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Review Article

Systematic Review of Chuna Manipulative Treatment for Ankle Sprain

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ABSTRACT

Background: This study was performed to review the efficacy of national and international randomized controlled trials (RCT) investigating Chuna manipulative treatment for ankle sprains.
Methods: Online databases (PubMed, Cochrane, EMBASE, CNKI, NDSL, OASIS), were searched for studies where Chuna treatment was performed for ankle sprains up to October 12th, 2017. Only RCT were selected that fulfilled the inclusion/exclusion criteria. Data were analyzed using the Cochrane risk of bias tool.
Results: There were 676 studies retrieved from the databases, resulting in analysis of 24 RCT. There was an average of 7 treatment visits over a 7 day period and the most frequent evaluation tool used was efficacy rate, with drug therapy being the most common control used in the trials. In 15 RCT, several Chuna methods were used in combination, amongst which, the osteopathic technique was most common. Statistically significant improvement in evaluation indices was reported in 19 RCT, and in 3 RCT, statistically significant improvement was reported, but not for all indices. In the remaining 2 RCT, there were no significant differences in any of the evaluation indices. No adverse reactions were reported in any of the RCT, although it was unknown whether all the trial protocols indicated that adverse reactions should be monitored, and for this reason, the risk of bias was unclear.
Conclusion: The review of 24 studies suggest that Chuna manipulative treatment for ankle sprains was effective in most cases, although, potential bias in these studies was difficult to evaluate.

Introduction

Sprains are caused when the ligament between the joints is or stretched contracted by an external force, resulting in pain and edema in the local area. Ankle sprains are one of the most commonly observed injuries in clinical practice, presenting with swelling, localized pain, tenderness, and subcutaneous bleeding symptoms [1]. Ankle sprains are usually treated with rest, ice, compression and elevation (RICE) to reduce inflammation, pain, swelling and bleeding. When the pain subsides, plantar flexion is initiated and dorsiflexion exercises are introduced to allow joint mobilization and stretching, ensuring that adduction and abduction is kept to a minimum. Sprains are categorized into 3 grades according to signs and symptoms. Grade 1 and Grade 2 sprains respond well to conservative treatment such as RICE. Conservative treatment is also preferred in Grade 3 sprains when plaster fixation or surgical treatment is offered because these treatments will require long-term recovery and there may be a risk of complications [2].

Untreated sprains, or sprains complicated by other ankle injuries, may result in a chronic relapse of the sprain and joint instability. Early diagnosis and treatment of the sprain will shorten the healing period and prevent weakening of the ankle [3].

It has been reported that treatment of an ankle sprain with acupuncture, Dongsi acupuncture, herbal acupuncture, acupotomy, moxibustion, bloodletting, embedding, Chuna or taping treatment are clinically effective [4].

Chuna treatment is usually applied by the practitioner's hand, other parts of the body, or ancillary equipment to stimulate the patient's skin [5]. There are 5 techniques for Chuna treatment; wave, friction, pressure, vibration and osteopathic. Each type of Chuna treatment can aid the recovery of skeletal structures, such

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as ankle joints, and also help recovery of muscle and ligament injuries, preventing chronic recurrence and instability. In Korea, studies on the Chuna treatment for ankle sprains have been consistently reported [6-11], but these are mostly case reports or studies without controls.

The purpose of this study was to review national and international, randomized controlled trials (RCT) of Chuna treatment for ankle sprains.

Materials and Methods

Data sources

To investigate the efficacy of Chuna treatment for ankle sprain injuries, searches were performed in the following databases to analyze studies published up until October 12, 2017: PubMed/MEDLINE, Cochrane, EMBASE, and the China National Knowledge Infrastructure (CNKI) for international publications, and the National Digital Science Library (NDSL), and Oriental Medicine Advanced Searching Integrated System (OASIS) for Korean publications.

The following keywords were used for the database searches with minor adjustments for each database: ("ankle" OR "ankle joint" OR "lateral ligament, ankle" OR "ankle injuries" OR "ankle pain" OR "ankle sprain") AND ("Chuna" OR "Tuina" OR "Chiropractic" OR "manipulation" OR "Chinese massage").

Eligibility criteria

Inclusion criteria

RCTs were included that reported on Chuna treatment of patients with an ankle sprain, with no differentiation placed on the Chuna treatment method. In addition, Chuna studies, with and without a control group, were selected and no restrictions on the year of publication were made.

