Title
Anesthesia for ovarian teratoma resection using remimazolam and remifentanil in a patient with anti-N-methyl-D-aspartate receptor encephalitis: two case reports

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Running title
Anesthesia in anti-NMDAR encephalitis

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Abstract

Background: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a type of autoimmune encephalitis that causes characteristic symptoms through the formation of antibodies against NMDA receptors. If ovarian teratomas are detected, surgical removal under general anesthesia is often considered. Many general anesthetic agents inhibit NMDA receptors. As such, anesthetic agents may have unexpected effects on disease progression. For anesthesiologists, providing general anesthesia for these patients is challenging.

Case: Two female patients were diagnosed with anti-NMDA receptor encephalitis and ovarian teratomas. Successful teratoma resection was performed under general anesthesia using remimazolam and remifentanil. After the surgery, one patient showed some improvement but died a month later. The other patient progressively improved over time.

Conclusions: Remimazolam and remifentanil are useful general anesthetic agents for patients with anti-NMDA receptor encephalitis. Further studies are warranted.

Keywords: Encephalitis; General anesthesia; NMDA receptor; Remifentanil; Remimazolam; Teratoma.
Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disease. Antibodies against the GluN1 subunit of the NMDA receptor are detected in the patient's serum or cerebrospinal fluid (CSF), resulting in characteristic symptoms [1]. Clinical manifestations range from prodromal symptoms such as fever, headache, nausea, vomiting and upper respiratory symptoms, to psychosis and seizures. Autonomic dysfunction and central hypoventilation can occur in severe cases [2]. The disease incidence is approximately 1.5 per million people annually. The majority of the patients are young women with a median age of 21 years. Tumors are detected in many of these patients, most of which are ovarian teratomas [3].

The first-line treatment for anti-NMDA receptor encephalitis includes immunotherapy and resection of the tumor if present [2]. Therefore, anesthesiologists occasionally encounter these patients in the operating room for tumor resection. Since the NMDA receptor is an important target of general anesthetic agents [4], we cannot exclude the possibility that these agents can exert inhibitory effects on NMDA receptors and adversely affect disease progression. Due to the rarity of this disease, reports on the appropriate anesthetic management of these patients are lacking. For anesthesiologists, providing general anesthesia for these patients can be challenging. To date, there have been no case reports of general anesthesia using remimazolam in patients with anti-NMDA receptor encephalitis.

In this report, we described two patients who underwent general anesthesia for ovarian teratoma resection using remimazolam, a novel sedative-hypnotic agent that does not act on NMDA receptors in combination with remifentanil, and discussed the appropriate anesthetic management for patients with anti-NMDA receptor encephalitis.
Case Reports

Case 1

In November 2021, a 21-year-old, previously healthy woman (ASA 1, 155 cm, and 53 kg) presented with headaches, fever up to 38.5°C, and myalgia. A few days later, her cognitive function declined and she was transferred from a nearby hospital to the emergency room of our hospital, suspecting meningitis. Initial diagnostic tests included computed tomography (CT) and magnetic resonance imaging (MRI) of the brain, all of which appeared normal. Electroencephalogram (EEG) suggested slow and disorganized posterior activity with diffuse irregular theta and delta slowing. Since there were no abnormal findings in the CSF study, viral or autoimmune meningoencephalitis was suspected, and acyclovir (600 mg every 8 h for 3 weeks) and steroid pulse therapy (glucocorticoid 1 g/day for 5 days) were administered.

Nevertheless, the patient’s symptoms worsened. She was mentally confused, and progressed to non-convulsive status epilepticus. Eventually, the patient became stuporous, and was transferred to the intensive care unit (ICU). In the ICU, additional antiepileptic drugs were initiated and midazolam was continuously administered to relieve seizures. Endotracheal intubation was performed to secure the airway, and a mechanical ventilator was used for respiratory support. One month later, a tracheostomy was performed. Subsequently, intravenous immunoglobulin (IVIG) therapy was initiated at 400 mg/kg/day for 5 days. A follow-up CSF test revealed anti-NMDA receptor antibodies, confirming the diagnosis of anti-NMDA receptor encephalitis. As the patient’s clinical status did not improve, rituximab and tocilizumab were administered as second-line therapies. The abdominal CT revealed a 7.4 cm-sized benign ovarian cystic tumor lesion of the right adnexa and laparoscopic right salpingo-oophorectomy under general anesthesia was considered. Informed consent for publication was obtained from the patient’s guardian.

