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Review

The efficacy and safety of medical leech therapy for osteoarthritis of the knee: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: It is controversial on whether medical leech therapy is effective in improving pain and functional outcome in patients with knee osteoarthritis (OA). Therefore, we perform a meta-analysis from randomized controlled trials (RCTs) to evaluate the efficacy and safety of medical leech therapy in patients with knee OA.
Materials and methods: The PubMed, EMBASE, ScienceDirect, and Cochrane Library databases were systematically searched for literature up to January 2018. RCTs involving medical leech therapy in patients with knee OA were included. Two independent reviewers performed independent data abstraction. The I^2 statistic was used to assess heterogeneity. A fixed or random effects model was adopted for meta-analysis. All meta-analyses were performed by using STATA 12.0.
Results: Four RCTs with 264 patients were included in this meta-analysis. The current meta-analysis showed that there were significant differences in terms of visual analogue scale (VAS) scores and WOMAC scores at 1 week, 4weeks and 7 weeks compared with control groups. However, leech therapy was associated with a significantly higher incidence of adverse events. The overall evidence quality is moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate.
Conclusion: Medical leech therapy was associated with a significantly improved outcome in pain relief and functional recovery in patients with symptomatic knee OA. However, given the inherent limitations in the included studies, this conclusion should be interpreted cautiously.

1. Introduction

Knee osteoarthritis (OA) is the most prevalent chronic joint disease. Cartilage is the central tissues affected by OA and causes subsequent symptoms include joint pain, stiffness and joint swelling, which diminishes the range of motion [1,2]. It is one of the major causes of deformity, resulting in huge medical expense and poor quality of life. It is reported that approximately 6% adults whose age above 30 years occurs symptomatic OA [3]. The number of patients with knee osteoarthritis has increased in tandem with population aging and it remains a huge healthcare challenge.

The goal of drug intervention is to relieve pain and improve functional outcome. Various strategies have been applied to treat the knee OA including local infiltration non-steroidal anti-inflammatory drugs (NSAIDs), peri-articular glucocorticoid, hyaluronic acid and platelet-rich plasma [4–7], however, a majority of patients complained of knee pain and the undesirable side effects. Currently, the optimal treatment remains controversial. Leech therapy is a kind of traditional treatment which is approved by the Food and Drug Administration (FDA) [8]. It has been used therapeutically for a few years and mainly for treating phlebitis and thrombosis due to the anticoagulant effect [9]. In the last decade, medical leech was found to have anti-inflammatory and anesthetic properties, thus studies have assessed the effect of leech therapy for reducing pain in knee OA. Michalsen et al. [10] reported that medical leech therapy appeared to be associated with a relieved pain from knee without major complications and it was less invasive than joint arthroplasty.

Currently, there remains controversial regarding the benefit effects of medical leech therapy for pain management in knee OA, due to the small sample size, inconclusive results and inaccurate evaluations of the published studies. Therefore, we perform a meta-analysis from randomized controlled trials (RCTs) to evaluate the efficacy and safety of medical leech therapy in patients with knee OA.

