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Original Article

The characteristics and prescription patterns of Chinese herbal medicine in clinical practice for the treatment of anemia

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ABSTRACT

Objective: Chinese herbal medicine (CHM) is frequently applied to patients to improve the symptoms and signs associated with anemia. The aim of this study is to use the claims data from the National Health Insurance Research Database (NHIRD) in Taiwan to analyze CHM prescription patterns and to identify the frequency and combinations of CHM commonly used to treat anemia.
Materials and methods: A total of 41,028 patients were diagnosed with anemia in Taiwan within the defined study period. After randomly equal matching for age and sex, data from 7682 patients characterized as CHM users and non-users were analyzed. Network analyses of the 30 most frequently applied herbs and formulas were used to indicate CHM combinations in patients with anemia.
Results: Those patients with anemia who were older, office workers, and lived in central areas of Taiwan had higher tendencies toward CHM usage. Based on considerations of comorbidities, anemia patients associated with chronic kidney diseases, diabetes mellitus, and hypertensive diseases preferred Western medical management and demonstrated a lesser likelihood of combining treatment with CHM; by contrast, those with coronary artery disease demonstrated a higher tendency for CHM use. Notably, *Astragalus membranaceus* (AM) and Gui-Pi-Tang (GPT) were the most commonly prescribed CHM single herb and formula, respectively. The core prescription pattern consisted of AM, *Salvia miltiorrhiza* (SM), *Angelica sinensis* (AS), GPT, and Si-Wu-Tang (SWT), as indicated by the associations and frequency of CHM utilization by traditional Chinese medicine (TCM) physicians.
Conclusion: This study demonstrates that CHM may be applied as an integral element of treatment for patients with anemia. It also provides insight regarding individual therapy and common clinical practices of TCM physicians in the treatment of anemia. Further research is required to explore potential interactions and possible mechanisms at play with CHM management of anemia.

Introduction

Anemia is a significant public health issue affecting people of all ages, particularly pregnant women and young children. According to research, 41.8% of pregnant women and 47.4% of preschool children are affected by this condition globally [1]. In 2010, global anemia incidence was estimated to be approximately 32.9%, with 68.36 million years lived with disability [2]. Anemia has significant health implications, and is characterized by signs of pallor, fatigue, dizziness, shortness of breath, and weakness; it is further associated with low hemoglobin and ferritin levels [3]. It may also lead to decreased cognitive abilities, weaker immune function, and increased rates of mortality without effective management.

According to the American Society of Hematology, there are several types of anemia, classified as iron-deficiency anemia (IDA),

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vitamin-deficiency anemia, aplastic anemia, hemolytic anemia, sickle cell anemia, and anemia caused by other diseases; of which IDA accounts for more than half of all cases [4]. While trauma and gastrointestinal bleeding are two other major causes of blood loss, the decreased production and uptake of iron and vitamins will induce iron-deficiency anemia and vitamin-deficiency anemia. Some forms are caused by increased breakdown associated with genetic disorders, these include aplastic anemia, sickle cell anemia, and anemia associated with certain autoimmune diseases. Anemia in elders or individuals associated with chronic diseases such as chronic kidney diseases, inflammatory bowel diseases, and chronic heart failure may lead to an increased risk of death, requiring increased supervision by physicians [5].

In terms of treatment, the blood transfusion is a common and effective method used to relieve signs and symptoms efficiently, based on hemoglobin levels. Meanwhile, there are two forms of pharmacotherapy iron supplementation. The oral form of ferrotherapy is a convenient, inexpensive, and effective option; however, there are side-effects which cannot be ignored, including gastrointestinal upset, muscle pain, and hives. The other form of ferrotherapy is through parenteral administration, administered based on considerations of oral ferrotherapy ineffectiveness, or inhibited absorption. However, long-term iron administration via the parenteral route will induce hemosiderin in various organs, and skin hyperpigmentation. Of concern, despite the advantages of iron supplementation, the long-term biologic effects of iron include the activating the generation of oxygen radicals leading to an increase of infectious disease morbidity [6]. Therefore, based on the limitations of Western medical treatments, finding an adjunct ferrotherapy to enable the reduction of the iron dose in traditional therapy is a challenge facing the health care community that needs to be addressed.

The National Health Insurance (NHI) system in Taiwan is well-organized, and recruits' data pertaining to both conventional Western medicine and TCM therapies. It has been become an important part of the health care system, and has provided valuable insight into the treatment of various diseases, including chronic myeloid leukemia [7], allergic rhinitis [8], heart disease [9,10], pulmonary disease [11], diabetes mellitus [12], hypertension [13], and precocious puberty [14]. Depending on the diagnostic pattern, TCM physicians will advise one or more herbal formulas combined with several single herbs for each prescription. In this study, we analyzed a cohort of one million beneficiaries from the NHIRD from 2001 to 2012 to evaluate and compare characteristics and prescription patterns between CHM users and non-users in patients with anemia.

