Kambakutaisoto treatment for children with night crying and arousal parasomnias developed during prolonged hospitalization for hematological and oncological diseases

Nozomu Kawashima*

*Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

***Corresponding author.** Nozomu Kawashima, MD, PhD. Assistant professor, Department of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, 466-8550 Japan, TEL: +81-52-741-2296, FAX: +91-52-744-2974, E-mail: kwnozomu@med.nagoya-u.ac.jp

Running head: Kambakutaisoto for night crying and parasomnia

Text word count: 2314 words, Number of Figures: 3, Tables: 2, Number of References: 26.

Abstract

Objective: The lack of an established treatment standard prompted an examination of whether kambakutaisoto, an herbal formula, is effective for non-rapid eye movement (NREM)-related parasomnias and night crying (provisionally defined as an infantile form of arousal parasomnia).

Methods: This study included 137 children aged median 4.1 years (range, 0.02–18.5) who were admitted for hematological and oncological diseases.

Results: Of 137, 3 children developed recurrent episodes of NREM-related parasomnias, and 3 developed night crying. The proportion of children with night-crying/parasomnia receiving invasive procedures was significantly higher than those without (100% vs. 47%, $P = .013$). All 6 children with night crying/parasomnia received kambakutaisoto at a dose of 0.13–0.22 g/kg *per os* and responded from the start of administration with a significant reduction in the number of episodes. No adverse effects were observed.

Conclusion: Kambakutaisoto may be a safe and promising therapy for night crying and NREM-related parasomnias in children.

Keywords: parasomnia, night crying, pediatric hematology/oncology, Japanese Kampo medicine, kambakutaisoto

Introduction

Children with hematological and oncological diseases are at a high risk of developing sleep disorders.[1] Besides treatment for malignancies affecting sleep behaviors in children,[1,2] adult survivors of childhood cancer are known to develop fatigue and poor sleep,[3-5] causing behavioral and neurocognitive impairment. However, studies have focused on insomnia and hypersomnia, and non-rapid eye movement (NREM)-related parasomnias, which are very common in children aged 3 years or more,[6,7] have rarely been studied among children undergoing treatment for cancer. Sleep-waking problems in infants and toddlers, occurring at night after 3 months of age and accompanied by signaling to parents, have been recently recognized as a distinctive entity from prolonged crying/infantile colic (which peaks at approximately 5–6 weeks of age with the crying occurring primarily during the daytime and evenings).[8] Sleep-waking problems in this age group are not yet defined in the International Classification of Sleep Disorders, 3rd edition.[9] However, traditional East Asian medicine has recognized this as an independent disease entity, since a century, designating the condition “night crying,” the nature of which is believed to be an infantile form of arousal parasomnia.[10] Both NREM-related parasomnias and night crying cast burdens on children and their caregivers, especially for children with hematological and oncological diseases, which require extended

hospitalization for chemotherapy and treatment for complications. Thus, recognizing and understanding these problems may improve overall treatment outcomes in children with hematological and oncological diseases.

Night crying has no specific treatments in modern medicine. Certain children with parasomnias are administered benzodiazepines and antidepressants.[11,12] However, the reported effects of these treatments are inconsistent, and concerns regarding the potential addiction and adverse effects such as disinhibition and sedation discourage the proactive use of psychotropic drugs in children. Kambakutaisoto is a formula derived from traditional Japanese Kampo medicine.[13,14] Kambakutaisoto is a decoction of Tritici Fructus (the dried fruit of wheat), Glycyrrhizae Radix (the dried root and stolon of Chinese licorice), and Zizyphi Fructus (the dried fruit of jujube). This formula was originally developed to treat hysteria. Kambakutaisoto has been traditionally administered to children with night crying and NREM-related parasomnias such as sleep terrors and sleepwalking.[10] It is currently covered by the National Health Insurance in Japan and can be administered during hospitalization.[15-17]

Given the limited treatment options for NREM-related parasomnias and night crying, kambakutaisoto is a promising treatment with a possible safety profile in children. In this study, we analyzed the etiology of NREM-related parasomnias and night crying

among children hospitalized for hematological and oncological treatments and evaluated the efficacy of kambakutaisoto treatment.

