Treatment of coronavirus disease 2019 with saikatsugekito: A case series

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ABSTRACT
Aim: Coronavirus disease 2019 (COVID-19) is a serious disease that has spread worldwide. In the absence of any effective treatment for mild-to-moderate-stage COVID-19, we report that treating patients with Kampo medicines could reduce or prevent disease progression. Herein, we report the current status of COVID-19 treatment with a Kampo medicine, saikatsugekito.

Methods: The clinical course of COVID-19 in patients treated with saikatsugekito was retrospectively investigated from January 2020 to January 2021 at a hospital designated for infectious diseases in Akita City.

Results: Saikatsugekito was administered to 30 COVID-19 patients, but the nine patients with infections caused by other pathogens or no symptoms and treated with steroids were excluded; finally, 21 patients were included in the study. Patients with symptoms such as fever and nasal discharge/obstruction were relieved about a week after hospitalization following treatment with saikatsugekito. However, hyposmia and ageusia persisted for a long time.

Conclusion: Most patients recovered within a week without worsening. Our study suggests that saikatsugekito may be considered a treatment choice to relieve symptoms of mild-to-moderate-stage COVID-19.

KEY WORDS: ageusia, COVID-19, hyposmia, Kampo medicine, saikatsugekito

INTRODUCTION
Coronavirus disease 2019 (COVID-19) has been spreading globally since its outbreak in Wuhan, China at the end of 2019 [1]. It is still under control in most prefectures, with some infected people in Akita Prefecture suffering from mild-to-moderate-stage COVID-19 as a result of the state of emergency and self-quarantine measures. Although the rate of severe COVID-19 is not high, it is more infectious than seasonal influenza. The number of critical patients increases concomitantly with a rapid increase in the number of infected patients [2], thus putting pressure on medical resources. Therefore, preventing the status of patients with mild-to-moderate stage COVID-19 from worsening is an important strategy for its treatment. Vaccination is expected to prevent infection and reduce COVID-19 severity. However, the preventive and long-term adverse effects on the human body of the first applied mRNA vaccine, which is being administered worldwide, remain unknown. Existing antiviral drugs (remdesivir, favipiravir, etc.) have been used; however, their effectiveness against COVID-19 remains uncertain.

Furthermore, side effects of these antiviral drugs have been reported; therefore, treatment with antiviral drugs is limited to moderate to severe stages of COVID-19.

In contrast to antiviral drugs (Western medicine), which specifically suppress primary pathogens, Kampo medicines, with acknowledged lower risks of side effects, can be prescribed for symptomatic conditions in general practice. We previously reported that Kampo medicines might prevent severe disease in mild-to-moderate-stage COVID-19 patients or can be used to prevent infection [3,4]. In particular, the Kampo medicine saikatsugekito (SKGT), used during the Spanish flu epidemic, has various pharmacological effects against viral infections [5]; however, its effectiveness in COVID-19 patients has not been demonstrated in clinical practice. We treated patients with mild to moderate COVID-19 admitted to a hospital designated for infectious diseases with SKGT, and this retrospective study reports the current status of COVID-19 treatment with SKGT.

METHODS
This single-center study retrospectively investigated the clinical course of patients with mild to moderate COVID-19 admitted to a hospital designated for infectious diseases in Akita City and treated with SKGT from January 2020 to January 2021. All patients tested positive for the RNA
### Table 1  Severity classification. Evaluation criteria used by healthcare workers

| Severity        | Oxygen saturation | Clinical state                                      | Examination points                                                                                       |
|-----------------|-------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Mild            | SpO₂ ≥ 96%        | No respiratory symptoms                             | • Condition will resolve naturally in most cases, but may also suddenly worsen                           |
|                 |                   | Coughing only; no shortness of breath               | • Patients with risk factors should be hospitalized                                                     |
| Moderate I      | 93% < SpO₂ < 96%  | Shortness of breath and pneumonia findings          | • Careful observation under hospitalization                                                               |
| Patient does not suffer respiratory failure |                   |                                                     | • Patient sometimes does not complain of respiratory distress even with hypoxemia                        |
|                 |                   |                                                     | • Also important to deal with patient anxiety                                                             |
| Moderate II     | SpO₂ ≤ 93%       | Oxygen administration required                      | • Estimate the cause of respiratory failure                                                               |
| Patient suffers respiratory failure     |                   |                                                     | • Consider transferring patient to a hospital that offers advanced medical treatment                     |
|                 |                   |                                                     | • Avoid using nasal high-flow and CPAP where possible and suppress aerosol generation                    |
| Severe          |                   | Admission to ICU or mechanical ventilator required | • Two classifications of severe pneumonia based on mechanical ventilator management (L-type and H-type) |
|                 |                   |                                                     | • L-type: Lungs are soft and ventilation amount increases                                                |
|                 |                   |                                                     | • H-type: Introduction of ECMO should be considered because of the positive pulmonary edema             |
|                 |                   |                                                     | • Difficult to determine the progress from L-type to H-type                                              |

CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

**Figure 1**  Number of symptoms during the time course. Day 0 indicates the date of the first positive PCR result.
| Case (no.) | Age (year old) | Gender | MH | Symptom | Tongue diagnosis | MBT (°C) | LVO₂ (%) | WBC (/μL), CRP (mg/dL) | DOA (days) | Other treatments | DOTH (day) | DOD (days) |
|------------|----------------|--------|----|---------|------------------|---------|----------|------------------------|------------|------------------|----------|----------|
| 1          | 41             | F      | None | • Fever  | • Pale red       | 37.3    | 93       | 5000, 0.04             | SKGT 7     | Acetaminophen    | 6        | 20       |
|            |                |        |      | • Headache | • Yellowish-white tongue coating |          |          |                        |            |                  |          |          |
|            |                |        |      | • Sore throat | • Slightly enlarged tongue and teeth marks |          |          |                        |            |                  |          |          |
|            |                |        |      | • Nausea | • Pale red       | 36.9    | 96       | 4900, 0.01             | SKGT 7     | Antitussive agent  | 2        | 13       |
|            |                |        |      | • Ageusia | • Pale red       | 36.9    | 94       | 6300, 0.10             | SKGT 7     | None             | 2        | 8        |
|            |                |        |      | • Hyposmia | • Pale red       | 36.9    | 92       | 3800, 0.54             | SKGT 7     | None             | 1        | 8        |
|            |                |        |      | • Nasal congestion | • Pale red       | 37.0    | 92       | 3800, 0.54             | SKGT 7     | None             | 1        | 8        |
|            |                |        |      | • Ageusia | • Pale red       | 37.0    | 92       | 3800, 0.54             | SKGT 7     | None             | 1        | 8        |
|            |                |        |      | • Hyposmia | • Pale red       | 37.0    | 92       | 3800, 0.54             | SKGT 7     | None             | 1        | 8        |
| 7          | 22             | M      | None | • Fever  | • Pale red       | 36.9    | 94       | 4500, 0.05             | SKGT 7     | Acetaminophen    | 8        | 11       |
|            |                |        |      | • Fatigue | • Yellowish-white tongue coating |          |          |                        |            |                  |          |          |
|            |                |        |      | • Headache | • Without a fissured tongue and teeth marks but with enlarged tongue |          |          |                        |            |                  |          |          |
| 8          | 27             | M      | None | • Fever  | • Pale red       | 36.9    | 94       | 4400, 0.23             | SKGT 7     | Acetaminophen    | 1        | 11       |
|            |                |        |      | • Sore throat | • No tongue coating |          |          |                        |            |                  |          |          |
|            |                |        |      | • Hyposmia | • Pale red       | 36.9    | 94       | 4400, 0.23             | SKGT 7     | Acetaminophen    | 1        | 11       |

(continued overleaf)
Table 2 (continued)