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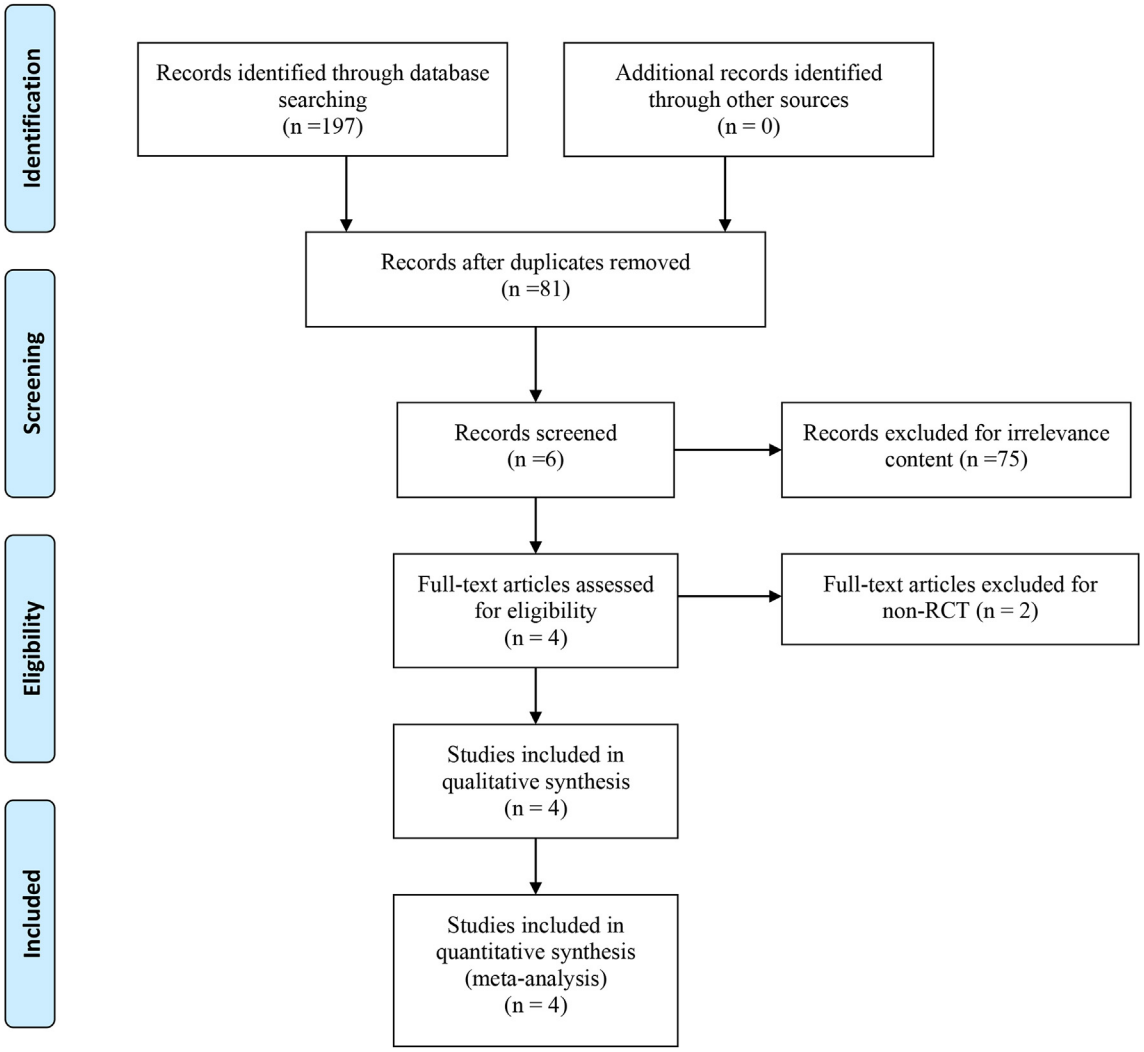

Fig. 1. Search results and the selection procedure.

2. Materials and methods

2.1. Search strategy

The PubMed, EMBASE, ScienceDirect, and Cochrane Library databases were systematically searched for literature up to January 2018. The searching strategy was applied as followings: "medical leech", "knee osteoarthritis" and "randomized controlled trial". Search terms were combined using the Boolean operators "AND" or "OR." Furthermore, the reference lists of manuscripts were also hand-searched to make sure some studies which were not identified by our original search were also be included in the present study. Moreover, there were no language restrictions. Two investigators independently selected articles according to the criteria described above. The full text were scanned to determine whether articles fit the inclusion criteria. We resolved disagreements by discussion until a consensus was search. If no consensus was reached, a third investigator was consulted.

2.2. Inclusion and exclusion criteria

The following inclusive selection criteria were applied: (a) population: patients with symptomatic knee OA; (b) Interventions: patients were treated by medical leech therapy; (c) Comparisons: in the control group, patients did not receive medical leech therapy; (d) outcome: visual analogue scale (VAS) scores, WOMAC scores and adverse effects; (e) design: RCTs. The exclusion criteria were as following: (a) letter, review, case report or comments (b) not focusing on the above-mentioned topic (c) duplicated studies or patients (d) animal or cell experiments (e) insufficient data.

2.3. Data extraction

The data extraction was independently completed by two investigators, and the following variables were extracted: the family name of the first author, publication year, the number of patients, the number of female in each study, the mean age of patients, intervention of each groups, and follow up duration. The clinical variables included VAS scores, WOMAC scores, and adverse effects. Corresponding authors were consulted to obtain incomplete outcome data.

2.4. Quality assessment

The risk of bias assessment of the included studies was performed by two authors independently using the tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). This tool included seven aspects which were sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias

Table 1
Trials characteristics.

