

A Prospective Randomized Study on the Preventive Effect of Japanese Herbal Kampo Medicine Goreisan for Recurrence of Chronic Subdural Hematoma

Naoaki FUJISAWA,¹ Soichi OYA,¹ Shinsuke YOSHIDA,¹ Tsukasa TSUCHIYA,¹
Takumi NAKAMURA,¹ Masahiro INDO,¹ and Toru MATSUI¹

¹Department of Neurosurgery, Saitama Medical Center, Saitama Medical University,
Kawagoe, Saitama, Japan

Abstract

Although the recurrence of chronic subdural hematoma (CSDH) after surgical treatment significantly affects the patients' quality of life, the recurrence rate has not improved in decades. Goreisan, a Japanese herbal Kampo medicine, promotes the hydragogue effect and has been empirically used in the treatment of CSDH in Japan. We conducted a prospective randomized study to investigate whether Goreisan treatment decreases the recurrence rate of CSDH. Between March 2013 and December 2018, a total of 224 patients who underwent initial burr hole surgery for CSDH were randomly assigned to receive Goreisan for 3 months (Group G) or no medication (Group N). The primary endpoint was symptomatic recurrence within 3 months postoperatively, and the secondary endpoint was complications, including the adverse effects of Goreisan. Of 224 randomized patients, 208 were included in the final analysis (104 in Group G and 104 in Group N). The overall recurrence rate was 9.1% (19/208). The recurrence rate of Group G was lower than that of Group N (5.8% vs 12.5%, $P = 0.09$), but the difference was not statistically significant. However, a significant preventive effect of Goreisan was found in 145 patients with high-risk computed tomography (CT) features, namely, homogeneous and separated types (5.6% vs 17.6%, $P = 0.04$). Although the present study did not prove the beneficial effect of Goreisan treatment, it suggested the importance of selecting patients with an increased risk of recurrence. A subset of patients whose hematoma showed homogeneous and separated patterns on CT image might benefit from Goreisan treatment.

Keywords: chronic subdural hematoma, Goreisan, prospective randomized trial, recurrence

Introduction

Chronic subdural hematoma (CSDH) can develop in all generations from infants to elderly individuals. It is common especially among the aged population and has been gradually recognized as “not benign” but serious clinical condition reflecting general frailty in elderly individuals.^{1,2} In Japan, CSDH develops in 13.1–20.6 per 100000 person in the general population.^{3,4} However, these numbers increase to 58.1–80.1 in individuals aged >65 years.^{3,4} Although a relatively simple surgical treatment usually consisting

of burr hole opening and drainage of the hematoma is effective, recurrence occurs postoperatively at 5.4–18.1%.^{5–16} In symptomatic reaccumulation of hematoma, repetitive drainage or craniotomy is often required, but redo surgery may have a negative impact on the neurological status and patients' quality of life. Several retrospective analyses have reported the benefit of adjuvant medical treatment, such as corticosteroid,^{17,18} atorvastatin,^{19,20} tranexamic acid,²¹ etizolam,²² and angiotensin-converting enzyme (ACE) inhibitor,²³ to lower the recurrence rate. Although some prospective trials for the abovementioned medications have been conducted, the effectiveness of these medical treatments has not been proven in the context of a prospective randomized study.^{24–27}

Regarding the mechanism of CSDH development, Gardner emphasized the role of the osmotic ingress of the cerebrospinal fluid into the cavity formed by

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the inner membrane of hematoma.²⁸⁾ In fact, an early study demonstrated the therapeutic effect of an osmotic diuretic agent, mannitol, as nonsurgical treatment of CSDH.²⁹⁾ Goreisan, a Japanese herbal Kampo medicine, is a mixture of five herbs including *Alisma Rhizome*, *Atractylodes Lancea Rhizome*, *Polyporus Sclerotium*, *Poria Sclerotium*, and *Cinnamon bark*.³⁰⁾ It is also known as *Oreongsan* in Korea.³¹⁾ Since it promotes the hydragogue effect, in Japan, Goreisan has been empirically administered in patients with CSDH.³⁰⁾ Although several small case series mostly from Japan showed the clinical effect of Goreisan to replace or enhance the effect of surgical treatment,^{30–36)} the reliable data collected in a prospective and randomized fashion are scarce. Recently, Katayama et al.³⁷⁾ conducted a prospective randomized trial for patients aged >60 years and evaluated whether Goreisan treatment lowers the recurrence rate. Although no beneficial effect for overall participants was observed, their subanalysis revealed that the recurrence rate was successfully lowered by Goreisan treatment in patients aged 60–74 years, indicating its potential benefit to relatively younger patients. This prospective randomized study on patients with CSDH, including young adults, aimed to investigate whether Goreisan treatment effectively reduces the recurrence rate of CSDH and which cluster of patients will benefit from this treatment.

