Prophylactic Consecutive Administration of Haloperidol Can Reduce the Occurrence of Postoperative Delirium in Gastrointestinal Surgery

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Postoperative delirium has in recent years been a common complication which can interfere with the recovery of patients after surgery. Unfortunately there is still no medical procedure available which can completely prevent the occurrence of postoperative delirium. Haloperidol is a psychopharmacological agent that has been used to treat the delirium and agitation, especially in geriatric patients. To assess the effectiveness and safety of the use of haloperidiol for the reduction of postoperative delirium, we performed a randomized, comparative clinical study in which 78 patients who underwent gastrointestinal surgery received either 5 mg of haloperidol intravenously postoperatively at 21:00 for 5 consecutive days, or normal saline with the same schedule. Postsurgical evaluation revealed the incidence of postoperative delirium to be only 10.5% (4 of 38 patients) in the group receiving haloperidol treatment, compared to 32.5% (13 of 40 patients) in the saline treatment group. No significant neuroleptic side effects were seen in any of the patients. These results suggest that daily postoperative administration of haloperidol can reduce the occurrence of postoperative delirium safely.

Key words: haloperidol; postoperative delirium

Delirium, defined as an acute disorder of cognition, wakefulness and attention, has been recognized as a relatively common postoperative complication in the elderly for some time, yet, to date, surprisingly little is known about effective procedures to reduce its occurrence. Postoperative delirium can result in increased morbidity, delayed functional recovery and prolonged hospital stay (Adams et al., 1986). Therefore, early diagnosis, assessment, prompt treatment and prevention of postoperative delirium are important objectives for improved management of elderly surgical patients.

Various hypotheses have been proposed to explain the pathogenesis of postoperative delirium (Adams et al., 1986). The responsible causative factors proposed are preoperative factors (e.g., aging, pathologic status in the brain, polypharmacy and drug interactions, metabolic problems, depression, dementia and anxiety), intraoperative factors such as type of surgery and anesthetic drugs and postoperative factors (e.g., hypoxia, hypocarbia and sepsis). Although preventative measures against postoperative delirium have been applied at preoperative, intraoperative and postoperative levels, there is still little definitive information available on successful prevention of postoperative delirium. The first consideration in the management of delirium is to find and treat any underlying organic cause of the presented state of confusion. When confusion is evident, prompt treatment is mandatory. The first therapy of choice for such cases is an antipsychotic drug such as haloperidol, which does not produce hypotension, aggravate diabetes, hepatic disease or renal disease nor does cause oversedation. The successful use of haloperidol in such cases makes it an interesting therapeutic candidate for testing in the prevention of postoperative delirium in surgical patients. So far, there has been no effective prevention of post-

Abbreviation: DSM, Diagnostic and Statistical Manual of Mental Disorders

Table 1. Demographic data of patients

	Haloperidol group		Saline group	
Number of patients randomized	40		40	
Postrandomization exclusion	2		0	
Number of evaluable patients	38		40	
Male/female ratio	24/14		26/14	
Age* (year)	72.4 ± 8.2		73.1 ± 9.3	
Ishemic heart disease	5	(13.2)	8	(20.0)
Hypertension	13	(34.2)	12	(30.0)
Respiratory disease	6	(15.8)	4	(10.0)
Diabetes mellitus	9	(23.7)	12	(25.0)
Liver disease	3	(7.9)	6	(15.0)
Premorbid cognitive impairment	2	(5.3)	4	(10.0)
Operation method				
Partial gastrectomy	20	(52.6)	23	(57.5)
Total gastrectomy	8	(21.1)	6	(15.0)
Colectomy	10	(26.3)	11	(27.5)

*Mean ± SD.
( ), percentage.

operative delirium with therapy which places emphasis on medication. We proposed, therefore, that prophylactic administration of haloperidol may have a potential application as a preventative medication for postoperative delirium in surgical patients.

The aim of the current study was to evaluate the effect and safety of daily postoperative administration of haloperidol as a preventative measure against the development of postoperative delirium, with special attention being paid to the sleep-wakefulness rhythm, in patients undergoing gastrointestinal surgery.

Subjects and Methods

Study design and subjects

Ethical comittee approval was obtained before commencement of this study. Eighty patients who were scheduled for elective gastrointestinal surgery and admitted to the High and Intensive Care Unit at Tottori University Hospital 1 or 2 weeks before the scheduled surgery, between April 1995 and August 1998, comprised the study population. After admission, the patients were interviewed, clinically examined and subjected to routine laboratory testing. Before entering the study, oral consent was required from each patient. The consenting patients were then randomized into 2 comparative study treatment groups. The randomization was conducted by way of a closed envelope system. Postoperatively, one group received daily administration of haloperidol intravenously, while the other group was given normal saline. After the 5th day of the postoperative study treatment, the 2 treatment groups were compared for the incidence of development of postoperative delirium.

