

The Effectiveness of Sho-Saiko-To for Subacute Necrotizing Lymphadenitis: A Retrospective Study

Kazuhiro Hirasawa^{1,2)}, Koji Otsuka¹⁾, Kiyooki Tsukahara³⁾

ABSTRACT

Objective: To confirm the efficacy of Sho-saiko-to, a Kampo medicine, in treating subacute necrotizing lymphadenitis.

Design: Single-center retrospective study

Materials and Methods: Twenty-four patients (age range 12-46 years, 14 women) who visited the Tokyo Medical University Ibaraki Medical Center and were diagnosed with subacute necrotizing lymphadenitis between January 2017 and May 2022 were enrolled. They were classified into symptomatic treatment, steroid use, and Sho-saiko-to use groups. The period from the onset to the disappearance of neck pain and fever was compared among the groups.

Results: The steroid and Sho-saiko-to use groups demonstrated a significantly shorter period from the onset to the disappearance of neck pain than the symptomatic treatment group ($p = 0.019$ and 0.004 , respectively), without a significant difference between the steroid and Sho-saiko-to use groups ($p = 0.888$). The steroid and Sho-saiko-to use groups demonstrated a significantly shorter period from the onset to the disappearance of fever than the symptomatic treatment group ($p = 0.030$ and 0.011 , respectively), without a significant difference between the steroid and Sho-saiko-to use groups ($p = 0.660$).

Discussions: Sho-saiko-to reduced the illness period of subacute necrotizing lymphadenitis, and its effects were comparable to that of steroids.

Conclusions: Sho-saiko-to might be effective for treating acute necrotizing lymphadenitis and could be comparable to steroids.

KEY WORDS

subacute necrotizing lymphadenitis, Sho-saiko-to, Kampo medicine, steroid

INTRODUCTION

Subacute necrotizing lymphadenitis causes peculiar necrotic lesions of the lymph nodes and was first reported by Kikuchi and Fujimoto *et al.* in 1972^{1,2)}. Theories state that it is caused by an infection, such as a virus, and autoimmunity; however, the actual cause remains unknown³⁾. Spontaneous healing often requires several months; nonetheless, there is no specific treatment, and steroids are commonly used to relieve the condition^{3,4)}.

By contrast, subacute necrotizing lymphadenitis often requires differentiation from malignant lymphoma and systemic lupus erythematosus³⁾, and easy steroid treatment may delay their diagnosis. Therefore, it is difficult to use steroids without a histological examination of the lymph nodes; nonetheless, clinicians often encounter cases that do not warrant a biopsy. In this study, we intended to follow up the patients with symptomatic treatment, and they continued to suffer for a prolonged period. This necessitated treatment methods other than steroid therapy.

Sho-saiko-to is a Kampo medicine used to treat infectious diseases and lymphadenitis in Japan. Previously, we reported two cases of sub-

acute necrotizing lymphadenitis that were successfully treated with Sho-saiko-to⁵⁾. Therefore, in this study, we aimed to collect data on the number of cases and to retrospectively examine the effectiveness of Sho-saiko-to for subacute necrotizing lymphadenitis.

MATERIALS AND METHODS

Between January 2017 and May 2022, 84 patients with cervical lymphadenitis visited the Department of Otorhinolaryngology, Tokyo Medical University, Ibaraki Medical Center. Of these patients, 30 were diagnosed (clinically or by biopsy) with subacute necrotizing lymphadenitis. The criteria depicted in Figure 1 were used for the clinical diagnosis. We included 24 patients, excluding patients two and four for whom we could not track the progress until symptom improvement and with an unknown detailed course in the medical records, respectively. We classified them into the following groups: symptomatic treatment only (symptomatic treatment group), steroids (steroid use group), and Sho-saiko-to (Sho-saiko-to use group). The treatment strategy was decided as follows: patients who underwent histological biopsy were adminis-

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1) Department of Otorhinolaryngology

