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Non-convulsive status epilepticus in the immediate postoperative period following spine surgery.

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Running title: Non-convulsive status epilepticus

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Abstract

**Background:** Non-convulsive status epilepticus (NCSE), in which continuous epileptiform discharges occur without seizure-like movement, is rare and unfamiliar to anesthesiologists, both of which make this condition overlooked in patients with decreased levels of consciousness following general anesthesia.

**Case:** We report on an elderly female patient who developed NCSE in the immediate postoperative period after spine surgery. Initially, delayed emergence from anesthesia was suspected, but the electroencephalogram confirmed NCSE and anticonvulsant therapy was initiated.

**Conclusions:** Delayed emergence is commonly attributed to cerebrovascular events or residual anesthetic effects but NCSE must be included in the differential diagnosis, especially in elderly patients. Anticonvulsant therapy should be initiated as soon as possible for a better prognosis.

**Keywords:** General anesthesia; non-convulsive status epilepticus; post anesthesia care unit.
Non-convulsive status epilepticus (NCSE) can be defined as a condition of continuous or intermittent clinical epileptic activity without convulsion, lasting at least 30 minutes with the electroencephalogram (EEG) evidence of seizure [1]. The main clinical features of NCSE is a change in behavior or consciousness: mutism, mild amnesia to stupor, agitation [1, 2]. However, there is as yet no universally accepted definition of NCSE.

A decreased level of consciousness after general anesthesia could be attributed to residual anesthetic effects, cerebrovascular events such as hemorrhage or ischemia, and other metabolic derangements and it is not an easy task to distinguish among the many possible causes of decreased consciousness or lack of responsiveness. The occurrence of NCSE in the immediate postoperative period is so rare to estimate prevalence. We found only two reported cases of NCSE in the immediate postoperative period after brain surgery [3-4]. Single report from India documented two patients with NCSE after extracranial surgery but the patient was thought to have NCSE based on the circumstantial evidence not on EEG finding [5]. To our knowledge, the presentation of NCSE immediately after non cranial surgery has never been published.

The following case describes an elderly female patient who developed NCSE in the immediate postoperative period and presents a discussion that highlights the importance of NCSE in the differential diagnosis of decreased consciousness.
Case Report

A 75-year-old woman with well-controlled hypertension and diabetes mellitus (height 154.1 cm and weight 52.8 kg) was scheduled to undergo a transforaminal lumbar interbody fusion of L3-S1. She had previously undergone uneventful surgery with general anesthesia for a laminectomy eight years ago. She was taking oral hypoglycemic and antihypertensive agents with analgesics for back pain. She had no history of psychiatric illness or drug addiction. Her preoperative vitals and biochemical parameters were unremarkable. General anesthesia was induced with propofol and maintained with air, oxygen, desflurane, remifentanil, and muscle relaxation with vecuronium. A mean arterial pressure (MAP) was maintained around 75 mmHg with intermittent bolus injection of ephedrine, and her MAP was never below 55 mmHg at any point in time during surgery. There was no episode of hypoxia and peripheral oxygen saturation was 100% throughout the surgery. The body temperature measured with esophageal stethoscope was 36.1 °C at the beginning of the surgery and gradually decreased even though the air warmer was applied, and at the end of the surgery, became 35.1 °C. Anesthesia lasted eight hours 10 minutes, with the majority performed in the prone position. An estimated blood loss was 300 ml with hemoglobin level of 10.2 g/dl without transfusion. At the end of anesthesia, the residual neuromuscular block was reversed with neostigmine 2.0 mg and glycopyrrolate 0.4 mg and a train-of-four ratio of 100% was confirmed. The patient did not respond to verbal commands but breathed spontaneously with adequate tidal volume and entropy was maintained over 95. Therefore, her condition was judged to be appropriate for extubation.