Study drug

Haloperidol (Serenase, Dainippon Pharmaceutical, Osaka, Japan) at a dose of 5 mg in 1.0 mL was administered intravenously daily at 21:00 from the 1st through the postoperative day. This dose of haroperidol was considered adequate for providing comparable sedation for the patients. An equal volume of normal saline for injection (0.9% NaCl, Otsuka Pharmaceutical, Tokushima, Japan) was administered by the same route and schedule as the comparative group of patients not receiving haloperidol.

Study measurements and evaluation

On the 5th day after surgery, postoperative data were collected from the patients and their nursing charts regarding i) cognition, with particular attention to signs and symptoms of delirium, ii) use of pain medication and iii) sleep pattern, with special attention being paid to the sleep-wakefulness rhythm. Psychotic diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, DSM-III-R (American Psychiatric Association, 1987).

Statistical methods

The chi-square test and unpaired student *t*-test were used for the statistical analyses of the results, which are presented as mean ± SD. A *P* value of less than 0.05 was regarded as statistically significant.

Results

During the study, 80 patients scheduled for gastrointestinal surgery were selected for random placing into the 2 treatment groups, 40 into the haloperidol treatment group and 40 into the saline control group. Two patients who had entered the Intensive Care Unit had to be excluded before randomization into the study. The 2 groups were comparable with respect to baseline criteria (e.g., age, sex, preexisting dis-

Table 2. The incidence of postoperative delirium in patients with haloperidol treatment and saline treatment

	Delirious	Non-delirious
Haloperidol	4*	34
Saline	13	27
Total	17	61

*$P < 0.05$ compared to the saline treament patients.

eases, preoperative medications, duration of operation and anesthesia, conditions during anesthesia as event of hypotension and hypoxemia, and intraoperative blood loss). The demographic data of the 78 evaluable patients are listed in Table 1, and there were no statistically significant demographic differences between the 2 groups.

Postoperative delirium developed in 17 of 78 patients (21.8%). Postoperative delirium began 2 to 4 days after surgery. Four of the 38 patients (10.5%) were clinically diagnosed as having postoperative delirium in the study group. On the other hand, there were only 13 out of 40 (32.5%) in the control group (Table 2). Intensity and duration of postoperative delirial symptoms in the control group were severe and longer respectively than those in the study group. Several other factors (e.g., drugs and method for postoperative pain control, hypoxia and infection) were examined and not found to be associated with the occurrence of
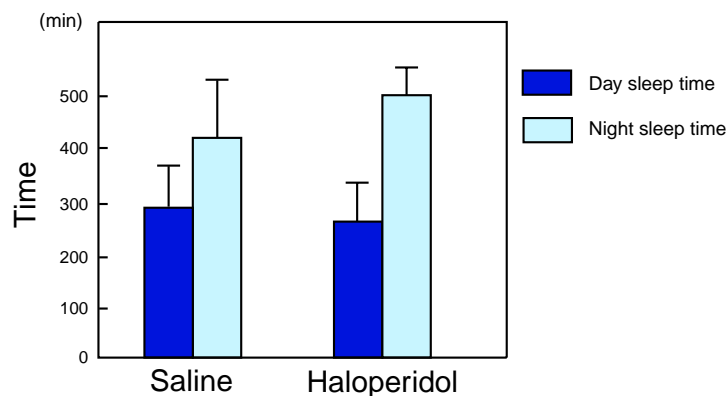

Fig. 1. Comparison of postoperative sleeping times for saline treatment patients and haloperidol treatment patients during the day and night during the first 5 postoperative days. Values are expressed as mean ± SD.
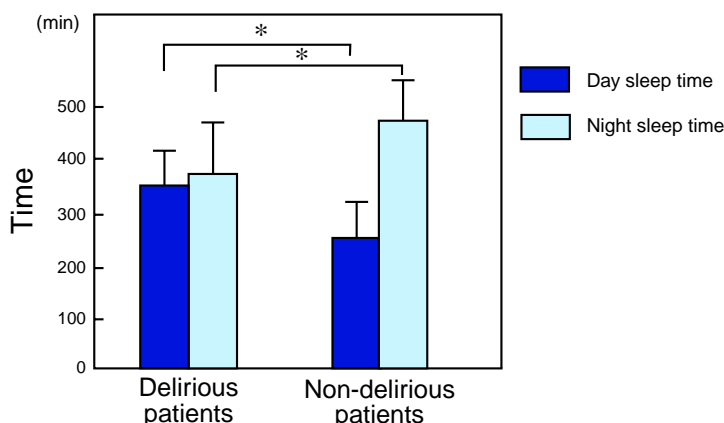
Fig. 2. Comparison of postoperative sleeping times for delirious and non-delirious patients during the day and night during the first 5 postoperative days. Values are expressed as mean ± SD. There are statistically significant differences in day and night sleeping times between the delirious and non-delirious group ($P < 0.05$).

postoperative delirium. The patients who developed postoperative delirium in the control group were administered haloperidol immediately until the delirial symptoms disappeared. Furthermore, the patients who developed postoperative delirium in the haloperidol group also were administered more haloperidol and flunitrazepam to control sleep-wakefulness rhythm.

