



Case Report

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Psychogenic coma after general anesthesia with remimazolam and remifentanyl -a case report-

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Background: Delayed emergence from general anesthesia is associated with life-threatening conditions with pharmacological, neurological, metabolic, and rarely, psychiatric causes. This case report was presented to report psychogenic coma after recovery from anesthesia with remimazolam and remifentanyl.

Case: An elderly woman was unresponsive after recovery from anesthesia with remimazolam and remifentanyl. Physical examination, laboratory testing, and radiographic imaging did not reveal any obvious organic causes. Pharmacological or metabolic abnormalities were not found. Absence of those causes strongly suggests that prolonged unconsciousness is related to psychiatric origin. The patient spontaneously regained consciousness after 48 h without any neurological complications.

Conclusions: Anesthesiologists should be aware of the possibility of psychogenic coma for patients with unexplained delay in emergence from anesthesia after the exclusion of other causes.

Keywords: Benzodiazepines; Coma; Delayed emergence from anesthesia; General anesthesia; Postoperative complications; Unconsciousness.

In recent anesthesia, the introduction of short-acting anesthetics has enabled patients to awaken rapidly after general anesthesia. Thus, today it is relatively uncommon for patients to experience delayed emergence from anesthesia or changes in their level of consciousness after general anesthesia. When such events do occur, they are usually associated with serious problems, such as cerebrovascular incidents or drug-related side effects [1]. Psychogenic causes can cause unconsciousness, but only rarely [2].

General anesthesia was induced and maintained in our patient using remimazolam and remifentanyl, short-acting benzodiazepine, and opioid. The patient experienced prolonged unconsciousness after waking up from anesthesia. We excluded organic causes through extensive testing and speculated that she experienced psychogenic coma. Psychogenic coma occurs very rarely and seems serious, but it resolves spontaneously without special treatment [2]. Here, we would like to share our experience because psychogenic coma is typically unfamiliar to anesthesiologists and responsible clinicians may experience distress until the patient regains consciousness.

Case Report

A written informed consent was obtained for publication of this case report. A 93-year-old woman was scheduled for bipolar hemiarthroplasty under general anesthesia. She had a medical history of hypertension, hypothyroidism, depression, insomnia, and somatic symptom disorder and was diagnosed as having sick sinus syndrome nine months ago. A cardiologist had recommended that she needed a pacemaker implanted, but she rejected it. She was taking levothyroxine, antihypertensive agent, analgesics with several psychiatric drugs, including benzodiazepine, zolpidem, and pregabalin, and two more unidentified drugs prescribed by a local clinic. Laboratory testing on admission revealed hyponatremia with sodium levels of 124 mEq/L, which was slowly improving. Thyroid function test was within normal range. A preoperative electrocardiogram showed normal sinus rhythms and a heart rate of 78 beats/min. Transthoracic echocardiography showed an ejection fraction of 56%. Her condition was otherwise evaluated as normal.

On arrival in the operating room, standard monitoring, namely by electrocardiogram, non-invasive blood pressure monitoring, and pulse oximetry of the patient was begun. Preoperative vital signs were normal. The radial artery was catheterized, and general anesthesia was induced and maintained using remimazolam and remifentanyl. Remimazolam was started with a loading dose of 6 mg/kg/h until loss of consciousness and thereafter was maintained at a rate of 1 ml/kg/h. Remifentanyl was adjusted to effect site target concentration of 2–10 ng/ml during the operation.

During the operation, mean arterial pressure was maintained above 80 mmHg and there were no episodes of arrhythmia. Adequate depth of anesthesia was maintained with a bispectral index (BIS) of 40–60. The operation proceeded uneventfully, and anesthesia lasted for 155 min. Remimazolam was discontinued when skin suture was commenced 20 min before extubation. At the end of anesthesia, 25 µg of fentanyl was injected intravenously for pain management followed by 200 mg of sugammadex and subsequently the train-of-four ratio showed 98%. Shortly, the patient responded to verbal commands and adequately breathed spontaneously and BIS remained over 95. She was extubated and brought out to the post anesthesia care unit (PACU).

On arrival in the PACU, the patient was fully awake and normothermic. The patient complained of pain with numeric rating scale (NRS) of 8 that we administered 30 µg of fentanyl. After 15 minutes, the patient was fine with NRS of 2. One hour after admission to the PACU, the patient's vital signs remained stable, so we decided to transfer her to the general ward. Immediately after

the patient was prepared for transfer to the general ward, she suddenly became unresponsive to verbal commands and any external stimuli. Her eyes were closed firmly, and her eyes were directed downwards when we opened her eyelids (Fig. 1). She had adequate spontaneous ventilation and was hemodynamically stable. The train-of-four ratio was 98% and her BIS was 77. Arterial blood gas analysis performed in the PACU showed that her blood pH level was 7.414, PaCO₂ level was 33 mmHg, PaO₂ level was 114 mmHg, bicarbonate level was 22 mmol/L and glucose level was 143 mg/dl. Oxygen saturation was 98% with oxygen mask 5 L/min. Serum electrolytes and other serum chemistries were within normal limits. Out of concern for residual effects of remimazolam or opioid overdose, we intravenously administered flumazenil 0.3 mg twice and naloxone 0.04 mg four times intermittently. However, the patient was still comatose with a Glasgow Coma Scale score of 3. We quickly performed brain computed tomography, which showed no evidence of brain hemorrhage or acute ischemic infarction. She was subsequently transferred to the intensive care unit (ICU) for further observation.

