

Original Article

# Yokukansan for the treatment of preoperative anxiety and postoperative delirium in colorectal cancer patients: a retrospective study

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## Abstract

**Background:** Yokukansan (YKS), a Japanese traditional herbal medicine for neurosis and insomnia, is speculated to be useful for perioperative psychiatric symptoms in cancer patients, but there exists little empirical evidence. This study provides preliminary data about the efficacy, feasibility, and side effects of YYS for the treatment of preoperative anxiety and postoperative delirium in cancer patients.

**Methods:** We retrospectively reviewed the medical records of colorectal cancer patients who took YYS for preoperative anxiety, evaluating the following: (1) patient characteristics, (2) feasibility of taking YYS, (3) changes in preoperative anxiety based on the Clinical Global Impression (CGI) scale and Edmonton Symptom Assessment System-revised (ESAS-r-anxiety), (4) incidence of postoperative delirium and (5) YYS-related side effects.

**Results:** We reviewed 19 medical records. There was a significant difference between ESAS-r-anxiety scores ( $P = 0.028$ ) before and after taking YYS, but no difference between CGI scores ( $P = 0.056$ ). The incidence of postoperative delirium was 5.2% (95% CI = 0.0–14.5). One patient could not complete the course of YYS during the perioperative administration period, but there were no side effects of Grade 2 or worse according to the Common Terminology Criteria for Adverse Events v4.

**Conclusions:** Cancer patients could safely take YYS before surgery. There was a significant improvement in preoperative anxiety after taking YYS, and the incident rate of postoperative delirium was lower than in previous studies. These results suggest that YYS may be useful for perioperative psychiatric symptoms in cancer patients. Further well-designed studies are needed to substantiate our results.

**Key words:** Yokukansan, neoplasms, surgery, anxiety, delirium

## Introduction

Cancer patients experience many perioperative psychiatric symptoms, preoperative anxiety being the most common (1,2). Anxiety reduces decision-making ability and treatment compliance, exacerbates cancer symptoms and reduces patients' quality of life (2). In the surgical setting, it is also suggested that anxiety prolongs postoperative pain (3), decreases endocrine and immune function, and affects the progression and long-term prognosis of cancer (4–7). Therefore, reducing preoperative anxiety should provide meaningful benefits throughout the course of cancer treatment.

Postoperative delirium, which is a clinical syndrome characterized by the acute disruption of attention and cognition (8), is also a common complication in cancer patients. Previous studies reported that the prevalence of postoperative delirium (9–13) ranged from 11.5% in a prospective study of head and neck cancer patients (9) to 50% in a retrospective study of esophageal cancer patients (10), and it is associated with poor outcomes such as longer length of hospital stay, functional disability, decline of cognitive function, high mortality and high hospital costs (14–18). Therefore, it is necessary to prevent postoperative delirium in cancer patients.

Benzodiazepines are widely used to treat anxiety. However, they have muscle relaxant effects and increase the risk of falls (19). They are also suggested to cause delirium when used in vulnerable patients such as the elderly and those with dementia (20–24). Although antipsychotics are commonly prescribed for delirium, they may cause over-sedation in a dose-dependent manner, as well as adverse reactions such as extrapyramidal symptoms and long QT syndrome (25–27). Therefore, it is risky to use these drugs in elderly patients and those with heart disease. For these reasons, there is a growing interest in safe methods of preventing and treating perioperative psychiatric symptoms.

Yokukansan (YKS), which is a Japanese traditional herbal kampo medicine, could be another possible treatment for perioperative psychiatric symptoms in cancer patients. YKS is generally used to treat neurosis and insomnia, as well as agitation in infants. In addition, some studies reported that YKS improved behavioral and psychological symptoms of dementia (BPSD), such as delusions, hallucinations, agitation/aggression, dysphoria, anxiety, irritability/lability and aberrant motor activity (28–33). There exists speculation that YKS may prevent delirium due to the fact that its clinical symptoms are similar to those of BPSD. One pilot randomized clinical trial with a small number of subjects demonstrated favorable effects and safety of YKS for postoperative delirium after cardiovascular surgery in Japan (34). Moreover, YKS has severe side effects such as pseudohyperaldosteronism, but it happens only one out of 3141 cases (35), so it is comparatively easy to administer to elderly individuals, patients with dementia, or those who have undergone surgery.

