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Nonsurgical treatment of chronic subdural hematoma with Chinese herbal medicine

A STROBE-compliant retrospective study

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Abstract

The aim of the study was to observe the efficacy of nonsurgical treatment with Chinese herbal medicine (CHM) for chronic subdural hematoma (CSDH). This study includes clinical results of a STROBE-compliant retrospective study.

Forty patients diagnosed with CSDH were recruited from outpatient. Different CHM prescriptions were dispensed for each patient based on syndrome differentiation until the patient had a stable neurologic condition for 2 weeks and/or CSDH completely resolved according to the computed tomography scan. Markwalder grading scale for neurologic symptoms and head computed tomography scan for hematoma volumes were performed before and after CHM treatment to evaluate efficacy.

Patients received uninterrupted CHM treatment for 2.81 ± 1.45 months (0.75–6 months). The hematoma volume significantly reduced from 73.49 ± 35.43 mL to 14.72 ± 15.94 mL ($P < .001$). The Markwalder grading scale scores of patients at the end of CHM treatment decreased significantly, from 1.3 ± 0.69 to 0.15 ± 0.36 ($P < .001$). Ninety percent of the patients showed >50% decrease in the hematoma volume and complete improvement in neurologic symptoms. The linear regression analysis suggested that change in hematoma was significantly related to the duration of CHM treatment ($R^2 = 0.334$; $P < .001$; $Y = 25.03 + 11.91X$). *Leonurus heterophyllus* Sweet (Yi-Mu-Cao, 90.5%), *Semen persicae* (Tao-Ren, 88.8%), and *Acorus tatarinowii* Schott (Shi-Chang-Pu, 86.2%) were the top 3 single Chinese herbs prescribed in CHM treatment.

The CHM treatment for CSDH based on syndrome differentiation with appropriate duration relieved neurologic symptoms quickly and promoted hematoma absorption effectively. It could be an effective nonsurgical therapy for CSDH.

Abbreviations: CHM = Chinese herbal medicine, CSDH = chronic subdural hematoma, CT = computed tomography, IL = interleukin, MGS = Markwalder grading scale, TCM = traditional Chinese medicine.

Keywords: Chinese herbal medicine, chronic subdural hematoma, *Leonurus heterophyllus* Sweet, nonsurgical treatment

1. Introduction

Chronic subdural hematoma (CSDH) is a common intracranial hemorrhagic disease, especially among the elderly population. It is an old blood collection between the cortical surface and the dura. The incidence of CSDH has increased as a result of an aging population and the increasing clinical use of anticoagulant and antiplatelet drugs. The incidence of CSDH is approximately 1 to 13 of 100,000 annually in the general population, while in people aged 80 years or older, the number rises up violently to 127.1 of 100,000.[1] Neurosurgical therapy is the current consensus on the treatment of radiologically confirmed CSDH. Surgical treatment of symptomatic CSDH can improve neurologic symptoms rapidly[2]; however, the high recurrence rate of about 25.6% in high-risk patients[3] is important to note. The mortality has increased from 11.1% to 13.5%[4] in surgically treated patients to 38.4%, independent of treatments, in patients aged 90 years or older.[5] Effective nonsurgical treatments are highly desirable owing to the high mortality and often complex medical problems in this age group. Though many studies have suggested agents including steroids, angiotensin-converting enzyme inhibitors, tranexamic acid, and atorvastatin as nonsurgical treatments for CSDH,[6–10] a clear evidence-based guideline is unavailable so far.

Chinese herbal medicine (CHM) and methods of arresting bleeding based on the traditional Chinese medicine (TCM) theory, such as improving blood circulation and arresting bleeding, benefiting qi and controlling blood, and warming meridians and arresting bleeding, have been used for treating hemorrhagic diseases for thousands of years and have an

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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indispensable important role in the adjuvant therapy of hemorrhagic diseases, including intracranial hemorrhage.[11–14] Syndrome differentiation and treatment are the essence of TCM, and CHM treatment should be adjusted to fit individual clinical manifestations of patients, even if they may share the same medical diagnosis. To our best knowledge, few clinical data are available regarding the treatment of CSDH with CHM based on syndrome differentiation so far. The present study aimed to explore the short- and long-term efficacy of CHM treatment based on syndrome differentiation for CSDH.

