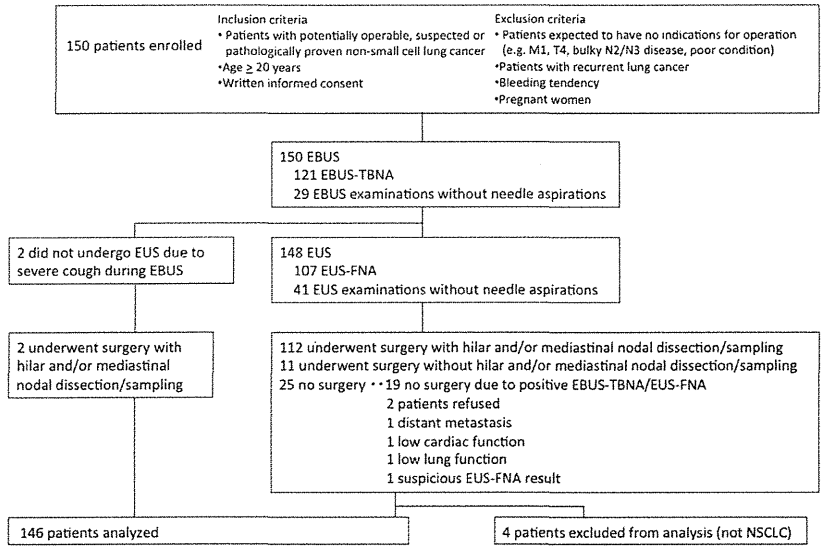

FIGURE E1. CONSORT diagram showing the clinical course of patients enrolled in the study.

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ORIGINAL ARTICLE

Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial

Shinji Fukata · Yasuji Kawabata · Ken Fujisiro · Yuichi Katagawa · Kojiro Kuroiwa · Hirotoshi Akiyama · Yasuhito Terabe · Masahiko Ando · Takashi Kawamura · Hideyuki Hattori

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Abstract
Purpose Postoperative delirium is the most common postoperative complication in the elderly. The purpose of this study was to evaluate the safety and effectiveness of the preventive administration of low-dose haloperidol on the development of postoperative delirium after abdominal or orthopedic surgery in elderly patients.
Subjects A total of 119 patients aged 75 years or older who underwent elective surgery for digestive or orthopedic disease were included in this study.
Methods Patients were divided into those who did (intervention group, $n = 59$) and did not (control group, $n = 60$) receive 2.5 mg of haloperidol at 18:00 daily for 3 days after surgery; a randomized, open-label prospective study was performed on these groups. The primary endpoint was the incidence of postoperative delirium during the first 7 days after the operation.
Results The incidence of postoperative delirium in all patients was 37.8 %. No side effects involving haloperidol were noted; however, the incidences of postoperative delirium were 42.4 and 33.3 % in the intervention and control groups, respectively, which were not significantly different ($p = 0.309$). No significant effect of the treatment was observed on the severity or persistence of postoperative delirium.
Conclusions The preventive administration of low-dose haloperidol did not induce any adverse events, but also did not significantly decrease the incidence or severity of postoperative delirium or shorten its persistence.

Keywords Haloperidol prophylaxis · Postoperative delirium · Elderly patients · Randomized open-label prospective trial · NEECHAM

Introduction

The incidence of diseases in the elderly requiring surgery, such as femoral neck fractures and colorectal cancer, has

S. Fukata · Y. Kawabata · K. Fujisiro · Y. Katagawa
Department of Surgery, National Center for Geriatrics and Gerontology, Obu, Japan

S. Fukata (✉)
Department of Perioperative Medical Care, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka, Obu, Aichi 474-8511, Japan
e-mail: fukatash@ncgg.go.jp

K. Kuroiwa
Department of Surgery, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

H. Akiyama
Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Y. Terabe
Department of Restorative Medicine, National Center for Geriatrics and Gerontology, Obu, Japan

M. Ando
Center for Advanced Medicine and Clinical Research, Nagoya University Graduate School of Medicine, Nagoya, Japan

T. Kawamura
Kyoto University Health Service, Kyoto, Japan

H. Hattori
Department of Psychiatry, National Center for Geriatrics and Gerontology, Obu, Japan

increased with the aging of the population in Japan [1, 2]. An advanced age is not considered to be a contraindication for surgery worldwide, and surgery is actively performed on patients in their 90 s [3]. However, postoperative management of the elderly is accompanied by many risks. In particular, postoperative delirium, which is the most common postoperative complication [4], represents a major issue in the postoperative treatment of the elderly. It is characterized by a disturbance in consciousness/attentiveness/understanding/cognition and a disorder in the sleep–wake rhythm. It develops suddenly and is likely to vary over the course of a day, inducing various psychiatric symptoms and abnormal behavior [5]. Since postoperative delirium develops in the postoperative recovery phase, it makes postoperative management difficult, disturbs postoperative care and recovery, and is associated with various risks, such as the disturbance of medical care due to the removal of a drip infusion, electrodes and monitors. It also puts an excess burden on medical care workers due to frequent nurse calls and violence, and due to the trauma and fractures caused by tumbles and falls. Moreover, restlessness frequently occurs at night when the nursing staff is shorthanded, which is a serious issue in ward management, and causes excess labor and load on nurses and the patients' families. Postoperative delirium also costs more because it delays the postoperative management and prolongs the hospital stay [6].

