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Review Article

An herbal medicine prescription (Oreongsan) developed as a new alternative treatment in patients with chronic subdural hematoma: a narrative review

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ABSTRACT

An herbal medicine prescription, Oreongsan (ORS), which is composed of Polyporus, Alismatis Rhizoma, Atractylodis Rhizoma, Poria (Hoelen), and Cinnamomi Cortex Spissus, has been used as treatment in patients with various symptoms such as thirst, diminished urination, edema, hangover, and diarrhea. ORS is the representative prescription of the 'inducing diuresis' (*isu*) effect, which traditionally means the effect of controlling the water balance. Advancement of modern science has enabled the determination of the action mechanism of herbal medicine complexes. As a result, ORS has been used in the treatment of patients with chronic subdural hematoma (CSDH), representing a novel indication. ORS inhibits the upregulation of aquaporin-4, which is involved in the development of brain edema in the central nervous system. Both aquaporin-1 and aquaporin-4 are expressed in the outer membrane of the CSDH; through its effect as aquaporin-4 inhibitor, ORS prevents the inflow of fluid into the hematoma, thereby preventing the development and recurrence of hematoma. In this study, we reviewed the relationship between the inducing diuresis effect of ORS and aquaporin, conservative treatment approach in patients with CSDH, and the prevention of recurrence in patients undergoing combined burr hole surgery and treatment with ORS.

1. Introduction

In modern society, traditional medicine using treatment tools that have been used in the past has been used in patients. In the past, traditional East Asian medicine was constructed on the basis of the Yin and Yang, Five-elements philosophy which is one of the ancient recognized systems.[1] In particular, the theory of the use of traditional herbal medicine was constructed on the basis of qi and flavor.[2] In modern society, pharmacological review of each herb or herbal complex has become possible[3]; as a result, it is possible to determine the specific therapeutic mechanism of traditional herbal medicine, thereby enabling indications of use that were not be previously identified through combined biomedical information for each disease. Oreongsan (ORS), a representative example, is referred to as the representative prescription of the 'inducing diuresis' *(isu)* effect, which means the effect of controlling the balance of the water. ORS has been used as treatment in patients with various symptoms such as vomiting, diarrheal gastroenteritis, urinary disease with edema, headache, and dizziness.[4] Recently, it has been reported that ORS acts on aquaporin, a water channel in the body, and has been applied to the treatment of chronic subdural hematoma (CSDH),[5] highlighting the case in which a prescription known to regulate water balance has been applied to the treatment of hemorrhagic disease. Thus, the prescription of traditional medicine has been used for novel indications based on scientific mechanism. In this review, we reviewed the scientific background, and reports related to practical applicability of ORS for known and novel indications.

2. Scientific studies on the herbal medicine prescription, Oreongsan

2.1. The origin of the inducing diuresis effect of Oreongsan

The herbal medicine, ORS was first recorded in the Chinese medical classic, Treatise on Cold Damage and Miscellaneous Diseases. ORS which is composed of Polyporus, Alismatis Rhizoma, Atractylodis Rhizoma, Poria (Hoelen), and Cinnamomi Cortex Spissus has been used for the treatment of patients with symptoms

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and diseases related to the body's water metabolism such as thirst, diminished urination, edema, hangover, and diarrhea.[4,6] It is known as a representative prescription for the inducing diuresi effect, a concept specific to traditional East Asian medicine alone which differs from that of the diuretic. Diuretic refers to the effect of in vivo urine production irrespective of the water distribution; whereas, inducing diuresis refers to adjustment of the imbalance of water distribution in the digestive tract or tissue. An experimental study including mice under conditions of water-deprivation and water-overloading demonstrated the inducing diuresis effect of ORS.[7] In the water-overloaded model, mice were injected with desmopressin, an antidiuretic drug, and a large amount of physiological saline (90 mL/kg, i.p.) was injected into the abdominal cavity with complete urination. The water-deprivation models were developed by maintaining the fasting state for 4 hours. In both models, Furosemide administered orally (5 mg/kg) significantly increased the urinary volume to similar level. In contrast, compared to the urinary volume at pretreatment, the administration of ORS showed significant increase of the urinary volume in water-overloaded mice and no change in the urinary volume in water-deprived mice. Thus, the inducing diuresis (*isu*) effect that is induced by the ORS may be considered as equivalent to the effect of adjusting the water balance by treating the water distribution abnormality unlike the effect of diuretics.

