The effect of goreisan on the prevention of chronic subdural hematoma recurrence – multicenter, randomized controlled study

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Abstract

The relatively high rate of postoperative recurrence in the treatment of chronic subdural hematoma (CSDH) is a significant problem. Goreisan is an herbal medicine that exhibits a hydragogue effect by inhibiting the expression of aquaporins, and its efficacy in preventing postoperative CSDH recurrence has been suggested by several case trials. This multicenter, prospective, randomized controlled trial was performed to investigate the preventative effect of goreisan on postoperative CSDH recurrence.

Patients with symptomatic CSDH over 60 years old undergoing burr hole surgery were enrolled in this study. The patients were randomly allocated to the control group or the goreisan group, in which oral administration of goreisan (7.5 g daily) was continued for 12 weeks. The primary endpoint was the post-operative recurrence rate at 12 weeks, and the secondary endpoint was hematoma volume reduction rates on CT scan at 12 weeks. The analyses were performed not only on patients of all ages older than 60 years, but also on patients divided into those over or under 75 years old.

One hundred and eighty patients were followed and analyzed (the control group; n = 88, the goreisan group; n = 92). The recurrence rates considering patients of all ages and patients under 75 years old were relatively low in the goreisan group but without a significant difference. The hematoma volume reduction rates showed no significant difference. Based on the results of the present study, a larger-scale study including more cases is necessary in future to confirm the efficacy of goreisan.

Key words: aquaporin-4; chronic subdural hematoma; goreisan, prevention of postoperative recurrence of CSDH; randomized controlled trial

Introduction

Chronic subdural hematoma (CSDH) is a common neurosurgical disease in elderly people. The number of such patients is increasing, because its incidence is known to rise with age and an aging- or aged society is and has been a reality in many developed countries.[1, 2] Its annual incidence in Japan is currently reported as 20.6 per 100,000 population.[2]

CSDH is not a difficult disease to treat, as burr hole surgery is a well-established method to treat symptomatic CSDH. However, the postoperative recurrence rate is not low and has been reported in the literature as between 8 and 22%.[1,3] This is thus the critical problem to be solved in treating CSDH. There have therefore been several trials for the prevention of postoperative recurrence.

Several reports have suggested that corticosteroids could prevent the recurrence of CSDH[4,5] due to its anti-inflammatory effect.[4] However, randomized, controlled trials have not been performed and adverse events should be considered, especially in the elderly.[6] Intraoperative irrigation with thrombin solution proved to be effective for the prevention of postoperative recurrence of CSDH in our previous study, but it could not find application because it is off-label in Japan.[7] Angiotensin converting enzyme (ACE) inhibitor was reported to have lowered the risk of the development and recurrence of CSDH;[8] however, a randomized, controlled trial did not show any significant difference between patients with ACE inhibitor and patients with placebo in the recurrence rate of postoperative CSDH.[9] Therefore, no treatments have been established for preventing the recurrence of postoperative CSDH.

Goreisan is an herbal medicine that exerts a hydragogue effect and is generally effective when used for systemic edema, nephrotic syndrome, uremia and other associated symptoms. It also includes low risk of adverse effects and low cost. Moreover, this herbal medicine is also sometimes used for the treatment of asymptomatic CSDH and prevention of postoperative

recurrence of CSDH in several countries, with expectations arising from its hydragogue effect. In this regard, case reports[10] and case trials[11,12] with low case numbers have been published, showing its effectiveness in preventing postoperative recurrence of CSDH. Recently, Yasunaga carried out a retrospective observational study using a national Japanese inpatient database that showed a significant reduction in postoperative recurrence rate with goreisan administration.[13]

However, its effect has not been established, because a prospective, randomized controlled study has not been carried out. We performed a multicenter, prospective randomized controlled trial to examine the efficacy of goreisan in the prevention of postoperative CSDH recurrence.

