The aim of this study was to examine pharmacopuncture treatment for lateral epicondylitis, and to contribute to developing a standardized treatment regimen by reviewing trends in clinical trials. Five randomized controlled trials, 1 case-control study, and 8 cohort studies published after 1999, that involved pharmacopuncture for lateral epicondylitis, were selected from Korean and international online databases \((n=8)\). The type of pharmacopuncture, dose, frequency, efficacy, and adverse events were analyzed. Seven types of pharmacopuncture were used, namely Bee Venom, Illicium henryi Diels, Akebiae Caulis, Angelicae sinensis Diels, Ligusticum chuanxiong Hort, Hominis Placenta, and Salviae Miltiorrhizae Radix. Dose, treatment duration, and treatment frequency varied widely. One study assessed the treatment efficacy according to frequency. Nine studies lacked data on adverse events. The quality of 5 randomized controlled trials was low. Although pharmacopuncture treatment appeared to be effective for lateral epicondylitis, it was difficult to standardize the regimen for lateral epicondylitis.

©2020 Korean Acupuncture & Moxibustion Medicine Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Lateral epicondylitis (“tennis elbow”) is a condition that causes local tenderness at the origin of the extensor muscles of the lateral and upper parts \[1\]. Repeatedly excessive pulling force applied to the periosteum or tendon of the lateral humerus, results in fine fibrosis of the fascia joints, periosteum, synovial membrane, and tendon \[2\]. It mainly affects middle-aged people in their 40s and 50s, who overuse their elbows \[3\].

Treatment of lateral epicondylitis may be surgical or conservative treatment. If there is no response to conservative treatment i.e. severe discomfort is still experienced, surgical treatment is performed to remove the degenerated fascia. Conservative treatment involves the use of oral/topical non-steroidal anti-inflammatory drugs, anti-inflammatory drugs \[4\] or hyaluronic acid injections \[5\], topical steroid injections \[6\] and physical therapy such as silver spike point therapy or extracorporeal shock waves \[7\].

In Korean medicine, various treatments such as herbal medicines \[8\], acupuncture \[9\], fire acupuncture \[10\], electro-acupuncture stimulation \[11\] and Chuna therapy \[12\] are selected as conservative treatments.

Pharmacopuncture has the effect of controlling the meridians of the acupuncture treatment, and the treatment of conditions/diseases through the pharmacological reaction of the medicines \[13\]. Kim et al \[14\] reported a case of bee venom treatment, Park et al \[15\] reported 2 cases of scolopendra pharmacopuncture as a treatment, Choi et al \[16\] reported a case of anti-inflammatory pharmacopuncture as a treatment, and Uhm et al \[17\] reported 4 cases of combined pharmacopuncture treatment for lateral epicondylitis.

However, there are no systematic literature reviews that can confirm the safety, methodology and therapeutic effects of pharmacopuncture treatment for lateral epicondylitis. The authors conducted an analysis of the latest clinical studies in Korea and abroad on the treatment of lateral pharmacopuncture. The purpose

Keywords: lateral epicondylitis, pharmacopuncture, tennis elbow
of this study was to evaluate studies to contribute to developing a standardized treatment regimen for the treatment of lateral epicondylitis.

Materials and Methods

Materials

Among the studies that used pharmacopuncture for lateral epicondylitis, randomized controlled trials (RCTs), case control studies (CCS), case series (CS) and systematic reviews (SR) were selected with the exception of laboratory studies (in vivo or in vitro). CS with less than 10 cases, and duplicate studies were excluded.

Conditions that were excluded from this study were cervical lateral epicondylitis, rheumatoid arthritis, elbow fracture, tuberculosis, and tumors. Search terms for pharmacopuncture, that were excluded were patches, external preparations, and drug fumigations. Studies that had steroid injections were also excluded because this is not a natural product extract. In this study pharmacopuncture and medicines were tested as independent variables in the intervention group.