Upon arrival at the post anesthesia care unit (PACU), the patient still did not respond to verbal commands - ‘open your eyes’, ‘what is your name’, ‘squeeze my hand’, exhibiting only painful moaning with firmly closed eyes and mouth. Her condition remained unchanged for the next three hours during her stay in the PACU and we could only guess from her facial expressions and moaning that she was in pain. A blanket and warmer were applied to treat hypothermia (35.1 °C).
throughout the stay in the PACU and her temperature reached 36.1 °C just before transfer to the ward. Hypoglycemia and electrolyte abnormalities were ruled out (blood glucose concentration, 204 mg/dl; serum sodium, potassium, calcium, magnesium, and chloride, 140, 4.0, 8.7, 2.1, and 106 mEq/L, respectively). Her pupillary reflex could not be checked because her eyes were tightly closed and a detailed neurological examination could not be performed due to her non-cooperation, but there has been no evidence of a cerebrovascular accident (CVA). She was hemodynamically stable, with a blood pressure of 140 – 170/ 60 – 90 mmHg and an SpO2 of 97 – 98% on room air. Modified Aldrete’s score was 8 due to unresponsiveness. We decided to transfer her to the general ward and obtain a neurology consultation for further evaluation.

On the day after surgery, she was transferred to the neurology service for evaluation and work-up of her mental status change and possible CVA occurrence. Neurological examination by a specialist showed no abnormal findings suggestive of a CVA. She voluntarily moved all four extremities upon occasion and responded to painful stimuli but remained mute and unresponsive to verbal commands. However, at most times, she seemed awake and possibly aware of her surroundings. At postoperative 18 hours, magnetic resonance imaging (MRI) and EEG were performed to differentiate between ischemic stroke and NCSE in relation to speech impairment or unresponsiveness after anesthesia. The MRI findings were normal, and the EEG showed a large amount of generalized slow waves and periodic lateralized epileptiform discharge-like patterns appeared occasionally over the right hemisphere (Fig. 1). After ruling out CVA and confirming the EEG pattern, she was given an intravenous loading dose of lacosamide 200 mg and maintained on an oral dose of lacosamide 50 mg twice a day starting on postoperative day 1. Over the next two days, she gradually became more alert and followed verbal commands, and started ambulation on the third postoperative day. Thereafter, she was maintained on lacosamide and no further episodes indicating NCSE were reported during her two-month follow-up period.
Discussion

Decreased responsiveness or alertness after general anesthesia poses many difficulties to anesthesiologists. Although there is no established definition of delayed emergence, even after long periods of anesthesia, patients usually restore their response to stimuli and consciousness within one hour after discontinuing anesthetics.

Several factors are attributed to the delayed recovery from anesthesia in the immediate postoperative period. First, pharmacologic factors should be excluded. The residual effects from various anesthetics such as volatile anesthetics, opioids, and neuromuscular blocking agents could be responsible for delayed emergence or unresponsiveness. In our case, complete recovery from neuromuscular blocking agents was confirmed with a neuromuscular transmission monitor. The patient received a total of 3 mg of remifentanil and desflurane with an end-tidal concentration of 4% for the maintenance of anesthesia, which lasted almost eight hours. Long anesthesia time could contribute to delayed emergence but it was quite unusual that the residual anesthetic effects lasted so long, considering that remifentanil and desflurane are known for their short duration of action.

Next, metabolic causes, such as hypothermia, hypoglycemia, and electrolyte imbalance, should be considered for this circumstance. Upon arriving at the PACU, her temperature was 35.1 °C and gradually rose to reach 36.1 °C. However, her condition remained unchanged despite a rise in body temperature. Moreover, the patient’s electrolyte concentrations were within the normal ranges blood and hypoglycemia was not noted. After ruling out the usual causes for delayed emergence, neurologic events, which are relatively uncommon, but with serious sequelae, should also be considered as possible etiology. The patient's non-cooperation made it impossible to complete a neurologic examination in the immediate postoperative period. However, there was no lateral sign implying CVA, and the subsequent MRI study and complete neurologic examination by neurologist confirmed that. If a patient was suspected of having a stroke, we would have called for a neurologist...
immediately. However, a surgical emergency was excluded based on benign physical exam and the patient's cardiovascular system was stable, and we decided to consult neurologist the next day. But it is often beneficial to obtain neuroimaging and neurology consult quickly.

NCSE is a condition with symptoms ranging from subtle muscle twitches to generalized coma and is difficult to diagnose unless an EEG shows the presence of seizure activity. The condition might be confused with delayed emergence or hypoactive delirium after anesthesia, especially in geriatric patients. Until now, no clinical case of NCSE immediately after non cranial surgery has been reported.