2.2. The relationship between Oreongsan and aquaporin-4

The mechanism of the inducing diuresis effect of ORS is explained through the function of aquaporin (AQP), a water channel. In the past, under common assumption of the kidney as functional target of ORS, studies mainly focused on the kidney. However, ORS has been used as treatment in patients with various systemic diseases such as the diseases of the digestive system, neurological diseases, as well as kidney diseases[4,6]; therefore, it was considered to have a systemic effect. Based on this point of view, it is likely that ORS has action on the AQP water channel distributed throughout the body.

AQP is a water-channel protein located in the biomembrane in humans, with a major role in maintaining water homeostasis.[8] AQP has 14 isoforms that are distributed throughout the body with involvement in various biological functions.[9] Reports indicated that AQP-1, 4, and 9 were mainly expressed in the central nervous system in humans[10]; AQP-1 was expressed in the structures of the cerebral nervous system that produce cerebrospinal fluid (CSF) such as the choroidal plexus[11,12]; indicating its role in the formation of brain edema and increase of water flow through tissue in the presence of brain disease. Moreover, AQP-4 was mainly expressed in the basolateral membranes of ependymal cells and glial cells at the blood–brain and brain–CSF interface,[13] with reported involvement in the movement of water between the blood–brain and brain–CSF, and as the main action mechanism in the development of cytotoxic edema in patients with brain disease.[14] With regard to these functions, ORS is known to inhibit the upregulation of AQP-4 which is known to be involved in the formation of brain edema.

A study evaluating the inhibitory effect of mercury ions, known to inhibit water permeability, and ORS on AQP using oocytes from the African Xenopus,[15] reported that the AQP activity was significantly suppressed in the ORS group, with selective inhibition of the AQP-3, 4, and 5 isoforms, whereas mercury ions inhibited the AQP-1 and 2 isoforms. In particular, Atractylodis Rhizoma as component of ORS was reported to play a role in the inhibition of AQP-4 through the action of its manganese content.[16] Other experimental studies reported that ORS inhibited the upregulation of AQP-4 in the juvenile hypoxic-ischemic encephalopathy model,[17] and the ischemic stroke model,[18] thereby preventing the occurrence of brain edema.

2.3. AQP4 is a factor affecting CSDH development and hematoma expansion

AQP, which plays a major role in the formation of brain edema in patients with brain neurological disease, has recently attracted attention as one of the factors affecting the growth of CSDH. Several studies reported the expression of AQP-1 and AQP-4 in the outer membrane of CSDH[11,19]; specifically, AQP-1 was expressed in the sinusoid capillaries of the outer membrane of CSDH,[11] and AQP4 in the vascular endothelium of the outer membrane of CSDH.[19] Collectively, both vascular endothelium known as a target area for frequent inflammatory cell invasion, and AQP-4 as the possible main cause of fluid movement to the subdural space have a potential role to contribute to the occurrence of CSDH and hematoma enlargement.

Therefore, the effect of ORS to inhibit upregulation of AQP4 was expected to be involved in the non-surgical treatment effect on the regression of CSDH and preventive effect against postoperative recurrence. ORS-mediated inhibition of AQP-4 located on the outer membrane of CSDH may restrict fluid movement into the subdural hematoma and interfere with the development and expansion of the hematoma. Based on this pharmacological mechanism, the administration of ORS in patients with CSDH became an ongoing treatment mainly in Japan and Korea, with relevant clinical reports.[20–37]

2.4. CSDH without burr-hole surgery

Burr-hole surgery, the most frequently used treatment for CSDH, showed high effectiveness.[38] However, in patients without symptoms or with mild symptoms, conservative treatments including pharmacotherapy can be attempted. In addition, in the case of lack of consent for surgical treatment of the elderly patients or caregivers, doctors should consider conservative treatments.

