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A Novel Approach to the Prevention of Postoperative Delirium in the Elderly After Gastrointestinal Surgery

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Abstract

Purpose. Postoperative delirium (POD) is known to be one of the most critical complications of major operative procedures in elderly patients. Since disorders of the sleep-wake cycle have been reported to be one of the key factors in POD, we attempted to clarify the effectiveness of improving sleep-wake cycle disorders with medication after surgery to prevent POD, by conducting a prospective randomized study of 42 elderly patients who underwent resection of either gastric or colon cancer through an open laparotomy.

Methods. The delirium-free protocol (DFP) group was given an intramuscular injection of diazepam at 20:00 h each night, as well as a continuous intravenous infusion of flunitrazepam and pethidine administered over 8 h, for the first three nights postoperatively. Two patients were excluded because of failure to complete the DFP.

Results. The incidence of POD was 7/20 (35.0%) in the non-DFP group and 1/20 (5.0%) in the DFP group, this difference being significant ($P = 0.023$). Morning lethargy produced by the DFP was observed in 40% of the DFP group; however, no other side effects were seen.

Conclusions. These findings indicate that DFP treatment is effective for controlling POD in elderly patients after general surgery and does not appear to be associated with severe complications or side effects. To our knowledge, this is the first report proposing artificial control of the sleep-awake rhythm by medication as a means of preventing POD in elderly patients.

Key words Postoperative delirium · Sleep disorder · Gastrointestinal surgery

Introduction

Postoperative delirium (POD) is one of the most common complications of major surgery, especially in elderly patients.[1–3] Although almost all patients who suffer from POD recover spontaneously within a few days,[3,4] critical postoperative accidents, including the pulling out of drainage tubes, as a result of POD often lead to severe complications, delayed recovery, prolonged hospital stay, and sometimes even a fatal outcome.[2,5] As the indications for surgical treatment of elderly patients have been increasing, POD must be recognized as a critical complication and diagnosed immediately and correctly to prevent the serious consequences of this disorder.

We previously reported a 13.7% incidence of POD in a retrospective study on 1057 consecutive patients who underwent surgery under general anesthesia in Hiratsuka City Hospital, Japan.[1,4] That incidence was consistent with several reports on the incidence of POD, such as 26%–61% after hip fracture, 17%–77% after open-heart surgery, and 7%–17% after general surgery.[2,5] Since two thirds of patients with POD complain of insomnia,[4] we hypothesized that sleep disorders are one of the critical factors in the etiology of POD in patients treated in the intensive care unit (ICU) after surgery. Thus, in the present study, we focused on the significance of the relationship between the development of POD and sleep disorders.

We attempted to control disturbances of the sleep-wake cycle by medication after surgery as a mean of preventing POD, but bearing in mind there was a risk that artificial regulation of the sleep rhythm would have significant side effects that outweighed its benefits. We devised a "delirium-free protocol" (DFP) employing diazepam, flunitrazepam, and pethidine given on the first three nights after surgery to maintain the sleep rhythm at night. In our preliminary trial, one of ten patients aged over 80 years old on the DFP protocol experienced POD after surgery, whereas our previous study of patients over 80 years old had revealed an incidence of POD of approximately 40%.[1] Therefore, we designed a prospective study to evaluate the effec-

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tiveness of the DFP in preventing POD after general surgery in elderly patients.

Materials and Methods

Study Design

This controlled clinical trial applied a prospective but non-double-blinded design to compare patients treated with DFP (DFP group) with those not given DFP (non-DFP group) as a control, in Hiratsuka City Hospital, Japan. Random assignment of the subjects to the DFP group or non-DFP group was performed immediately after surgery. To avoid critical disadvantages to patients as a result of side effects of the DFP, placebos were not administered to the patients in the non-DFP group because it would have been difficult for medical staff to make a prompt response to side effects of the DFP treatment if a strictly blinded study with placebos had been designed. Delirium is defined in the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) as a disturbance of consciousness and change in cognition that develops over a short period of time as a result of surgery or postoperative intensive care, especially in elderly patients.[6]

Patients

A total of 42 consecutive patients aged over 70 years old, but less than 86 years old, who underwent resection of gastric or colorectal cancer through an open laparotomy under general anesthesia in our department, were registered between November 1996 and March 1999. Patients with liver cirrhosis or liver dysfunction, defined by a serum total bilirubin level >2.0 mg/dl, renal dysfunction, defined by a serum creatinine level >2.0 mg/dl, respiratory disturbance, defined by a pCO_2 >45 mmHg, other poor risk factors, mental disorders, visual impairment, or patients who required extended resection of other organs or emergency surgery were excluded from enrolment in the study. The preoperative evaluation of the patients' condition was based on the following factors: age, sex, performance status (PS) (Table 1), and respiratory, cardiac, hepatic, and renal function, with no significant differences between the two groups. Informed consent for enrolment in this study was obtained preoperatively from all patients.