Although YKS is speculated to be useful for perioperative psychiatric symptoms, there exists little empirical evidence. One study compared the effects of diazepam with YKS for preoperative anxiety and showed that the two drugs had comparable therapeutic effects (36). The aims of this study were to provide preliminary data about the efficacy, feasibility, and side effects of YKS for the treatment of preoperative anxiety and postoperative delirium in cancer patients.

## Patients and methods

### Setting and subjects

This study was a retrospective investigation of medical records of patients who were (1) scheduled to undergo tumor resection in the

department of colorectal surgery, National Cancer Center Hospital in Japan; (2) referred to the department of psycho-oncology; (3) received YKS for their preoperative anxiety and (4) followed up after surgery for at least 5 days between March and April in 2016. During the study period, the surgical and psycho-oncology teams collaborated intensively with the perioperative mental care team, and we clinically administered YKS for patients with preoperative anxiety. We used the Clinical Global Impression (CGI) scale (37) to evaluate the anxiety of all patients scheduled to undergo tumor resection in the department of colorectal surgery. Beginning 2 days before surgery, we administered 7.5 g of YKS (TJ-54, Tsumura & Co., Tokyo, Japan) to patients with an anxiety severity score of 2 or higher on the CGI scale. Each patient completed the Edmonton Symptom Assessment System-revised (ESAS-r) anxiety item (38,39) before and after taking YKS. We assessed whether delirium, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (40), appeared during the 5-day postoperative period. We set the evaluation period of delirium to 5 days after surgery because several previous studies suggested that postoperative delirium usually appeared in 2 or 3 days after surgery (10,11,13,41–43).

We conducted a review of each medical record and evaluated the following: (1) demographic variables and patient characteristics, (2) feasibility of taking YKS, (3) change in anxiety scores, (4) incidence of postoperative delirium and (5) YKS-related side effects.

This case series study was conducted in accordance with the principles of the Declaration of Helsinki. We were not required to receive approval by the Institutional Review Board or obtain patient informed consent because this was a retrospective chart review.

## Measures

### Demographic and clinical characteristics

All demographic data and clinical characteristics were obtained from the patients' medical records by a trained psychiatrist (S.W.).

### Preoperative anxiety

*CGI:* The CGI scale is a commonly used measure of symptom severity and therapeutic response in studies of treatments for patients with mental disorders. Many researchers, while recognizing the validity of the scale, consider it to be subjective as it requires comparison of the subject to typical patients in the researcher's experience.

The Clinical Global Impression-Severity (CGI-S) scale is a 7-point scale that requires the researcher to rate the severity of the patient's illness at the time of assessment, relative to the researcher's past experience with patients with the same diagnosis. Possible scores are as follows: 1, normal/not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; and 7, extremely ill.

The Clinical Global Impression-Improvement (CGI-I) scale is a 7-point scale that requires the researcher to assess how much the patient's illness has improved or worsened relative to baseline at the beginning of the intervention, and is rated as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse.

We used the CGI scale to assess patients' anxiety rated by observers.

*ESAS-r:* The ESAS-r is a self-reported symptom measurement tool. It consists of an 11-point numerical rating scale for the self-report of nine common symptoms of cancer, with a 10th item for a patient-specific symptom. Cronbach's alpha coefficient of the Japanese version of ESAS-r was 0.87. The intraclass correlation

coefficient in the test–retest examination was 0.84 for anxiety score. The ESAS-r anxiety item was moderately correlated with the emotional functioning subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items, with Pearson correlation coefficients of  $-0.67$ .

We used the ESAS-r to assess patients' anxiety reported by themselves.

### Postoperative delirium

**DSM-5:** The DSM-5 offers a standard criterion for the classification of mental disorders. Many mental health professionals use the manual to determine a patient's diagnosis and to communicate this diagnosis to other practitioners. DSM-5 criteria can be used clinically by psychiatrists to determine whether delirium is present or not.

### Feasibility

As for feasibility, we judged whether patients could completely take YKS and there was no refusal of taking it during the perioperative administration period.

