Kampo Medicine – Current Research

Effectiveness of Goreisan for Eliminating Brain Edema due to Intracranial Malignant Brain Tumors

Akimune Hayashi, M.D.
Department of Neurosurgery, Kanagawa Cancer Center
Yokohama, Japan

ABSTRACT

Objectives: Hypertonic solutions and corticosteroids are widely used to eliminate brain edema complicated by malignant brain tumors. However, side effects sometimes prevent long-term use of them. To reduce brain edema, the author studied a traditional oriental medical prescription, *goreisan*, which promotes diuresis and eliminates dampness, and is known for inhibiting the aquaporin 4 activity.

Methods: Between February 2003 and October 2010, *goreisan* was prescribed to 60 patients (73 cases) with malignant brain tumors (Male 33, Female 27. Age: 24 to 82 years old, Mean 56.5). The efficacy was evaluated by the level of improvement of subjective symptoms or neurological deficits: excellent (improvement rate≧50%), good (improvement rate 30~50% or 50% or more reduction in other medical decompression agents), and no effect (improvement rate <30 %).

Results: An acceptable level of symptom relief was observed in 52 cases (71.2 %). There were no cases of deterioration, and no significant complications were observed.

Conclusion : *goreisan* can be used for eliminating mild to moderate brain edema and can be a substitute for hypertonic solutions and corticosteroids.

Key words: *goreisan*, brain tumor, brain edema, aquaporin

[Introduction]

Treatment of cerebral edema is a critical issue in the field of neurosurgery, but, for several decades, almost no advancement has been made to the therapy.

Current medical therapy for reducing intracranial pressure in cerebral edema is limited to two types of medicine: hyperosmotic diuretics and adrenocortical hormones. No new medical treatment has been introduced for at least 30 years; that is the current situation surrounding cerebral edema. In clinical practice, excluding D-sorbitol and D-mannitol infusion used mainly in the acute phase, concentrated glycerin/fructose infusion, isosorbide liquid (oral), and adrenal corticosteroids (oral/ drip infusion) are the most-commonly-prescribed hyperosmotic diuretics. However, they have some challenges that need to be resolved.

The most problematic point is that concentrated glycerin/fructose infusion can only be administered intravenouly. Another disadvantage is that the current national health-insurance system in Japan defines the estimated usage period as 2 weeks, or at most 3 weeks. Dehydration and electrolyte abnormalities must be carefully checked for long-term use. Corticosteroids can be taken either orally or intravenously and are significantly effective. However, they can cause complications including higher susceptibility to infection and hemorrhage in the upper gastrointestinal tract. Hence, corticosteroids are not suitable for long-term use. Isosorbide, an oral agent, is difficult to take because of the taste (too sweet/ bitter). It is a liquid medicine, which can be inconvenient.

From a kampo (Japanese traditional medicine)

point of view, the pathological condition of cerebral edema was diagnosed as local stasis of body fluid (suidoku). Therefore, appropriate diuretics should improve the condition. In this report, the author takes up *goreisan* (*Poria Powder with Five Herbs*), a representative Kampo diuretic prescription, to examine its efficacy in improving the symptoms of cerebral edema. The author also reviewed the efficacy from a modern medical point of view to determine whether *goreisan* can become an alternative drug to the modern drugs for reducing brain edema.

[Cases and methods]

From February 2003 to October 2010, 60 patients (73 cases in total) with malignant brain tumors were treated with *goreisan*: 33 male and 27 female. Age 24-82 years old (mean 56.5). The following is the details of the brain tumors by type: 18 patients with primary brain tumor (8 glioblastoma, 5 malignant glioma, 3 primary cerebral malignant lymphoma, 1 meningioma, and 1 primary neuroectodermal tumor); 39 patients with metastatic brain tumor (13 lung cancer, 9 breast cancer, 3 stomach cancer, 3 kidney cancer, 2 esophageal cancer, 2 colon cancer, and 1 each of pancreatic cancer, bladder cancer, ovarian cancer, thyroid cancer, hepatic cancer, malignant melanoma, and nasopharyngeal cancer); 3 patients with delayed radiation necrosis of the brain.

31 patients showed symptoms related to raised intracranial pressure such as headache, nausea and vomiting, and 54 patients with focal neurological symptoms (some patients had multiple symptoms).