Patients and Methods

Study cohort and kambakutaisoto administration

The study retrospectively analyzed the medical records of all 137 children aged <19 years who had been consecutively admitted at the Department of Pediatrics, Nagoya University Hospital from January 2014 to April 2016. This cohort included 6 children who developed NREM-related parasomnias or night crying, and received kambakutaisoto treatment. In our hospital, children were generally hospitalized during induction and consolidation chemotherapy, returning for only a few days to their homes between chemotherapy courses. This meant at least 3 months of hospitalization. Children receiving hematopoietic stem cell transplant were hospitalized at least 3 months after transplant. Red blood cells were transfused to maintain hemoglobin levels at >8 g/dL. All patients routinely underwent brain computed tomography and/or magnetic resonance imaging at admission to rule out infection and tumoral invasion. Patients underwent electroencephalography examination before and after undergoing hematopoietic stem cell transplant. Electroencephalography was also indicated for children with parasomnias to rule out

epilepsy. Polysomnography was not obtained in this cohort. Blood tests were obtained twice or thrice a week during hospitalization.

Pharmaceutical-grade kambakutaisoto extract granules (Tsumura & Co, Tokyo, Japan) were used at a dose of 0.13–0.22 g/kg *per os* daily in either 1 dose or 2 divided doses (maximum of 7.5 g/day). A high-performance liquid chromatography fingerprint of the extract is shown in Figure 1. Kampo diagnosis and prescription was exclusively performed by fellows of the Japan Society for Oriental Medicine and board-certified members of the Japanese Society of Pediatric Hematology/Oncology.

This retrospective study was approved by the ethics committee of the Nagoya University Graduate School of Medicine (Approval Number 2016-0076).

Definition

Of the several parasomnia subtypes defined in the International Classification of Sleep Disorders, 3rd Edition, only disorders of arousal from NREM sleep were considered in this study. Parasomnias usually associated with rapid eye movement (REM) sleep and other parasomnias were excluded. Confusional arousals are defined as a condition where children are confused and disoriented to time and space. This condition may also involve automatic behaviors such as the opening of the eyes, mumbling, and lack of motor activity or sympathetic hyperactivity. Sleepwalking is defined as disoriented consciousness

involving a spectrum of activity such as sitting up in bed before walking, ambulating aimlessly, and performing inappropriate behaviors. Sleep terrors in children is defined as an episode involving abrupt awakening from sleep with a scream and unresponsiveness to attempts to calm them down.[18] In this study, an episode of parasomnia was defined as an event from the onset of symptoms specific to each subtype of parasomnia until the child could sleep again.

Night crying is defined as a condition in infants and toddlers involving sleeping for <5 h with waking and signaling (fussing/crying with a high voice) at night.[8,19] An episode of night crying was defined as an event from the onset of night crying that was not attenuated by merely leaving the sickrooms until the infant or toddler goes back to sleeps. Children who presented with NREM-related parasomnias or night crying for at least 5 days a week were included.

Invasive procedures were defined as surgical operations, hematopoietic stem cell transplant, and organ transplant. Radiation therapy, surgeries for settling central venous tunneled catheters, and biopsies of skin and superficial lymph nodes were not considered invasive in this study.

Statistical analyses

Data were retrospectively reviewed and analyzed as of September 2017. Statistical

analysis was performed using the Fisher's exact test for categorical variables and the Mann–Whitney's U test for continuous variables. The Wilcoxon signed-rank test was used for paired samples. Cumulative incidence of night crying/parasomnia with discharge from the hospital as a competing variable was calculated using Gray's method. A probability (*P*) value < .05 was considered to indicate statistical significance. All statistical analyses were conducted using JMP Pro 12.0.0 (SAS Institute Inc., NC, USA).