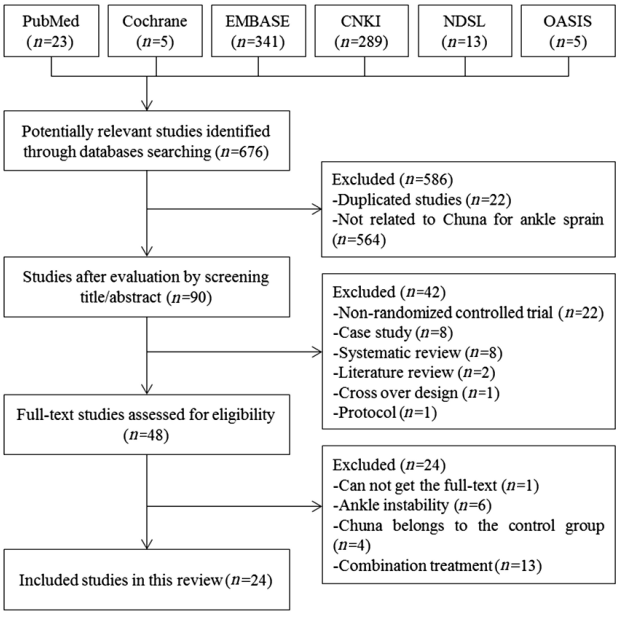

Fig. 1. Flow diagram of selection process.

Exclusion criteria

Studies of ankle instability, case–control studies, laboratory studies, review articles, protocols, case reports and case series were all excluded. Furthermore, Chuna treatment studies that had combined treatment were excluded. Studies with only abstracts published or studies whose original text was unavailable, were also excluded.

Data collection and risk of bias

Studies that satisfied the inclusion criteria were selected and then 2 reviewers performed data extraction and assessment independently. In cases of disagreement, the matter was reassessed by a 3rd reviewer. The risk of bias in RCTs was assessed using the Cochrane risk of bias tool [12].

Results

A total of 676 studies were retrieved from 6 online databases until October 12, 2017. Of the 676 papers retrieved, PubMed had 23, Cochrane 5, EMBASE 341, CNKI 289, NDSL 13 and OASIS 5. From the 676 studies, 22 duplicates were removed, along with 564 non-related studies, 90 dissertations and, 42 non-RCTs. Of the 48 studies remaining, 1 study was excluded as it did not have the original text, 6 studies excluded due to ankle instability, 4 studies where Chuna belonged to the control group, and 13 studies where Chuna was included as part of combination therapy. This provided a final selection of 24 studies for analysis (Table 1; Fig.1). Of the 24 studies, 17 [13-29] were in China, 4 [30-33] were in the United States, and 3 [9-11] were published in Korea.

Year of publication

Analysis by year showed that from 1989 to 2017, 20 studies (83%) were conducted in the last 10 years (Fig.2).

Sample size of study

The total number of subjects in the experimental group and control groups was analyzed. Of the 24 studies, 4 studies (17%) had less than 50 patients, 11 studies (46%) had 50 to 75 patients, 2 studies (8%) had 75 to 100 patients, and 7 studies (29%) had more than 100 patients (Fig.3).

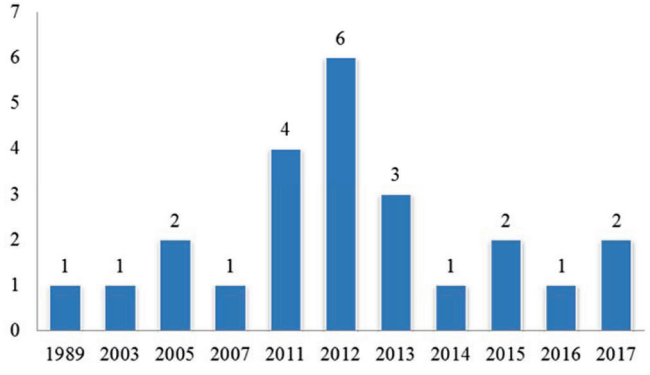

Fig. 2. Analysis of publication year.

Table 1. Key Data of Studies.