Author	Study design	Sample size	Mean age	Female patient	BMI	Experiential group	Control group	Follow up
		(E/C)	(E/C)	(E/C)	(E/C)			
Michalsen, 2003	RCT	24/27	63/66	15/18	28/27	2 leeches were placed proximal to the patella and 1 each at the medial and lateral joint line, while the knee was placed comfortably in extension	No medical leeches therapy	6 months
Andereya, 2008	RCT	73/40	68/64	41/30	29/27	Leeching, single application of 4 leeches (proximal, medial, and lateral to the patella)	28-day topical diclofenac regimen	6 months
Stange, 2012	RCT	22/18	65/64	17/12	27/28	Leeching, single application of 8 leeches (above, below, medially, and laterally the patella	Transcutaneous electrical nerve stimulation, single application of 2 electrodes (above and below the patella)	3 weeks
Shakouri, 2017	RCT	30/30	63/65	20/19	29/27	Leeching, single application of 4 leeches (maximally painful periarticular sites)	Transcutaneous electrical nerve stimulation	6 months

E: Experimental, C: Control, RCT: randomized controlled trial.

Table 2
Methodological quality of the randomized controlled trials.

Table 3
Risk of bias.

(baseline balance and fund). Additionally, each of the aspects was ranked low risk of bias, high risk of bias, and unclear risk of bias. The evidence grade was assessed using the guidelines of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group [11] including the following items: risk of bias, inconsistency, indirectness, imprecision and publication bias. The recommendation level of evidence was classified into the following categories: (1) high, which means that further research is unlikely to change confidence in the effect estimate; (2) moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate; (3) low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; and (4) very low, which means that any effect estimate is uncertain. GRADE pro Version 3.6 software is used for the evidence synthesis.

2.5. Statistical analysis

All meta-analyses were performed by using STATA 12.0 (College Station, TX, USA). For dichotomous parameters, the risk difference (RD) and 95% confidence intervals (CI) was used to analyze the results. As for continuous clinical parameters, weighted mean difference (WMD) were utilized. And heterogeneity was determined to be significant at $I^2 > 50\%$ or $p < 0.1$. The random effects model was used when heterogeneity was significant, and a fixed effects model was used if homogeneity.

3. Results

3.1. Search results

A total of 197 relevant studies were identified by the initial database search. 116 were excluded because of duplicate studies, and 75 studies were excluded based on the titles and abstracts. The remaining 6 full-text articles were reviewed for more detailed evaluation, and 2 of them were then excluded for non-RCTs. Finally, for RCTs [12–15] fulfilled the predefined inclusion criteria and were included in the final systematic review and meta-analysis. The selection process was shown in

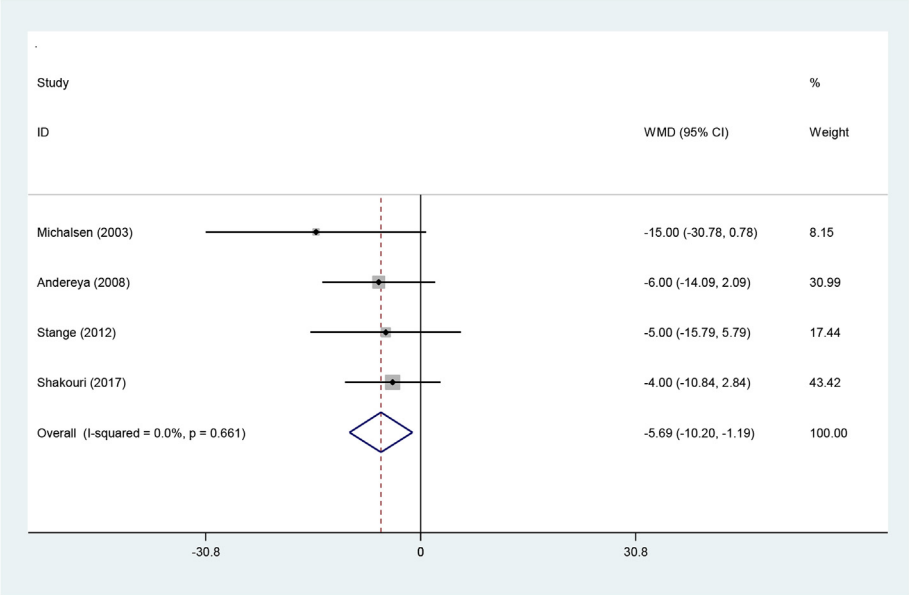

Fig. 2. Forest plot diagram showing WOMAC scores at 1 week.

