SYSTEMATIC REVIEW

Qingkailing injection for the treatment of acute stroke: a systematic review and Meta-analysis

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Abstract

OBJECTIVE: To evaluate systematically the clinical efficacy and safety of Qingkailing (QKL) injection in the treatment of acute stroke.

METHODS: Searches for randomized controlled trials into acute stroke treated with QKL injection were performed in the China National Knowledge Infrastructure Database, China Science and Technology Journal Database, Wan fang Database, Chinese Biomedical Literature Database, PubMed and Cochrane Library, from January 1979 to March 2013. Two reviewers independently retrieved the RCTs and extracted the information. The Cochrane risk of bias method was used to assess the quality of the included studies, and a Meta-analysis was conducted with Review Manager 5.2 software.

RESULTS: A total of 13 studies with 1110 participants were included. The quality of the studies was generally low. The Meta-analysis indicated that the combined use of QKL and Western Medicine was significantly superior to control group therapy in terms of the total effective rate. The relative risk (RR) in the acute cerebral hemorrhage (ACH) sub-group was 1.17 [95% confidence interval (CI) (1.08, 1.26), P=0.0001]. In the acute cerebral infarction (ACI) sub-group, RR was 1.27 [95% CI (1.14, 1.42), P<0.0001], and in the ACH and ACI mixed sub-group, RR was 1.34 [95% CI (1.20, 1.50), P<0.00001]. Additionally, QKL promoted the absorption of hematoma [mean difference (MD) = -3.73, 95% CI (−4.48, −2.98), P<0.000 01], decreased neurological damage in ACI [MD = -5.60, 95% CI (−8.50, −2.70), P=0.0002] and ACH [MD = -4.08, 95% CI (−8.00, −0.16), P=0.04], promoted the recovery of awareness [RR=1.56, 95% CI (1.09, 2.21), P=0.01] and reduced the whole blood viscosity coefficient [MD = -0.75, 95% CI (−1.47, −0.03), P=0.04]. There were no adverse drug reactions reported in the included studies.

CONCLUSION: Based on this systematic review, QKL combined with conventional therapy was effective compared with control treatment. However, because the articles used in the study were not of high quality, further studies should be conducted into the efficacy and safety of QKL in treating acute stroke.

Key words: Qingkailing injection; Stroke; Acute cerebrovascular disease; Meta-analysis; Randomized controlled trials; Review
INTRODUCTION

In Western Medicine (WM), acute stroke is also known as acute cerebrovascular disease. It includes acute cerebral infarction (ACI), acute cerebral hemorrhage (ACH), cerebral embolism and subarachnoid hemorrhage.1 Stroke can be divided into two types: ischemic stroke and hemorrhagic stroke. Ischemic stroke includes cerebral infarction and cerebral thrombosis, and the most common case of hemorrhagic stroke is cerebral apoplexy. Stroke has one of the highest incidences of the cerebrovascular diseases. It results in high rates of morbidity, mortality and disability, and often contributes to sequelae that may seriously threaten human health. The majority of survivors (60%) require the help of medical institutions; their lives may be dramatically affected and the possibility of recurrence is high. At the same time, stroke is one of the most expensive diseases to treat, which can bring a great deal of economic burden to patients.2-4 Results of some studies have shown that the incidence of stroke is increasing. Therefore, methods to treat acute stroke effectively and reduce the impact of its sequelae have become foci for research.1

Qingkailing injection (QKL) is derived from Angongniuhuang pills. Its main ingredients include Niuhuang (Calculus Bovis), Shuinijiao (Cornu Bubali), Huangqin (Radix Scutellariae Baicalensis), Jinyinhua (Flotis Lonicerae), and Zhizi (Fructus Gardeniae). It has a variety of functions: as an antifebrile agent and hepato-protectant, in regulating immunity, promoting the absorption of intracranial hematoma and reducing cerebral edema.5 QKL is used widely in the clinical setting in the areas of cerebrovascular disease, acute infectious diseases, pediatric diseases and otorhinolaryngologic diseases, among others. It has achieved significant effects in the treatment of stroke, hepatitis, and in cardiovascular and pediatric diseases.5 Recently, more and more clinical cases have been reported describing QKL as an emergency treatment for acute stroke with fever.6 All of these reports have shown that QKL could increase the efficacy rate of emergency rescue in Traditional Chinese Medicine (TCM).