Tokyo Medical University Ibaraki Medical Center

3-20-1 Chuo, Ami-machi, Inashiki-gun, Ibaraki 300-0395, Japan

2) Kampo Medicine Center, Tokyo Medical University Hospital

6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

3) Department of Otorhinolaryngology, Head and Neck Surgery

Tokyo Medical University

6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

Correspondence to: Kazuhiro Hirasawa

(e-mail: hirakazu@tokyo-med.ac.jp)

ORCID ID:

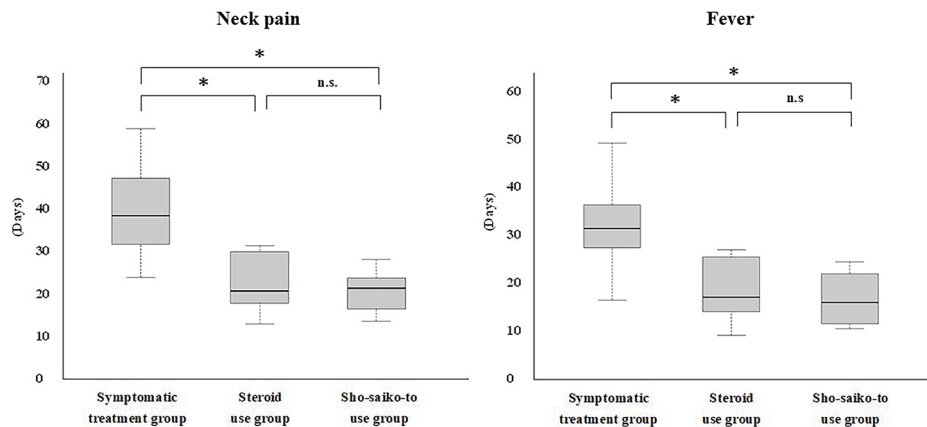
Kazuhiro Hirasawa: 0000-0001-6337-071X

Kiyooki Tsukahara: 0000-0002-4198-9615

Table 1: Patient characteristics in the three groups

	Age (years)	Sex	CRP value at first visit (mg/dl)	Period from onset to treatment initiation
Symptomatic treatment group (n = 9)	16-46 Mean (28.8)	3 men 6 women	0.04-3.25 Mean (0.90)	—
Steroid use group (n = 7)	14-36 Mean (27.7)	3 men 4 women	0.04-4.59 Mean (1.54)	5-25 days Mean (14.9 days)
Sho-saiko-to use group (n = 8)	12-43 Mean (26.3)	4 men 4 women	0.07-3.24 Mean (1.24)	5-19 days Mean (11.6 days)

Abbreviations: CRP, C-reactive protein

**Figure 1. Period from the onset to the disappearance of neck pain and fever**

*, significantly different; n.s., not significant

tered steroids from the date of biopsy; when patients did not warrant biopsy, attending physicians who were not familiar with Kampo medicine selected symptomatic treatment, while those who were familiar used Sho-saiko-to. We compared the period from the onset to the disappearance of neck pain among the groups, which was used as the primary endpoint. Moreover, we compared the period from the onset to the disappearance of fever in the groups and used this as the secondary endpoint. Furthermore, we compared the period from the treatment initiation to the disappearance of neck pain and fever between the steroid and Sho-saiko-to use groups, which were also used as the secondary endpoints. In addition, we compared the age, sex, and C-reactive protein (CRP) levels during a consultation with the patient characteristics of all three groups. Furthermore, the period from the onset to the treatment initiation was compared between the steroid and Sho-saiko-to use groups.

For statistical analysis, we performed the Fisher's exact test for the sex distribution among the three groups. We performed the Kruskal–Wallis test to compare other items among the groups. Upon observing a significant difference in the Kruskal–Wallis test, we used the Steel–Dwass method for multiple tests. A p -value < 0.05 was considered statistically significant. The Mann–Whitney U test was performed to compare any two groups. Statistical significance was defined as a two-tailed p -value < 0.05 .

This retrospective study was conducted in compliance with the tenets of the Declaration of Helsinki and the ethical guidelines for medical research targeting humans and was approved by the Tokyo Medical University Medical Ethics Review Board (approval number: T2022-0113). The need for informed consent was waived owing to its retrospective nature.