A neurologist in the ICU conducted a neurological examination but did not find any abnormal results. The day after the operation, brain magnetic resonance imaging and electroencephalography were conducted, and their results were normal. Thus, intracranial abnormalities, cerebrovascular incidents, and seizure were excluded as potential causes of the coma. A psychiatrist was then consulted, and they recommended to simply wait while providing her with supportive care.

After 36 h of no response, a nurse in the ICU heard the patient suddenly saying 'I'm cold' and appearing drowsy. At 48 h of no response, she opened her eyes and followed verbal commands. After recovery, the patient had no memory of the surgery but remembered hearing enough noise that she couldn't sleep while she was in the ICU. She seemed to remember, at least faintly, of the times that she was unresponsive. She was transferred to the general ward and the remainder of her hospitalization was unremarkable.



Fig. 1. Eyeballs directed downwards on opening the patient's eyelids.

able. The patient was discharged without any neurological complications.

Discussion

With the use of fast-acting general anesthetic drugs, we expect patients to awake within a few minutes after surgery. Rarely, patients may not regain consciousness quickly after general anesthesia as a result of various causes, including pharmacological, metabolic, and neurological causes [1]. Occasionally, residual anesthetic drugs may delay emergence from anesthesia as a result of overdosing or recurarization [1]. There are also nonpharmacological causes, such as seizure, stroke, and, in rare cases, psychogenic disease [3]. Psychogenic coma can be diagnosed as the cause when all other organic causes have been ruled out [4]. It is difficult for an anesthesiologist to immediately suspect psychogenic coma when the patient fails to regain consciousness after anesthesia, because it occurs rarely and can be diagnosed at the end of the evaluation [5].

The mechanisms and causes of psychogenic coma are poorly understood. Previous cases involved being female, undergoing general anesthesia, undergoing head or neck surgery, having psychiatric disease, and experiencing stress as predisposing factors [2]. Psychogenic coma has several characteristics that differentiate it from true coma. As in our case, patients close their eyes tightly and consistently look either upward or downward [6]. During the hand drop test, patients with psychogenic coma show hand drop avoidance [7]. In addition, often the results of the doll's eye or caloric examinations are not abnormal, which would be the case if there was a neurological problem [8]. In most cases, self-respiration is sufficiently preserved even in the comatose state [9]. Patients generally regain consciousness spontaneously in 3–48 h without any special treatment [2].

Our patient awakened after general anesthesia but fell into coma shortly thereafter in the PACU. Resedation after remimazolam reversal with flumazenil has been reported to be effective in such situations as the blood concentration of flumazenil decreases [10]. In our case, the patient was awakened without flumazenil administration in the operating room and was alert upon arrival in the PACU. As flumazenil and naloxone administration was ineffective, resedation due to the residual effects of the anesthetic drugs can be excluded as the cause of the coma. As in our case, another patient was reported to have fully woken up immediately after surgery but to have then lost consciousness again several hours later [5]. She experienced psychogenic coma each of the three times she underwent general anesthesia thereafter. Therefore, in patients with a history of psychogenic coma, there is a

possibility of repeated episodes following anesthesia.

Decreased levels of consciousness during the perioperative period can be confused with hypoactive delirium, especially in elderly patients. During hypoactive delirium, EEGs slow as the level of consciousness approaches stupor [11,12]. Our patient was determined to be in a psychogenic coma, not experiencing hypoactive delirium, because her EEG was normal while she was comatose. Furthermore, the patient appeared to be experiencing a significant psychogenic burden as indicated by the many psychiatric medications she took for uncontrolled anxiety, insomnia, and somatic symptoms as determined during the preoperative checkup.

Treatment of psychogenic coma is largely limited to relieving the anxiety of the patient and caregivers with supportive care. Clinicians should not repeat stimuli to wake the patient. Anxiety is believed to be a contributing factor to psychogenic coma, so more noxious stimuli may cause greater anxiety in patients and delay recovery even more [13]. Anxiolytics, such as lorazepam, have been suggested for recovery [5]. In this respect, the present case was unique because remimazolam, a short-acting benzodiazepine, was used to maintain anesthesia. Various anesthetics were used in previous cases of psychogenic coma, including sevoflurane, isoflurane, propofol, and thiopental [2]. There seems to be no correlation between anesthetic type and the occurrence of psychogenic coma.

In conclusion, psychogenic coma may be a rare cause of delayed recovery of consciousness after anesthesia. Its poorly understood etiology and low incidence rate make it difficult to diagnose. Anesthesiologists should consider this rare condition for patients with unexplained delay in emergence from anesthesia. Appropriate examinations and treatments can improve patient prognosis.

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Conflicts of Interest

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