Prescriptions Combined with Conventional Western Medicine for Cognitive-Related Disorders Meta-Analysis and Data Mining

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Abstract: The increasing aging of society has led to a yearly increase in the incidence of cognitive-related disorders. It happens that prescriptions have significant advantages in treating such multifactorial symptoms and diseases. Therefore, we investigated the effectiveness of prescriptions combined with conventional western medicine in the treatment of cognitive-related disorders through meta-analysis. Based on this, we also obtained new prescriptions through data mining to find better prescriptions for the treatment of cognitive-related disorders. This will provide a basis for clinical drug use and subsequent prescription development.

Keywords: Cognitive, Prescriptions, Western medicine, Meta-analysis, Data mining

1 INTRODUCTION

Cognitive-related disorders are mainly related to the nervous system and have many influencing factors[1–2]. For example, Alzheimer's disease, Parkinson's disease, cerebral stroke, and vascular dementiame can all have an impact on cognitive abilities[3–5]. As our society ages, the incidence of these cognitive-related disorders is increasing significantly[6]. And more critically, once the individual suffers from a cognitive-related disorder, the quality of life is greatly affected, both for the individual and the family. Once the social group of cognitive-related disorders increases, and cannot be well controlled later. Even the development of the whole society will be affected[7].

Currently, cognitive-related disorders are treated with corresponding conventional western medicine to control the patient's symptoms[8]. However, this type of treatment is difficult to cure. Moreover, as the disease progresses and the drugs are used for a long time, adverse effects such as fluctuations in symptoms and complications can occur[9]. Chinese materia medica has unique characteristics and significant advantages in the treatment of such diseases[10]. Through the principle of dialectical treatment, different prescriptions are selected for treatment according to the patient's condition and symptoms. Combined treatment with conventional western medicine is often very effective[11].

ICICA 2022, December 02-04, Chongqing, People's Republic of China

DOI 10.4108/eai.2-12-2022.2328045

To this end, this study conducted a meta-analysis of prescriptions combined with conventional western medicine for the treatment of cognitive-related disorders. And the high-frequency medicinal substances and grouping patterns for the treatment of cognitive-related diseases were screened out through data mining. With this we hope to provide some basis for clinical use and follow-up research.

2 META-ANALYSIS

2.1 Study sources and study screening

A thorough search was carried out in CNKI, Wangfang, Weipu, Web of Science, PubMed, and the Cochrane Library. The search period is from the establishment of the library until April 7, 2022. A joint search of Medical Subject Headings (MeSH) terms and free terms was used. The English and Chinese search terms included "Drugs, Chinese Herbal", "Chinese Herbal Drugs", "Chinese Drugs, Plant", "Chinese Plant Extracts", "Traditional Chinese Medicine", " Cognitive", "Cognition", "Randomized Controlled Trial", "RCT", etc.

First, duplicates were removed from the literature. Then the initial screening was performed by browsing the titles and abstracts. Literature such as inconsistent studies, meta-analyses, systematic reviews, reviews, and cellular or animal experiments were excluded. Then the full text was read, and literature such as non-randomized controlled trials and inconsistent outcome indicators was excluded. The primary outcome indicator examined in this study was the MMSE (Mini-Mental State Examination). In addition to this, MoCA (Montreal Cognitive Assessment) and TE (therapeutic effect) were secondary outcome indicators to be examined. This resulted in the final including literature. Based on the inclusion and exclusion criteria of the studies, a total of 2019 relevant studies were obtained from the initial search. After removing duplicates, 657 studies remained. After reading the article titles and abstracts, 577 studies were again excluded. Finally, by reading the full text, 14 studies met the criteria and were retained[12-25]. The study screening process is shown in Figure 1A.

2.2 Study quality assessment

Bias risk assessment adopted the recommended RCT bias risk assessment tool in the Cochrane handbook 6.3. The evaluation entries contained random sequence generation, allocation concealment and blinding, incomplete outcome data, selective reporting and other bias. The quality of the included literature was evaluated separately according to the above entries. The results were classified as low risk of bias, unclear risk of bias, and high risk of bias. The quality evaluations of the included studies were conducted independently by two investigators. Two people reviewed each other if there was a disagreement. A third investigator then reviewed and combined the opinions of the three investigators to determine the final inclusion. The results of the bias risk assessment are shown in Figure 1B.