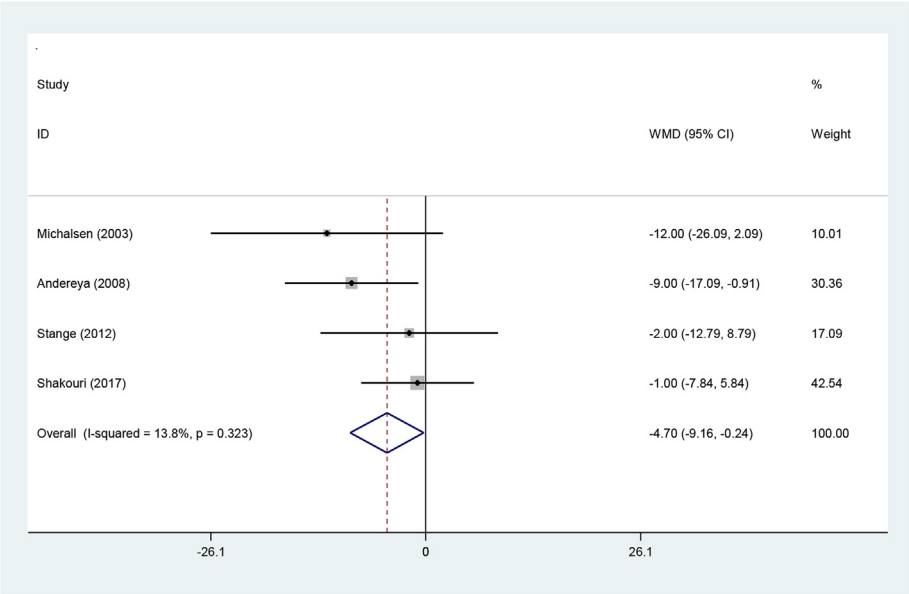

Fig. 3. Forest plot diagram showing WOMAC scores at 4 weeks.

Fig. 1.

3.2. Study characteristics

The main characteristics of included studies were described in Table 1. Statistically similar baseline characteristics were observed between both groups. All included studies were English publications which published between 2003 and 2017. The sample size ranged from 40 to 113 (a total of 264, 149 in medical leech therapy group and 115 in control groups) and mean age ranged from 63 to 66 years old. Duration of follow up ranged from 3 weeks to 6 months.

3.3. Risk of bias assessment

RCT quality was assessed based on the Cochrane Handbook for Systematic Review of Interventions (Table 2). All RCT stated clear inclusion and exclusion criteria and performed adequate methodology of randomization by computer. Two of them [12,15] used sealed envelopes for allocation concealment. None RCTs reported double-blinding to the surgeons and participants. One study [15] showed that assessor was blinded. Low risk of bias due to incomplete outcome data and selective outcome reporting were detected. Judgments regarding each risk of bias item were presented as percentages across all the included RCTs in Table 3.

3.4. Primary outcome

3.4.1. WOMAC scores at 1 week

All RCTs [12–15] reported the WOMAC scores at 1 week. There was no significant statistical heterogeneity ($\chi 2 = 1.59$, df = 3, $I^2 = 0.0\%$, P = 0.661); therefore, a fixed-effect model was adopted. Our study revealed that medical leech therapy was associated with a significantly reduction of WOMAC scores at 1 week compared with control groups (WMD = −5.69, 95% CI: −10.195 to −1.185, P = 0.013; Fig. 2).

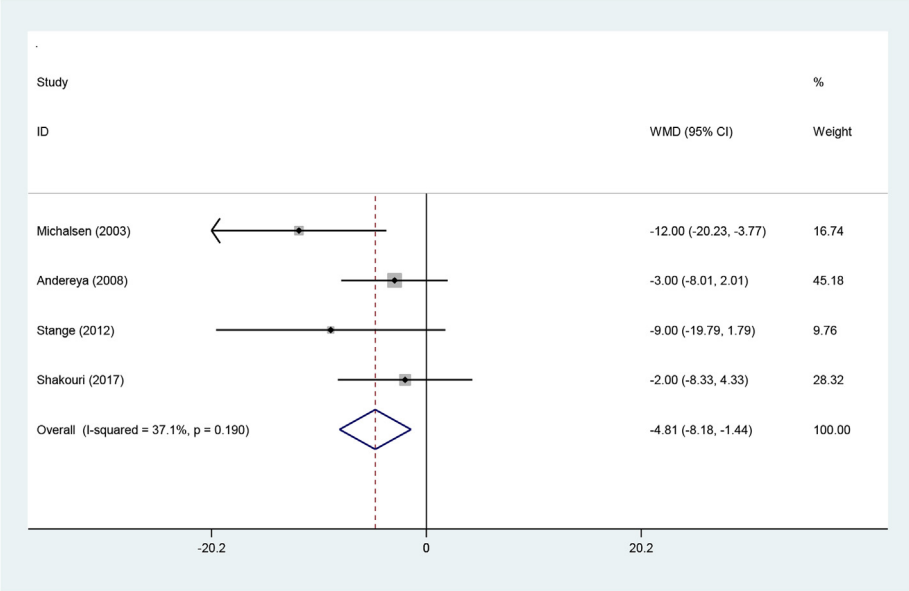

Fig. 4. Forest plot diagram showing WOMAC scores at 7 weeks.