Once postoperative delirium develops, only symptomatic treatment with drugs (haloperidol) is currently available, and the effect is insufficient in many cases. A high dose may be necessary, which can markedly influence many patients' physical condition. Therefore, methods to prevent postoperative delirium, to rapidly detect the signs of delirium, to prevent progression to a more severe state and to reduce the persistence of the condition need to be established.

Our previous studies confirmed that the NEECHAM confusion scale (NEECHAM) is useful and objective for the evaluation of postoperative delirium; the incidence of postoperative delirium in 75-year-old or older surgical patients was 55 % when evaluated using the NEECHAM scale. Age, preoperative cognitive dysfunction (a low Mini-Mental State Examination (MMSE) score) and a low preoperative NEECHAM score, but not the surgical department or anesthesia type, were significantly correlated with the development of postoperative delirium, and the incidence of postoperative delirium was higher than 80 % in patients with MMSE and NEECHAM scores lower than 25 and 27 before surgery, respectively, which indicated that these patients represent a high-risk group [7]. We considered that the evaluation of the MMSE and NEECHAM before surgery and the NEECHAM during the postoperative course can facilitate the prevention and early treatment of postoperative delirium in elderly patients.

Pharmacological prevention of postoperative delirium by prophylaxis with antipsychotic medication has been reported in several studies [8]. Oral administration of risperidone and olanzapine reduced the incidence of postoperative delirium in patients undergoing cardiac surgery and hip or knee surgery, respectively [9–11]. However, these drugs are not applicable for many patients, because they are unable to have oral intake for a period of time following surgery. In this respect, either ondansetron or haloperidol, whose intravenous injection has been shown to be effective for the treatment of postoperative delirium [12], can be used. Since the aim of our present study was to incorporate routine drug prophylaxis for surgical patients, ondansetron, whose use is not covered by the health insurance system in Japan, was considered to be unfavorable, leaving haloperidol as the only approved injectable medication that could be used. The effects of haloperidol prophylaxis have already been examined in some studies [13–16], but its efficacy for decreasing the occurrence of postoperative delirium, especially in the elderly, is controversial [13–18].

On the basis of these considerations and the results of our previous studies, we performed a randomized, open-label prospective study to investigate the efficacy and safety of the daily postoperative administration of low-dose haloperidol on postoperative delirium in 75-year-old or older patients who underwent abdominal or orthopedic surgery.

Subjects and methods

Ethical considerations

This study was performed in conformity to the ethical principles based on the Declaration of Helsinki and the 'Ethical Guidelines for Clinical Studies' (notification of the Ministry of Health, Labour and Welfare).

(1) The patients were only included in the study when informed consent was obtained.
(2) The patients' privacy was respected, the secrecy of the recorded results was strictly kept and no information obtained from the study results was used for objectives other than research. To prepare the patient evaluation tables, the patients' privacy protection was sufficiently considered, and patients were identified using identification codes.

Regarding the prophylactic intervention study for postoperative delirium in elderly patients, approval had already been obtained from the Ethics and Conflict of Interest Committee of the National Center for Geriatrics and Gerontology. Other study cooperative institutions started the collection of patients after approval by their respective ethics committee.

Study design and objectives

This was a randomized, open-label prospective trial, and the objective was to evaluate the effect of low-dose haloperidol (2.5 mg/day, for the first 3 days after surgery) on the development, severity and persistence of postoperative delirium, and to evaluate the safety of its preventive intravenous administration to patients 75-year old or older who underwent abdominal or orthopedic surgery.

Patients

The subjects consisted of 121 75-year-old or older patients who underwent elective abdominal surgery under general anesthesia or elective orthopedic surgery under general/spinal anesthesia and gave consent to participate in this study at one of five cooperative institutions (National Center for Geriatrics and Gerontology, Tokyo Metropolitan Geriatric Hospital, Yokohama City University Graduate School of Medicine, Aichi-Saiseikai Hospital and Shizuoka-Saiseikai Hospital) between January 2007 and December 2012. Their age, gender, disease treated with surgery, cognitive function (Mini-Mental State Examination: MMSE [19, 20]), activities of daily living (ADL; Barthel Index [21]), NEECHAM confusion scale (NEECHAM) [22–24], and the presence or absence of psychoneurological complications, urinary incontinence, excitement/hyperkinesia during previous hospitalization and the use of psychotropic drugs before admission were evaluated prior to surgery. Patients, who underwent emergency surgery, had a preoperative NEECHAM score below 20, and with periodic dosing with newly added or switched antipsychotics, antidepressants, hypnotics or anti-Parkinson agents within 2 weeks prior to surgery were regarded as ineligible. Patients previously treated with haloperidol for delirium after surgery before the initiation of postoperative preventive haloperidol administration were also excluded.