Study retrieval

A total of 8 online databases were used to retrieve studies up to October 20, 2018, including 4 international online databases [PubMed, Cochrane library, Excerpta Medica database (EMBASE), China National Knowledge Infrastructure (CNKI)], and 4 Korean online databases [National Digital Science Links (NDSL), Oriental medicine Advanced Searching Integrated System (OASIS), Korean studies Information Service System (KISS), Research Information Sharing Service (RISS)] shown in Table 1.

The search terms used were (“lateral epicondylitis” or “tennis elbow” or “tennis arm” or “radiohumeral epicondylitis”) and (“pharmacopuncture” or “herbal acupuncture” or “extract” or “aquapuncture”).

The actual search was modified and changed according to the characteristics of each database. When searching Korean and Chinese databases, the above-mentioned English terms were also used.

Table 1. Online Databases Used for This Study.

<table>
<thead>
<tr>
<th>Online database</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td><a href="http://www.pubmed.com">http://www.pubmed.com</a></td>
</tr>
<tr>
<td>Cochrane library</td>
<td><a href="http://www.cochranelibrary.com">http://www.cochranelibrary.com</a></td>
</tr>
<tr>
<td>EMBASE</td>
<td><a href="http://www.embase.com">http://www.embase.com</a></td>
</tr>
<tr>
<td>CNKI</td>
<td><a href="http://search.cnki.net">http://search.cnki.net</a></td>
</tr>
<tr>
<td>NDSL</td>
<td><a href="http://www.nndl.kr">http://www.nndl.kr</a></td>
</tr>
<tr>
<td>OASIS</td>
<td><a href="http://oasis.kiom.re.kr">http://oasis.kiom.re.kr</a></td>
</tr>
<tr>
<td>KISS</td>
<td><a href="http://kiss.kstudy.com">http://kiss.kstudy.com</a></td>
</tr>
<tr>
<td>RISS</td>
<td><a href="http://www.riis.kr">http://www.riis.kr</a></td>
</tr>
</tbody>
</table>

EMBASE, Excerpta Medica database; CNKI, China National Knowledge Infrastructure; NDSL, National Digital Science Links; OASIS, Oriental medicine Advanced Searching Integrated System; KISS, Korean studies Information Service System; RISS, Research Information Sharing Service.

Retrieval and screening

Study retrieval and screening was conducted independently by 2 researchers where the titles and abstracts were checked to determine if they fitted the selection criteria for this study. Two researchers reviewed the full articles and agreed upon the selected studies. In case of disagreement between the 2 researchers, a third researcher judged the appropriateness of the study and decided whether a study was included.

Analyzing and reviewing

Using EndNote X8.2 the selected articles were reviewed for title, first author, publication year, type of research, number of subjects, treatment content, number and duration treatment, and adverse events.

Evaluating risk of bias

There were 5 RCT studies where Cochrane’s risk of bias [18] was used by the 2 researchers to evaluate the risk of bias using the evaluation table. For the 7 items including selection of participants, confounding variables, measurement of intervention (exposure), blinding for outcome assessment, incomplete outcome data, and selective outcome reporting, “high risk of bias” was marked when the risk of bias was high, and “low risk of bias” was marked when the risk of bias was low. An “unclear risk of bias” was marked when the risk of bias was unclear. In case of disagreement between the 2 researchers in the evaluation, a third researcher was consulted.

Results

Outcome

A total of 209 articles were retrieved from PubMed (n = 8), Cochrane (n = 4), EMBASE (n = 17), CNKI (n = 136), NDSL (n = 19), OASIS (n = 4), KISS (n = 12) and RISS (n = 9). Of these, 42 duplications were removed. There were 21 studies performed before 1999, and 120 which did not apply pharmacopuncture for lateral epicondylitis. After the first screening, there were 26 articles left to review. There were 12 studies including 2 articles with no access, 9 articles with less than 10 cases, and 1 article with secondary lateral epicondylitis which were also excluded from this current study. A total of 14 articles were selected for this study and were analyzed based on the publication year, research design, number of subjects, treatment method, evaluation index and treatment efficiency. The process of selection of articles was plotted in a flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) as shown in Fig. 1.