| Case (no.) | Age (year old) | Gender | MH | Symptom | Tongue diagnosis | MBT (°C) | LVO₂ (%) | WBC (/μL), CRP (mg/dL) | DOA (days) | Other treatments | DOtH (day) | DOD (days) |
|------------|----------------|--------|----|---------|------------------|---------|---------|------------------------|------------|------------------|-----------|-----------|
| 9          | 32             | F      | None | Nasal congestion | Pale red | 36.9   | 96      | 3300, 0.19             | SKGT 7     | None             | 1         | 10        |
|            |                |        |      | Sore throat | White tongue coating |        |         |                        |            |                  |           |           |
|            |                |        |      | Ageusia   | Without a fissured tongue and teeth marks but with enlarged tongue | |         |                   |            |                  |           |           |
|            |                |        |      | Hyposmia  |                      |         |         |                        |            |                  |           |           |
| 10         | 23             | M      | None | Fever    | Pale red | 37.7   | 96      | 3800, 0.08             | SKGT 7     | Acetaminophen    | 1         | 11        |
|            |                |        |      | Headache  | Yellowish-white tongue coating |        |         |                        |            |                  |           |           |
|            |                |        |      | Cough     |                      |         |         |                        |            |                  |           |           |
|            |                |        |      | Ageusia   |                      |         |         |                        |            |                  |           |           |
|            |                |        |      | Hyposmia  |                      |         |         |                        |            |                  |           |           |
| 14         | 70             | F      | DL   | Fever    | Pale red | 37.7   | 94      | 6800, 1.14             | SKGT 7     | None             | 2         | 9         |
|            |                |        |      | Hyposmia  | No tongue coating |        |         |                        |            |                  |           |           |
| 15         | 57             | F      | HT   | Fever    | Red     | 37.3   | 94      | 5040, 0.80             | SKGT 7     | None             | 0         | 19        |
|            |                |        |      | Headache  | Yellowish-white tongue coating |        |         |                        |            |                  |           |           |
|            |                |        |      | Ageusia   |                      |         |         |                        |            |                  |           |           |
|            |                |        |      | Hyposmia  |                      |         |         |                        |            |                  |           |           |
|            |                |        |      | Post-thyroid cancer surgery | |         |                   |            |                  |           |           |
| 17         | 56             | M      | HT   | Fever    | Pale red | 36.5   | 94      | 5300, 0.06             | KT 5→SKGT 7 | None             | 0         | 31        |
|            |                |        |      | Ageusia   | White tongue coating |        |         |                        |            |                  |           |           |
|            |                |        |      | Hyposmia  |                      |         |         |                        |            |                  |           |           |

CRP, C-reactive protein; DL, dyslipidemia; DOA, duration of administration; DOD, duration of disease; DOtH, duration from onset to hospitalization; HT, hypertension; KT, kakkonto; KTSS, kakkontokasenkyushin'; LVO₂, lowest value SpO₂; MBT, maximum body temperature; MH, medical history; SKGT, saikatsugekito; WBC, white blood cell.
| Case (no.) | Age (y.o.) | Gender | MH | Symptom | Tongue diagnosis | MBT (°C) | LVO₂ (%) | WBC (/μL), CRP (mg/dL) | DOA (day) | Other treatments | DOnH (day) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 18 | 66 | F | DM | Fatigue, Nasal discharge, Cough | Dark red, Yellowish-white tongue coating, Without a fissured tongue and teeth marks but with enlarged tongue | 37.6 | 94 | 7100, 3.89 | SKGT 7 | Expectorant | 5 |
| 19 | 28 | M | None | Fatigue, Nasal discharge, Ageusia, Hyposmia, Dyspnea | Dark red, White tongue coating, Without teeth marks but with enlarged tongue | 36.8 | 98 | 4400, 0.03 | SKGT 7 | None | 12 |
| 21 | 47 | F | None | Fever, Fatigue, Nasal discharge, Nasal congestion, Sore throat | Dark red, Yellowish-white tongue coating, Without a fissured tongue and teeth marks but with enlarged tongue | 37.0 | 97 | 3300, 0.04 | SKGT 7 | Acetaminophen | 0 |
| 23 | 66 | M | DM, HT, DL | Ageusia, Hyposmia | Pale red, No tongue coating, Without a fissured tongue and teeth marks but with enlarged tongue | 37.2 | 96 | 5000, 0.59 | SKGT 7 | None | 0 |
| 24 | 70 | M | DL | Fever, Nasal discharge, Nasal congestion, Sore throat, Ageusia, Hyposmia | Pale red, Yellowish-white tongue coating, Without a fissured tongue and teeth marks but with enlarged tongue | 37.6 | 95 | 3700, 0.29 | KT 1—SKGT 7 | None | 4 |

(continued overleaf)
| Case (no.) | Age (y.o.) | Gender | MH | Symptom | Tongue diagnosis | MBT (°C) | LVO₂ (%) | WBC (/μL), CRP (mg/dL) | DOA (day) | Other treatments | DOtH (day) | DOD (day) |
|-----------|------------|--------|----|---------|-----------------|---------|---------|--------------------------|-----------|-----------------|-----------|-----------|
| 25        | 64         | M      | • DM, • HT, • Hyperuricemia | • Fever, • Fatigue, • Cough, • Diarrhea | • Dark red, • White tongue coating | 38.8    | 94      | 4700, 1.02                | SKGT 2 — SSKKS | Acetaminophen    | 0         | 5         |
| 27        | 50         | F      | • SLE, • HBV carrier | • Sore throat, • Cough | • Pale red, • White tongue coating, • Without a fissured tongue but teeth marks and with enlarged tongue | 36.7    | 95      | 2900, 0.06                | SKGT 7 | None            | 2         | 12        |
| 28        | 41         | F      | None | • Fever, • Fatigue, • Cough | • Pale red, • Yellowish-white tongue coating, • Without a fissured tongue but teeth marks and enlarged tongue | 37.0    | 97      | 6400, 0.03                | SKGT 7 | None            | 7         | 18        |
| 29        | 66         | F      | • DM, • HT, • DL | • Fever, • Fatigue, • Cough | • Pale red, • Yellowish-white tongue coating, • Without a fissured tongue but teeth marks and enlarged tongue | 38.5    | 94      | 6500, 3.88                | SKGT 7 | Acetaminophen    | 4         | 32        |
| 30        | 41         | F      | None (pregnant) | • Nasal discharge, • Nasal congestion | • Pale red, • No tongue coating, • Without a fissured tongue and teeth marks but with enlarged tongue | 36.7    | 98      | 5000, 0.34                | SKGT 7 | None            | 1         | 8         |