Although there have been several previous Meta-analyses regarding stroke,7-15 their focus has been on either cerebral infarction or cerebral hemorrhage only. Rather, this systematic review aims to evaluate the scientific basis for its clinical use in acute stroke, the possibility of recurrence is high. At the same time, stroke is one of the most expensive diseases to treat, which can bring a great deal of economic burden to patients.2-4 Results of some studies have shown that the incidence of stroke is increasing. Therefore, methods to treat acute stroke effectively and reduce the impact of its sequelae have become foci for research.1

Efficacy criteria predominantly referred to a reduction of patients with progress)/total number ×100% . Efficacy criteria predominantly referred to a reduction of patients with progress)/total number ×100% .

MATERIALS AND METHODS

Study search

Two reviewers retrieved randomized controlled trials (RCTs) by searching the following databases from January 1979 to March 2013: the China National Knowledge Infrastructure Database, Wän fang Database, China Science and Technology Journal Database, Chinese Biomedical Literature database, PubMed, and the Cochrane Library. The search terms included “Qingkailing” as a MeSH term and then “stroke or cerebrovascular diseases” for secondary retrieval. Studies published in English or Chinese were considered.

Inclusion criteria

Studies meeting the following criteria were included. Clinical RCTs used QKL to treat acute stroke, regardless of blinding. The diagnostic criterion in terms of TCM was “apoplexy diagnostic efficacy assessment standards”; that used in terms of WM was “the various types of cerebrovascular disease diagnostic points”, as determined in 1995.13 Diagnoses were validated using computer tomography or magnetic resonance imaging scanning. The courses of disease were 7 days or shorter; this is considered the acute phase of stroke. All patients were experiencing the first onset of stroke, and no limits were placed on age, gender, race or severity of disease. The control group was treated with predominantly two types of conventional WM: patients with cerebral hemorrhage received hemostatics, drugs lowering intracranial pressure, anti-hypertensives and anti-infectives; patients with cerebral infarction received vasodilators and anti-hyperlipidemias. Both types of patients required brain cell activators. The experimental group was treated with WM on the same basis as the control group, but combined with QKL. None of the therapies was combined with any other Chinese medicine, surgery or acupuncture. The dosages and treatment courses were not limited. The primary outcome was the total effective rate, using the following formula: total effective rate=(number of recovered patients + number of patients with significant progress + number of patients with progress)/total number × 100% .
reactions (ADR)/adverse drug events (ADE) identified. The degree of absorption of the cerebral hematoma was judged by hematoma size and the following absorption rate calculation formula: \( V = \frac{1}{2} \times L \times S \times \text{the slice} \), where \( L \) is the longest diameter of the largest hematoma, \( S \) is the width, and the ‘slice’ is the layers of lesion. The absorption rate of the hematoma = (before treatment – after)/treatment before × 100%. The judgment of the degree of neurological deficit was based on the standard score of the degree of neurological deficit of stroke, as determined in 1995: light 0-15 points, medium 16-30 points and heavy 31-45 points. The evaluation of clinical efficacy = (points before – after)/points before treatment × 100%.

Data extraction and quality assessment
For the included studies, two reviewers extracted the data and screened them according to the inclusion criteria. Any disagreements on data extraction and study evaluation were resolved through discussion. The extracted data included study type, patients' characteristics, and information about treatment. We assessed the risk of bias in the included trials strictly according to the Cochrane risk of bias tool. This addressed random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. For each item, there were three grades of risk: low risk of bias, unclear, and high risk of bias. When inadequate information was presented in the article and we were unable to explicitly judge "high" or "low", the item was judged as "unclear". Two researchers independently completed and mutually checked the allocated grades. Any dispute was resolved through discussion or with the assistance of a third researcher.