Measurements and procedures

Eligible patients were enrolled through an internet website on the morning of postoperative day 1 after obtaining consent, and were automatically assigned at that time to the intervention or non-intervention group on a computer using the age, gender and department as adjustment factors.

Haloperidol 0.5A (2.5 mg) was dissolved in 100 ml of saline and intravenously administered by drip infusion once daily at 18:00 from postoperative days 1 to 3 to the intervention group. The dosing time-point of 18:00 was selected because delirium is more likely to occur at night, and also to recover and maintain the sleep–wake rhythm. Regarding the administration method and dose of haloperidol, an intravenous injection of 5–10 mg of haloperidol was recommended as the first-line treatment for orally untreatable delirious patients in the Guidelines for the Treatment of Delirium published by the Japanese Society of General Hospital Psychiatry [25, 26]. The low dose was set in consideration of the physical characteristics of the elderly and the prophylactic nature of the intervention. The duration of administration was decided based on the previous findings in which the development of delirium increased after 24 h, and because severe symptoms continued for approximately 3 days [7]. The development and severity of postoperative delirium were evaluated for 8 days, from postoperative days 0 to 7, using the NEECHAM score.

The NEECHAM score includes the results of an evaluation of three categories: the cognitive information processing function, behavior and physiological control, and the most unfavorable condition over each 24-h period was regarded as the condition on that day. The maximum score of 30 points decreases as the severity of postoperative delirium increases. Patients with a NEECHAM score of 27 or higher, 25–27, 20–24 and 19 or lower were considered to be non-problematic, at high risk of delirium, with mild delirium and with moderate to severe delirium, respectively. This scale has high internal consistency and high reliability regardless of differences among raters, and has been correlated with the Diagnosis and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnostic criteria [27].

The non-intervention group did not receive preventive treatment, and delirium was evaluated in the same way as in the intervention group (Fig. 1).

When delirium developed, conventional treatments, such as the administration of an intravenous antipsychotic drug (such as haloperidol), were administered in both groups.

Assessment and outcomes

Patient data were collected through the internet website, and the identification of personal information was prevented by coding. After completing the data collection from 121 patients, exceeding the planned number of cases, study team members not involved in the medical care of the patients evaluated and analyzed all baseline data and the results. The development and severity of postoperative delirium were evaluated using the NEECHAM score. When the NEECHAM score decreased to below 20 after surgery, the patient was regarded as having developed postoperative delirium.

The primary endpoint was a lower incidence of postoperative delirium in the intervention group than in the non-intervened control group. The secondary endpoints were the severity and persistence of the postoperative delirium in a time-course analysis of the NEECHAM score during the observation period, and the presence or absence of adverse events assumed to be associated with the intervention.

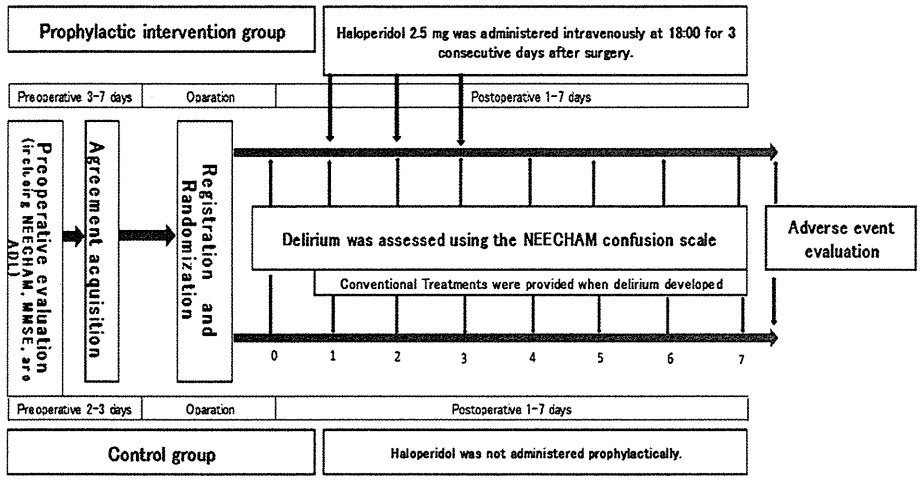

Fig. 1 The study protocol. *NEECHAM* NEECHAM confusion scale, *MMSE* Mini-Mental State Examination, *ADL* Activities of daily living

Discontinuation criteria were withdrawal of consent or a change/discontinuation of treatment requested by the patient or her/his legal representative, the development of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 2 or more severe adverse events associated with haloperidol, difficulty continuing due to severe physical postoperative complications, and judgment that continuing the trial would be difficult by the physician in charge.