Results

Patient characteristics of the cohort

This study included 137 children aged median 4.1 years (range, 0.02–18.5 years) with a diagnosis of hematological or oncological disease (Table 1). They were hospitalized for a median 184 days (range, 1–723 days). Six of the 137 children (4%) developed NREM-related parasomnias or night crying. The 1-year cumulative incidence of night crying/NREM-related parasomnias was 0.0832 (Figure 2). The diagnoses of the children were almost equally divided between hematological diseases and solid tumors. Invasive treatments were performed in 68 children. Of these, 41 children (30%) underwent surgical operations, excluding less-invasive tunneled catheter insertions and biopsies. Hematopoietic stem cell transplant was performed in 35 children (26%) and none

received organ transplantation during the study period. Nightmare disorder, REM sleep behavior disorder, enuresis, and restless legs syndrome were not clinically evident in the 137 children included in this study cohort.

Characteristics of children with night crying or parasomnia

In this study, of 6 children in the night crying/parasomnia group, 3 developed night crying and 3 developed NREM-related parasomnia (Table 2). Age at admission, sex, and disease diagnosis were not significantly different between the night crying/parasomnia and non-night crying/parasomnia groups (Table 1). Interestingly, all 6 children in the night crying/parasomnia group received invasive procedures before they developed night crying/parasomnia. This proportion of patients who underwent invasive procedures was significantly higher than the proportion that did not undergo invasive procedures (non-night crying/parasomnia group) (100% vs. 47%, $P = .013$; Table 1).

Table 2 summarizes the patient characteristics of the 6 children who developed night crying/parasomnia. Three were diagnosed with hematological diseases and underwent allogeneic hematopoietic stem cell transplant, 1 was diagnosed with neuroblastoma and underwent autologous hematopoietic stem cell transplant, and the other 2 were diagnosed with rhabdomyosarcoma, which involved tumors that were completely resected during the intermission between chemotherapy and radiotherapy. The

6 children developed night crying/parasomnia within a median 10 weeks (range, 2–52 weeks) after undergoing the invasive procedures. The tendency for problematic parasomnias is known to be clustered in families,[6] but 2 children with parasomnias had no family history (Table 2). No patients manifested insomnia, and none had gastroesophageal reflux or iron deficiency. Of the 3 children with NREM-related parasomnias, 1 (KBT01) manifested both sleepwalking and sleep terrors, whereas the other 2 manifested sleep terrors and autonomic symptoms. The number of night crying/parasomnia episodes was a median twice (range, 1–4 times) per night.

Kambakutaisoto treatment of night crying and parasomnia

All 6 children in the night crying/parasomnia group received kambakutaisoto (Table 2), and fulfilled the Kampo indication for receiving kambakutaisoto ("heart blood deficiency" and "heart spleen deficiency" in 3 and 3 patients, respectively). The kambakutaisoto dosage administered was a median of 0.19 g/kg/day (range, 0.13–0.22 g/kg/day). Three patients received kambakutaisoto once daily before sleeping and the other 3 received it twice daily (morning and evening). Surprisingly, on the first night of kambakutaisoto administration, 5 of the 6 children had no episodes of night crying/parasomnia. One (KBT02) had a residual episode of NREM-related parasomnia, although the number of episodes decreased from 4 per night to 1. Four days after the start of treatment, KBT02

no longer had episodes. Recurrence of episodes during kambakutaisoto treatment was observed in 1 child (KBT03) with night crying. However, after the kambakutaisoto treatment was divided into 2 while maintaining the same total dosage per day, the child no longer experienced night crying episodes. In hindsight, 1 child (KBT04) exhibited daytime sleepiness, although he had no episodes of night crying after on the initiation of kambakutaisoto. After kambakutaisoto was divided into 2, he showed complete resolution of sleep disorders. The children received kambakutaisoto for a median 19 days (range, 2–372 days). Interestingly, even though they completed the kambakutaisoto course, no recurrent episodes of night crying/parasomnia were noticed to date.