Several medications including corticosteroids, tranexamic acid, mannitol, angiotensin converting-enzyme inhibitors, statins and inhibitors of platelet activating factor receptor mediated the resolution of hematoma.[39] However, the efficacy of these medications was not definitive. Therefore, the approach using herbal medicines was suggested, with ORS as representative example. Several reports indicated the effect of conservative treatment using ORS on CSDH (Table 1).[20–30] To date, most reports indicated the high effective rate of 80–100%, and duration of medication of 1.8–6.0 months. All reports were case reports or case series. Therefore, the use of ORS in elderly patients who refuse surgical treatments, asymptomatic patients, or patients with mild symptoms is worth considering. However, due to the poor quality of evidence, the conclusion on the effect of ORS as conservative therapy in patients with CSDH cannot be confirmed.

2.5. Inhibitory effect on postoperative recurrence of CSDH

Previous studies indicated that 5–30% of CSDH cases showed recurrence after burr-hole surgery which is standard therapy.[31] Therefore, the prevention of postoperative recurrence is an important issue in the treatment of patients with CSDH.

In a retrospective chart review study,[32] 199 patients with CSDH after burr-hole surgery were identified. The patients were divided into four groups according to the types of medication administered (ORS ($n = 48$); tranexamic acid ($n = 46$); combination of ORS and tranexamic acid ($n = 35$); and control (no additional treatment, $n = 70$)) and the recurrence rate of CSDH after burr-hole surgery was compared. The recurrence rate by group was 8.3% in the ORS group, 10.9% in the tranexamic acid group, 2.9% in the combination group, and 5.7% in the control group. There was no significant group-wise difference; however, the combination of ORS and tranexamic acid

Table 1
Efficacy of ORS in the Conservative Treatment of Patients with Chronic Subdural Hematoma

First author (yr)	Number of patients	Patients' age (average)	Effective cases (%)	Average treatment period (mo)
Seki (1995)[20]	8	74	4 (50)	Unknown
Onuki (2005)[21]	1	75	1 (100)	6.0
Muramatsu (2005)[22]	11	>80(88)	10 (91)	4.6
Sato (2007)[23]	1	63	1 (100)	1.8
Miyagami (2009)[24]	22 (27 with CSDH)	50–98(78)	23 (85)	2.8
Yokomizo (2010)[25]	3	59–82(74)	3 (100)	4.0
Okamoto (2011)[26]	3	65–92(74)	3 (100)	3.2
Murakami (2012)[27]	1	73	1 (100)	3.0
Shigemori (2014)[28]	1	0.75	1 (100)	1.6
Tsutsumi (2014)[29]	3	60–67(65)	3 (100)	4.7
Mitsuhashi (2015)[30]	8 (11 with CSDH)	64–88(78)	9 (82)	2.5
Total cases	70	74*	59 (84)	3.4

CSDH, chronic subdural hematoma; ORS, Oreongsan.
* Average patients' age excluding infant's data.

showed the lowest recurrence rate. This result suggested that the combination therapy of ORS and conventional therapy (tranexamic acid) showed the best preventive effect on the recurrence of CSDH after burr-hole surgery. However, in this study, the lack of statistical significance may have been due to the different number of patients included in each group.