Antiepileptic drugs were continued on the day of the surgery. Continuous infusions of intravenous
midazolam (2 mg/h), propofol (40 mg/h), norepinephrine (0.25 mcg/kg/min) and morphine (1.5 mg/h) that were being administered in the ICU were maintained during the intraoperative period. Remimazolam and remifentanil were selected as the main anesthetic drugs. The preanesthetic baseline values were as follows: the bispectral index (BIS), 96; SpO2 at room air, 94%; body temperature, 38.1°C; heart rate, 102 beats/min; and non-invasive blood pressure (NIBP), 102/65 mmHg. Preoperative mental status assessment in the operating room before induction revealed that the Richmond Agitation-Sedation Scale (RASS) was -4 and the Glasgow Coma Scale (GCS) was E:4/V:T/M:1. Concurrently the patient presented with myoclonus on both feet. Due to her unstable respiratory ability, manual positive pressure ventilation was performed through a tracheostomy tube to support the patient’s ventilation during transfer to the operating room. The ventilator was connected to the patient’s tracheostomy tube through a breathing circuit. General anesthesia was induced with a continuous infusion of remimazolam (3 mg/kg/h) and remifentanil (0.2 mcg/kg/min) for 3 minutes until the patient’s eyes were closed. Rocuronium (40 mg) was also administered to achieve appropriate neuromuscular blockade. Anesthesia was maintained with a continuous infusion of remimazolam (1 mg/kg/h) and remifentanil (0.3–0.4 mcg/kg/min). During surgery, the BIS values remained between 70 and 78 and did not fall below 70 despite intermittent intravenous bolus administration of 2 mg of remimazolam. The vital signs remained stable between mean arterial pressure (MAP) of 90–110 mmHg and heart rate of 70–100 beats/min until the end of surgery. The resection was completed without any problems. Continuous infusion of remimazolam and remifentanil was stopped at the time of skin closure. To reverse the neuromuscular blockade, we administered intravenous pyridostigmine (10 mg) and glycopyrrolate (0.4 mg) and the train-of-four ratio soon reached 100%. Approximately 15 min after the discontinuation of remimazolam and remifentanil, the patient opened her eyes and the BIS value increased to 95. Immediately before leaving the operating room, the patient's vital signs were stable, with a body temperature of 37.6°C.
NIBP of 121/80 mmHg and heart rate of 80 beats/min. The duration of the operation and anesthesia were 50 min and 90 min, respectively.

No myoclonic movement was observed during ICU transfer. The biopsy result of the resected ovarian mass confirmed it to be a mature cystic teratoma containing 15% neural tissue and mild lymphocytic infiltrates. During the postoperative period, the patient continuously experienced intermittent seizures and the EEG results did not improve. Her mental status was assessed daily but did not return to the patient’s preoperative status. The continuous infusion of propofol and midazolam used to control the patient's seizures gradually tapered as the incidence of seizures slightly decreased and enable the patient’s consciousness to improve. One week after surgery, propofol was completely stopped and the continuous infusion of midazolam was stopped on postoperative day 13. Instead, an intravenous bolus of lorazepam or midazolam was administered intermittently when seizure activity recurred. On postoperative day 15, the patient's spontaneous breathing partially recovered. On postoperative day 20, IVIG 400 mg/kg/day was readministered for 5 days to remove the remaining antibodies because of persistent seizure activities. Her spontaneous breathing ability completely recovered and mechanical ventilation was discontinued 2 weeks later. The patient’s blood pressure was also well maintained, so norepinephrine infusion was stopped. The MAP was maintained well above 60 mmHg, so additional cardiovascular drugs for hemodynamic support were not initiated. However, the patient’s mental status did not improve, and she continuously experienced intermittent seizure activities. Eventually, on postoperative day 40, the patient died of brain injury from status epilepticus.