Study	Sample size	Intervention	Control	Treatment		Evaluation index	Result (A > B, C)	Chuna type
				N°	Period			
Chen (2016) [13]	56	A: CMT (n = 28)	B: RICE (n = 28)	7×	7d	1. AOFAS 2. Efficacy	1. $p < 0.05$ 2. $p < 0.05$	Osteopathic
Wang (1989) [14]	66	A: CMT (n = 44)	B: Ultrashort wave (n = 22)	12×	10wk	1. Cured 2. Efficacy	1. $p < 0.05$ 2.A = 100%, B = 93.2%	Wave, Pressure, Osteopathic
Huang (2012) [15]	60	A: CMT + B (n = 30)	B: Drug (internal medicine + external application) (n = 30)	9×	18d	1. Efficacy	1. $p < 0.05$	Wave, Pressure, Osteopathic
Li (2011) [16]	87	A: CMT (n = 43)	B: RICE (n = 44)	7×	7d	1. AOFAS 2. Efficacy	1. $p < 0.05$ 2. $p > 0.05$	Pressure
Chen (2012) [17]	108	A: CMT (n = 54)	B: Drug (external application) (n =54)	7×	7d	1. MPQ 2. VAS 3. PPI	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$	Friction, Osteopathic
Gao (2014) [18]	184	A: CMT (n = 92)	B: Drug (internal medicine + external application) (n = 92)	15×	15d	1. Efficacy	1. $p < 0.05$	Wave, Friction, Pressure, Osteopathic
Chen (2011) [19]	70	A: CMT + B (n = 35)	B: Drug (external application) (n = 35)	7×	7d	1. Efficacy	1. $p < 0.05$	Wave, Pressure, Osteopathic
Yao (2013) [20]	64	A: CMT + B (n = 32)	B: Drug (external application) (n = 32)	4×	10d	1. Efficacy 2. NRS	1. $p < 0.05$ 2. $p < 0.05$	Wave, Friction, Pressure, Osteopathic
Gao (2015) [21]	40	A: CMT (n = 21)	B: RICE (n = 19)	7×	14d	1. Takakura score	1. $p < 0.05$	Wave, Friction, Pressure, Osteopathic
Gao (2015) [22]	106	A: CMT (n = 54)	B: RICE (n = 52)	6×	14d	1. VAS 2. ° swelling	1. $p > 0.05$ 2. $p < 0.05$	Wave, Friction, Pressure, Osteopathic
Wang (2011) [23]	84	A: CMT + B (n = 42)	B: RICE (n = 42)	14×	14d	1. Efficacy 2. Pain relief time/ Recovery time	1. $p > 0.05$ 2. $p < 0.05$	Wave, Pressure, Osteopathic
Ma (2017) [24]	136	A: CMT (n = 68)	B: Drug (internal medicine + ice pack) (n = 68)	-	-	1. Efficacy	1. $p < 0.05$	Wave, Pressure, Osteopathic
Wang (2012) [25]	162	A: CMT (n = 81)	B: Drug (internal medicine + ice pack) (n = 81)	20×	20d	1. Clinical symptom score 2. Efficacy	1. $p < 0.05$ 2. $p < 0.05$	Wave, Pressure, Osteopathic
Chen (2012) [26]	108	A: CMT (n = 54)	B: Drug (external application) (n = 54)	7×	7d	1. Clinical symptom score	1. $p < 0.05$	Friction, Osteopathic
Huang (2012) [27]	160	A: CMT (n = 80)	B: Exercise (n = 80)	42×	8wk	1. AOFAS 2. Efficacy	1. p <0.05 2. p <0.05	Wave, Friction, Osteopathic
Yu (2007) [28]	60	A: CMT + B (n = 30)	B: Acupuncture (n = 30)	15×	30d	1. Efficacy 2. Cured	1. $p < 0.05$ 2. $p < 0.05$	Friction, Osteopathic
Cao (2015) [29]	72	A: CMT + B (n = 36)	B: Acupuncture (n = 36)	4×	14d	1. Clinical symptom score 2. Efficacy	1. $p < 0.05$ 2. $p < 0.05$	Osteopathic
Zhao (2017) [30]	62	A: CMT + C (n = 21)	B: Placebo (n = 21) + C C: RICE (n = 19)	2×	3d	1. SF12v2* 2. AOFAS 3. VOFAL 4. ROM 5. VAS	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.05$ 5. $p < 0.05$	Pressure
Cleland (2013) [31]	74	A: CMT + B (n = 37)	B: Exercise (n = 37)	8×	4wk	1. FAAM ADL 2. FAAM sports 3. LEFS 4. NRS	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.05$	Osteopathic
Eisenhart (2003) [32]	55	A: CMT + B (n = 28)	B: RICE (n = 27)	1×	1d	1. ° swelling 2. ROM 3. VAS	1. $p > 0.05$ 2. $p < 0.05$ 3. $p > 0.05$	Friction, Pressure, Osteopathic
Salo (2012) [33]	17	A: CMT (n = 7)	B: Placebo (n = 10)	1×	1d	1. VAS	1. $p > 0.05$	Osteopathic
Koo (2005) [9]	60	A: CMT (n = 30)	B: Massage (n = 30)	7×	14d	1. Dorsiflexion 2. Single support time 3. VAS	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$	Vibration
Lee (2005) [10]	24	A: CMT + B (n = 12)	B: Acupuncture (n = 12)	3×	7d	1. VAS	1. $p < 0.05$	Osteopathic
Lee (2011) [11]	45	A: CMT + C (n = 15)	B: Herbal Acupuncture (n = 15) C: Acupuncture (n = 15)	3×	10d	1.NRS	1. $p > 0.05$	Osteopathic