Methods

Study design

This study was an investigator-indicated, multicenter, prospective, randomized controlled trial with blinded outcome assessment, performed at five neurosurgical institutions in Aomori prefecture, Japan, between October 2014 and March 2016. This study was performed in accordance with ethics principles originating from the Declaration of Hersinki and in compliance with ethical guidelines for clinical research. The study protocol received ethics committee approval from all of the participating centers. All participants or their legal representatives provided written, informed consent. This trial is registered with the Universal Hospital Medical Information Network Clinical Trials Registry (No. UMIN000015970).

Study population

Patients over 60 years old with CSDH presenting any neurological deficits considered due to CSDH and undergoing burr hole surgery were eligible for this study. Exclusion criteria were as follows: (1) severe liver dysfunction, (2) severe renal dysfunction, (3) prior administration of goreisan or corticosteroids before operation. The reason why patients treated with corticosteroids were excluded was that corticosteroids were reported to have preventative effects in the postoperative recurrence of CSDH.

Randomization

After burr hole surgery was performed, participants were randomized into one of the following two groups. Control group patients were treated by burr hole surgery alone. In the goreisan group, administration of 2.5 g goreisan-ryo (Tumura ＆ Co., Tokyo, Japan) orally three times per day was started within 72 hours after surgery and continued for 12 weeks. Three packets (7.5 g) of this medicine contain 2.0 g of goreisan extract of the following mixed, crude herbs: Alismatis

Rhizoma (4.0 g), Poria (3.0 g), Polyplus (3.0 g), Atractylodis Lanceae Rhizoma (3.0 g), and Cinnamomi Cortex (1.5 g). The study drug assignments were kept in sealed envelopes that were opened by site study investigators who were involved neither in patient care nor in end points assessment.

Operation and post-operation management

Burr hole surgery was performed under local anesthesia. The hematoma was irrigated with sterile saline and a silicone drainage tube was inserted into the frontal side of the hematoma cavity. We also replaced air in the hematoma cavity with sterile saline after skin suture and connected the tube with a closed-system drainage.

The patients received intravenous drip infusion of antibiotics and a proton-pump-inhibitor for 48 hours; they were not given hemostatic agents or corticosteroids. All drainage catheters were removed within 24 hours post-operation following CT scanning.

Clinical assessment, radiology, and end points

Assessment of neurological findings and CT examinations were performed in all patients preoperatively and on the 1st, 7th, 14th days, 4, 8 and 12 weeks after surgery, Neurological findings and CT findings were assessed by two site investigators who were blind to the allocation. Primary end-point was recurrence of CSDH, which was defined as increased hematoma volume with neurological deficits and need for re-operation.

Serial CT images were sent to the central office and hematoma volumes were calculated there by two independent, blinded reviewers. The hematoma volume was calculated by the XYZ/2 method.[14] The hematoma drainage rate was calculated by dividing the preoperative hematoma volume by the postoperative hematoma volume. Hematoma reduction rate, the secondary

end-point, was calculated by a following formula:

$$\textit{Hematoma reduction rate} = \quad (1 - A/B) * 100\ [\%]$$

where *A* is post-operative hematoma volume and *B* is the pre-operative hematoma volume.

Statistics

We compared the two groups for patient characteristics, recurrence rate and hematoma reduction rate in postoperative CSDH (paired *t-test* and Fisher exact test). In addition, we examined all cases separated by age, under 75 years old or over 75 years old, because postoperative recurrence occurs more readily in patients over 75 years old.[15] Statistical calculation was done with JMP 13.0, and a p-value below 0.05 was accepted as statistically significant. When goreisan use significantly affected any endpoint by univariate analysis, multivariate analysis was performed using logistic regression by including possible confounding factors. Factors with a p-value below 0.2 or factors reported to have an influence on any end point were selected as possible confounding factors.