Abstract

Three of the 14 selected studies were published in Korea, and 11 were published in China. There were 8 studies published within the last 10 years, of which 4 studies were published in 2012. The study design of the included articles were RCT (n = 5), CCS (n = 1) and CS (n = 8). No SR were performed with pharmacopuncture for lateral epicondylitis.

Outline and characteristic analysis (shown in Tables 2 and 3)

Sample size of studies

There were a total of 1,214 participants across all studies. The smallest study had 13 participants in the intervention group and 21 subjects in the control group. The largest study had 300
participants in the intervention group and 178 subjects in the control group. There are 5 studies with less than 50 participants, 6 studies with more than 50 participants less than 100, and 3 studies with more than 100 participants.

Purpose of studies
There were 3 studies that compared the effect with other treatments, 5 studies observed the effect of integrated treatment, 3 studies observed the effect of a single treatment, 2 studies compared the effects of additional treatments with existing treatments, and 1 study compared the integrated effect with other treatments.

Frequency of pharmacopuncture in treatment
As pharmacopuncture treatment, bee venom (BV), was used in 6 studies, Illicium henryi Diels in 2 studies, Akebiae Caulis in 2 studies, Angelicae sinesis Diels in 1 study, Ligusticum chuaxiong Hort in 1 study, mixed pharmacopuncture with Ligusticum chuaxiong Hort and Homonis Placenta, and mixed pharmacopuncture with Salviae Miltiorrhizae Radix and Akebiae Caulis in 1 study.

Volume of pharmacopuncture treatment
The volume of pharmacopuncture varied from at least 0.1 mL to 4 mL. There were 4 studies using less than 1 mL of pharmacopuncture, 2 studies using less than 2 mL, 5 studies using 2 mL or more, and 3 studies where the volume of pharmacopuncture could not be confirmed. In 1 study, the volume

Table 2. Data of Included Studies.

<table>
<thead>
<tr>
<th>First author [ref]</th>
<th>Year</th>
<th>Study type</th>
<th>Sample</th>
<th>A : Intervention group</th>
<th>B : Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Chen [29]</td>
<td>2012</td>
<td>RCT</td>
<td>100</td>
<td>A. n = 50 : CA + B + TDP + BV</td>
<td>B. n = 50 : Prednisolone acetate + Lidocaine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; CCS, case control study; CS, case series; BV, bee venom; CA, common acupuncture; U/S, ultra sound therapy; IR, infrared therapy; B, blood letting cupping; TDP, tending Diancibo Pu (specific electromagnetic waves); TENS, transcutaneous electrical nerve stimulation.
of each treatment point was 0.1 mL.

The number and period of treatment
In 14 studies, the number of treatments ranged from 1 to more than 10, and a maximum of 15 treatments were performed (in those studies that indicated the number of treatments). There were 6 studies with less than 5 treatments, 7 studies with 5 or more treatments, and 1 study where the number of treatments varied from 1 to more than 10. The period of treatment ranged from 3 days to 3 weeks or more. There was 1 study with less than 2 weeks, 6 studies with less than 3 weeks, and 3 studies with more than 3 weeks. There were 4 studies that did not confirm the period of the treatment.

Evaluation index
Of the 14 studies, 1 evaluation index was used in 13 studies,
and only 1 study used 2 evaluation indexes. There were 3 types of evaluation indexes used. There were 11 studies that were based on the efficacy rate, 2 studies used the visual analogue scale (VAS), and 1 study used the VAS and grip strength index simultaneously.

**Pharmacopuncture point**

All 14 studies selected a local painful point, and in 1 of these studies, the marginal part of the elbow cartilaginous membrane and the elbow joint, were selected as treatment points with the painful points.

