Kampo Medicine for Neurosurgery

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Kampo is being reappraised as complementary alternative medicine due to emerging clinical evidence from randomized controlled studies and partial elucidation of the mechanism of actions from basic studies. In this paper we introduce our clinical experience and some clinical reports to describe the effectiveness of two widely prescribed Kampo extract in neurosurgery: goreisan for the treatment of chronic subdural hematoma, and yokukansan for dementia.

Key words: goreisan, chronic subdural hematoma, yokukansan, dementia

Introduction

Kampo medicine is traditional Japanese medicine that evolved distinctly from its origin, traditional Chinese medicine, over the past 1800 years. While Kampo prospered during the Edo period, the adoption of western (German) medicine in 1869 by the Meiji government led to its gradual decline. Juntendo University was a renegade at the time for establishing a western medicine school 30 years prior to Japanese government’s adoption of western medicine. Despite the historical setbacks, a renewed appreciation for Kampo is on the rise in large part due to clinical and basic research generating robust evidence on why and how Kampo actually work. In this paper we will highlight two Kampo extract, goreisan and yokukansan, which are frequently used in neurosurgery.

1. Goreisan for chronic subdural hematoma

Chronic subdural hematoma (CSDH) can be treated by relatively simple surgery; however, the recurrence rate is about 10%1), and a single surgical intervention may not be curative. Meanwhile, conservative therapy with mannitol and steroids has been studied in the past as there are cases of spontaneous absorption2). In recent years, the prevention of recurrence and exacerbation by goreisan has been increasingly reported3)-5), and we have witnessed many such cases as well. In this report, we’d like to interweave two forms our experience and some published reports.

CSDH is dark–red flowing hematoma that is trapped between the inner layer of the dura mater (outer membrane) and the arachnoid mater (inner membrane). Typically, a hematoma gradually increases in size between three weeks and two to three months after a minor trauma, and produces symptoms by compressing the brain. Because the hematoma lacks coagulation factors, it does not
solidify even if left in open air\textsuperscript{6}.

The pathogenesis of CSDH has been proposed as follows. A minor trauma causes slight hemorrhage immediately beneath the dura mater where a part of the arachnoid membrane is also injured and the cerebrospinal fluid and blood from the hemorrhage are mixed and trapped beneath the dura. Thereafter, an outer membrane on the dura side and an inner membrane on the arachnoid side are at once formed. In order to liquefy and absorb the blood clot beneath the dura mater, local fibrinolysis is activated in the outer membrane. In spite of the temporary clotting and hemostasis, clots are re-lysed and bleeding recurs. The leakage of persistent blood components from the sinusoidal vessels of the outer membrane is considered to contribute to hematoma expansion\textsuperscript{6}. It is thought the hematoma expansion and absorption is balanced, however if it tends to expand, it becomes symptomatic, and if it tends to absorb, it may shrink naturally\textsuperscript{7}.

\section*{Goreisan}

Goreisan is a representative Kampo medicine for regulating and dispersing water accumulation. It is composed of takusha (\textit{Alismatis Rhizoma}), chorei (\textit{Polyporus}), bukuryo (\textit{Hoelen}), sojyutsu (\textit{Atractylodis Lanceae Rhizoma}), and keishi (\textit{Cinnamomi Cortex}). Classical indications include dry mouth, urinary retention, and edema, yet many modern chronic conditions may not present these signs and symptoms. For example, diarrhea, rhinitis, spontaneous perspiration and any disorders of body fluid secretion, headache, dizziness, and palpitations are also signs and symptoms of water imbalance that may indicate the use of goreisan\textsuperscript{8}.

Some aspects of its mechanism of action have been elucidated. For instance, Isohama\textsuperscript{9} has revealed that goreisan activates aquaporin (AQP), a selective water channel that allows only water molecules present in the cell membranes to pass through. Goreisan has been shown to inhibit water permeability of a cell membrane in a dose-dependent manner and induce a similar effect as that of mercuric ion, a typical AQP inhibitor, at doses 1.0 mg/dl and greater. Among the 13 AQP isoforms, goreisan has been confirmed to inhibit the activity of AQP4, a highly expressed channel in the brain.

