Therapeutic Effect of Combined Therapy of Tui-na and Oral Chinese Medicine on Osteoarthritis of Knee – a Randomized Controlled Trial

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Research Article

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Abstract

Background

Knee osteoarthritis (KOA) is a common degenerative joint condition that causes disability and pain in the elderly population. The prevalence of KOA among persons aged 63 or above is approximately 30%. Previous studies have reported the positive effect of Tui-na treatment and the Chinese herbal formula Du-Huo-Ji-Sheng Decoction (DHJSD) for KOA treatment. However, the therapeutic effects of the combination of these two methods are unknown. The current study aims to evaluate the therapeutic effect of the combined therapy of Tui-na and oral administration of DHJSD on KOA using a randomized controlled design.

Methods

We conducted a prospective, randomized, wait-list controlled clinical trial. Seventy study subjects with KOA were randomly assigned to the treatment and wait-list control groups in a 1:1 ratio. Both the treatment and wait-list control groups received eight sessions of Tui-na manipulation for 4 weeks. The DHJSD were given to the study subjects in the treatment group, but not the wait-list group. Outcomes were assessed using the WOMAC score and EQ-5D-5L, a health-related quality of life with 5-level EQ-5D version.

Results

The analysis of WOMAC scores and EQ-5D-5L in both groups showed statistically significant improvement with time. The mean WOMAC Pain subscale score was significantly lower in the treatment group than in the wait-list control group at week 8 follow up (P = 0.048). The mean WOMAC Stiffness subscale score was significantly lower in the treatment group than in the wait-list control group at week 2 and week 8 follow up (P = 0.035 and 0.008). The mean EQ-5D index value was significantly improved in the treatment group than in the wait-list control group at week 2 (P = 0.022). No significant adverse effects were found during the trial.

Conclusion

Combined Tui-na and the herbal medication were effective in relieving pain and improving stiffness as well as quality of life (QOL) in patients with KOA. The combined treatment was generally safe and well tolerated.

Trial registration

The study was registered at the ClinicalTrials.gov (website: https://clinicaltrials.gov/ct2/show/NCT04492670, registry number: NCT04492670), registered on 30 July 2020.

Background

Knee osteoarthritis (KOA) is a common degenerative joint condition and one of the most common causes of disability and pain amongst the elderly. The prevalence of KOA amongst persons aged 63 or above is 33.0%, and this figure increases with age [1].
According to a recent study conducted in Hong Kong, by the year 2036, it is predicted that 30% of Hong Kong residents will be aged 65 or above [2], implying an estimated 10% of Hong Kong residents may suffer from KOA. Since the morbidity rate of KOA is extremely high in Hong Kong, it is of utmost important for us to establish an effective method to treat KOA.

The effectiveness of conventional therapies for KOA is limited for many reasons including an array of adverse side effects and drug resistance from the use of approved pharmacological drugs [3, 4]. Currently, the ultimate solution is surgery but prolonged waiting periods and effectiveness of Total Knee Replacement (TKR) makes this option unfavorable. According to the data in 2021, the 90th percentile waiting time for total joint replacement surgery is approximately 62 months in Hong Kong [5]. Although mortality after primary TKR was low in public hospitals in Hong Kong [6], the probability of the occurrence of the postsurgical pain of TKR is approximately 53% [7].

Historically, traditional Chinese medicine techniques such as Tui-na were used to treat KOA and over the years this method has been refined and standardized. Tui-na can relieve the symptoms of KOA due to an increase in local blood circulation in the affected muscles [8]. The effect of Tui-na is well studied and widely reported. It has fewer associated adverse effects than other treatment schemes and is generally well taken by patients.

Hong Kong is a “East meets West” place in which the Chinese medicine is very popular. Tui-na for KOA is highly demanded but owing to the limited number of Tui-na practitioners, the treatment cannot be fully maximized. There are 18 Tripartite Chinese Medicine Clinic cum Training and Research Centre supported by the Hospital Authority, 13 of them provide Tui-na services, but each Tui-na practitioner is only able to deliver the service to approximately 10 patients per day. With a view of maximizing the treatment effects so that the number of service sessions can be reduced and satisfy the demand, we aimed to explore a complementary treatment, Chinese medicine to Tui-na to increase the synergistic effect. This was predicted to reduce the number and frequency of Tui-na sessions required for KOA patients to be able to observe its effectiveness.

Du-Huo-Ji-Sheng Decoction (DHJSD) is a widely used traditional Chinese herbal medicine for the treatment of arthritis in Asia [9, 10]. In animal studies, DHJSD has demonstrated significant anti-inflammatory effects through promoting lymphatic drainage function [11], and it can improve clinical symptoms, knee function and quality of life (QOL) for patients with KOA by inhibiting cartilage apoptosis [12]. In addition, DHJSD showed a lower risk of adverse events than standard western treatments [13]. There are very limited published reports about the clinical effectiveness of DHJSD. Hence this study aimed to evaluate the effectiveness and safety of DHJSD in KOA. During the study, Tui-na was administered to the study subjects in both groups as a supportive treatment.

**Methodology**

**Study design**

This was a multicenter, prospective, randomized, wait-list controlled trial in patients with KOA. The study subjects were randomized to receive either Tui-na and DHJSD or Tui-na alone for 10 weeks.

**Study population**

Study subjects were recruited from the general public via daily outpatient services (Yan Oi Tong - The Chinese University of Hong Kong Chinese Medicine Clinic cum Training and Research Centre (Tuen Mun District) and Yan Oi Tong - The University of Hong Kong Chinese Medicine Clinic cum Training and Research Centre (Islands District)
and advertisements in posters and leaflets from September 2020 to September 2021. Study subjects interested in participating in the study were referred to or self-approached the study sites to undergo eligibility assessment. They were pre-screened through a telephone interview. Potential study subjects for recruitment to the study had a face-to-face interview arranged to confirm the eligibility. During the interview, assessors explained the overall objectives and nature of the study, described the informed consent, and assessed the study subjects’ eligibility. All study subjects were assessed using Chinese medicine theory by the Chinese medicine practitioners (CMPs), and the baseline data on their symptoms and medical histories were recorded.