Delirium-Free Protocol

The DFP group was given diazepam, flunitrazepam, and pethidine, according to the regimen shown in Table 2. Diazepam (0.1 mg/kg) was intramuscularly injected at 20:00 h, and a continuous intravenous infusion of 0.04 mg/kg of flunitrazepam, to maintain sleep, and 1 mg/kg of pethidine, to maintain analgesia, was started at 20:00 h and continued for 8 h. The same regimen was administered each night for the first three nights after surgery.

Assessment

The operative factors of the patients are shown in Table 1, based on operation time, amount of blood loss, blood transfusion, and surgical procedure. We also strictly monitored the patients' condition in the ICU immediately after surgery by APACHE II scoring,[7] which enables objective scoring of a patient's condition, including respiratory state, cardiovascular function, and hepatic and renal function, which severely affect mental condition (Table 1).

A psychiatrist who was unaware of the patients' group assignments and had no role in DFP treatment examined the patients to assess whether or not they were suffering POD. Even though placebos were not used, the psychiatrist was unable to identify the group to which the patient belonged because the agents were administered by drip infusion or as a single intramuscular injection without labeling the infusion containers or syringes. The psychiatrist performed the screening interview strictly twice a day for 7 consequent days after

Table 1. Comparison of backgrounds, operative factors, and postoperative state between the groups

	DFP (n = 20)	non-DFP (n = 20)	P value
Age (years)	75.9 ± 4.5	76.2 ± 4.1	0.892
Sex (male/female)	15/5	11/9	0.370
PS 0	18	18	
1	2	2	>0.999
Operation time (min)	280 ± 88	250 ± 67	0.229
Blood loss (g)	538 ± 462	375 ± 305	0.181
Blood transfusion (+)	2	3	
(−)	18	17	0.633
Operative procedure			0.548
Gastrectomy	9	11	
total	5	5	
distal	4	6	
Colectomy	11	9	
partial	2	1	
regional	8	7	
extended	1	1	
APACHE II score	8.3 ± 1.4	7.6 ± 1.7	0.168

Values are mean ± standard deviation
DFP, delirium-free protocol; PS, performance status; colectomy-regional: sigmoidectomy, right colectomy, left colectomy, or low anterior resection; colectomy-extended: abdomino-anal resection and abdomino-perineal resection

surgery, according to the criteria of the DSM-IV.[5] POD was judged by the following four criteria: a disturbance of consciousness; a change in cognition or the development of a perceptual disturbance; the development of a disturbance within a short period of time; and evidence that the disturbance was caused by the direct physiological consequences of a medical condition.

The incidence of POD and accidents caused by POD in the DFP group and the non-DFP group was calculated for the first 7 postoperative days (Table 3). Accidents caused by POD mainly consisted of the traumatic pulling out of important tubes, including surgical drains, central vein lines, arterial lines, or urinary catheters. We also calculated the incidence of mental disorientation and lethargy induced by DFP treatment during the first 7 postoperative days and evaluated the length of hospital stay after surgery in both groups (Table 3).

The unpaired Mann-Whitney *U*-test was used to analyze continuous variables in the study to determine statistical differences between the DFP group and the non-DFP group. Fisher's exact probability test was also utilized to analyze PS and the incidence of POD, accidents caused by POD, or side effects of the DFP treatment.

Results

Of the 42 patients enrolled in this study, 2 were excluded due to incomplete administration of the agents at the beginning of the protocol. The remaining 40 patients (20 in each group) were evaluated as described in Materials and Methods. The preoperative background factors of age, sex, and PS were not significantly different between the two groups (Table 1). Table 1 also shows that there were no significant differences between the DFP group and the non-DFP group in intraoperative factors. We compared the patients' condition immediately after surgery in the ICU, by calculating the APACHE II scores. The APACHE II scores in the DFP and non-DFP groups were 8.3 ± 1.5 and 7.6 ± 1.7, respectively, which were not significantly different. This demonstrated that there were no significant differences in the condition of patients from the two groups before the start of DFP treatment, or immediately after surgery. Furthermore, all patients were

Table 2. Delirium-free protocol (DFP)

		Day of operation	Postoperative	
			Day 1	Day 2
Diazepam	0.1 mg/kg intramuscularly	20:00 h	20:00 h	20:00 h
Flunitrazepam	0.04 mg/kg drip infusion	20:00–04:00 h	20:00–04:00 h	20:00–04:00 h
Pethidine	1 mg/kg drip infusion	20:00–04:00 h	20:00–04:00 h	20:00–04:00 h