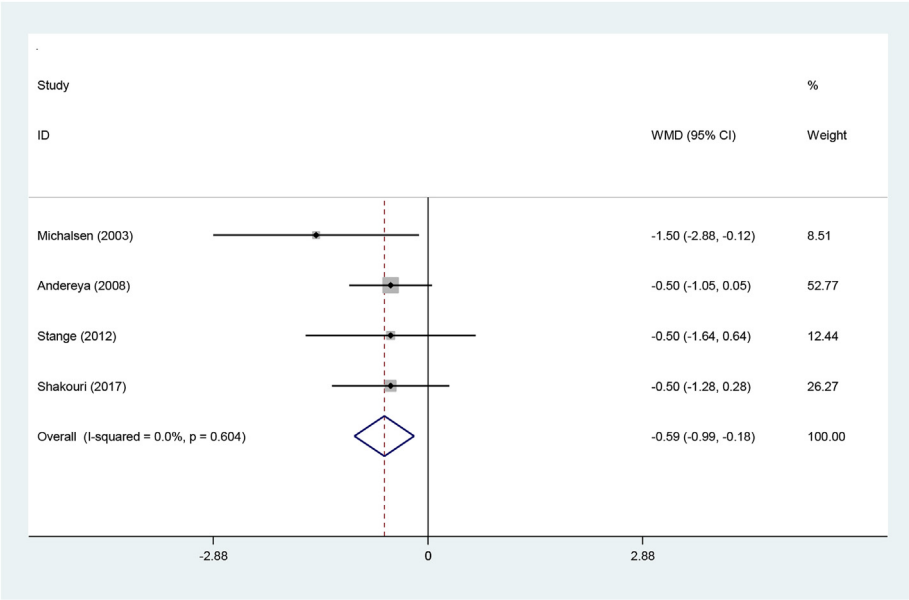

Fig. 5. Forest plot diagram showing VAS at 1 week.

3.4.2. WOMAC scores at 4 weeks

WOMAC scores at 4 weeks was shown in all RCTs [12–15], no significant heterogeneity was found and a fixed-effect model applied ($\chi 2 = 3.48$, df = 3, $I^2 = 13.8\%$, P = 0.323). There was significant difference between groups regarding WOMAC scores at 4 weeks (WMD = 4.701, 95% CI: −9.160 to −0.242, P = 0.039; Fig. 3).

3.4.3. WOMAC scores at 7 weeks

Four RCTs [12–15] provided the outcome of WOMAC scores at 7 weeks. There was no significant statistical heterogeneity ($\chi 2 = 4.77$, df = 3, $I^2 = 37.1\%$, P = 0.190); therefore, a fixed-effect model was used. WOMAC scores at 7 weeks in the leech therapy groups was significantly lower than that in the control groups (WMD = −4.809, 95% CI: −8.178 to −1.440, P = 0.005; Fig. 4).

3.4.4. VAS at 1 week

All RCTs [12–15] showed the VAS at 1 week. No significant statistical heterogeneity was found ($\chi 2 = 1.85$, df = 3, $I^2 = 0.0\%$, P = 0.604); therefore, a fixed-effect model was adopted. The present meta-analysis indicated that medical leech therapy was associated with a significantly reduction of VAS at 1 week compared with control groups (WMD = −0.585, 95% CI: −0.987 to −0.183, P = 0.004; Fig. 5).

3.4.5. VAS at 4 weeks

VAS at 4 weeks was provided in four RCTs [12–15]. A fixed-effect model was adopted because no significant heterogeneity was identified ($\chi 2 = 1.94$, df = 3, $I^2 = 0.0\%$, P = 0.586). There was significant difference between groups regarding VAS at 4 weeks (WMD = −0.434, 95% CI: −0.846 to −0.846, P = 0.039; Fig. 6).

3.4.6. VAS at 7 weeks

Three studies [12–14] showed the outcome of VAS at 7 weeks. A fixed-effect model was applied ($\chi 2 = 0.88$, df = 2, $I^2 = 0.0\%$,