If the study subject had bilateral KOA and both knees fulfil the eligibility criteria, only the most symptomatic knee was treated and evaluated for the outcome assessment throughout the whole study period.

**Eligibility criteria**

Study subjects aged 50 years or older, met the criteria of KOA according to the American College of Rheumatology [14], with Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [15, 16] score 39 or above were recruited and a willingness to participate in the study.

We excluded study subjects who had other disorders that might affect the knee (e.g., infection, malignant or autoimmune diseases); who had knee surgery or arthroscopy in the past year; who had knee chondroprotective or intra-articular injection, or received systemic corticoid treatment in the past 4 months; who had local antiphlogistic treatment, acupuncture, physiotherapy in the past 2 weeks; who took anticoagulants, antiplatelets, corticosteroids, psychiatric drugs, hormones, antiarrhythmic drugs or diuretics drug; who had uncontrolled hypertension; who had comorbidities including severe cardiovascular, cerebral, hepatic, renal, or hematopoietic diseases; who had a history of mental illness; or who had allergic reaction to or had drug interaction with the study herbs.

**Randomization and masking**

Before randomization, there were 2 weeks screening period for pre-study blood test assessments, and study subjects needed to stop taking antiphlogistic treatment, acupuncture or physiotherapy during this period. Eligible study subjects were randomly assigned to the treatment group and wait-list control group in 1:1 ratio. An independent assessor used the random number function in Microsoft Excel 2019 to generate the randomization sequence. Study subjects were informed of their assigned group. However, Tui-na practitioners and statisticians were blinded to randomization but follow standard operation procedure (SOP).

**Interventions**

Treatment group received the standardized Tui-na and DHJSD, while wait-list control group received Tui-na alone during the study period. Study subjects in treatment group underwent 8 sessions of 20 minutes Tui-na with the same manipulation by well-trained independent, blinded Chinese medicine practitioner investigators, and took DHJSD orally twice daily concomitantly over 4 weeks. The wait-list control group only received standardized Tui-na in the same manner of the treatment group but were given the same regimen of DHJSD after the completion of week 8 follow-up assessments at study subjects’ discretion. The procedures of Tui-na manipulation are shown in Appendix I. Names and details of acupoints used in Tui-na manipulations are listed in Table 1. Prescription of the core formula and the addition of herbs are listed in Table 2, and the composition and the action of DHJSD are listed in Table 3.
<table>
<thead>
<tr>
<th>Name of acupoints*</th>
<th>Areas</th>
<th>Special qualification</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuehai (SP10)</td>
<td>When the knee is flexed, 2 cun above the medical superior border of the patella on the bulge of the medial portion of m. quadriceps femoris</td>
<td>-</td>
<td>Irregular menstruation, heavy uterine bleeding, amenorrhea; urticaria, eczema, erysipelas; abdominal distension, diarrhea, jaundice; abdominal pain, difficulty in micturition, edema; pain and swelling in the knees</td>
</tr>
<tr>
<td>Liangqiu (ST34)</td>
<td>On the line connecting the anterior superior iliac spine and the lower lateral border of the patella, 2 cun above the upper lateral border of the patella</td>
<td>Xi-Cleft Point</td>
<td>Stomach pain; knee pain, atrophy and paralysis of the legs; mastitis</td>
</tr>
<tr>
<td>Hedeng (EX-LE2)</td>
<td>Above the knee, in the depression of the midpoint of the superior patellar border</td>
<td>-</td>
<td>Knee pain, weakness of the leg and foot, and palsy</td>
</tr>
<tr>
<td>Dubi (ST35)</td>
<td>When the knee is flexed, at the lower border of the patella, in the depression lateral to the patella ligament</td>
<td>-</td>
<td>Swelling and pain in the knees, difficulty in flexing and extending the knees and beriberi</td>
</tr>
<tr>
<td>Neixiyan (EX-LE4)</td>
<td>In the depression medial to the patellar ligament when the knee is flexed</td>
<td>-</td>
<td>Pain in the knee, atrophy or paralysis of the lower limbs</td>
</tr>
<tr>
<td>Yanglingquan (GB34)</td>
<td>In the depression anterior and inferior to the small head of the fibula</td>
<td>He-Sea Point; Lower He-Sea Point of the Gallbladder; One of the Eight Influential Points</td>
<td>Jaundice, bitter taste in mouth, hiccups, vomiting; pain in the hypochondric region; swelling and pain of the knee, atrophy or paralysis in the lower limbs</td>
</tr>
<tr>
<td>Weizhong (BL40)</td>
<td>On the midpoint of the transverse crease of the popliteal fossa, between the tendons of the biceps femoris and semitendinous</td>
<td>He-Sea Point; Lower He-Sea Point of the Bladder</td>
<td>Lumbar pain, spasm of the popliteal tendons, weakness or paralysis in the lower limbs; difficulty in urination, enuresis; erysipelas, urticaria, furuncles</td>
</tr>
<tr>
<td>Chengshan (BL57)</td>
<td>In the centre of the posterior aspect of the lower leg, between Weizhong (BL40) and Kunlun (BL60), in the triangle depression formed below the bellies of the gastrocnemius muscle when the foot is stretched</td>
<td>-</td>
<td>Pain and spasm in the lumbar region and legs; haemorrhoids, constipation</td>
</tr>
</tbody>
</table>