Safety, feasibility, and tolerability of kambakutaisoto treatment, focusing on serum potassium levels

All children could to take kambakutaisoto *per os*. No adverse effects due to kambakutaisoto were observed (Table 2). One child (KBT05) had chronic diarrhea, possibly an adverse effect of an extensive course of chemotherapy. However, the diarrhea improved a week after taking kambakutaisoto, indicating a possible favorable side effect of the decoction (Table 2).

Kambakutaisoto includes relatively higher amounts of Chinese licorice, raising concerns for pseudoaldosteronism.[20] The primary symptoms of pseudoaldosteronism are

hypokalemia and body weight gain. Thus, these parameters were compared before and after initiating kambakutaisoto. Serum potassium levels and body weight were not significantly different 1 and 2 weeks after initiating kambakutaisoto treatment (Fig. 3). Hypertension, edema, and rhabdomyolysis were also not observed under kambakutaisoto treatment.

Discussion

This study is the first to assess the rare but serious problem of NREM-related parasomnias among children admitted for hematological and ontological treatments. Night crying was also included in this study based on a theory from traditional medicine that night crying and NREM-related parasomnia represent the same disease spectrum,[10] and the success of the kambakutaisoto treatment may reinforce this hypothesis. NREM-related parasomnias, irrespective of the type, have genetic predispositions.[21] While night crying in infants and toddlers has been regarded more as a social issue, it presents a burden on caregivers, and necessitates the development of an effective treatment. The establishment of a link between night crying and a family history of NREM-related parasomnias in this study may indicate a possible common pathophysiology between parasomnias and night crying. Parasomnia can be triggered by stressors such as certain medications, alcohol abuse, sleep

deprivation, and febrile episodes,[12] consistent with the observations in this study, wherein all 5 children who developed night crying/parasomnia had undergone invasive procedures.

Kambakutaisoto is a decoction derived from traditional Japanese Kampo medicine, and its pharmaceutical-grade extract granules (7.5 g) are decocted from 20 g of Tritici Fructus, 5 g of Glycyrrhizae Radix, and 6 g of Zizyphi Fructus. Pharmacological studies revealed that kambakutaisoto inhibited sodium, calcium, and potassium uptake in neurons and pentylenetetrazol-induced bursting activity, and it prolonged hexobarbital-induced sleeping time.[22,23] Kambakutaisoto successfully treated 12 children with breath-holding spells without adverse effects despite prolonged administration.[13] The precise mechanism underlying these effects is not fully understood; however, an impairment in the regulation of 5-hydroxytryptamine activity is suspected in patients with sleepwalking, causing transient increase in the excitability of serotonergic neurons.[24] Serotonergic neurons are regulated by γ-aminobutyric acidergic and noradrenergic neurons, providing a basis for benzodiazepines and selective serotonin reuptake inhibitors in the treatment of NREM-related parasomnias. Neuronal ion channels are promising targets for neuronal hyperexcitability,[25] and kambakutaisoto may stabilize neuronal membrane potential by interfering with ion channels. Although further basic and clinical research is needed, kambakutaisoto may be a potent candidate as a new drug class.

A major limitation in this study is the small number of study subjects in a single-center analysis. The prevalence of NREM-related parasomnias including night crying was 4% for this study, which is lower than that of a cross-sectional sampling survey targeting junior and junior-high school students in Japan, which was 7%.[26] A possible reason for this may be the inclusion in this study of more severe forms of night crying/parasomnias with a higher number of episodes (at least 5 days per week). Another major limitation is that polysomnography was not obtained, although 3 patients with parasomnias and 1 with night crying underwent electroencephalography to rule out epilepsy. Furthermore, the efficacy of polysomnography in infants/toddlers remains to be elucidated. Future studies should include polysomnographic tests to understand the mechanisms of night crying.

Conclusion

Kambakutaisoto is a promising candidate therapy for NREM-related parasomnias and night crying in children. Future clinical research should include sleep studies to evaluate a possible common pathophysiology underlying parasomnias and night crying.

Acknowledgments

The author thanks all patients and their families as well as the physicians and caregivers who made this study possible.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Japan Society for the Promotion of Science, KAKENHI (grant number: 18K12273).