Table 3. Evaluation of the DFP treatment according to its efficacy and side effects

	DFP (n = 20)	non-DFP (n = 20)	P value
Efficacy			
Incidence of POD (+)	1	7	
(−)	19	13	0.023
Accident by POD (+)	1	5	
(−)	19	15	0.101
ICU stay (days)	1.3 ± 0.6	1.9 ± 1.7	0.314
Surgical complications (+)	5	6	
(−)	15	14	0.723
Hospital stay (days)	25.6 ± 9.4	29.9 ± 16.2	0.740
Side effects			
Mental disorientation caused by DFP	0	—	
Morning lethargy caused by DFP	8	—	
Complications caused by DFP	0	—	

Values are mean ± standard deviation. POD, postoperative delirium; ICU, intensive care unit

given epidural anesthesia for pain control for 2 or 3 days after surgery.

Evaluation of POD by the psychiatrist during the first 7 postoperative days yielded an incidence of 7/20 (35.0%) in the non-DFP group and 1/20 (5.0%) in the DFP group, showing a significantly higher incidence of POD in the non-DFP group according to Fisher's exact probability test ($P = 0.0234$). While the incidence of accidents caused by POD was higher in the non-DFP (5/20) than in the DFP group (1/20), the difference was not significant ($P = 0.101$) (Table 3). Six of the total eight patients with POD from both groups experienced several accidents; five pulled out their nasal-gastric tube, one pulled out a central vein line, and all showed uncontrollable, strange behavior like peeling off their dressing gauze or fumbling with their tubes. There were no differences between the two groups in the incidence of surgical complications, the duration in ICU, or hospital stay (Table 3).

Morning lethargy produced by DFP treatment was observed in 40% of the DFP group, and this was clearly the most critical event associated with DFP treatment. However, the morning lethargy was never accompanied by accidents, such as tube removal. No other complications or side effects caused by DFP treatment were observed, based on cardiopulmonary, respiratory, renal, liver, and brain function monitoring.

Discussion

The surgical indications for elderly patients have increased dramatically with advances in medicine. The concept of POD has been recognized for centuries,[8] and is well known to be a common complication after surgery, especially in elderly patients.[1–5] We conducted two earlier retrospective studies to characterize the features of POD and reported finding a high incidence of POD in patients over 80 years old, with an incidence of almost 40%, and an overall incidence without regard to age of 14%.[1,4] When POD occurs in a patient intubated with vital tubes, including surgical drains, central vein lines, or arterial lines, the patient is at risk of accidentally removing the tube, which sometimes leads to lethal complications.[3,4] In fact, a mortality rate of 4% was reported in 117 delirious patients after elective noncardiac surgery,[9] suggesting that prevention of POD is an important strategy in the successful postoperative management of elderly patients.

Deep sleep stages 3, 4, and rapid eye movements (REM), which are important to maintain normal mental function, were found to be severely suppressed in patients in ICU after surgery, who had been deprived of total sleep.[10] We previously reported a close relationship between POD and sleep disorders and that 68% of delirious patients suffered from insomnia.[4] The present trial was based on the hypothesis that the aggressive prevention of sleep disorders by the artificial induction of a good sleep-wake rhythm with medication would be effective in preventing POD, although strictly speaking, the artificial induction of sleep with medication is not the same as natural normal sleep, including the deep sleep stages 3, 4, and REM.

The findings of this study demonstrated the benefit of DFP in that it could at least prevent patients with POD from pulling out important tubes. Although not experienced in this study, a patient with POD could escape from their room and move to somewhere dangerous, even out of the hospital, suffering an accident resulting in severe injuries or complications. While the hospital stay did not differ significantly between the two groups, DFP kept the patients' state of mind after surgery secure without severe accidents. The only disadvantage of DFP was the high incidence of morning lethargy in the DFP group, but no severe adverse effects such as respiratory complications resulted from the DFP, and the morning lethargy stopped immediately after completion of the DFP. On the other hand, most patients with POD suffered insomnia, which also sometimes caused morning lethargy.

In summary, we conclude that DFP proved effective for controlling POD in elderly patients after general surgery, and that it would be beneficial for patients with any symptoms of POD or for those at high risk of its development. While morning lethargy was recognized as the only disadvantage of the DFP, no other severe complications or side effects were observed in the DFP group. To the best of our knowledge, this is the first report proposing artificial control of the sleep-awake rhythm by medication as a means of preventing POD in elderly patients.

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