

Efficiency of Japanese herbal medicine shokenchuto for nocturnal enuresis

An observational study

Keiko Ogawa-Ochiai, MD, PhD^{a,b} , Kazunori Ohama, MD, PhD^{c,*}

Abstract

Japanese traditional (Kampo) medicine has been empirically used for nocturnal enuresis (NE). This study aims to investigate the efficacy of one of the most popular formulas, shokenchuto (SKT). We retrospectively analyzed 110 patients with NE who were referred to our department. Following the diagnosis of NE, treatment was started with either alarm or/and desmopressin (DDAVP) therapy. Patient refractory to DDAVP monotherapy or to combination therapy consisting of DDAVP and bedwetting alarm were selected. SKT (Tsumura Co., Tokyo, Japan) extract at a dose of 2.5 g was administered orally to all intractable cases twice daily before meals. The treatment outcomes and safety were assessed. In total, 24 cases were patient refractory to DDAVP monotherapy or to combination therapy consisting of DDAVP and bedwetting alarm. SKT was highly effective in 8, effective in 7, and ineffective in 9. A significant difference was observed between ages 10 and over ($P = 0.031$). SKT was significantly effective as a treatment for NE in patients aged ≥ 10 years and could be a good alternative if alarm or DDAVP therapies are ineffective. We proposed evaluating SKT prospectively for NE.

Abbreviations: DDAVP = desmopressin, NE = nocturnal enuresis, SKT = shokenchuto.

Keywords: children, desmopressin, Kampo medicine, nocturnal enuresis, shokenchuto

1. Introduction

Nocturnal enuresis (NE) refers to involuntary urination at night in the absence of congenital or acquired central nervous system defects among children >5 years of age.^[1] By 5 years of age, 90% to 95% of children are nearly continent during the day, and 80% to 85% are continent at night. Monosymptomatic enuresis is defined as enuresis in children without any other lower urinary tract symptoms and without a history of bladder dysfunction.^[2] NE that occurs more than twice per night can have a substantial adverse effect on the patient's quality of life, and in many cases, might require treatment. The treatment of NE begins with counseling, behavioral therapy, alarm therapy, and drug therapy, such as with antidiuretic hormone (desmopressin; DDAVP).^[3] The success rate of alarm therapy for NE is around 2/3 in children ≤ 15 years old, and the dropout rate is 10% to 30%.^[3] In contrast, DDAVP therapy completely cures 30% of patients. Furthermore, it reduces the frequency of NE by 40% with an effective rate of about 70%. However, the recurrence rate after discontinuation is as high as 60% to 70%.^[4] If neither alarm nor DDAVP therapies are independently successful, they can be combined. The combination therapy significantly reduced the frequency of NE; however, the long-term benefits are not clear.^[4] In addition, it is reported that when alarm therapy was administered in combination

with DDAVP in resistant patients, there was no significant difference in the cure rate between the alarm therapy and the placebo group, but the frequency of NE decreased significantly during the 8-week treatment.^[5] Nevertheless, some reports have revealed that therapy does not exceed the cure rate of monotherapy.^[6] Kampo formulas can be prescribed for NE that is unresolved by the standard treatments. Shokenchuto (SKT, see <http://mpdb.nibiohn.go.jp/stork/>) is typically prescribed in such cases; however, there are only a few case studies or reports about this form of treatment.^[7] Therefore, in this study, we examined whether SKT is effective as the next treatment after DDAVP and alarm therapy.