Another retrospective chart review evaluated the recurrent factors and the efficacy of ORS on CSDH after percutaneous subdural tapping performed in 125 patients with unilateral hematoma and measurable initial hematoma pressure.[33] In that study, several risk factors for the recurrence of CSDH including the patients' age, sex, alcohol consumption, diabetes mellitus, antiplatelet agent or anticoagulant agent administration, history of trauma, severity of neurological deficits, midline shift, hematoma volume, initial hematoma pressure, volume of removed hematoma, and ORS administration were examined. Among 125 patients, 35 (28.0%) showed recurrence. A greater midline shift ($p = 0.033$) and initial hematoma pressure ($p = 0.031$) were risk factors that could predict recurrence at post-percutaneous subdural tapping. ORS was prescribed before or after percutaneous subdural tapping in the ORS group, and percutaneous subdural tapping alone was performed in the control group. The rate of recurrence was 27.7% in the ORS group and 29.0% in the control group, without significant difference between the two groups ($p = 1.000$). Based on these results, ORS was ineffective in preventing recurrence at postoperative period in patients with CSDH. However, the study was conducted using the ORS dose of only 2.5 g, compared with the standardized ORS dose of 7.5 g/day, suggestive of inadequate dose of ORS.

Recently, to overcome the limitations of previous studies, a study evaluated the effect of ORS on re-operation rates after burr-hole surgery in patients with CSDH through analyzing the Japanese inpatient database[34]; the re-operation rate after burr-hole surgery of the ORS group and control group was compared. As a result of primary search, there were 3889 patients in the ORS group and 32,131

Table 2
Efficacy of ORS in the prevention of postoperative recurrence of chronic subdural hematoma

First author (yr)	Subjects, design, and intervention	Results
Wakabayashi (2012)[32]	199 patients with CSDH underwent burr-hole surgery Retrospective chart review ORS group: burr-hole surgery + ORS Tranexamic acid group: burr-hole surgery + tranexamic acid ORS + tranexamic acid group: burr-hole + ORS + tranexamic acid Control group: burr-hole surgery only	Total recurrence rate: 7% ORS group: 8.3% Tranexamic acid group: 10.9% ORS + tranexamic acid group: 2.9% Control group: 5.7% (no significant difference between the four groups)
Okamura (2013)[33]	125 patients with unilateral CSDH underwent percutaneous subdural tapping Retrospective chart review ORS group: Subdural tapping + ORS Control group: Subdural tapping alone	Recurrence rate: 27.7% (26/94) in the ORS group vs. 29.0% (9/31) in the control group ($p = 1.0$)
Yasunaga (2015)[34]	7758 patients with CSDH underwent burr-hole surgery within 2 d after admission Retrospective chart review (using a national Japanese inpatient database, one-to-one propensity – score matching) ORS group: ORS (within 2 d after surgery) + conventional therapy Control group: conventional therapy	Re-operation rate: 4.8% in the ORS group vs. 6.2% in the control group ($p = 0.001$)
Goto (2018)[35]	256 patients with CSDH underwent burr-hole surgery Retrospective chart review ORS A group: burr-hole surgery + ORS (early postoperative administration) ORS B group: burr-hole surgery + ORS (administration in case tendency to recur was observed) Control group: burr-hole surgery only	Recurrence rate: 5% in the A group vs. 12% in the Control group ($p = 0.046$) 6.1% in A + B groups vs. 12% in the Control group ($p = 0.082$)
Katayama (2018)[36]	180 patients with CSDH underwent burr-hole surgery (age, >60 yr-old) Multicenter, RCT, observer blinded ORS group: Burr-hole surgery + ORS (within 72 hr after surgery) for 12 weeks Control group: Burr-hole surgery only	Recurrence rate at 12 weeks: 9.8% (9/92) in the ORS group vs. 12.5% (11/88) in the Control group (no significant difference)

CSDH, chronic subdural hematoma; ORS, Oreongsan.

patients in the control (ORS non-administration) group. Among these, 3879 pairs were created by one-to-one propensity-score matching which were calculated based on the hospital characteristics (the hospital type, average annual number of CSDH patients treated at each hospital, and admission year) and the patients' background (the age, sex, body mass index, Barthel index, consciousness level, comorbidities, and the administration of antithrombotics, mannitol, and corticosteroid). The reoperation rate was significantly lower in the ORS group than in the control group (4.8% vs. 6.2%, $p = 0.001$).