ADL, Activities of Daily Living; AOFAS, American Orthopedic Foot and Ankle Score; CMT, Chuna Manipulative Treatment; FAAM, Foot and Ankle Ability Measure; LEFS, Lower Extremity Functional Scale; MPQ, McGill Pain Scale; NRS, Numeric Rating Scale; PPI, Present Pain Intensity; RICE, Rest·Ice·Compression·Elevation; ROM, Range of Motion; VAS, Visual Analogue Scale; VOFAL, Volumetric measurement Of the Foot·Ankle and Lower leg.
*SF12v2, Quality of Life Outcome.
A, Intervention group; B·C, Control group

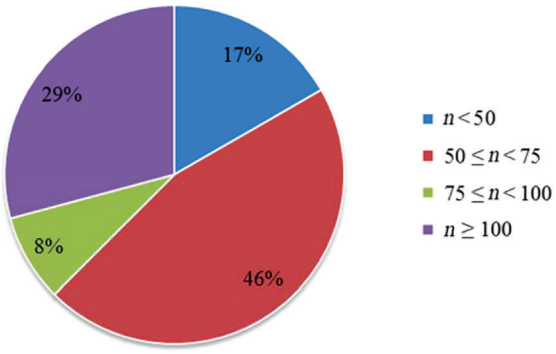

Fig. 3. Sample size analysis of studies.

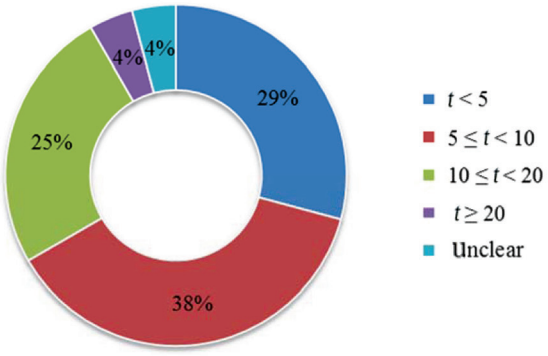

Fig. 4. Analysis of treatment number of times.

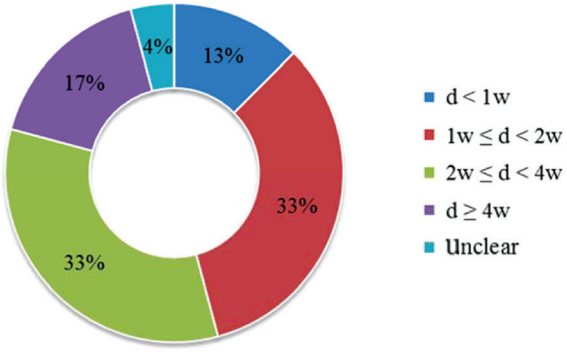

Fig. 5. Analysis of treatment period.

Treatment number of times and period

In 23 of 24 studies, (except for 1 study in which the number and period of Chuna treatment were not recorded accurately), the data values were all calculated as mean values.