RESULTS

Patient characteristics (Table 1)

There were nine, seven, and eight patients in the symptomatic treatment group, steroid use group, and Sho-saiko-to use group, respectively. Their age distribution ranged from 16 years to 46 years (average age

28.8 years), 14 years to 36 years (average age 27.7 years), and 12 years to 43 years (average age 26.3 years) in the symptomatic treatment group, steroid use group, and Sho-saiko-to use group, respectively. There were three men and six women in the symptomatic treatment group, three men and four women in the steroid use group, and four men and four women in the Sho-saiko-to use group. The CRP value at the first visit was 0.04–3.25 mg/dl (average, 0.90 mg/dl), 0.04–4.59 mg/dl (average, 1.54 mg/dl), and 0.07–3.24 mg/dl (average, 1.24 mg/dl) in the symptomatic treatment group, steroid use group, and Sho-saiko-to use group, respectively. There were no significant differences in age, sex, or CRP level at the first visit among the three groups ($p = 0.902$, 0.874, and 0.578, respectively). The period from onset to the treatment initiation ranged from 5 days to 25 days (average, 14.9 days) and 5 days to 19 days (average, 11.6 days) in the steroid use group and Sho-saiko-to use group, respectively. There was no significant difference between the groups ($p = 0.322$).

Period from the onset to the disappearance of neck pain (Figure 1)

The period from the onset to the disappearance of neck pain ranged from 23 days to 59 days (average, 39.6 days), 12 days to 31 days (average, 22.3 days), and 13 days to 28 days (average, 20.3 days) in the symptomatic treatment group, steroid use group, and Sho-saiko-to use group, respectively ($p = 0.002$ in the Kruskal–Wallis test). It was significantly shorter in the steroid and Sho-saiko-to use groups than that in the symptomatic treatment group ($p = 0.019$ and 0.004, respectively). There was no significant difference between the steroid and Sho-saiko-to use groups ($p = 0.888$).

Period from the onset to the disappearance of fever (Figure 1)

The period from the onset to the disappearance of fever ranged from 16 days to 49 days (average, 31.3 days), 9 days to 27 days (average, 18.9 days), and 10 days to 24 days (average, 16.3 days) in the symptomatic treatment group, steroid use group, and Sho-saiko-to use group, respectively ($p = 0.005$ in the Kruskal–Wallis test). It was significantly shorter in the steroid and Sho-saiko-to use groups than that in the symptomatic treatment group ($p = 0.030$ and 0.011, respectively). There was no significant difference between the steroid and Sho-saiko-to use