Statistical analysis

Eligible patients were randomly assigned 1:1 to the intervention or non-intervention group by the minimization method according to age (<75/≥75 years), gender (female/male), MMSE score (<25/≥25) and institution. The proportions of patients with severe postoperative delirium, defined as at least one episode of a NEECHAM score <20, were compared between the treatment groups using the Chi-square test. This study was designed to have 80 % power to detect a 25 % difference in the proportion of severe postoperative delirium at a two-sided significance level of 0.05. A multivariate logistic regression including the patient age, gender, MMSE score and the preoperative NEECHAM score as covariates was performed to evaluate the effects of the prophylactic haloperidol treatment after adjustment for potential confounding factors. An odds ratio <1 indicated that the factor was protective against severe postoperative delirium. A supportive analysis using the generalized estimating equation regression model was conducted to compare the incidence of severe delirium between treatment groups during the first 7 days after the operation. The statistical analyses were performed using the SAS software program, version 9.3 (SAS Institute, Cary, NC, USA).

Results

In total, 59 and 62 patients were allocated to the prophylactic intervention and control groups, respectively (121 patients overall). The ages of the intervention and control groups were 80.5 ± 0.5 (mean ± standard deviation) and 80.2 ± 0.5 years, respectively. There were 64 male patients (32 each in the intervention and control groups) and 57 female patients (27 and 30, respectively). Abdominal surgery was performed in 107 patients (52 and 55, respectively); orthopedic surgery in nine patients (five and four) and other surgeries (including vascular surgery) were performed in five patients (two and three patients, respectively, in the intervention and control groups). The preoperative MMSE scores in the intervention and control groups were 23.3 ± 0.7 and 23.0 ± 0.7, and the preoperative Barthel Indices were 85.5 ± 3.1 and 84.0 ± 3.0, respectively, with no significant differences observed between the two groups. The preoperative NEECHAM scores were 27.3 ± 0.4 and 28.1 ± 0.4, respectively, with the intervention group having a slightly lower score, although not significant. No significant differences were noted between the two groups in the presence or absence of urinary incontinence, a past medical history of excitement/hyperkinesia or the preoperative use of oral psychotropic drugs, antidepressants, hypnotics or anti-Parkinson agents. The preoperative baseline data of all patients are shown in Tables 1 and 2.

Postoperative NEECHAM measurements were completed in 119 patients (59 and 60 in the intervention and control groups, respectively) because haloperidol was administered to treat delirium on the day of surgery in two of the 62 patients in the control group (Fig. 2). Postoperative delirium (NEECHAM score lower than 20) developed in 45 patients (37.8 %); 20 (33.3 %; 95 %CI 21.7–46.7 %) and 25 patients (42.4 %; 95 %CI 29.6–55.9 %) in the

Table 1 The baseline data of the patients

Preoperative demographics and characteristics	Prophylactic intervention group (*n*:59)	Control group (*n*:62)	*p* value
Age, mean ± SE	80.5 ± 0.5	80.2 ± 0.5	0.723
Male/female ratio	32/27	32/30	0.773
Type of operation			0.852
Abdominal	52	55	
Orthopedic	5	4	
Other	2	3	
MMSE, mean ± SE	23.3 ± 0.7	23.0 ± 0.7	0.740
NEECHAM score, mean ± SE	27.3 ± 0.4	28.1 ± 0.4	0.133
ADL (Barthel index), mean ± SE	85.6 ± 3.1	84.0 ± 3.0	0.736
Urinary incontinence, yes/no	9/50	8/54	0.710
History of excitement, yes/no	1/58	3/59	0.334
Use of anti-Parkinson agents, yes/no	0/59	1/61	0.327
Use of antipsychotic agents, yes/no	1/58	3/59	0.334
Use of antidepressants, yes/no	4/55	1/61	0.154
Use of hypnotics, yes/no	10/49	7/55	0.371

NEECHAM NEECHAM confusion scale, *MMSE* Mini-Mental State Examination, *ADL* Activities of daily living, *Barthel Index* Representative index of the ADL

Table 2 The underlying diseases and type of surgery

Diseases, surgery	Prophylactic intervention group (*n*:59)	Control group (*n*:62)
Abdominal	52	55
Malignancy	36	39
Gastric, gastrectomy/others	11/0	14/2
Colonic, colectomy/others	14/1	14/0
Rectal, LAR/APR/others	2/2/1	4/2/1
Hepatobiliary, hepatectomy/PD/others	1/1/2	1/0/1
Others	1	0
Benign	16	16
Cholelithiasis, cholecystectomy/ choledochotomy	0/4	2/2
Abdominal aortic aneurysm, graft	6	7
Others	6	5
Orthopedic	5	4
Others	2	3

LAR low anterior resection, *APR* abdominoperineal resection, Miles operation, *PD* pancreatoduodenectomy

control and intervention groups, respectively. There was no significant effect on the prevention of postoperative delirium ($p = 0.309$).