*According to "Acupuncture and Moxibustion" edited by Shi XM, (China Press of Traditional Chinese Medicine, 2002)
Table 2
Prescription of the core formula and the addition of herbs*

<table>
<thead>
<tr>
<th>The Basic DHJSD</th>
<th>Concentrated Chinese Medicine granules</th>
<th>Corresponding raw herbs dose</th>
<th>Highest dosage recommended by Chinese Medicine Information System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du-huo (Angelicae Pubescentis Radix)</td>
<td>2g</td>
<td>10g</td>
<td>10g</td>
</tr>
<tr>
<td>Sang-ji-sheng (Taxilli Herba)</td>
<td>3g</td>
<td>15g</td>
<td>15g</td>
</tr>
<tr>
<td>Du-zhong (Eucommiae Cortex)</td>
<td>2g</td>
<td>10g</td>
<td>10g</td>
</tr>
<tr>
<td>Niu-xi (Achyranthis Bidentatae Radix)</td>
<td>2.4g</td>
<td>12g</td>
<td>12g</td>
</tr>
<tr>
<td>Xi-xin (Asari Radix et Rhizoma)</td>
<td>0.2g</td>
<td>1g</td>
<td>1g</td>
</tr>
<tr>
<td>Qin-jiao (Gentianae Macrophylae Radix)</td>
<td>2g</td>
<td>10g</td>
<td>10g</td>
</tr>
<tr>
<td>Fu-ling (Poria)</td>
<td>3g</td>
<td>15g</td>
<td>15g</td>
</tr>
<tr>
<td>Fang-feng (Saposhnikoviae Radix)</td>
<td>2g</td>
<td>10g</td>
<td>10g</td>
</tr>
<tr>
<td>Chuan-xiong (Chuanxiong Rhizoma)</td>
<td>1.2g</td>
<td>6g</td>
<td>10g</td>
</tr>
<tr>
<td>Dang-shen (Codonopsis Radix)</td>
<td>3g</td>
<td>15g</td>
<td>30g</td>
</tr>
<tr>
<td>Gan-cao (Glycyrrhiza Radix et Rhizoma)</td>
<td>1.2g</td>
<td>6g</td>
<td>10g</td>
</tr>
<tr>
<td>Bai-shao (Paeoniae Radix Alba)</td>
<td>2.4g</td>
<td>12g</td>
<td>15g</td>
</tr>
<tr>
<td>Di-huang (Rehmanniae Radix)</td>
<td>3g</td>
<td>15g</td>
<td>15g</td>
</tr>
<tr>
<td>Ji-xue-teng (Spatholobi Caulis)</td>
<td>2.4g</td>
<td>12g</td>
<td>15g</td>
</tr>
<tr>
<td>Cu-yan-hu-suo (Corydalis Rhizoma)</td>
<td>0.6g</td>
<td>3g</td>
<td>3g</td>
</tr>
</tbody>
</table>

*According to


<table>
<thead>
<tr>
<th>Herb</th>
<th>Conc. of Granules</th>
<th>Raw Herb Dose</th>
<th>Highest Dose Recommended by CMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addition of herbs to study subjects with excess dampness pattern</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fang-ji (Stephaniae Tetrandrae Radix)</td>
<td>2g</td>
<td>10g</td>
<td>10g</td>
</tr>
<tr>
<td>Yi-yi-ren (Coicis Semen)</td>
<td>3g</td>
<td>15g</td>
<td>30g</td>
</tr>
<tr>
<td>Cang-zhu (Atractylodis Rhizoma)</td>
<td>1.8g</td>
<td>9g</td>
<td>9g</td>
</tr>
<tr>
<td><strong>Addition of herbs to study subjects with blood stasis pattern</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tao-ren (Persicae Semen)</td>
<td>2g</td>
<td>10g</td>
<td>10g</td>
</tr>
<tr>
<td>Hong-hua (Carthami Flos)</td>
<td>1.2g</td>
<td>6g</td>
<td>10g</td>
</tr>
</tbody>
</table>

*According to:


<table>
<thead>
<tr>
<th><strong>Table 3</strong></th>
<th>The composition and the action of DHJSD*</th>
</tr>
</thead>
</table>
| **Angelicae Pubescentis Radix** | TCM: Dispels wind, eliminates dampness, frees cold, stops pain.  
Pharmaceutical study: Apply to wind-cold and damp impediment, pain of waist and knees, subside wind of Shao Yin and headache, headache and toothache. |
| **Taxilli Herba** | TCM: Dispels wind-damp, supplements liver and kidney, strengthens sinew and bone, secures fetus.  
Pharmaceutical study: Apply to cold pain in the waist and knees, weakness of bones and muscles due to flaccidity, hemiplegia, rheumatic arthralgia, lightheadedness and dizziness, restless fetal movement, metrorrhagia and metrostaxia. |
| **Eucommiae Cortex** | TCM: Supplements the liver and kidney, strengthens sinew and bone, calms the fetus.  
Pharmaceutical study: Apply to aching pain in the loins and knees, weakness of legs and knees, drenching and unsmooth urination, vaginal dampness and itch, fetal leakage and abortion, restless fetal movement, hypertension. |
| **Achyranthis Bidentatae Radix** | TCM: Supplements liver and kidney, strengthens sinew and bone, invigorates blood, frees channels, conducts the blood to move downward, promotes urination.  
Pharmaceutical study: Apply to sour pain of waist and knees, tired and soft of lower limbs, blood stasis and amenorrhea, dysmenorrhea, abdominal pain after giving birth, aggregation-accumulation, retention of placenta after giving birth, heat strangury, blood strangury, injury of trauma, abscess swelling and sore, throat swelling and pain. |
| **Asari Radix et Rhizoma** | TCM: Resolvers exterior, disperses cold, dispels wind, stops pain, warms lung, transforms fluids, frees nose.  
Pharmaceutical study: Apply to exterior disease induced by pathogenic wind-cold, headache, toothache, wind-damp impediment, dyspnea with cough due to phlegm and retained fluids, nasal obstruction, rhinorrhea with turbid discharge, mouth sore. |
| **Gentianae Macrophyllae Radix** | TCM: Dispels wind-damp, comforts sinews, clears deficiency heat.  
Pharmaceutical study: Apply to wind-damp impediment, contracture of bones and muscles, sour pain of bone and joint, afternoon tidal fever, infantile malnutrition with fever. |
| **Poria** | TCM: Promotes urination, leaches out dampness, fortifies the spleen and stomach, calms spirit.  
Pharmaceutical study: Apply to dysuria, edema, phlegm and retained fluid and cough, vomiting, less intake due to deficiency of spleen, diarrhea, and fright and nervous, insomnia and amnesia, spermatorrhea and gonorrhea. |
| **Saposhnikoviae Radix** | TCM: Resolves the exterior, disperses wind, eliminates dampness, relieves tetany.  
Pharmaceutical study: Apply to exterior syndrome due to wind-cold, headache, dizziness, rigid neck, rheumatic arthralgia with wind-cold, joint pain and sour, convulsion of limbs, tetanus. |
| **Chuanxiong Rhizoma** | TCM: Invigorates the blood, eliminates stasis, moves Qi, opens stagnation, dispels wind, relieves pain. |

