Meta-Analysis of the Effectiveness and Recanalization of Warfarin Combined With Low Molecular Weight Heparin in the Treatment of Intracranial Venous Sinus Thrombosis

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Abstract

Objective
The incidence of intracranial venous sinus thrombosis is low, but the rate of death and disability is high. The clinical treatment is usually warfarin or low molecular weight heparin or symptomatic lowering of intracranial pressure. The therapeutic efficacy and safety of warfarin combined with low molecular weight heparin are lacking. Related research requires further clinical evaluation. This study systematically evaluated the efficacy and recanalization rate of warfarin combined with low molecular weight heparin in the treatment of venous sinus thrombosis, and provided reference for clinical treatment.

Results
By searching databases such as CNKI, Wanfang, Weipu, China Biomedical Literature Database, pubmed, Cochran library, embase, etc., to collect published warfarin combined with low molecular weight heparin for intracranial venous sinus from the establishment of the database to March 2020 Clinical randomized controlled trials of thrombosis, extract relevant raw data from the literature, and conduct a meta-analysis of the effective rates of the two groups of treatment.

Conclusion
The recanalization rate of warfarin combined with low-molecular-weight heparin in the treatment of intracranial venous sinus thrombosis is 1.57 times that of single therapy, and the effective rate is 1.28 times that of single therapy, which provides a certain reference value for clinicians in the diagnosis and treatment of the disease.

Key words: Warfarin; Low molecular weight heparin; venous sinus thrombosis.

Introduction
Cerebral venous sinus thrombosis (CVST/ CVT) is a rare and special cerebrovascular disease. CVT mostly occurs in children and adolescents. Its pathogenesis is unknown, and it is related to genetic factors, environmental factors, and self-resistance[1]. Because of its unobvious clinical features, it is easy to miss and misdiagnose clinically, causing delays in treatment, and has a high fatality rate and disability rate[2]. The clinical treatment methods often use warfarin or low molecular heparin alone, but alone therapy the clinical effect is not ideal[3]. The purpose of this study is to systematically evaluate the efficacy and recanalization rate of warfarin combined with low molecular weight heparin (combination therapy) in the treatment of venous sinus thrombosis, and to provide reference value for clinical treatment.

Materials and methods

Literature source

Inclusion criteria

1) Study type: The type of study needs to be a randomized controlled trial; 2) Research object: Patients with intracranial venous sinus thrombosis diagnosed for the first time, and the diagnostic criteria are in line with the 2012 "Chinese Guidelines for the Diagnosis and Treatment of Intracranial Venous System Thrombosis" , No major organ damage and absolute contraindications, etc., not limited to men and women, age ≥18 years; 3) Intervention measures: the test group is a combination therapy of warfarin and low molecular weight heparin, and the control group is warfarin alone or alone Low-molecular-weight heparin or conventional treatments such as dehydration alone to lower intracranial pressure; 4) Outcome indicators: total effective rate of treatment = {number of markedly effective cases + number of effective cases} / total number of cases*100% According to the evaluation criteria established by the Fourth National Cerebrovascular Conference in 1996, the evaluation criteria are as follows: 1) Effective: After treatment, clinical manifestations and signs such as headache and consciousness disturbance completely disappeared as obvious effect; 2) Effective: clinical
symptoms and symptoms after treatment. Signs have improved significantly, but some of the symptoms have not completely disappeared as effective; ③Invalid: After treatment, the patient still has headaches and convulsions and other clinical symptoms and signs are invalid.

Exclusion criteria
① The type of study is a non-randomized controlled trial or the type of trial is not clearly explained; ② The age of the research object is ≤18 years old; ③ The original literature research is systematic review, individual case, meeting, etc.; ④ The research content does not match, Intervention measures are inconsistent; ⑤ Outcome indicators are inconsistent or meta-analysis cannot be performed.

Search strategy
Through searching PubMed, Cochrane Library, Embase, China Knowledge Network (CNKI), WanFang Database (WANFANG Database), VIP database (VIP), China Biomedical Literature Database (CBM), etc. The search date is from the establishment of the database to March 2020. The search uses a combination of subject terms and free words. The Chinese search subject terms are venous sinus thrombosis, sinus thrombosis, sinus thrombosis, warfarin, low molecular heparin; the English search subject terms are Intracranial Sinus Thrombosis, Warfarin, Low molecular weight heparin.

Data extraction
At least two reviewers (Xiaorui Ma, Shasha Fang Resident) independently carry out research inclusion and data extraction, and then check the summary. Once there is a disagreement, the third researcher (Xue Xiao Chief Physician) decides whether to include. Including; the first author of the literature, the year of publication, the sample size of the experimental group and the control group, gender, age, intervention measures, total effective rate and other relevant data.

