

Evaluation of Recurrence Factors and Gorei-san Administration for Chronic Subdural Hematoma after Percutaneous Subdural Tapping

Akitake OKAMURA*, Yukihiro KAWAMOTO, Eiichirou SAKODA,
Taro MURAKAMI and Takeshi HARA

Department of Neurosurgery, Hiroshima City Asa Hospital, Hiroshima 731-0293, Japan

ABSTRACT

Recent reports have shown that administration of Gorei-san (Tsumura, Tokyo, Japan) can prevent recurrence of chronic subdural hematoma (CSDH). However, no report has shown its potential, including its correlation with other recurrent clinical factors. We retrospectively evaluated the recurrent factors and the effects of Gorei-san on CSDH using percutaneous subdural tapping. Between April 2009 and February 2012, we performed percutaneous subdural tapping on 160 patients with intact CSDH. Of this population, 125 patients with unilateral hematoma and measurable initial hematoma pressure were included in this study. From April 2010, Gorei-san was routinely administered to patients. Patient characteristics such as age, sex, neurological grading, alcohol, diabetes mellitus, antiplatelet agent, anticoagulant agent, trauma, midline shift on CT images, hematoma volume on CT images, initial hematoma pressure, volume of the removed hematoma, and administration of Gorei-san were analyzed. Recurrence was recognized in 35/125 (28.0%) patients. Multivariate analysis revealed that a greater midline shift on CT images ($p = 0.033$) and initial hematoma pressure ($p = 0.031$) predicted recurrence. Gorei-san was administered to 94/125 (75.2%) patients, but they showed no changes in recurrence (27.7% vs. 29.0%; $p = 1.0$). Among 13 patients for whom Gorei-san administration was started before surgery, CSDH recurrence was reported in only 1 (7.7%). However, the group showed a significantly lower number of recurrent factors. Patients with a greater midline shift in their CT images or higher initial hematoma pressure need close postsurgical observation. The potential of Gorei-san for preventing recurrence of CSDH needs further examination.

Key words: *Chronic subdural hematoma, Recurrence, Gorei-san, Percutaneous subdural tapping*

Although many risk factors for the recurrence of chronic subdural hematoma (CSDH) have been reported^{2,8,11,15,17-19,23}, only a few reports show a potential for intervention, with the exception of surgery^{5,27}. Recent reports have shown that administration of Gorei-san (Tsumura, Tokyo, Japan) can prevent recurrence of CSDH. However, these reports contained only a small number of cases and none examined the effects of multiple factors^{9,10,12,26}.

Percutaneous subdural tapping¹⁾ has been adopted as a standard surgical procedure in our institute for intact CSDH since 2009, and we are free from procedural selection bias. We retrospectively evaluated the recurrent factors and the effects of Gorei-san on CSDH using percutaneous subdural tapping to present the optimal management of CSDH.

MATERIALS AND METHODS

Between April 2009 and February 2012, we performed percutaneous subdural tapping on 160 patients and burr hole surgery on 6 patients with intact CSDH at Hiroshima City Asa Hospital. Of these 166 patients, we excluded those with burr hole surgery (6 patients), bilateral CSDH (22 patients), and unmeasurable initial hematoma pressure (13 patients). Thus, this study included 125 patients with unilateral hematoma and measurable initial hematoma pressure. Gorei-san was routinely administered to the patients from April 2010 as a single 2.5 g dose before mealtime. We examined several risk factors for the recurrence of CSDH, including age, sex, neurological grading, alcohol, diabetes mellitus, antiplatelet agents,

*Corresponding author: Akitake Okamura, MD, Department of Neurosurgery, Hiroshima City Asa Hospital, 1-1, Kabeminami 2-chome, Asakita-ku, Hiroshima 731-0293, Japan

Tel: 082-815-5211

Fax: 082-814-1791

E-mail: akitake-okamura@hotmail.co.jp

anticoagulant agents, trauma, midline shift based on CT images, hematoma volume based on CT images, initial hematoma pressure, volume of removed hematoma, and administration of Gorei-san. The characteristics of the recurrence and the non-recurrence groups were analyzed and then the effect of the time of initiation of Gorei-san administration was also analyzed.