2. Methods

2.1. Patients

This was a single-center, retrospective, observational study of CSDH patients who received CHM treatment at outpatient of the Department of Traditional Chinese Medicine, Beijing Tiantan Hospital, Capital Medical University, between June 2016 and October 2018. Ethics approval (KY 2019-330-01) for the present study was obtained from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, China. All patients provided informed consent for their clinical records to be used for research purposes before enrollment.

Patients who fulfilled the following inclusion criteria were enrolled continuously: age ≥18 and <90 years old; diagnosed with CSDH using head computed tomography (CT) scans or magnetic resonance imaging; neurosurgeon made a judgment that cerebral hernia would not occur and surgical operation might not be performed in a short time; conservative treatment was adopted. Patients who met any of the following conditions were excluded: known hypersensitivity to CHM; history of TCM treatment after diagnosis in 1 month; coma (Glasgow coma scale <9); severe hematoma with herniation warranting surgical operation; hematoma caused by tumors, blood, and other known comorbidities; abnormal liver function; dysfunction of coagulation; and history of oral or intravenous steroid treatment in the last 2 weeks.

2.2. CHM treatment

Two attending TCM physicians and an experienced chief TCM physician diagnosed the syndrome differentiation cooperatively in the light of the Diagnostics of Traditional Chinese Medicine.[15] There were 5 common syndromes in patients with CSDH and about 2 to 4 syndromes in different patients. The diagnostic criteria for syndromes and corresponding herbs were listed in Supplemental Tables 1, http://links.lww.com/MD/E703, and 2, http://links.lww.com/MD/E704. Based on the aforementioned syndrome differentiation and fundamental prescriptions, Chinese herbal prescriptions were made up and adjusted for each patient and the prescription might be modified at regular outpatient visits about every 4 weeks. Chosen herbs of the prescription were boiled to produce decoction. The decoction of one set of herbs was taken orally per day. The CHM treatment was discontinued when the patient had a stable neurologic condition for 2 weeks and/or CSDH completely resolved according to the CT scan. Anytime during CHM treatment when the patients were in a clinically urgent state, including conditions such as a sudden increase in the hematoma volume, cerebral hernia, and exacerbated neurologic dysfunction, they were switched to neurosurgery for surgery.

2.3. Efficacy evaluation

All patients underwent head CT scan before and after CHM treatment. CT examination was performed using 64-slice spiral CT scanners (Discovery CT750HD; GE Healthcare Technologies, Milwaukee, WI). The hematoma volume (in milliliters) was calculated from CT using 3D slicer 4.8.1, an open-source software platform for medical image processing (https://www.slicer.org).

Neurologic functions were evaluated using Markwalder grading scale (MGS) before and after CHM treatment. The efficacy of CHM treatment was evaluated as "completely improved," "significantly improved," "partially improved," and "not improved" by changes in neurologic symptoms and hematoma volume as follows: completely improved: hematoma absorption sufficient according to CT scans and complete improvement in neurologic symptoms; significantly improved: decrease in the hematoma volume of >50% but <100%, and partial or complete improvement in neurologic symptoms; partially improved: decrease in the hematoma volume of <50% and partial improvement in neurologic symptoms; and not improved: increase in the hematoma volume or a new CSDH, with aggravated neurologic symptoms.

2.4. Statistical analysis

The statistical analysis was performed using SPSS 22.0 (International Business Machines Corporation, Chicago, IL). According to the last observation carried forward principle, missing data during the treatment period were replaced with the last available data. After the test of normality, data of changes in the hematoma volume and MGS before and after CHM treatment were analyzed using the paired-sample *t* test. A linear regression analysis was conducted to explore a correlation between length of CHM treatment and changes in the hematoma volume. A P value <.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics of the study population

A total of 40 patients with CSDH, including 30 males and 10 females, were enrolled retrospectively in the current study. The mean age was 66.83 ± 14.6 years (27–86 years). Eighteen patients (18/40, 45%) had recurrent CSDH after neurosurgical treatment. The demographics and clinical characteristics were summarized in Supplemental Table 3, http://links.lww.com/MD/E705.