Case 2

In March 2022, a 21-year-old woman (ASA 2, 155 cm and 75 kg) visited emergency room of our hospital with headaches lasting 10 days, memory disturbance, and confusion that occurred 7 days
before. There were no known underlying diseases other than being diagnosed with COVID-19 9 days before admission.

Brain CT and MRI did not reveal any significant abnormalities. EEG showed rare ill-defined sharp waves in the bitemporal region. Initially, meningoencephalitis due to viral, tuberculosis or autoimmune causes was suspected, and acyclovir (600 mg every 8 h), anti-tuberculosis medication and steroid pulse therapy (glucocorticoid 1 g/day) were promptly started. However, no virus or tuberculosis was detected in the subsequent CSF analysis. The abdominal CT revealed a mature cystic teratoma, measuring 4 cm in diameter, in the right ovary. An additional CSF study for antibody analysis was conducted. Surgical resection of the teratoma was scheduled with anti-NMDA receptor encephalitis suspected. Two days later, on hospital day 7, laparoscopic right salpingo-oophorectomy was performed under general anesthesia. Informed consent for publication was obtained from the patient’s guardian.

On arrival to the operating room, the preanesthetic baseline vital signs indicated a SpO2 of 99% at room air, body temperature of 37.0°C, heart rate of 60 beats/min, and NIBP of 140/85 mmHg. The initial BIS value was 96 and the GCS score was E:4/V:4/M:6 indicating irritability and confusion. General anesthesia was induced with a continuous infusion of remimazolam (6 mg/kg/h) and remifentanil (0.2 mcg/kg/min) for 5 minutes. Rocuronium (50 mg) for the neuromuscular blockade was administered. Anesthesia was maintained with a continuous infusion of remimazolam (1-2 mg/kg/h) and remifentanil (0.1-0.3 mcg/kg/min). The BIS values remained between 60 and 65 during surgery. The patient’s vital signs were stable during the surgery and the teratoma was successfully resected without any complication. Remimazolam and remifentanil infusions were discontinued after the resection. Muscle relaxation was successfully reversed with intravenous pyridostigmine (15 mg) and glycopyrrolate (0.4 mg). The train-of-four ratio was 100%. Flumazenil (250 mcg) was administered to fully awaken the patient. After the patient regained consciousness, successful tracheal extubation
was performed, and she was transferred to ICU for postoperative care. The duration of the operation and anesthesia were 30 minutes and 85 min, respectively.

The biopsy result of the resected ovarian mass confirmed a mature cystic teratoma with neural elements. The result of the CSF analysis performed before surgery was available 2 days after surgery, which confirmed the presence of anti-NMDA receptor antibodies. The patient was diagnosed with anti-NMDA receptor encephalitis. The next day, IVIG was administered at a dose of 400 mg/kg/day for 5 days. The patient’s condition gradually improved and she was discharged 12 days after the surgery for further management at another hospital.
Discussion

Anti-NMDA receptor encephalitis is a type of autoimmune encephalitis, a disease in which patients’ antibodies to the GluN1 subunit of the NMDA receptor reduce NMDA receptor density through antibody-mediated capping and internalization, resulting in characteristic neuropsychiatric symptoms [5]. The exact incidence is unknown. The estimated disease incidence is approximately 1.5 per million people per year. It is most prevalent in young women (80% of all the patients), with a median age of 21 years [3].