Percutaneous subdural tapping is performed under local anesthesia, as described by Aoki¹¹. The procedure consists of hematoma evacuation, oxygen replacement, and saline irrigation of the hematoma cavity. In this procedure, liquid hematoma ascends through an extension tube when the dura mater is penetrated. Initial hematoma pressure is defined as the height of the hematoma from the openings of the external acoustic meatus when the head is in the median position. Although the original procedure is done at the bedside, we perform this procedure in the operating room.

We used the Markwalder neurological grading system as follows⁷. Our indication for surgery was a Grade 1 or higher, or even Grade 0 if the patient opted for surgery.

Grade 0: patient neurologically normal.

Grade 1: patient alert and oriented; mild symptoms, such as headache; absent or mild neurological deficit, such as reflex asymmetry.

Grade 2: patient drowsy or disoriented with variable neurological deficit, such as hemiparesis.

Grade 3: patient stuporous but responding appropriately to noxious stimuli; severe focal sign, such as hemiplegia.

Grade 4: patient comatose with absent motor responses to painful stimuli; decerebrate or decorticate posturing.

Recurrence was defined as the re-accumulation of hematoma on the operation side requiring a second operation. Hematoma volume was calculated using the formula $A \times B \times C/2$, where A represents hematoma thickness, B represents anteroposterior hematoma length, and C represents craniocaudal hematoma length based on CT images¹⁶.

Univariate analysis was performed using the Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The chi-squared test for trend was also used for neurological grading. Multivariate analysis using stepwise logistic regression was performed to identify factors predicting recurrence. The patients were assigned to 3 groups according to initial time of Gorei-san administration, and the Kruskal-Wallis test was used to assess the differences among groups. *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed using the R software, ver-

sion 2.15.2 (R Development Core Team, www.r-project.org).

Outcomes from the initial 71 patients, including 19 patients with recurrent CSDH, were included in our previous study¹⁵. This study was approved by the Hiroshima City Asa Hospital Institutional Review Board.

RESULTS

Of 125 patients who had received percutaneous subdural tapping for intact unilateral CSDH and with measurable initial hematoma pressure, 35 (28.0%) experienced recurrence. Table 1 illustrates the characteristics of the recurrence and the non-recurrence groups. Univariate analysis revealed that the recurrence group had a significantly greater midline shift on CT images (10.0 mm vs. 6.6 mm; $p = 0.00026$), hematoma volume on CT images (127 ml vs. 102 ml; $p = 0.015$), initial hematoma pressure (14.8 cmH₂O vs. 12.1 cmH₂O; $p = 0.0050$), and removed hematoma volume (126 ml vs. 103 ml; $p = 0.022$). The recurrence group showed a more severe neurological grading, although this characteristic was not statistically significant ($p = 0.084$).

Multivariate analysis revealed that a greater midline shift on CT images (odds ratio [OR] 1.12 mm, 95% confidence interval [CI] 1.01-1.24, $p = 0.033$) and initial hematoma pressure (OR 1.11 cmH₂O, 95% CI 1.10 -1.21, $p = 0.031$) predicted CSDH recurrence (Table 2).

Both the recurrence group and the non-recurrence group were administered Gorei-san equally (74% (26/35) vs. 76% (68/90); $p = 1.0$). Gorei-san was administered to 94/125 (75.2%) patients. Of the 94 patients given Gorei-san, 26 patients recurred (27.7%), and among 31 patients who did not receive Gorei-san, 9 patients recurred (29.0%). Gorei-san thus showed no significant changes in the recurrence rate (27.7% vs. 29.0%; $p = 1.0$). The effect of time of initiation of Gorei-san administration was also analyzed (Table 3). Of the 13 patients who received Gorei-san before surgery during their outpatient visit, only 1 patient recurred (7.7%). Of the 81 patients who were administered Gorei-san after surgery, 25 patients recurred (30.9%). Among the 31 patients who did not receive Gorei-san during their clinical course, 9 patients recurred (29.0%). The differences in recurrence rates among the 3 groups, however, were not statistically significant ($p = 0.23$). On the other hand, the three groups showed differences in the risk factors for recurrence. Those administered Gorei-san before surgery on their outpatient visit showed a significantly milder neurological grading ($p = 0.041$) compared to the other 2 groups. Additionally, the members of this group showed a smaller midline shift on CT images and lower initial hematoma pressure.

