Kampo Medicine - Current Research

Effect of Goreisan on Chronic Subdural Hematoma —From the Goreisan Symposium 2010"—

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Introduction

Chronic subdural hematoma (hereafter CSDH) is a gradual accumulation of blood below the dura mater over more than three weeks, generally after a minor head injury. The hematoma is encapsulated, in which old liquefied blood is found. In recent years, increases in the number of the elderly and image analyzing examinations such as CT/MR images have contributed to an improved detection of CSDHs, for which surgery is a recognized and established method of treatment. However, even if CSDH shows up on CT images, some patients do not exhibit the signs and symptoms indicative of CSDH or merely show very mild symptoms. There are also patients who do not desire an operation. Moreover, the recurrence of CSDH after surgery occurs in 10 to 20%[12,19,23] of patients. Patients who are prone to bleeding or have complications are hesitant to undergo surgery. On the other hand, it must be kept in mind that CSDHs may heal spontaneously,[3,16] which is said to occur in 2.8 to 21% of patients with mild mass effect who do not show signs and symptoms or have very mild symptoms.[4,15,17] For this reason, non-operative treatment may be selected depending on the patient. In terms of non-operative procedures for CSDHs, hyperosmolar therapy[8,22] with mannitol and steroid hormone therapy[1,2,18] have been reported. Recently, practitioners in the field of neurosurgery have had another look at Kampo treatment and treatment of CSDH with Kampo medicines [9,10,14,21,15] for CSDHs has occasionally been seen. However, only a few case reports have been published and Kampo treatment has not been established for CSDH.

Since January 2006, we have used *goreisan* for some patients with CSDH and studied its efficacy.[11] This study reports the efficacy of the medicine for CSDH obtained through conducting CTs with long-term follow-up.

Subjects and Methods

As stated above, surgery is an accepted treatment for CSDH. However, we used *goreisan* for CSDH in the following types of patients (with their consent and that of their family members): (1) those who did not desire surgery, (2) those who did not exhibit signs or symptoms, or very mild symptoms, and (3) those who were prone to bleeding or presented with systemically bad health conditions. The subjects enrolled in the trial were 22 patients with CSDH (the number of hematomas was 27). Their ages ranged from 50 to 98, with 18 subjects 70 years old or above. Nine subjects had right-sided hematomas, 8 had left-sided, and 5 had bilateral. Fourteen subjects had experienced trauma. Two subjects developed recurrent CSDH after surgery as the first treatment. At the start of treatment after CSDH developed, 8 patients presented without any symptoms, 7 had headaches or dizziness, and 5 had mild motility disorder. In terms of complications, 5 patients had dementia. Each subject had one of the following complications: diabetes mellitus, dialysis, cerebral infarction, cerebral hematoma, terminal colon cancer, or jaundice.

The CT findings were examined for the maximum width of the hematomas and their CT density. Twenty hematomas, the largest number, had a maximum width of 10 to 19 mm just before treatment, 4 hematomas had 20 to 25 mm, and 3 had 9 mm or less. The CT density at the start of treatment with *goreisan* was evaluated as iso, high, or mixed in 14 hematomas and low in 13 hematomas. The period of follow-up by CT was 4–29 weeks (Table 1).

	case	age/sex	location	hematoma density	maximum thickness of hematoma before (administration of Gorei-san)	after	follow (weeks)
1.	T T	87/F	L	mixed	18	0	13
2.	K H	79/F	L	mixed	20	0	14
			R	mixed	10	0	7
3.	K Y	95/M	L	mixed	25	12	29
4.	K T	62/M	R	mixed	15	0	6
5.	RS	50/M	L	mixed	18	12	4
6.	SY	81/F	L	mixed	10	0	8
7.	SK	93/M	L	mixed	12	5	8
			R	iso	10	0	8
8.	IM	89/F	L	iso	15	0	11
9.	KS	74/F	R	iso	18	8	7
10.	AY	59/M	L	high	20	10	7
			R	high	8	2	7
11.	TM	66/M	R	high	15	0	20
12.	T K	74/M	R	low	20	12	24
13.	N T	78/M	L	low	15	10	3
14.	HF	85/F	R	low	7	0	4
15.	KK	83/F	L	low	8	0	8
16.	AS	92/M	L	low	15	8	17
			R	low	10	0	17
17.	NK	82/M	R	low	10	0	10
18.	HT	72/M	R	low	18	7	19
19.	HY	78/M	R	low	10	3	8
20.	A T	80/F	L	low	15	15	24
			R	low	12	12	24
21.	IT	75/M	L	low	13	12	4
22.	YI	98/M	R	low	15	15	6

Table 1. Summary of cases with chronic subdural hematomas treated with *goreisan*..

