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No psychological emergence reactions in schizophrenic surgical patients immediately after propofol, fentanyl, and ketamine intravenous anesthesia

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Abstract

Purpose. We attempted to determine the frequency of adverse psychological events after total intravenous anesthesia with propofol-fentanyl-ketamine (PFK) in surgical schizophrenic patients.

Methods. PFK was used in 25 schizophrenic patients undergoing various surgical procedures from 1995 to 1997. Adverse events occurring during and after anesthesia were recorded. Psychiatric follow-up was also done during the first 3 postoperative weeks at least.

Results. One patient died postoperatively of airway obstruction from concomitant severe malignant thyroid disease, but in the remaining patients neither respiratory nor cardiovascular states during or after anesthesia became unstable. None of the patients developed adverse psychological emergence reactions immediately after anesthesia. Two patients undergoing major surgical procedures exhibited delirium in the early postoperative days despite taking their routine antipsychotic drugs postoperatively.

Conclusions. We suggest that PFK maintains stable respiratory and cardiovascular states, and causes no psychological emergence reactions in schizophrenic surgical patients. However, adverse psychological events may occur postoperatively, probably due to continued psychic stress. We therefore recommend appropriate perioperative management and further psychological studies for such patients.

Key words: Schizophrenia, Intravenous anesthetic agents, Ketamine, Propofol, Complications

Introduction

Ketamine, when combined with droperidol and fentanyl (DFK), has recently been reported to be a satisfactory anesthetic for surgical patients with schizophrenia [1], although ketamine itself may induce psychological emergence reactions with a deterioration in the psychic state of such patients [2–4]. Propofol may also cause psychological events, such as hallucinations, in schizophrenic patients [5,6], although one clinical report noted that an infusion of propofol was used without such sequelae in a schizophrenic surgical patient [7]. Thus, the true picture of psychological reactions occurring immediately after intravenous anesthesia with propofol plus ketamine in such patients remains unclear.

Since propofol became clinically available in Japan in 1995, total intravenous anesthesia with combined propofol, fentanyl, and ketamine (PFK) has been a routinely given to more than 5000 non-psychotic patients, as well as to 25 schizophrenic patients, for various surgical procedures in our department. This study aimed to determine the frequency of adverse events occurring during and after PFK in schizophrenic surgical patients. Psychiatric follow-up was also done for at least the first 3 postoperative weeks.

Patients and methods

This study was performed at the University of Hirosaki School of Medicine and its four affiliated hospitals, with Hospital Ethics Committee approval. Twenty-five schizophrenic patients were studied from 1995 to 1997 (Table 1). In all patients anesthesia was induced with intravenous (i.v.) administration of fentanyl 1–3 $\mu g \cdot kg^{-1}$, ketamine 0.5–1.0 $mg \cdot kg^{-1}$, and propofol 0.5–1.0 mg in divided doses. Tracheal intubation was facilitated with either i.v. suxamethonium chloride 0.8 $mg \cdot kg^{-1}$ or i.v. vecuronium bromide 0.1 $mg \cdot kg^{-1}$. Anesthesia was maintained with continuous infusions of propofol 3–10 $mg \cdot kg^{-1} \cdot h^{-1}$ and ketamine 0.5–1.0 $mg \cdot kg^{-1} \cdot h^{-1}$ in combination with a total dose of

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Table 1. Preoperative profiles of 25 schizophrenic patients