The postoperative NEECHAM score showed a pattern similar to that previously reported: the score decreased on postoperative day 1 and then gradually increased and returned to the preoperative level on postoperative days 5–7 [7]. The time-course changes in the mean NEECHAM scores in the control and intervention groups are shown in Fig. 3. The mean postoperative NEECHAM scores on postoperative days 1–7 were lower in the intervention group than in the control group, but no significant differences in the severity or incidence of delirium were noted in the intervention group. The mean durations of the persistence of delirium were 1.10 (95 % CI 0.58–1.62 days) and 1.38 days (95 %CI 0.83–1.95 days) in the control and intervention groups, respectively, with no significant difference between them ($p = 0.356$). The incidences of postoperative delirium were 43.2 % (95 %CI 27.1–60.5 %) and 52.8 % (95 %CI 35.5–69.6 %), when the patients were limited to those with a preoperative MMSE <25, and were 64.3 % (95 %CI 35.1–87.2 %) and 66.7 % (95 %CI 43.0–85.4 %), when limited to those with a preoperative NEECHAM score <27, for the control and intervention groups, respectively, which indicated that no significant effect was noted even when patients were limited to those at high risk for postoperative delirium (preoperative MMSE <25 and preoperative NEECHAM <27; $p = 0.415$ and 0.884, respectively).

When a logistic multivariate analysis was performed that included the presence or absence of the intervention as a parameter (Table 3), the incidence of postoperative delirium was significantly higher in patients at an advanced age with low preoperative MMSE and NEECHAM scores [age: odds ratio = 1.12 (for a 1-year increase in age), $p = 0.043$; preoperative MMSE: odds ratio = 1.15 (for a 1-point decrease in the MMSE score), $p = 0.014$; preoperative NEECHAM: odds ratio = 1.23 (for a 1-point decrease in the NEECHAM score), $p = 0.037$]; however, no significant differences associated with gender or the presence or absence of the intervention were noted ($p = 0.953$ and $p = 0.558$, respectively).

Furthermore, when the analysis was conducted after additionally limiting the subjects to those who underwent abdominal surgery, the odds ratio of the prophylactic administration of haloperidol was 1.25 (95 %CI 0.50–3.12), leading to the same conclusion as expected from our previous work which showed no significant difference in the incidence of postoperative delirium between the patients in the department of surgery and orthopedics [7].

To confirm the reliability of the results of the logistic multivariate analysis, an analysis using the generalized estimating equation was performed. The results are shown

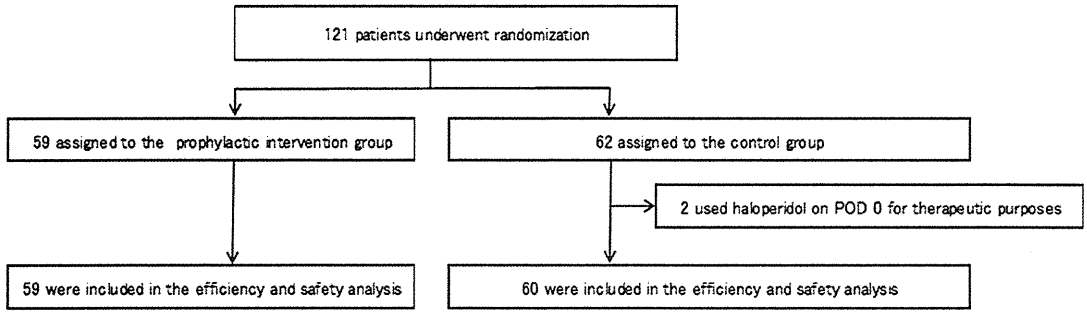

Fig. 2 A flow diagram of the study

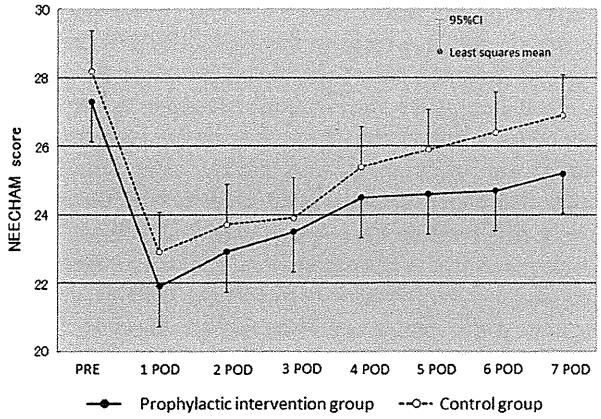

Fig. 3 The preoperative and postoperative changes in the NEECHAM scores in the prophylactic intervention group and control group The preoperative and postoperative (POD1-7) changes in the NEECHAM score in the prophylactic intervention and control groups. The percentages of patients with postoperative delirium (NEECHAM <20) in the prophylactic intervention and the control groups were 42.4 and 33.3 %, respectively (95 % confidence intervals (CI) 29.6–55.9 and 21.7–46.7 %; $p = 0.309$). The duration of the delirium (NEECHAM <20) was 1.38 versus 1.10 days in the intervention and control groups, respectively (95 %CI 0.83–1.95 days and 0.58–1.62 days; $p = 0.356$). *Open circle* shows the least-squares mean score of the control group. *Filled circle* shows the least-squares mean score of the prophylactic intervention group. The *vertical line* in the least-squares mean score shows the 95 %CI

in Table 4, which are consistent with the data shown in Table 3. The odds ratio of the prophylactic administration of haloperidol was 1.48 (95 %CI 0.33–6.71), which indicated no postoperative delirium-decreasing effect ($p = 0.611$). The age, preoperative MMSE score and number of days after surgery were significantly correlated with the development of postoperative delirium.