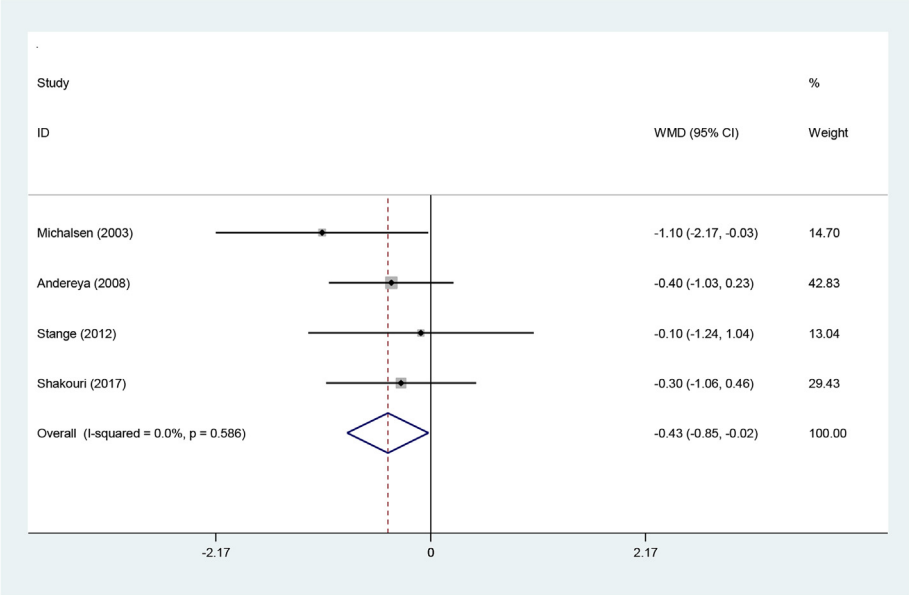

Fig. 6. Forest plot diagram showing VAS at 4 weeks.

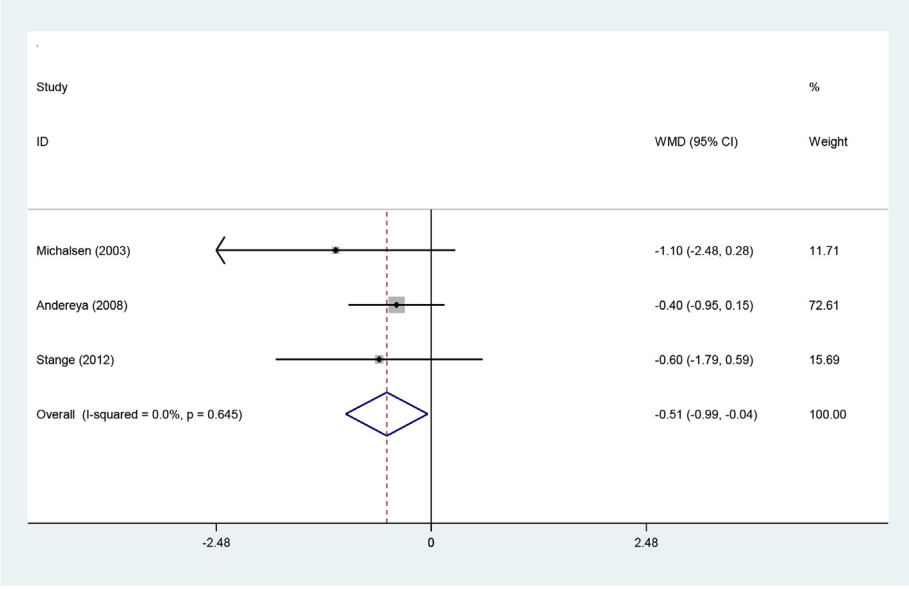

Fig. 7. Forest plot diagram showing VAS at 7 weeks.

P = 0.645). VAS at 7 weeks in the leech therapy groups was significantly lower than that in the control groups (WMD = −0.531, 95% CI: −0.985 to −0.041, P = 0.033; Fig. 7).

3.4.7. Adverse events

Adverse events were reported in all included RCTs [12–15], such as local skin reaction, bleeding and infection. No significant heterogeneity was shown between pooled results ($\chi 2 = 10.47$, df = 9, $I^2 = 14.0\%$, P = 0.314) and thus, a fixed-model was performed. Leech therapy was associated with a significantly higher incidence of adverse events (WMD = 0.050, 95% CI: 0.022 to 0.077, P = 0.000; Fig. 8).

3.4.8. Evidence level and recommendation strengths

Quality of evidence were evaluated by the GRADE system. The evidence quality for each outcome was moderate. Therefore, we agreed that the overall evidence quality was moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate (Table 4).

4. Discussion

To the best of our knowledge, it was the first meta-analysis from RCTs to evaluate the efficacy and safety of medical leech therapy for OA of the knee. The most important finding of the present meta-analysis was that medical leech therapy was associated with a significant reduction in WOMAC scores and VAS at 1 week, 4 weeks and 7 weeks. However, there was an increased risk of adverse events in medical leech groups. The overall evidence quality was moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate.