\section*{Case report}

Patient: 81 year old male  
Chief complaint(s): Disturbed consciousness, right hemiparesis.  
Past history: none.  
Present illness: On February Y, 201X, the patient was transported to ER due to disturbed consciousness and right hemiparesis. And head CT revealed bilateral CSDH. So he was hospitalized to undergo emergency operation.  
Consciousness: Japan Coma Scale (JCS): II-10, Glasgow Coma Scale (GCS) = E3V3M5.  
Physical findings: Height, 164 cm; body weight, 67 kg; BT, 36.0\degree C; BP, 153/100 mmHg; HR, 87 bpm and regular; right hemiparesis, 3/5 on Manual Muscle Testing (MMT).  
Blood test: CBC and blood chemistry including coagulation factors within normal limits.  
Head CT: Bilateral CSDH with mild midline shift due to compression from thickened left hematoma. Sulci of the right brain are visible (upper part of Figure-1).  
Clinical course: Operation was performed on the day of admission to relieve symptomatic CSDH. Burr hole drainage was performed only on the left side under local anesthesia despite the bilateral CSDH. And a drainage was placed subdural space without irrigation.  
This was because midline shift due to compression from the left side was mild, and sulci of the right brain was visible.  
The total volume of SDH was 140 ml after surgery. Consciousness level improved to GCS = E4V5M6 and right hemiparesis improved to MMT5. The drain was removed after confirming improvement in both neurological findings and brain imaging. Goreisan extract (TSUMURA) was prescribed at a dosage of 7.5 g/day to prevent recurrence of left CSDH and improve right CSDH. The patient discharged to home on post-operative day 7 with a 30-day prescription of goreisan. At the one month follow-up examination, the patient had not been worsening symptoms and head CT showed steady improvement of left CSDH. The density of right CSDH transformed to near the density of the brain parenchyma with a slight reduction in thickness. The patient continued goreisan for another month, and head CT showed complete resolution of left CSDH at two months.
after surgery. Right CSDH changed from high to iso
density and shrank further, suggesting continued
improvement (bottom part of Figure-1).

Literature review of goreisan
Okamoto, et al. 3) retrospectively analyzed the
recurrence rate of 171 CSDH patients who under-
went surgery after 2010. Thirty-nine patients
treated by burr hole surgery alone (“surgical
group”) were compared to 132 patients who
received goreisan after the burr hole surgery
(“goreisan” group). The postoperative recurrence
rates were 15.4% and 5.3% (surgical group vs
goreisan group) with a statistically significant
difference between the two groups.

Yasunaga 10) performed a propensity score match-
ing of Diagnosis Procedure Combination (DPC)
data to analyze the reoperation rate and total
inpatient cost of CSDH patients (goreisan users
group vs non-users group) and thereby determine
the clinical effectiveness of goreisan. Among the
3,879 matched pairs (n=7,758), there were no
significant differences in background characteris-
tics, reoperation rates were 4.8% and 6.2%, and
mean inpatient costs were 643,000 JPY vs 671,000
JPY (goreisan users group vs non-users group).
Furthermore, a significant correlation was detected
between the reduction in reoperation rate and
post-operative administration of goreisan after
homogenizing the background factors of the two
groups via the propensity score matching method.

Given that CSDH may spontaneously resolve, the
efficacy of goreisan if given alone should be viewed
with discernment. Nevertheless, there are many
neurosurgeons who have experience of its clinical
effectiveness, and statistically it has been shown to
prevent recurrence. For these reasons, goreisan
should become a sensible treatment option to
prevent recurrence and exacerbation of CSDH.

2. Yokukansan for behavioral and psychological
symptoms of dementia
In this section, we would like to discuss yokukan-
san for the treatment of dementia in light of its
prevalence and growing impact in a rapidly aging
society. There are the three dominant types of
dementia with Alzheimer’s disease (AD), vascular
dementia (VaD), and dementia with Lewy bodies
In all three types of dementia, cerebrovascular disorders are thought to be involved to varying degrees, such that dementia is now presumed to be a mixed disease with multiple etiologies.