TCM: Traditional Chinese Medicine

*According to Hong Kong Baptist University Chinese Medicinal Material Images Database, Medicinal Plant Images Database and Chinese Medicine Specimen Database.*
### Codonopsis Radix
**TCM:** Supplements the center, boosts Qi, fortifies the lung, boosts the spleen.

**Pharmaceutical study:** Apply to weakness of spleen and lung, short breath and palpitations, anorexia and loose stool, dyspnea and cough due to deficiency of the lung, feverish dysphoria and diabetes.

### Glycyrrhizea Radix et Rhizoma
**TCM:** Supplements the spleen, boosts Qi, clears heat, resolves toxin, disperses phlegm, relieves cough, relaxes tension, relieves pain, harmonizes the nature of other medicinal.

**Pharmaceutical study:** Apply to weakness of the spleen and stomach, weariness and debilitation, coughing with asthma, excessive phlegm, palpitation and shortness of breath, pain of gastric cavity, contraction and pain in four limbs, anthracia and sores, relieving drug toxicity, severity of toxicity.

### Paeoniae Radix Alba
**TCM:** Nourishes the blood, regulates menstruation, calms the liver, relieve pain, astringes yin, stops sweating.

**Pharmaceutical study:** Apply to thoracic, abdominal and costal pains, abdominal pain due to dysentery, spontaneous perspiration and night sweat, fever with yin deficiency, irregular menstrual periods, metrorrhagia and metrostaxis, leukorrhea.

### Rehmanniae Radix
**TCM:** Clears heat, cools blood, nourishes yin, and engenders fluids.

**Pharmaceutical study:** Apply to acute pyreticosis, fever and coma, macular eruption, hydrodipsia due to depletion of body fluids, hematemesis due to hemopyretic bleeding, non-traumatic hemorrhage, metrorrhagia and metrostaxis, hemafecia, mouth and tongue ulcers, swelling pain in the throat, coughing with over-strained fever, injury pains from falls, anthracia.

### Spatholobi Caulis
**TCM:** Supplements blood, invigorates blood, frees network vessels.

**Pharmaceutical study:** Apply to irregular menstrual periods, hemasthenic flaccidity, numbness and paralysis, rheumatic arthralgia.

### Corydalis Rhizoma
**TCM:** Invigorates blood, disperses stasis, moves Qi, stops pain.

**Pharmaceutical study:** Apply to chest impediment and heart pain, flank and abdomen pain, headache, waist pain, hernis pain, sinew and bone pain, dysmenorrhea, amenorrhea, postpartum blood stasis and abdominal pain, injury from falls.

### Stephaniae Tetrandrae Radix
**TCM:** Promotes urination, reduces swelling, dispels wind, relieves pain.

**Pharmaceutical study:** Apply to edema and beriberi, difficulty in micturition, wind-damp impendment, rheumatic arthralgia, hypertension.

### Coicis Semen
**TCM:** Fortifies the spleen, percolates dampness, eliminates impediment, relieves diarrhea.

**Pharmaceutical study:** Apply to edema, beriberi, dysuria, damp arthralgia and contracture of tendons and vessels, diarrhea due to spleen deficiency.

### Atractylodis Rhizoma
**TCM:** Dries dampness, fortifies the spleen, dispels wind, disperses cold, and brightens the eyes.

**Pharmaceutical study:** Apply to chest impediment and heartache, chest pain, swollen pain of falls wound, irregular menses, amenorrhea, dysmenorrheal, abdominal mass and pain, headache, wind-damp impediment.

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* According to Hong Kong Baptist University Chinese Medicinal Material Images Database, Medicinal Plant Images Database and Chinese Medicine Specimen Database.
Follow-up visits

Both groups are assessed at week 2, week 4 and were further followed up at week 8 (post 4 weeks intervention) with any symptoms of the knee and adverse events being assessed at each visit. All outcome assessments were done before the treatment at each follow up, this was to assess the treatment efficacy since last treatment instead of the immediate effect.