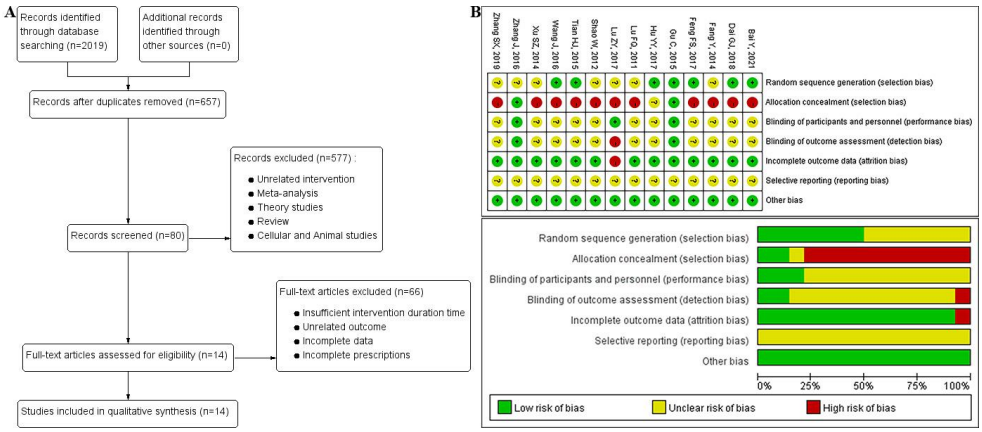

Figure 1. (A) Flow diagram of study screening. (B) Summary of main quality assessment of included studies.

2.3 Statistical analysis

The meta-analysis was performed using RevMan 5.4.1 software provided by the Cochrane Collaboration. Inconsistent methods and units of measurement for continuous variables are indicated as standardized mean difference (SMD). Dichotomous variables were expressed as relative risk (RR). All are expressed as effect values and 95% confidence intervals (95% CI). Chi-square (χ^2) and I^2 tests were used to analyze the heterogeneity between studies. Heterogeneity between studies was significant if $P < 0.10$, $I^2 \geq 50\%$. A random-effects model was used to analyze the data. There was no significant heterogeneity among studies if $P \geq 0.10$, $I^2 < 50\%$. A fixed-effects model was used to analyze the data. For the major outcome indicators, if the included study was ≥ 10, the funnel plot was used to qualitatively detect publication bias.

(1) Mini-Mental State Examination

In all included studies, the MMSE was used as an outcome indicator. There were 529 cases in the experimental group and 527 cases in the control group. Since the treatment modalities were not all the same across the groups. Therefore, SMD was used to indicate. A test of heterogeneity showed that P=0.16, I^2=28%. Therefore, a fixed-effects model was used for the combined analysis. The combined MMSE effect size for both groups was [SMD=0.62, 95% CI (0.50, 0.74), P<0.00001] (Figure 2A). The above results suggest that conventional western medicine combined with prescriptions for cognitive disorders has a significant advantage in improving MMSE scores. The funnel plot (Figure 2B) between the 14 included studies showed significant left-right symmetric differences, indicating some risk of publication bias.

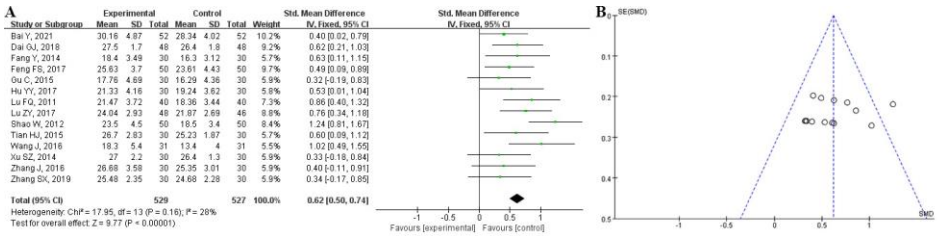

Figure 2. (A) Forest plot of the meta-analysis of the experimental and control groups affecting MMSE scores. CI: Confidence interval. (B) Funnel plot of the experimental group versus the control group affecting MMSE scores.

(2) Montreal Cognitive Assessment

Seven studies used MoCA as an outcome indicator[12,13,15,16,20,22,25]. There were 288 cases in the experimental group and 286 cases in the control group. Heterogeneity tests showed no heterogeneity in the included studies. Therefore, a fixed-effects model was used for the analysis (Figure 3). The results showed that conventional western medicine combined with prescriptions for cognitive-related disorders had a significant advantage in improving MoCA scores. The difference was statistically significant [SMD=0.56, 95% CI (0.39, 0.73), P<0.00001].