Results

Patient Population

A flow diagram according to the Consolidated Standards of Reporting Trials guideline is shown in Figure 1. Between October 2014 and March 2016, 236 CSDH patients were admitted to our institutions. Of these cases, 208 met both the inclusion criteria and consented to participate in this study. These 208 cases were randomly divided into two groups. Twenty-eight patients were lost to follow-up because these patients defaulted from outpatient appointments and were thus excluded from analysis. Eighty-eight patients in the control group and 92 patients in the goreisan group underwent analysis. Goreisan was continued for 12 weeks in all of 92 patients.

The baseline characteristics of all patients are shown in Table 1. No significant differences were seen between the characteristics of the two groups.

Effect of goreisan

Postoperative recurrence in patients for all investigated ages occurred in 9 cases (9.8%) in the goreisan group, which was lower than 11 cases (12.5%) in the control group; however, a statistically significant difference was not apparent between them (Table 2). Dividing the patients into two populations, under- or over 75 years old, the recurrence rate for CSDH in the cases under 75 years old was significantly lower in the goreisan group compared to the control group (control group vs. goreisan group; 17.4% vs. 3.0%, $p = 0.04$) (Table 2). In the cases over 75 years old, the recurrence rate of postoperative CSDH showed no significant difference between the two groups.

Serial changes in hematoma volume reduction rates are shown in Figure 2. In all patients at all ages, the hematoma volume reduction rates after the operation showed no significant

difference between the two groups at any period after operation (Fig. 2A). When analysis was done by dividing patients into two populations, under- or over 75 years old, there were no statistically significant differences in the hematoma reduction rates between the two groups (Fig. 2B, C).

The goreisan arm had almost double the number of bilateral CSDH. Therefore, we assessed the difference in the recurrence rate by separating unilateral CSDH from bilateral CSDH (Table 3). The recurrence rate in the control group was twice that in the goreisan group without any statistically significant difference in patients with unilateral CSDH (control group vs. goreisan group; 11.7% vs. 5.6%, $p = 0.25$). In patients with bilateral CSDH, there was no difference (control group vs. goreisan group; 18.2% vs. 25%, $p = 0.81$).

Multivariate analyses were performed in order to evaluate the factors associated with postoperative recurrence and the preventative efficacy of goreisan. As confounding factors, those reported to have an influence on postoperative CSDH recurrence, such as use of goreisan,[13] ages (over 75 years old),[15] use of anticoagulant,[16] and bilateral CSDH were selected.[17] Multiple logistic analysis showed that bilateral CSDH was an independent risk factor for recurrence of postoperative CSDH (odds ratio: 3.43, p = 0.02, 95%CI: 1.196 - 9.819). Goreisan use was not the factor that reduced the recurrence of CSDH (Table 4). Multivariate analysis was also performed for the patients under 75 years old, because univariate analysis showed that goreisan use significantly reduced postoperative CSDH recurrence in those under 75 years old. Multiple logistic analysis showed that no factors were not significantly associated with postoperative recurrence of CSDH (Table 5).

Discussion

Surgical treatment for CSDH is well-established[18] and is not difficult; however, the postoperative recurrence rate remains high and is a problem that needs to be solved. Brain atrophy or its causative factors have been reported as risk factors in the recurrence of CSDH. Older patients (≥ 75 years old),[15] bilateral CSDH, obesity (body mass index ≥ 25.0 kg/m^2)[15] and poor re-expansion of brain after the operation[1] are considered as risk factors of CSDH recurrence through inducing brain atrophy. Therefore, postoperative recurrence will become a more serious problem with aging- or an aged society. However, no preventative medical treatment has been established, although several following trials have been done.