Materials and Methods

Study design

This study was approved by the institutional review board (No. 705-III). Patients who underwent initial surgery for symptomatic CSDH confirmed on computed tomography (CT) images were recruited in this study. The primary endpoint was the symptomatic recurrence of CSDH, and the secondary endpoint was the complications, including the adverse side effects of Goreisan. The sample size was determined as follows. We previously reported that the recurrence rate of CSDH at our institution was 8.9%.³⁸⁾ Therefore, we postulated an estimated recurrence rate of 10% in the control group and 2% in the group receiving Goreisan. The estimated sample size for the two-tailed t-test was determined to be 224 when Type I and Type II errors were considered at 0.05 and 0.20, respectively. Enrollment was conducted between March 1, 2013, and December 31, 2018. Written informed consent was obtained from all enrolled patients. Patients aged ≤ 18 years, those with a history of surgery for CSDH and hematological disorders, and those who had been using Goreisan before surgery were excluded. Additionally, patients with other intracranial lesions, such as brain

tumors or arachnoid cysts, were also excluded because these conditions have been reportedly associated with risk of CSDH.^{39,40)} The study protocol was registered at a clinical trial registry (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000011717) with number UMIN000010006. Data collected include age, sex, history of recent head injury, history of infarction, alcohol consumption, hypertension, diabetes, and hemodialysis. Moreover, current use of medications, such as antiplatelets, anticoagulants, and ACE inhibitors, statins, and steroids, was analyzed. Heavy drinking was defined as alcohol intake of ≥ 60 g/day. We also conducted radiological classification based of CT images into four subtypes according to the Nakaguchi classification.⁴¹⁾ Homogeneous type was defined as hematoma exhibiting homogenous density regardless of low or high. Lamellar type was defined as hematoma consisting of two or more layers with different densities. Hematomas were defined as separated type when they had a border of density (upper low, lower high). Trabecular type was defined as heterogeneous hematoma containing trabeculae running between the inner and outer membranes of hematoma.

Patient enrollment

We recruited participants in this study from March 2013 to November 2018. During this period, a total of 381 patients with CSDH underwent initial surgical treatment from March 2013 to November 2018 at our institution. By initial survey, four patients aged < 18 years, two patients who had craniotomy based on hematoma characteristics, and one patient under treatment for myelodysplastic syndrome were excluded. Another patient was not enrolled because she had large arachnoid cyst on the same side of CSDH. After the detailed explanation of the study protocol, 149 patients refused to participate in this study. Consequently, the study registration was terminated when 224 patients agreed to participate and were randomly assigned by drawing lots to the group receiving Goreisan (Group G) or the group receiving no medication (Group N).

Burr hole surgery

Our surgical indication and protocol are shown elsewhere.³⁸⁾ Briefly, a single burr hole was opened on the skull over the CSDH, and the hematoma was irrigated with saline solution under local anesthesia. Then, a closed drainage system using a silicone tube was placed in the hematoma cavity for 12–24 h postoperatively except patients for whom tube placement was considered dangerous. Postoperatively, CT was performed immediately after surgery and day 1 to exclude adverse events, such as postoperative

