

Kampo Medicine - Current Research

Effect of Goreisan on Cerebral Infarction

— *From the Goreisan Symposium 2010*—

Hiroshi Kimoto, Internist

Saito Clinic, Medical Corporation Eizukai

Introduction

Goreisan, whose source is “shang han lun”, has long been known as a common agent in Chinese herbal medicine. It is considered to be an aquaretic drug and alleviates aqueous moisture metabolic abnormality. Using this medicine to treat headaches has recently come to light in Japan.⁽¹⁾ In this paper, we review the indications for *goreisan* on cerebral infarction, a pathologic condition in cerebral stroke. At present, its application for cerebral infarction is being conducted only by the author, and there is a clinical comparison⁽³⁾ with the 2002 Japan Standard Stroke Registry Study (JSSRS),⁽²⁾ as described later.

Background

Acute cerebral infarction is a disease that is classified into types of cerebral stroke and itself is a risk factor in elderly persons. A guideline for the treatment of cerebral stroke has been published by the Cerebral Stroke Joint Guideline Committee (the Committee), starting in 2003 and continuing in 2003, 2004, and 2009.⁽⁴⁾ At each of those times, treatment based on scientific foundations was recommended. In the process, various drugs such as thrombolytics and radical scavengers have been developed, which has resulted in a greater number of patients with favorable prognoses. On the other hand, statistically, many patients have residual disabilities such as paralysis, which reduces a patient’s quality of life (QOL) and causes social problems such as patient care. Thus, further development of drugs and treatment for the disease has been desired.

In Japan, the use of Chinese herbal medicines

for cerebral stroke has been described in various historical literature.⁽⁵⁾ While *daisaikoto*, *san’oshashinto*, and *zokumeito*, etc., are indicated for treatment at the acute stage, a record of the use of *goreisan* has not been found. The reason is presumed to be because its diagnostic findings in Chinese medicine varied historically due to a large number of hemorrhagic pathologic conditions such as cerebral hemorrhage, which might result in various prescriptions of Chinese herbal medicines; it was also impossible to understand the lesions in the brain in detail as can now be done by CT or MRI, etc., and consequently, it was impossible to detect cerebral edema, a pathologic condition induced by cerebral stroke in many cases.

In cerebral infarction, signals are detected on diffusion images of MRI at the initial stage or later after onset, and thus the local pathologic condition of cerebral edema at the lesion appears. It is expected that controlling the edematous condition will enable protection from necrosis of cerebral nervous tissue induced by the infarction, which indicates the great contribution to a prognosis. However, only edaravone, which is available as a cerebral protector, has a certain effect, but it is not a cure-all.

Process till application of *goreisan*

In 2000, the author reported a case of a patient with external hydrocephalus secondary to traumatic subarachnoid hemorrhage and the prognosis could be controlled favorably by administration of aquaretic drugs such as *inchingoreisan* and *shinbuto*. In addition, aquaretic drugs of Chinese herbal medicine were applicable for an edematous pathologic condition in the cranium.⁽⁶⁾

Taking these findings and the above-described pathologic conditions of cerebral infarction into consideration, the author devised a method in which Western drugs and Chinese herbal

medicines were combined⁽⁷⁻⁹⁾ and the treatment was described in case reports during the period from 2001 to 2002. The outline of the method is as follows:

A small dose of argatroban (10 mg/day; a prescribed dose is 60 mg/day for the first two days and 20 mg/day for the subsequent five days) and *goreisan* extract (7.5 mg/day) were combined for all cases, and for abdominal symptoms, *saikokeishito*, *san'oshashinto*, *orengedokuto*, etc., were added (see reference for details). The functional prognoses after discharge were sufficiently satisfactory.

Comparison with the 2002 Japan Standard Stroke Registry Study

Based on the above-described case report, the author describes a comparative study of the severity at admission and findings in follow-up observations after discharge of 14 inpatients with lacunar and atherothrombotic cerebral infarction who were treated by a combined therapy with Chinese herbal medicines at the author's clinic during the period from October 2000 to October 2002, and those findings were compared with those in the 2002 Japan Standard Stroke Registry Study (JSSRS).^(2,3)

The subjects were 14 patients (seven males and seven females aged 68–99; mean age, 78.0±9.1), of whom 9 had a lacunar type disease, 4 had an atherothrombotic type disease, and 1 was unknown. The time until consultation at the clinic ranged from one to 84 hours after onset (mean time, 19.3±26.6 hours).