No.	Age (years)	Sex (M/F)	Weight (kg)	Major daily antipsychotic drugs	Duration (years)[a]	Surgical procedure
1	26	M	70	Levomepromazine 350 mg	1	Suture of the abdominal wall
2	49	F	49	None	0	Posterior fusion of the lumbar supine
3	53	F	63	Timiperone 13 mg, levomepromazine 10 mg	35	Vaginal hysterectomy
4	38	F	63	Zotepine 75 mg, haloperidol 2 mg	6	Ovarian cystectomy
5	51	F	43	Haloperidol 4 mg	10	Removal of thoracic spinal tumor
6	29	M	67	Levomepromazine 150 mg, zotepine 150 mg	6	Bilateral tonsillectomy
7	54	F	52.5	Zotepine 50 mg	16	Abdominal hysterectomy
8	45	F	55	Levomepromazine 50 mg	18	Vaginal hysterectomy
9	44	M	62.2	Levomepromazine 50 mg	19	Left vitrectomy
10	45	M	70	Chlorpromazine 50 mg, haloperidol 6 mg	15	Skin graft (upper extremities and truncus)
11	24	M	93.4	Haloperidol 6 mg, etizolam 1 mg	1	Skin graft (face and chest)
12	29	F	43.7	Levomepromazine 75 mg	9	Subtotal glossectomy, radical neck dissection
13	64	F	50	Promethazine hydrocholoride 100 mg	26	Left mastectomy
14	62	F	70.7	Chlorpromazine 50 mg	34	Oophorectomy
15	59	F	56	Levomepromazine 150 mg	37	Mastectomy
16	59	F	54	Nemonapride 60 mg, levomepromazine 25 mg	13	Open reduction of Fx left tibia
17	65	F	60	Chlorpromazine 300 mg	36	Open reduction of Fx right humerus
18	49	M	65	Pipamperone hydrochloride 320 mg	22	Open reduction of Fx right pattela
19	70	F	48	Haloperidol 13 mg, sulpiride 150 mg	31	Total thyroidectomy, neck dissection
20	60	F	50	Chlorpromazine 300 mg	20	Open reduction of Fx left tibia
21	47	M	77	Levomepromazine 85 mg	30	Open reduction of Fx pubic bone
22	70	M	63	Levomepromazine 50 mg	23	Nephrectomy
23	58	M	54	Levomepromazine 50 mg	18	Total gastrectomy
24	71	F	57	Clocapramine hydrochloride 150 mg	46	Right hemicolectomy
25	45	F	69	Promethazine hydrochloride 20 mg	20	Abdominal hysterectomy
Mean (SD)	50.6 (13.8)		60.2 (11.4)		19.7 (12.5)	

Fx, Fracture.
[a]Duration of treatment.

fentanyl of 2–10 $\mu g \cdot kg^{-1}$, given in divided doses. Intraoperative muscle relaxation was maintained with i.v. vecuronium bromide as needed.

Postanesthetic follow up

The patients were closely observed in the recovery room during the immediate postoperative period for at least 1 h after tracheal extubation. Eight patients required analgesics such as i.v. pentazocine and bupronorphine during their stay in the recovery room. The regimens used for postoperative pain relief in the recovery room were similar in our university hospital and the four affiliated hospitals, but the regimens differed in the wards. Anesthesiologists routinely visited each patient three times during the first postoperative week, and recorded the details of the patient's condition, including their psychic state (e.g., delirium). The patients' charts were reviewed during the first 3 postoperative weeks by one of authors (HI), and the patients' postoperative

psychic state was also monitored by the psychiatrist in charge of each patient. The presence or absence of exacerbation of psychosis, changes in antipsychotic drugs, or other important events, such as postoperative death, were recorded during a follow-up of at least the first 3 postoperative weeks.

Results

The preanesthetic profiles of the 25 schizophrenic patients are shown in Table 1. All but one of the patients had been using phenothiazine derivatives or other antipsychotic drugs for at least the preceding 1 year, with the mean duration of treatment being 19.7 ± 12.5 (SD) years. These drugs had been administered until the morning of the operative day, with or without diazepam as premedication. Drug administration was restarted postoperatively when the patients were allowed by the surgeon, anesthesiologist, or psychiatrist to take the drugs. One patient (no. 23) was unable to take the antipsychotic drugs during the first postoperative week because of continued paralytic ileus (Table 2).

Respiratory and cardiovascular states were stable during and after PFK. Desaturation, monitored by a pulse oximeter, was not observed in any of our patients during or after anesthesia. Neither vasopressors nor antiarrhythmic drugs were required during or after PFK. Although the propofol infusion was discontinued at the end of the surgical procedures in most patients, two patients (no. 2 and no. 5) required more than 60 min after end of the surgery to respond to verbal commands. No psychological emergence reactions occurred during the patients' stay in the recovery room. The incidence of postoperative psychological complications is shown in Table 3 together with findings reported after DFK in our previous study [1]. Most patients had an uneventful course during the first 3 postoperative weeks after anesthesia, but three patients experienced episodes of delirium. One patient (no. 5) who was not allowed to move after surgery, experienced hallucinations and delirium on the fifth postoperative day. She cut her intravenous line with a knife by herself. Levomepromazine 30 mg, haloperidol 2 mg, and flunitrazepam 2 mg were added to her routine antipsychotic drugs immediately after this event. Subsequently her postoperative course was uneventful. Another patient (no. 22), who had undergone nephrectomy, experienced frequent episodes of delirium from the first to the sixth postoperative day, although administration of routine antipsychotic drugs had been restarted on the first postoperative day. During this period the patient removed his arterial and intravenous lines by himself. Intravenous midazolam temporarily relieved these psychotic events, and this psychotic complication resolved spontaneously after the seventh postoperative day. Patient no. 23, who could not take routine antipsychotic drugs postoperatively due to continued paralytic ileus, experienced frequent episodes of delirium from the second postoperative day. Intravenous haloperidol 5 mg improved the psychological state on each occasion. Neither delirium nor excitement was observed after readministration of routine preoperative antipsychotic drugs, through the ileostomy, commenced on the eighth postoperative day.