Table 1. Characteristics and clinical findings in recurrent and non-recurrent group

	Recurrence Group (n = 35)		Non-recurrence Group (n = 90)		p value
Age (mean ± SD) years	77.6 ± 13.0		80.4 ± 8.4		0.45
Male (%)	22	(63%)	65	(72%)	0.39
Alcohol (%)	8	(23%)	23	(26%)	0.82
Diabetes Mellitus (%)	5	(14%)	10	(11%)	0.76
Antiplatelet agent (%)	6	(17%)	21	(23%)	0.63
Anticoagulant agent (%)	4	(11%)	12	(13%)	1
Trauma (%)	20	(57%)	50	(56%)	1
Gorei-san Administration	26	(74%)	68	(76%)	1
Neurological grade (Markwalder)					0.084
Grade 0 (%)	2	(6%)	7	(8%)	
Grade 1 (%)	11	(31%)	41	(46%)	
Grade 2 (%)	19	(54%)	38	(42%)	
Grade 3 (%)	2	(6%)	4	(4%)	
Grade 4 (%)	1	(3%)	0	(0%)	
Midline shift (CT) (mean ± SD) mm	10.0 ± 4.7		6.6 ± 4.3		0.00027
Hematoma volume (CT) (mean ± SD) ml	127 ± 50		102 ± 48		0.015
Initial hematoma pressure (mean ± SD) cmH ₂ O	14.8 ± 5.2		12.1 ± 4.4		0.0050
Removed hematoma volume (mean ± SD) ml	127 ± 47		103 ± 41		0.022

Univariate analysis was performed using the Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The chi-squared test for trend was also used for neurological grade.
SD, standard deviation

Table 2. Multivariate analysis for risk factors for recurrence of CSDH

Variable	Adjusted OR	95% CI for Adjusted OR	p value
Midline shift (CT), mm	1.12	1.01-1.24	0.033
Initial hematoma pressure, cmH ₂ O	1.11	1.01-1.21	0.031
Removed hematoma volume, ml	1.01	0.99-1.02	0.099

Multivariate analysis using stepwise logistic regression was performed to identify factors predicting recurrence.

CI, confidence interval; CSDH, chronic subdural hematoma; OR, odds ratio

Although the 2 parameters did not differ among the 3 groups ($p = 0.06$, $p = 0.20$, respectively), our multivariate analysis showed that these factors were strongly associated with CSDH recurrence.

DISCUSSION

The rate of postoperative CSDH recurrence ranges from 5% to 30%^{2,5,8,11,15,17-19,23}. Many factors for CSDH recurrence have been identified and cat-

egorized into four groups, namely; patient background, hematoma character, postsurgical administration, and surgical option¹⁷. Our results showed that the recurrence group had a significantly greater midline shift on CT images, hematoma volume on CT images, initial hematoma pressure, and removed hematoma volume. Additionally, the recurrence group had a more severe neurological grading, although the trend was not statistically significant. These results are

Table 3. Characteristics and clinical findings according to initial time of Goreisan administration

Timing of starting Gorei-san	Before surgery (n = 13)	After surgery (n = 81)	No administration (n = 31)	p value
Recurrence (%)	1 (7.7%)	25 (30.9%)	9 (29.0%)	0.23
Age (mean ± SD) years	79.8 ± 5.7	80.4 ± 10.9	77.3 ± 8.4	0.076
Male (%)	10 (76.9%)	55 (67.9%)	22 (71.0%)	0.79
Alcohol (%)	6 (46.2%)	21 (25.9%)	4 (12.9%)	0.063
Diabetes Mellitus (%)	1 (7.7%)	10 (12.3%)	4 (12.9%)	0.88
Antiplatelet agent (%)	2 (15.4%)	22 (27.2%)	3 (9.7%)	0.11
Anticoagulant agent (%)	1 (7.7%)	12 (14.8%)	3 (9.7%)	0.65
Trauma (%)	8 (61.5%)	44 (54.3%)	18 (58.1%)	0.86
Neurological grade (Markwalder)				0.041
Grade 0 (%)	1 (7.7%)	4 (4.9%)	4 (12.9%)	
Grade 1 (%)	10 (76.9%)	34 (42.0%)	8 (25.8%)	
Grade 2 (%)	2 (15.4%)	39 (48.1%)	16 (51.6%)	
Grade 3 (%)	0 (0%)	4 (4.9%)	2 (6.5%)	
Grade 4 (%)	0 (0%)	0	1 (3.2%)	
Midline shift (CT) (mean ± SD) mm	5.2 ± 2.4	8.2 ± 4.8	6.9 ± 4.9	0.059
Hematoma volume (CT) (mean ± SD) ml	96.5 ± 36.9	118 ± 52.1	88.8 ± 39.3	0.0055
Initial hematoma pressure (mean ± SD) cmH ₂ O	10.5 ± 3.3	13.0 ± 4.2	13.4 ± 6.3	0.20
Removed hematoma volume (mean ± SD) ml	97.2 ± 43.4	117.9 ± 44.5	93.7 ± 37.4	0.012