3.2. Frequency of Chinese herbs used in CHM treatment for CSDH

In this study, 116 TCM prescriptions were made up for patients with CSDH who received CHM treatment, and an average of 12.2 ± 0.12 (9–16) Chinese herbs was included in a single prescription. *Leonurus heterophyllus* Sweet (Yi-Mu-Cao, 90.5%) was the most frequently single Chinese herb prescribed for patients with CSDH, followed by *Semen persicae* (Tao-Ren, 88.8%) and *Acorus tatarinowii* Schott (Shi-Chang-Pu, 86.2%). Details of the top ten single Chinese herbs most commonly prescribed by TCM physicians are shown in Table 1.

3.3. Efficacy evaluation of CHM treatment for CSDH

The treatment was stopped when CSDH completely resolved according to the CT scan and/or patients were in a stable

Table 1

Top 10 single Chinese herbs prescribed in Chinese herbal medicine treatment for patients with chronic subdural hematoma.

Pharmaceutical name	Chinese name	Number	Frequency
Leonurus artemisia Sweet	Yi-Mu-Cao	105	90.5%
Semen persicae	Tao-Ren	103	88.8%
Acorus tatarinowii Schott	Shi-Chang-Pu	100	86.2%
Flos carthami	Hong-Hua	92	79.3%
Achyranthes bidentatae Radix	Huai-Niu-Xi	91	78.4%
Astragalus membranaceus	Huang-Qi	82	70.7%
Chuanxiong rhizoma	Chuan-Xiong	81	69.8%
Poria cocos	Fu-Ling	74	63.8%
Atractylodes macrocephala Koidz	Bai-Zhu	51	44.0%
Hirudo	Zhi-Shui-Zhi	50	43.1%

neurologic condition. In this study, patients received CHM treatment for 2.81 ± 1.45 months (0.75–6 months) without interruption.

After CHM treatment, the volume of hematoma significantly reduced from 73.49 ± 35.43 (12.2–168.8) mL to 14.72 ± 15.94 (0–55.35) mL ($P < .001$) (Fig. 1). The neurologic symptoms of enrolled patients were headache, dizziness, vertigo, tinnitus, barylalia, poor memory, gait disturbance, and weakness of limbs. During CHM treatment, none of the enrolled patients were switched to surgery or suffered deteriorated neurologic symptoms. The MGS scores of patients at baseline were 1.3 ± 0.69 (0–2). Among all patients, neurologic symptoms improved prior to complete hematoma absorption. The neurologic symptoms improved significantly in 0.57 ± 0.33 months (0–1.5 months) since the beginning of CHM treatment. The MGS scores of patients at the end of CHM treatment decreased significantly to 0.15 ± 0.36 (0–1) ($P < .001$) (Fig. 2). For efficacy evaluation of CHM treatment, 15 patients (37.5%) were assigned to the grade of "completely improved," 21 patients (52.5%) were "significantly improved," and 4 patients (10%) were "partly improved."

The CT scan images before, during, and after CHM treatment of 2 patients, cases 3 and 39, with complete improvement are shown in Figure 3.

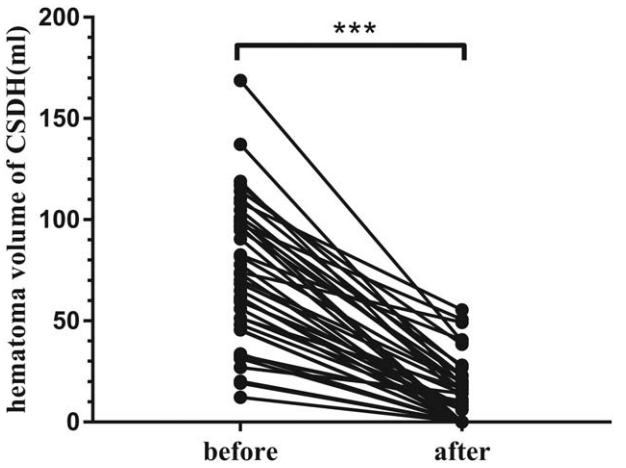

Figure 1. The hematoma volumes of chronic subdural hematoma (CSDH) patients reduced significantly after Chinese herbal medicine treatment.

3.4. Linear regression analysis of length of CHM treatment and change in the hematoma volume

The linear regression analysis of length of CHM treatment and change in the hematoma volume showed that change in hematoma volume was significantly related to the duration of CHM treatment ($R^2 = 0.334$; $P < .001$; $Y = 25.03 + 11.91X$) (Fig. 4).