In diagnosing the disease, except for one case, the infarct site becoming a culprit lesion was determined by neurological symptoms and detectable lesion sites on diffusion images of MRI performed two to three hours after onset. The severity at admission was evaluated according to the Japan Stroke Scale (JSS), the clinical evaluation at discharge was determined by the degree of neurological improvement on the JSS,

and the degree of recapitulative functional improvement was evaluated based on the Modified Rankin Scale.

The results obtained could not undergo a test of significant difference between both sets of data because the number of cases was insufficient and individual data in JSSRS were not available. In the group treated with combined Chinese herbal medicines, the ages of the subjects were higher (78.0±9.1 years vs. 68.0±11.4 in JSSRS lacunar type and 68.0±10.2 in JSSRS atherothrombotic type), and the period (days) of hospitalization was shorter (29±18 vs. 33±25 in JSSRS lacunar type and 36±23 in JSSRS atherothrombotic type). The JSS at admission was higher (8.9±5.9 vs. 2.1±3.5 in JSSRS lacunar type and 4.9±6.5 in JSSRS atherothrombotic type), indicating a severer condition, and the JSS at discharge was lower (0.3±1.2 vs. 1.3±4.1 in JSSRS lacunar type and 3.6±6.6 in JSSRS atherothrombotic type), indicating a neurological improvement. As for the Modified Rankin Scale at discharge, the proportion of the scores of 0 or 1 that indicates normal or very slight pathologic condition without any clinical problem, was 93% versus 67% in JSSRS lacunar type and 45% in JSSRS atherothrombotic type, which is an unquestionably favorable outcome. As for the clinical results from the different treatment methods, the variation in JSS was 8.6±6.20 in the group treated with combined Chinese herbal medicines versus 2.7±6.11 in the group treated with argatroban in JSSRS and 1.7±4.44 in the group with ozagrel in JSSRS, which was a more favorable result than the groups treated with each single Western drug. As for safety, no side effect or harmful event was found in the treatment with combined Chinese herbal medicines.

Subsequent reports

Based on a search of the literature, no clinical studies appear to have been published after the

above-described report. However, the author presented a report at the end of 2003, in which a mechanism for the effect related to the above results is indicated.⁽¹⁰⁾ The report was about a patient with atherothrombotic cerebral infarction in the anterior cerebral arterial region, where the variations in the lesion on an MRI three hours and seven days after onset were compared. The results revealed that the extent of the infarct lesion seven days after onset was far less than the expected range in an untreated case, which strongly indicates a cerebral protective action of the combined Chinese herbal medicines. The author also presented data (in this journal) from a comparison of variations in urinary volume during treatment with *goreisan* administered to patients with other diseases such as vertigo. According to the report, the urinary volume increased significantly with the treatment for cerebral infarction, which strongly indicates a cause and effect relationship between the treatment effect and the administration of an aquaretic drug, namely *goreisan*, for cerebral infarction.

The author hasn't presented further clinical studies and similar additional reports about cerebral infarction have also not been presented. Therefore, further studies are required.

Viewpoint of current medicine for cerebral edema

In 2004–2005, Nagai et al. from Kumamoto University and Isohama et al. presented the treatment effects of *goreisan* on fatal cerebral edema induced by water intoxication in rats, reporting that the mechanism for this is due to the active inhibition of aquaporin 4, and the basis of the inhibitors of aquaporin 4 were mineral components such as manganese contained in *cang-shu* and *zhu-ling*, both of which are constituent crude drugs of *goreisan* (see reference 11). Subsequently, the relationship between cerebral edema with various pathologic conditions and the pharmacokinetics of aquaporin

4 was studied and reported.⁽¹²⁾ Although the mechanism cannot always be explained only by the action of aquaporin 4, clinically, evidence of the effects of Western drugs such as glyceol on cerebral edema have not been apparent and the role of *goreisan* as an anti-cerebroedema drug is thus anticipated.

Summary

Although no additional reports have currently been presented with respect to cerebral infarction, there have been clinical reports on cerebral edemas induced by chronic intradural hematoma, dialysis uneven syndrome, etc.^(13–15) As such, recently, the efficacy of *goreisan* on various cerebral edemas has been strongly indicated by clinical reports and animal experiments from independent facilities. Accordingly, *goreisan* is now considered to be effective for treatment of edematous pathologic conditions accompanying various cerebral diseases. There is currently no effective Western drug for the treatment of cerebral edema, but the clinical applications for *goreisan* have been strongly indicated and they therefore remain to be clarified by future studies.

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