Another retrospective study focused on the role of ORS in the prevention of recurrence of CSDH,[35] included three groups: the ORS A group (early ORS administration after burr-hole surgery), ORS B group (delayed ORS administration in cases with tendency to recur after burr-hole surgery) and control group (absence of treatment after burr-hole surgery). At postoperative day 1, 6, 1 month, and subsequent every month, the recurrence of CSDH was examined using the brain CT image until the absence of visible subdural space; as a result, the recurrence rate was significantly lower in the ORS A group than the control group (5% vs. 12%, $p = 0.046$).

In a multicenter, prospective, observer blinded, randomized controlled trial, 180 included patients with CSDH at post-burr-hole surgery were randomly assigned to either the ORS group or control (no treatment) group and administered treatment for 12 weeks' period.[36] The recurrence rate after operation was 9.8% in the ORS group and 12.5% in the control group, without significant difference ($p = 0.56$). Despite the absence of statistical difference, the ratio of recurrence rates between the ORS group and control group was similar to those reported in the previous study.[34] Furthermore, the bilateral CSDH was a significant affecting factor for the recurrence at postoperative period (OR: 3.43, $p = 0.02$; 95% CI: 1.2–9.8) in the ORS group versus the control group (ORS vs. control: 21.7% (20/92) vs. 12.5% (11/88), $p = 0.09$). Therefore, a well-designed, large-scale clinical trial should be performed to estimate the efficacy of ORS in preventing postoperative recurrence of CSDH.

We experienced a case of successful prevention of the recurrence of CSDH using ORS after the fourth burr-hole surgery.[37] An 84-year-old man with previous three burr-hole surgeries and recurrences, underwent treatment using ORS to prevent the fourth recurrence. After the fourth surgery and 79 days' treatment with ORS, there were no signs of recurrence, and the brain CT image was normalized. In addition, there was no recurrence at 1 year 6 months' follow-up although ORS was not administered. In another case report,[31] ORS was administered for the purpose of preventing CSDH in 10 patients with unruptured intracranial aneurysm who showed increasing subdural fluid collection (SFC) at 2 weeks after clipping and arachnoidplasty; of these, nine patients showed reduced SFC at 1 to 2 months' treatment duration, which indicated that ORS had the potential to prevent the occurrence of CSDH after burr-hole surgery as well as other surgical approaches of stereotactic craniotomy (Table 2).

2.6. Safety of ORS on treating CSDH

It is known that the administration of ORS on CSDH is considerably safe. A retrospective study reported that no side effect of ORS was reported in 164 patients who administered ORS.[35] Other studies[20–34,36,37] did not specifically report adverse events.

3. Conclusion

Traditionally known for its inducing diuresis effect, ORS has long been used as treatment for a variety of symptoms, including vomiting, diarrhea, headache, and edema. The effects of ORS are possibly mediated through the water channel, AQP. Based on this pharmacological mechanism, ORS has recently been applied for the conservative treatment of CSDH, and in the prevention of the recurrence of CSDH at post-burr-hole surgery, with ongoing related reports in the literature. In this report, we performed the literature review on the effect of ORS on CSDH. Evidence to date indicated that ORS could be used as an alternative and conservative therapy for the purpose of preventing postoperative recurrence of symptomatic CSDH after burr-hole surgery, and in treating the cases of asymptomatic or mild-symptomatic CSDH. However, most published studies as a case report or retrospective chart review did not provide high-level evidence. Therefore, it is necessary to perform prospective clinical trials with higher quality and evidence level.

4. Clinical recommendation

ORS could be used to prevent the recurrence of CSDH following burr hole surgery. It is recommended to prescribe 2.5–3.0 g of ORS extract, 2–3 times a day. In this case, it is advisable to evaluate the effect of ORS after an administration period of about 3 weeks. ORS could be also used as a conservative treatment even in patients who are very elderly or who refuse surgery.

Conflicts of interest

All authors declare that there is no conflict of interest.

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