Ethical Approval

This retrospective study was approved by the ethics committee of the Nagoya University Graduate School of Medicine (Approval Number 2016-0076).

References

1. İnce D, Demirağ B, Karapınar TH, et al. Assessment of sleep in pediatric cancer patients. *Turk J Pediatr.* 2017;59(4):379-386.
2. Rosen G, Harris AK, Liu M, Dreyfus J, Krueger J, Messinger YH. The effects of dexamethasone on sleep in young children with acute lymphoblastic leukemia. *Sleep Med.* 2015;16(4):503-509.
3. van Kooten JAMC, Maurice-Stam H, Schouten AYN, et al. High occurrence of sleep problems in survivors of a childhood brain tumor with neurocognitive complaints: The association with psychosocial and behavioral executive functioning. *Pediatr Blood Cancer.* 2019;66(11):e27947.
4. Rach AM, Crabtree VM, Brinkman TM, et al. Predictors of fatigue and poor sleep in adult survivors of childhood Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. *J Cancer Surviv.* 2017;11(2):256-263.
5. Mulrooney DA, Ness KK, Neglia JP, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). *Sleep.* 2008;31(2):271-281.
6. Kotagal S. Parasomnias in childhood. *Sleep Med Rev.* 2009;13(2):157-168.
7. Paruthi S, Chervin RD. Approaches to the assessment of arousals and sleep disturbance in children. *Sleep Med.* 2010;11(7):622-627.
8. St James-Roberts I, Peachey E. Distinguishing infant prolonged crying from sleep-waking problems. *Archives of disease in childhood.* 2011;96(4):340-344.
9. Sateia MJ. International Classification of Sleep Disorders-Third Edition. *CHEST.* 2014;146(5):1387-1394.
10. Kawashima N, Yamaguchi H. Origin of Kambakutaisoto for Night Crying (Yatei) and Fright Crying (Kyotei): Research on the Medical History. *Jounal of the Japan Pediatric Society for Oriental Medicine.* 2017(30):43-50.
11. Stores G. Aspects of parasomnias in childhood and adolescence. *Archives of disease in childhood.* 2009;94(1):63-69.
12. Manni R, Toscano G, Terzaghi M. Therapeutic Symptomatic Strategies in the Parasomnias. *Curr Treat Options Neurol.* 2018;20(7):26.
13. Murata R, Matsuoka O, Hattori H, et al. Efficacy of kan-baku-taiso-to (TJ-72) on breath-holding spells in children. *Am J Chin Med.* 1988;16(3-4):155-158.
14. Hijikata Y, Makiura N, Kano T, et al. Kampo medicine, based on traditional medicine theory, in treating uncured glossodynia: efficacy in five clinical cases. *Am J Chin Med.* 2008;36(5):835-847.