CRP, C-reactive protein; DL, dyslipidemia; DM, diabetes mellitus; DOA, duration of administration; DOD, duration of disease; DOtH, duration from onset to hospitalization; HBV, Hepatitis B virus; HT, hypertension; KT, kakkonto; LVO₂, lowest value SpO₂; MBT, maximum body temperature; MH, medical history; SKGT, saikatsugekito; SSKKS, shosaikotokakikyosekko; SLE, systemic lupus erythematosus; WBC, white blood cell.
polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical data such as information from symptom onset to undergoing PCR, symptoms at presentation, medical history, disease duration, blood sampling, chest radiographs, and tongue diagnosis were obtained. Disease duration was defined as the time from onset of any of the following symptoms until improvement in all these symptoms (fever, below 37°C; hyposmia, improving odorless condition): fever, dyspnea, nausea, sore throat, cough, nasal discharge, nasal congestion, hyposmia, ageusia, headache, fatigue, and diarrhea. Because of COVID-19’s characteristics, doctors practicing Kampo medicine could not be in direct contact with patients; thus, the findings were confirmed only by tongue inspection.

COVID-19 severity was determined using the Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers (Version 3) (Table 1) [6]. We included patients with mild to moderate disease on admission. Additionally, since the SKGT extract was unavailable, it was substituted with a combination of kakkonto (KT) extracts and shosaikotokakikyosekko (SSKKS) (http://mpdb.nibiohn.go.jp/stork/). Informed consent was obtained from patients or their families. The study was approved by the Ethics Committee of Akita University (approval number: 19605).

| Table 4 | Patient characteristics, medical history and symptoms |
| No. (%) | Mean ± SD | Median | IQR | Range |
| No. of patients | 21 (100) | | | |
| Male | 9 (42.9) | | | |
| pregnant | 1 (4.8) | | | |
| Age | 44.4 ± 18.7 | 41 | 36 | 12–70 |
| DOtH | 2.8 ± 3.2 | 2 | 3 | 0–12 |
| DOD | 13.0 ± 7.5 | 11 | 8 | 4–32 |
| Medical histories | | | | |
| No medical history | 11 (53.4) | | | |
| DL | 6 (28.6) | | | |
| HT | 5 (23.8) | | | |
| DM | 4 (19) | | | |
| Cancer (post operation) | 3 (14.3) | | | |
| HBV carrier | 1 (4.8) | | | |
| Hyperuricemia | 1 (4.8) | | | |
| Cardiovascular disease | 1 (4.8) | | | |
| SLE | 1 (4.8) | | | |
| Symptoms | | | | |
| Hyposmia | 15 (71.4) | | | |
| Ageusia | 13 (61.9) | | | |
| Fever | 12 (57.1) | | | |
| Nasal congestion/discharge | 9 (42.9) | | | |
| Sore throat | 7 (33.3) | | | |
| Fatigue | 7 (33.3) | | | |
| Cough | 6 (28.6) | | | |
| Headache | 4 (19) | | | |
| Diarrhea | 3 (14.3) | | | |
| Dyspnea | 1 (4.8) | | | |
| Nausea | 1 (4.8) | | | |

DL, dyslipidemia; DM, diabetes mellitus; DOD, duration of disease; DOtH, duration from onset to hospitalization; HBV, Hepatitis B virus; HT, hypertension; IQR, interquartile range; SLE, systemic lupus erythematosus.
RESULTS

Thirty-three patients with mild to moderate COVID-19 were treated, among whom 30 were prescribed SKGT. Pneumococcal pneumonia or Chlamydophila pneumonia (suspected) were detected in two patients. In two other patients, symptoms had already improved at the time of admission, and the indication for Kampo medicines was doubtful. Moreover, five patients were treated with steroids after hospitalization; thus, after excluding these patients, 21 patients were finally included in this study. None of the 21 patients received any specific treatment such as antiviral therapy agents.