For safety concern, we recorded medical history and adverse events during the interventions and follow-up period, and gave appropriate treatment or referral if needed. Interventions were suspended immediately should a treatment-related serious adverse events occurred. Further assessments were needed to decide whether the trial should be suspended. There had a designated hotline for adverse event reporting. Study subjects could call the hotline during office hours but were advised to attend Emergency Department at the nearest hospital during non-office hours if severe adverse event was found. At the end of the intervention, the study subjects received post-study blood tests, included complete blood picture tests, liver and renal function tests for safety monitoring.

In order to encourage study subjects’ continued compliance, they were contacted by telephone one to two days prior to each visit. For the treatment group who had study medications, leftover packages were counted to monitor each study subject’s compliance. The consumption of topical drugs and non-steroidal anti-inflammatory drugs (NSAIDs) rescue medication was also recorded at each visit.

Outcome Measurements

Primary outcome measure

The primary outcome measure was rated using the WOMAC in Chinese version [16, 17] at 4 weeks after randomization. The WOMAC is a validated tool for self-administration. It is a 3-dimensional questionnaire that assesses pain, stiffness and physical functional disability in study subjects with KOA using a series of 24 questions. It is a five-point scale from 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme).

Secondary outcome measures
Secondary outcome measured WOMAC in Chinese version at 2 weeks and 8 weeks after randomization. The health-related quality of life using the EQ-5D-5L in Chinese version [18, 19] was also used. Outcomes were documented at 2 weeks, 4 weeks after randomization and follow-up (8 weeks). The EQ-5D-5L is used to assess health-related quality of life and particularly utility values. It shows high responsiveness in study subjects and it can also show important changes clinically [20]. The EQ-5D-5L essentially consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS can be used as a quantitative measure of health outcome that reflects the study subjects’ own judgment. It recorded the study subjects’ self-rated health on a vertical visual analogue scale.

Ethics Consideration

The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Review Committee (CREC Ref. No. 2019.538). And the study was registered at the ClinicalTrials.gov (website: https://clinicaltrials.gov/ct2/show/NCT04492670, registry number: NCT04492670).

Study Monitoring

A dedicated team from the Hospital Authority Chinese Medicine Department (HACMD) that was completely uninvolved in the running of the study and had no competing interests were responsible for study monitoring.

Sample Size Calculation And Statistical Analysis

The sample size calculation was based on the primary outcome, the WOMAC. We assumed Tui-na combined with DHJSD could have a 20-point superior than the wait-list control group at week 4. According to the previous study, the massage could decrease WOMAC 17.44 with standard deviation 23.61 [21]. The sample size could be calculated according to the following formula

$$n = \frac{2\sigma^2 \left( t_\alpha + t_\beta \right)^2}{(\mu_1 - \mu_2)^2}$$

The $\mu_1-\mu_2$ was the difference in means, 2.616. The $\sigma$ was 23.61. We define $\alpha$ as 0.05 and $\beta$ as 0.1, the $t_\alpha$ and $t_\beta$ were 1.96 and 1.282 respectively. The sample size for each group was 29. Considering 20% drop-out, the total sample size was 70.

All efficacy and safety analyses were conducted according to the intention-to-treat (ITT) principle. Missing values were imputed by the last-observation-carried forward method. The statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) for Windows, version 27.0. Statistical significance was defined as a two-sided $P$ value of < 0.05. Baseline characteristics were reported as mean ±SD.

Analysis of covariance (ANCOVA) was used to adjust the potential confounding variables on the outcomes. In this study, WOMAC Stiffness subscale score and WOMAC Physical Function subscale score (shopping) were potential confounding variables that were adjusted. The changes in scores from baseline to the end-point of treatment were
tested using paired t-test. Within-subject differences were assessed using repeated measure analysis of covariate (ANCOVA) and paired t test for underlying non-normal distributed data.

Results

Study subjects and baseline characteristics

Between September 2020 to September 2021, 117 study subjects were screened according to the inclusion criteria, and 46 (39.3%) were excluded. 71 eligible study subjects were enrolled. 1 was post-randomization excluded due to unavailable treatment appointment. The remaining 70 study subjects were randomly divided into two groups. Out of 70 randomly assigned study subjects, 1 from the wait-list control group was withdrawal due to working reason, all the rest completed the 4-week course of treatment and were assessed at week 8. A flow chart of this study is presented in Fig. 1. There was no significant difference between the two groups in age, gender, body mass index (BMI) and other demographic characteristics. Baseline characteristics of the study subjects are presented in Table 4. Before treatment, there was no significant difference in WOMAC total scores and the EQ-5D descriptive system as well as EQ VAS between two groups (P > 0.05).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment group (n = 35)</th>
<th>Wait-list control group (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.8 (7.5)</td>
<td>64.5 (5.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (25.7)</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (74.3)</td>
<td>29 (82.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.4 (11.3)</td>
<td>65.8 (12.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.0 (8.3)</td>
<td>156.0 (6.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.1 (3.8)</td>
<td>27.1 (4.9)</td>
</tr>
<tr>
<td>Pain area, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Knee</td>
<td>20 (57.1)</td>
<td>19 (54.3)</td>
</tr>
<tr>
<td>Right Knee</td>
<td>15 (42.9)</td>
<td>16 (45.7)</td>
</tr>
<tr>
<td>Pain duration (months)</td>
<td>99.1 (93.6)</td>
<td>101.1 (85.9)</td>
</tr>
</tbody>
</table>

Note: Values are presented as mean (SD) except where noted.

SD: standard deviation; BMI: body mass index (calculated as weight in kilograms divided by height in meters squared).