TSUMURA *Goreisan* Extract Granules (Extract of *goreisan*, 7.5 g divided into 3 doses in three times a day, basically before meals) was orally administered to all patients with CSDH regardless of the patients' pathological conditions from the Kampo perspective. The patients who were able to take the medicine for four weeks or more were assigned to the study. With the disposition of the primary doctor, hemostatic agents (tranexamic acid and carbazochrome sodium sulfonate) were used in combination for 7 non-selected subjects. The effectiveness of *goreisan* was assessed based on whether the hematoma had resolved or decreased in size as determined by a CT. Results (Figure 1, 2)

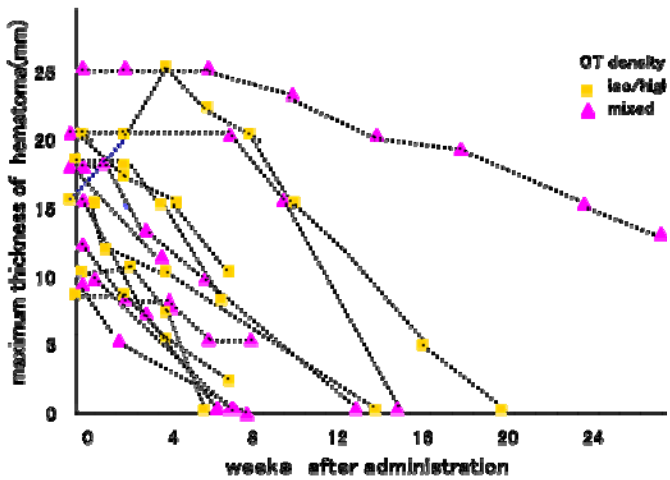

Figure 1. Change in maximum thickness of hematomas with iso/high (■) or mixed (▲) density on a CT after administration of *goreisan*.

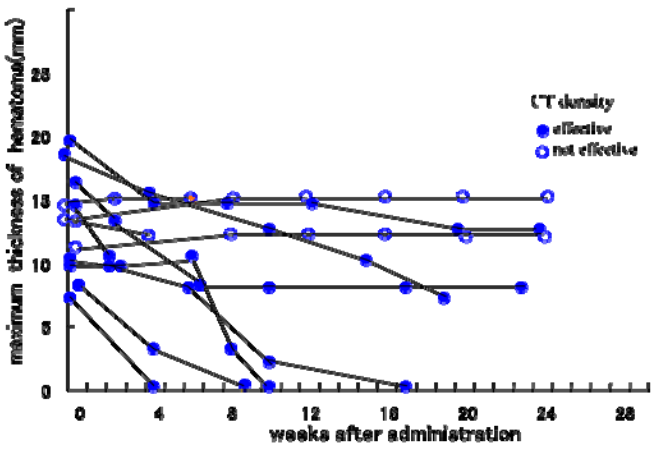

Figure 2. Change in maximum thickness of hematomas with low density on a CT after administration of *goreisan*. ● effective cases ○ineffective cases

Results

The treatment with *goreisan* resulted in a high level of improvement in 23 (85%) of 27 CSDHs, including hematomas that had disappeared or shrunk, whereas treatment was ineffective for 4 CSDHs (15%) since they remained unchanged after administration of the medicine. In the 23 CSDHs responsive to *goreisan*, 12 hematomas disappeared and 11 shrank (Table 1). In 17 CSDHs (74%) out of the 23 CSDHs that showed improvement, the hematomas began to shrink within four weeks after administration and then they gradually shrank further or disappeared. Of the 12 CSDHs that disappeared, 10 took less than 14 weeks to disappear. None of the hematomas grew after administration of *goreisan* for four weeks or more, so there were also no CSDH cases that needed surgery. In the meantime, there were no adverse effects associated with the medication in any of the cases.