Extrapyramidal side effects have not developed during the use of this protocol; however, one patient who was administered haloperidol developed transient tachycardia, but this did not substantially interfere with clinical management. No other complications or side effects of haloperidol use occurred with this protocol. Between the 2 groups, there was no considerable variability in the duration of sleep time in the day or night. As a result, the difference in the average and total time of sleep between the 2 groups was not statistically significant (Fig. 1). The ratio of sleep time during the day and night was lower during the use of haloperidol. In contrast, special attention was paid to the patients who had developed postoperative delirium, and there was close correlation between the development of postoperative delirium and deprivation of sleep rhythm, that is, a short sleep period during the night and a long sleep period during the day (Fig. 2).

Discussion

Postoperative delirium and other organic mental syndromes have been frequent and problematic complications, often requiring aggressive medical management. Notably cardiotomy and organ transplantation have appeared to involve several additive risk factors for the occurrence of postoperative mental disorders. Postoperative delirium has also been a common problem in the field of gastrointestinal surgery. Unfamiliar surroundings and a sense of alienation appear to be factors which make patients more likely to develop postoperative delirium. We recently reported that sleep deficiency is likely to predispose elderly patients to postoperative delirium and so techniques designed to prevent sleep deprivation may be of considerable value in reducing the incidence of postoperative delirium (Kaneko et al., 1997).

Haloperidol, a high-potency antipsychotic agent, is considered to be the drug of choice for rapid control of delirium in the critically ill patient. Unlike other neuroleptic agents, haloperidol has minimal adverse effects on hemodynamic and respiratory function and does not aggravate other functions (Fish, 1991). For this reason and because the number of elderly pa-

tients in the operative population who are at risk in developing postoperative delirium has been increasing, we felt that haloperidol would be a suitable candidate medication to test for prevention of postoperative delirium.

Several authors have proposed dosage guidelines for haloperidol use in the treatment of acute delirium. The initial intravenous dose of haloperidol prescribed for acute delirium varies with the degree of delirium from only 0.5–2 mg for mild agitation, to 2–5 mg for moderate agitation, to 10–20 mg for severe agitation (Fish, 1991). On the other hand, Levenson (1995) reported a case of delirium following lung transplantation that required 2,842 mg of haloperidol intravenously over 4 days. Though the maximally tolerated total daily dosage of haloperidol has not been fully established, it has been reported to range from 100 mg to over 530 mg (Korp et al., 1985; Levenson, 1995; Kaneko et al., 1997) and to be as high as 975 mg (Levenson, 1995). One case has been reported in which the intravenous administration of 7.5 mg of haloperidol appeared to cause cardiac arrest (Menza et al., 1987). Thus, for the current study, it was important to design a protocol of haloperidol dose and schedule that not only was potentially therapeutically effective, but also safe for use in our patient population. Our consideration on the safety of our haloperidol administration protocol depended on several factors, which included its limitations of use in an intensive care setting, frequent reassessment of the patients mental state and careful monitoring for side effects.

As haloperidol is rapidly absorbed after both oral and intramuscular administration, rapid control of acute delirium with extreme agitation is best accomplished with intravenous delivery. Moulaert (1989) recommended intravenous administration of haloperidol because the absorption may be erratic when the drug is given by the intramuscular route. Moreover, the pain of intramuscular injection may be added to the patient's confusion. Menza and colleagues (1987) also recommended intravenous administration of haloperidol in the immunosuppressed patient due to the lower frequency of extrapyramidal side effects when it was de-livered by the intravenous route. The reason for this route of administration-related difference in toxicity is not clear.

The use of haloperidol in physically compromised patients with delirium is not entirely without complications. As a high-potency neuroleptic agent, haloperidol has increased potential to cause extrapyramidal side effect symptoms. These effects are not dose-related and are sudden in onset. Extrapyramidal symptoms are seldom observed with the use of haloperidol administered by the intravenous route.

Craven (1990) first reported on the prophylactic intravenous administration of a small dose of haloperidol 4 times daily, and demonstrated its effectiveness and safety in the management of postoperative delirium in lung transplant recipients. Although further systematic investigation is required to determine the full potential of clinical effectiveness for haloperidol administration in the prevention of postoperative delirium, we have not found any increased frequency of postoperative delirium. These preliminary findings suggest that this study protocol of daily postoperative intravenous haloperidol administration may be both an effective and a safe means of preventing the occurrence of postoperative delirium in patients undergoing gastrointestinal surgery, particularly in elderly patients who are at a higher risk of development of postoperative delirium.

This prospective study is the first systematic evaluation of the use of prophylactic administration of intravenous haloperidol to reduce the occurrence of postoperative delirium. The mechanism by which haloperidol reduces the occurrence of postoperative delirium is not clear. Some studies suggest that actions other than the blockade of central dopamine receptors may be responsible for haloperidol's calming effect in patients with delirium (Korp et al., 1985; Tesar and Stern, 1988). It is also not clearly understood why prophylactic administration of haloperidol reduced the incidence of postoperative deliriums after gastrointestinal surgery; we intend to perform further investigation of the optimization of dosage and timing of haloperidol administration.

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