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Conservative Treatment of Chronic Subdural Hematoma with Gorei-san

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Abstract

Most asymptomatic patients with chronic subdural hematoma (CSDH) are followed conservatively but can require surgical treatment if the hematoma expands. We conducted a retrospective evaluation of the effect of Gorei-san on CSDH. This study included patients treated between April 2013 and March 2015. In total, 289 patients were diagnosed with CSDH and 110 patients received conservative management. Finally, 39 patients who met the requirements were registered. We retrospectively examined the age, gender, medical history, hematoma thickness, clarity of sulci below hematomas, and midline shift of the patients. The primary outcome was the median surgery-free interval, and the secondary results were the rate of CSDH shrinkage and surgery avoidance. A comparison of patient characteristics between the Gorei-san (G) and non-Gorei-san (NG) groups found no significant differences in the percentage of men, average ages, past history, thickness of CSDH (15.0 ± 3.1 mm vs. 15.3 ± 2.6 mm, p = 0.801), or midline shift (2.0 ± 2.7 mm vs. 4.0 ± 5.0 mm, p = 0.230). The median surgery-free interval was significantly different between the G and NG groups [n. r. vs. 41 days (95% CI: 5-79), log-rank p = 0.047]. The CSDH avoidance rate was not significantly different between the two groups (70.0% vs. 34.4%, p = 0.071). Additionally, the CSDH shrinkage rate was significantly different between the two groups (60.0% vs. 10.3%, p = 0.004). This retrospective study demonstrated that CSDH treatment with Gorei-san reduces hematoma significantly more than treatment that does not include Gorei-san.

Keywords: chronic subdural hematoma, conservative treatment, Gorei-san, hematoma shrinkage, Kampo

Introduction

Chronic subdural hematoma (CSDH) is one of the most common intracranial hematomas. CSDH forms when the veins of the brain bridging the draining dural-venous sinuses are torn after head trauma.[1)] It then gradually spreads through the subdural space. Surgery is the standard treatment for symptomatic patients with large CSDH. Asymptomatic and mildly symptomatic patients with CSDH can be managed conservatively. However, some require aspiration drainage due to hematoma expansion.[2,3)] Recent research suggests that Gorei-san, a traditional Japanese Kampo medicine, can reduce the risk of CSDH recurrence following surgery operation through hydrostatic modulation.[4-7)]

The rate of spontaneous shrinkage of CSDH is reportedly between 20.8% and 50%.[3,8,9)] In comparison, research into Gorei-san treatment of CSDH has shown resulting CSDH reduction rates of 75% to 90.1%.[6,10,11)] However, this research included only asymptomatic or mild cases. Because somewhere between 2.8% and 21% of mild cases of CSDH dissipate without treatment,[4)] the extent of Gorei-san's effects on the rates of shrinkage and surgery avoidance in CSDH in these studies is unclear. To address this, we conducted a retrospective comparison of hematoma shrinkage and surgery avoidance rates between patients with CSDH treated with Gorei-san and those managed conservatively without Gorei-san.

