SYSTEMATIC REVIEW

Effect of Tianshu capsule in treatment of migraine: a meta-analysis of randomized control trials

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OBJECTIVE: To review the efficacy of Tianshu capsule in the treatment of migraine.

METHODS: Retrieving papers from Pubmed, Cochrane central register of controlled trials (CENTRAL), Weipu database (VIP), China biology medicine (CBM), China national knowledge infrastructure (CNKI), and Wanfang Data. Two reviewers retrieved and extracted the information independently. Retrieval time scale is up to August 2012.

RESULTS: A total of 10 studies including 937 migraine patients. The merged data shows Tianshu capsule had a higher effective rate in treating migraine, and there is no significant heterogeneity between Tianshu capsule group and control group ($\chi^2=6.33$, $df=9$, $P=0.71$, $I^2=0\%$), $OR=4.18$ [95% CI (2.93, 5.95)]. Tianshu capsule alone compared to conventional therapy also showed advantages, and there was low heterogeneity ($\chi^2=4.53$, $df=3$, $P=0.21$, $I^2=34\%$), $OR=3.95$ [95% CI (2.32, 6.72)]. Meta-analysis results show that clinical efficacy of Tianshu capsule was better than that of the control group in the treatment of migraine and there was a significant difference ($P<0.00001$).

CONCLUSION: Tianshu capsule had better efficacy in the treatment of migraine with fewer adverse effects.

INTRODUCTION

Migraine is a chronic neurological disorder. Its symptoms include one side or bilateral headaches, often accompanied by nausea, vomiting or visual disturbances. Studies show that about 6.5% of men and 18.2% of women suffer from migraine. Most patients are women at the age of 20-40. Flunarizine is the only effective calcium antagonist medicine in preventing migraine proved by evidence-based research. Traditional Chinese Medicine (TCM) has a long history in the treat-
ment of migraine. Tianshu capsule (Kanion pharmaceutical, Lianyungang, Jiangsu, China) is an effective Chinese patent medicine for the disease, which can, in terms of TCM theory, soothe liver, activate blood, and relieve pain. It can be traced back to Da Xiong Wan, a classic prescription in Sheng Ji Zonglu in the Song Dynasty (A.D. 1117). This study performed a meta-analysis of the randomized controlled trials (RCTs) conducted to evaluate the efficacy of Tianshu capsule on migraine.

**MATERIALS AND METHODS**

*Literature retrieval*

Two reviewers searched the RCTs conducted for Tianshu capsule in treating migraine both in English and Chinese from the database of Pubmed (1966-2012.8), Cochrane central register of controlled Trials (CENTRAL) (2012, Issue3), Weipu database (VIP, 1989-2012.8), China biology medicine (CBM, 1979-2012.8), China national knowledge infrastructure (CNKI, 1994-2012.8), and Wanfang Data (1980-2012.8). The search term were Tianshu capsule, and migraine.

*Inclusion criteria*

1) Definite diagnosis: the final diagnosis of migraine, in terms of the diagnostic criteria: "the International Classification of Headache Disorders;" 2) RCTs; 3) Homogeneity between groups was required, and the research was comparable; 4) Evaluation of effectiveness of the medication should be the generally accepted at home and abroad; 5) The experiment group was treated with Tianshu capsule, the control group’s intervention was conventional therapy.

*Exclusion criteria*

1) Any non-RCTs studies; 2) Diagnosis complicated with pregnancy, stroke, endocrine diseases, or severe diseases of heart, liver, kidney, and hematopoietic system; 3) Data could not be utilized in the study.

*Data extraction and assessment of methodological quality*

Two reviewers independently perused the papers retrieved, screened out the unaccepted ones according to the inclusion and exclusion criteria and had their outcomes cross-checked. If there was any difference, they would make a decision to keep or discard by deliberation. The risk of bias of those included trials were assessed strictly according to the Cochrane Collaboration the system evaluators manual version 5.1. Assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each entry corresponded respectively to yes, no, or unclear.