The number of Chuna treatments ranged from 1 to 42, with 7 treatments being the most common. When expressed as a range, there were 7 studies (29%) with < 5 treatments, 9 studies (38%) with 5 to 10 treatments, 6 studies (25%) with 10 to 20 treatments, 1 study (4%) with > 20 treatments, and 1 study (4%) that did not report the exact number (Fig.4).

The period of Chuna treatment also ranged from 1 day to 10 weeks, with 7 days being the most common, followed by 14 days. When expressed as a range, there were 3 studies (13%) with < 1 week of treatment, 8 studies (33%) with 1 to 2 weeks of treatment, 8 studies (33%) with 2 to 4 weeks, 4 studies (17%) with > 4 weeks, and 1 study (4%) did not report the exact period (Fig.5).

Evaluation index

In a single study, 1, or at most 5 evaluation indicators were used, and a total of 1,960 subjects were evaluated for 18 evaluation indices, in a total of 24 studies. There were 13tudies that used the efficacy rate according to the degree of symptom improvement as the evaluation index. Next, there were 7 studies using Visual Analogue Scale (VAS), then 4 studies using American Orthopedic Foot and Ankle Score (AOFAS), 3 studies using Numeric Rating Scale (NRS), 3 studies using clinical symptom score, 2 studies using Range of Motion (ROM), degree of swelling, and cured rate, respectively, and 10 other evaluation indices were used once for each scoring scale (Fig.6).

Type of Chuna manipulative treatment

Analysis of Chuna treatment was classified into 5 types; wave (kneading method), friction (scrubbing, rubbing, and wiping method), pressure (pressing and twirling method), vibration (vibration method) and osteopathic (traction, pulling, rotation, flexion/extension, and inside/outside method). There were 9

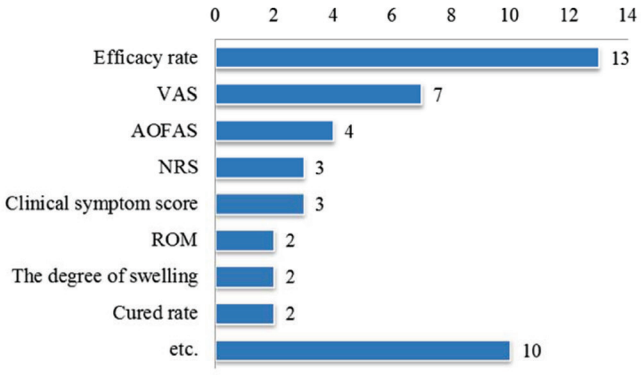

Fig. 6. Analysis of evaluation index.

AOFAS, American orthopedic foot and ankle score; NRS, numeric rating scale; ROM, range of motion; VAS, visual analogue scale.

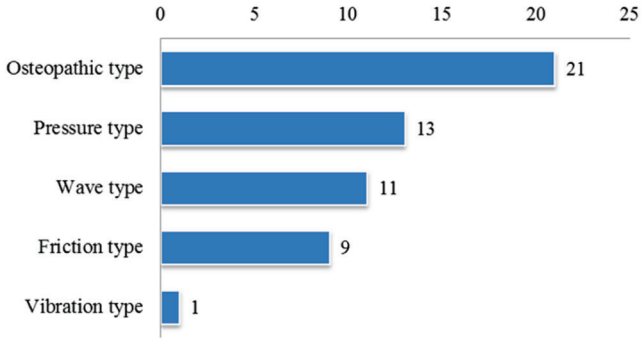

Fig. 7. Analysis of Chuna manipulative treatment type.

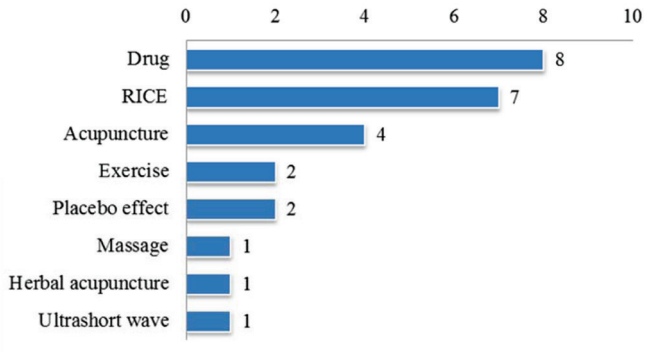

Fig. 8. Analysis of control group treatment.