Statistical analysis
The Revman 5.2 software package that produced and updated by the Nordic Cochrane Centre was used to analyze the collected data. Relative risk (RR) was used for dichotomous data, and mean difference (MD) was used for continuous variables, both with a 95% confidence interval (95% CI), \( P<0.05 \) was considered statistically significant between experimental and control group. The Chi-square test was used for checking the heterogeneity between studies, and \( I^2 \) was used to show the size of heterogeneity. If \( P>0.1 \) and \( I^2<25\)%, there was determined to be little heterogeneity between studies, then we used a fixed effect model, otherwise we should use a random effect model. If the number of included trials was sufficient, a funnel plot would be carried out to assess publication bias. Because we focused on stroke comprehensively in the study, the comparison was split into three sub-groups: ACI, ACH and a mixed sub-group. This took into account the differences in therapy between the different sub-groups. Sensitivity analysis was performed on "the total effective rate" indicators, to indicate the stability of the result.

RESULTS
Analysis of literature and assessment of quality
In this review, 484 articles were retrieved from the databases listed above. After excluding duplications, reviews and obviously irrelevant studies by reading the titles and abstracts, 141 papers were downloaded for further assessment. After reading the full texts, studies that did not meet the inclusion criteria, non-RCTs, studies in which there was a lack of information regarding the control group, or individual clinical cases, were excluded. A total of 13 studies were eventually included, all published in Chinese Journal Literature Databases from 1995 to 2011 (Figure 1).
Therefore, 1110 patients were included in the systematic review. The QKL group consisted of 585 patients, while the control group consisted of 525 patients. All of the patients were undergoing their first onset of stroke, and received treatment in hospital within a week. The average age of the patients was approximately 62.9 years, and all of the trials included more males (60%) than females. All of the interventions consisted of QKL combined with WM, and the dosage of QKL was 30-80 mL every day. The duration of treatment for both experimental and control groups was not more than 28 days. More details regarding the individual trials are presented in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex (M/F)</th>
<th>AVG age (extension)</th>
<th>Disease diagnose</th>
<th>N (Q/C)</th>
<th>Course of disease (h)</th>
<th>Therapy of experiment group</th>
<th>Therapy of control</th>
<th>Treatment (weeks)</th>
<th>Outcome</th>
<th>ADR/ ADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang S 2011</td>
<td>34/26</td>
<td>58 (42-72)</td>
<td>ACH</td>
<td>30/30</td>
<td>24</td>
<td>QKL 50 mL/q.d. + WM</td>
<td>WM</td>
<td>14</td>
<td>Total effective rate, the absorption of hematoma, the score of neurological deficit</td>
<td>Unclear</td>
</tr>
<tr>
<td>Wang QF 2011</td>
<td>40/16</td>
<td>55 (41-78)</td>
<td>ACH</td>
<td>28/28</td>
<td>24</td>
<td>QKL 50 mL/q.d. + WM</td>