2. Patients and Methods

Between January 2013 and December 2018, 110 patients with NE were referred to our department. The inclusion criteria for patients as monosymptomatic NE were as follows: intermittent urinary incontinence during sleep in children ≤ 15 years of age; without urinary incontinence and other lower urinary tract symptoms, irrespective of the time of the day; at least 1 NE episode/mo for >3 months; and nocturnal urination recurring for >4 d/wk was defined as frequent and nocturnal urination occurring for ≤ 3 d/wk was defined as infrequent. Nocturnal

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^aClinic of Kampo Medicine, Public Central Hospital of Matto Ishikawa, 3-8, Kuramitsu, Hakusan City, Ishikawa, Japan, ^bDepartment of Japanese Traditional (Kampo) Medicine, Kanazawa University Hospital, 13-1 Takaramachi, Kanazawa City, Ishikawa, Japan, ^cDepartment of Pediatric Surgery, Public Central Hospital of Matto Ishikawa, 3-8, Kuramitsu, Hakusan City, Ishikawa, Japan.

*Correspondence: Kazunori Ohama, Department of Pediatric Surgery, Public Central Hospital of Matto Ishikawa, 3-8, Kuramitsu, Hakusan City, Ishikawa 924-8588, Japan (e-mail: k-ohama@mattohp.com).

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urine volume and bladder volume were measured to guide the choice of treatment. Nocturnal polyuria was defined in Japan as nocturnal urine volume of 200 mL or more at 6 to 9 years old and 250 mL or more at ≥10 years old, and the expected bladder capacity was defined as (age +2) × 25 mL.^[8] The effects of treatments were determined according to the International Children's Continence Society standard^[2]; the efficacy was defined as highly effective when a 100% reduction or frequency of <1NE/mo was achieved; effective when a reduction of 50% to 99% of NE/mo was achieved; and ineffective when a reduction of 0% to 49% of NE/mo was achieved.

Following diagnosis, treatment for NE (Fig. 1) was started with either alarm or/and antidiuretic hormone therapy. Patients showing no improvement to both treatments were diagnosed with intractable NE. SKT is derived from the following: *Cinnamomi cortex*, *Paeoniae radix*, *Glycyrrhiza radix*, *Zingiberis rhizoma*, *Zyzyphi fructus*, and *Saccharum granorum*. SKT extract (Tsumura Co., Tokyo, Japan) (Table 2) at a dose of 2.5 g was administered orally to all intractable cases twice daily before meals. Pseudoaldosteronism is the most relevant adverse effect of SKT,^[9] which has not been reported in pediatric patients under 10 years old. Moreover, we set the dose of SKT extract at 5 g/day, making the dose per body weight relatively smaller in patients ≥10 years of age.

When the effect of the SKT was confirmed, the dose of the antidiuretic hormone was gradually reduced; then, the dose of SKT was gradually reduced and eventually discontinued. The subjects were evaluated monthly to investigate the incidence of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [Common Terminology Criteria for Adverse Events, v5.0. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Accessed April 12, 2018)].

The study protocol was designed in accordance with the ethical principles of the Declaration of Helsinki and regional regulations. All patients provided informed consent prior to the SKT administration.

Statistical analysis was done with the Kruskal–Wallis test and Mann–Whitney *U* test (IBM SPSS Statistics, ver.26.0, IBM Corp.) *P* = .031 is considered to be significant.