Patient characteristics are shown in Tables 2–4. The median age was 41 (range, 12–70) years, and the male-to-female ratio was 9:12. The most common symptom was hyposmia in 15 patients, followed by ageusia, fever, and nasal discharge/obstruction. The most common medical history in order of prevalence was dyslipidemia, hypertension, and diabetes mellitus. White, yellowish-white, or yellow-thick tongue was observed in 14 patients on tongue inspection, with 11 showing improvement after administering SKGT. The accumulated time course of the four major symptoms in the 21 patients is shown in Fig. 1, with day 0 being the time of PCR positivity and fever, nasal discharge, and congestion being resolved within approximately a week after admission; however, some cases of hyposmia and ageusia persisted for a long time. All patients were discharged without any exacerbation.

DISCUSSION

This study showed that most patients with mild to moderate COVID-19 treated with SKGT recovered from fever within a week, and there were few cases of long-term residual hyposmia or ageusia. Furthermore, all patients were discharged without any exacerbation.

The original source for SKGT is ‘Shokan-un’yo’ by Wu Shou of the Ming dynasty; however, there are three types with the same name (Table 5) [7]. Asada Souhaku’s father, Seian, removed jujube and ginseng from the drug combination of KT and shosaikoto and added Gypsum to produce a new type of SKGT (Asada family’s original blend). Futsugo yakushitsu hokan kuketsu [8] said, ‘SKGT cures patients presenting with a combination of diseases of early and late yang, headache, dry nose and throat, insomnia, tingling pains in the extremities, and tachycardia’, and its effect is better than that of SKGT in ‘shokan-rokusho’. SKGT was also reportedly used to treat the Spanish flu, which spread widely more than 100 years ago, and this was found to improve patients’ health [2].

Patients with mild COVID-19 are generally expected to recover within 1–2 weeks [9], and 74% of hyposmia cases improve within approximately four weeks [10].

However, exacerbation occurs approximately 7–10 days after onset [11]. In this study, the symptoms started with fever, nasal congestion, and discharge, followed by hyposmia and ageusia.
These symptoms persisted for a long time, even after the fever broke and the upper respiratory symptoms improved. When patients presented to the hospital, they already had a white or yellowish-white tongue, which is observed in the middle and late yang stage patterns. This suggests that a combination of Kampo medicines for the half-exterior, half-interior pattern to the interior pattern is necessary next to diaphoretics such as keishito, KT, and maoto. Kashima et al. [12] reported that large doses of Platycodon root and Gypsum improved antipyretic and inflammatory reactions and oxygenation promptly. Since the timing of prescription discontinuation and resumption was also consistent with disease kinetics, the inclusion of Gypsum in the formula was expected to treat COVID-19 symptoms effectively.

In this study, although there were risk factors such as old age, diabetes mellitus, and hypertension, we could not determine the extent to which SKGT contributed in treating patients with mild to moderate COVID-19 because most patients recovered without exacerbation by symptomatic treatment. Furthermore, most of the included patients were in the low-mortality age group.

However, the antiviral agents undergoing clinical trials have not been shown to be effective at this stage, and there are also the problems of side effects and resistance. Conversely, Kampo medicines are expected to have antiviral effects by activating autoimmunity [13,14], are relatively safe in clinical use, and have few side effects in patients at this stage. Kampo medicines for common cold or bronchitis are permitted in the national health insurance system according to the symptoms, which is an advantage of Kampo medicines that is not found for other treatments. The side effect, which seemed to be caused by the ephedrine included in KT, occurred in an elderly patient excluded from the study, and she could not continue taking the Kampo medicines. Considering ephedrine side effects in elderly patients, it might be better to administer maobushishaishinto instead of KT or administer SSKKS only.

In conclusion, we have reported the current status of COVID-19 treatment with SKGT. Although the clinical efficacy of SKGT for mild to moderate COVID-19 has not been clarified, SKGT may currently, in the absence of any effective treatment, be considered a treatment choice for symptom relief in mild COVID-19. We await the results of a multicenter randomized controlled trial by the Integrative Management in Japan for Epidemic Disease on the use of Kampo medicine, kakkonto with shosaikotokakikyosekko, in mild-to-moderate COVID-19 patients for symptomatic relief and the prevention of severe disease [15].

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CONFLICT OF INTEREST

All authors declare to have no conflicts of interest associated with this manuscript.

INFORMED CONSENT

We obtained consent from the patients’ families for their treatment and for publication of this report.

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