<td>WM</td>
<td>20</td>
<td>Total effective rate, the absorption of hematoma Total effective rate</td>
<td>Unclear</td>
</tr>
<tr>
<td>Guo CE 2008</td>
<td>70/62</td>
<td>66 (52-78)</td>
<td>ACH</td>
<td>66/66</td>
<td>144</td>
<td>QKL 60 mL/q.d. + WM</td>
<td>WM</td>
<td>28</td>
<td>Total effective rate</td>
<td>Unclear</td>
</tr>
<tr>
<td>Li YQ 2005</td>
<td>55/35</td>
<td>67 (34-80)</td>
<td>ACH</td>
<td>45/45</td>
<td>48</td>
<td>QKL 40 mL/q.d. + WM</td>
<td>WM</td>
<td>28</td>
<td>Total effective rate, the absorption of hematoma Total effective rate</td>
<td>None</td>
</tr>
<tr>
<td>Zeng H 2003</td>
<td>36/28</td>
<td>(47-77)</td>
<td>ACI</td>
<td>34/30</td>
<td>24</td>
<td>QKL 60 mL/q.d. + WM</td>
<td>WM</td>
<td>20</td>
<td>Total effective rate, the score of neurological deficit</td>
<td>Unclear</td>
</tr>
<tr>
<td>Hou B 2006</td>
<td>53/27</td>
<td>63</td>
<td>ACI</td>
<td>40/40</td>
<td>48</td>
<td>QKL 30 mL/q.d. + WM</td>
<td>WM</td>
<td>15</td>
<td>Total effective rate, the score of neurological deficit</td>
<td>Unclear</td>
</tr>
<tr>
<td>Zhang YY 2003</td>
<td>46/24</td>
<td>63 (43-76)</td>
<td>ACI</td>
<td>40/30</td>
<td>72</td>
<td>QKL 60 mL/q.d. + WM</td>
<td>WM</td>
<td>28</td>
<td>Total effective rate</td>
<td>Unclear</td>
</tr>
<tr>
<td>Liang SH 2000</td>
<td>47/33</td>
<td>61</td>
<td>ACI</td>
<td>40/40</td>
<td>72</td>
<td>QKL 30 mL/q.d. + WM</td>
<td>WM</td>
<td>28</td>
<td>Total effective rate</td>
<td>None</td>
</tr>
<tr>
<td>Xu J 1998</td>
<td>54/14</td>
<td>67 (32-84)</td>
<td>ACI</td>
<td>38/30</td>
<td>72</td>
<td>QKL 40-60 mL/q.d. + WM</td>
<td>WM</td>
<td>28</td>
<td>Total effective rate, blood viscosity</td>
<td>None</td>
</tr>
<tr>
<td>Wang AJ 2006</td>
<td>64/56</td>
<td>69 (22-79)</td>
<td>ACI/ACH 54</td>
<td>60/60</td>
<td>72</td>
<td>QKL 40-80 mL/q.d. + WM</td>
<td>WM</td>
<td>15</td>
<td>Total effective rate, blood viscosity</td>
<td>None</td>
</tr>
<tr>
<td>Liu Q 2004</td>
<td>56/64</td>
<td>64 (48-86)</td>
<td>ACI</td>
<td>60/60</td>
<td>168</td>
<td>QKL 40 mL/q.d. + WM</td>
<td>WM</td>
<td>15</td>
<td>Total effective rate</td>
<td>None</td>
</tr>
<tr>
<td>Wang Y 2000</td>
<td>43/25</td>
<td>62 (41-83)</td>
<td>ACI/ACH 23</td>
<td>34/34</td>
<td>48</td>
<td>QKL 40 mL/q.d. + WM</td>
<td>WM</td>
<td>7</td>
<td>Total effective rate</td>
<td>Unclear</td>
</tr>
<tr>
<td>Shou XY 1995</td>
<td>68/34</td>
<td>60</td>
<td>ACI 81</td>
<td>70/32</td>
<td>72</td>
<td>QKL 60-80 mL/q.d. + WM</td>
<td>WM</td>
<td>28</td>
<td>Total effective rate</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Notes: M: male; F: female; AVG: average; Q: QKL; C: control; ACH: acute cerebral hemorrhage; ACI: acute cerebral infarction; QKL: Qingkailing injection; WM: conventional therapy with Western Medicines, including therapy for ACI with dextran 40, citicoline and other drugs, and therapy for ACH with mannitol and other drugs; ADR: adverse drug reaction; ADE: adverse drug event.
Study quality was evaluated by the Cochrane risk of bias tool. All of the studies referred to randomization, but did not describe the method of randomization and blinding. Two studies appeared to have incomplete outcome data (Figures 2 and 3).

