritic pain and underlying mechanisms should be further investigated.

Keywords: Carpometacarpal joint; Leech therapy; Osteoarthritis; Randomized trial

1. Introduction

Medicinal leeches were applied widely in ancient times to relieve regional pain, including that of osteoarthritis [1,7]. We previously could show that a single topical application of leeches effectively relieves pain and improves joint function in osteoarthritis of the knee [18,19]. To date, it is unknown if leeches therapy is also beneficial in other forms of joint osteoarthritis. More than 30 biological active substances have been identified in leech saliva, among them are a variety of potent anti-inflammatory substances, hyaluronidase and several thrombin-inhibitors [3,26,27]. For the most potent thrombin-inhibitor in leech saliva, hirudin, antiinflammatory effects have been described [15], and arthritis is

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linked to local and systemic activation of coagulation and fibrinolysis pathways [34].

In view of the potential of leech therapy in osteoarthritis and the current lack of randomized trials, we designed this trial to assess the symptomatic effectiveness of leech therapy in symptomatic osteoarthritis of the first carpometacarpal joint. The first carpometacarpal joint is commonly targeted by the osteoarthritic process. According to a recent European study 36% of subjects aged > 55 years have radiographic signs of osteoarthritis of the first carpometacarpal joint [5]. Estimates of the prevalence of this form of osteoarthritis show a female preponderance and a rate of up to 20% of postmenopausal women being affected by this type of osteoarthritis [2,9]. Osteoarthritis of the first carpometacarpal joint frequently leads to painful dysfunction of the thumb joint and hand function, thus impairing daily life activities and quality of life. Conventional treatment strategies are limited and consist of analgetic medication, topical administration of NSAIDs, intraarticular injections of corticosteroids and hyaluronic acid [8], and, in more severe cases surgical interventions [38]. We aimed to evaluate the symptomatic effect of leech therapy compared to topical NSAIDs in osteoarthritis of the first carpometacarpal joint and hypothesized that leeches therapy is more effective than commonly used topical diclofenac therapy.

2. Methods

The study was designed as a randomized controlled open trial. The study protocol was reviewed and approved by the Ethics Committee of the University Hospital Essen and by the German Federal Institute for Drugs and Medical Devices. Patients were screened and recruited between August and December 2005. Patient treatments and follow-ups were completed by April 2006. All study procedures and data collection were performed at the outpatient clinic of the Kliniken Essen – Mitte, academic teaching hospital of the University Duisburg – Essen.

2.1. Study procedures

We recruited participants through a press release. Eligibility was determined during telephone screening interviews. Candidates then were scheduled for enrolment visits. A study physician performed a targeted physical examination and pain ratings were performed. If patients had not had radiographs the preceding 3 months, they were taken at this study visit. Enrolled patients were invited for a second study visit during which they completed baseline questionnaires and underwent testing of grip strength. Thereafter, the participant was randomly assigned to either leech or topical diclofenac therapy and the allocated treatment started. During subsequent study visits on days 7, 30 and 60 all outcomes were assessed except grip strength by vigorimetry, which was assessed on days 7 and 60 only. Due to technical problems measurement of grip strength was not available in the first six of enrolled patients.

2.2. Study participants

Patients were eligible if they were female, >40 years old and met radiographic criteria of osteoarthritis of the first metacarpal joint according to Eaton Classification [6]. Symptoms had to have lasted at least 3 months. In addition, patients were required to have a pain rating of >40 mm in one of the three pain scales (Visual Analog Scales (VAS) 0–100 mm) for pain at rest, in motion, during grip). We excluded subjects with clinical evidence for rheumatoid arthritis and those that had undergone surgery of the joint or intraarticular injections within the previous 3 months. Further criteria for exclusion were anticoagulation or haemophilia, anaemia, polyneuropathy, or coexisting serious illnesses. Patients regularly taking rescue medication with NSAIDs or analgetics were not excluded if the mean weekly dosage and type of administration had not been altered during the preceding 3 months.

2.3. Randomization

Patients were randomly allocated to the treatments by a non-stratified block-randomization with varying block lengths and by preparing sealed, sequentially numbered opaque envelopes containing the treatment assignments. Randomization and envelopes were prepared by the study biometrician. When a patient fulfilled all enrolment criteria the study physician opened the lowest numbered envelope to reveal that patient's assignment.