### Side effects of Yokukansan

We considered side effects of YKS to be present if they were rated as more severe than Grade 2 based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.

### Statistical analysis

Descriptive statistics were used to describe baseline characteristics and outcome measures. We considered age, the duration of operation, the duration of anesthesia, and the amount of blood loss to be continuous variables, while other factors were nominal categorical variables. The independent samples *t*-test was used to evaluate differences in anxiety before and after taking YKS. *P* values  $<0.05$  were considered statistically significant. Analyses were performed using R.

## Results

### Patient demographics and characteristics of the surgical procedure

Of 26 patients who underwent tumor resection in the colorectal division, 19 (73.1%) had anxiety with severity rated as 2 or higher on the CGI-S. Table 1 shows data on patient demographics and characteristics of the surgical procedure. Subjects averaged 63.5 years of age (range 49–82), and the majority were male (63.2%). Twelve patients had comorbidities such as hypertension (36.8%), diabetes mellitus (15.8%), history of cerebral infarction (10.5%), and history of cancer (10.5%). One patient took benzodiazepines and another took opioids, but none was treated with antipsychotics. Open abdominal surgery was performed in 11 patients (57.9%). The mean operation time was 4.5 h, and the mean anesthesia time was 5.5 h.

### Change in preoperative anxiety

Table 2 and Fig. 1 show changes in preoperative anxiety from baseline. The mean ESAS-r anxiety item scores before and after taking YKS were 5.1 (SD = 3.2) and 4.7 (SD = 3.1), respectively ( $P = 0.028$ ). On the other hand, there were no significant differences in the mean CGI-S scores (before YKS, 3.2 (SD = 1.4); after YKS, 2.9 (SD = 1.0);  $P = 0.056$ ). The mean CGI-I score was 3.4 (SD = 0.9).

**Table 1.** Patient demographics and characteristics of the surgical procedure ( $n = 19$ )

	<i>n</i>	%
Age, mean (SD), years	63.5 (8.9)	
Sex		
Male	12	63.2
BMI, mean (SD), kg/m <sup>2</sup>	23.3 (3.3)	
ASA physical status		
1	5	26.3
2	12	63.2
3	2	10.5
4	0	0.0
Comorbidities		
Hypertension	7	36.8
Diabetes mellitus	3	15.8
History of cerebral infarction	2	10.5
History of cancer	2	10.5
Preoperative drug use		
Benzodiazepine	1	5.2
Antipsychotics	0	0.0
Opioid	1	5.2
Primary cancer site		
Colon	12	63.2
Rectum	7	36.8
Cancer stage		
1	6	31.6
2	3	15.8
3	9	47.4
4	1	5.2
Type of surgery		
Laparoscopic surgery	8	42.1
Open abdominal surgery	11	57.9
Type of anesthesia		
Inhalational anesthesia	18	94.7
Total intravenous anesthesia	1	5.2
Epidural anesthesia performed	12	63.2
Duration of operation, mean (SD), hours	4.5 (2.1)	
Duration of anesthesia, mean (SD), hours	5.5 (2.1)	
Blood loss, mean (SD), ml	257 (321)	

SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologist class.

### Incidence of postoperative delirium

Only one patient (5.2%; 95% CI = 0.0–14.5) developed postoperative delirium.

### Feasibility and side effects of Yokukansan

One patient could not complete the course of YKS due to stomach ache after taking a laxative for surgical preparation. There were no side effects of CTCAE v4 Grade 2 or higher, and also pseudohyperaldosteronism.