**Total effective rate**

All the studies compared the total effective rate between two groups. The analysis was divided into three sub-groups, according to the classification of stroke: ACH, ACI and the mixed sub-group containing both ACI and ACH. There were four studies in the ACH sub-group, five studies in the ACI sub-group and four studies in the mixed sub-group. Following the tests of heterogeneity, the fixed effects model could be used for all three sub-groups, for which the result of the test of heterogeneity of the ACH sub-group was $P=0.27$, $I^2=23\%$, the ACI sub-group was $P=0.51$, $I^2=0\%$ and the mixed sub-group was $P=0.83$, $I^2=0\%$. Compared with the control group, QKL combined with WM was more effective in treating any type of stroke. There was a statistically significant difference between the two groups in all of the sub-groups. The RR in the ACH sub-group was 1.17 [95% CI (1.08, 1.26), $P=0.0001$], in the ACI sub-group was 1.27 [95% CI (1.14, 1.42), $P<0.0001$] and in the mixed sub-group was 1.34 [95% CI (1.20, 1.50), $P=0.0001$] (Figure 4). Because there was heterogeneity between the three subgroups ($P=0.11$, $I^2=55.1>25\%$), we did not merge the results.

**Sensitivity analysis**

To confirm the stability of the total effective rate results, we removed the most and the least weighted of every sub-group, and changed from fixed mode to random mode. In the ACH sub-group, after removing the most weighted (Guo et al 18), the result was $RR=1.17$ [95% CI (1.01, 1.37), $P=0.04$]. The result of removing the least weighted (Wang et al 17) was $RR=1.15$ [95% CI (1.05, 1.24), $P=0.001$], and the result of changing the mode was $RR=1.15$ [95% CI (1.05, 1.25), $P=0.002$]. Processing the other two groups in a similar way, the results for the ACI sub-group were: $RR=1.26$ [95% CI (1.10, 1.43), $P=0.0005$], $RR=1.22$ [95% CI (1.09, 1.36), $P=0.0006$] and $RR=1.25$ [95% CI (1.12, 1.38), $P<0.0001$]. The results for the mixed sub-group were: $RR=1.36$ [95% CI (1.18, 1.56), $P=0.0001$], $RR=1.32$ [95% CI (1.18, 1.48), $P=0.0002$] and $RR=1.34$ [95% CI (1.20, 1.49), $P=0.0001$]. There was no clear difference compared with the previous results, so the degree of sensitivity of the study was not high.

**Degree of absorption of cerebral hematoma**

Two studies mentioned hematoma size and absorption. Following the test for heterogeneity ($P=0.93>0.1$, $I^2=0<25\%$), we used a fixed model. The Meta-analysis showed that QKL combined with WM was better than WM alone in promoting the absorption of hematoma. The statistical difference between the two groups was significant [MD= - 3.73, 95%CI ( - 4.48, - 2.98), $P<0.00001$] (Figure 5).
### Figure 4: Meta-analysis of the total effective rate of QKL plus WM vs WM in treating acute stroke

QKL: Qingkailing injection; WM: conventional therapy with Western Medicines.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Qingkailing</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Li YO 2005</td>
<td>44</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td>Guo CE 2008</td>
<td>62</td>
<td>66</td>
<td>54</td>
</tr>
<tr>
<td>Zhang S 2011</td>
<td>28</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Wang GF 2011</td>
<td>27</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>169</strong></td>
<td><strong>169</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>161</td>
<td>138</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.91, df = 3 (P = 0.27), I² = 23%
Test for overall effect: Z = 3.84 (P < 0.0001)