All thirty-five study subjects in the treatment group completed the whole Tui-na treatment (8 sessions). In the wait-list control group, 3 study subjects (8.57%) did not receive the whole Tui-na treatment. In the treatment group, 3 study subjects (8.57%) took less than 80% of the prescribed dosage over the study period.
All thirty-five study subjects in the treatment group were prescribed the basic study medication, DHJSD. Eight of them (22.86%) manifested excessive dampness patterns at the baseline and were prescribed DHJSD with Fang-ji (Stephaniae Tetrandrae Radix), Yi-yi-ren (Coicis Semen) and Cang-zhu (Atractylodis Rhizoma), one of them did not manifest this pattern at week 2 and the remaining medication had changed to the basic study medication. Ten of them (28.57%) manifested blood stasis patterns at baseline and were prescribed DHJSD with Tao-ren (Persicae Semen) and Hong-hua (Carthami Flos), one of them did not manifest this pattern at week 2 and the remaining medication had changed to the basic study medication. One study subject (2.86%) manifested both excessive dampness and blood stasis pattern and was prescribed DHJSD with the five additional herbs.

**Primary and secondary outcomes**

The WOMAC total scores in the treatment group and the wait-list control group were similar at 4 weeks (t = -1.295, P = 0.20) with the mean (SD) 37.0 (16.2) compared with 42.1 (16.3) (Table 5). However, the analysis of WOMAC total scores and all the subscales scores in both groups showed statistically significant improvement with time, when comparing baseline versus week 4 and baseline versus week 8 (P < 0.001 and P < 0.001 respectively). On comparison between two groups, the treatment group showed a trend of improvement than the wait-list control group.

<table>
<thead>
<tr>
<th>WOMAC and EQ-5D-5L score over time by group, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (baseline)</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>WOMAC Total score</td>
</tr>
<tr>
<td>Pain subscale</td>
</tr>
<tr>
<td>Stiffness subscale</td>
</tr>
<tr>
<td>Physical Function subscale</td>
</tr>
<tr>
<td>EQ-5D Index value</td>
</tr>
<tr>
<td>EQ VAS</td>
</tr>
</tbody>
</table>

* The difference between two groups is statistically significant.

In addition, there was a statistical difference in mean WOMAC Pain subscale score at week 8 follow up between the two groups (P = 0.048). The mean difference (MD) was 1.76 with 95% confidence interval (CI) of 0.02 to 3.5. The treatment group demonstrated better improvement in pain relief than control group.

Besides, there were statistical differences of mean WOMAC Stiffness subscale scores between the two groups at week 2 (MD 0.74, 95%CI 0.05 to 1.42, P = 0.035) and week 8 (MD 0.95, 95%CI 0.26 to 1.65, P = 0.008).
For EQ-5D-5L, the analysis of EQ-5D index values and EQ VAS scores in both groups showed statistically significant improvement with time, when comparing baseline versus week 4 and baseline versus week 8 (P < 0.001). Besides, there were statistical differences of mean EQ-5D index values for the two groups at week 2 (MD 0.17, 95%CI 0.02 to 0.31, P = 0.022) (Table 5).

As WOMAC Stiffness subscale score and WOMAC Physical Function subscale score (shopping) significantly affected (P = 0.014 and 0.026 respectively) the WOMAC scores and EQ-5D-5L between both groups at baseline. ANCOVA was performed to compare the effect of intervention groups the independent variable (treatment group versus wait-list control group) on WOMAC and EQ-5D-5L (dependent variables) separately at 4 different time periods. The ANCOVA results shown that interventions (treatment group versus wait-list control group) were not statistical difference in the mean of WOMAC, EQ-5D index values and EQ VAS scores at week 4 and week 8.

Additional drugs

Both groups showed decreasing consumption of topical drugs and non-steroidal anti-inflammatory drugs (NSAIDs) during treatment. Twenty-one subjects (60.0%) from each group used additional drugs to relieve knee pain at the baseline. After the 8-week trial, only 4 (11.4%) and 5 (14.3%) study subjects consumed additional drugs in the treatment group and the wait-list control group respectively. There was significant difference in time for both groups (P < 0.001), but no significant difference between groups (P = 0.73).

Safety outcomes

Adverse events

During the 8-week trial, there were no report on serious adverse events. 2 study subjects (5.7%) from the treatment group and 6 (17.1%) from the wait-list control group reported mild local pain in the lower limbs after receiving Tui-na manipulation. There was no significant difference in the occurrence of adverse events between two groups (P = 0.12). Besides, in the treatment group, seven (20.0%) adverse drug reactions were potentially related to the medication, involving change in stool frequency and abdominal distention. All these adverse events were mild and subsided in a short of time without medical care.

Laboratory investigations

After 4-week intervention, there were few abnormal findings in the liver function test. 2 study subjects (5.7%) from the treatment group and 3 (8.6%) from the wait-list control group showed alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin slightly increased in the blood tests. There was no significant difference in the occurrence of abnormal blood test results between two groups (P = 0.62). These study subjects showed no symptoms or signs related to the abnormal liver function and all returned to normal after having re-check blood tests 2 weeks later.

For other examinations, there were no significant changes in the vital signs, blood tests including complete blood picture tests and renal function tests after the intervention in both groups.

Discussion

The present study demonstrated that there was improvement in pain relief, stiffness knee function, as well as QOL in both groups during the 4-weeks intervention. And the improvement kept on going at week 8 followed up. These
results suggest that Tui-na or the combined treatment have positive effects in terms of WOMAC scores, as well as the quality of life of KOA patients.

The treatment group showed significant improvements in WOMAC Pain subscale score at week 8, the results demonstrated Tui-na was effective for immediate relief of pain, while oral Chinese medicine as an add-on effect was effective in long-term pain relief. As herbal Chinese medicine can help to suppress inflammatory reactions [22] that make the analgesic effect more progressive.

Besides, the treatment group showed significant improvements in WOMAC Stiffness subscale score at week 2 and week 8, as the herbal Chinese medicine can protect articular cartilage [23], it may help the joints’ motion smoother. But the WOMAC Physical Function subscale score did not show significance add-on effect when compared to the treatment group, it is because the herbal medicine might not alter abnormal alignment and the degenerative process [24, 25].

