Pain relief effect of TT knee remedy on knee osteoporosis

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ABSTRACT
Objective: Evaluate the analgesic effect of TT knee remedy on patients with knee osteoarthritis. Method: prospective clinical trial study, comparing before and after controlled study. Results: TT knee remedy has pain relief effect on patients with knee osteoarthritis, this effect appears after seven days (VAS score decreases by 30.19%) and gradually lasts to 28 days (decreases by
76.34%). The analgesic effect of TT knee on patients with osteoarthritis was better than the controlled group using glucosamine 1500mg (p <0.001).

Keywords: TT knee, pain relief, knee osteoarthritis

1. INTRODUCTION
Knee osteoporosis is nowadays one of the most frequent chronic diseases worldwide as well as Vietnam, with a prevalence of 15 – 34%. Women have a greater prevalence than men; the incidence rate increases with age. The disease can develop slowly, characterized by disorders of the structure and function of the joints, including cartilage, subarticular cartilage, ligaments, joint muscles, and synovial membrane. When have knee osteoarthritis, the structure, and function of the articular cartilage cell decline, the level of joint mucus excreted decreases gradually leading to wear-and-tear arthritis; Knee symptoms are pain with mechanical properties, the practitioner may hear grinding or popping sounds, range of motion can be decreased (An and Lan, 2016).

According to traditional medicine, knee osteoporosis has belonged to define of “painful obstruction” and “arthrosis of the knee”. The disease arises due to impaired organ function, combined with wind-cold – dampness to block meridians (Chau, 2006). Traditional medicine treatments focus on improving the righteous spirit, promoting the functioning of the organs, thereby limiting the effects of the etiologies. Much research showed that traditional medicine has the effect of reducing symptoms, limiting the progression of the disease, and being safe for patients even when used long term. “TT knee” is made on the formula of the ancient medicine “San bi tang”, which is adjusted to suit the source of available pharmaceutical materials in the country (Department of Traditional Medicine, 2018). TT knee was used at Tue Tinh Hospital, initially showing positive results in patients with knee osteoarthritis, improve some symptoms of patients. TT knee has been tested for acute toxicity at the Department of Pharmacology of Military Medical University; the results confirm safety. However, no author has assessed the effectiveness of this remedy. Therefore, we conduct this topic with the goal: of evaluating the analgesic effect of the knee joint remedy for knee osteoarthritis patients. TT knee has been studied for acute toxicity at the Department of Pharmacology of Military Medical University; the results confirm safety. However, there are no research has evaluated the effect of TT knee. Therefore, the study was undertaken with the aim: of evaluating the analgesic effect of TT knee on knee osteoarthritis patients.

2. MATERIALS AND METHODS
The ingredients for TT knee: Codonopsis pilosula 8 gm, Astragalus membranaceus 12 gm, Angelica sinensis 12 gm, Ligusticum striatum 12 gm, Paeonia lactiflora 12 gm, Eucommia ulmoides 10 gm, Achyranthes bidentata 16 gm, Wolfiporia Extensa 12 gm, Dipsacus japonicus 16 gm, Asarum heterotropoides 04 gm, Ramulus cinnamoni 08 gm, Justicia gendarussa 12 gm, Angelica pubescens 12 gm, Ledebouriella seseloides 10 gm, Glycyrrhiza uralensis 06 gm, Rhizoma Homalomenae 10 gm, Leea Rubra Blume 15 gm.

Dosage form
TT knee is decomposed by the chromatograph machine of KYUNG SEOMACHINE - Korea, one decoction takes 300ml of solution, closes two bags (the volume of each bag is 150ml). TT knee was manufactured at the Pharmacy Department of Tue Tinh Hospital. A randomized controlled trial, 60 patients diagnosed with knee osteoporosis according to ACR-1991 standard, stages 1 and 2 according to Kellgren and Lawrence(Scott and Gishen, 1999), belong to wind-cold-damp with liver and kidney deficiency of Traditional medicine, Inpatient treatment at Tue Tinh Hospital from June to December 2018. Patients are divided randomly into two groups:
- Treatment group: 30 patients, taking " TT knee ", one decoction per day, taking 300ml divided into two times morning-afternoon after meals.
- Control group: 30 patients, taking glucosamine 1500mg, one sachet, mixed with drinking water after eating.