RICE, rest·ice·compression·elevation.

studies that used only 1 type of technique, and 15 studies that used a combination of 2 to 4 types of Chuna techniques. In 24 studies, a total of 55 types of Chuna treatment were used in duplicate. Amongst them, 21 studies used the osteopathic technique and was the most common. Next, there were 13 studies that used pressure, 11 studies using the wave technique, 9 studies using friction, and 1 study using vibration (Fig.7).

Treatment of control group

In 22 of 24 studies, 1 control group was set up for each study, whilst in the remaining 2 studies, 2 control groups were set up.

For controls, 8 studies used drug treatment, including an internal medicine and an external application, which were the most common. Next, there were 7 studies using Rest·Ice·Compression·Elevation (RICE) treatment and 4 studies using acupuncture. There were 2 studies each using exercise as a therapy, such as joint functional exercise, home exercise programs, and sham acupressure and sham manipulation as a placebo. Lastly, 1 study used massage therapy (effleurage), and 1 study used Hwangryunhaedoktang herbal acupuncture therapy, with microwave therapy as a control group (Fig.8).

In the 8 studies using drug treatment as a control, there were 4 studies using an external application alone, 2 studies using an internal medicine and an external application, and 2 studies using an internal medicine and the ice pack.

Therapeutic effect

Efficacy of Chuna treatment was measured in the 24 selected studies, the experimental and control effects of treatment in the 50 groups were analyzed and evaluation indices in the Chuna treated groups showed improvement after treatment. The comparison of treatment results between the experimental group and the control group was made as a baseline before treatment and after the treatment to assess the therapeutic effects.

In 18 studies, the experimental group showed a statistically significant improvement for each evaluation index compared to the control group.

In the remaining 6 studies, Li et al [16] showed that AOFAS had a statistically significant beneficial effect on the experimental group compared to the control group, but the efficacy rate showed no significant difference between the 2 groups. In the study by Gao et al [22], the reduction in the degree of swelling after treatment was statistically significant, but VAS was not significantly different between the control group and the treatment group, but the VAS value (1.30 ± 1.54) in the experimental group was lower than the VAS value (1.73 ± 1.16) in the control group. In the study by Wang et al [23], the efficacy rate recorded at 14 days after treatment was not significant between the control group and the treatment group, but the efficacy rate at 7 days was significantly different ($p < 0.05$), and the pain relief time and recovery time were significantly different. Eisenhart et al [32] showed a statistically significant difference in ROM between the control group and the treatment group after treatment. The difference of swelling and VAS was not significant but all showed improvement. In the other 2 studies, there was no statistically significant difference in each evaluation index. In the study by Salo et al [33], there was no statistically significant difference in the NRS values amongst the Chuna group, herbal acupuncture group, and acupuncture group after treatment. However, Chuna group and herbal acupuncture group showed a larger NRS fall width than that of the acupuncture group and showed the greatest decrease width in the Chuna treatment group. In the remaining study by Lee et al [11], VAS was measured after one treatment and both groups showed improvement, but there was no statistically significant difference between the control group and the treatment group.

Adverse reaction

None of the 24 studies reported adverse reaction.

Risk of bias assessment

The risk of bias was assessed for 24 studies using Cochrane risk of bias tool (Figs.9, 10).

Random sequence generation

Low risk was observed in 3 studies (13%), 2 studies used a

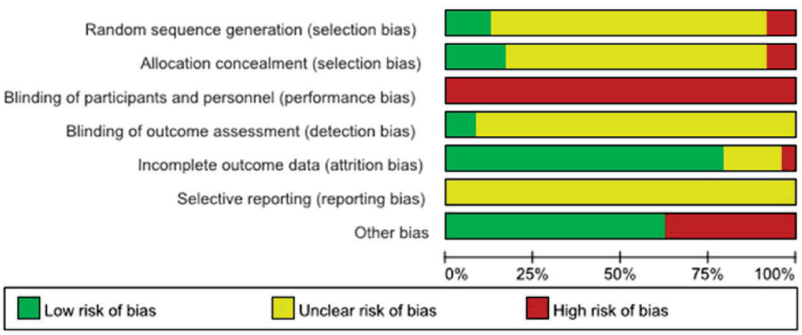

Fig. 9. Risk of RCT bias graph.