We studied the time-dependent changes in the density level of hematomas after administration of *goreisan*. The medicine was effective in all 14 CSDHs with density levels of mixed or high/iso on a CT before treatment. That is, 14 CSDHs all improved with 8 resolved hematomas and the other 6 shrank (Figure 1). Of the 13 CSDHs with lower density on a CT, 9 showed an improvement with the hematoma disappearing or shrinking, while 4 CSDHs remained unchanged and non-responsive to the administration of *goreisan* (Figure 2). The results of the study show that CSDHs with hematoma density levels of iso/high or mixed were more responsive to *goreisan*. We consider that further research with many more patients will be needed.

A representative case

Case: K. H. (Figure 3)

79 years old, female: Bilateral chronic subdural hematoma (CSDH) (L>R).

On November 19, X year, the patient fell down and banged her head. On January 10 of the following year, she visited our facility, complaining of a mild gait disorder. CT examination revealed a bilateral CSDH (right: 8 mm, left: 5 mm) with iso density and the administration of hemostatic agents (carbazochrome sodium sulfonate 3 tablets and tranexamic acid 3 tablets a day) was commenced. A CT scan during a follow-up visit on February 7 indicated enlarged hematomas, having a maximum width of 10 mm on the right and 20 mm on the left, with mixed density on both sides. For this reason, *goreisan* 7.5 g (divided into 3 doses) was commenced with the hemostatic agents. The hematomas began to decrease in size after seven weeks: the right hematoma disappeared and the left one remained unchanged with a maximum width of 20 mm. However, the extent of the hematoma tended to decrease. On April 20, the density decreased to low and shrinkage was obvious. In the 14th week, the CSDH dissolved completely (Figure 3). The gait disorder also disappeared and she recovered her normal gait.

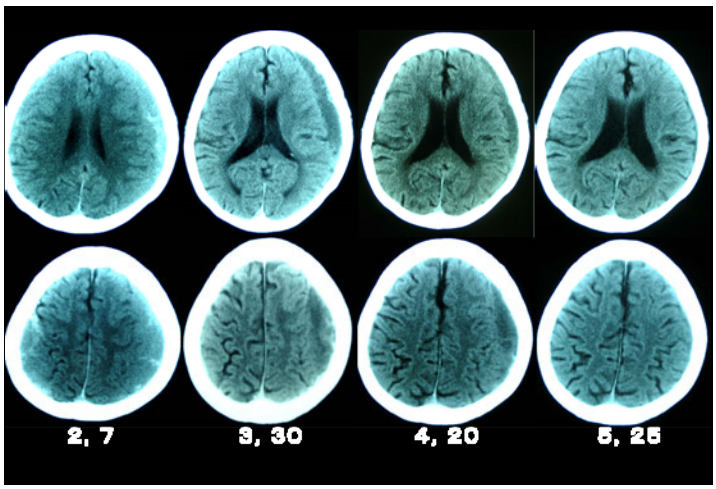

Figure 3. CT scan of case 2 (K.H.) before and after administration of *goreisan*. 06,2,7; before administration, 06,3,30;, 06,4,20;, and 06,5,25; 7, 10 and 14 weeks after administration of *goreisan*.

Discussion

A widely-accepted theory[13] of the etiology and growth mechanism of CSDH is that hematoma enlargement occurs through blood leakage and constant or intermittent bleeding from neovascular vessels in a false membrane into the

capsule and the cavity of a hematoma in order to enhance local fibrinolytic activity inside the hematoma and its outer membrane. On the other hand, the old theory of osmosis pressure is still prevalent, but the cause is not known in detail. As nonsurgical management of CSDHs, the use of diuretics or steroids has been claimed to be effective. More specifically, effectiveness has been reported for mannitol 20% osmotherapy by Suzuki, et al.[22] and Kinjyo, et al.;[8] the combination therapy with steroid hormone and 50% glucose by Ambrosetto, et al.; [1] and the steroid-alone hormone therapy by Glover, et al.[2] and Rudiger, et al.[18]

In recent years, CSDH has occasionally been treated using the aquaretic Kampo medicines of "*goreisan*" and "*saireito*." Seki, et al.[21] used *goreisan* in 8 cases of CSDH and obtained improvement in 4 cases. Onuki[10] and Ueno, et al.[25] reported that hematomas had resolved in all cases with the combination treatment of *goreisan* and prednisolone. Muramatsu, et al.[14] reported the effectiveness of *goreisan*; they used the Kampo medicine alone in 11 cases and in 10 of the cases, the hematomas disappeared or shrank. Kitahara[9] had favorable results using *saireito*, which is made up of two formulae: "*goreisan*" and "*shosaikoto*". Kitahara reported that improvement could be obtained even if administration of antithrombogenic agents continued.