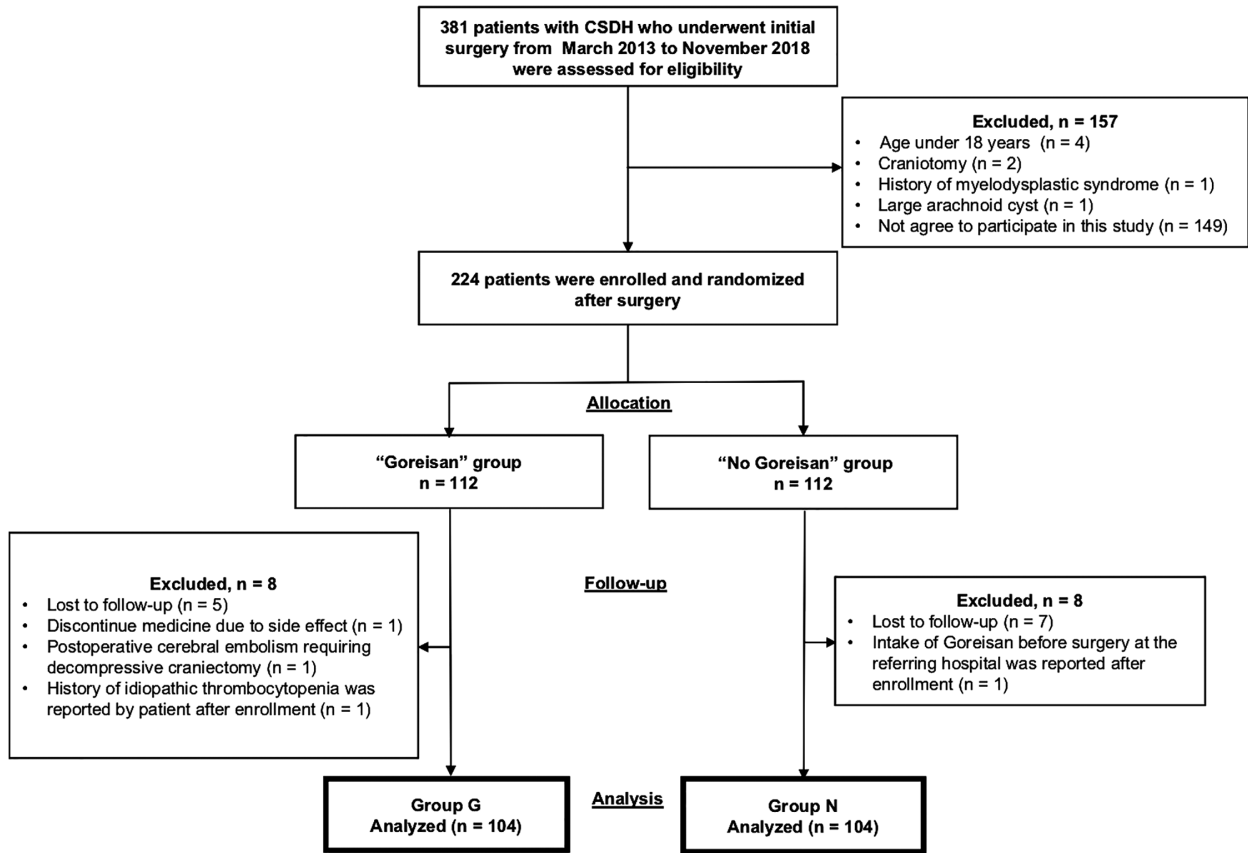


Fig. 1 CONSORT flow diagram for patient screening and randomization.

bleeding before discharge. In patients with bilateral CSDH, only the symptomatic side was treated. When both sides were regarded as symptomatic, surgery was conducted for both sides. Irrigation was conducted on both side when both sides were considered symptomatic. Patients on antiplatelet therapy underwent immediate surgery without discontinuing the antiplatelet treatment, whereas those using anticoagulants underwent elective surgery after the anticoagulative effect was reversed with vitamin K2 or fresh frozen plasma until normalization of prothrombin time or international normalized ratio was confirmed.

Goreisan administration and follow-up strategy

Postoperatively, patients assigned to the Group G started to receive oral Tsumura Goreisan extract granules (Tsumura & Co., Tokyo, Japan), 7.5 g, three times a day within a few days. Patients were instructed to continue Goreisan for at least 3 months unless they developed any side effect of Goreisan. Three months postoperatively, continuation of Goreisan was allowed as per surgeons' judgment when a significant amount of hematoma remained on CT. Most patients were discharged home within a week and visits our outpatient clinic regularly for checkup.

Recurrence was defined as reaccumulation of symptomatic CSDH. In some patients who were sent to rehabilitation centers before returning home and unable to visit our outpatient clinic, whether the patient had symptomatic recurrence was assessed on the phone at 3–6 months postoperatively.

Statistical analysis

Pearson's chi-square test and Fisher's exact test (if any of the cells in 2×2 table is <5) were used to compare categorical variables. Continuous variables with non-normal distributions were presented as median (interquartile range) and compared using the Wilcoxon–Mann–Whitney test. Multiple logistic regression analysis for calculation of odds ratios (ORs) to determine the characteristics associated with increased recurrence risk. P values <0.05 were considered statistically significant. All analyses were performed with JMP 14 (SAS Institute, Cary, NC, USA).