2.4. Interventions

The method of leeching was performed as previously described for the treatment of knee osteoarthritis [20]. In brief, 2–3 medicinal leeches (Hirudo medicinalis, Fa. Zaug, Biebertal, Germany) were applied once to the periarticular soft tissue of the affected thumb joint with preference to maximum pain points during examination and palpation. Leeches were left in place until they detached by themselves, after a mean of 50 min. The leeched area then was bandaged. Patients were asked to remove the bandage the next day and returned 7 days later for the first repeated measurement. Control group patients were given two tubes of 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 throughout days 0–30 and to discontinue application thereafter. Compliance with diclofenac gel treatment was assessed from the diaries and by interviewing the patients.

2.5. Outcome measures

The primary outcome measure was change in total pain score from day 0 to 7 as derived from the mean of the three single 100 mm VAS pain scores (pain at rest, in motion, during grip). Quality of life was defined as a secondary endpoint and assessed by the Medical Outcomes Study 36-Item -Short-Form (SF-36) [39]. Prespecified other secondary outcomes included functional impairment measured by DASH-questionnaire (Disabilities of the Arm, Shoulder and Hand) developed by the Upper Extremity Collaborative Group (UECG) [11] and grip strength of the thumb joint (lateral pinch power) mea-

sured with a specially designed device (Laboratory for Electronic Devices, Hannover Medical School, Hannover, Germany). Peak strength of three consecutive grip efforts was recorded and the total maximum value used.

Adverse effects and the use of oral rescue medication were monitored by means of the patient's diaries from day 0 to 60, and by interviews at days 7, 30 and 60. Blinded treatment of leeching is not feasible due to the specific nature of the treatment. To control for non-specific 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.

Trained, unblinded research assistants collected patient-reported data, and research personnel blinded to group allocation performed data entry and monitoring.

2.6. Sample size determination and statistical analysis

Following O'Brian and Fleming [25] the study was planned as a superiority trial and conducted according to a 3-stage group sequential design with pre-planned analyses after $n = 32$, 46 and 60 patients. The trial specific one-sided type I error rate was set at $\alpha = 2.5\%$ (corresponding to a two-sided level of 5%), Consequently, we fixed the adjusted two-sided significance levels for the three analyses at $\alpha_1 = 0.21\%$, $\alpha_2 = 0.97\%$ and $\alpha_3 = 2.16\%$ and defined to stop the trial for futility whenever the observed p-value exceeded 60%. We assumed that the overall pain would decrease by 24 ± 8 mm from baseline to day 7 in the leech therapy group and by 10 ± 8 mm in the diclofenac group. For this, a maximum sample size of 60 patients was calculated to achieve a power of 80% [40].

All outcome criteria were analysed by intention-to-treat analysis with repeated measurement analyses of covariance (ANCOVA) which took time as the within-subject factor, group as a between-subject factor, and the respective baseline value as a covariate. Missing data were multiply imputed following the suggestions of Little and Rubin [14]. In detail, we used the MCMC method of the MI procedure of the SAS/STAT® software [31], imputed missing values for each treatment group separately, and created 20 different sets of data, analysed them separately with the above described ANCOVA models and combined the results with the SAS MIANALYZE procedure.

Only one interim analysis of the primary outcome criterion was conducted. This analysis resulted in a p-value of $p = 0.0003$ which was substantially smaller than $\alpha_1 = 0.21\%$ so that the study was stopped.

Ancillary analyses of the overall pain score were done to adjust for the effects of possibly confounding variables, namely outcome expectation. Here, we added these variables as covariates to the ANCOVA models and estimated the group differences in the presence of these covariates.

3. Results

After first telephone screening 36 patients were invited for further assessment. Of these, 32 fulfilled all study criteria and agreed to study participation. Sixteen patients were randomly assigned to the leech therapy, 16 to topical diclofenac. One patient (diclofenac) was unwilling to return for further visits to the study center and withdrew from the study immediately at day 1. Compliance with diclofenac application was well with regular application in 14 of 15 patients at day 7 and 13 of 15 patients at day 30. The trial profile is summarized in Fig. 1.

Treatment groups were comparable at baseline with the exception of higher motion pain ratings in the leech group (Table 1). All patients had radiographically confirmed osteoarthritis of the first carpometacarpal joint and had received previous treatments against osteoarthritis.