15. Kawashima N, Deveaux TE, Yoshida N, Matsumoto K, Kato K. Choreito, a formula from Japanese traditional medicine (Kampo medicine), for massive hemorrhagic cystitis and clot retention in a pediatric patient with refractory acute lymphoblastic leukemia. *Phytomedicine.* 2012;19(12):1143-1146.
16. Kawashima N, Sekiya Y, Narita A, et al. Kampo patterns and radiology in children receiving choreito for hemorrhagic cystitis after hematopoietic stem cell transplantation. *Traditional & Kampo Medicine.* 2016;3(2):136-144.
17. Kawashima N, Ito Y, Sekiya Y, et al. Choreito Formula for BK Virus–associated Hemorrhagic Cystitis after Allogeneic Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation.* 2015;21(2):319-325.
18. Kotagal S. Sleep-Wake Disorders of Childhood. *Continuum (Minneap Minn).* 2017;23(4, Sleep Neurology):1132-1150.
19. Blunden SL, Thompson KR, Dawson D. Behavioural sleep treatments and night time crying in infants: challenging the status quo. *Sleep Med Rev.* 2011;15(5):327-334.
20. Takahashi K, Yoshino T, Maki Y, et al. Identification of glycyrrhizin metabolites in humans and of a potential biomarker of liquorice-induced pseudoaldosteronism: a multi-centre cross-sectional study. *Arch Toxicol.* 2019;93(11):3111-3119.
21. Heidbreder A, Frauscher B, Mitterling T, et al. Not Only Sleepwalking But NREM Parasomnia Irrespective of the Type Is Associated with HLA DQB1*05:01. *J Clin Sleep Med.* 2016;12(4):565-570.
22. Tsuda T, Kubota K, Yasuda K, Nishikawa S, Sugaya A, Sugaya E. Effects of Chinese herbal medicine "kanbaku-taiso-to" on transmembrane ionic currents and its local anesthetic action. *J Ethnopharmacol.* 1986;17(3):257-261.
23. Tsuda T, Kubota K, Yasuda K, Sugaya A, Sugaya E. Effect of Chinese herbal medicine "kanbaku-taiso-to" on neuropharmacological tests. *J Ethnopharmacol.* 1986;15(3):289-296.
24. Juszczak GR, Swiergiel AH. Serotonergic hypothesis of sleepwalking. *Medical Hypotheses.* 2005;64(1):28-32.
25. Paoletti P, Ellis-Davies GCR, Mourot A. Optical control of neuronal ion channels and receptors. *Nature Reviews Neuroscience.* 2019;20(9):514-532.
26. Itani O, Kaneita Y, Ikeda M, et al. Disorders of arousal and sleep-related bruxism among Japanese adolescents: a nationwide representative survey. *Sleep Med.* 2013;14(6):532-541.

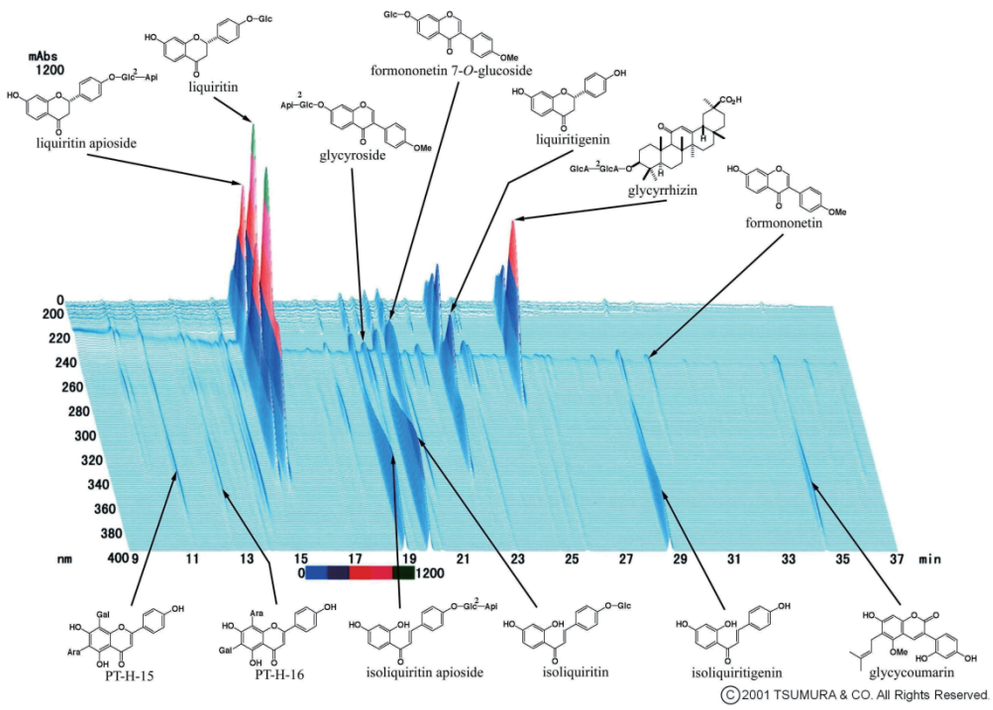

Figure 1

246x175mm (300 x 300 DPI)

Figure 1. Three-dimensional high-performance liquid chromatography of kambakutaisoto extract granules.