3.5. Safety assessment

During the course of TCM therapy, no significant changes in blood cell counts, hematologic and liver functions, and drug allergy reaction were reported. None of the patients switched to surgery.

4. Discussion

The prevalence of CSDH has increased worldwide due to an aging population and the increasing clinical use of anticoagulant and antiplatelet drugs. Neurosurgical therapy is the current

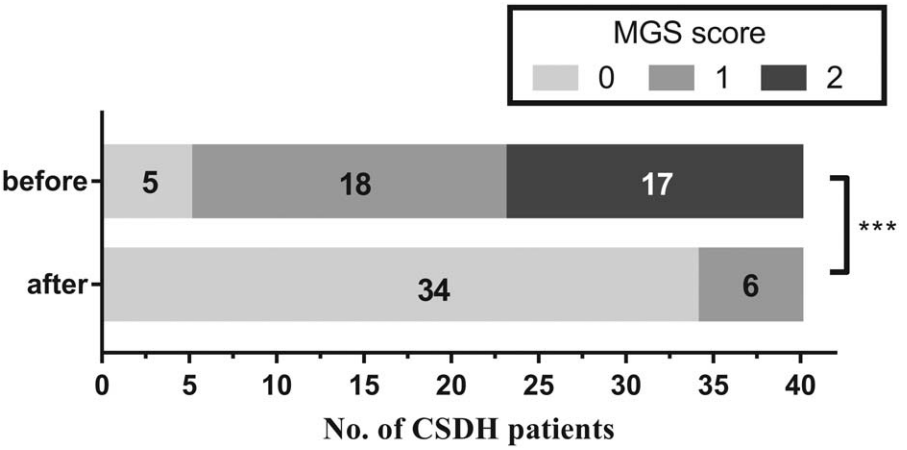

Figure 2. The Markwalder grading scale (MGS) scores of chronic subdural hematoma (CSDH) patients decreased significantly after Chinese herbal medicine treatment.