### Figure 5: Meta-analysis of the degree of absorption of cerebral hematoma using QKL plus WM vs WM in acute stroke

QKL: Qingkailing injection; WM: conventional therapy with Western Medicines.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Qingkailing</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Wang Y 2000A</td>
<td>29</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>Shou XY 1995</td>
<td>60</td>
<td>70</td>
<td>22</td>
</tr>
<tr>
<td>Liu Q 2004</td>
<td>56</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Wang AJ 2006</td>
<td>56</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>201</strong></td>
<td><strong>125</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>201</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.86, df = 3 (P = 0.83), I² = 0%
Test for overall effect: Z = 5.27 (P < 0.00001)

### Figure 6: Meta-analysis of the improvement of neurological deficit using QKL plus WM vs WM in acute stroke

QKL: Qingkailing injection; WM: conventional therapy with Western Medicines.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Qingkailing</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Hou B 2006</td>
<td>6.8</td>
<td>7.2</td>
<td>39</td>
</tr>
<tr>
<td>Zeng H 2003</td>
<td>5.16</td>
<td>6.07</td>
<td>34</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>73</strong></td>
<td><strong>68</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.81; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 3.79 (P = 0.0002)

### 1.3.2 the improvement of neurological deficit of ACH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Qingkailing</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Zhang S 2011</td>
<td>13.13</td>
<td>7.24</td>
<td>30</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>30</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)

Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%

Figure 6 Meta-analysis of the improvement of neurological deficit using QKL plus WM vs WM in acute stroke

QKL: Qingkailing injection; WM: conventional therapy with Western Medicines.
**Improve**ment of neurological deficit

Three studies\(^{16,20,21}\) mentioned the improvement of neurological deficit scores. One study\(^6\) was in the ACH sub-group, the compared result was \(MD = -4.08\) [95% CI ( - 8.00, - 0.16), \(P=0.04\)]. There was little difference between the two groups. The test for heterogeneity of the ACI sub-group (\(P=0.19>0.1, F=41>25\%\)) indicated that a random model should be used. The Meta-analysis showed that combined with WM, QKL was more effective in improving neurological deficit. There was a statistically significant difference between the two groups [\(MD = -5.60, 95\%\) CI ( - 8.50, - 2.70), \(P=0.0002\)] (Figure 6).

**Improvement of awareness**

Only one study\(^{27}\) that in the sub-group of mixed mentioned improvement of awareness. The Meta-analysis showed that QKL could improve the disturbance of consciousness, and the statistical difference between the experimental and control group was significant [\(RR=1.56, 95\%\) CI (1.09, 2.21), \(P=0.01\)].

**Whole blood viscosity coefficient**

Hyperviscosity can lead to slower blood flow, which makes it easy for blood to form thrombose and cause subsequent stroke. Two studies\(^{24,25}\) referred to the blood viscosity coefficient, the results showing that QKL could reduce the whole blood viscosity coefficient. The result in the ACI group was statistically significantly different [\(MD = -0.71, 95\%\) CI ( - 0.87, - 0.55), \(P<0.00001\)]; the result of the mixed ACI and ACH sub-groups showed less statistically significant difference [\(MD = -0.75, 95\%\) CI ( - 1.47, - 0.03), \(P=0.04\)].

**Safety**

Only 5 studies\(^{18,23-26}\) mentioned clearly that there were no ADRs reported in the included studies. While the other 8 studies did not pay sufficient attention to the safety aspects of QKL use, accordingly, we could not conclude that QKL was absolutely safe.

**DISCUSSION**

Following the literature analysis, we concluded that based on WM, QKL was effective when used for any pattern of acute stroke. It could improve the total effective rate, promote the absorption of brain hematoma, decrease the degree of neurological deficit, and reduce awareness restoration time and blood viscosity. This could be expected to not only save patients’ lives, but also reduce the degree of sequela and recurrence of acute stroke. The result of this Meta-analysis was supported by the findings of previous research.\(^{9-15}\)