Clinical manifestations range from prodromal symptoms such as fever, headache, nausea, vomiting and upper respiratory symptoms to psychosis and seizures. In severe cases, autonomic dysfunctions (hyperthermia, tachycardia, bradycardia, hypotension and hypertension) and central hypoventilation requiring mechanical ventilation support may occur [2]. Brain MRI sometimes presents FLAIR or T2 signal hyperintensity in some brain regions. However this is not observed in all patients. EEG results typically show nonspecific, generalized slow rhythmic delta or theta activity. A definitive diagnosis can be made by detection of IgG GluN1 antibodies in CSF analysis and at the same time accompanied by the rapid onset (<3 months) of one or more typical symptoms including psychiatric behavior, speech dysfunction, seizure, movement disorders, decreased level of consciousness, autonomic dysfunction and central hypoventilation [6].

The primary treatment strategies include immunotherapy such as steroids, IVIG, and plasma exchange, and tumor resection if there is a tumor present. Patients with a diagnosed tumor and treated with surgical removal within 4 months of the onset of neurological symptoms showed better outcomes compared to patients with an untreated tumor or one that was treated 4 months after the onset of neurological symptoms. Earlier interventions generally lead to a higher incidence of complete recovery and fewer or more minor deficits. Furthermore, the reported median time from the onset of symptoms to early signs of improvement is approximately 8 weeks (range, 2-24 weeks) for early
tumor resection group, versus 11 weeks (range, 4-40 weeks) for the late or untreated group [1]. Second-line immunotherapy may include rituximab or cyclophosphamide and 80% of patients with tumors and 48% of patients without tumors show significant improvement with first-line immunotherapy [2].

The NMDA receptor is a complex of four subunits (GluN1, GluN2A-B, and GluN3A-B) [7]. NMDA receptors mediate excitatory neurotransmission in the central nervous system (CNS) and are important targets of general anesthetic agents. In addition to nitrous oxide (N2O) and ketamine, which have a major inhibitory effect on NMDA receptors, propofol and volatile anesthetics (isoflurane, sevoflurane, desflurane) are also known to have inhibitory effect on NMDA receptors to some extent [4].

Considering this, it can be hypothesized that the use of these anesthetic agents in patients with anti-NMDA receptor encephalitis who present with various clinical symptoms may produce unexpected effects or even worsen their clinical status. However, only a few studies have been conducted on which anesthetic method is the most appropriate for these patients. Few case reports have been described the use of combination of propofol and volatile anesthetics [8,9] or total intravenous anesthesia (TIVA) with propofol and remifentanil [10,11] for general anesthesia. Moreover, the effects of TIVA or inhalational agents in patients with anti-NMDA receptor encephalitis are controversial.

Some patients who underwent general anesthesia with TIVA did not develop major complications and their symptoms improved [10,11]. In one case report, propofol 80 mg and sufentanil 15 mcg were used for induction and then propofol and remifentanil were continuously administered at a rate of 270 mg/h and 0.1 mcg/kg/min respectively for 1 h and 5 min of total surgical duration. After the surgery, the patient’s condition improved, and she was discharged 20 days after surgery [10]. However, in other studies which used propofol for induction and volatile anesthetic agents for
maintenance, patient outcomes did not improve and for some, patient outcomes worsened [8,9]. In one case report, 50-150 mg/h of propofol was continuously administered to the patient before surgery for several days, and 100 mg of propofol was used as the induction dose for general anesthesia. Sevoflurane was used to maintain anesthesia. After surgery, propofol was continuously administered at a rate of 50-80 mg/h for sedation, and the patient’s symptoms worsened, resulting in dyskinesia and generalized tonic-clonic seizures. These symptoms improved after discontinuation of the propofol infusion. Therefore, the authors of this case report concluded that propofol and sevoflurane aggravated NMDA receptor inhibition and exacerbated disease symptoms. Based on this, they recommended anesthetic management using benzodiazepines, opioids, and curare to minimize the potential effects on NMDA receptors in their conclusion [9].