An inflammatory process has been considered important in the pathogenesis of CSDH occurrence and growth, because inflammatory cells or inflammatory-associated substances induce angiogenesis[19-21] and/ or growth of the CSDH outer membrane[22]. Therefore, corticosteroids have been tried for the prevention of postoperative recurrence, anticipating the benefit of the anti-inflammatory and anti-angiogenesis effect.[4,5] However, this has not prevailed as treatment, because adverse events therefrom should be considered, especially in the elderly.[6]

Preoperative anticoagulants[16, 23] or antiplatelets[24] also have been reported as risk factors in postoperative recurrence. We reported the effectiveness of intraoperative irrigation with thrombin solution in reducing the CSDH recurrence rate in high-risk patients.[7] However, this treatment has also not prevailed, because intracranial use of thrombin is off-label in Japan.

Recently, aquaporins (AQPs) were reported as one of the factors affecting CSDH growth. AQPs are water channel proteins that exist in biomembranes and play an important role in maintaining homeostasis. AQPs have 13 subtypes and, of those, AQP1, AQP4, and AQP9 are subtypes expressed in particular in the human central nervous system.[25] AQP1 is expressed in the choroid plexus and other structures producing cerebrospinal fluid (CSF) and is considered to

contribute to an increase in water flow through tissues, and to edema.[26, 27] AQP4 is concentrated in glial membranes facing blood – brain and brain – CSF interfaces and in the basolateral membranes of ependymal cells.[28] It plays a key role in the movement of water between blood and brain and between brain and CSF, as it provides a principal pathway for water influx in cytotoxic brain edema.[29]

AQP1 and AQP4 have been reported to be expressed within the CSDH outer membrane.[26,30] Basaldella et al.[26] reported that AQP1 is expressed in the endothelium of the CSDH outer membrane sinusoid capillaries. They consider that AQP1 in the outer membrane might be the source of CSDH enlargement. Utsuki et al.[30] reported that AQP4 is also expressed in the vascular endothelium of CSDH outer membranes, especially in portions where inflammatory cell invasion is frequent. AQP4 may cause fluid to flow into the subdural space, and contribute to hematoma occurrence and enlargement.

Goreisan has been thought to inhibit the expression of AQPs. Kurita T et al. reported that goreisan inhibits mRNA expression in AQP 2, 3 and 4 in rat kidney.[27] Nagai et al.[31] reported that *Atractyloides lanceace rhizome* (sohjutsu), which is contained in goreisan, inhibits the function of AQP4, while manganese, a component of sohjutsu, plays a key role in the inhibitory effect. Based on these effects of goreisan on AQP4, it is sometimes used with the aim of treating asymptomatic CSDH or the prevention of postoperative recurrence, although the evidence has not been determinative.

A retrospective observational study by Yasunaga has shown that 187 (4.8%) of 3879 goreisan users and 241 (6.2%) of 3879 goreisan nonusers suffered recurring CSDH after surgery, which was significantly different.[13] The present, first multicenter, prospective, randomized controlled trial was performed to determine the efficacy of goreisan in postoperative CSDH patients. The results of this study showed no significant effect of goreisan in the prevention of postoperative

CSDH recurrence not only in the cases of all investigated ages but also when patients were divided into those under or over 75 years old. In spite of the lack of a significant difference, the ratio of the recurrence rates of goreisan group and the control group in the present study seems to correspond to the previous observational report by Yasunaga.[13] Therefore, based on the present study, a large clinical trial should be performed in future to confirm the efficacy of goreisan in preventing postoperative recurrence of CSDH by setting a higher, more appropriate case number.

Furthermore, it is necessary to consider the age of the patients and the laterality of CSDH when future studies are designed, because the result of the present study suggests that severe brain atrophy may interfere with the effect of goreisan in CSDH recurrence. In the present study, goreisan significantly reduced the recurrence rate of postoperative CSDH in the cases under 75 years of age in univariate analysis, although goreisan did not reduce the recurrence rate in the cases over 75 years old. Goreisan also reduced the recurrence rate almost by half in the cases of unilateral CSDH in spite of the lack of any statistically significant difference; however, there is no difference in the cases of bilateral CSDH. The over 75 years old and bilateral CSDH cases could both have had brain atrophy as background, which may associate with the lack of efficacy of goreisan in CSDH recurrence.