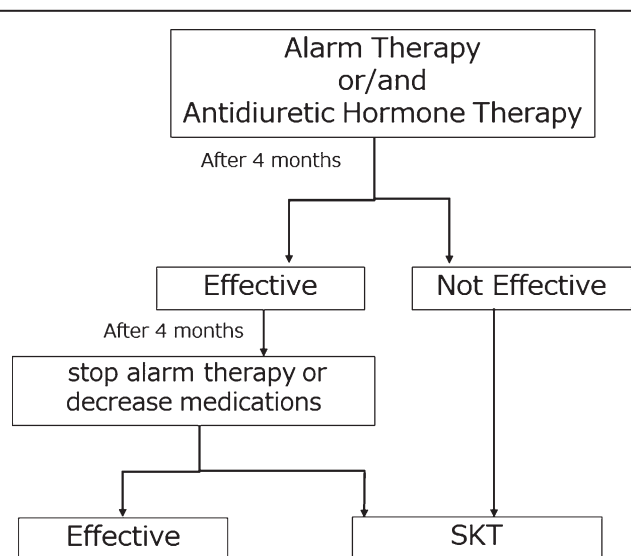


Figure 1. The protocol for the treatment of monosymptomatic NE. Initially, pharmacotherapy and/or alarm therapy is performed, and the therapeutic effect is evaluated 4 mo later. If therapy is determined to be not effective, SKT would be added. Even when effective, if reduction in the number of hormonal medications or discontinuation of the alarm therapy causes recurrence of NE, then SKT would be added. NE = noneffective, SKT = shokenchuto.

Table 1

Composition of the SKT extract granules.

Component	Weight (g)
JP peony root	6.0
JP cinnamon bark	4.0
JP jujube	4.0
JP ginger	1.0
JP <i>Glycyrrhiza</i>	2.0

A 15.0 g portion of Tsumura shokenchuto extract granules (hereafter TJ-99) contains 3.75 g of a dried extract of the following mixed crude drugs and 10.0 g of JP Koi. <p>JP = the Japanese Pharmacopoeia, SKT = shokenchuto.

3. Results

Thirty-four patients (M:F = 25:9) were ≥10 years of age (group A10) and 76 patients (M:F = 49:27) were ≤10 years of age (group U10). In group A10, 13 of 34 patients (38.2%) (M:F = 12:1) were refractory to DDAVP monotherapy or to combination therapy consisting of DDAVP and bedwetting alarm, while 11 of 76 patients (14.5%) (M:F = 8:3) were in group U10. In total, 24 cases were refractory to DDAVP monotherapy or to combination therapy consisting of DDAVP and bedwetting alarm (Table 1). The ages ranged from 6 to 12 years old, and the median was 10. SKT was prescribed to them as monotherapy or in addition to standard therapy. SKT was highly effective in 8, effective in 7, and ineffective in 9. A significant difference was observed between ages 10 and over (*P* = .031). There were no significant differences in SKT efficacy by gender. The following classifications were noted: polyuria, 14 cases (10 in group A10, 9 in group U10); bladder, 9 cases (3 in group A10, 6 in group U10); normal, (1 in group U10). There were no significant differences in SKT efficacy by NE types. There were no side effects from the SKT treatment.

4. Discussion

As described in the introduction, there are cases in which DDAVP therapy, alarm therapy, and their combination therapy are ineffective. In our cases, 38.2% in group A10, while 14.5% in group U10, were patients refractory to DDAVP monotherapy or to combination therapy consisting of DDAVP and bedwetting alarm. This suggests that NE tends to be intractable in patients ≥10 years of age.

Kampo therapy has been often administered to patients refractory to DDAVP monotherapy or to combination therapy consisting of DDAVP and bedwetting alarm. The advantages of Kampo medicine are that it is easily administered to pediatric patients, it can be administered as a prolonged treatment, it improves peripheral symptoms, and it serves as a convenient change from combination therapy to monotherapy. It has the following disadvantages: many cases do not respond to treatment immediately, the mechanisms of effectiveness are not clear, and it is often difficult for children to continue to take Kampo formulas because of its taste and difficulty in swallowing.

Paeoniflorin, a chief active ingredient in the root of *Paeoniae radix*, is effective in relieving colorectal distention-induced visceral pain in rats with visceral hyperalgesia induced by neonatal maternal separation. The adenosine A1 receptor partly mediates the analgesic effect of paeoniflorin.^[10] Moreover, shakuyakukanzoto, a formula composed of equal proportions of *Glycyrrhizae radix* and *Paeoniae radix*, both of which are included in SKT, significantly ameliorates muscle contraction disorders in patients with a broad array of underlying diseases, such as abdominal pain, extremities muscle pain, constipation, and more.^[11,12] These results suggest that *Glycyrrhizae radix* and *Paeoniae radix* might