There is substantial variability in the reported incidence of NCSE, reflecting the lack of a universally accepted definition and difficulty in diagnosis [6,7]. NCSE is likely to occur in any condition that causes brain tissue injury such as subarachnoid hemorrhage, traumatic brain injury, and intracranial surgery [8-10]. NCSE has been increasingly reported in other comatose patients in intensive care units [11]. The actual incidence is hard to determine, considering that NCSE is easily missed, but higher than reported. NCSE is particularly difficult to recognize in the postoperative period and often misinterpreted as residual anesthetic effects. NCSE is often a diagnosis of exclusion and a high degree of suspicion is important. Jordan et al. suggested that NCSE should be suspected if consciousness is not restored for a long period of time after all types of surgery that have a high risk of brain dysfunction [12]. Old age and critical illness are known risk factors for NCSE development [13,14].

The prognosis of NCSE highly related to the underlying disease, and when it is excluded, the prognosis may vary depending on the presenting level of consciousness [15]. “De novo” reactive (situation-related) absence status in the elderly, subtype of NCSE, is a morbid condition, with mortality ranging up to 57% [1]. But the prognosis in certain subsets of “de novo” absence status is benign, such as our patient, who had no concomitant brain or systemic injury. However, this does not mean
that treatment decision should be based solely on the expected outcome. Especially in postoperative patients, the risk of delayed ambulation and its associated potential complications, unnecessary diagnostic studies, and hospital cost should be considered. Although rare, delay in diagnosis and initiation of treatment could leave neurological sequelae if persisted [1,2].

With regard to treatment options, the response to an initial treatment with benzodiazepines such as lorazepam is usually good, but sometimes delayed in ‘de novo’ reactive status in the elderly [2]. Devarajan et al. reported that the seizures slowly decreased after 8 hours of initiating treatment and persisted for another 5 hours in elder patient with newly developed NCSE in immediate postoperative period [3]. The follow up EEG is not mandatory to confirm the therapeutic effect of antiepileptic medications and the patient's symptoms gradually recovered over the two days in our case.

The presence of seizure activity in the EEG is essential for the diagnosis and treatment of NCSE but EEG is not one of the routine diagnostic tests in the presence of delayed emergence in the PACU and obtaining an emergency EEG after hours and during weekends is unavailable in some institutions. The patient stayed in the PACU for about three hours from 5 PM and it wasn't until around 6 PM that the patient's condition called our attention. Since we put more possibility on the hypoactive delirium and it was not a regular working hours, the subsequent examination and referral was decided to be performed early the next day. However, as mentioned earlier, if circumstantial evidence highly suggestive of NCSE, neurologic consultation should be sought as soon as possible for diagnosis and treatment.

Decreased consciousness can arise from serotonin syndrome and overlapping feature with NCSE may lead to a misdiagnosis. Serotonin syndrome resulted from serotonin excess usually presents as a triad of neuromuscular hyperactivity, autonomic instability, and mental status changes and patient’s history reveals current exposure to serotonergic agent [16]. The patient was prescribed
75/650 mg oral tramadol/acetaminophen twice daily, 5/2.5 mg oral oxycodone/naloxone twice daily and 100 mg celecoxib twice daily for back pain. Fentanyl was also administered for pain control at PACU. Opioids have been considered as serotonergic agents which are associated with serotonin syndrome, and tramadol, oxycodone, and fentanyl are among them [17]. Fentanyl in the setting of other serotonergic opioids might have caused the serotonin syndrome in our patient. This hypothesis, however, is not supported by patient’s symptom- patient didn’t show any autonomic instability including hyperthermia, hypertension and diaphoresis or neuromuscular hyperactivity such as muscle rigidity, tremor and bilateral Babinski sign. Initially, serotonin syndrome was ruled out based on symptoms and later NCSE was confirmed with the help of EEG.

This case describes de novo NSCE development in an elderly woman after general anesthesia. This condition can be easily misdiagnosed, particularly in an unusual clinical setting such as the immediate postoperative period and surgical locations other than the brain. The presence of NCSE after intracranial surgery or any other type of surgery, for that matter, should be considered in patients with an unexplained impairment of consciousness after anesthesia. Patients receiving an appropriate diagnostic approach and quick treatment are more likely to have a better prognosis.
References


**Fig. 1.** Electroencephalogram obtained during the patient’s initial EEG recording on postoperative day 1 shows large amount of generalized slow waves and periodic lateralized epileptiform discharge-like patterns (arrows) appeared occasionally over right hemisphere.