## Discussion

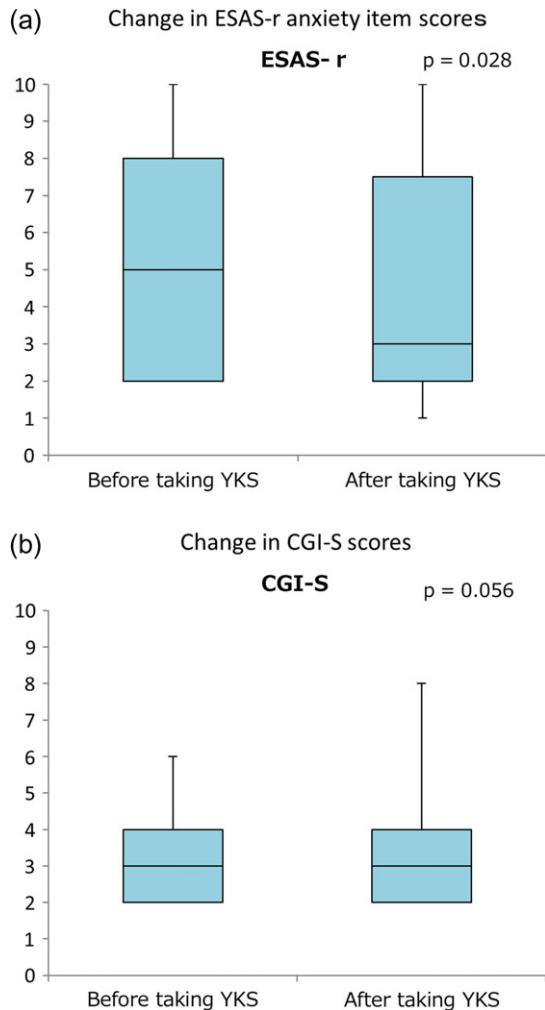
In this study, we examined the efficacy, feasibility, and side effects of YKS for the treatment of preoperative anxiety and prevention of postoperative delirium in cancer patients. Although YKS is an herbal medicine that is used to neurosis and insomnia, there are insufficient clinical data about the drug. Our retrospective investigation showed a favorable effect of YKS on preoperative anxiety, providing a basis for moving forward with randomized placebo-controlled trials. In this

**Table 2.** Anxiety outcomes

	Before taking Yokukansan	After taking Yokukansan	P values
ESAS-r anxiety item score, mean (SD)	5.1 (3.2)	4.7 (3.1)	0.028
CGI-S score, mean (SD), days	3.2 (1.4)	2.9 (1.0)	0.056
CGI-I score, mean (SD)		3.4 (0.9)	

SD, standard deviation; ESAS-r, the Edmonton Symptom Assessment System-revised; CGI-S, the Clinical Global Impression-Severity; CGI-I, the Clinical Global Impression-Improvement.

P values were obtained via *t*-test.



**Figure 1.** Change in preoperative anxiety before and after taking YKS. Box plot explanation: upper box boundary, 75th percentile; lower box boundary, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile.

study, the incidence of postoperative delirium was 5.2% (95% CI = 0.0–14.5). This is low compared with previous studies (9–13), although there were differences in patient characteristics and surgical settings. Besides from the effect of YKS, several reasons could be considered why the incidence rate of postoperative delirium was low in

this study. For example, this study included many laparoscopic surgeries, which were few burdens of the surgery for the patients and previous studies have suggested that the onset of delirium after laparoscopic surgery may decrease (44–46). As another reason, we introduced fast-track surgery which include early mobilization and oral feeding, which may have decreased postoperative delirium (47,48).

There is no evidence about the adequate duration of YKS administration. In previous studies that demonstrated a beneficial effect of YKS for BPSD, subjects took YKS for at least 2 weeks (28–33), but we considered this duration to be too long in a real surgical setting. Since YKS treatment for 2 days appeared to have been effective in this study, short-term administration of YKS may be useful for surgical patients.

This study has some limitations. First, we may have failed to identify various symptoms and diagnoses because this was a retrospective medical record review and incomplete documentation may sometimes occur. Second, this study included only colorectal cancer patients, which could limit the generalizability of our results to other cancer patients. Finally, all participants could take orally administered YKS, which could limit the generalizability of our results to patients unable to ingest oral medications, such as those with ileus or dysphasia. Because of such limitations, it is necessary to be careful when adapting our findings to other cancer settings.

Despite these drawbacks, our results provide preliminary information on the effects of YKS on perioperative psychiatric symptoms especially preoperative anxiety in cancer patients, and demonstrate that such patients can take YKS safely before surgery. Our findings also suggest the possibility of YKS for treatment of prevention of postoperative delirium in cancer patients, which is not statistically confirmed, and further investigation is necessary for this point. This is a first step in providing preliminary data about the efficacy and feasibility of YKS. Further well-designed studies are needed to substantiate these results.

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**Conflict of interest statement**

None declared.

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