Three-dimensional high-performance liquid chromatography was performed using a representative lot of pharmaceutical-grade kambakutaisoto extract granules (Tsumura & Co, Tokyo, Japan) administered in this study. This chart was provided by Tsumura & Co.

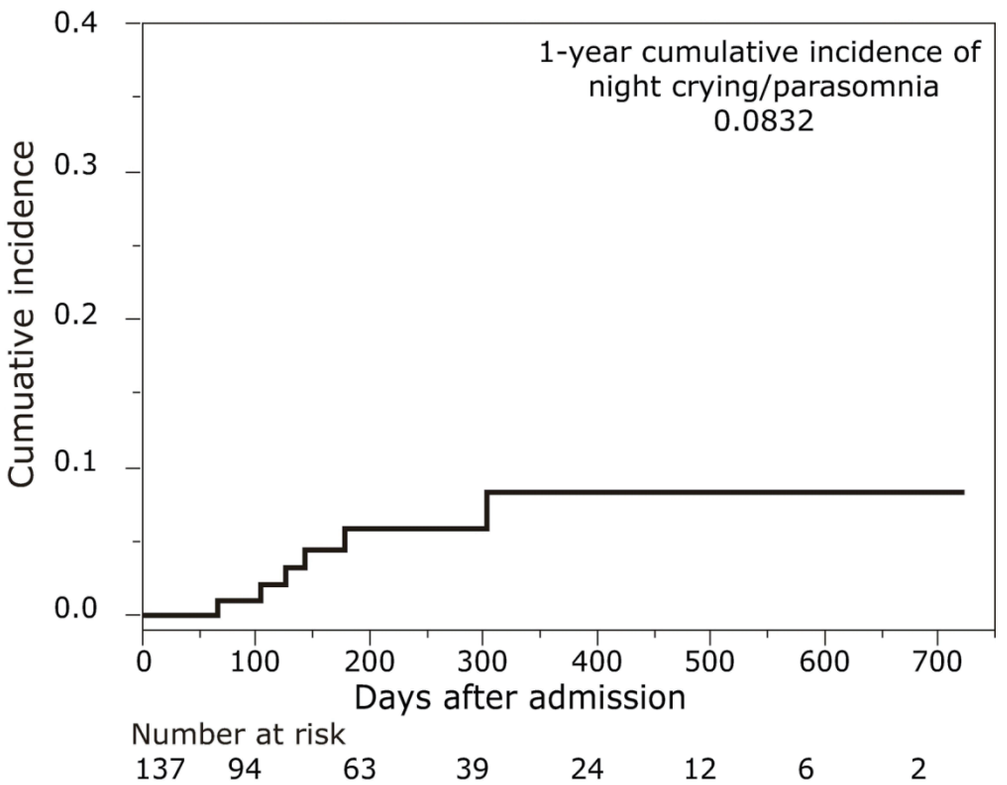

Figure 2

146x115mm (300 x 300 DPI)

Figure 2. Cumulative incidence of night crying and non-rapid eye movement-related parasomnias in the study cohort.

The 1-year cumulative incidence of night crying/parasomnia was 0.0832.

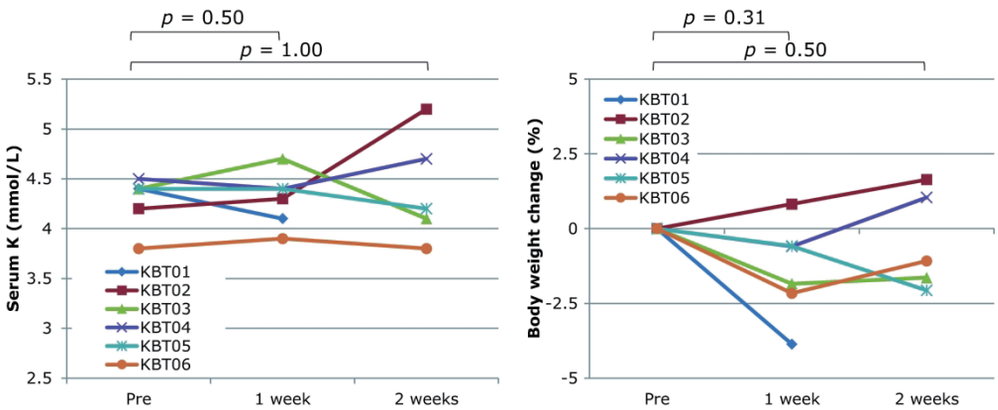

Figure 3

223x90mm (600 x 600 DPI)

Figure 3. Serum potassium and body weight change after kambakutaisoto treatment.