**Treatment efficacy (statistical analysis)**

Of the 2 studies that were statistically processed for the total efficacy rate of the evaluation indexes, 1 study reported statistically significant treatment effects for pharmacopuncture in the intervention group, and 1 study was not statistically significant. In 2 studies, pharmacopuncture was statistically significantly effective at decreasing the VAS score, and 1 of those studies pharmacopuncture did not statistically significantly increase the grip strength index. In the remaining 10 studies, the total effective rate, and the decrease in VAS score was reported without statistical analysis of the evaluation index.

**Reporting adverse effect**

In 3 of the 14 studies, a skin test was performed using the BV used in therapeutic pharmacopuncture. In addition, 1 study reported no cases of infection in the course of the study, and 1 study reported no adverse events. There were no reports of adverse events in the rest of the 9 studies.

**Risk of bias**

Among the 14 studies, 5 RCT were conducted using the Cochrane’s risk of bias (Figs. 2 and 3).

**Randomized sequence generation**

In all 5 RCT, “random assignment” was used, but it was not classified by a random number table, computer random generator, date of birth, date of admission or clinical record number. All 5 studies were classified “unclear risk of bias.”

**Allocation concealment**

All 5 RCT were classified as an “unclear risk of bias” because there was no mention of the sequencing order used, such as sealed envelopes or central allocation.

**Blinding of participant and personnel**

In 1 study, the pharmacopuncture was not injected into the control group and was considered to be a “high risk of bias.” In the remaining 4 studies, blinding of the participants was conducted because both control and intervention groups were treated with either acupuncture or injections. However, it was classified as “high risk of bias” because it was considered that there was a difference between the intervention group and the control group for injecting with other treatments.

**Blinding of outcome assessment**

All 5 RCT were classified as an “unclear risk of bias” because there was no mention of an outcome evaluation.

**Incomplete outcome data**

All 5 RCT were classified as “low risk of bias” because no missing values were reported.

**Selective reporting**

All 5 RCT did not show any missing results, but were classified as “unclear risk of bias because there was no protocol at the design stage of the study.

**Other bias**

All 5 RCT were classified as “high risk of bias.” In 4 studies, there was a difference in the number of treatments between the intervention group and the control group, and it was judged that there was a bias that could affect the results. In 1 of these studies, it was concluded that the combined therapy, which could be an independent variable in the intervention group, could not be used to evaluate the effect of the single treatment. In the other study, the number of treatments was not clearly specified in both the control group and the intervention group.

**Discussion**

Lateral epicondylitis is a condition in which local tenderness occurs in the lateral epicondy and the upper part, due to direct trauma in the elbow, repetitive use of the upper limbs.
such as tennis and racket exercise [33]. The symptoms of lateral epicondylitis are consistent with edema, pain, erythema, and warmth, suggestive of tendinitis, but the cause is often due to overuse of the upper extremity, so lateral epicondylitis shows chronic degenerative change. There is also the opinion that it should be perceived as tendinosis, a degenerative condition that undergoes fine rupture, transformation, and subsequent injury [34].

The clinical tests used to diagnose lateral epicondylitis include Cozen’s test and the Chair test. If the pain is reproduced on the lateral epicondylyle when performing the 2 tests, lateral epicondylitis is diagnosed [35]. Ultrasound is used as a radiological diagnostic method, and the images of the traumatic region and the radial articular surface, are checked to confirm the thickening of the tendon of extensor carpi radialis brevis, which is the main muscle causing the lateral epicondylitis [36].