3.1. Outcome measures

A greater benefit from leech therapy than from topical diclofenac was observed in the primary outcome measure, change of total pain of the thumb joint after day 7. The total (±SD) pain score was reduced from 59.6 (±13.8) to 27.1 (±20.6) in 7 days in the leech therapy group and from 50.6 (±13.3) to 46.9 (±18.5) in the diclofenac group (Fig. 2) resulting in a highly significant between group difference −26.5 (95%CI −40.3; −12.7; $p = 0.0003$, repeated measurement ANCOVA). The group difference persisted at day 30 (−26.5; 95%CI −40.4; −12.7) and increased with day 60 (−34.1, 95%CI: −47.9; −20.2; $p < 0.0001$). A significant and comparable group difference favoring the leech therapy was evident among all three subscales of pain (Table 2).

In addition, disability in daily life as assessed by the DASH score improved rapidly with leech therapy. This effect was maintained at days 30 and 60 and resulted in significant group differences favoring leech therapy at all time points. Quality of life was reduced at baseline in both groups and improved only in the leech therapy group to a relevant extent resulting in significant between group differences at days 30 and 60 (Table 3). Grip strength increased in the leech group from 42.5 ± 14.1 N to 50.8 ± 14.6 N at day 7 and 57.6 ± 10.2 N at day 60. In the control group grip strength remained unaffected at day 7 (47.5 ± 16.1 N to 47.4 ± 7.0 N) and slightly increased with day 60 (50.7 ± 16.6 N) resulting in a mean group difference of 10.2 (95%CI 1.8 to 18.5; $p = 0.021$).

The use of rescue medication was comparable in both groups throughout the study. Within the first 7 days two patients in each group had taken any oral rescue medication. On average, recourse to rescue medication was needed on fewer than 3% of all study days without significant differences between the groups.

3.2. Outcome expectation

Outcome expectation was significantly higher in the leech group compared to diclofenac group. However,

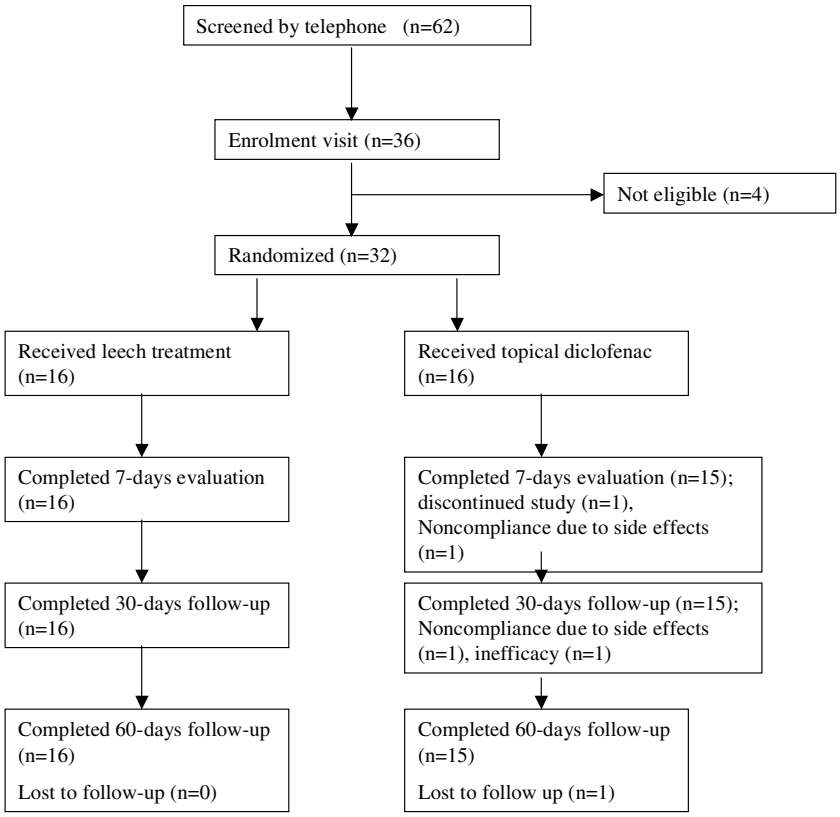

Fig. 1. Trial profile.

after adjustment for baseline outcome expectation, group differences between all outcomes remained largely unaffected. Thus, there was no indication that outcome was largely determined by treatment expectation (Fig. 3).