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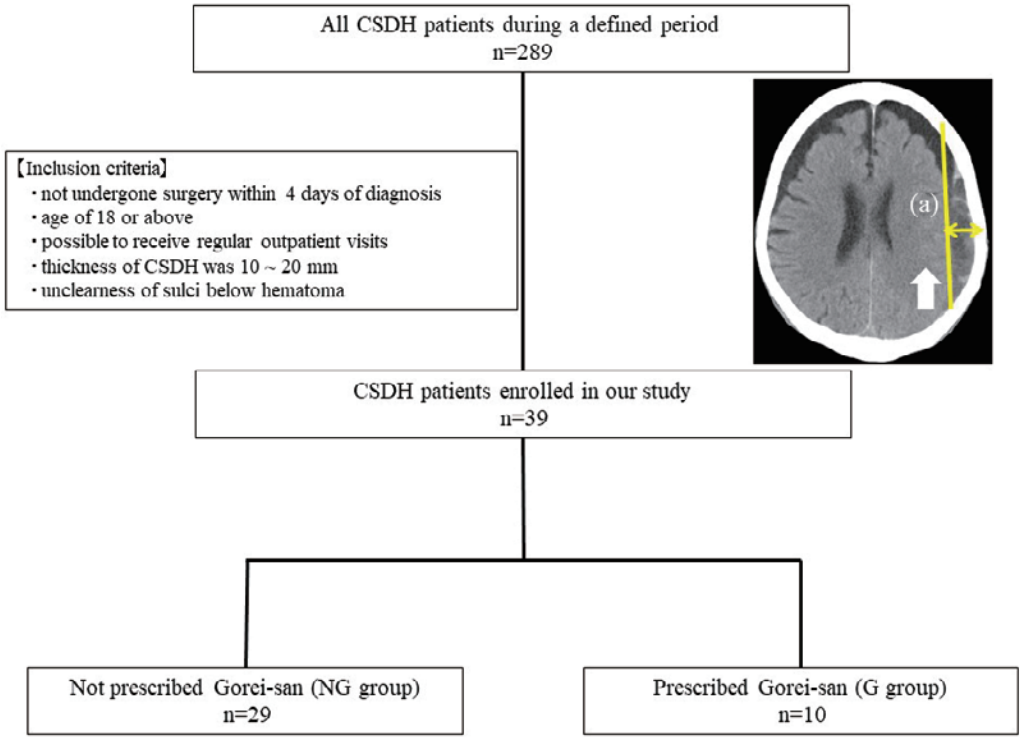

Fig. 1 Flow diagram of included patients and definition of the thickness and unclearness of sulci.
We retrospectively studied 39 patients diagnosed with chronic subdural hematoma who presented to the neurosurgery departments of four hospitals.
The thickness of the chronic subdural hematoma of each patient was measured by slice axial computed tomography or axial magnetic resonance imaging (a). Sulci were defined as unclear when there was almost no cerebrospinal fluid space between the sulci below the hematoma.

Materials and Methods

The Ethics Committee of the University of Tsukuba Hospital approved this study (R03-156). The consent requirements of patients were waived by the ethics committee.

This was a retrospective, multicenter, cohort study. Data from patients with CSDH admitted to the University of Tsukuba Hospital, Ibaraki Seinan Medical Center Hospital, Kobari General Hospital, and the University of Tsukuba Mito Medical Center from April 2013 to March 2015 were retrospectively collected and analyzed. Patients with CSDH were diagnosed with cerebral computed tomography (CT) or cerebral magnetic resonance imaging (MRI). Neurosurgeons treating each case determined the need for surgery.

The inclusion criteria were (a) conservative management without surgical treatment within four days of diagnosis, (b) aged 18 or above, and (c) regular outpatient visits. The exclusion criteria were (a) CSDH less than 10 mm thick, (b) CSDH more than 20 mm thick, and (c) clear sulci below the hematoma.

Patients who were prescribed Gorei-san were categorized into the G group; patients who were not prescribed Gorei-san, into the NG group (Fig. 1). Gorei-san was administered orally at a dose of 7.5 g/day (2.5 g thrice a day with water). Patients attended outpatient appointments and regularly received imaging tests (cerebral CT or MRI). All medical records, including imaging, were retrospectively reviewed for each patient's pre- and post-treatment clinical course and neurological status.

To evaluate mass effects, we gathered data on age, gender, hematoma thickness (mm), clarity of sulci images below the hematoma, and midline shift (mm). Hematoma thickness was defined as the widest thickness (mm) measured vertically from the inner skull plate to the brain surface on the CT or MRI image at the time of diagnosis. Unclear sulci were defined as cerebral CT or MRI images at the time of diagnosis in which no cerebrospinal fluid cavity was apparent in the sulcus beneath the hematoma (Fig. 1).

The primary outcome was the median surgery-free interval, with the CSDH surgery avoidance and shrinkage rates as secondary outcomes. Shrinkage was described as the condition wherein the hematoma was considered to have been resolved by imaging studies by neurosurgeons.