One patient (no. 5) complained of anxiety during the night after surgery. Intramuscular amobarbital 250 mg with levomepromazine 25 mg immediately improved her psychic state. No further psychotic complication was observed in this patient. One patient (no. 19) died of airway obstruction, due to advanced malignant thyroid carcinoma, on the 34th postoperative day. One patient (no. 2) was diagnosed postoperatively with a chronic subdural hematoma in the right frontal lobe by brain computed tomography; this would have played a role in her delayed recovery from anesthesia. Other postoperative complications included constipation (patient. 9) and paralytic ileus (patient 23).

Discussion

Our experience with anesthetics in 143 schizophrenic surgical patients in our department over a period of 21 years has shown that these patients frequently have liver damage, as well as autonomic nervous system dysfunction, due to long-term treatment with antipsychotic drugs [8,9]. Compared with inhalational anesthesia, intravenous anesthesia with either DFK or PFK was found not to exacerbate postoperative liver damage [10]. Accordingly, we have not given inhalational anesthesia to schizophrenic patients since 1989. However, according to our previous experience, emergence reactions, delirium and/or excitement in such patients could be prevented by relatively deep inhalational anesthesia as well as the additional administration of analgesics or antipsychotic drugs during and immediately after anesthesia. In contrast, an increase in anesthetic requirements during anesthesia with PFK seems unlikely, as judged by the total amount of each anesthetic drug used in the present study. The postoperative pain management regimen used with the previous inhalational anesthesia differed from that used with the present PFK. Consequently, we could not compare PFK with inhalational anesthesia in terms of the postoperative psychic state in schizophrenic patients.

In the present study none of the schizophrenic patients experienced apparent psychological emergence reactions immediately after PFK for up to 1 h after the trachea had been extubated, while two patients experi-

Table 2. Anesthetic and postoperative profiles of 25 schizophrenic patients

No.	Surgery duration (min)	Total propofol (mg)	Total fentanyl (μg)	Total ketamine (mg)	Recovery time (min)	Restart of antipsychotic drugs (POD)	Postoperative complications (POD)	Remarks
1	20	245	200	55	25	3		
2	320	903	1000	337	75	5	Delayed recovery	Chronic subdural hematoma
3	75	435	400	127	10	3		
4	115	500	250	200	5	3		
5	157	600	550	210	130	1	Excitement, delayed recovery	Cut off IV line
6	58	700	300	140	15	0	Sleep disturbance	
7	42	80	200	64	10	2		Diabetes mellitus
8	50	143	200	48	5	2		
9	120	800	200	100	15	2	Constipation	
10	95	440	400	80	10	7		
11	274	4700	800	300	15	2		
12	850	2500	800	406	15	2		
13	100	615	250	40	5	2		
14	40	200	300	90	5	2		
15	50	262	300	71	3	2		
16	224	950	450	300	10	2		
17	122	390	300	120	5	2		
18	79	460	400	140	5	2		
19	154	800	700	300	15	5	Respiratory failure	Died on 34th POD
20	169	550	450	150	5	2		
21	185	1000	200	200	40	2		
22	151	840	400	220	25	1	Excitement	Self removal of IV line
23	232	1300	650	200	20	8	Excitement, paralytic ileus	Self removal of IV line
24	107	690	300	90	20	3		
25	134	1033	400	145	30	2		
Mean (SD)	157 (163)	845 (938)	416 (219)	165 (100)	20.7 (27.4)	2.7 (1.8)		

POD, Postoperative day; delayed recovery, recovery from anesthesia more than 60 min after the end of surgery.

Table 3. Incidence of postanesthetic psychological complications

	PFK	DFK[a]
Number of patients studied	25 (%)	14 (%)
Adverse emergence reactions immediately after anesthesia	0 (0)	0 (0)
Anxiety or sleep disturbance during the night after surgery	1 (4)	1 (7)
Delirium or excitement within the 1st postoperative week	3 (12)	0 (0)
Exacerbation of psychotic condition within the 1st 3 weeks	0 (0)	0 (0)

PFK Propofol, fentanyl, and ketamine intravenous anesthesia; DFK, droperidol, fentanyl, and ketamine intravenous anesthesia.
[a] Data derived from our previous report [1].

enced delirium within the first postoperative week despite taking their routine antipsychotic drugs.