Quality assessment
According to the Cochrane Deviation Risk Assessment Tool (5.3), the literature quality of the included studies was evaluated. Evaluation indicators include: ① Random allocation method; ② Hidden allocation plan; ③ Blind method of researchers and subjects; ④ Blind method evaluation of research results; ⑤ Completion of data results; ⑥ Selective report of research results; ⑦ Others Source of bias. In response to the results of each study, the above seven items were judged as “low risk”, “high risk”, and “unclear”.

Statistical analysis
Use State software for Meta-analysis (provided by Cochrane Collaboration). The effect size refers to the amount of change in the value or observation index that has clinical significance or actual value. When the observation index is a categorical variable data, the relative risk (RR) is used; when the observation index is a numerical variable data, the mean difference (MD) is used as the analysis statistic. Each effect size is expressed with a 95% confidence interval (CI). The heterogeneity between the results of the included studies is tested by Chi-square. If the included studies have sufficient consistency (P>0.05, I²<50%), the fixed-effects model is used for analysis; if there is heterogeneity in the included studies, it is necessary to further analyze the causes of heterogeneity, and conduct subgroup analysis and sensitivity analysis on the factors that may lead to heterogeneity. If the results are still heterogeneous after excluding certain factors, random effects models are used for analysis.

Results

Document search results
433 documents were retrieved according to the inclusion criteria, and then 425 documents were excluded according to the exclusion criteria, and finally 8 documents were included, including 3 Chinese science and technology core journals and 5 general journals. The total number of cases was 476. Among them, there were 239 cases in the test group and 237 cases in the control group. Through searching PubMed, Cochrane Library, etc., no foreign literature that meets the requirements was found, so it was not included in foreign research. (Figure 1)

The basic characteristics of the included studies and the risk assessment of bias
The basic characteristics of the eight included literature studies are shown in Table 1. The bias risk evaluation of the eight included studies is shown in Figure 2.

Meta-analysis

Heterogeneity test
The 8 documents with an effective rate in this study, after the heterogeneity test, I²=0%<50%, and the Q test P=0.61>0.1, and the 3 papers researching the recanalization rate, After the heterogeneity test: I²=0%<50%, and the Q test P=0.23>0.1, suggesting that the heterogeneity between the selected documents in this study is not statistically significant, and the fixed-effects model should be selected for Meta-analysis.

Meta-analysis of the fixed-effect model
The efficacy analysis of the 8 count data study: RR=1.31, 95%CI (1.19, 1.43), statistical significance test Z=5.50, P=0.00001, suggesting that the combination therapy has excellent efficacy for single treatment such as warfarin or low molecular weight heparin or conventional treatment. Analysis of the recanalization rate of three count data studies: RR=1.57, 95%CI (1.25, 1.97), statistical significance test Z=3.88, P<0.00001, suggesting the recanalization rate of combined therapy for intracranial venous sinus thrombosis It is 1.57 times that of single therapy. (Figure 3, Figure 4)

Offset test
In this study, the RR values of the 8 efficient studies and the 3 studies of the recanalization rate were used as the abscissa, and...
Table 1: Basic characteristics of included research literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiaoli Dou[4]</td>
<td>2020</td>
<td>Control group 40.39±5.49 Treatment group 39.47±5.21</td>
<td>0.855 0.964</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group 39/55 Warfarin Warfarin + Low molecular weight heparin</td>
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<tr>
<td>Aijun Hu [5]</td>
<td>2017</td>
<td>Control group 36.4±6.9 Treatment group 36.9±5.5</td>
<td>0.733 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group Nov-30 Oct-30 Warfarin Warfarin + Low molecular weight heparin</td>
<td></td>
</tr>
<tr>
<td>Honglong Liu [6]</td>
<td>2017</td>
<td>Control group 35.2±5.2 Treatment group 36.2±5.0</td>
<td>0.625 0.875</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group Sep-24 Oct-24 Warfarin Warfarin + Low molecular weight heparin</td>
<td></td>
</tr>
<tr>
<td>Wei Qin[7]</td>
<td>2019</td>
<td>Control group 32.5±8.5 Treatment group 32.5±9.5</td>
<td>0.727 0.909</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group 04-Nov 05-Nov Routine symptomatic Warfarin Warfarin + Low molecular weight heparin</td>
<td></td>
</tr>
<tr>
<td>Qinhuo Xiao[8]</td>
<td>2017</td>
<td>Control group 34.7±7.4 Treatment group 34.7±7.4</td>
<td>0.667 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group - - Warfarin Warfarin + Low molecular weight heparin</td>
<td></td>
</tr>
<tr>
<td>Lifu Tan[9]</td>
<td>2016</td>
<td>Control group 34.89±2.35 Treatment group 35.28±2.77</td>
<td>0.647 0.944</td>
</tr>
<tr>
<td></td>
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<td>Control group Dec-17 Nov-18 Routine symptomatic Warfarin Warfarin + Low molecular weight heparin</td>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Outcome</th>
<th>p-value 1</th>
<th>p-value 2</th>
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<td>Liangwei Lin[10]</td>
<td>2019</td>
<td>Control group 31.32±8.14</td>
<td>Treatment group 31.45±9.96</td>
<td>18/33</td>
<td>0.636</td>
<td>0.879</td>
</tr>
<tr>
<td>Qingyan Wang[11]</td>
<td>2016</td>
<td>Control group 37.6±10.8</td>
<td>Treatment group 37.5±12.1</td>
<td>17/37</td>
<td>0.73</td>
<td>0.947</td>
</tr>
</tbody>
</table>