Regarding postoperative adverse events, grade 2 events were noted in two patients (convulsions and temporary loss of consciousness 2 days after completing the preventive administration of haloperidol and T-tube removal) and grade 3 events occurred in one (no abnormality was noted during haloperidol administration, but the patient fell on

Table 3 The results of the multivariate analysis of the factors affecting the development of postoperative delirium (logistic regression analysis)

	Odds ratio	95 % CI	*p* value
Prophylactic administration of haloperidol	1.30	0.54–3.17	0.558
Age	1.12[a]	1.01–1.27	0.043
Gender (male)	1.03	0.41–2.60	0.953
Preoperative NEECHAM score	1.23[b]	1.01–1.51	0.037
Preoperative MMSE score	1.15[b]	1.03–1.30	0.014

The multivariate logistic regression analysis was performed to include the patient age, gender, preoperative MMSE score and preoperative NEECHAM score as covariates to evaluate the effects of prophylactic haloperidol treatment after adjustments for potential confounding factors. An odds ratio >1 indicated that the factor conferred a greater risk of severe postoperative delirium

NEECHAM NEECHAM confusion scale, *MMSE* Mini-Mental State Examination

[a] For each 1-year increase

[b] For each 1-point decrease in the score

day 7, leading to a femoral neck fracture) in the intervention group. However, the grade 3 event was unlikely to have had any causal relationship with the preventive haloperidol treatment, considering that the half-life of intravenous haloperidol is 14.1 ± 3.2 h [28], and no other adverse events of grade 3 or more were noted.

Discussion

No significant preventive effect of the daily administration of low-dose haloperidol on postoperative delirium was noted in this randomized, open-label prospective study. The incidence of postoperative delirium was not significantly lower in the intervention group than in the control group, and no significant effect was noted on the severity or persistence of the delirium. Moreover, no significant effect was observed even in the group at high

Table 4 The results of the multivariate analysis of the factors affecting the development of postoperative delirium (GEE analysis)

	Odds ratio	95 %CI	*p* value
Prophylactic administration of haloperidol	1.48	0.33–6.71	0.611
Age	1.30[a]	1.07–1.58	0.008
Gender (male)	0.39	0.08–1.86	0.238
Preoperative NEECHAM score	1.05[b]	0.78–1.40	0.752
Preoperative MMSE	1.69[b]	1.05–2.73	0.032
Postoperative day (postoperative days 1–7)	0.67[c]	0.52–0.85	0.001

A supportive analysis using the generalized estimating equation regression model was conducted to compare the incidence of severe delirium between the treatment groups throughout first 7 days after the operation

GEE generalized estimating equation, *NEECHAM* NEECHAM confusion scale, *MMSE* Mini-Mental State Examination

[a] For each 1-year increase

[b] For each 1-point decrease in the score

[c] For each 1-day increase

risk for postoperative delirium with preoperative MMSE and NEECHAM scores below 25 and 27, respectively.

There have been several contradictory reports regarding the efficacy of haloperidol in preventing delirium. Kaneko et al. [13] reported that it significantly decreased the incidence of delirium after surgery involving the digestive organs in a small-scale clinical study, and Wang et al. [14] reported that 12-h continuous preventive administration of haloperidol significantly decreased the incidence of delirium in elderly patients admitted to an ICU, excluding those after cardiac surgery. In contrast, Kalisvaart et al. [15] reported that haloperidol reduced the severity and persistence of delirium, but did not decrease its incidence in patients following orthopedic surgery in a RCT where they received oral preventive treatment with low-dose haloperidol.

The absence of a preventive effect of haloperidol on postoperative delirium may have been due to the low dose used and short administration period. However, although the dose was lower than 5 mg/day for 5 days, as reported by Kaneko et al., the preventive administration of the dose of 2.5 mg/day for 3 days was still markedly higher than the intravenous bolus injection of 0.5 mg of haloperidol, followed by continuous infusion at a rate of 0.1 mg/h for 12 h (total dose per day: 1.7 mg) reported by Wang et al. High-dose haloperidol may be necessary for the primary prevention of delirium, but such treatment may increase the frequency and severity of adverse effects, particularly in vulnerable patients. It has been suggested that haloperidol should ideally be administered to elderly patients at a low dose for a short time [29].

It is also possible that the initiation of preventive administration in the present study may have been too late. In the time-course of the NEECHAM scores after surgery (Fig. 3), the lowest score was noted on postoperative day 1 in both the intervention and control groups, and it slowly improved thereafter. The NEECHAM score may have rapidly decreased immediately after surgery within one postoperative day. The drug was administered early after surgery in the studies by Kaneko et al. and Wang et al., in which an effect was observed. We performed our study on the assumption that the intervention would be administered in general wards of general hospitals, and decided to start haloperidol administration on postoperative day 1 in consideration of the patient safety; however, this timing was not before the decrease in the NEECHAM score was observed. This may have been the reason for the absence of an effect due to the intervention. Although it may have been better to initiate the intervention on the night after the surgery, an intervention immediately after surgery to patient in unstable general conditions is difficult unless it is strictly monitored in the ICU, as reported by Wang et al. When preventive administration is initiated immediately after surgery, the influence of anesthesia remains, and the respiratory and circulatory dynamics are unstable, which may have a negative influence on the postoperative course and increase the possibility of severe adverse events.