Results

A flow diagram for patient enrollment and randomization is presented in Fig. 1. Between March 2013 and November 2018, a total of 224 patients were

Table 1 Patient demographics and CT classifications of chronic subdural hematoma

Factor	Group G (Goreisan)	Group N (No Goreisan)	<i>P</i> value
No. of patients	104	104	
Age, median (IQR), years	74 (66, 83)	74 (66, 81)	0.52
–39	2	0	
40–49	4	2	
50–59	6	8	
60–69	21	26	
70–79	34	39	
80–	37	29	
Sex, male, n (%)	78 (75.0)	75 (72.1)	0.63
Current antiplatelet therapy, n (%)	13 (12.5)	11 (10.6)	0.66
Current anticoagulant therapy, n (%)	8 (7.7)	0 (0)	0.004
Current ACE inhibitor therapy, n (%)	2 (1.9)	4 (3.9)	0.68
Current statin therapy, n (%)	8 (7.7)	13 (12.5)	0.25
Current steroid therapy, n (%)	0 (0)	2 (1.9)	0.16
History of cerebral infarction, n (%)	8 (7.7)	7 (6.7)	0.79
History of hypertension	51 (49.0)	47 (45.2)	0.58
History of diabetes mellitus	16 (15.4)	20 (19.2)	0.46
History of recent head injury, n (%)	61 (58.7)	69 (66.3)	0.25
Heavy drinking	4 (3.9)	8 (7.7)	0.23
Hemodialysis	1 (1.0)	1 (1.0)	1.00
CT classification, n (%)			0.60
1. Homogeneous type	56 (53.8)	53 (51.0)	
2. Lamellar type	23 (22.1)	18 (17.3)	
3. Separated/gradation type	15 (14.4)	21 (20.2)	
4. Trabecular type	10 (9.6)	12 (11.5)	

ACE: angiotensin-converting enzyme, CT: computed tomography, IQR: interquartile range.

enrolled in this study. From Group G, seven patients were excluded because of lost to follow-up ($n = 5$), discontinuation of Goreisan due to side effect ($n = 1$), and postoperative cerebral embolism occurring on postoperative day 1 requiring decompressive craniectomy ($n = 1$). Additionally, protocol violation was confirmed after enrollment: one patient reported history of idiopathic thrombocytopenic purpura immediately after enrollment. In Group N, seven patients were also excluded due to lost to follow-up. Moreover, a protocol violation was reported after enrollment ($n = 1$): one patient had been receiving Goreisan preoperatively at a referring hospital. Consequently, both Group G and Group N comprised 104 patients.

Patient demographics and CT classifications of CSDH are shown in Table 1. All characteristics except for the use of anticoagulant ($P = 0.004$) were

matched between two groups. Table 2 demonstrates the primary and secondary outcomes. The overall recurrence rate was 9.1% (19/208). The recurrence rate of Group G was lower than that of Group N, but it was not statistically significant (5.8% vs 12.5%; OR, 0.42; 95% confidence interval [CI], 0.15–1.17; $P = 0.09$). Although it was not significant, there was a tendency that patients aged <70 years receiving Goreisan treatment less frequently had recurrence than those not receiving Goreisan treatment (3.0% vs 16.7%; OR, 0.15; 95% CI, 0.02–1.34; $P = 0.11$). No therapeutic effect of Goreisan treatment was observed among patients aged >70 years (7.0% vs 10.3%; OR, 0.66; 95% CI, 0.20–2.19; $P = 0.50$). The occurrence of wound infection was not significant between the two groups ($P = 0.57$). No seizure was observed in Group G. Among three patients complaining of severe headache, diarrhea, and abdominal

Table 2 Primary and secondary outcomes according to the intake of Goreisan

Outcomes	Group G n = 104	Group N n = 104	OR (95% CI)	P value
Primary outcome				
Recurrence, n (%)				
All	6(5.8)	13(12.5)	0.42 (0.15–1.17)	0.09
Age <70 (n = 69)	1(3.0)	6(16.7)	0.15(0.02–1.34)	0.11
Age ≥70 (n = 139)	5(7.0)	7(10.3)	0.66(0.20–2.19)	0.50
Secondary outcome				
Wound infection, n (%)	1(1.0)	2 (1.9)	0.50 (0.04–5.60)	0.57
Seizure, n (%)	0	1 (1.0)	NC	NC
Adverse effects of Goreisan, n (%)	3 (2.9)	–	NC	NC

NC: not calculable, OR: odds ratio.

discomfort, one patient with headache was not able to tolerate and discontinued Goreisan treatment.