RCT, randomized controlled trials.

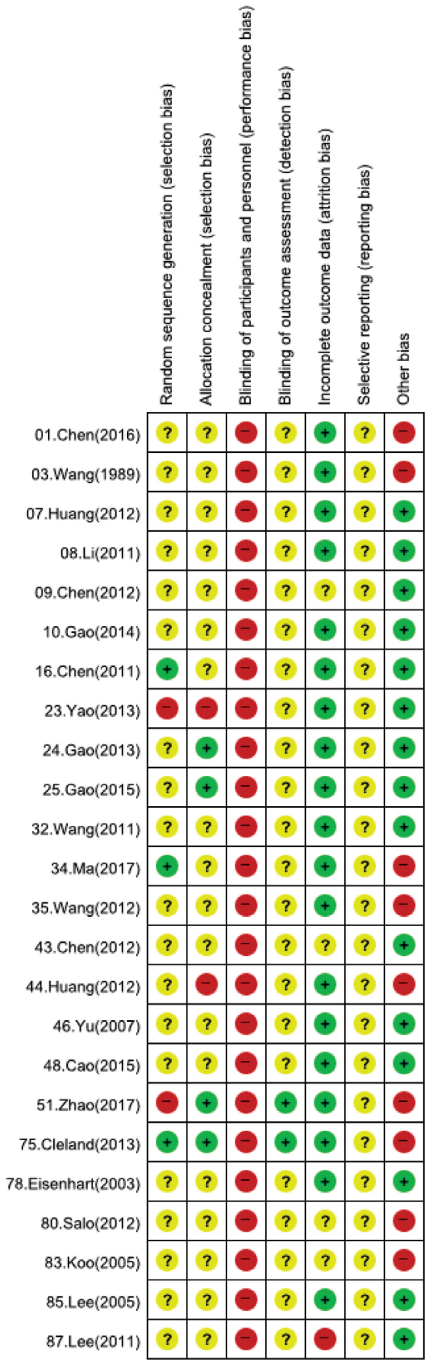

Fig. 10. Risk of RCT bias summary.

(+), Low risk of bias; (-), High risk of bias; (?), Unclear of bias.
RCT, randomized controlled trials.

random number table, and 1 study used computers for random sequence generation. High risk was observed in 2 studies (8%), 1 study was randomized by visited order, and 1 study randomized by gender. In the remaining 19 studies (79%), the level of risk was unclear, because of the random division of the group without description of the randomization method.

Allocation concealment

Low risk was observed in 4 studies (17%), 2 studies used the central randomization method, and 2 studies used sealed envelopes with serial numbers. The highest risk was observed in 2 studies (8%). One study was randomly assigned by visit order, and the order of placement was not concealed. The other study used opaque envelopes, but not serial numbers or sealed envelopes, so it was judged to be a random envelope placement that had no safety devices. The remaining 18 studies (75%) were classified as unclear risk because there was no mention of concealment or lack of judgment.

Blinding of participant and personnel

All 24 studies (100%) were categorized as high risk because the studies were not completed blind, due to the characteristic of Chuna treatment. In 2 studies, sham treatment was used but the study was unblinded for both participants and researchers due to the characteristic of Chuna.

Blinding of outcome assessment

The 2 studies (8%) that were partially blinded were classified as low risk because the outcome assessment was not aware of the group allocation status and was considered to have been blinded. In the other 22 studies (92%), all of them were classified as unclear risk because there was no mention of blinding of outcome assessment.

Incomplete outcome data

Low risk was observed in 19 studies (79%). There were 2 studies where incomplete outcome data existed but these 2 studies did not affect the outcome significantly, and there were 17 studies that had complete data. High risk was observed in 1 study (4%), and it was judged that the incomplete data outcome could affect the results because there was no mention that it did not significantly affect the outcome. Unclear risk was observed in 4 studies (17%), there were 2 studies that did not report the reason for the incomplete outcome, and the remaining 2 studies stated that they did not know if there was an incomplete outcome.

Selective reporting

All 24 studies (100%) were categorized as unclear risk because there was no report of protocols and predefined plans.