Goreisan used in this study was TSUMURA *goreisan* Extract Granules (2.5g/pack), manufactured by Tsumura Co., Ltd. Patients with raised intracranial pressure that required urgent administration of hyperosmotic diuretics and adrenocortical hormones were excluded from this study. In this study, *goreisan* was prescribed, not based on Kampo medical findings (sho) , but on the Western medicine diagnosis of cerebral edema.

Prior to the commencement of the therapy, patients were informed that “edema” is one of the indications for *goreisan* covered by the national health insurance system. Patients received 3 packs per day, in accordance with the instruction of usage. When the improvement of the symptoms was insufficient, *goreisan* was immediately replaced by steroids or another cerebral decompression therapy.

The efficacy was assessed based on the improvements of subjective symptoms of raised intracranial pressure or neurological symptoms using the overall ratings: markedly improved (≧ 50%), effective (30% to less than 50% improvement), or concomitant cerebral decompression drugs reduced to at least 50% or discontinued.); ineffective (less than 30% improvement).

[Results]

Improvements were observed in 52 cases (71.2%): markedly improved in 19 cases (26.0%), effective in 33 (45.2%), and ineffective in 21 (28.8%). Some of the patients who showed no improvement with *goreisan* did not respond to steroids either. For headache (31patients), improvement was observed in 26 cases (83.9%): markedly improved in 11 (35.5%), effective 15 (48.4%), ineffective in 5 (16.1%), and no aggravated case. When a favorable response was observed, the efficacy appeared in a short time, at

the latest within several days. Furthermore, no side-effects were reported for *goreisan*.

[Representative case]

Effective case (Fig. 1). 52 year-old female with metastatic cerebellar tumor caused by lung cancer. She complained of headache, nausea and vomiting, and ataxic gait. She is very close to developing obstructive hydrocephalus.

According to her diagnostic images, most physicians would choose the cerebellar decompression therapy by infusion. In this study, however, both *goreisan* (TJ17) 7.5g and *saireito* (*Minor Bupleurum Decoction*) (TJ114) 7.5g were administered. Then the above symptoms were relieved. The co-administration of the two drugs was intended to double the dosage of *goreisan*.

Ineffective case (Fig. 2/ Left). 66-year old female with metastatic brain tumor from lung cancer. Left-sided hemiparesis. No improvement in neurological symptoms with *goreisan* because the motor area in the brain was directly damaged.

Right side: 82-year-old male with metastatic brain tumor from colon cancer which triggered agnosia. *goreisan* was not effective. Oral steroids were not effective either. The potential factors that render *goreisan* ineffective are as follows:

1) Large tumor,

2) Growth speed of tumors is fast,

3) Rapid development of edema associated brain tumors,

4) Associated cerebral edema is small in volume. The above factors were more prevalent in tumors developed in smaller areas with scarce space for buffering intracranial pressure such as in the posterior cranial fossa. When a tumor was directly causing neurological deficits, no improvement in neurological symptoms was observed. They did not respond to steroids either.

[Discussion]

In Shang Han Lun (Treatise on Febrile and Miscellaneous Disease), *goreisan* is mainly used for symptoms of wind-stroke (syndrome of Taiyang stricken by wind) associated with fever, which do not resolve in 6 to 7 days, and a severe condition with exterior and interior symptoms, become thirsty and crave for water, but drinking of water makes patients vomit like a non-stop fountain. These descriptions are often explained as gastrointestinal symptoms. However, when wind stroke, heat sensation, and vomiting are examined from the perspective of neurosurgery, they could resembled a headache, disturbed consciousness, and vomiting attributable to a raised intracranial pressure. The pathological concept of “symptoms coming from the increased intracranial pressure” likely did not exist when the Shang Han Lun was written. However, there is a strong possibiliy that *goreisan* was prescribed based on the diagnosis of signs and symptoms. In addition, there is a published article confirming that our Japanese pioneers were using *goreisan* at the dawn of the history of brain tumor treatment[1)].