Tui-na, Chinese massage, is an important part of Tradition Chinese Medicine with more than 2000 years history [26]. It is a treatment based on meridian system. Practitioners use hands and arms to manipulate soft tissue, which stimulate the acupoints and mobilize joints by different techniques of Tui-na such as rolling, kneading and pulling to dredge the meridian system and promote the Qi and Blood circulation [27]. This method was used to treat different disorders, such as muscle weaknesses, and joint pains. Tui-na was included as a component of physiotherapy intervention for KOA in the 2018 Expert Consensus on Step Treatment of Knee Osteoarthritis statement in China [28]. It is one of the most popular therapies for KOA because it is a non-invasive treatment and is widely accepted by patients.

KOA is a degenerative disease and the most common cause of disability in the elderly [29]. The major symptoms of KOA include knee pain, muscle weakness and loss of joint function. Compare to current pharmacological treatment, Tui-na is more beneficial to the patients and health care system because of its simple operation, fewer side-effect and lower financial cost [30, 31].

Many studies had shown that the effectiveness of treating KOA with Tui-na is without doubt [32–34]. The results in this study are comparable to previous clinical trials. In this study, the quadriceps femoris and knee cap are manipulated. The function of quadriceps muscle is to maintain the stability of knee [35]. The weakness of quadriceps muscle is a common clinical sign for KOAs’ patients. The reason why manipulating the muscle is that massaging the quadriceps femoris not only can relieve pain, but also can improve the muscle strength and knee function in KOA patients [36–40]. Increased quadriceps strength also reduces the risk of symptomatic knee osteoarthritis [41]. The underlying mechanisms include: increased lymph and blood flow of the joint, increased clearance of blood lactate and absorption of inflammatory substances, promote the metabolism and nutrients supplication of articular cartilage [42–46].

In traditional Chinese medicine theory, there is a theory called muscle-region theory. A large proportion of muscles around the knee belong to the region of Foot Yang-ming. Patients with KOA showed a major damaged in the muscle region of Foot Yang-ming [47]. Hence, by rolling manipulated around this region, pressing and kneading the acupoints around the knee in this study, these can dredge the channels and promote the circulation of Qi and blood around the knee and disperses stasis. As a result, the channels are cleared and warmed [48, 49]. These manipulations were used to reduce swelling, break up adhesions and alleviates pain [26]. Besides, the knee joints were mobilized by rotating it clockwise and anti-clockwise respectively. The joints were then undergone a slight
pulling and shaking. These manipulations were used to lubricate the joints, restoring the joints’ full range of movement, and help muscle relaxation by stimulating inhibitory reflex and Golgi tendon organ [50, 51].

In this study, herbal medication, DHJSD, was used as an additional treatment on KOA apart from Tui-na. Various researches on DHJSD have been conducted over these years. It was proved that DHJSD can reduce the swelling volume, the number of inflammatory cells and inflammatory factors in joints fluid, relieve synovium pathological changes and suppress inflammatory signals in rats with induced KOA [52]. The clinical therapeutic effect of DHJSD may explain by its mechanism on inhibition of the inflammatory reaction in knee osteoarthritis by regulating the micro RNA signal pathway [53]. It is to believe that DHJSD can inhibit chondrocytes apoptosis [54, 55] and promote the progression of chondrocytes [56] in joints’ cartilage, thus it slows down the degenerative progress of KOA, and explain the nourishing and tonifying effect of DHJSD.

Pattern differentiation is one of the most important principles in the Chinese Medicine therapies. Chinese medicine practitioners analyse patients’ signs and symptoms data through observation, listening, questioning and palpation, all information obtained will be summarized and differentiated to different patterns. Chinese medicine is prescribed according to which patterns patients are.

According to traditional Chinese medicine theory, the most common pattern for KOA is kidney-yang deficiency with excessive dampness and blood stasis [10]. For patients related to kidney-yang deficiency, they present knee pain with aching pain in lumbar vertebrae, deafness, hair loss, teeth loosen and urinary incontinence. For patients related to excessive dampness, they present knee pain with heavy pain, heavy feeling in the body, pain worse in the rainy days and slippery tongue coating. For patients related to blood stasis, they present knee pain with fixed stabling pain, purple lips and purple tongues [57].

DHJSD is used for patients with KOA related to kidney-yang deficiency [10]. In our study, DHJSD was the basic formula for the treatment group. DHJSD aims to stop pain by dispelling wind-dampness, nourish the liver and kidney and tonify Qi and blood [58]. According to the Chinese herbology theory [59], Du-huo (Angelicae Pubescentis Radix), Qin-jiao (Gentianae Macrophyllae Radix) and Fang-feng (Saposhnikoviae Radix), each has the key function to dispel wind-dampness and release wind-cold. Xi-xin (Asari Radix et Rhizoma) is a warming herb with a remarkable pain-relieving power by disperse cold and wind. Chuan-xiong (Chuanxiong Rhizoma) and Cu-yan-hu-suo (Corydalis Rhizoma) both belong to blood-invigorating herbs which activate Qi and blood circulation and relieve pain. Research has found that alkaloids in Cu-yan-hu-suo (Corydalis Rhizoma) extracts are responsible for its anti-inflammatory effect [60]. Another study showed that Chuan-xiong (Chuanxiong Rhizoma) and Xi-xin (Asari Radix et Rhizoma) compounds demonstrate a synergistic analgesic effect [61]. Ji-xue-teng (Spatholobi Caulis) and Niu-qi (Achyranthis Bidentatae Radix) both activate blood circulation along with tonifying power. Ji-xue-teng (Spatholobi Caulis) would also tonifies blood while Niu-xi (Achyranthis Bidentatae Radix) nourishes liver and kidney and strengthens bones and tendons. Du-zhong (Eucommiae Cortex) and Sang-ji-sheng (Taxilli Herba) are often used in pair in many prescriptions because of their characteristics to tonify liver and kidney and strengthen bones and sinews. Dang-sheng (Codonopsis Radix), Gan-cao (Glycyrrhizae Radix et Rhizoma) and Bai-shao (Paeoniae Radix Alba) are tonic herbs to elevate Qi and blood level of the body.