This study has some limitations. One is that 10% of patients were lost to follow up, which may have influenced the result. Another is that adequate sample size could not be calculated before planning this study, because no previous study had been performed, which might have led to the lack of significant results. Therefore, this study should be considered a preliminary study, with the next trial expected to include a larger number of cases.

Conclusion

The present, preliminary study showed that goreisan did not significantly reduce the recurrence rate or the hematoma volume reduction rate in post-operative CSDH. In order to confirm the efficacy of goreisan, a large clinical trial should be performed based on the present study.

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Author Disclosure Statement

No competing financial interests exist.

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Figure legend

Figure 1: Flow diagram of the trial patient recruitment according to the Consolidated Standards of Reporting Trials guideline.

Figure 2: Transition of hematoma reduction rate: all cases (A), cases under 75 years old (B), cases over 75 years old (C). No significant difference between the two groups, respectively.

TABLE 1. BASELINE CHARACTERISTICS

	Control N = 88	Goreisan N = 92	P
Age, Mean ± SD	75.8 ±9.53	75.9 ±8.08	0.93
Sex, N (%)			0.99
Male	67 (76.1)	70 (76.1)	
Female	21 (23.9)	22 (23.9)	
Laterality, N (%)			0.09
Unilateral	77 (87.5)	72 (78.3)	
Bilateral	11 (12.5)	20 (21.7)	
Medication			
Anticoagulant	7	5	0.49
Antiplatelet	3	8	0.13
Preoperative hematoma (ml) Mean ± SD	121.1 ±39.5	115.7 ±37.4	0.34
SDA at 1st day (ml) Mean ± SD	13.1 ±16.1	10.2 ±11.8	0.19

SD, standard deviation; SDA, Subdural air

TABLE 2. RECURRENCE RATE

	Control N (%)	Goreisan N (%)	P
All patients	11/88 (12.5)	9/92 (9.8)	0.56
< 75 years old	6/35 (17.4)	1/33 (3.0)	0.044
≥ 75 years old	5/53 (9.4)	8/59 (13.6)	0.49

TABLE 3. RECURRENCE RATE IN PATIENTS WITH UNILATERAL OR BILATERAL CSDH

	Control N (%)	Goreisan N (%)	P
Unilateral CSDH	9/77 (11.7)	4/72 (5.6)	0.25
Bilateral CSDH	2/11 (18.2)	5/20 (25.0)	0.81

CSDH, chronic subdural hematoma

TABLE 4. ASSESSMENTS OF FACTORS AFFECTING CSDH RECURRENCE IN ALL CASES

	OR	P	95%CI
Age	1.45	0.48	0.529-3.989
Sex (male)	1.42	0.56	0.434-4.619
Goreisan use	0.68	0.44	0.257-1.810
Bilateral CSDH	3.43	0.02	1.196-9.819
Antiplatelet	—†	—†	—†
Anticoagulant	0.64	0.69	0.0715-5.842