The possible influence of other factors was investigated (Table 3). Univariate analysis revealed that heavy drinking was associated with increased risk of recurrence (21.1% vs 4.2%, $P = 0.003$). After multivariate analysis adjusting for Goreisan use, heavy drinking was an independent risk factor for increased recurrence rate (OR: 5.47, 95% CI: 1.31–20.0, $P = 0.02$). We also found that the recurrence rates were different according to CT classification (Fig. 2A). Although no significant difference was found between any groups ($P = 0.27$), the risk of recurrence after surgery for laminar or trabecular type of CSDH was sufficiently low considering the overall recurrence rate (Fig. 2B). Therefore, we confined the analysis for these high-risk hematomas, namely, homogeneous and separated types, and found that the recurrence rate was significantly lower in patients receiving Goreisan treatment than those not receiving Goreisan treatment (5.6% vs 17.6%, $P = 0.04$, Fig. 2C).

Discussion

Although burr hole opening and drainage of hematoma is a well-established and safe treatment for CSDH, the recurrence rate of CSDH has not decreased in recent decades,²⁾ indicating the necessity to improve current treatment strategy. In addition to surgical treatment, several studies have investigated the benefit of additional medical treatments, including corticosteroid, atorvastatin, tranexamic acid, etizolam, and ACE inhibitor to minimize the risk of recurrence.^{17,21,22,42,43)} Although these retrospective studies demonstrated some positive effects to lower the recurrence rates, the result of previous prospective

randomized trials implies the limited effect of these adjuvant therapies to prevent the recurrence of CSDH.²⁷⁾ The present study did not show the beneficial effect of Goreisan to lower the recurrence rate. However, it suggested that Goreisan treatment might be effective for CSDH manifesting homogeneous and separated types on CT.

Therapeutic mechanism of Goreisan treatment

Although the mechanism of the therapeutic effect of Goreisan remains to be elucidated, an immunohistochemical study demonstrated that the outer membrane of CSDH expressed aquaporin-4 (AQP4).⁴⁴⁾ AQP4 is the major water transporter protein in the central nervous system and increases water permeability of cell membranes.⁴⁵⁾ A recent experimental study suggested that the possible mechanism of the hydragogue effect of Goreisan is via its suppressive effect on the expression and function of AQP4.⁴⁶⁾

Treatment outcome of Goreisan administration

In Japan, Goreisan has been empirically administered to patients with CSDH in expectation of its hydragogue effect.³⁰⁾ In addition to small case series reporting its therapeutic effect,^{30–36)} a recent retrospective large observational study using a national inpatient database in Japan demonstrated that the reoperation rate of patients with CSDH who started receiving Goreisan treatment within 2 days postoperatively was lower than that of those who did not receive Goreisan treatment.⁴⁷⁾ This robust statistical analysis of 36020 patients, including 3889 patients treated with Goreisan, showed that Goreisan treatment was associated with a reduction of reoperation rate from 6.2 to 4.8%. Such findings prompted us to start the prospective randomized trial to verify the effect of adjuvant Goreisan treatment. Three randomized

Table 3 Variables analyzed for their correlation with CSDH recurrence

Factor	Univariate analysis			Multivariate analysis		
	Recurrence n = 19	No recurrence n = 189	P value	OR	95% CI	P value
Age, median (IQR), years	74 (66, 79)	74 (67, 82)	0.69			
Sex, male, n (%)	14 (73.7)	139 (73.5)	0.98			
Current antiplatelet therapy, n (%)	3 (15.8)	21 (11.1)	0.54			
Current anticoagulant therapy, n (%)	0 (0)	8 (4.2)	0.36			
Current ACE inhibitor therapy, n (%)	2 (10.5)	4 (2.1)	0.10			
Current statin therapy, n (%)	3 (15.8)	18 (9.5)	0.42			
Current steroid therapy, n (%)	0 (0)	2 (1.1)	1.00			
History of cerebral infarction, n (%)	2 (10.5)	13 (6.9)	0.56			
History of hypertension	10 (52.6)	88 (46.6)	0.61			
History of diabetes mellitus	3 (15.8)	33 (17.5)	0.85			
History of recent head injury, n (%)	11 (57.9)	119 (63.0)	0.66			
Heavy drinking	4 (21.1)	8 (4.2)	0.003	5.47	1.31–20.0	0.02
Hemodialysis	0 (0)	2 (1.1)	1.00			
Goreisan treatment, n (%)	6 (31.6)	98 (51.9)	0.09	0.46	0.16–1.26	0.13