The usage of CHM granules is covered by the NHI in Taiwan. These Chinese herbal products, including single Chinese herbs and multi-herbal Chinese formulas are permitted to be prescribed by TCM practitioners. All of the CMH granules covered by the NHI program are manufactured by Good Manufacturing Practice (GMP)-certified pharmaceutical companies. The actual daily CMH granule prescriptions in clinical practice are recorded in the NHI database. The specific purpose of this study is to investigate CHM utilization and prescription patterns in patients with anemia. We conducted a population-based retrospective cohort study of the NHI database to evaluate demographic differences, common prescriptions, and relevant single herb and formula combinations which offers insightful information regarding the use of CHM as a complementary and alternative option for the treatment of patients with anemia.

Patients and methods

This study used the Longitudinal Health Insurance Dataset of 2000 (LHID2000) as a data source. LHID2000 is a sampling dataset of the NHIRD which randomly selects 1 million beneficiaries from total beneficiaries, and contains all medical records of those one million subjects from 1996 to 2013. The demographic characteristics between the LHID2000 and the general NHIRD showed no difference after Chi-square test ($\chi 2 = 1.74$, df = 1, p-value = 0.187). With a 99% coverage rate, the NHIRD records many criteria of beneficiary data, including basic individual information (sex, date of birth, living area, insurance type, etc.), ambulatory care data, inpatient data, detailed drug information, and other relative medical data on an annual basis. Both ambulatory care data and inpatient data included disease diagnosis code in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). A disease diagnosis without valid clinical findings may be considered a medical fraud by the NHI with a penalty of a 100-fold payment as claimed by the treating physician or hospital. Detailed drug information recruited the scientific and/or commercial name, number of drugs, dosages and drug use duration. Before release for research, each beneficiary identification code in the NHIRD was transformed into a set of dummy numbers, in order to avoid exposure of beneficiary personal information.

The study cohort with anemia was identified by ICD-9-CM code: 280–285, including only those subjects diagnosed with anemia at least twice (n = 58,597). After the exclusion criteria, there were 41,028 subjects with anemia included in this study. Of those subjects, 27,558 were classified as CHM users after been diagnosed with anemia; among them, 4741 subjects used CHM specifically for the treatment of anemia (anemia CHM users). This study matched CHM users and non-CHM users by 1:1 frequency matching. There were in total 3841 subjects included in each group, identified as CHM users and non-CHM users. All steps of the study population selection are shown in Fig. 1.

The demographic characteristics of the study population included sex, age, job type and area of residence. The population was further sorted into four age groups: < 20, 20–39, 40–59, ≥60. In accordance with insurance type, employment was classified as office worker, manual worker, or other. The four areas of residence were classified as northern Taiwan, central Taiwan, southern Taiwan, and eastern Taiwan and offshore islands, respectively. Comorbidities with anemia were included as follows: coronary artery disease (ICD-9-CM: 410–413, 414.01–414.05, 414.8, 414.9), congestive heart failure (ICD-9-CM: 398.91, 402.01, 402.11, 402.91, and 428), chronic liver disease and cirrhosis (ICD-9-CM: 571), chronic kidney disease (ICD-9-CM: 250.4, 403.XX, 404.XX, 585, 586), chronic obstructive pulmonary disease and allied conditions (ICD-9-CM: 491, 492, 493, 496), diabetes mellitus (ICD-9-CM: 250, A181), and hypertensive disease (ICD-9-CM: 401–405, A260, A269). All comorbidities were required to have been diagnosed at least twice to be included in this study.

As for statistical analysis applied in this study, Chi-square test was used to evaluate the association between CHM and non-CHM cohorts for identification of demographic characteristics and comorbidities. Differences of average age between CHM users and non-CHM users were tested by two-sample student's t-tests. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated by univariate analysis and multivariable logistic regression. The combination patterns of Chinese herbal products were demonstrated by network analysis. The significance level was set at $\alpha = 0.05$. All statistical analyses were processed by applying the statistical software package, SAS, version 9.4 (SAS Institute, Inc., Cary, NC). The network analysis was carried out by open-sourced freeware NodeXL (http://nodexl.codeplex.com/). The spot indicates the frequency of each herb or formula use. The line bar indicates the association between each two connections with different thickness. The thicker of spot and line are concomitant with the higher frequency and association.