SPSS software was used for statistical analyses (v.22.0; SPSS, Inc., Chicago, IL, USA). Quantitative data were reported as mean with standard deviation or median. Pearson chi-square test, t-test, or two-tailed Fisher's exact test

Table 1 Clinical characteristics of the study population

	G group $n = 10$	NG group $n = 29$	p value
Male sex (%)	90.0	68.9	0.402+
age	70.2 ± 15.5	78.9 ± 8.8	0.120§
Hypertension (%)	40.0	41.3	1.000+
Hyperlipidemia (%)	10.0	13.7	1.000+
Diabetes (%)	10.0	3.4	0.452+
Antithrombotic drug (%)	40.0	31.0	0.704+
Liver disease (%)	0	3.4	1.000+
Active drinker (%)	0	3.4	1.000+
Plate ($\times 10^4/\mu L$)	22.2 ± 6.7	20.4 ± 4.5	0.432§
Thickness of CSDH (mm)	15.0 ± 3.1	15.3 ± 2.6	0.801§
Midline shift (mm)	2.0 ± 2.7	4.0 ± 5.0	0.230§

Patient demographics and clinical information. There were no significant differences in the sex ratios, age, medical histories, thickness of the chronic subdural hematoma, or midline shift between the two groups.
+Fisher's exact test.
§t-test.

Table 2 Primary and secondary outcomes

	G group $n = 10$	NG group $n = 29$	p value
Median surgery-free interval (days)	n. r.	41 (95% CI: 5-79)	0.047*
Surgery avoidance rate (%)	70.0	34.4	0.071+
Shrinkage rate of CSDH (%)	60.0	10.3	0.004+

The results for our primary and secondary outcomes. Between the two groups, the median surgery-free interval was significantly different. The shrinkage rates were significantly different between the two groups.
*log-rank test.
+Fisher's exact test.

was used to compare the frequencies of categorical variables where applicable. Cumulative survival curves were constructed using the Kaplan-Meier method, and log-rank test was used to assess surgery-free intervals. For all tests, $p < 0.05$ was considered significant.

Results

Overall, 289 patients were diagnosed with CSDH in the four hospitals during the period defined for this study. Of these, 110 patients were managed conservatively and 179 patients were excluded as they underwent emergency surgery within four days of diagnosis. Additionally, one patient was excluded because he was under 18 years, and three patients were excluded because their regular follow-up was impossible. The remaining exclusion criteria applied to 67 of the 106 patients (CSDH thickness < 10 mm: 38 patients; CSDH thickness more than 20 mm: 12 patients; and clear sulci below the hematoma: 17 patients). The remaining 39 patients were included in our study.

Of these 39 patients, 10 (25.6%) were in the G groups and 29 patients (74.4%) were in the NG group. Table 1 presents patient data, and Table 2 presents median surgery-free interval and the CSDH surgery avoidance and shrinkage rates. A comparison of the patient variables between the two groups showed no significant differences in the ratio of men [9 (90.0%) vs. 20 (68.9%), $p = 0.402$], average ages in years (70.2 ± 15.5 vs. 78.9 ± 8.8, $p = 0.120$), past history of hypertension [4 (40.0%) vs. 12 (41.3%), $p = 1.000$], hyperlipidemia [1 (10.0%) vs. 4 (13.7%), $p = 1.000$], diabetes [1 (10.0%) vs. 1 (3.4%), $p = 0.452$], liver disease [0 (0%) vs. 1 (3.4%), $p = 1.000$], antithrombotic drug [4 (40.0%) vs. 9 (31.0%), $p = 0.704$], active drinker [0 (0%) vs. 1 (3.4%), $p = 1.000$], count of plate ($22.2 \pm 6.7 \times 10^4/\mu L$ vs. $20.4 \pm 4.5 \times 10^4/\mu L$, $p = 0.432$), the thickness of CSDH (15.0 ± 3.1 mm vs. 15.3 ± 2.6 mm, $p = 0.801$), or midline shift (2.0 ± 2.7 mm vs. 4.0 ± 5.0 mm, $p = 0.230$) (Table 1).

In our study, 74 patients with a hematoma thickness of 10-20 mm and unclear sulci below the hematoma were operated on within 4 days of diagnosis. These patients were categorized as the S group and compared with the G and NG groups. A comparison of the patient variables between the two groups found significant differences in the ratio of men [S group: 37 (50.0%) vs. G and NG groups: 29 (74.3%), $p = 0.013$] and no significant differences in the average ages in years (S group: 75.8 ± 10.8 vs. G and NG groups: 76.6 ± 22.3, $p = 0.705$). The thickness of CSDH (S group: 16.7 ± 2.8 mm vs. G and NG groups: 15.2 ± 2.7 mm, $p = 0.010$) and midline shift (S group: 6.6 ± 4.3 mm vs. G and NG groups: 3.5 ± 4.5 mm, $p < 0.001$) showed significant differences between the two groups.