Fang-ji (Stephanieae Tetrandrae Radix), Yi-yi-ren (Coicis Semen) and Cang-zhu (Atractylodis Rhizoma) were added if patients with excessive dampness patterns. Fang-ji (Stephanieae Tetrandrae Radix) can delay the progression of KOA by regulating lymphatic drain function [62], while Yi-yi-ren (Coicis Semen) and Cang-zhu (Atractylodis Rhizoma) can remove damp, relax muscles and tendon [63]. On the other hand, Tao-ren (Persicae Semen) and
Hong-hua (Carthami Flos) were added if patients with blood stasis patterns. The function of Tao-ren (Persicae Semen) and Hong-hua (Carthami Flos) is to improve microcirculation [64].

For the EQ-5D-5L, there are statistical differences of mean EQ-5D index values for the two groups at week 2. It is believe that DHJSD complementary to Tui-na had improved study subjects’ mobility and pain relief, DHJSD might also improve anxiety/depression and contributed to this result. In fact, Fu-ling (Poria) has a Chinese therapeutic effect to calm the Spirit and treat Spirit disturbance symptoms like insomnia and palpitations caused by deficiency of heart and spleen [63]. Gan-cao (Glycyrrhizae Radix et Rhizoma) is traditionally combined with other herbs to treat Zang-zao disorder – a condition associated with disturbed sleep and emotional instability. It is believed that Gan-cao (Glycyrrhizae Radix et Rhizoma) treats this by tonifying Qi and nourishing the heart [63].

Certain herbs in DHJSD also showed a sedative pharmacological effect in experiments on animals. Oral administration of Chuan-xiong (Chuanxiong Rhizoma) decoction to mice and rats has a sedative effect to the central nervous systems and counteracted the stimulation produced by caffeine [63, 65]. Ji-xue-teng (Spatholobi Caulis) has shown a sedative and hypnotic influence in rats while Cu-yan-hu-suo (Corydalis Rhizoma) has demonstrated a sedative and tranquilizing effect in rabbits, mice, dogs and monkeys [63].

In this study, the compliance rate was high, possibly because most of the study subjects were elderly and retired, with more time for treatment than those still working. Besides, they all lived close to the clinics, and many of them said that they found the interventions and the setting comfortable.

DHJSD complementary to Tui-na for KOA are safe and well tolerated. The adverse events were mild, transient and disappear spontaneously without the need for discontinuing interventions. They are safe, relatively inexpensive, and effective way to relieve knee osteoarthritis.

There were several limitations to our study. First, neither study subjects nor assessors were blinded to group allocation, possibly resulting in overestimation of the effects of the combined intervention. But it is recommended to have a third party to be assessors in the future studies. Second, there may be a selection bias as study subjects were enlisted through outpatient clinic-based recruitment and advertisements with posters and leaflets, they were already interested in being active and caring for themselves were more willing to participate. Third, most of the study subjects were women as they are more active in community activities, this may have increased the gender bias. Fourth, the treatment period of only 4 weeks was relatively short; therefore, we cannot assess long-term results. Last, self-rating scales were used as outcome measurements, some study subjects may have recall bias when interpreting results.

Further studies are required to carry out in the future. First, this study was conducted on a limited sample. It is recommended to repeat the study on larger samples. Second, increasing the duration of treatments and follow-up can clarify whether the analgesic effect can be progressive. Third, it is suggested to use imaging examination, such as X-ray, Computed Tomography scan (CT) or magnetic resonance imaging (MRI), which can help to make diagnosis and can also be one of the outcome measurements. Fourth, as Tui-na may also improve knee muscle function [36]. It is required to introduce objective outcomes to assess, such as knee muscle strength and balance using the Five-Times-Sit-to-Stand Test (FTSST) and the Timed Up and Go Test (TUG). Last, as various Tui-na manipulations were used in this study, different manipulations have to be found out each mechanism and therapeutic effect.
Conclusion

This study aimed to explore the efficacy and safety of Tui-na and herbal medication for KOA. The trial demonstrated that the herbal medication has add-on effect in pain relief, improving stiffness as well as QOL in patients with KOA and this combined treatment was generally safe and well tolerated. The findings highlight the potential of Tui-na and herbal medication as complementary treatment regimens for KOA. Large-scale clinical trials and double-blinded studies are needed to substantiate clinical evidence on the benefits of KOA and to identify the mechanisms underlying its efficacy.

Abbreviations

BMI: Body mass index; CREC: Clinical Research Ethics Review Committee; DHJSD: Du-Huo-Ji-Sheng Decoction; EQ VAS: EQ visual analogue scale; EQ-5D-5L: 5-level EQ-5D version; HACMD: Hospital Authority Chinese Medicine Department; ITT: intention-to-treat; KOA: Knee osteoarthritis; QOL: Quality of life; SD: Standard deviation; SOP: Standard operation procedure; SPSS: Statistical Packages for the Social Sciences; TKR: Total Knee Replacement; WOMAC: Western Ontario and McMaster University Osteoarthritis Index.

Declarations

Conflicts of interest

All authors declare that they have no conflict of interest.

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CRediT authorship contribution statement


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References


Figures
Figure 1

Flow chart of the study design