Patients were given the corresponding drugs for each group continuously for 28 days. Monitoring the pain level of patients on a VAS (Visual Analog Scale) scale at times D0, D7, D14, D21, D28. The effect of the knee joint remedy was assessed by comparing VAS scores at the time between the two groups.
**Statistical analysis**

The qualitative variables are presented as a percentage (%); the quantitative variables are expressed as mean and standard deviation (± SD). Data were processed by the biomedical method with the support of SPSS 16.0 software. Using algorithm χ2 (chi-2) with qualitative data, compare before and after treatment using the paired-sample T-test pairwise algorithm, compare with the algorithm of verification of the average value of two independent samples of independent-sample T-test.

3. RESULTS

**Table 1.** Age distribution of the two research groups

<table>
<thead>
<tr>
<th>Ages</th>
<th>EG (n = 30)</th>
<th></th>
<th>CG (n = 30)</th>
<th></th>
<th>Total (n =60)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Fre (%)</td>
<td>n</td>
<td>Fre (%)</td>
<td>n</td>
<td>Fre (%)</td>
</tr>
<tr>
<td>40 – 49</td>
<td>4</td>
<td>13,3</td>
<td>1</td>
<td>3,3</td>
<td>5</td>
<td>8,3</td>
</tr>
<tr>
<td>50 – 59</td>
<td>16</td>
<td>53,3</td>
<td>17</td>
<td>56,7</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>60 – 69</td>
<td>8</td>
<td>26,7</td>
<td>12</td>
<td>40,0</td>
<td>20</td>
<td>33,3</td>
</tr>
<tr>
<td>≥ 70</td>
<td>2</td>
<td>6,7</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3,4</td>
</tr>
<tr>
<td>X ± SD</td>
<td>56,30 ± 8,66</td>
<td>58,03 ± 6,47</td>
<td>57,17 ± 7,57</td>
<td></td>
<td></td>
<td>&gt; 0,05</td>
</tr>
</tbody>
</table>

In our study, KOS age mainly focused on ages ≥ 50, accounting for 91.7%, of which the elderly accounted for 86.7%, the control group accounted for 96.7%. Age of knee degeneration in the age group ≤ 49 accounts for 8.3%, in the elderly accounted for 13.3%; the control group accounted for 3.3%.

**Table 2.** Clinical symptoms of the two groups before the study

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>EG (n =30)</th>
<th></th>
<th>CG (n = 30)</th>
<th></th>
<th>Total (n =60)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Fre(%)</td>
<td>n</td>
<td>Fre(%)</td>
<td>n</td>
<td>Fre(%)</td>
</tr>
<tr>
<td>Knee pain</td>
<td>30</td>
<td>100</td>
<td>30</td>
<td>100</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Limiting movement</td>
<td>30</td>
<td>100</td>
<td>30</td>
<td>100</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Rust’s sign</td>
<td>26</td>
<td>86,7</td>
<td>28</td>
<td>93,3</td>
<td>54</td>
<td>90</td>
</tr>
<tr>
<td>Crackling sounds</td>
<td>30</td>
<td>100</td>
<td>28</td>
<td>93,3</td>
<td>58</td>
<td>96,7</td>
</tr>
<tr>
<td>Patella glide test</td>
<td>27</td>
<td>90</td>
<td>26</td>
<td>86,7</td>
<td>53</td>
<td>88,4</td>
</tr>
<tr>
<td>Hot skin at joint</td>
<td>3</td>
<td>10</td>
<td>1</td>
<td>3,3</td>
<td>4</td>
<td>6,7</td>
</tr>
<tr>
<td>p</td>
<td>&gt; 0,05</td>
<td>&gt; 0,05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The most common signs in the study: joint pain, movement limitation accounted for 100% in both study groups; crackling sounds accounted for 100% in the experimental group and 93.3% in the control group. Erosion of the articular surface accounts for 86.7% in the experimental group, while in the control group accounts for 93.3%. Patella apprehension – patellar instability signs in the experimental group, accounted for 90%, in the control group accounted for 86.7%. Heat skin at joints accounts for a very low rate of 10% in the experimental group and 3.3% in the control group.

