The Relationship Between the Perioperative Transition of Serum Anticholinergic Activity and Postoperative Delirium in Patients Undergoing Esophagectomy and Gastrectomy

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Purpose: Delirium is one of the most common postoperative complications among elderly patients undergoing major surgery. However, biomarkers for delirium have not yet been elucidated. We therefore investigated the relationship between postoperative delirium and the serum anticholinergic activity (SAA).

Materials: Patients undergoing elective esophagectomy or gastrectomy under combined thoracic epidural and general anesthesia were prospectively studied.

Methods: The levels of SAA were measured inside the operating room after the induction of anesthesia before the surgery began, and immediately after the surgery had finished, but before the patient awoke from anesthesia. The occurrence of postoperative delirium was determined using the Confusion Assessment Method (CAM).

Results: Postoperative delirium was identified in 41.2% of the 34 patients enrolled in this study. Compared with the non-delirious group, the delirious group had a significantly higher number of preoperatively SAA (+) patients whose elevated SAA levels were still detectable after surgery (p < 0.05).

Conclusions: Patients who had incomplete or no ability to compensate for the elevated anticholinergic activity were more likely to develop postoperative delirium.

Key words: serum anticholinergic activity, delirium, esophagectomy, gastrectomy

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV, delirium is described as an acute and fluctuating disturbance of consciousness with a reduced ability to focus, maintain or shift attention, accompanied by changes in cognition and perceptual disturbances secondary to a general medical condition. Delirium is an important issue, especially among elderly patients in emergency departments, surgical and oncology wards, intensive care units (ICU) and nursing homes. Patients undergoing surgical procedures and anesthesia are at high risk for developing postoperative delirium. In addition, postoperative delirium is associated with a prolonged hospital stay, increased mortality and increased morbidity.

Although its etiology is not fully understood, the following mechanisms are postulated to relate to delirium: changes in neurotransmitters, inflammation, physiological stressors, metabolic derangements, electrolyte disorders and genetic factors. Since acetylcholine plays an important role in...
consciousness, the disturbance of the central cholinergic system is often presumed to be the major pathogenic mechanism of delirium \(^6\). It is difficult to directly evaluate the cholinergic neurotransmissions in the brain. However, it has been suggested that the SAA levels adequately reflect the central anticholinergic activity \(^7\).

Despite the fact that previous studies have suggested an association between elevated SAA levels and delirium among medical and surgical patients \(^8\)–\(^12\), the relationship between postoperative delirium and SAA remains unclear. In this study, we evaluated the changes in the serum levels of SAA during the pre- and postoperative periods, and investigated the relationship between the levels of SAA and the occurrence of postoperative delirium.

**Methods**

**Patients**

Following the approval of the institutional review board and after obtaining written informed consent, 34 patients were enrolled in this study. The operations were performed at Juntendo University Hospital, which included esophagectomy (n = 17 patients) and gastrectomy (n = 17 patients).

**Exclusion criteria**

The exclusion criteria were as follows: preoperative impairment of consciousness and/or mental status, aphasia, respiratory dysfunction, liver dysfunction, and type I diabetes mellitus.

**Anesthesia**

No premedication was given. After placement of thoracic epidural anesthesia between either the T7/8 or T9/10 intervertebral space, general anesthesia was induced using propofol (1-2 mg/kg) and continuous infusion of remifentanil at the rate of 0.3–0.5 μg/kg/min. Rocuronium (0.6–0.9 mg/kg) was administered to facilitate orotracheal intubation. After the epidural administration of morphine (2–3 mg) and 0.375% ropivacaine (4–6 ml), anesthesia was maintained with sevoflurane (0.8–1.0 minimum alveolar concentration) and remifentanil infusion (0.2–0.5 μg/kg/min). Postoperative pain control consisted of epidural continuous infusion of 0.2% ropivacaine (2–5 ml/h) and morphine (1.4–4 μg/kg/h).

Medications known to have anticholinergic effects such as atropine and diazepam were not used.