The Kruskal-Wallis test was used to assess the differences among groups.

consistent with previous reports^{15,19)} and thus ensure the validity of the present study.

Patient background and hematoma character cannot be intervened for patients' specific problems. For example, discontinuation of antiplatelet and anticoagulant agents brings an unacceptable risk for systemic thrombotic events because the follow-up period needs several months for CSDH. Therefore, patients who possess these factors require close observation during their outpatient visits due to the difficulty of risk reduction.

Etizolam, ibudilast, steroids, angiotensin converting enzyme inhibitors, Gorei-san, and Saireito have been reported as recurrence-preventing agents for CSDH^{3,10,12,14,20,24-26,28)}. Gorei-san has been associated with minimal adverse effects, and we have administered it since 2010 to decrease CSDH recurrence. This report considers 94 patients who received Gorei-san and discusses its recurrence-preventing effect.

Gorei-san inhibits aquaporin-4 (AQP4)⁴⁾, which is expressed on the outer membrane of chronic subdural hematoma²⁴⁾. Most reports on the effects of Gorei-san on CSDH recurrence are based on case series, and no report has statistically proved

its actual effect on CSDH recurrence^{9,10,12,26)}. The current report shows no recurrence-preventing effect of Gorei-san. Among the 13 patients who received Gorei-san before surgery during their outpatient visit only one patient recurred, but they also showed a milder neurological grading, smaller midline shift on CT images, and lower initial hematoma pressure. This result may derive from appropriate timing of surgery. Further investigation is needed to assess the clinical effectiveness and the mechanism of action of Gorei-san.

The surgical options can be intervened in terms of timing and procedure. For neurologically normal patients, deferment of surgery may be beneficial because a mature hematoma reduces the recurrence rate for CSDH¹³⁾. However, the decision-making process of whether to perform or defer surgery may be difficult when only a slight neurological deficit is recognized. The results of this study showed that patients with a smaller hematoma volume and lower neurological grade were associated with a lower CSDH recurrence rate. Prompt surgery may be recommended when a hematoma worsens or when a slight neurological

deficit is detected.

While burr hole surgery has been performed worldwide as a standard procedure for CSDH²⁷⁾, percutaneous subdural tapping has also been commonly performed¹⁾. We selected percutaneous subdural tapping as a first-choice procedure because it is less invasive and for ease of perioperative control. Although a higher CSDH recurrence rate has been reported with percutaneous subdural tapping²⁷⁾, we consider this procedure beneficial in terms of the shorter time to patient discharge, which is usually 1 day after surgery, and because no sutures are required.

Percutaneous subdural tapping allows noninvasive measurement of initial hematoma pressure²²⁾, which we reported as one of the risk factors for CSDH recurrence¹⁵⁾. In this report, we evaluated a larger number of cases, which, in turn, further increases its statistical significance to CSDH recurrence. Because intracranial pressure increases brain elastance (dP/dV) and a high elastance brain tends to re-expand poorly^{2,6)}, initial hematoma pressure may thus indirectly represent brain-surface elastance¹⁵⁾. However, Sundstrøm et al did not find an association between repeat surgery and CSDH pressure in burr hole surgery²¹⁾. Further studies associated with initial hematoma pressure are needed.

Our study has the limitations of a retrospective design and a small number of cases. The compatibility of recurrent factors may be weak because the recurrent factors have been mainly studied in relation to burr hole surgery and not percutaneous subdural tapping.

CONCLUSIONS

Our results indicate that patients with a greater midline shift in their CT images or higher initial hematoma pressure need close postsurgical observation. The current report shows no recurrence-preventing effect of Gorei-san, and further investigation is needed to assess the clinical effectiveness and action mechanism of Gorei-san.

CONFLICT OF INTEREST

The authors have no personal, financial or institutional interest in any of the drugs, materials, or devices mentioned in the article.

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