**Table 3.** Comparison of average pain relief performance by VAS at different times

<table>
<thead>
<tr>
<th>Time of research</th>
<th>Average pain score according to VAS (± SD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Research group (n = 30)</td>
<td>Control group (n = 30)</td>
</tr>
<tr>
<td>D0</td>
<td>5,20 ± 1,09</td>
<td>5,33 ± 0,99</td>
</tr>
<tr>
<td>D7</td>
<td>3,63 ± 0,72</td>
<td>4,53 ± 1,07</td>
</tr>
<tr>
<td>D14</td>
<td>2,70 ± 1,12</td>
<td>3,80 ± 0,76</td>
</tr>
<tr>
<td>D21</td>
<td>1,76 ± 1,27</td>
<td>3,03 ± 0,88</td>
</tr>
</tbody>
</table>
Performance reduction | D28 – D0 | 1,23 ± 1,35 | 2,43 ± 1,07 | p<0,001
---|---|---|---|---
P(28 - 0) | < 0,001 | < 0,001
Performance reduction | D7 – D0 | 30,19% | 15%
| D14 – D0 | 48,07% | 28,7%
| D21 – D0 | 66,15% | 43,15%
| D28 – D0 | 76,34% | 54,40%

**Figure 1.** Change average VAS at times

Comment: According to the results (Table 3), before treatment the average pain level (VAS) of the study group was 5.2 ± 1.09 (points), the control group was 5.33 ± 0.99 (score), the difference between the two groups is not statistically significant (p> 0.05).

After seven days of treatment, the average VAS score of the EG group was 3.63 ± 0.72 (points) decreased by 30.19% compared to the first day D0, in the control group was 4.53 ± 1.07 (points) 15% reduction compared to D0. The difference between the two groups is statistically significant, with p < 0.001.

After 14 days of treatment, the average VAS score of the EG group decreased by 48.07% compared to the time of D0, while in the control group, it decreased by 28.7% compared to D0. Two groups had a statistically significant difference with p < 0.001.

At D21, the average VAS score of the research group decreased by 66.15% compared to D0, in the control group, it decreased by 43.15% compared to D0, the difference between the two groups was statistically significant with p < 0.001.

After 28 days of treatment, the average VAS score in the EG decreased more than D0 by 76.34%, while in the CG group decreased 54.40% compared to D0, the difference between the two groups was statistically significant with p < 0.001.

4. DISCUSSION

According to the research results (Table 1), the distribution of morbidity rates by age showed that the majority of patients aged ≥ 50 years old, accounting for 91.7%. That rate in the experimental group was 86.7%, while the control group accounted for 96.7%. There was no significant difference between the two groups with p> 0.05. Our research results are similar to those of domestic and foreign authors on the influence of age on knee osteoarthritis. In the research of Nguyen Giang Thanh (2012), patients over 50 years old in the experimental group accounted for 86.7%, while the control group accounted for 93.3%. In the research of author Nguyen Thi Bich (2014), the proportion of patients over 50 years old in the experimental group accounted for 93.3%, while the control group accounted for 96.7%. The average age is similar to the results in the study of author Thanh NG (2011) 65.5 ± 9.69 (age), author Nguyen Thu Thuy (2014) 60.15 ± 11.35 (years), (Thanh, 2012, Thuy, 2014).

In our study (Table 2), all patients had clinical symptoms of knee osteoarthritis such as arthralgia, decreased range of motion of the knee joint, crackle sound when moving, Rust’s sign, Patellar glide test. There was no statistically significant difference between the two patient groups in the study. Common symptoms in two groups are knee pain (100%), limited movement (100%), Rust’s sign...
(86.7% in the experimental group, 93.3% in the control group), crepitus (in the experimental group was 100%, the control group was 93.3%), the patellar glide test (in the experimental group was 90%, in the control group was 86.7%). This research result is also consistent with the diagnostic criteria of the American College of Rheumatology (ACR) in 1991 and is similar to the results of author Nguyen Thu Thuy (2014), Nguyen Thi Bich (2014).

Assessing the average VAS index (Table 3) prior to the treatment, the pain level calculated by the VAS scale in the experimental group was 5.02 ± 1.09, and the control group 5.33 ± 0.99. There is no significant difference (p > 0.05).