It should be noted that we were unable to exclude the possibility of a psychological effect arising from the patients' awareness of having received a haloperidol drip infusion, because this trial was not performed in a double-blinded manner. However, a lack of blinding would introduce potential bias in favor of the haloperidol prophylactic group, which was not observed in the present study. Therefore, the non-double-blinded nature of the study does not appear to have affected the conclusions regarding the treatment.

No severe adverse event corresponding to grade 3 or more that was assumed to be associated with the preventive haloperidol administration was noted. Although high-dose haloperidol administration (from 5 mg to more than 20 mg) was necessary when postoperative delirium developed, no adverse event assumed to be induced by the haloperidol was noted even in these cases, which suggested that haloperidol can be relatively safely administered even during the unstable postoperative period. The safety of haloperidol for postoperative elderly patients has also been confirmed in other studies [13–15]. Combining its high tolerability and low cost, expanding the clinical experience using this antipsychotic drug will broaden the range of applications for other conditions.

Nevertheless, this study suggests that intravenous treatment with low-dose haloperidol is unlikely to be used widely in hospital wards as prophylactic intervention to prevent postoperative delirium in elderly surgical patients who are not orally treatable. High-dose haloperidol may be

effective, but it has been advised that haloperidol should be administered to elderly patients at a low dose to prevent adverse effects [25, 26, 29].

Several studies have shown various non-pharmacological measures that can contribute to reducing the incidence of delirium [30–33]. Inouye et al. [30] proposed a multifactorial intervention that included specific protocols for cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration by showing significant reductions in the number and duration of episodes of delirium in hospitalized general medicine patients aged 70 or older. Marcantonio et al. [32] reported that geriatric consultation decreased delirium in elderly surgical patients after hip fracture by over one-third. More recently, Colombo et al. [33] showed that the timely use of a re-orientation strategy was correlated with a significantly lower occurrence of delirium in patients admitted to the ICU. In fact, the proportion of patients who developed postoperative delirium in the present study (38 % of all patients) was lower than that reported in our previous study (55 %) [7]. This may have been due to the protocol used in this study, in which patients who developed delirium on the day of surgery or on the following morning were not included. However, alternatively, it could have been because the preceding studies on delirium motivated the participating medical staff and nurses to be more aware of postoperative delirium, thus promoting the care of patients at risk and decreasing the incidence of delirium.

The NEECHAM score was employed to diagnose delirium and to evaluate its severity. A pattern similar to that in our previous report [7] was noted in the present study, which confirmed its reproducibility and usefulness as a score to evaluate delirium. The incidence of postoperative delirium has been shown to vary markedly (10 % to higher than 50 %) among reports [29, 34–38], and this may have been due to the fact that many studies were retrospective, and the definition of the development of delirium has been ambiguous or different among these studies. The DMS-IV [39] and Delirium Rating Scale (DRS) [40] are known as diagnostic criteria that can also be used to evaluate delirium; however, it is difficult for nurses who directly take care of patients with postoperative delirium to judge delirium accurately using the DMS-IV and DRS. On the other hand, the severity and condition of delirium can be simply and objectively determined by general physicians and nurses using the NEECHAM score. In this study, postoperative delirium was continuously and prospectively evaluated in consecutive cases using the NEECHAM score by nurses in direct contact with patients all day at clinical sites. The efficacy of the intervention was judged based on this evaluation, and its reliability should have been high.

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Conflict of interest The authors of this report have no conflicts of interest.

References

1. Committee for Osteoporosis Treatment of The Japanese Orthopaedic. Association. Nationwide survey of hip fractures in Japan. J Orthop Sci. 2004;9(1):1–5.
2. Isobe H, Takasu N, Mizutani M, Kimura W. Management of colorectal cancer in elderly patients over 80 years old (in Japanese). Nippon Ronen Igakkai Zasshi. 2007;44(5):599–605.
3. Blansfield JA, Clark SC, Hofmann MT, Morris JB. Alimentary tract surgery in the nonagenarian: elective vs. emergent operations. J Gastrointest Surg. 2004;8(5):539–42.
4. Amemiya T, Oda K, Ando M, Kawamura T, Kitagawa Y, Fukata S, et al. Activities of daily living and quality of life of elderly patients after elective surgery for gastric and colorectal cancers. Ann Surg. 2007;246(2):222–8.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Text Revision (DSM-IV-TR). Washington, DC, American Psychiatric Association, 2000.
6. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. Arch Intern Med. 2002; 162(4):457–63.
7. Hattori H, Kamiya J, Shimada H, Akiyama H, Yasui A, Fukata S, et al. Assessment of the risk of postoperative delirium in elderly patients using E-PASS and the NEECHAM Confusion Scale. Int J Geriatr Psychiatry. 2009;24:1304–10.
8. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013;54(2):124–31.
9. Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. Anesthesiology. 2012; 116(5):987–97.
10. Larsen KA, Kelly SE, Stern TA, Bode RH Jr, Price LL, Hunter DJ, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics. 2010;51:409–18.
11. Prakanrattana U, Prapajtrakool S. Efficacy of risperidon for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care. 2007;35:714–9.
12. Tagarakis GI, Voucharas C, Tsolaki F, Daskalopoulos ME, Papaliagkas V, Parisis C, et al. Ondasetron versus haloperidol for the treatment of postcardiotomy delirium: a prospective, randomized, double-blinded study. J Cardiothorac Surg. 2012;7:25.
13. Kaneko T, Cai J, Ishikura T, Kobayashi M, Naka T, Kaibara N. Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery. Yonago Ada Med. 1999;42:179–84.
14. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med. 2012;40:731–9.
15. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip surgery patients at risk fur delirium: A randomized placebo-controlled study. J Am Geriatr Soc. 2005;53:1658–66.
16. Schrader SL, Wellik KE, Demaerschalk BM, Caselli RJ, Woodruff BK, Wingerchuk DM. Adjunctive haloperidol prophylaxis