With the aging population, the incidence of knee osteoarthritis is increasing and it becomes a serious social problem. The pathological process includes inflammation and structural changes of knee joints. Thus, it may result in pain and deformity. The therapeutic goal is to

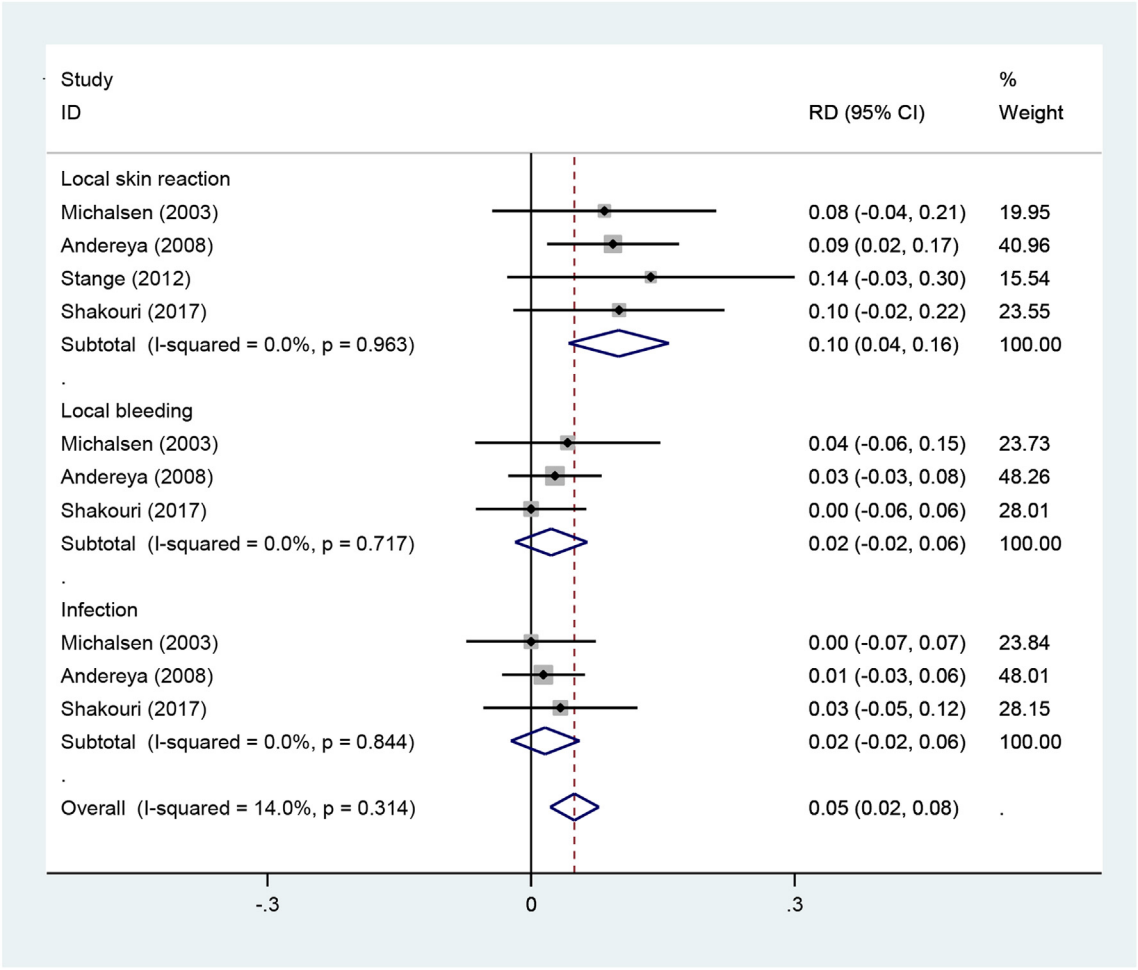

Fig. 8. Forest plot diagram showing the adverse effects.

Table 4
The GRADE evidence quality.

Quality assessment						No of patients		Effect	Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Leech groups	Control groups			
WOMAC scores at 1 weeks										
4	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	149	115	WMD = −5.69, 95% CI: −10.195 to −1.185	MODERATE	CRITICAL
WOMAC scores at 4 weeks										
4	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	149	115	WMD = −4.701, 95% CI: −9.160 to −0.242	MODERATE	CRITICAL
WOMAC scores at 7 weeks										
4	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	149	115	WMD = −4.809, 95% CI: −8.178 to −1.440	MODERATE	CRITICAL
VAS at 1 weeks										
4	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	149	115	WMD = −0.585, 95% CI: −0.987 to −0.183	MODERATE	CRITICAL
VAS at 4 weeks										
4	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	149	115	WMD = −0.434, 95% CI: −0.846 to −0.846	MODERATE	CRITICAL
VAS at 7 weeks										
3	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	119	85	WMD = −0.531, 95% CI: −0.985 to −0.041	MODERATE	CRITICAL
Adverse effect										
4	RCT	serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	149	115	RD = 0.050, 95% CI: 0.022 to 0.077	MODERATE	CRITICAL