The reported incidence of excitement following propofol anesthesia was 1.3% in a multicenter study of adverse events, evaluated by anesthesiologists and post-anesthesia care unit nurses, in 25 981 patients [11]. Hallucinations and disinhibited behavior have often been reported following propofol in anesthesia non-psychotic patients, as occurs with other anesthetic drugs [5,12,13]. Bricker [5] reported on 130 patients who had propofol-fentanyl anesthesia for minor gynecologic vaginal procedures. Twelve percent of the patients displayed amorous and disinhibited behavior. Prolonged delirium, lasting 4–5 h after a propofol infusion, was reported in a healthy 19-year-old woman [14]. Although disinhibition can occur in patients after light propofol anesthesia or during sedation [12,13], these findings suggest that possible adverse psychological emergence reactions could be possible immediately after propofol anesthesia in patients with schizophrenia [6].

Boey and Lai [15] reported recovery side effects after propofol and thiopental anesthesia given for electroconvulsive therapy in 31 psychotic patients, including 23 with schizophrenia. Although the side effects were minimal and the differences between anesthetic drugs were not significant on 62 occasions of delivery of anesthesia, the side effects for propofol: thiopental were headache (6:1), restlessness (3:5), flushing (1:1), euphoria (0:1), and withdrawal (0:1). To our knowledge, there is only one clinical report of an infusion of propofol given to a schizophrenic surgical patient [7]. The patient had been taking antipsychotic drugs for 10 years, and underwent bilateral tonsillectomy under propofol-fentanyl-nitrous oxide anesthesia. Anesthesia and post-anesthetic courses were uneventful, in conjunction with intravenous haloperidol 5 mg and intramuscular biperiden 1 mg given immediately after surgery.

The above evidence, as well as the results of the present study, suggest that propofol can be given safely to most schizophrenic patients without apparent emergence reactions. Further, the incidence of anxiety during the night after operation was low with PFK, similar to that noted with DFK [1].

The N-methyl D-aspartate (NMDA) receptor has been implicated in the pathophysiology of schizophrenia, and the NMDA receptor antagonist, ketamine, may affect psychotic symptoms as well as cognitive function [4]. Subanesthetic doses of ketamine (less than $0.5\,mg{\cdot}kg^{-1}$) delayed psychotomimetic effects, such as exacerbation of psychosis with visual hallucinations in schizophrenic patients, for up to 24 h after administration [3]. One clinical report described deterioration in psychosis following ketamine anesthesia, although the author did not describe this in detail [2]. In contrast, Shpilenia [16] reported that ketamine was therapeutically effective in 29 schizophrenic patients who did not respond to conventional antipsychotic drugs. Recently we reported that ketamine, when combined with fentanyl and droperidol, was safe in 14 surgical patients with schizophrenia in terms of the low incidence of adverse emergence reactions and psychotic deterioration [1]. Although one report showed that haloperidol failed to block ketamine-induced psychosis [3], the concomitant use of droperidol, a butyrophenone neuroleptic, with ketamine would exert an antipsychotic effect similar to that observed with haloperidol [17]. Most antipsychotic drugs interfere with the actions of dopamine as a neurotransmitter, particularly at D_2 and D_2-like receptors [18]. Although it is not clear whether propofol affects dopamine receptors [19,20], ketamine may inhibit the neural uptake of dopamine as well as that of noradrenaline and serotonin [21]. As reported previously [1,17] the concomitant administration of droperidol and ketamine would have the least adverse effect on the psychic state of schizophrenic patients.

Since propofol became clinically available in Japan, we have used ketamine in conjunction with propofol for total intravenous anesthesia in our department, as ketamine has cardio-stimulatory effects [22] that overcome the cardio-depressant effects of propofol [23]. This cardiovascular stability would also be suitable

for schizophrenic patients who are at risk of unexpected cardiovascular collapse and autonomic nervous dysfunction because of long-term treatment with antipsychotic drugs [9]. This favorable effect was confirmed in the 25 patients in this study.

Three patients in this study experienced episodes of delirium within the first postoperative week, although two of them had been taking their routine antipsychotic drugs since the first postoperative day. One of the two patients was not allowed to move voluntarily after removal of a thoracic spinal tumor. However, the contributory factor in the postoperative delirium experienced by the other patient, who underwent a nephrectomy, remains unclear.

The continued psychic stress experienced during the early postoperative period may have played a role in this adverse psychological event, rather than effects of anesthetic drugs and/or postoperative pain, as the patient had recovered from anesthesia uneventfully in the recovery room, and relief of these psychotic events was obtained without administration of analgesics. However, further psychological studies during the early postoperative period after PFK are required in schizophrenic patients.

In conclusion, neither cardiovascular complications nor psychological emergence reactions during or immediately after PFK in our 25 schizophrenic surgical patients, would allow us to use this anesthetic method for such patients. Nonetheless, appropriate perioperative management and further psychological studies are mandatory in order to reduce the risk of mortality and morbidity in these patients.

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