**Figure 2:** Evaluation of the risk of bias in the included studies

**Figure 3:** Forest plots of Comparison of the total effective rate between the two groups

the reciprocal of the RR value was used as the ordinate to draw the funnel chart. It can be seen that the funnel chart is left and right. Basically symmetrical, indicating that the publication bias is small. (Figure 5, Figure 6)
**Figure 4:** Forest plot of comparison of recanalization rates between the two groups

**Figure 5:** The total effective rate of the two groups of publication bias funnel

**Figure 6:** The total recanalization rate of the two groups of publication bias funnel

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Discussion

This is the first study of the Meta analysis of warfarin combined with low molecular weight heparin. Most of these studies describe patients who are followed up in tertiary hospitals. The sample size, follow-up time, and dosage of drugs are slightly different, but the data shows no heterogeneity. These numbers indicate that the absolute risk is very low, indicating that the study has certain reference value. Intracranial venous sinus thrombosis is a neurological disease that is not easy to find. We found that due to the low incidence, the lack of large-scale multi-center clinical research is fatal, and the majority of case reports, the currently identified risk factors are the use of oral contraceptives, chronic sinus or ear infections, and obesity[12]. Conventional clinical treatment includes anticoagulation, lowering intracranial pressure and other symptomatic treatments. At present, it is believed that anticoagulation therapy is still the first choice for patients with acute CVT. Studies have shown that anticoagulation therapy is safe and effective for intracranial venous sinus thrombosis. Reduce the fatality rate and disability rate, and at the same time there is no risk of aggravating intracranial hematoma[13-15]. Because of ethical issues, there is still no clear evidence to show the efficacy and safety of intravascular treatment in acute CVT[16], however, it has been clinically found that low-molecular-weight heparin or warfarin is not satisfactory for the clinical effect of CVT. Therefore, Huafarin combined with low-molecular-weight heparin began to be gradually applied to the clinic, and the combination therapy is significantly better than the single therapy in terms of therapeutic effect, but its safety and efficacy need further clinical evaluation. Therefore, we conducted a meta-analysis to further evaluate warfarin. The efficacy of combined low-molecular-weight heparin in the treatment of CVT. Since it is included in Chinese literature, its clinical safety is rarely mentioned, so this article evaluates its efficacy and recanalization rate.

Our research provides a certain reference value for the clinical treatment of intracranial venous sinus thrombosis. Our research results show that: (1) Effectiveness: Combination therapy (warfarin combined with low molecular heparin therapy) can be significantly better than single therapy Reduce the fatality rate and disability rate of intracranial venous thrombosis. (2) Recanalization rate: Combination therapy for intracranial venous sinus thrombosis is 1.57 times that of single therapy, and the use of fixed-effect model meta-analysis has good reliability, and the results have certain reference effects for clinical treatment.

Since this study is a secondary study and its quality depends on the quality of the original study, there may be some limitations: (1) the treatment duration included in the study is different. A small number of warfarin and low molecular weight heparin use different doses, and the treatment duration needs to be different. Further included literature research; (2) This study has no collection of unpublished literature, and the search languages are only Chinese and English, and there may be database bias and language bias; (3) Only a few studies mention the disadvantages of combination drugs Response, safety needs further verification; (4) The number of included studies is small, and more large-scale studies are needed for further verification.

In summary, through this Meta-analysis, it can be concluded that low-molecular-weight heparin combined with warfarin can significantly reduce the morbidity and mortality of patients. Compared with monotherapy, it has an advantage in effectiveness and recanalization rate. Warfarin combined with low-molecular-weight heparin is 1.57 times that of monotherapy. However, due to the lack of relevant safety studies and limited research samples, large multi-center RCTs are needed to confirm our findings.

References

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