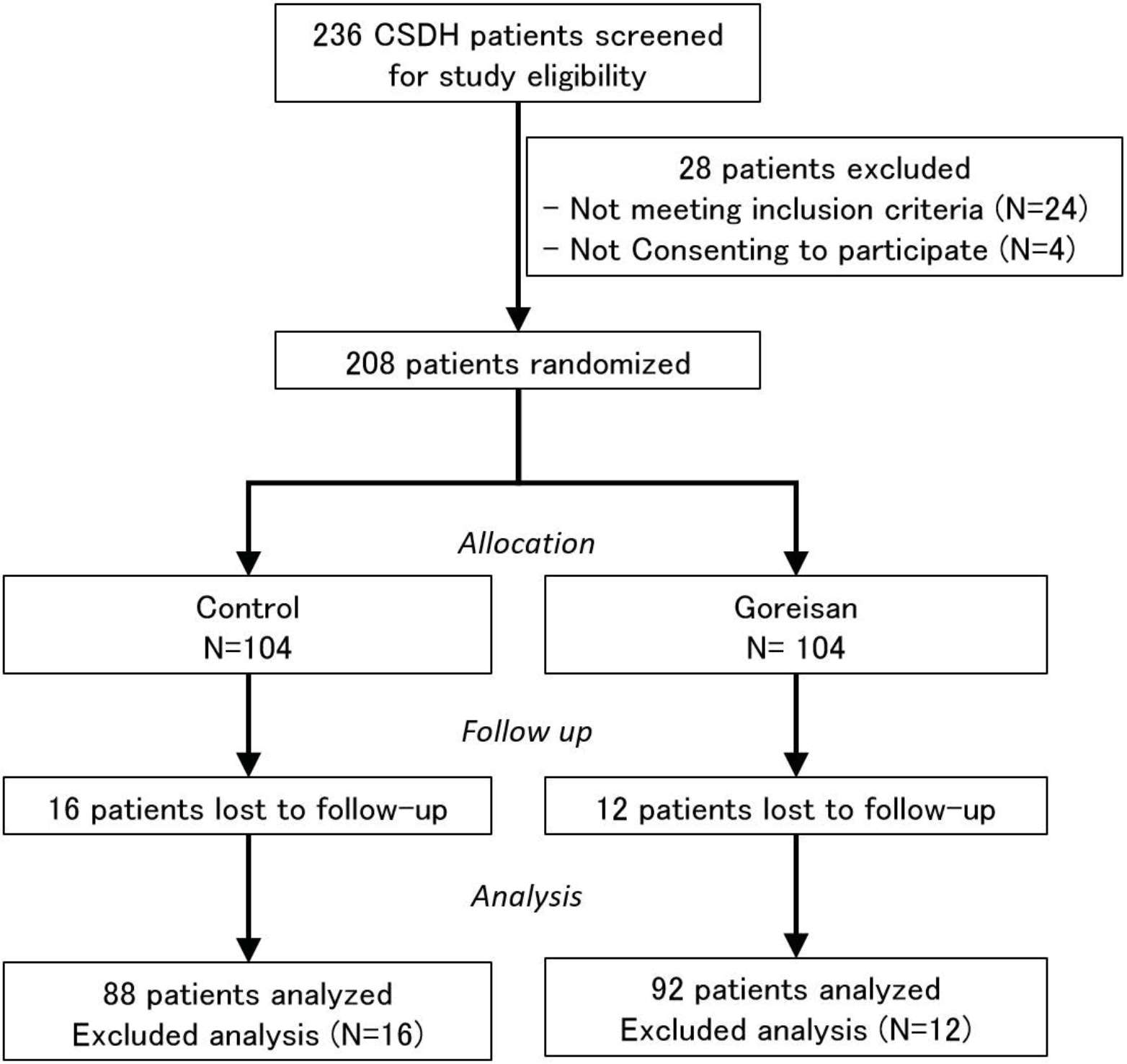
† Could not be calculated because of small number.

