Kampo Medicine - Current Research

Effect of Poria Powder with Five Herbs on Chronic Subdural Hematoma

Mitsusuke Miyagami
Takenozuka Neurosurgical Rehabilitation Hospital
Sonoda Daiichi Hospital Neurosurgery

Introduction

Chronic subdural hematoma (hereafter CSDH) is a gradual accumulation of blood below the dura mater over more than three weeks, generally after a very 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% 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, 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. For this reason, non-operative treatment may be selected depending on the patient. In terms of non-operative procedures for CSDHs, hyperosmolar therapy with mannitol and steroid hormone therapy have been reported. Recently, practitioners in the field of cranial nerve surgery have had another look at Kampo treatment and treatment of CSDH with Kampo medicines 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 Poria Powder with Five Herbs for some patients with CSDH and studied its efficacy. This study reports the efficacy of the medicine for CSDH obtained through conducting CTs with long-term follow-up.

CT Subjects and Methodology

As stated above, surgery is an accepted treatment for CSDH. However, we used Poria Powder with Five Herbs 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, encephalorrhagia, 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 Poria Powder with Five Herbs 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).
Table 1. Summary of cases with chronic subdural hematomas treated with Gorei-san.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Location</th>
<th>Hematoma Density</th>
<th>Maximum Thickness of Hematoma Before Administration of Gorei-san</th>
<th>Maximum Thickness of Hematoma After Administration of Gorei-san</th>
<th>Follow-up (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>87</td>
<td>M/F</td>
<td>L</td>
<td>mixed</td>
<td>10</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2.</td>
<td>74</td>
<td>M/F</td>
<td>L</td>
<td>mixed</td>
<td>20</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>3.</td>
<td>95</td>
<td>M/F</td>
<td>L</td>
<td>mixed</td>
<td>10</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>4.</td>
<td>62</td>
<td>M/F</td>
<td>R</td>
<td>mixed</td>
<td>15</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>5.</td>
<td>56</td>
<td>M/F</td>
<td>L</td>
<td>mixed</td>
<td>15</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>6.</td>
<td>81</td>
<td>M/F</td>
<td>R</td>
<td>mixed</td>
<td>15</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>7.</td>
<td>91</td>
<td>M/F</td>
<td>L</td>
<td>mixed</td>
<td>15</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>8.</td>
<td>89</td>
<td>M/F</td>
<td>L</td>
<td>iso</td>
<td>10</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>9.</td>
<td>74</td>
<td>M/F</td>
<td>R</td>
<td>iso</td>
<td>10</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>10.</td>
<td>59</td>
<td>M/F</td>
<td>L</td>
<td>high</td>
<td>10</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>11.</td>
<td>66</td>
<td>M/F</td>
<td>R</td>
<td>high</td>
<td>15</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>12.</td>
<td>74</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>13.</td>
<td>78</td>
<td>M/F</td>
<td>L</td>
<td>low</td>
<td>15</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>14.</td>
<td>85</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>15.</td>
<td>83</td>
<td>M/F</td>
<td>L</td>
<td>low</td>
<td>15</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>16.</td>
<td>92</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>17.</td>
<td>82</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>18.</td>
<td>72</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>19.</td>
<td>78</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>20.</td>
<td>80</td>
<td>M/F</td>
<td>L</td>
<td>low</td>
<td>15</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>21.</td>
<td>75</td>
<td>M/F</td>
<td>L</td>
<td>low</td>
<td>15</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>22.</td>
<td>98</td>
<td>M/F</td>
<td>R</td>
<td>low</td>
<td>15</td>
<td>15</td>
<td>6</td>
</tr>
</tbody>
</table>

TSUMURA Goreisan Extract Granules (Extract of Poria Powder with Five Herbs, 7.5 g divided into 3 doses, 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 Poria Powder with Five Herbs was assessed based on whether the hematoma had resolved or decreased in size as determined by a CT. Results (Figure 1, 2)
The treatment with *Poria Powder with Five Herbs* 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 *Poria Powder with Five Herbs*, 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 shrunk 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 *Poria Powder with Five Herbs* 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 *Poria Powder with Five Herbs*. 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 *Poria Powder with Five Herbs* (Figure 2). The results of the study show that CSDHs with hematoma density levels of iso/high or mixed were more responsive to *Poria Powder with Five Herbs*. 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) 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, *Poria Powder with Five Herbs* 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.

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.\textsuperscript{22} and Kinjo, et al.;\textsuperscript{8} the combination therapy with steroid hormone and 50% glucose by Ambrosetto, et al.;\textsuperscript{1} and the steroid-alone hormone therapy by Glover, et al.\textsuperscript{2} and Rudiger, et al.\textsuperscript{18}

In recent years, CSDH has occasionally been treated using the aquaretic Kampo medicines of “Poria Powder with Five Herbs” and “Minor Bupleurum Decoction, Poria Powder with Five Herbs.” Seki, et al.\textsuperscript{21} used Poria Powder with Five Herbs in 8 cases of CSDH and obtained improvement in 4 cases. Konuki\textsuperscript{10} and Ueno, et al.\textsuperscript{25} reported that hematomas had resolved in all cases with the combination treatment of Poria Powder with Five Herbs and prednisolone. Muramatsu, et al.\textsuperscript{14} reported the effectiveness of Poria Powder with Five Herbs; they used the Kampo medicine alone in 11 cases and in 10 of the cases, the hematomas disappeared or shrank. Kitahara\textsuperscript{9} had favorable results using Minor Bupleurum Decoction, Poria Powder with Five Herbs, which is made up of two formulae: “Poria Powder with Five Herbs” and “Minor Bupleurum Decoction”. 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 Poria Powder with Herbs have been published and all of these reports suggest its usefulness.

We treated 22 cases of CSDHs (27 hematomas): Poria Powder with Five Herbs alone was administered in 15 cases, and Poria Powder 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 Poria Powder with Five Herbs 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 Poria Powder with Five Herbs, 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 Poria Powder with Five Herbs, 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 Poria Powder with Five Herbs, 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.

Poria Powder with Five Herbs, 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\textsuperscript{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.\textsuperscript{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. 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 Poria Powder with Five Herbs inhibits the action of the aquaporins. According to Isohama, the constituent crude drugs of Poria Powder with Five Herbs, especially atractylodes lancea rhizoma, polyponus sclerotium, and tuckahoe (pora 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 endocapillary cells, is said to be involved in water permeability. Atractylodes lancea rhizoma, the crude drug of the atractylodes family contained in Poria Powder with Five Herbs used for CSDH treatment, has been used in many medicines as well as the ones used in our experiment. Ueno, et al. have also reported that Poria Powder with Five Herbs containing atractylodes ovatae rhizoma was effective for CSDHs.

Our experiment suggests that Poria Powder with Five Herbs 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.

Poria Powder with Five Herbs is orally administered for treatment, unlike mannitol or steroid drugs, and it did not cause any adverse effects in the cases in our study and in other reported cases. We consider Poria Powder with Five Herbs to be an easy-to-use medicine and useful for the future nonsurgical management of CSDHs.

Conclusion
1. Poria Powder with Five Herbs 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. Poria Powder with Five Herbs 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.

References
5. ISOHAMA Y: Working Mechanisms of
Aquaretic Drug “Goreisan”, Kampo Igaku 29:13–215, 2005
6. ISOHAMA Y: Goreisan wa Aquaporin-4 wo Sogaisuruka, Aquaporin wa Risui wo Setumeisuru Bunshi? ISOM/Japan Goreisan Symposium (October 31, 2010), Japan Chapter of the International Society of Oriental Medicine, 1st Special Symposium Abstracts p. 15