reduce pain, improve patient's satisfaction, quality of life and slow the progression of the disease. Since traditional long-term therapy for knee OA treatment poses potential risk of serious adverse effects, and innovative therapeutic option should be studied. Medical leech therapy has been applied in medical history for pain management, however, it was rarely studied in a modern medicine. In a non-RCT, medical leech

therapy was reported to be associated with clinically significant improvements in patients with knee OA [10]. Additionally, leech therapy was effective in improving functional outcome. The possible mechanism was that: (1) bioactive substances such as protein compounds were detected in leech saliva, which may act as painkillers and anesthetics to reduce pain in the joints [16]; (2) Leech therapy could induce pain relief through anti-inflammatory effect in the joint [17]; (3) leech therapy has a powerful placebo effect [18]. Koeppen et al. [19] demonstrated that leech saliva contained active ingredients with anti-inflammatory and blood-circulation enhancing properties. Pain relief from leech therapy was rapid, effective and long-lasting in many conditions. In our study, pain was assessed using a 10-point VAS score. The present meta-analysis revealed that leech therapy was associated with a significantly reduction VAS score at 1week, 4 weeks and 7 weeks. Andereya et al. [13] provided the use of pain medication between groups and found that leech treatment groups was associated with significantly reduction of pain medication. However, no statistically significant difference was found regarding the analgesic rescue medication used in another study. Due to the limited RCTs, we failed to perform a meta-analysis. More well-designed RCTs were required for further investigation.

The pathogenesis of osteoarthritis contains stress-induced mechanisms, phenotype shifts, and abnormal cellular activities in cartilage and synovium [20,21]. As a result, intra- and extracellular proinflammatory mediators is activated. Then aseptic inflammatory reaction of knee joints may cause cartilage degeneration and hyperosteogeny, which results in twist, unstable and stiffness and develops into deformity ultimately [22,23]. Minimizing inflammatory response can alleviate the progression of the pathological changes and then maintain physical function of knee joints. Previous studies have demonstrated that the clinical effect of medical leech therapy for functional recovery in knee OA with mixed results. Andereya et al. [13] reported a long-term reduction of joint stiffness and improved function in the activities of daily living. Michalsen et al. [12] showed no significant difference regarding the joint stiffness at 3–6 months between treatment groups. As outcome measures, WOMAC scores was used for evaluating the functional restoration. The present meta-analysis indicated that medical leech therapy could significantly improve the functional outcome of joint.

Clinical benefits was not the only concern when evaluating the effectiveness of medical leech therapy. Isik et al. [24] reported that 31 of 46 patients occurred a mild local itching and skin redness in leech groups and 3 of them were severe and attended the emergency department with the diagnosis of cellulitis. Backer et al. [25] showed that 2 of 20 patients experienced a reduction of systolic blood pressure (20 and 15 mm Hg) with a mild sensation of dizziness after leech therapy. Mild bleeding is an intended therapeutic effect and no prolonged bleeding was found. Our study showed an increased risk of adverse effects following leech therapy, all of them were mild and required no further treatment. Large sample size of RCTs were still required to assess the safety and further study should focus on the comparison of conventional medical therapy and medical leech therapy.

Several potential limitations should be noted: (1) Only four RCTs were included, all of which had a relatively small sample size; (2) Methodological weaknesses exist in all included studies which might affect the persuasion of the conclusion; (3) Due to the limited studies, we failed to perform a subgroup analyses to investigate the other confounding factors, such as gender, age, and body mass index, thus we could not determine the source of heterogeneity; (4) Short-term follow-up may lead to an underestimation of complications. (5) All included RCTs were English and Chinese publications, thus, publication bias was unavoidable.

5. Conclusion

Medical leech therapy was associated with a significantly improved outcome in pain relief and functional recovery in patients with symptomatic knee OA. However, given the inherent limitations in the included studies, this conclusion should be interpreted cautiously.

Ethical approval

Ethical approval is not needed, it is a meta-analysis based on the published RCTs.

Sources of funding

No funding.

Author contribution

Haixia Wang: finish manuscript.
Jing Zhang: data collections and data analysis.
Liyan Chen: study design.

Conflicts of interest

There is no conflict of interest among patients.

Trial registry number

None.

Research registration number

Unique Identifying Number (UIN): reviewregistry 424.

Guarantor

Liyan Chen.

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None.

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