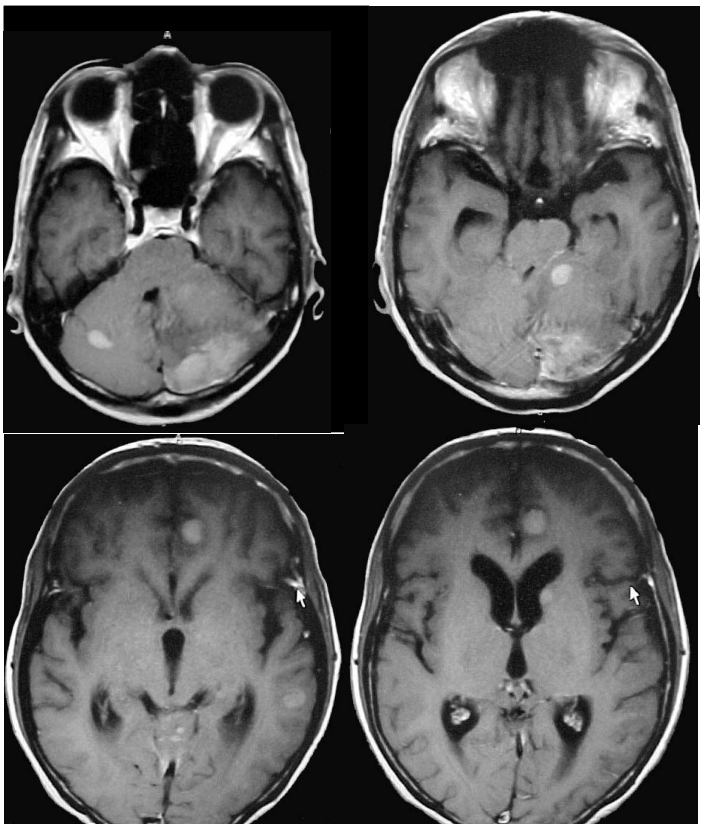

Figure 1
Effective case. 52-year-old female with metastatic cerebellar tumor caused by lung cancer.

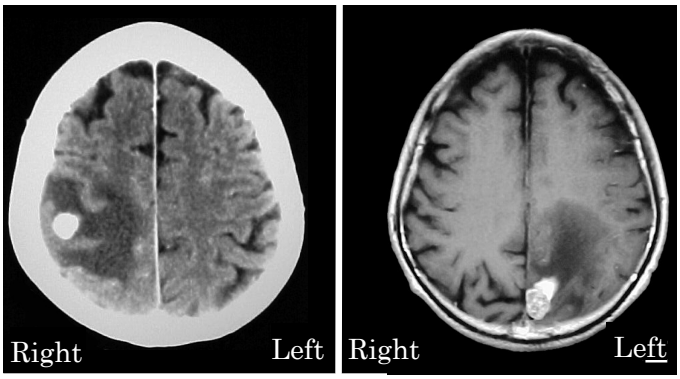

Figure 2
Ineffective case. Left: 66-year-old female with metastatic brain tumor caused by lung cancer. Her left hemiparesis did not resoled by gireisan.
Right: 82-year-old male with metastatic brain tumor by colon cancer complained of agnosia. Did not respond to oral steroids either.

Treating the symptoms of raised intracranial pressure complicated with cerebral edema is essential for treating not only the brain tumors, but also head injury and cerebrovascular disorder. Urea, 50% hypertonic glucose, and other diuretics used to lower the pressure at the early stage of the treatment have become outdated. That was due to the rebound phenomenon where the intracranial pressure is elevated again after administration of the agents mentioned above. Hyperosmotic diuretics and adrenocortical hormones are the two best drugs, among the currently available therapies, for lowering the intracranial pressure. However, as mentioned before, they cannot be regarded as the ideal treatment due to various constraints on the usage and side effects.

On the other hand, oriental medicine defines cerebral edema as a localized stasis of cerebral fluid (suidoku). Therefore, the "promoting diuresis and eliminating dampness" therapy could be used as one of the treatment methods. *Goreisan*, one of the representative diuretics[2)3)] has a very different diuretic property from Western medicines. Although it acts to adjust the systemic water balance, it rarely causes local electrolytes abnormality. The risk of creating dehydration[4)] is low. This makes *goreisan* a highly safe drug for usage.

The efficacy of *goreisan* for cerebral edema complicated with intracranial malignant brain tumor was examined in this study. The overall improvement rate was 71.2%. The improvement in headache alone was 83.9%. Since the relieving of the cerebral edema will not improve the neurological damages caused directly by tumors, the overall improvement rate of 71.2% is satisfactory. In spite of a selection bias, this study still supports the value of *goreisan* as an

option against mild to moderate symptoms.

The pharmacological mechanism of the water draining property in *goreisan* hasn't been uncovered yet; however, the effects on aquaporins (AQP), known as a water channel has gathered attention[5)6)] in recent years.

