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Case Scenario: Postoperative Delirium in Elderly Surgical Patients

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DELIRIUM is increasingly recognized as a major adverse event occurring postoperatively in elderly surgical patients. Once the diagnosis has been established, the main goal of delirium therapy is to identify important, potentially life-threatening, treatable, organic causes responsible for this syndrome. The purpose of this clinical pathologic conference is to highlight key points essential for the diagnosis and treatment of delirium occurring after anesthesia and surgery.

Case Report

An 81-yr-old woman presented with delirium 4 days after undergoing laparoscopic colon surgery under general anesthesia. She had a history of major tobacco consumption (2 cigarette packs/day for 45 yr) and still smokes. She also had moderate hypertension and peripheral vascular disease for which she had been treated with bare metal stents in both iliac arteries and the left femoral artery 3 yr ago. Chronic medications consisted of clopidogrel (75 mg/day), simvastatin (20 mg/day), bromazepam (6 mg/day), valsartan (160 mg/day), and bisoprolol (10 mg/day). She was admitted for laparoscopic surgical treatment of sigmoid diverticulitis complicated by sigmoido-vaginal fistula. Several episodes of polymicrobial urinary tract infections had been treated with antibiotics before admission. Preoperative examination revealed satisfactory cardiopulmonary status. Blood electrolytes were normal, troponin Ic was less than 0.04 ng/ml, hemoglobin was 12.9 g/dl, and platelet count was 260 g/l. Electrocardiogram showed regular sinus rhythm, blood pressure was 168/78 mmHg, and stress-echocardiography was negative for ischemia but showed left ventricular diastolic dysfunction with left ventricular hypertrophy. Doppler ultrasound examination of the carotid arteries was normal.

Clopidogrel, simvastatin, bromazepam, and bisoprolol were continued until the day of surgery, whereas valsartan was discontinued 2 days before surgery. Anesthesia was induced with propofol, sufentanil, and atracurium, and it was maintained with desflurane in O_2/N_2O 50:50. After an uneventful 3-h operation that consisted of sigmoidectomy, colorectal anastomosis, and ileostomy, residual neuromuscular blockade was reversed with neostigmine and atropine, the trachea was extubated, and the patient was transferred to the postanesthesia care unit (PACU) and then to the surgical ward. Postoperative analgesia consisted of intravenous propacetamol (500 mg 4 doses per day), nefopam (20 mg 3 doses per day), and morphine titration in the PACU. Patient-controlled analgesia with morphine hydrochloride (bolus = 1 mg, refractory interval = 7 min) was used during the first 48 postoperative hours. Epidural analgesia was not used in this case.

On postoperative day 4, the patient experienced several episodes of confusion, logorrhea, and disorientation. Glasgow Coma Scale score was 15. Temperature was 37.2°C but had a transient peak to 38.4°C the day before. Physical examination revealed slight abdominal tenderness, diarrheic stool in the ileosotomy, and normal cardiac and pulmonary auscultation. Blood leukocytes were 10,000/ml, hemoglobin was 12.9 g/dl, blood electrolytes were normal, and computed tomographic scan revealed a 3-cm diameter fluid collection at the colorectal anastomosis (fig. 1).

Discussion

Important issues to consider in this case include the following.

1. *How Is Delirium Diagnosed in the Postoperative Period?* Delirium, defined as an acute decline in attention and cognition, represents a serious complication in patients

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Fig. 1. Abdominal computed tomography scan performed on the fourth postoperative day revealing a 3-cm diameter fluid collection at the colorectal anastomosis (*arrow*).

after anesthesia and surgery and is predictive of mortality at 6 months in intensive care unit (ICU) patients.[1] There is increasing evidence that delirium precedes development of postoperative cognitive dysfunction after ICU admission.[1] Delirium exhibits both hyperactive and hypoactive forms, the latter being more common in the elderly and more often unrecognized.[2] The main clinical features of delirium are summarized in table 1. Diagnosis in the postsurgical setting is based on validated clinical scales. However, to date, most postoperative patients admitted to the PACU or the ICU have not been formally assessed for delirium or cognitive dysfunction with appropriate preoperative tests, which makes the time of onset of symptoms uncertain. The Confusion Assessment Method for Intensive Care Unit Patients Scale has been validated in medical and coronary ICU patients as a reliable tool to detect delirium.[3] Diagnostic criteria include abrupt onset and fluctuating course, inattention, and either disorganized thinking or coma. However, the capacity of Confusion Assessment Method for Intensive Care Unit Patients Scale for detecting delirium in the PACU is inferior to recently reported scales.[4] The Nursing Delirium Screening Scale includes five items scored 0–2: disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and psychomotor retardation. Delirium is indicated by a score ≥ 2. The Delirium Detection Score has been adapted to the PACU and includes five items scored 0–7: orientation, hallucination, agitation, anxiety, and paroxysmal sweating. Diagnosis of delirium is based on a Delirium Detection Score ≥ 7. The Nursing Delirium Screening Scale and Delirium Detection Score might be useful as additional tools to pain scores for ensuring patient comfort and restoration of postoperative brain function in the PACU. In this case, delirium was indicated by each of these scales (Confusion Assessment Method for Intensive Care Unit Patients Score = 3/4, Nursing Delirium Screening Scale Score = 6, Delirium Detection Score = 12).

