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Case report

Five patients with severe burns and refractory infections treated using the traditional Japanese medicine juzentaihoto

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ABSTRACT

Immunodeficient patients such as those with severe burn injuries are usually at risk for systemic infection with methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant *Pseudomonas aeruginosa* (MDRP). Juzentaihoto (JTT) is a traditional Japanese herbal complex used for the treatment of fatigue, anemia, weakness, hypotension, malaise following illness or surgery, and chronic wasting diseases. We treated 5 patients with severe burn injuries and concurrent MRSA, MDRP, or *Candida* infections using JTT. All patients had flame burns (40%–85% body surface area) and inhalation injuries. The patients developed MRSA, MDRP, or *Candida* infections following burn injuries, and antibiotics such as arbekacin, vancomycin, teicoplanin, or antimycotic drugs failed to control the infections. Subsequent to antibiotic failure, JTT was administered. Four patients showed negative bacterial cultures following JTT treatment. Thus, we conclude that JTT may be useful as a treatment against anemia and infection caused by severe burns.

1. Introduction

Immunodeficient patients including those with severe burn injuries are usually at risk for systemic infection with methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Pseudomonas aeruginosa* (MDRP), or fungal infection. Thus, it is important to prevent and control these subsequent infections in order to improve the prognosis of patients with severe burn injuries.

Juzentaihoto (JTT) is a traditional Japanese herbal complex used in the treatment of fatigue, anemia, weakness, hypotension, malaise following illness or surgery, chronic wasting diseases, and weakness caused by radiation therapy or anticancer drugs [1–3]. JTT can enhance immunological functions [4], thereby affecting not only the acquired immune system but also the innate immune response through macrophages. JTT also has protective effects against *Candida*, *Salmonella*, and malarial infections [5–8]. However, only a few clinical reports have been published on the use of JTT in the treatment of patients with burns [9].

Here, we report the cases of 5 patients with severe burn injuries, who subsequently developed refractory MRSA, MDRP, or *Candida* infections and were treated using JTT.

2. Case series

2.1. Patients

Five patients (2 men and 3 women) with a median age of 64 years (range, 35–78 years) presented with flame burns (Table 1). The median total burn surface area (TBSA) of the patients was 59% (40%–85%). The median burn index (BI) was 59 (40–67.5) with a median prognostic burn index (PBI) of 118 (102.5–131). All patients were also diagnosed with inhalation injury. Three of the patients survived and 2 died; death in both fatal cases was due to sepsis subsequent to pneumonia.

JTT in the form of a granular extract (TJ-89; Tsumura & Co, Tokyo, Japan) was administered through a nasogastric tube. The JTT extract comprised 10 crude drugs mixed in specific ratios (Table 2).

Abbreviations: juzentaihoto, JTT; burn index, BI; prognostic burn index, PBI; hospital day, HD; hemoglobin, Hb.

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Table 1
Clinical data of patients.

No	Age (years)	Gender	TBSA (%)	BI	PBI	Type	Inhalation injury	Starting HD of JTT	Duration of JTT administration	Number of skin grafts	Outcome
1	35	M	85	67.5	102.5	Flame	+	18	49 days	4	Survived
2	64	M	40	40	104	Flame	+	43	83 days	3	Survived
3	78	F	40	40	118	Flame	+	40	42 days	5	Survived
4	72	F	63	59	131	Flame	+	49	6 days	4	Died (HD 95)
5	61	F	60	60	121	Flame	+	72	67 days	2	Died (HD 143)

M: male, F: female, TBSA: total body surface area, BI: burn index, PBI: prognostic burn index, HD: Hospital day, JTT: juzentaihoto.

Ultrasonication was used for 30 min to extract JTT from the crude drugs using 20 mL methanol. The solution was filtered and then submitted for High-performance liquid chromatography (HPLC) analysis [10]. HPLC equipment was controlled with an HPLC pump (LC-10AD; Shimazu, Kyoto, Japan) running at 1.0 mL/min, using a TSK-gel® (Tosoh Bioscience Japan, Tokyo, Japan) and ODS-80TS column (4.6φ × 250 nm). Elution was performed using solvents (A) 0.05 M $AcONH_4$ (pH 3.6) and (B) CH_3CN. A linear gradient of 100% A and 0% B was converted over 60 min to 0% A and 100% B was used. The eluate from the column was monitored, and the three-dimensional data were processed using a diode array detector (SPD-M10A; Shimadzu, Kyoto, Japan). The three-dimensional HPLC profile of the methanol solution of JTT is shown in Fig. 1. JTT was administered when the patient had all of following 3 symptoms: (1) infection refractory to antibiotics, (2) anemia, and (3) protracted wound healing. The median hospital day (HD) when JTT administration was started was HD 43 (HDs 18–72). The median duration of JTT administration was 49 days (6–83 days). Skin grafting was performed a median of 4 times (2–5 times).