Table 2**Profile of patients.**

Case	Age	Gender	Type	Alarm therapy	Desmopressin	Anticholinergic drug	Prognosis	Duration of SKT (mo)
1	12	M	P	–	+	–	HE	14
2	12	M	P	+	+	+	NE	14
3	11	M	P	–	+	–	HE	5
4	11	M	B	–	+	–	E	4
5	11	M	P	–	+	–	HE	7
6	11	F	P	–	+	–	HE	9
7	10	M	B	+	+	–	HE	10
8	10	M	P	+	+	–	HE	10
9	10	M	P	+	+	+	NE	4
10	10	M	P	+	+	–	NE	4
11	10	M	P	+	+	–	HE	15
12	10	M	B	–	+	–	E	9
13	10	M	P	–	+	–	E	4
14	9	M	Normal	+	+	+	HE	18
15	9	M	B	+	+	+	NE	4
16	9	M	B	+	+	–	NE	8
17	9	M	P	+	+	–	NE	4
18	8	M	B	+	+	+	NE	4
19	8	F	B	+	+	+	NE	5
20	8	M	P	+	+	–	E	21
21	8	F	B	+	+	–	E	9
22	7	M	P	–	+	–	NE	17
23	6	F	B	+	+	–	E	3
24	6	M	P	+	+	+	E	21

B = bladder capacity reduction-type, E = effective, HE = highly effective, NE = noneffective, P = polyuria-type, SKT = shokenchuto.

control bladder smooth muscle and NE. *Zyzyphi fructus* and *Glycyrrhiza radix* improve digestive function and in addition to these, *Saccharum granorum* is sweet, which makes SKT more palatable for children.

In this study, we set the dose of SKT extract at 5g/day, so the dose per body weight was relatively smaller in patients ≥ 10 years of age. Since pediatric patients often have difficulty in taking Kampo medicine, the dosage was adjusted to a smaller dose, compared to the standard dose according to body weight. In future research, we could consider increasing the dose to 10g/day in cases where 5g/day SKT is ineffective.

In our cases, the treatment results were better in patients > 10 years of age, although there is no difference in age-related effects for patients with the duration of SKT of 10 months or more in both groups. This may be because the older patients were more motivated to achieve remission of NE,^[13] and compliance for SKT may be better in group A10 than in group U10. The side effects of SKT are pseudoaldosteronism, myopathy, and hypersensitivity, although the incidence of adverse reactions is not known (https://www.tsumura.co.jp/english/products/pi/JPR_T099.pdf).

Another Kampo medicine, yokukansan, has been reported to be effective in pediatric NE with insomnia.^[14] Several other Kampo medicines have also been reported in Japanese literature as effective treatments for NE; however, they are limited to empirical reviews or case reports.

The limitation of this study is that our study is retrospective, and the sample size is relatively small to lead to generalizable results. In future research, we would like to perform a prospective study, preferably with a placebo control, and to study other Kampo medicines, besides SKT, for NE. Evidence-based use of SKT/Kampo demands studies for efficacy and safety in a rigorous controlled clinical trial so that healthcare providers can decide whether SKT/Kampo should be considered as an alternative medicine in children with monosymptomatic enuresis who have not responded to standard treatment.

5. Conclusion

SKT may be a good alternative treatment for NE if alarm therapy or DDAVP treatment is ineffective. We propose that prospective evaluation of the efficacy of SKT for NE is required to provide further proof of its use as a complementary and alternative therapy for NE.

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Author contributions

Conceptualization: Keiko Ogawa-Ochiai.
 Formal analysis: Keiko Ogawa-Ochiai.
 Methodology: Kazunori Ohama, Keiko Ogawa-Ochiai.
 Project administration: Kazunori Ohama.
 Resources: Kazunori Ohama.
 Writing – original draft: Keiko Ogawa-Ochiai.
 Writing – review & editing: Kazunori Ohama.

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