reduces postoperative delirium severity and duration in at-risk elderly patients. Neurologist. 2008;14(2):134–7.
17. Seitz D, Gill SS. Perioperative haloperidol to prevent postoperative delirium. J Am Geriatr Soc. 2006;54(5):861; author reply 861–3.
18. Wang MD. Perioperative haloperidol usage for delirium management. J Am Geriatr Soc. 2006;54(5):860–1; author reply 861–863.
19. Cockrell JR, Folstein MF. Mini-mental state examination (MMSE). Psychopharmacol Bull. 1988;24:689–92.
20. Anthony JC, LeResche L, Niaz U, von Korff MR, Folstein MF. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. Psychol Med. 1982;12:397–408.
21. Mahoney FL, Barthel DW. The Barthel. Index. Maryland. State. Mad J. 1965;14:61–5.
22. Neelon VJ, Champagne MT, Carlson JR, Funk SG. The NEECHAM confusion scale: construction, validation, and clinical testing. Nurs Res. 1996;45(6):324–30.
23. Matsushita T, Matsushima E, Maruyama M. Early detection of postoperative delirium and confusion in a surgical ward using the NEECHAM Confusion Scale. Gen Hosp Psychiatry. 2004;26(2):158–63.
24. Schuurmans MJ, Deschamps PI, Markham SW, Shortridge-Baggett LM, Duursma SA. The measurement of delirium: review of scales. Res Theory Nurs Pract. 2003;17(3):207–24.
25. American Psychiatric Association. Practice guideline for the treatment of patients with delirium. Am J Psychiatry. 1999;156(suppl):1–20.
26. Hatta K. Clinical Guideline for the Treatment of Delirium Japanese Society of General Hospital Psychiatry Practice Guidelines 1. Tokyo: Seiwa Shoten; 2005. p. 19–47.
27. Immers HE, Schuurmans MJ, van de Bijl JJ. Recognition of delirium in ICU patients: a diagnostic study of the NEECHAM Confusion Scale in ICU patients. BMC Nurs. 2005;4:7.
28. Forsman A, Ohman R. Pharmacokinetic studied on haloperidol in man. Curr Ther Res Exp. 1976;20:319–36.
29. Cole MG. Delirium in elderly patients. Am J Geriatr Psychiatry. 2004;12:2–7.
30. Inouye SK, Bogardus ST, Carpenter PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340:669–76.
31. Cole MG, Primeau F, McCusker J. Effectiveness of intervention s to prevent delirium in hospitalized patients: a systematic review. CMAJ. 1996;155:1263–8.
32. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc. 2001;49:516–22.
33. Colombo R, Corona A, Praga F, Minari C, Giannotti C, Castelli A, et al. A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. Minerva Anestesiol. 2012;78(9):1026–33.
34. Demeure MJ, Fain ML. The elderly surgical patient and postoperative delirium. J Am Coll Surg. 2006;203:752–7.
35. Robinson TN, Kiseman U. Postoperative delirium in the elderly: diagnosis and management. Clin Interv Aging. 2008;3:351–5.
36. Olin K, Eriksdotter-Jonhagen M, Jansson A, Herrington MK, Kristiasson M. Permert Jet. Postoperative delirium in elderly patients after major abdominal surgery. Br J Surg. 2005;92(12):1559–64.
37. Goldenberg G, Kiselev P, Bharathan T, Baccash E, Gill L, Madhav V, et al. Predicting postoperative delirium in elderly patients undergoing surgery for hip fracture. Psychogeriatrics. 2006;6:43–8.
38. Santana SF, Wahlund LO, Varli F, Tadeu VI, Eriksdotter JH. Incidence, clinical features and subtypes of delirium in elderly patients treated for hip fractures. Dement Geriatr Cogn Disord. 2005;20(4):231–7.
39. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM IV-TR).
40. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res. 1988;23:89–97.