3.3. Safety

There were no serious adverse events in both study groups. A frequent initial minor adverse effect of leech therapy was local mild itching and skin reddening emerging 2–3 days after leech therapy in 13 out of 16 patients, which lasted for a mean of 4 days. In the diclofenac group 5 out of the 16 patients reported mild local skin reactions. Pain associated with the leeching procedure was rated as not severe by all patients in that group. A slight disgust in the face of leech therapy was reported by two subjects, and was not at all present in the other 14 subjects of the leech group. At the end of the study period 15 out of 16 patients in the leech therapy group and 13 out of 15 in the diclofenac group perceived their study treatment as very well tolerable.

Table 1
Baseline characteristics of study patients

Characteristic	Leech therapy ($n = 16$)	Topical diclofenac ($n = 16$)
Age (years)	64.1 ± 6.4	64.3 ± 9.1
Sex, female	16	16
Mean duration of symptoms ± SD (months)	74.1 ± 66.9	85.5 ± 80.1
Mean body mass index ± SD (kg/m^2)	27.3 ± 7.2	26.6 ± 4.9
Mean weight ± SD (kg)	74.9 ± 19.9	73.4 ± 11.5
Hypertension, *n* (%)	7 (44)	8 (50)
Mean overall pain score ± SD	59.6 ± 13.8	50.6 ± 13.3
Mean SF-36 physical quality of life score ± SD	42.3 ± 5.2	39.5 ± 7.4
Mean DASH sum score	47.0 ± 14.7	42.8 ± 9.8
Mean maximum grip power	42.5 ± 14.1	47.5 ± 16.1

SF-36, short-form 36 health survey; DASH, disabilities of the arm, shoulder hand questionnaire.

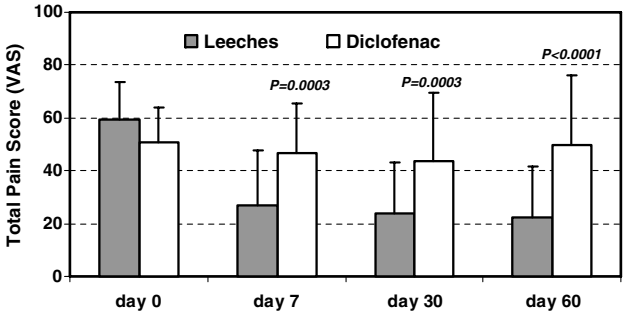

Fig. 2. Total pain score. Means ± SD of the total VAS pain score in the leech and topical diclofenac treatment groups in the study course. *p*-values were calculated from repeated measurement ANCOVA.

Table 2
Severity of joint pain at rest, in motion, during grip and group differences for change on treatment

	Baseline	Day 7	Day 30	Day 60
Rest pain				
Leech therapy	37.9 ± 21.7	12.0 ± 13.2	10.1 ± 9.7	8.6 ± 5.5
Diclofenac	27.0 ± 22.1	29.4 ± 22.2	32.7 ± 26.4	36.9 ± 27.6
Group difference (95%CI)		−21.3 (−33.9; −8.6)	−26.5 (−39.1; −13.8)	−32.2 (−44.9; −19.6)
p-value		0.0014	<0.0001	<0.0001
Motion pain				
Leech therapy	61.3 ± 18.6	29.0 ± 24.8	26.8 ± 23.4	23.7 ± 21.3
Diclofenac	48.4 ± 13.0	45.3 ± 20.8	44.0 ± 26.9	49.9 ± 28.2
Group difference (95%CI)		−25.4 (−40.9; −9.9)	−26.4 (−41.9; −10.9)	−35.3 (−50.8; −19.8)
p-value		0.0018	0.0012	<0.0001
Grip pain				
Leech therapy	79.8 ± 11.5	40.3 ± 27.2	35.3 ± 28.7	34.2 ± 29.9
Diclofenac	76.4 ± 13.6	66.1 ± 21.6	55.0 ± 27.8	61.8 ± 29.4
Group difference (95%CI)		−28.9 (−46.4; −11.5)	−22.9 (−40.3; −5.4)	−30.7 (−48.2; −13.3)
p-value		0.0017	0.0120	0.0009

Mean values ± SD and estimated group difference (95%CI), negative values indicate superiority of leech therapy.