Since 2008, a number of reports on the treatment of initial and recurrent CSDHs with *goreisan* have been published and all of these reports suggest its usefulness.

We treated 22 cases of CSDHs (27 hematomas): *goreisan* alone was administered in 15 cases, and *goreisan* and hemostatic agents were administered in combination in 7 cases, resulting in effectiveness in 23 hematomas — 12 hematomas were resolved and the other 11 shrank. We believe this improvement was due to the effectiveness of *goreisan* rather than spontaneous healing. This is based on the following: (1) cases that had a tendency for the hematomas to grow before the administration of *goreisan*, and many cases that did not have a tendency for the hematomas to shrink were included; (2) there were cases that showed a tendency for the hematomas to shrink from an early stage after the administration of *goreisan*; and (3) higher rates of effectiveness of the treatment were shown compared to the frequency of spontaneous resolution of CSDHs in the past. In general, the hematomas started to shrink three to four weeks after the start of administration of *goreisan*, and they disappeared within 14 weeks after administration in most cases. There were only a few cases in which shrinkage started within 2 weeks. To assess the effect of CSDH treatment with this Kampo medicine, a continued administration for at least three to four weeks or more is required.

Goreisan, which consists of the five crude drugs of arisma rhizoma, tuckahoe, polyporus sclerotium, atractylodes lancea rhizoma, and cassia twig, is a typical diuretic Kampo medicine. This diuretic medicine clinically has anti-edema action[6,20] and is generally prescribed for pathological conditions such as headache, cerebral edema, ascites, gastroenteritis, ophthalmic disorders, hangover, and pain. Although the mechanism of the effect of the medicine on CSDHs is unclear, the diuretic actions may be the main contributing factor as the usefulness of mannitol osmotic diuretic agents has been reported.[8,22]

Unlike the diuretic agents used in Western medicine such as mannitol, this Kampo diuretic medicine is characterized by the role of antidiuretic actions in a hydrated state and the role of regulating the actions of water metabolism in a hyperhydrated state.[24] It is said that the diuretic mechanism is involved in the inhibition of water channel aquaporins (AQPs), which increase water permeability in cell membranes, whereas *goreisan* inhibits the action of the aquaporins.[5,20] According to Isohama,[5] the constituent crude

drugs of *goreisan*, especially atractylodes lancea rhizoma, polyporus sclerotium, and tuckahoe (poria sclerotium), inhibit cell membrane water permeability. In particular, AQP4, which is most abundant in the brain but also distributed in large numbers in astroglia cells adhered to capillary endothelial cells, is said to be involved in water permeability.[6] Atractylodes lancea rhizoma, the crude drug of the atractylodes family contained in *goreisan* used for CSDH treatment, has been used in many medicines as well as the ones used in our experiment. Ueno, et al.[25] have also reported that *goreisan* containing atractylodes ovatae rhizoma was effective for CSDHs.

Our experiment suggests that *goreisan* is more effective if the hematoma density on a CT is iso, high, or mixed, compared to low density. The reasons, however, are not known in detail. Meanwhile, in the cases of relatively new hematomas with iso density or high density, hematoma capsules often show the sinusoidal channel layer, which is filled with capillaries. On the other hand, in the hematomas with low density, old bleeding to a certain extent can possibly be found with relatively fewer vessels. This means that CSDHs with low density have a comparatively long course and the vessels in the hematoma capsule may be relatively scarce. So, it is possible that AQP4 surrounding the vessels are also relatively reduced, causing the reduced inhibition of water permeability.

goreisan is orally administered for treatment, unlike mannitol or steroid drugs, and it did not cause any adverse effects in the cases in our study[11] and in other reported cases.[10,14,21,24,25] We consider *goreisan* to be an easy-to-use medicine and useful for the future nonsurgical management of CSDHs.

Conclusion

1. *Goreisan* was administered in 22 cases of CSDH with 27 hematomas for four weeks or more and the results showed it was effective in 23 hematomas (85%) with the hematomas disappearing or shrinking.
2. *Goreisan* did not cause any obvious adverse effects in the cases in our own study and in reported cases to date. It is a safe and useful drug for nonsurgical therapy of chronic subdural hematomas.

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