Children receiving kambakutaisoto were followed up to monitor serum potassium levels and body weight changes for signs of pseudo-aldosteronism. Potassium level was essentially unchanged after 1 and 2 weeks after initiating kambakutaisoto treatment (Wilcoxon signed-rank test, *P* = 1.0 and *P* = 1.0, respectively). Similarly, body weight was unchanged after one and two weeks after initiating kambakutaisoto treatment (Wilcoxon signed-rank test, *P* = .25 and *P* = 1.0, respectively).

Table 1. Characteristics of the study cohort.

		Total cohort	Night crying/parasomnia		
			No	Yes	
		N = 137	*n* = 131	*n* = 6	*P*
Age at hospitalizaion, median year (range)		4.1 (0.02-	4.1 (0.02-	2.5 (0.3-	0.230
Sex	Male, *n*	77	76	1	0.086
	Female, *n*	60	55	5	
Disease, *n*	Hematological malignancy	46	45	1	0.573
	Non malignancy	28	26	2	
	Solid tumor	63	60	3	
Invasive procedures, *n* (%)	Operation*	41 (30%)	39 (30%)	2 (33%)	1.000
	Stem cell transplant	35 (26%)	31 (24%)	4 (67%)	0.037
	Operation or transplant	68 (50%)	62 (47%)	6 (100%)	0.013

*Operations for catherter insertion or biopsy were excluded.

Table 2. Clinical characteristics of children with night crying and parasomnia

ID	Age	Sex	Dx	PMH	Family history of parasomnia	Invasive proceture	Duration from procedure (wk)	Daytime sleepiness	Insomnia	Night crying	Confusional arousal	Sleep-walking	Sleep terrors	Autonomic symptoms	Episode (/night)	Kampo dx	Dosage of kambaku-taisoto (g/kg/d)		Episode on the start of therapy (/night)	Duration of kambaku-taisoto (d)	Recurrence of episodes	Side effect
KBT01	10.5	F	AA	PRES	-	BMT	17	+/-	-	-	-	+	+	-	1	Heart Blood deficiency	0.22	bid	0	5	-	-
KBT02	3.6	F	AA	-	-	BMT	12	-	-	-	-	-	+	+	4	Heart Spleen deficiency	0.21	hs	1	20	-	-
KBT03	2.0	F	RMS	-	Sleepwalking	Op	5	-	-	+	-	-	-	-	2	Heart Blood deficiency	0.15	hs	0	372	+ (resolution after changed to	-
KBT04	0.6	M	RMS	-	Confusional arousa	Op	2	+/-	-	+	-	-	-	-	2	Heart Blood deficiency	0.19	hs	0	18	-	-
KBT05	2.0	F	ALL	-	-	BMT	52	-	-	+	-	-	-	-	2	Heart Spleen deficiency	0.13	bid	0	56	-	Diarrhea improvement
KBT06	3.5	F	NB	-	-	aPBSCT	7	-	-	+	-	-	+	+	1	Heart Spleen deficiency	0.20	bid	0	2	-	-

Abbreviations: M, male; F, female; Dx, diagnosis; AA, aplastic anemia; RMS, rhabdomyosarcoma; ALL, acute lymphoblastic leukemia; NB, neuroblastoma; PMH, past medical history; PRES, posterior reversible encephalopathy syndrome; BMT, bone marrow transplant; aPBSCT, autologous peripheral blood stem cell transplant; Op, resection of the tumor; bid, twice a day; hs, before sleep.