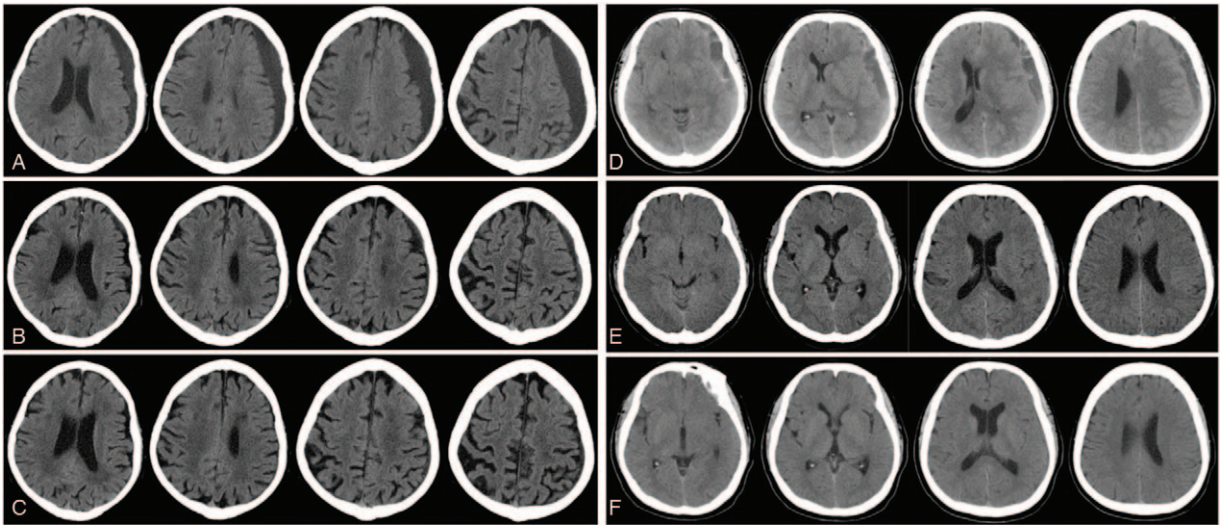

Figure 3. Case 3 (A–C, head computed tomography scan) was an 84-year-old male patient with a recurrent chronic subdural hematoma (CSDH) in left frontal parietal 2 weeks after burr-hole drainage operation. He had a definitive history of head trauma before first CSDH. He suffered from headache, dizziness, and weak limbs, and the score of Markwalder grading scale (MGS) was 2 when enrolled in this study. The hematoma volumes were measured as 99.03 mL (A), 18.86 mL (B), and almost undetectable (C) before, after Chinese herbal medicine (CHM) treatment lasting for 3 months, and in 6 months after CHM treatment termination. Case 39 (D–F, head computed tomography scan) was a 62-year-old female patient who suffered from headache 1 week, with a definitive history of head trauma and MGS 2. She had left frontotemporal subdural hematoma of 77.86 mL (D), with midline shift to right and cerebral hernia. After CHM treatment lasting for 2 months, the hematoma volume reduced to 5.55 mL (E) without midline shift and cerebral hernia, and at the end of CHM treatment, the hematoma was almost undetectable (F).

consensus on the treatment of radiologically confirmed CSDH. However, neurosurgical therapy is not suitable for the whole CSDH population because of relatively high recurrence rates, high hospitalization costs, surgical contraindication, and heavy psychologic burden of operation. Hence, effective and low-cost nonsurgical treatments are highly desirable.

To our best knowledge, few clinical data are available regarding the treatment of CSDH with CHM based on syndrome differentiation. This preliminary retrospective study investigated the clinical efficacy of TCM treatment based on syndrome differentiation for CSDH. Forty patients with CSDH received CHM treatment based on syndrome differentiation for 2.81 ± 1.45 months (0.75–6 months) without interruption. The data showed that the hematoma volume and neurologic symptoms of these patients improved significantly. At the end of CHM treatment, the hematoma volume of all enrolled patients with CSDH decreased and neurologic symptoms improved significantly compared with the baseline. None of the patients switched to surgery. Ninety percent of the patients showed a decrease in the hematoma volume of >50% and complete improvement in neurologic symptoms. One of the advantages of TCM treatments based on syndrome differentiation is to relieve the current symptoms of patients and improve their quality of life. The current study showed that CHM treatment could improve neurologic symptoms of patients with CSDH much earlier than hematoma absorption. The MGS scores decreased significantly at the end of CHM treatment than at the beginning.

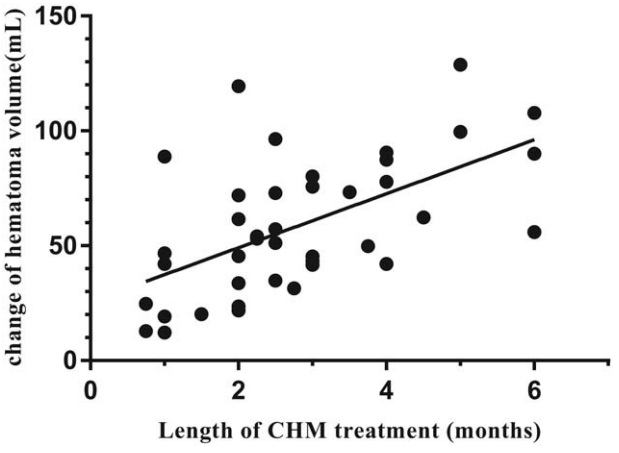

Figure 4. Linear regression analysis of length of Chinese herbal medicine (CHM) treatment and change of hematoma volume in chronic subdural hematoma patients.

The formation mechanism of CSDH has historically been considered as a result of head trauma; however, emerging recent evidence suggests that more complex processes are involved. The development and recurrence of CSDH is associated with localized inflammation (CSDH membrane and fluid formation), angiogenesis (formation of new immature vessels) and fibrinolysis (clot breakdown).[16] It is believed that inflammation plays a pivotal role in the development of CSDH. A range of inflammatory cells and cytokines, both the pro- and anti-inflammatory molecules, mediate the inflammation in CSDH in some pathways. High levels of cytokines and chemokines such as interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor-α, monocyte chemoattractant protein-1, and eotaxin-3 have been shown in CSDH fluid compared with serum.[16–19] Localized inflammation induces disruption of the endothelial cell barrier, resulting in formation of new immature and "leaky" vessels.[20,21] The high level of fibrin/bibrinogen degradation products found in the CSDH fluid is considered to represent excessive fibrinolysis (clot breakdown) and therefore persistent bleeding.[16]