Other bias

High risk was observed in 9 studies (38%). Amongst them, 2 studies were considered to be at potential risk of bias due to the nature of the research that included home treatment, where there maybe concerns regarding whether the treatment was performed properly. The exact number of treatments was not reported in 2 studies, with 2 more studies did not report the specific treatment method, and 1 study had unequal treatment and control subjects. All of these studies were considered to have a risk of bias. Two of the studies were found to have other problems with typographical errors and were also classified as high risk. The remaining 15 studies (62%) were classified as low risk because there was no possibility of additional bias.

Discussion

To evaluate the efficacy of Chuna therapy for ankle sprains, 6 online databases were searched and 24 RCT were selected for systematic review.

Of the 24 studies, 17 were published in China, 4 in the United States, and 3 in Korea. In the last 10 years, 20 studies (83%) have been conducted, indicating increasing interest in Chuna treatment for ankle sprains.

In 7 studies (29%), the number of Chuna treatments received was set at 7, which was the most common number of treatments. There were 6 studies (25%) with 7 days of treatment, which was the most common, followed by 5 studies (21%) with treatment completed at 14 days. This suggests that 7 Chuna treatments for ankle sprains every day, or every other day may have a beneficial therapeutic effect.

A total of 18 evaluation indicators were used in the 24 studies. In only 4 studies, comparative, objective indicators such as the degree of swelling, volumetric measurement of the foot, ankle and lower leg (VOFAL), range of motion (ROM), dorsiflexion, and single support time were used to evaluate treatment effects. In most studies, indicators were used to assess the subjective symptoms of the patient making it difficult to completely exclude the possibility of an evaluation error. Therefore, further evaluation using objective indicators will be necessary in the future.

The treatment methods of Chuna were classified into 5 types. In 24 studies, a total of 55 types were used in duplicate, suggesting that more than 1 technique was used for the treatment of ankle sprains. Among the 5 types, the osteopathic technique was used most frequently. However, it was difficult to classify Chuna treatment when the technique was descriptive and not named, and there were limitations in the definition and classification of Chuna treatment, due to the variety of types and techniques. Further studies to more clearly identify Chuna treatment methodology will be needed.

In the control treatment setting, 8 studies used medication and 7 studies used RICE. This showed that comparing basic treatment RICE and Korean medicine drug therapy with Chuna treatment for ankle sprain was a common therapeutic approach.

In the 24 studies, the experimental group and the control group were compared. In each evaluation index of 18 studies, the experimental group showed a statistically significant difference compared to the control group, indicating that Chuna therapy was a beneficial treatment for ankle sprain. In 4 of the remaining 6 studies, there was a significant difference in several evaluation indices. In the other 2 studies, the difference between the control group and the treatment group was not statistically significant in each evaluation index.

There were no reports of adverse reactions in any of the 24 studies suggesting that Chuna therapy was a safe treatment for ankle sprain.

Bias is a systematic error where the findings have deviated from the true value of the outcome or estimation. Understanding bias is important because it can lead to underestimating or overestimating the intervention effect [34]. In this study, the risk of bias assessment was evaluated in 7 areas using Cochrane's risk of bias (RoB) tool [12] (random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). The characteristic of the overall risk assessment of bias was that most of the 24 studies had "unclear risk" items. Only 5 out of 24 studies were describing random sequence generation, and only 6 studies described allocation concealment. The blinding of patient and staff was attempted using sham treatment only in 2 studies, but this proved to be difficult and it was reported that participants and staff became unblinded due to the nature of the Chuna treatment. Selective reporting areas were not mentioned in all studies. Analysis of bias risk showed that in most studies, explanations of research methods to avoid bias were overly concise, or not even described in the random sequence generation, allocation concealment or selective reporting area. These results suggest that researchers require greater awareness of bias when conducting RCT. Thus, in order to demonstrate the efficacy of Chuna treatment for ankle sprain, improved design of clinical studies with low bias will be required by referring to RCT guidelines such as CONSORT 2010 [35]. However, there is a limit to effectively designing a blinded trial due to the interventional nature of Chuna treatment, therefore future research will be needed to improve study designs and controls for Chuna research studies.

In conclusion these results suggest that Chuna treatment is statistically more effective than commonly used treatments such as RICE, internal medicine and external application. However, interpretation of these results is limited as it is difficult to classify the treatment method of Chuna accurately and to evaluate bias.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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