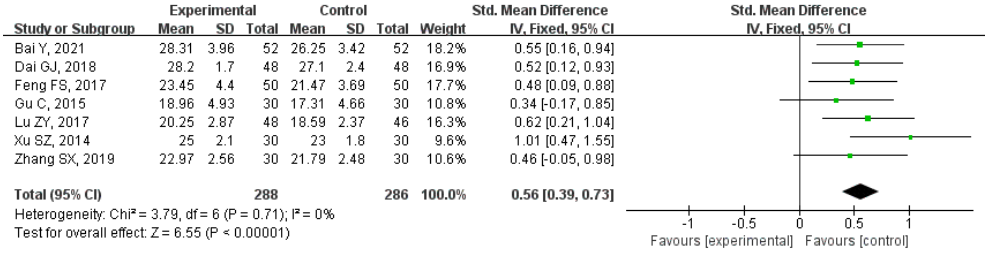

Figure 3. Forest plot of meta-analysis of experimental and control groups affecting MoCA scores.CI: Confidence interval.

(3) Therapeutic Effect

A total of nine studies used TE as an outcome indicator[12,14,15,19–23,25]. There were 321 cases in the experimental group and 321 cases in the control group. The results of the heterogeneity test suggested that there was no heterogeneity in the included studies, so a fixed-effect model was used (Figure 4). The results showed that the TE of conventional western medicine combined with prescriptions for the treatment of cognitive-related disorders was better than that of conventional western medicine alone, and the difference was statistically significant [RR=1.26, 95% CI (1.16, 1.37), P<0.00001].

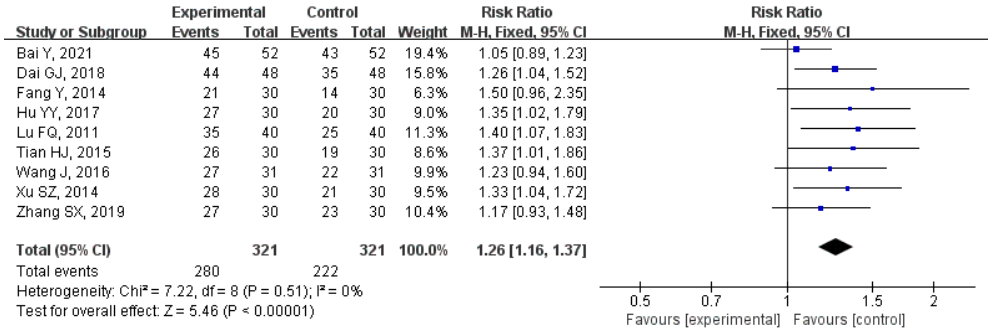

Figure 4. Forest plot of meta-analysis of experimental and control groups affecting therapeutic effect. CI: Confidence interval.

3 DATA MINING

3.1 Dataset creation

The prescriptions involved in the included studies were extracted as the data set. Standardize the names of medicinal substances with reference to the Pharmacopoeia of the People's Republic of China. Uniform naming of medicinal substances that differ by origin or concoction method, etc.

3.2 Calculation of frequency statistics and association rules

Data mining was performed on the dataset using the Apriori algorithm. A threshold value of Support ≥ 0.10 and Confidence ≥ 0.80 is used to obtain association rules. And analyze the most frequent items involved in medicinal substances. They are calculated as follows:

$$\text{Support}(A \Rightarrow B) = P(AB) = \frac{\text{num}(AB)}{\text{num}(\text{AllSamples})} \quad (1)$$

$$\text{Confidence}(A \Rightarrow B) = P(B|A) = \frac{P(AB)}{P(A)} \quad (2)$$

In the above operations, the num (AB) is the number of prescriptions containing both medicinal substance A and medicinal substance B. The num (AllSamples) is the total number of prescriptions in the dataset. The P(AB) is the probability of containing both medicinal substance A and medicinal substance B in a prescriptions, and the P(B|A) is the conditional probability of a prescriptions containing medicinal substance A provided that it also contains medicinal substance B.

Finally, 950 association rules were obtained. Among them, the most frequent item medicinal substances contained 27, as shown in Table 1.

Table 1. The most frequent items of medicinal substance involved in association rules.