In the present study, there was an average of 12.2 ± 0.12 (9–16) Chinese herbs were included in a single prescription and *L heterophyllus* Sweet (Yi-Mu-Cao, 90.5%) was the most

frequently single Chinese herb prescribed for patients with CSDH. *L heterophyllus* Sweet is a common clinical Chinese medicine, with the effect of activating blood circulation and regulating menstruation, inducing diuresis to alleviate edema, and clearing heat and detoxification, according to the Pharmacopoeia of the People's Republic of China (2015). Stachydrine and leonurine, the major bioactive alkaloid ingredients of *L heterophyllus* Sweet, have been demonstrated to exert protective effect against traumatic brain injury and endothelial injury, anti-inflammatory, anti-oxidative, and anti-apoptotic effects *in vivo* and ex vivo.[20,22–27] The second and third most commonly single Chinese herb prescribed for patients with CSDH are *S persicae* (Tao-Ren, 88.8%) and *A tatarinowii* Schott (Shi-Chang-Pu, 86.2%). Amygdalin is an effective monomer component of *S persicae*, which has the effects of anticoagulation, anti-inflammation, antineoplastic, and antitumor.[28] Modern pharmacologic studies have shown that extract of *A tatarinowii* Schott has a variety of biologic activities, such as antioxidant, anti-Alzheimer disease, antimicrobial, anticonvulsive, and antiepileptic effects.[29] Nevertheless, there is little evidence about of the potential mechanism of Chinese herbs for CSDH. The high proportions of *L heterophyllus* Sweet, *S persicae*, and *A tatarinowii* Schott which included in a single prescription suggested that they may play a crucial role in promoting CSDH absorption. The novelty of our research was that it provided an innovative idea for herb screening, and further clinical experiments and pharmacologic research on the nonsurgical treatment of CSDH using TCM and Chinese herbs.

The linear regression analysis of length of TCM treatment and change in the hematoma volume was performed to explore the correlation between them. Data showed that the change in hematoma was significantly related to the duration of TCM treatment. It is well known that Chinese herbal formulas are advantageous in body regulation.[30,31] It is believed that appropriate TCM treatment and sufficient duration can improve the microenvironment of the body, redress disequilibrium among qi, blood, yin, and yang, reduce the excess syndrome, reinforce the deficiency condition, and promote the hematoma absorption gradually. The harmonization of qi, blood, yin, and yang can further prevent hematoma recurrence. Although CSDH is a neurosurgical disease, the vast majority of patients are elderly, often complicated with a variety of basic diseases. Surgery is a great test for patients' body and mind, and the higher recurrence rate of surgery further reduces the benefits of patients. Our study shows that CHM treatment for CSDH is low-risk, convenient, and may improve neurologic symptoms as well as promote of hematoma absorption, which will be a beneficial choice as nonsurgical therapy.

This was a preliminary exploratory study with some unavoidable limitations. First, patient selection bias was likely because this was a retrospective study and the patients in our study were enrolled at outpatient and generally with relatively mild station. Second, the study was conducted in a single center, which also consequently limited its generalizability. Third, the Chinese herb prescription and treatment period of the patients was not equalized and evaluated, but our study may be more representative of actual clinical conditions. So prospective, randomized, controlled, and multicenter clinical trials with equalized CHM treatment should be carried out to estimate the efficacy of CHM for CSDH in the future. A number of studies have identified the beneficial effects of CHM[31,32]; however, the exact mechanisms of action of CHM are still mostly unknown.

5. Conclusion

Collectively, the present retrospective study preliminarily suggested that CHM treatment based on syndrome differentiation was an effective nonsurgical therapy for CSDH. CHM treatment could relieve neurologic symptoms quickly and promote hematoma absorption effectively with few recurrences. Change in the hematoma volume was significantly correlated with CHM duration, indicating that appropriate and sufficient CHM treatment length was necessary for a favorable clinical outcome. The high proportions of *L heterophyllus* Sweet, *S persicae*, and *A tatarinowii* Schott that included in a single prescription suggested that they may play a crucial role in promoting CSDH absorption. This study may provide a preliminary basis for further clinical studies with regard to CHM treatment as a nonsurgical therapy for some neurosurgical diseases, including CSDH.

Author contributions

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