Based on these previous studies, we decided to use remimazolam and remifentanil for general anesthesia induction and maintenance in both cases. Remimazolam is a novel sedative-hypnotic agent, classified as a benzodiazepine, which enhances the effects of GABA receptor, a major target of general anesthesia [12]. Some of the benefits of remimazolam anesthesia include a lower incidence of hypotension and rapid reversal of the sedative effect by flumazenil when the patient's awakening is delayed, compared to propofol anesthesia [13]. In addition, remifentanil is an ultra-short acting opioid that acts on the mu-opioid receptor and effectively controls intraoperative hemodynamic responses [14].

In our first case, the patient was sedated with a continuous low-dose infusions of midazolam, propofol, and morphine for several weeks before surgery due to status epilepticus. Nevertheless, intermittent seizure events were present and the preanesthetic baseline BIS value in the operating room was as high as 96. Therefore, we judged that although her mental status was affected by the disease, the sedative effect of these low-dose infusions was only modest, and sudden cessation of the sedatives could trigger adverse events such as generalized seizures. Therefore, we decided to add...
remimazolam and remifentanil for general anesthesia while maintaining the preoperative drug infusion status during the entire intraoperative period.

However, the remimazolam induction dosage was arbitrarily reduced by half to prevent unexpected oversedation from interacting with other sedatives administered concurrently. In addition, in both cases, a much higher maintenance dose was administered because the BIS values did not fall within the appropriate ranges for general anesthesia during the intraoperative period. Based on this, we hypothesized that the depth of anesthesia was not shallow, but the abnormal electrical activities due to the damaged brain may not have correctly corresponded to the patients’ consciousness level [15], thereby resulting in incorrect and high BIS values. In both cases, the operations were completed without any patient movement or excessive change in the vital signs.

We predicted better outcome in our two patients compared to previous studies in which the patient underwent anesthesia with propofol and sevoflurane [9] because remimazolam and remifentanil did not have any inhibitory effects on NMDA receptor function, and the amount of propofol used in our first case was smaller (40 mg/h). In our first case, the patient's incidence of seizures decreased, and she recovered normal spontaneous breathing ability over time after surgery. However, her mental status remained stuporous and she died 40 days after surgery. We suspected that the delay in teratoma resection, which was performed 83 days after hospitalization, could be one of the reasons why the patient's clinical condition did not improve dramatically. During this long period, the patient's brain was likely already irreversibly damaged by persistent seizure activities from NMDA receptor antagonism. In addition, the continued use of propofol in the ICU during the postoperative period may have contributed in part to the undesired outcome. If sedation is required after surgery in other patients with this disease, benzodiazepine such as midazolam and remimazolam, or dexmedetomidine may be preferable to propofol. As dexmedetomidine is an α2 agonist that is widely used for sedation, and at the same time does not have NMDA receptor inhibitory potential. In our second case, propofol
was not used perioperatively, the diagnosis and treatment were earlier, which may contributed to more favorable outcomes.

Anti-NMDA receptor encephalitis was first identified a few years ago. However, there are currently few studies on the most appropriate anesthetic management for patients with the disease. Furthermore, most of the general anesthetic agents currently used have antagonistic effects on NMDA receptor function. General anesthesia using these agents can worsen the patient's disease course or produce unanticipated effects. We recommend the use of remimazolam, a novel general anesthetic agent that does not have any effect on NMDA receptors, and has a rapid onset and offset after prolonged continuous infusion, an appropriate drug for general anesthesia and sedation in patients with anti-NMDA receptor encephalitis. Furthermore, remimazolam is associated with fewer hypotensive events compared to propofol [13], which can assist anesthesiologists in managing intraoperative blood pressure and can be another potential advantage in patients with advanced anti-NMDA receptor encephalitis who present severe hemodynamic instability due to autonomic dysfunctions. Although our patient in first case died, the patient in the second case who underwent general anesthesia only with remimazolam and remifentanil had a positive outcome. To date, there are no reported studies on the use of remimazolam in patients with anti-NMDA receptor encephalitis. This is the first case report. Future studies on the use of remimazolam in patients with anti-NMDA receptor encephalitis will help establish an appropriate anesthetic plan for the management of general anesthesia for these patients.
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