*Data analysis*

Cochrane Collaboration the Review Manager 5.1 was used for data analysis. For count data odds ratio (OR) was be used with confidence interval (CI) of 95%, and for heterogeneity between studies Chi-square test analysis used. If \( P > 0.1, I^2 < 50\% \), it signified no significant heterogeneity. The fixed effects model was chosen if there was no significant heterogeneity. If there was heterogeneity, subgroup analysis could be performed first. However, the random effects model analysis would be used if there was still heterogeneity. Potential publication bias would be checked with funnel plot.

*Search results*

We collected a total of 39 articles initially, Wanfang \((n=31)\), CBM \((n=43)\), VIP \((n=59)\), CNKI \((n=57)\), Pubmed \((n=0)\), CENTRAL \((n=0)\). After 25 duplicates were removed, 14 records remained for study; further, four of them were excluded due to incomplete data; finally 10 RCTs were available. They were involved in 937 patients. The basic characteristics are shown in Figure 1, Figure 2 and Table 1, Table 2.

*Effective rate meta-analysis*

The clinical efficacy of Tianshu capsule was compared with that of conventional therapy by 10 trials. No significant heterogeneity between studies \((\chi^2=6.33, df=\)
Fixed effects model analysis was used. The result showed that Tianshu capsule combined with other drugs had a higher effective rate than that in the control group (\(P<0.00001\), Figure 3). The funnel-shape was a little asymmetrical, indicating that there might be publication bias in those studies. The reason might be that all studies conducted in China and some researchers were unwilling to publish negative results.

### Table 1 Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients (T/C)</th>
<th>Age (T/C)</th>
<th>M/F</th>
<th>Disease course (T/C)</th>
<th>Intervention (T/C)</th>
<th>Dose usage (T/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chai JJ 2009*</td>
<td>55/40</td>
<td>16-52/ Unclear</td>
<td>10/45 vs Unclear</td>
<td>&gt;2 Months</td>
<td>Tianshu capsule+Flunarizine Hydrochloride capsule /Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid po+ 1capsule qd/1capsules qd</td>
</tr>
<tr>
<td>Ji XL 2006*</td>
<td>40/40</td>
<td>16-54/ 15-52</td>
<td>16/24 vs 15/25</td>
<td>&gt;3 Months/ &gt;3 Months</td>
<td>Tianshu capsule+Flunarizine Hydrochloride capsule /Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid po+unclear/ unclear</td>
</tr>
<tr>
<td>Ma XD 2011*</td>
<td>50/50</td>
<td>14-53</td>
<td>45/55</td>
<td>&gt;3 Months</td>
<td>Tianshu capsule+Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid po+4g tid/1capsule qd</td>
</tr>
<tr>
<td>Ma XD 2012*</td>
<td>40/40</td>
<td>15-55</td>
<td>35/45</td>
<td>&gt;3 Months</td>
<td>Tianshu capsule+Flunarizine Hydrochloride capsule /Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid po+1capsule qd/1capsule qd</td>
</tr>
<tr>
<td>Meng DJ 2004*</td>
<td>59/59</td>
<td>35.2±9.87</td>
<td>48/70</td>
<td>Unclear</td>
<td>Tianshu capsule/Doufugusogan tablet</td>
<td>4 capsules tid/2 pills qd</td>
</tr>
<tr>
<td>Meng L 2008*</td>
<td>40/46</td>
<td>21-55</td>
<td>40/50</td>
<td>&gt;3 Months</td>
<td>Tianshu capsule+Stellate ganglion block/Stellate ganglion block</td>
<td>4 capsules tid po</td>
</tr>
<tr>
<td>Qiao SL 2008*</td>
<td>51/45</td>
<td>18-57/ 17-49</td>
<td>18/33 vs 16/29</td>
<td>(4±2) Years/ (5±2) Years</td>
<td>Tianshu capsule/Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid+2 capsules qd</td>
</tr>
<tr>
<td>Qin JW 2009*</td>
<td>48/40</td>
<td>18-57/ 17-49</td>
<td>26/22 vs 16/24</td>
<td>Unclear</td>
<td>Tianshu capsule/Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid+2 capsules qd</td>
</tr>
<tr>
<td>Sun XJ 2009*</td>
<td>58/32</td>
<td>47±16/ 35±10</td>
<td>20/38 vs 6/16</td>
<td>(7±7) Years/(7±8) Years</td>
<td>Tianshu capsule/Compound Paracetamol tablet</td>
<td>4 capsules tid po/1pill qd</td>
</tr>
<tr>
<td>Zhao R 2008*</td>
<td>50/50</td>
<td>16-54/ 15-52</td>
<td>21/29 vs 24/26</td>
<td>&gt;3 Months/ &gt;3 Months</td>
<td>Tianshu capsule+acupuncture/ Flunarizine Hydrochloride capsule</td>
<td>4 capsules tid po+ acupuncture qd/5 mg qd</td>
</tr>
</tbody>
</table>