Culture results are shown in Table 3. MRSA was detected in 4 patients, MDRP in 1 patient, and *Candida albicans* in 4 patients. Tests for pathogens including MRSA or *C. albicans* were negative in 4 patients (negative rate, 80%) following administration of JTT. The median hemoglobin (Hb) level at the beginning of JTT administration was 9.0 g/dL (6.7–9.6 g/dL). The median Hb level at completion of JTT administration was 10.1 g/dL (7.2–10.9) (Table 4). The increase in Hb levels following treatment was significant ($p = 0.0431$).

No adverse events related to JTT were observed in any patient.

BI was calculated as follows:

$$\mathrm{BI} = \text{body surface area(BSA) of deep dermal burn} \times 1/2 + \text{BSA of deep burn}$$

PBI was calculated as follows:

$$\mathrm{PBI} = \text{Age(years)} + \mathrm{BI}$$

Inhalation injury was diagnosed on the basis of bronchoscopic examination. Data for all parameters are expressed as median values with their ranges. Differences were evaluated for significance using Wilcoxon's signed rank test. A *P* value of less than 0.05 was considered significant.

Table 2
The 10 crude drugs that compose juzentaihoto extract and their weight ratios.

Latin names	Crude drugs	Weight (g)
Astragali radix	*Astragalus* root	3.0
Cinnamomi cortex	Cinnamon bark	3.0
Rehmanniae radix	*Rehmannia* root	3.0
Paeoniae radix	*Peony* root	3.0
Cnidii rhizome	*Cnidium* rhizome	3.0
Atractylodis lanceae rhizome	*Atractylodes lancea* rhizome	3.0
Angelicae radix	Japanese Angelica rhizome	3.0
Ginseng radix	Ginseng root	3.0
Hoelen	Hoelen	3.0
Glycyrrhizae radix	*Glycyrrhiza* root	1.5

2.2. Case presentation (Case 3)

A 78-year-old woman was admitted with a full thickness 40% BSA flame burn sustained during an accident involving the candle of a family Buddhist altar. The burn involved areas of the face, scalp, anterior chest, back, abdomen, and both upper limbs. The patient was also diagnosed with an inhalation injury. The BI was 40 and PBI was 118. Skin grafting was performed 3 times in the 26 days immediately following injury. MRSA was detected in the sputum culture on HD 24. Prolonged pneumonia due to MRSA infection was observed despite treatment with various antibiotics. *Torulopsis glabrata* and MRSA were detected in urine culture. Antibiotics including arbekacin failed to control the MRSA infection. The patient was also found to be anemic (Hb level, 8.3 mg/dL: hematocrit, 25.4%). The administration of JTT (5.0 g/day) was initiated on HD 40. By HD 54, the patient's condition was stable, and skin grafting was performed for the fourth time. The postoperative course was favorable, and the patient was discharged from the intensive care unit on HD 65. Following a sputum culture that was negative for MRSA, the administration of JTT was halted on HD 81. A fifth skin grafting was performed on HD 96, and epithelization of burn wounds was completed. The patient had cerebral infarction on HD 101 and was transferred to a geriatric rehabilitation center on HD 206.

3. Discussion

JTT comprises the following 10 herbs: *Astragalus* root, cinnamon bark, *Rehmannia* root, *Peony* root, *Cnidium* rhizome, *Atractylodes lancea* rhizome, Japanese angelica rhizome, ginseng root, hoelen, and *Glycyrrhiza* root. From a pharmacologic view, JTT contains various immunomodulatory substances. Ginsenoside Rh1 from the ginseng root has been shown to have antiallergic and anti-inflammatory activities [11]. Glycyrrhizin extracted from the *Glycyrrhiza* root and extracts of *Astragalus* root have also shown anti-inflammatory activities [12,13]. Other research has suggested that the extracts from ginseng root, cinnamon bark, *Glycyrrhiza* root, *Peony* root, and *Astragalus* root have antioxidative activities [14–17]. Another study reported that ginseng root, *Glycyrrhiza* root, *Atractylodes lancea* rhizome, and *Cnidium* rhizome play crucial roles in the protective effect of JTT against *Candida* infection [5]. Liu reported that JTT activated and enhanced phagocytosis in macrophages [18]. This evidence suggests that JTT enhances the immunological functions. JTT affects not only the acquired immune system but also the innate immune response through macrophages [19].

JTT has also shown protective effects against lethal *Candida*, *Salmonella*, and malarial infections in animal models [5–8].

Schwartz calculated the BI on the basis of burn area and depth [20], and a BI of more than 10–15 is classified as a severe injury. PBI is a convenient index used to indicate the prognosis of patients. A patient with a PBI less than 70 is likely to survive, while