Table 1. Clinical Features and Factors Contributing to Postoperative Delirium in Elderly Surgical Patients

Main Clinical Features of Delirium
Acute onset*
Fluctuating course*
Inattention*
Disorganized thinking*
Alteration in consciousness
Cognitive deficit (memory, orientation, executive functions)
Hallucinations (30% of the patients)
Psychomotor disturbances
Lethargy (hypoactive delirium)
Agitation (hyperactive delirium)
Alteration in the sleep-wake cycle
Emotional disturbances

Factors Contributing to Postoperative Delirium	
Patient-related factors	**Patient-unrelated factors**
Pain	Use of physical restraint
Hypoxemia	Cardiac surgery
Hypercarbia	Central nervous system drugs (anesthetics, sedatives, benzodiazepines, anticholinergics)
Hypotension	Sleep deprivation
Metabolic disorders (hyponatremia, hypercalcemia, hypoglycemia)	
Sepsis	
Drug withdrawal	
Pre-existing disease (depression, dementia)	

* Included in the confusion assessment method for intensive care unit patients diagnosis scale.[5]

2. *What Is the Pathophysiology of Postoperative Delirium in the Elderly?*

The pathophysiology of delirium after anesthesia and surgery remains obscure and is multifactorial. Hypothetical mechanisms for postoperative delirium include disordered neurotransmission, inflammation, and stress. Evidence supports the role of reduced cholinergic transmission or excessive dopaminergic tone in delirium. Proinflammatory cytokines such as tumor necrosis factor-α or interleukin-1, which have also been implicated, can alter neurotransmission, enhance neurotoxicity, and increase blood-brain barrier permeability.[5] Genetic factors have also been identi-

fied as risk factors for developing postoperative delirium in the elderly.[6] The aging brain exhibits both quantitative and qualitative changes in neuronal circuitry[7,8] that could account for the greater sensitivity of elder patients to delirium.

3. *What Are the Causes of Postoperative Delirium?*

On diagnosis of delirium, efforts turn to identification of the cause. Factors contributing to delirium in the postoperative period are listed in table 1. Factors related to the patients include pain, hypoxemia, hypotension, metabolic disorders, sepsis, and drug or alcohol withdrawal. Intense postoperative pain is a cause of hyperactive delirium with agitation.[9] Pain-induced delirium caused by undiagnosed urinary retention is common because residual bladder volume is elevated after anesthesia and surgery in the PACU[10] Hypoxemia and hypotension can cause delirium. Electrolyte disorders can also cause delirium, as with hyponatremia, because of absorption of water during endourologic or endogynecologic surgery. Hypernatremia and hypoglycemia in diabetic patients can also cause postoperative delirium. Hypoactive delirium can occur in patients with Parkinson disease because levodopa is given only orally. Patients addicted to nicotine, ethanol, opioids, or benzodiazepines are at high risk of developing delirium in the postoperative period. The incidence of postoperative confusion is increased in older persons taking chronic benzodiazepines.[11] Delirium tremens must also be considered and prevented in the case of alcoholic patients.

Factors not related to the patient include use of physical restraints, cardiac surgery, drugs (including anesthetics), and sleep deprivation. Perioperative acute ischemic stroke is an important cause of morbidity and mortality associated with both cardiac and noncardiac surgery, particularly in elderly patients.[12] Delirium without any sensory or motor deficit can be the only clinical manifestation of stroke in this context. Residual effects of muscle relaxants can contribute to delirium/agitation because of depression of pharygolaryngeal muscle activity and hypoxemia. Residual paralysis is frequently observed in the patients in PACU because of the underuse of neuromuscular function monitoring and incomplete antagonism of the effects of neuromuscular blockers, which increases postoperative respiratory complications, particularly hypoxemic episodes.[13] Drug-induced delirium is an obvious concern after anesthesia, because many drugs used in the perioperative period can contribute to delirium in older persons.[14] The use of anticholinergic agents is associated with delirium, particularly in older patients.[15] Delirium induced by ketamine has also been reported in this context.[16] Propofol has been associated with an increased incidence of emergence delirium in children.[17] In long-duration laparoscopic surgery performed in elderly patients under an anesthetic regimen with propofol-based anesthesia, an increase in the severity, but not incidence, of delirium on postoperative days 2 and 3 has been reported in comparison with a sevoflurane-based anesthetic regimen.[18] Although the use of nitrous oxide in elderly patients has been challenged recently, no data support an increase in the incidence of postoperative delirium in high-risk surgical patients undergoing anesthesia and surgery.[19] On the other hand, statins have been reported to attenuate delirium in patients undergoing cardiac surgery.[20]