ACE: angiotensin-converting enzyme, CI: confidence interval, IQR: interquartile range, OR: odds ratio.

controlled studies including the present study have been conducted on the effect of Goreisan to prevent recurrence, but none of those could prove the benefit of Goreisan treatment.^{27,37)} Although some previous studies have discussed the surgical strategy might affect the recurrence rate,^{12,48)} it would have little impact on those negative results because the recurrence rates of control patients in two previous studies were 9.8% and 12.5%; it was quite comparable to the result of our study (Group N, 12.5%). The number of participants of the three prospective trials including the present study ranged from 180 to 224 and failed to show significant decrease in the recurrence rate due to Goreisan treatment. These facts appear to indicate that we might have overestimated the favorable effect of Goreisan.

Patient selection to prevent CSDH recurrence by Goreisan treatment

There is still a possibility that a certain cluster of patients might benefit from Goreisan treatment. For example, a study by Katayama et al. found that Goreisan had a favorable effect in patients aged 60–74 years while no beneficial effect was observed in patients aged ≥ 75 years.³⁷⁾ Our data also showed a similar tendency in patients aged < 70 years. We conducted additional analysis to seek the relevance of CT findings because some previous studies demonstrated the association between the radiological features on CT image and recurrence rate of

CSDH.^{10,41)} Our data demonstrated that Goreisan might effectively lower the recurrence rate specifically for patients with high-risk characteristics on CT image. The importance of risk stratification based on CT images in Goreisan treatment was also confirmed on a recent retrospective analysis.⁴⁹⁾ Another randomized controlled study regarding adjuvant dexamethasone treatment with surgery for CSDH recently disclosed the result of the interim analysis.²⁵⁾ In their study, recurrence occurred significantly less frequently with dexamethasone administered for 2 weeks postoperatively (0% vs 21%). Although the result is promising, dexamethasone may cause various adverse effects, such as infection and wound dehiscence; it should also be avoided in patients with diabetes. In contrast, Goreisan is an herbal medicine with few side effects. Based on the analysis of the secondary outcome of the present study, it appears as another advantage of this supportive therapy.

While several factors, such as older age,^{6,9)} male sex,^{7,9)} current antiplatelet or anticoagulant therapy,⁸⁾ and alcohol abuse¹⁴⁾ have been reported to increase recurrence rate in large retrospective studies, only heavy drinking was independently associated with risk of recurrence in this study. This is probably because the present study is a prospective trial recruiting a smaller number of patients compared to the abovementioned retrospective studies. Eight patients using anticoagulants were all assigned to