Although etiologically diverse, the symptoms of dementia can be broadly categorized into three types: cognitive disorder that comprises the “core” symptoms, behavioral and psychological symptoms of dementia (BPSD) that constitute “peripheral” symptoms, and neurological and physical symptoms. The symptoms of dementia severely compromise the patient’s activities of daily life and social life and are major causes of diminished quality of life.

While yokukansan is commonly prescribed for BPSD in neurosurgery, there are many instances of broader applications such as hospital-induced delirium in elderly patients and excitability and agitation in frontal lobe symptoms after a head trauma. We will now highlight two studies of yokukansan for BPSD (as BPSD has become one of the most vibrant areas of Kampo research).

Yokukansan is indicated for the treatment of pronounced irritability, agitation and frequent displays of temper. The original indication is childhood convulsions and it is co-administered to the mother and child according to the classical kampo article. In modern practice, yokukansan is prescribed to patients with overexcitability and restless sleep. Yokukansan is composed of seven crude drugs: saiko (Bupleuri Radix), kanzo (Glycyrrhiza Radix), toki (Angelicae Radix), senkyu (Cnidii Rhizoma), soujyutsu (Atractylodis Lanceae Rhizoma), chotoko (Uncariae Uncis Cum Ramulus), bukuryo (Poria). Chotoko has sedative and antispasmodic effects, and together with saiko and kanzo relaxes tension and calms nervousness. Traditional indications include neurosis, insomnia, childhood night crying, night terrors, hysteria, and epilepsy.

The wisdom behind the mother-offspring co-administration is in leveraging the emotional synchronization that naturally occurs between a mother and child, more so than an attempt to administer yokukansan through breastmilk. Some physicians today who have embraced this clinical pearl and have applied it to the relation between a patient and caregiver.

Behavioral and psychological symptoms of dementia (BPSD) include agitation, irritability, excitability, disinhibition, hallucination, delusion, depression, anxiety, apathy, and abnormal eating behaviors. Clinically, yokukansan is considered most effective for symptoms related to overexcitability.

Literature review of yokukansan

Basic research on yokukansan has witnessed rapid progress in the past ten years, spurred in part by a clinical report published in 2005 by Iwasaki et al. They conducted an observer-blinded randomized controlled study in which 52 patients with Alzheimer’s disease (AD), vascular dementia (VaD), or dementia with Lewy bodies (DLB) were randomly assigned to either the yokukansan group (n = 27) or the control group (n = 25). BPSD were evaluated by the Neuro-Psychiatric Inventory (NPI) and activities of daily living were assessed by the Barthel Index (BI). The results from the study showed that both outcome measures improved significantly from baseline to post-treatment in the yokukansan group, whereas no improvements were observed in the control group.

In addition, Mizukami et al. conducted a multicenter, randomized crossover study in 106 patients with mild AD and DLB. Patients were randomly assigned to either group A (4-week yokukansan treatment followed by 4-week no-treatment period), or group B (4-week no-treatment period followed by 4-week yokukansan treatment). No other psychiatric medications were administered during the yokukansan treatment. The results from the study showed that NPI improved significantly during yokukansan treatment compared to the no-treatment period in both groups. In particular, delirium, hallucination, impatience, aggressiveness, depression, anxiety, and irritability markedly improved. Although the no-treatment period did not result in any improvement, the authors found that group A did not relapse after discontinuation of yokukansan, suggesting the likelihood of a positive carryover effect.

No serious side effects were noted in both studies, and yokukansan treatment appeared to be safe and effective. The inhibition of neuronal hyperactivity
through a partial agonist action and upregulation of 5-HT1A receptors\(^{16}\) and a downregulation of 5-HT2A receptors\(^{17}\) have been cited as the mechanistic underpinnings of yokukansan in BPSD.

Possible side effects of yokukansan include pseudoaldosteronism and associated hypokalemia, hypertension and edema and the accumulation of glycyrrhizic acid in kanzo has been found to cause these effects.

**Conclusion**

We have woven our case report with data from published reports on the effectiveness of two frequently used Kampo extract in neurosurgery.

**Acknowledgments**

The authors declare no conflict of interest and financial support.

**References**