4. Discussion

Symptomatic osteoarthritis of the thumb saddle joint is prevalent in ageing populations [5,9]. Since treatment options are limited, new therapeutic approaches should be considered. Leeches have been applied extensively to treat pain throughout medical history [24] and recently have been found to effectively relieve pain and improve joint function in osteoarthritis of the knee [18,19].

In this randomized trial, patients with osteoarthritis of the first carpometacarpal joint who were treated with leech therapy experienced clinically significant improvements in self-perceptions of pain for a period of at least 2 months. Moreover, the single course of leech therapy improved joint function, quality of life, and grip strength when compared with the results of a course of topical diclofenac.

The observed improvements are in accordance with the results of leech therapy for osteoarthritis of the knee and suggest that leech therapy may effectively alleviate the symptoms of osteoarthritis in other types of joints. At the outset the patients in the leech therapy group had slightly higher symptom scores, which might bias the results. But with the exception of pain with motion, the baseline differences were not significant, and since the study was randomized, these differences must have occurred by chance. Moreover, all reported results have been statistically adjusted for baseline differences.

Different mechanisms may explain the observed effects. First, a variety of pharmacological active substances besides hirudin have been described in leech saliva, such as histamin-like vasodilators, kallikrein and tryptase inhibitors, a variety of other proteinase inhibitors and anaesthetics [3,26,27,32]. Through the concomitant activity of a further leech saliva component, hyaluronidase [4] these substances might reach deeper tissue zones, and, possibly, the joint space. Hirudin itself is a potent thrombin-inhibitor and has recently been found to have potent antiinflammatory effects in arthritis [15,37]. In arthritis models, genes involved in coagulation showed enhanced expression, and arthritis was

Table 3
Physical quality of life (SF-36 questionnaire) and daily life disability (DASH-questionnaire) in study groups with group differences for change on treatment

	Baseline	Day 7	Day 30	Day 60
Quality of life				
Leech therapy	36.4 ± 6.4	39.1 ± 7.1	42.6 ± 9.1	42.8 ± 10.3
Diclofenac	39.7 ± 8.1	38.9 ± 6.4	38.4 ± 7.0	40.4 ± 7.1
Difference (95%CI)		2.4 (−1.9; 6.7)	6.5 (2.1; 10.8)	4.6 (0.3; 9.0)
p-value		0.2771	0.0043	0.0382
Disability-score				
Leech therapy	47.0 ± 14.7	30.3 ± 16.3	31.7 ± 19.8	24.8 ± 17.2
Diclofenac	42.8 ± 9.8	43.8 ± 13.2	42.7 ± 11.4	40.9 ± 16.7
Difference (95%CI)		−16.0 (−25.8; −6.2)	−13.5 (−23.4; −3.7)	−18.7 (−28.5; −8.5)
p-value		0.0019	0.0083	0.0003

Mean values ± SD and estimated group difference (95%CI).

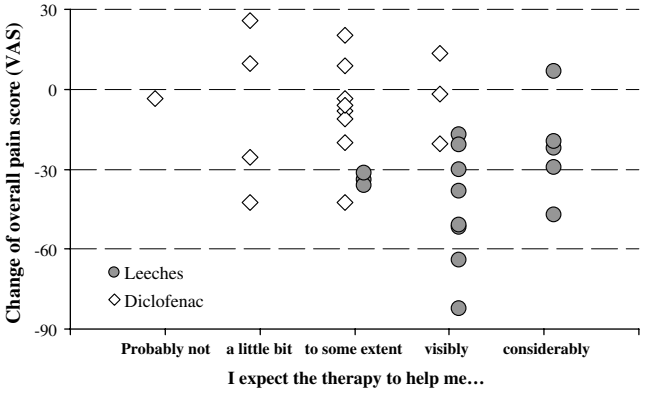

Fig. 3. Change of overall pain score (study day 7) and patient's expectations at baseline. Negative values indicate an improvement.

linked to local and systemic activation of coagulation and fibrinolysis pathways [30,34].

Second, nociceptive activation contributes to chronic pain [33] and leech therapy may alleviate pain by means of antinociceptive effects and by counterirritation. However, it is unclear to which extent leech bites may induce such mechanisms and it seems unlikely that the reduction of nociceptive input on a single occasion could have such lasting effects.