**Analysis of the SAA level**

Blood samples were collected inside the operating room after the induction of anesthesia before the surgery began and then immediately after the surgery had finished, but before the patient awoke from anesthesia; and the samples were allowed to clot at room temperature. After centrifugation of 2500 rpm for 10 min, the resulting serum samples were stored at ~80°C until they were assayed. The SAA level was assayed at Mitsubishi Chemical Medience Corporation Laboratory in Kumamoto, Japan according to the protocol described by Tune and Coyle \(^8\). Using this radioreceptor technique, the amount of muscarinic antagonist, 3H–quinuclidinyl benzoate (3H–QNB), inhibited by the blood sample was compared with that of a known concentration of atropine, and was expressed as “atropine equivalents”. Since the relationship between the atropine concentration and 3H–QNB counts were linear when the addition of atropine ranged between 1.95 pmol/ml and 25 pmol/ml, the patient was categorized as SAA (+) if the measurement was ≥1.95 pmol/ml \(^13\). In this manner, we categorized a level below 1.95 pmol/ml as SAA (±) and undetectable level as SAA (−). The SAA levels were analyzed using the raw data for the SAA (+) group and 0 pmol/ml for the SAA (−) group. For the SAA (±) group, the SAA level was set at 0.975 pmol/ml, since the results were below the quantitative limit.

**Assessment of the mental state**

The cognitive function of the patients was evaluated using the Mini–Mental State Examination (MMSE) prior to the operation and approximately seven days later, when their postoperative course had settled \(^14\). The MMSE was performed in a quiet environment, either in the general ward or in the ICU, by an investigator who had been trained by a neurologist.

The confusion assessment method for the intensive care unit (CAM-ICU) was used to assess the presence of delirium, on admission to the ICU and until the patient was transferred to the general ward \(^15\).
Fisher’s exact test was performed using the SPSS Statistics 21 software program (IBM, Armonk, NY), and a value of p < 0.05 was accepted as statistically significant.

Results

Clinical characteristics
The clinical characteristics of patients with and without delirium are shown on Table-1. Although both the preoperative and postoperative MMSE scores were lower in the delirious patients, there were no significant differences between the delirious group and the non-delirious group when the MMSE scores were classified into two groups: scores 23 and below, versus scores above 23.

Levels of SAA
Since there was no significant difference in the development of delirium among patients who underwent two different surgical procedures (esophagectomy and gastrectomy), all data were analyzed together.

Postoperative delirium was found in 14 of the 34 patients (41.2%). There was no significant difference between the delirious group and the non-delirious group concerning the MMSE score.

As shown in Figure-1, the elevation of the SAA levels was recognized in the preoperative serum samples. However, there was no significant difference between the preoperative SAA levels and the occurrence of delirium.

Figure-2 shows the SAA levels categorized into (+), (±) or (−), and the number of preoperatively SAA (+) patients who were SAA (+) or SAA (±) after the operation was significantly higher in the delirious group than in the non-delirious group (p < 0.05).

Discussion
SAA has generally been thought to arise from the exposure to anticholinergic drugs or their metabolites. However, the presence of endogenous anticholinergic substances related to fever, acute infection and/or stress has been postulated among ill elderly patients independent from anticholinergic medications.

To the best of our knowledge, the present study is the first to investigate the relationship between the perioperative transition in the level of SAA and delirium.
the occurrence of postoperative delirium.

Although none of the patients had taken medications known to be anticholinergic preoperatively, almost all of the patients were categorized into the SAA (+) or SAA (±) group preoperatively. This elevation of the SAA levels may be explained by stress, considering the production of endogenous anticholinergic substances in response to stress.

On the other hand, almost all of the postoperative serum samples were categorized into SAA (±) or SAA (−). Although the SAA levels were predicted to rise due to surgical stress, the normal function of the cholinergic system may have compensated for the anticholinergic activity in some of the patients, thus suggesting that their cognitive functions were well preserved.

A SAA level greater than the limit of detection at a quantitative level is commonly defined as SAA (+). According to the findings of our previous studies, SAA was considered to be positive when it was ≥1.95 pmol/ml and undetectable when it was <1.95 pmol/ml. However, because a small amount of SAA can induce anticholinergic activity in the central nervous system, we assumed that a SAA level between 0 pmol/ml and 1.95 pmol/ml is still meaningful and should be classified as SAA (±).

Our study showed that there were no significant differences between the delirious and non-delirious groups concerning the preoperative SAA level alone, but the preoperatively SAA (+) patients who remained SAA (+) or SAA (±) after surgery were more likely to develop postoperative delirium. It could be speculated that the cholinergic system failed to compensate for the elevation of the SAA level in patients who developed delirium. As we had excluded patients with characteristics which are thought to be related to delirium, this result may suggest the close relationship between SAA and postoperative delirium.

The present study is limited by the small number of patients. However, further investigation may lead to a better understanding of postoperative delirium and its relationship with SAA.

In conclusion, the perioperative transition of the SAA levels may be associated with the occurrence of postoperative delirium, and larger and more in-depth studies are warranted.

References