The median surgery-free interval was significantly different between the G and NG groups [n. r. vs. 41 days (95% CI: 5-79), log-rank $p = 0.047$; Fig. 2]. The CSDH avoidance rate was not significantly different between the two groups (70.0% vs. 34.4%, $p = 0.071$). The CSDH shrinkage rate was significantly different between the two groups (60.0% vs. 10.3%, $p = 0.004$) (Table 2).

Figure 3 shows the cerebral CT of a representative case. This case had a mild headache at the initial visit and was prescribed Gorei-san. He continued to take Gorei-san for 2 months, he was free from headaches, and CT showed that his hematoma shrunk. No serious adverse events resulted from the Gorei-san (Fig. 3).

The midline shift between the G and NG groups was not significant, but there was a difference (2.0 ± 2.7 mm and 4.0 ± 5.0 mm, respectively, $p = 0.230$). Therefore, we restricted both groups to patients with a midline shift less than 4 mm and analyzed them again.

There were seven patients (70%) in the G group and 20

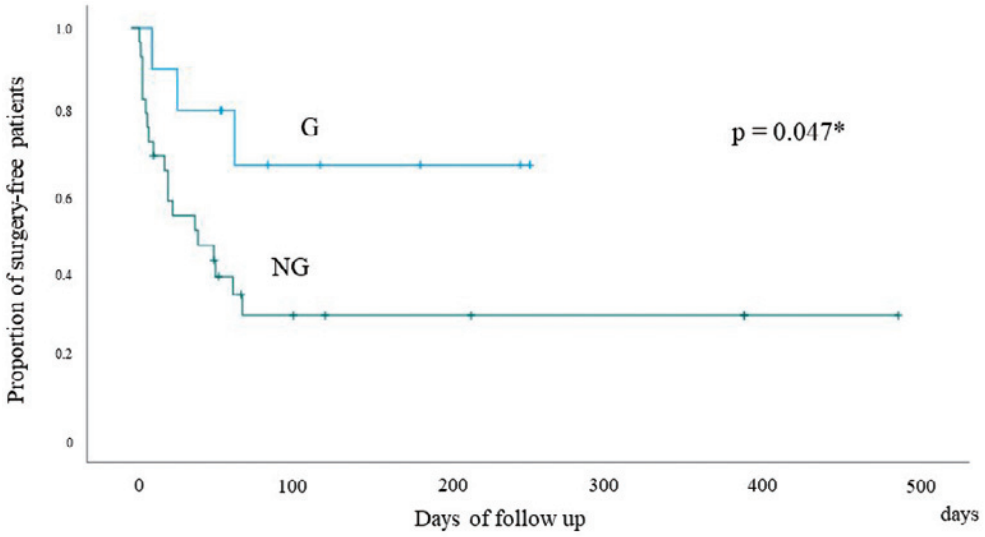

Fig. 2 Kaplan-Meier curve showing the proportion of surgery-free patients.
The follow-up time shows the Kaplan-Mayer estimate for surgery-free time intervals in the Gorei-san (G) and non-Gorei-san (NG) groups throughout the study.