The average VAS pain score of the two groups of patients improved gradually over time. After seven days, the VAS average pain score of both groups of patients started to decrease. The average VAS value of the experimental group was 3.63 ± 0.72 (decreased by 30.19%), in the control group was 4.53 ± 1.07 (decreased by 15%) compared to D0, statistically significant compared to the time before treatment (p <0.001). After 14 days of treatment, the average VAS score of 2.70 ± 1.12 in the experimental group was statistically different from the average VAS of the control group, with 3.80 ± 0.76. Thus, after 14 days of treatment, although there was a statistically significant difference between before and after treatment in both groups of patients on average VAS score of the experimental group using decoction “TT knee”, which made the average VAS index of experimental group decreased faster than in the control group taking oral glucosamine 1500mg. Moreover, the reduction in VAS after 14 days of treatment in the experimental group was 48.7%, higher than the control group with 28.7%, which is the statistical significance with p <0.001. At the next evaluation times D21, D28, the average VAS index decreased gradually, and the difference between the two groups at each evaluation time was statistically significant (p <0.001). The efficiency of VAS reduction at each evaluation time after treatment compared with the time before treatment between the two patient groups in the study has a statistically significant difference (p <0.001). In the experimental group, the rate of decreased VAS in each time of evaluation was higher than that of the control group with statistical significance with p <0.001. After 28 days of treatment in the experimental group, the effectiveness compared to the before treatment was 76.34%, while in the control group was 54.40%. Thus, in terms of treatment efficacy according to the average VAS index, the experimental group using decoction “TT knee” has a faster and stronger analgesic effect than the control group taking oral glucosamine 1500mg.

Classification of pain level in patients in the two groups before treatment, pain symptoms mainly focused from moderate to severe pain level according to VAS, of which the experimental group had 93.3% patient having moderate to severe pain, while the control group had 100% of patients with moderate to severe pain. The difference in the two groups was not statistically significant with p> 0.05. The pain level improved gradually over each evaluation period. After 28 days of treatment, the pain level, according to VAS of both groups improved (p <0.001), in which the level of pain reduction level was clearer in the experimental group. The experimental group, after 28 days of using decoction remedy “TT knee” had 50% of patients with no pain and 50% of patients with mild pain, and none of them had moderate and severe pain. Whereas in the control group taking oral medication glucosamine 1500mg, after 28 days of treatment, 10% of patients had no pain, 80% of patients had mild pain, and 10% had moderate pain. The difference in the results of the classification of pain level, according to VAS, after treatment between the two groups is statistically significant with p <0.001.

Involving the efficacy of VAS-scale treatment, both research groups, after 28 days of treatment, showed an improvement in the analgesic efficacy on the VAS scale, with a statistically significant difference in efficacy (p <0.001). The post-treatment experimental group with analgesic efficacy assessed at a good level accounted for 50%, fairly good accounted for 50%, none of the patients had poor treatment results. The control group had 10% of patients at a good level, accounting for 80%, while the patients achieved average results of 10%, and no patients achieved poor treatment results. Our research results are similar to those of Nguyen Thu Thuy (2014); the proportion of patients who achieved good and fairly good results according to VAS in the experimental group accounted for 93.3% in the control group accounting for 63.4%. (Thuy, 2014)

Thus, through the treatment of pain according to the VAS scale in experimental patients compared to patients in the control group, we can indicate that the “TT knee” remedy actually has an analgesic effect on patients with osteoporosis knee. To explain this effect, “TT knee” has a number of herbs such as Angelica pubescent, which is bitter, spicy and warm and can expel wind-cold-damp, remove the obstruction and relieve pain; Ledebouriella seseloides, Justicia gendarussa can expel wind and dry the dampness; Ramulus cinnamon can heat the interior and expel cold, cleat the blood vessels; Asarum heterotropoides, which is spicy and warm, and can expel cold, relieve the pain(Trac, 2005). The herbs in the medicine are work together to bring the systemic effect to relieve pain.

5. CONCLUSION

From the results obtained in 60 patients, we have the following conclusions: the remedy “TT knee” has a relief effect on patients with knee osteoporosis. This effect appears after seven days (VAS score decreases by 30.19%) and gradually increases to 28 days.
(decreases by 76.34%). The analgesic effect of “TT knee” in patients with knee osteoarthritis was better than in the control group using glucosamine 1500mg (p <0.001).

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Informed consent:** Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

**Ethical approval for study protocol:** The study was approved by the Medical Ethics Committee of Tue Tinh Hospital (ethical approval code: 09/TTH).

**REFERENCE**