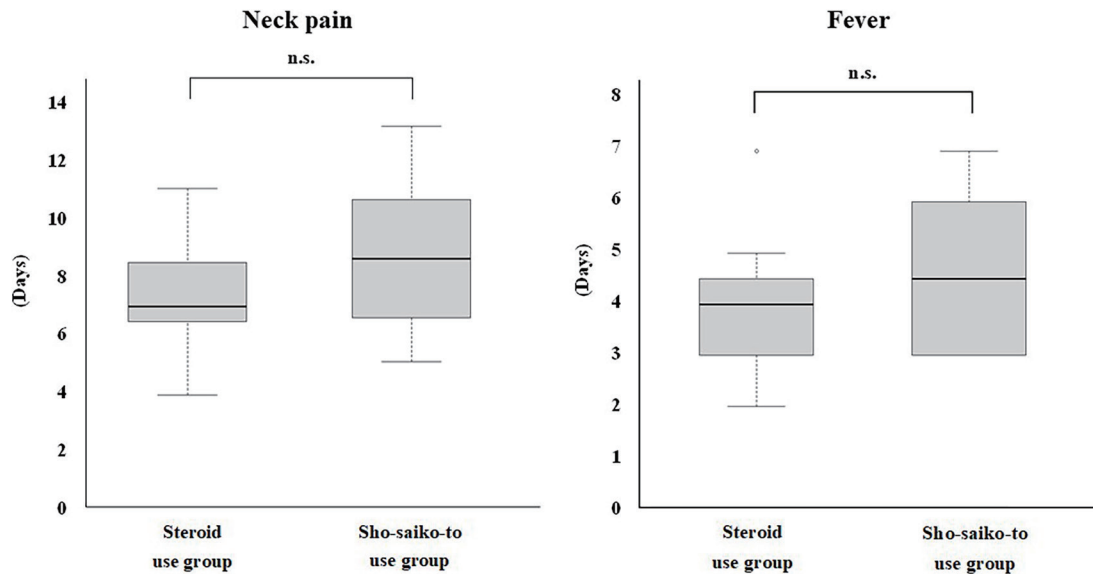


Figure 2. Period from treatment initiation to the disappearance of neck pain and fever
 *, significantly different; n.s., not significant

groups ($p = 0.660$).

Period from the treatment initiation to the disappearance of neck pain and fever (steroid use group vs. Sho-saiko-to use group) (Figure 2)

The period from the treatment initiation to the disappearance of neck pain ranged from 4 days to 11 days (average, 7.4 days) and 5 days to 13 days (average, 8.6 days) in the steroid use group and Sho-saiko-to use group, respectively. There was no significant difference between the two groups ($p = 0.447$). The period from the treatment initiation to the disappearance of fever ranged from 2 days to 7 days (average, 4.0 days) and 3 days to 7 days (average, 4.6 days) in the steroid use group and Sho-saiko-to use group, respectively. There was no significant difference between the two groups ($p = 0.514$).

DISCUSSION

Clinical diagnosis of subacute necrotizing lymphadenitis

Subacute necrotizing lymphadenitis is often accompanied by fever, in addition to painful cervical lymphadenitis^{3,6}. Blood tests often reveal a decrease in white blood cells and an increase in lactate dehydrogenase, and the CRP value remains marginally high despite an increase^{6,7}. Image

inspection reveals central necrosis of the lymph nodes⁸. Moreover, it is necessary to differentiate among malignant lymphoma, tuberculosis lymphadenitis, *Toxoplasma*, infectious mononucleosis, syphilis, and systemic lupus erythematosus³. We performed a clinical diagnosis of subacute necrotizing lymphadenitis with reference to these clinical features (Fig. 3). This disease may be accompanied by upper respiratory symptoms and sore throat^{3,6}; however, it is difficult to distinguish it from viral lymphadenitis only by the clinical symptoms. Therefore, patients with these symptoms were excluded from this study.

Sho-saiko-to reduces the illness period of subacute necrotizing lymphadenitis

Upon comparison between the symptomatic treatment and Sho-saiko-to use groups, the Sho-saiko-to use group displayed a significantly shorter period from the onset to the disappearance of neck pain. We obtained similar results for the period from the onset to the disappearance of fever. Thus, Sho-saiko-to may reduce the duration of subacute necrotizing lymphadenitis. Upon comparison between the symptomatic treatment group and the steroid use group, the steroid use group displayed a significantly shorter period until the symptoms disappeared. Furthermore, conventional treatment with steroids reduces the duration of subacute necrotizing lymphadenitis.

Lymphadenopathy persists in several cases even after the disappearance of neck pain and fever. However, lymphadenopathy is an objective finding, and the criteria differ depending on the physicians. In addition, unlike subjective symptoms, such as pain and fever, it is challenging to

- A. Fever, swelling, and pain in the neck
 - B. No upper respiratory symptom other than “A”
 - C. Blood test reveals low WBC count and high LDH levels
 - D. Ultrasonography reveals a blood flow defect in the cervical lymph nodes
 - E. Contrast-enhanced CT scan does not capture the inside of the cervical lymph nodes
 - F. Blood test results are negative for other lymphadenopathies
- Patients that satisfy criteria A, B, (C and/or D and/or E), and F were clinically diagnosed with subacute necrotizing lymphadenitis

Figure 3: Clinical diagnostic criteria of subacute necrotizing lymphadenitis
 Abbreviations: WBC, white blood cell; LDH, lactate dehydrogenase; CT, computed tomography

determine the exact time of lymphadenopathy disappearance during outpatient visits. Therefore, we did not include the time of lymphadenopathy disappearance as an endpoint.