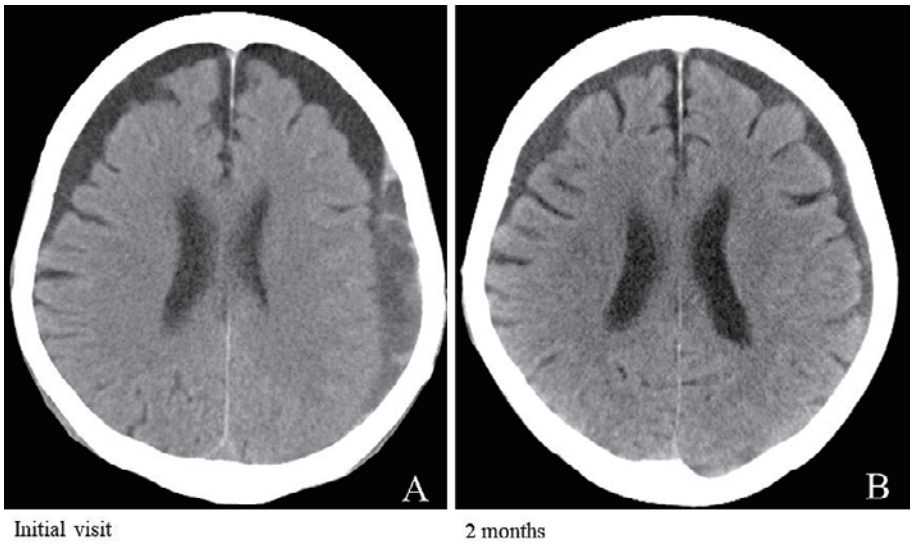

Fig. 3 A case of group G.
This patient from group G presented with a mild headache on his initial visit. He was diagnosed with chronic subdural hematoma and prescribed Gorei-san (A). After two months, his hematoma had shrunk (B).

patients (68.9%) in the NG group with a midline shift of 4 mm or less. In the two groups, there were no differences in the patient backgrounds. Although hematoma thickness did not differ between the two groups, the NG group had a much larger midline shift. The median surgery-free interval was significantly different [n. r. vs. 26 days (95% CI: 0-68), log-rank p = 0.020].

The surgery avoidance rate (85.7% vs. 35.0%, p = 0.033) and shrinkage rate (71.4% vs. 10.0%, p = 0.005) were significantly different between the two groups. Gorei-san may be more effective in patients with a midline shift of 4 mm or less.

Discussion

Surgery is the standard treatment for symptomatic CSDH, usually burr hole irrigation with or without drainage and craniotomy.[12,13] However, patients with asymptomatic or mildly symptomatic CSDH are managed conservatively. Reportedly, 20.8% to 50% of CSDHs will show spontaneous regression.[3,8,9,14] Kim et al. reported that 18.7% of patients with CSDH require surgical intervention after

conservative treatment.[15] Therefore, medical treatment should aim to reduce hematoma to avoid surgical intervention.

Most previous studies of CSDH treatment with Gorei-san have focused on its use to prevent recurrence after surgical treatment.[4,16] Few studies have considered using Gorei-san to shrink CSDH.[3,10,11] Furthermore, the effects of Gorei-san found in previous research are uncertain because most have been case reports or small case series with no control group.

Our study excluded CSDH patients with small and large hematomas because they are likely to shrink spontaneously if they are less than 10 mm thick[17] and hematomas more than 20 mm thick are likely to require emergency surgery. Therefore, patients with CSDH of 11-20 mm thickness and unclear sulci were selected to assess the effects of Gorei-san. Previous studies have not indicated the presence or absence of mass effects evaluated by CT or MRI, and they may have included patients with mild symptoms.[5] This makes it difficult to assess whether hematoma shrinkage is the spontaneous reduction that can occur in mild cases or is due to the effects of Gorei-san. This study set our inclusion and exclusion criteria to ensure an appropriate patient sample. The CSDH shrinkage rate in the group that received Gorei-san was 60.0%, significantly greater than the 10.3% rate of the group that received conservative treatment without Gorei-san.

Some Japanese studies have found Gorei-san to have hydrostatic effects on CSDH.[6,10,11,17] Gorei-san comprises five herbs (*Alismatis rhizoma*, *Atractylodis rhizoma*, *Polyporus*, *Poria*, and *Cinnamomi cortex*) used to treat nausea, dry mouth, edema, headaches, and dizziness.[4] The hydrostatic modulation effects of Gorei-san may explain its ability to decrease CSDH.[18,19]

Our study was limited by its retrospective design. A prospective randomized controlled study is needed for a more valid and reliable assessment of the effects of Gorei-san on CSDH.

Conclusion

Our retrospective comparative study showed a significantly longer median surgery-free interval in patients with CSDH having 10-20 mm thick hematomas and unclear sulci treated with Gorei-san. However, a further prospective clinical trial is needed to verify our findings.

Acknowledgments

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Abbreviations

CSDH, chronic subdural hematoma; CT, computed tomography; MRI, magnetic resonance imaging.

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Conflicts of Interest Disclosure

All authors have no conflict of interest.

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