In TCM, the basic pathogenesis of stroke is stagnation of blood. In the acute phase of the disease, patients may have inherent deficiency syndrome, while externally, a positive syndrome may be present.\(^{29}\) During the acute phase of stroke in particular, the positive syndrome is the main cause of pathogenesis such as liver wind, heat evil, phlegm and blood stasis, excess syndromes of the Fu-organs and auricular obstruction. Therefore, the treatment of stroke should start with heat-clearing detoxification, blood stasis-activating collaterals and awareness recovery. From the perspective of pathology, ACH and ACI may result in partial disorder of blood circulation, the formation of cerebral edema,\(^{30}\) breaking the blood-brain barrier and increasing free radicals. An animal experiment\(^{31}\) has shown that the degree of brain damage was significantly positively correlated with the increase of free radicals. The prognosis of stroke has a very close relationship with the effect of treatment in the acute phase.\(^{29}\)

Combining the opinions of TCM and Western Medicine, the choice of medicine in the acute phase is very important. QKL is derived from Angong-niuhuang pills. Its main actions are heatclearing and detoxifying, eliminating phlegm and freeing channels, tranquilizing and allaying agitation, recovering consciousness, and keeping the balance of \(Qi\) and blood. QKL can also scavenge free radicals effectively, which can reduce the occurrence of sequela.\(^{32}\) Recent research has indicated that QKL can also correct metabolic disorders, improve cerebral circulation and cerebral edema, and enhance brain cells’ tolerance to hypoxia. This can protect the brain cells, reduce infarct size, and promote the absorption of hematoma.\(^{30}\)

Based on the efficacy and pharmacological effects described above, QKL may be the first choice for the clinical treatment of acute stroke. Combining this with the results of the Meta-analysis, we can conclude that QKL combined with WM has a relatively good effect, regardless of stroke disease-type.

Though there was no ADRs reported in the Meta-analysis, the number of ADR reports regarding QKL has gradually increased in clinical practice.\(^{32}\) From this, we may assume that the clinical use of QKL for stroke may be relatively safe. Analyzing the ADR reports from the clinical setting, the results show that excessive dose is one of the reasons for QKL-related anaphylactic shock. In addition, the occurrence of ADRs may also be associated with the combining of drugs. Therefore, medical staff should pay special attention to controlling the dose, slowing down the rate of infusion, and strictly abiding by the requirement to avoid unnecessary drug combination, in particular for drugs proven to be incompatible.\(^{30-34}\)

In the clinical setting, as is emphasized in TCM, we should discontinue the medication as soon as we gain effect. It has been proven that 15 to 20 days is an appropriate course of treatment when using QKL to treat stroke.\(^{29}\) In summary, care should be taken to
avoid the occurrence of ADRs when using QKL in the clinical setting. By analyzing the results of the ACI sub-group, the total effective rate was \( RR = 1.18 < 1.2 \). This means that QKL used for ACI may not be ideal, although it showed a statistically significant difference. Accordingly, further studies are needed to evaluate QKL comprehensively, for example, whether the economic burden of patients will increase by using QKL, and whether using QKL will alleviate the suffering of patients. The result of the mixed sub-group warrants further research, as the total effective rate was \( RR = 1.34 \), which was greater than that for the ACI or ACH sub-groups. This could perhaps be related to the quality of the included studies. Thirteen trials were included in the review, but they were not large-scale RCTs, and none of them detailed any random allocation or methods of blinding. Further, all the included studies were published in databases, and there was a lack of negative results, which may have resulted in selection bias. More studies with rigorously designed RCTs are therefore needed. This systematic review showed that the combined use of QKL with WM was effective. The combination may increase the total effective rate, promote the absorption of hematoma, improve the degree of neurological damage and awareness, and decrease the whole blood viscosity coefficient, which can improve efficacy for treating acute stroke. Even though the safety of QKL used for stroke requires further research, it is still one of the first choices for the clinical treatment of stroke.

**REFERENCE**

1. **Wang JG.** How to prevent stroke. Qiu Yi Wen Yao 2011; 5: 4-5.