Effectiveness of Sho-saiko-to was not inferior to that of steroids

Upon comparison between the Sho-saiko-to and steroid use groups, there was no significant difference in the period from the treatment initiation to the disappearance of neck pain and fever (without a significant difference in the period from the onset to the treatment initiation between the groups). Therefore, Sho-saiko-to may exert a therapeutic effect, comparable to that of steroids.

The definitive diagnosis of subacute necrotizing lymphadenitis is based on a histological examination of the lymph nodes³. An easy administration of steroids without tissue biopsy delays the diagnosis of serious diseases, such as malignant lymphoma. However, we occasionally encounter cases in which the patient does not wish to undergo tissue biopsy, which makes steroid therapy difficult. In such cases, Sho-saiko-to is expected to be an alternative treatment to steroids.

Pharmacological action of Sho-saiko-to

Sho-saiko-to suppresses the cyclooxygenase activity of cyclooxygenase^{9,10}. Furthermore, saikosaponin, the primary component of the bupleurum root contained in Sho-saiko-to, comprises a steroid-like skeleton and exerts steroid-like action¹¹. Therefore, Sho-saiko-to exerts anti-inflammatory effects.

In addition, Sho-saiko-to regulates the expression of cytokines, which are immunoactive substances. Their effects are wide-ranging as follows: (1) induce interleukin (IL)-1 production, which enhances cellular and humoral immunity¹²⁻¹⁴; (2) induce IL-2 production, which promotes the proliferation of T lymphocytes¹⁵; (3) suppress IL-3 production, which may be involved in autoimmunity¹⁶; (4) induce IL-6 production, which regulates humoral immunity^{12,13}; (5) promote IL-12 production, which activates natural killer cells, and induce tumor necrosis factor-alpha production, which damages virus-infected cells^{14,17}; and (6) induce interferon-gamma production, which suppresses virus growth¹².

The cause of subacute necrotizing lymphadenitis remains unknown, despite theories about viruses and autoimmunity³. The anti-inflammatory effect, virus growth inhibitory effect, and damaging effect on infected cells are advantageous in case of an infection-mediated disease. Contrarily, the immunomodulatory action of regulating cytokines supposedly works favorably in case of autoimmunity.

Thus, Sho-saiko-to maybe a treatment method comparable to steroids for subacute necrotizing lymphadenitis. Only symptomatic treatment was available, particularly in cases that did not require tissue biopsy of the lymph nodes. The addition of Sho-saiko-to to the treatment options will likely enable aggressive treatment even in such cases.

This study had some limitations as follows: (1) small sample size, (2) our inability to generalize the findings to different populations, and (3) the potential for selection bias owing to the enrollment of participants from only one institution.

CONCLUSION

Sho-saiko-to reduced the illness period of subacute necrotizing lymphadenitis and its effect was not inferior to that of steroids. The anti-inflammatory and immunomodulatory effects of Sho-saiko-to were considered effective. Sho-saiko-to may be a treatment for acute necrotizing lymphadenitis, comparable to steroids.

ETHICAL STATEMENT

This retrospective study was conducted in compliance with the tenets of the Declaration of Helsinki and the ethical guidelines for medical research targeting humans and was approved by the Tokyo Medical University Medical Ethics Review Board (approval number: T2022-0113).

INFORMED CONSENT

The need for informed consent was waived owing to the retrospective nature of the study.

CONFLICT OF INTEREST

We have no financial relationships to disclose.

SUPPORTING INFORMATION

The Sho-saiko-to used in this study was an extract preparation from Tsumura & Co., Ltd., and the composition of 7.5 g of this drug was as follows: 7.0-g bupleurum root, 3.0-g scutellaria baicalensis, 5.0-g pinellia tuber, 3.0-g ginseng, 2.0-g licorice, 3.0-g jujube, and 1.0-g ginger.

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