Third, leech therapy might only induce a powerful placebo effect. In fact, all invasive treatments, including arthroscopic surgery [23], may have relevant placebo-like effects. In a recent randomized trial a sham device was more effective in relieving pain than a placebo pill [12]. Therefore, the non-specific and placebo-like effects of leech therapy may result from its being an uncommon and invasive procedure. But, this is relevant only if placebos are indeed effective in treating pain syndromes, which is still open to discussion [10]. Of course it is possible that all three mechanisms play a role in alleviating the symptoms of osteoarthritis.

An important limitation is the open nature of this study. That is, the placebo-like effects of leeches therapy cannot be precisely assessed.

A sham leech treatment is not available at present, and treatment blinding is not feasible due to the very specific character of the treatment procedure (leech bite, sucking period, >12 h bleeding). We assessed outcome expectation in order to approximate the placebo-like effects. Although the scores indicated that the leech therapy group had higher expectations, the overall results did not change after adjustment for the confounding effect of outcome expectation. Therefore, while leech therapy seems likely to have a non-specific relevant effect, our results indicate that it also has a specific effect.

Further study limitations are due to the nature of the control treatment. In the present study leech therapy was compared to a 4-week topical NSAIDs treatment. Topical NSAIDs have been shown to be effective in treating osteoarthritis [13,16] and are recommended for the management of hand osteoarthritis [42]. However, only a few trials have included patients with osteoarthritis of the first carpometacarpal joint and these studies differ in methods of pain assessment and observation period [17,29,41].

In the present study, topical diclofenac was preferred over oral NSAIDs in order to compare two modalities of local treatment. Whereas there is some controversy about the endurance of pain relief with topical NSAIDs, existing data consistently show that they are effective within the time period of our selected primary outcome, 1 week [16,22,28]. Moreover, in larger trials with longer periods of observation, topical diclofenac was as effective as oral diclofenac and was more effective for longer periods than other topical analgetics and NSAIDs [28,35,36].

Of note, the general pain relief observed with topical diclofenac in this study was rather modest. General pain was reduced by 7% and 14% after 1 and 4 weeks, respectively, and pain relief was relevant only for grip pain, which was reduced by 28% after 4 weeks of topical diclofenac. In the largest trial on different types of hand osteoarthritis topical diclofenac reduced general pain by 18% after 1 week and by 35% after 3 weeks. The reduced effectiveness of topical diclofenac in our study may be due to the selection of patients, the small sample size, and the lower outcome expectations of patients receiving diclofenac. Nonetheless, the pain relief of about 60% by leeches in this study clearly exceeds the observed effects of topical NSAIDs in other trials on osteoarthritis [13,17]. However, to avoid overestimating the effects of leech therapy, future trials should use control therapies whose non-specific effects are more pronounced, i.e. invasive treatments and/or acupuncture.

We do not know, whether our findings may be generalized to male patients with osteoarthritis of the first carpometacarpal joint. Furthermore, this study may not have lasted long enough to fully assess the long-term effect of leech therapy. The symptomatic improvement persisted until the end of the 2-months study period. However, in the trial on leech therapy for knee osteoarthritis, the beneficial effect decreased after 3 months [18]. It may be useful to repeat leech therapy on patient request when treating osteoarthritis of the first carpometacarpal joint on a long-term basis.

Due to the group sequential design of the study and the clear impact of leech therapy on the primary outcome, the resulting study groups were rather small. Yet, treatment effects were consistent, and the observed group differences with a small sample size were significant, indicating that leech therapy may be beneficial in treating the symptoms of osteoarthritis of the first carpometacarpal joint. However, the magnitude of the effects may be overestimated due to the small sample sizes [21].

Leech therapy as applied in this study was safe and well tolerated. A common minor side effect with leech therapy was local itching with erythema. Patients therefore should be informed about this frequent adverse effect.

In conclusion, a single course of leech therapy seems to be effective in relieving pain and improving joint function for at least 2 months in women with symptomatic osteoarthritis of the first carpometacarpal joint. However, since the sample size was small and the intervention unblinded, the results of this study are preliminary. The efficacy and safety of this treatment should be further tested in larger and long-term randomized trials using other treatments as controls.

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