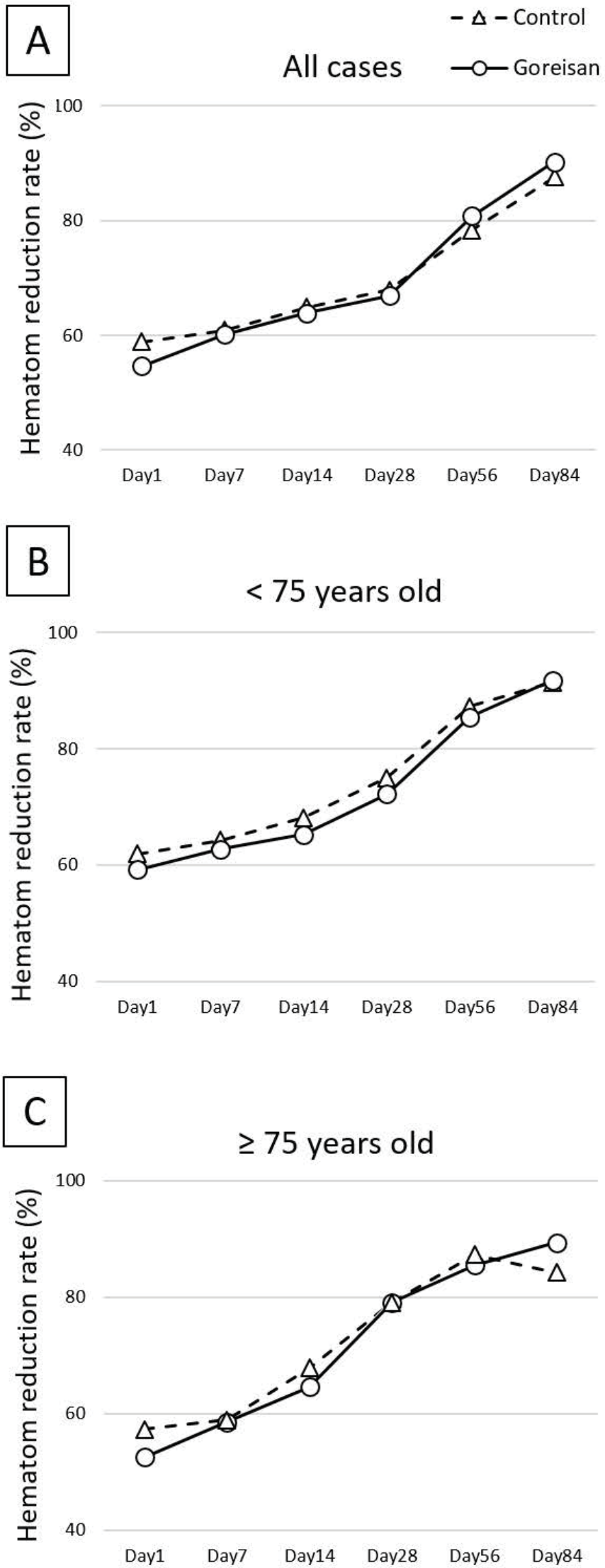
OR, Odd's ratio; CI, confidential interval; CSDH, chronic subdural hematoma

TABLE 5. ASSESSMENTS OF FACTORS AFFECTING CSDH RECURRENCE IN CASES UNDER 75 YEARS OLD

	OR	P	95%CI
Sex (male)	1.39	0.78	0.133-14.430
Goreisan use	0.13	0.07	0.013-1.194
Bilateral CSDH	4.97	0.08	0.843-29.331
Antiplatelet	—†	—†	—†
Anticoagulant	—†	—†	—†

† Could not be calculated because of small number.
OR, Odd's ratio; CI, confidential interval;
CSDH, chronic subdural hematoma


236 CSDH patients screened for study eligibility
28 patients excluded
- Not meeting inclusion criteria (N=24)
- Not Consenting to participate (N=4)
208 patients randomized
Allocation
Control N=104
Goreisan N= 104
Follow up
16 patients lost to follow-up
12 patients lost to follow-up
Analysis
88 patients analyzed
Excluded analysis (N=16)
92 patients analyzed
Excluded analysis (N=12)


A
All cases
Control
Goreisan
Hematom reduction rate (%)
100
80
60
40
Day1
Day7
Day14
Day28
Day56
Day84
B
< 75 years old
Hematom reduction rate (%)
100
80
60
40
Day1
Day7
Day14
Day28
Day56
Day84
C
≥ 75 years old
Hematom reduction rate (%)
100
80
60
40
Day1
Day7
Day14
Day28
Day56
Day84