The international, and Korean trends of acupuncture treatment of lateral epicondylitis, have been reported recently [9,37]. However, there was no analysis of the research trends of pharmacopuncture for lateral epicondylitis. The purpose of this study was to evaluate the efficacy of pharmacopuncture used for lateral epicondylitis and standardized the treatment of lateral epicondylitis with pharmacopuncture. Therefore, the types, doses, and treatment efficacy of pharmacopuncture was analyzed by performing a literature review of 8 online databases (PubMed, Cochrane, EMBASE, CNKI, NDSL, OASIS, KISS and RISS). The highest number of studies were published in 2012 (n = 4). Study design of the 14 articles included RCTs, CCS, and CSs. The purpose of the studies was to compare the effect of pharmacopuncture with other treatment in 3 studies, to observe the effect of integrated treatment in 5 studies, to observe the effect of a single treatment in 3 studies, to compare the effects of additional treatments with existing treatments in 2 studies, and compare the integrated effect with other treatments in 1 study. Since steroid injections are widely used as a conservative treatment, 3 studies comparing the treatment efficacy of pharmacopuncture and steroid injections may be of great clinical value.

The 7 types of pharmacopuncture used in the treatment were 6 kinds of BV, 2 kinds of Illicium henryi Diels, 2 kinds of Akebiae Caulis, 1 piece of Angelicae sinensis Diels, 1 piece of Liguisticum chuanxiong Hort, 1 mixture of Liguisticum chuanxiong Hort and Hominis Placenta and 1 mixture of Salviae Miltiorrhize Radix and Akebiae Caulis. BV seems to be the most actively studied in clinical practice, and it seems to have treatment efficacy through BV counter stimulation effects, immunoregulatory action, and circulation facilitation action [38].

All of 14 studies selected painful points, where 1 was chosen as a treatment point for the marginal region of the painful point, elbow cartilaginous membrane, and for the elbow joint. It seems to be the nature of lateral epicondylitis where the pain and lesion are confined to the lateral epicondyle. Drug dose, number of treatments and duration of treatment were analyzed as specific methods of pharmacopuncture treatment. One study in which the dose of each treatment point was confirmed, and the dose of each point was not confirmed, but 2 studies accurately indicating the total dose, but the treatment efficacy according to the dosage of the pharmacopuncture was not evaluated. There were 10 studies that were able to confirm the treatment duration, but there was no evaluation of effect according to treatment duration. In 14 studies, the number of treatments was confirmed, but only 1 study evaluated the treatment effect according to the number of treatments.

There were 3 indexes used as evaluation indexes. Efficacy rate was used in 11 studies, and VAS and Grip Strength were used as index in 3 studies each. Considering that lateral epicondylitis is the result of degenerative changes, consideration should be given to the recurrence rate after termination of treatment. It is necessary to diversify the evaluation indexes of the treatment such as the change of the forearm extensor group through ultrasound [39], and the quality of life of the patient.

Of the 5 studies that reported adverse events, 2 were non-serious adverse reactions, 3 were drug hypersensitivity reactions from skin tests, and 9 were not mentioned. The pharmacopuncture therapy in which pharmacopuncture is injected into the body, should clarify that the skin test was performed before treatment, and the adverse event report should be made at the end of the treatment.

Bias means deviating from the true value when estimation outcomes are due to errors in the research system, and it is essential to evaluate bias because the intervention effect can be overestimated or underestimated [40]. Of the 14 selected studies, a total of 7 areas of the RCT were evaluated for risk of bias. “Unclear risk of bias” was assessed in all 5 RCT in the 4 areas of random sequence generation, allocation concealment, blinding of outcome assessment and selective reporting. All 5 RCT were “high risk of bias” in 2 areas of binding of participants and personnel and other bias, and “low risk of bias” in 1 area of incomplete outcome data. The 4 areas evaluated as “unclear risk of bias” were not adequately explained in the study, and 2 areas rated “high risk of bias” were not adequately controlled.

Analysis of the latest clinical research trends through 14 studies in Korea (n = 3) and China (n = 11) revealed that pharmacopuncture improved the clinical symptoms of lateral epicondylitis and reduced pain. However, there was a high risk of bias in the 5 RCT included in this review. It difficult to evaluate the effects, and the significance of the change in the treatment method with the lack of diversity of evaluation indexes, and omission of adverse event reports. A more systematic large scale RCT study is needed in the treatment of lateral epicondylitis.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References