AQP, a membrane protein, was reported in 1990 as a water channel that selectively transport water molecules without moving electrolytes[7)]. Thirteen types of AQPs have been identified so far. Expressions of AQP1[3,4,5,8,9,11,12)] have been verified in the brain but the major AQP subtypes are two types; AQP1 and AQP4[8)]. AQP1 mainly appears in the choroid plexus epithelia. AQP4, which appears mainly in the central nervous system, is prevalent in the subarachnoid cavity, ventricles of the brain, and neuroglia cells close to cerebral blood vessels. They are all believed to be deeply engaged in the water metabolism of the brain. Therefore, the study on AQP4 has now become one of the most advanced research areas[9)].

Factors attributable to cerebral edema are classified into five types; vasogenic, cytotoxic, osmotic, hydrostatic, and interstitial. Major ones are vasogenic and cytotoxic. The most common type of cerebral edema caused by brain tumor is vasogenic edema triggered by a damage or loss of the blood-brain barrier.

According to an animal experiment using AQP4 null mice[10)], AQP4 works to protect cells against a cytotoxic cerebral edema, whereas it aggravates cerebral edema if it is vasogenic. This signifies that AQP4 promotes water flowing into cells if cerebral edema is cytotoxic, while promoting the excretion of water in vasogenic cerebral edema. In fact, with pathological conditions of malignant tumor, trauma, cerebrovascular damages, and "suidoku" -which result in forming vasogenic cerebral edema- it is known that the expression of AQP4 increases in the perivascular glial endfeet, which is an important component of the blood-brain barrier. Hence, it is assumed that AQP4 re-absorbs extracellular fluids, functioning in the direction of relieving cerebral edema. In malignant glioma, the expression of AQP4 significantly increases in the tumor itself rather than in the area of tumor infiltration, i.e. edema in tumor periphery. The degree of expression and the extent of brain edema formation seem to have co-relation[11)]. AQP4 seems to have bilateral natures, edema formation and edema relief, but further functions of AQP4 remain unknown. However, it is currently expected that the inhibition of the AQP4 could lead in reduction of cerebral edema[12)].

The expression of AQP1 increases in the cytoplasm of malignant glioma. The level of the expression co-relates with the degree of the malignancy and the expansion of the edema in the tumor periphery. There is a report[13)] that even when the expression of AQP1 is not observed in metastatic cerebral tumor, the increase in the AQP1 expression was confirmed in the edema in the tumor periphery. Based on this report, AQP1 inhibitors may also bring about a new treatment modality for cerebral edema complicated with malignant cerebral tumor.

Out of crude drugs composing *goreisan* (Arisma Rhizoma, Polyporous Schlerotium, Atratylodes Lancea Rhizoma, Tuckahoe, and Cassia Bark), it is reported that Polyporous Schlerotium, Atratylodes Lancea Rhizoma, and Tuckahoe inhibit AQP4 and control it in a concentration-dependent manner the water permeability of cell

membraines[14)15)]. Since no aggravation of the symptoms by *goreisan* was observed in any case in this study, at least, the AQP4 inhibiting effect of *goreisan* does not seem to promote brain edema. This suggests that *goreisan* could be a safe drug for an AQP4 inhibitor, and it is expected to reduce cytotoxic edema in tumors as well as vasogenic edema in the peripherial area of tumor.

For the future, measures must be taken to enhance *goreisan*'s clinical efficacy. Japanese extracts contain lower volumes of crude drugs compared to decoctions of Traditional Chinese Medicine. Thus, it is assumed that medicinal efficacy of Japanese extracts is inferior. To enhance the efficacy in a regular clinical practice, which uses the extracts as the main drug, the dosage-increase or combination with *choreito* (*Umbellate Fungus Decoction*) or *bukuryoin* (*Tuckahoe Decoction*) for the purpose of increasing the total volume of Polyporous Schlerotium, Atratylodes Lancea Rhizoma, and Tuckahoe may be considered. From the perspective of the combination usage of *goreisan* and steroids, the use of *saireito* (*Minor Bupleurum Decoction*) that could induce endogenous hormones is also worth considering.

[Conclusion]

Goreisan can be applied for treating cerebral edema complicated with malignant brain tumor. Since *goreisan* is safe and suitable medicine for long-term usage, it can be used as an alternative and complimentary medicine to Western oral drugs such as steroids and isosorbide.

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