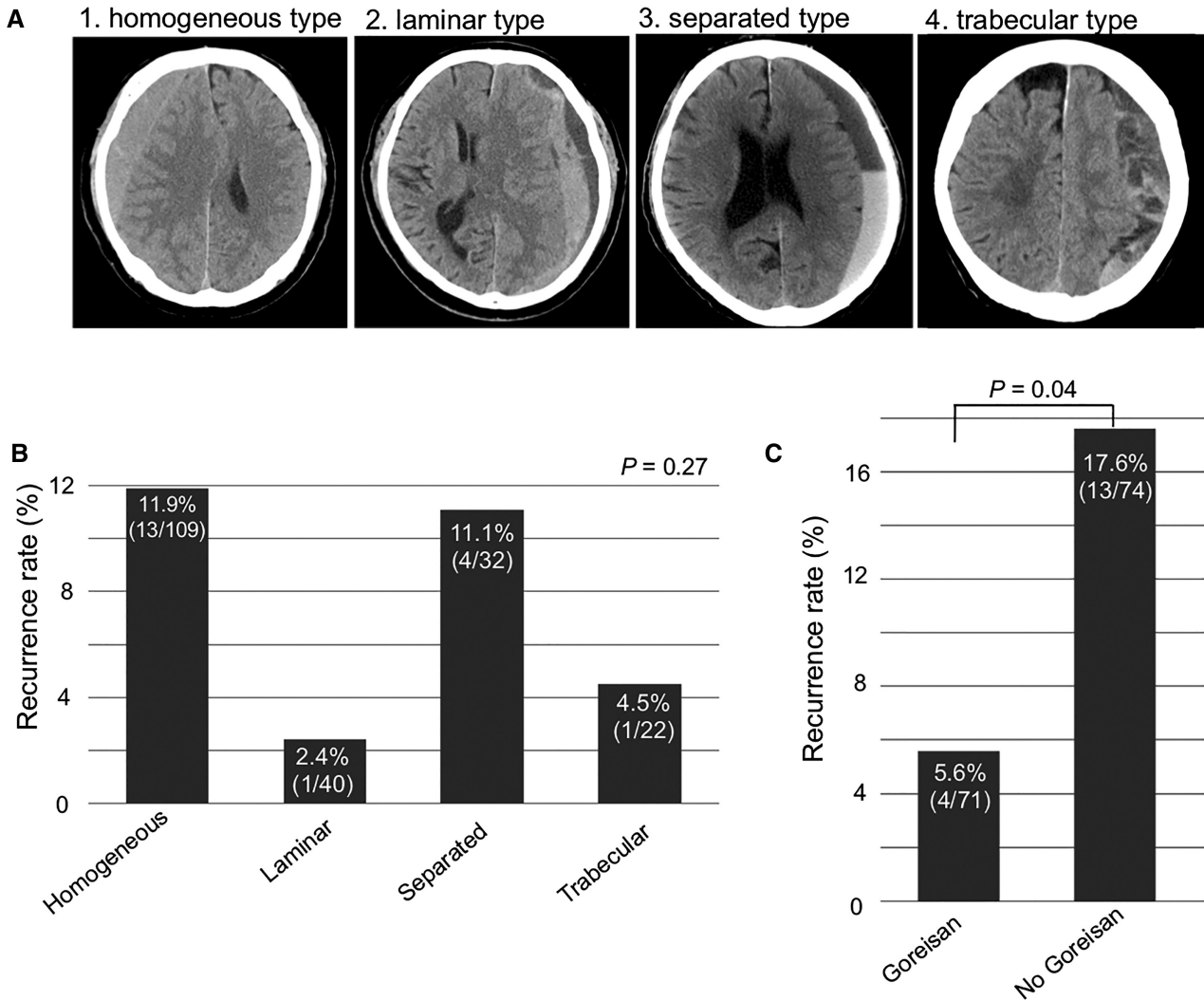


Fig. 2 (A) Subtypes of CT scan finding used in this study according to Nakaguchi classification.⁴¹⁾ (B) Bar graphs showing the recurrence rates according to CT classifications of hematoma. There was no significant difference in recurrence rate between each CT classification ($P = 0.27$). Note that recurrence occurs at $\geq 10\%$ for homogeneous- and separated-type hematomas, while the risks of recurrence are sufficiently low for laminar- and trabecular-type hematomas. (C) Bar graphs demonstrating the preventive effect of Goreisan for chronic subdural hematoma recurrence in patients with homogeneous and separated types (5.6% vs 17.6%, $P = 0.04$). CT: computed tomography.

Group G in this study as a result of randomization. Although views are split regarding whether the use of anticoagulant increases the risk of recurrence,^{5,8–10,38,50)} the consequence is that none of these patients had recurrence in this study; however, it remains unknown whether this excellent outcome in patients on anticoagulant is attributable to Goreisan treatment.

Study limitations

There are some limitations in our study. First, we might have overestimated the favorable effect due to the lack of preliminary data and available studies, which might lead to recruitment of an insufficient

number of patients and the negative result for primary outcome. Second, this study was conducted at a single center; therefore, it should be validated in the form of multi-institutional approach.

Conclusions

The present prospective randomized study did not prove the beneficial effect of adjuvant Goreisan treatment, although it approached significance to lower the recurrence rate in overall patients. However, it suggested the importance of selecting patients with high risk of recurrence. Based on our data, a

subset of patients whose hematoma showed homogeneous and separated patterns on CT image might benefit from Goreisan treatment.

Conflict of Interest Disclosure

The authors have no conflict of interest to declare.

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Corresponding author: Soichi Oya, MD, PhD
 Department of Neurosurgery, Saitama Medical Center,
 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan.
 e-mail: sooya-ky@umin.ac.jp