Name of item	Support (%)
ACORI TATARINOWII RHIZOMA	66.67
CHUANXIONG RHIZOMA	40
POLYGONI MULTIFLORI RADIX	40
ALPINIAE OXYPHYLLAE FRUCTUS	33.33
CISTANCHES HERBA	33.33
CITRI RETICULATAE PERICARPIUM	33.33
CURCUMAE RADIX	33.33
GLYCYRRHIZAE RADIX ET RHIZOMA	33.33
PINELLIAE RHIZOMA	33.33
PORIA	33.33
REHMANNIAE RADIX	33.33
ANGELICAE SINENSIS RADIX	26.67
ATRACTYLODIS MACROCEPHALAE RHIZOMA	20
AURANTII FRUCTUS	20
CARTHAMI FLOS	20
COPTIDIS RHIZOMA	20
PAEONIAE RADIX RUBRA	20
SALVIAE MILTIORRHIZAE RADIX ET RHIZOMA	20
ALISMATIS RHIZOMA	13.33
CORNIFRUCTUS	13.33
CUSCUTAE SEMEN	13.33
GINSENG RADIX ET RHIZOMA	13.33
PERSICAE SEMEN	13.33
PHERETIMA	13.33
POLYGALAE RADIX	13.33
SCUTELLARIAE RADIX	13.33
TESTUDINIS CARAPACIS ET PLASTRI COLLA	13.33

3.3 Clustering calculation

Cluster analysis was performed on the association rules obtained using the Apriori algorithm. And adjust the mesh clustering map to show link strengths ≥ 0.10. The obtained mesh clustering map was analyzed to obtain potential combinations of medicinal substances with improved cognition. As shown in Figure 5A, the link strength ≥ 0.10 was used as the threshold value to filter the 950 association rules. After being presented as a visual network, it can be found that it mainly consists of 9 core medicinal substances. Further analysis of the mesh clustering map shows that it is mainly composed of two clusters (Figure 5B and Figure 5C).

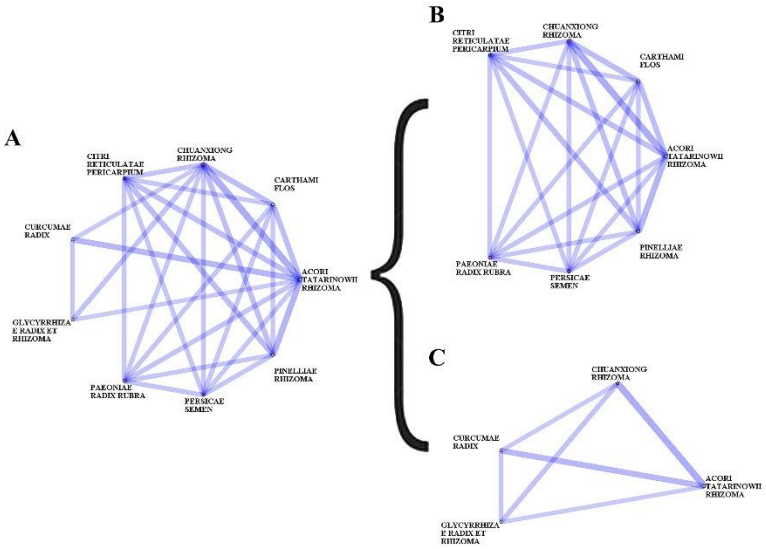

Figure 5. Association rule clustering analysis. When the link strength is higher, the thicker and darker the edge is displayed. (A) Visual network of association rules. (B) Clustering I. (C) Clustering II.

4 DISCUSSION

In 2020, a study estimated that about 38.77 million people in China suffer from cognitive-related disorders[26]. The use of prescriptions in combination with conventional western medicine to treat cognitive-related disorders in order to control patients' symptoms and even cure them is an urgent task. Therefore, the meta-analysis of this study pooled 14 studies involving 1056 patients to explore the differences between the treatment of cognitive-related disorders with prescriptions in combination with conventional western medicine and conventional western medicine alone.

The results of the meta-analysis showed that prescriptions combined with conventional western medicine were better than conventional western medicine alone in the treatment of cognitive-related disorders. This was reflected in improved MMSE, MoCA, and TE of subjects. Thus, based on the excellent performance of prescriptions for cognitive-related disorders. The method of data mining prescription patterns, screening high-frequency medicinal substances, and clusters association rules. Twenty-seven medicinal substances with frequent items and two combinations of medicinal substance with improved cognitive function in patients were successfully identified.

Through meta-analysis, we found the superiority of prescriptions combined with conventional western medicine for the treatment of cognitive-related disorders. Through data mining, we identified 27 frequent medicinal substances that may improve cognitive function and obtained two combinations of medicinal substances that may have cognitive improvement effects on patients. This will provide a basis for clinical use and subsequent prescription development.

Acknowledgments. This work was financially supported by the National Key Research & Development Program (2017YFE0118200), and the National Natural Science Foundation of China (82104065, 32061143045).

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