Notes: T: test group, C: control group; Some studies** only provided a total data about age.

### Subgroup analyses

Evaluation of a single drug and combination of the drug with Tianshu capsule in the treatment of migraine: 4 studies* took only Tianshu capsule as experimental group, 6 studies* used both Tianshu capsule and other drugs as experimental group, the control groups were given conventional therapy. There was no significant heterogeneity (\(\chi^2=4.53, df=3, P=0.21, F=34\%\)), the fixed effects model analysis was used. The re-
Results showed that the groups of Tianshu capsule plus other drug had higher effective rate than that in their control groups, and the difference was statistically significant ($P<0.00001$, Figure 4).

Sensitivity analysis
Compared to their control groups, the ORs for the group of Tianshu capsule combined with other drugs and the group used Tianshu capsule only were 4.18 [95% CI (2.93, 5.95)] and 3.95 [95% CI (2.32, 6.72)] respectively. There was no obvious change of OR values under different interventions, which indicates the good stability of this result.

Adverse reactions
Seven studies $^{8,10-11,14-17}$ mentioned adverse reactions. Adverse reactions were mainly abdominal discomfort. No liver and kidney injuries were reported. The analysis showed no significant difference between the experiment group and the control group ($P=0.07$).

DISCUSSION
The meta-analysis was proved to be one of the reliable methods for the evaluation of some drugs’ efficacy and safety in the treatment regimen. Migraine is called "Pian Tou Feng" in Traditional Chinese Medicine (TCM). It considers that the cause of the condition is Qi stagnation due to liver cold. Cold pathogen invades the Liver Meridian, and then goes upward to the top through the liver Meridian and cause headache. Other pathogenic factors like wind, fire, phlegm, blood stasis are also playing an important role in migraine onset. The disease is involved in liver and gallbladder viscera in terms of TCM theory. The pathogenesis is the disturbance of Qi-movement, and the pathological feature is manifested as Qi stagnation and blood stasis.

Tianshu capsule was prepared with Chinese herbal medicinal compounds had muti-target effect. The formulas of tianshu capsule is composed of Tianma ($Rhi zoma Gastrodiae$), Chuanxiong ($Rhizoma Chuanxiong$). Rhizoma Gastrodiae functions as calming the liver and suppress-...
Figure 4 Meta-analysis of subgroups

Figure 5 Meta-analysis of adverse reactions

Complicated by Qi disorder. It contains volatile oil, tetramethylpyrazine, perlolyrine.22 With fewer adverse reactions, Tianshu capsule contains this two herbs and has definite effect on migraine.

Limitations of this systematic review and direction for future clinical research

This review included a total of 10 trials, but they lacked large-scale, multi-centered RCTs and few of them adopted blinding method. So rigorously designed RCTs are needed to further provide more accurate data so as to verify the efficacy of Tianshu capsule on migraine.

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