4. *What Was the Probable Cause of Delirium in This Case?*

The most likely explanation of acute postoperative delirium in this case was postoperative peritonitis, which can precipitate delirium.[21] The fever the day before surgery supports this diagnosis, a nonspecific but frequent physical sign present in peritonitis. Fever as a sign of infection can be blunted or absent in older patients with infection.[22] Although the pathophysiology of sepsis-induced delirium remains poorly understood, several lines of evidence suggest that sepsis can alter the blood-brain barrier through the production of proinflammatory cytokines, such as interleukin 1-β, promoting leukocyte endothelial adhesion, and endothelial damage.[5] Interestingly, patients with sustained septic shock exhibit abnormal magnetic resonance imaging findings with various degrees of encephalopathy and damage to white matter tracts.[23] Altered synaptic transmission and excitability of hippocampal pyramidal neurons have been reported in an animal model of sepsis.[24] Sepsis-induced delirium might also be explained in part by an increase in oxygen requirements or hypoxia.

Subsequent Course

The patient received broad spectrum antibiotics and returned to surgery for exploratory laparotomy. Peritonitis caused by leakage of the colorectal anastomosis was confirmed by peritoneal fluid cultures positive for *Escherichia coli*. The postoperative course was complicated by respiratory, circulatory, and renal failure requiring mechanical ventilation with continuous intravenous sedation (midazolam and fentanyl) and inotropic support. The patient's condition slowly improved and she was extubated 8 days later. The day after extubation, a second episode of delirium ensued with disorganized thinking, inattention, and olfactory hallucinations. Her physical status remained stable, with no fever, normal electrolytes and no recurrence of circulatory, respiratory, or renal failure. Abdominal computed tomography scan was normal. Current medications, including antibiotics, could not account for the delirium.

5. *What Was the Cause and Treatment of the Second Delirium Episode?*

Because organic causes and persistent intraabdominal sepsis were unlikely, withdrawal syndrome was considered the most likely cause of this delirium episode. Benzodiazepine withdrawal syndrome could also have contributed to the first episode of delirium as a predisposing factor in addition to sepsis. The patient had been taking bromazepam chronically but had not received it since the second operation. She had also received 8 days of continuous

intravenous sedation with midazolam while being mechanically ventilated. She was therefore at high risk of developing benzodiazepine withdrawal syndrome.[25] Opioid withdrawal could not be excluded, because fentanyl was administered intravenously for 8 days.[25] Nicotine withdrawal has also been reported in ICU patients,[26] but a nicotine patch failed to reverse the delirium in this case. Bromazepam was then administered orally and the delirium resolved within 2 h. The patient was discharged from the hospital 8 days later and remains well 1 yr later.

6. *How Can Postoperative Delirium Be Treated or Prevented in Elderly Patients?*

Only dangerous agitation associated with delirium requires emergent pharmacologic intervention, whereas alternative strategies, including searching for an organic cause, must be considered first. Because of increased sensitivity of elderly persons to drugs, starting with small dosages and titration to effect is advised.[14] Neuroleptics such as haloperidol, a well-tolerated, easily titratable, nonrespiratory depressant butyrophenone antipsychotic, can be used for sedation.[27] In a randomized placebo-controlled trial, haloperidol prophylaxis decreased the severity and duration, but not the incidence, of postoperative delirium in high-risk elderly patients undergoing hip replacement.[28] Implementation of a delirium assessment tool in the ICU can reduce haloperidol use by allowing considerable reduction in the dosage and duration of treatment.[29] Reduced incidence of delirium in hospitalized elderly patients can be achieved by management of cognitive dysfunction, sleep deprivation, immobility, visual and hearing impairment, and dehydration.[30] Preventive strategies, such as preservation of sleep and multimodal physiotherapy, should be considered as well. Recently, a strategy for rehabilitation consisting of interruption of sedation and physical and occupational therapy during the early days of critical illness resulted in a reduction in the duration of delirium in ICU patients.[31] Sleep deprivation is also a common cause of delirium in ICU patients, who exhibit both qualitative and quantitative alterations of sleep.[32] Sleep disorders predispose to development of cognitive dysfunction in ICU patients,[2] such that improving sleep quality is an important goal. The α2-adrenoceptor agonist dexmedetomidine increases the number of delirium-free days in mechanically ventilated ICU patients and could become the preferred strategy for sedation in the ICU.[33]

Basic Science: Neuropathogenesis of Delirium

The etiology of delirium, particularly in the postoperative period, is most often multifactorial and difficult to diagnose.[34] Interactions between patient risk factors, medical illness, and therapy can produce such a complex neuropsychiatric syndrome. Drugs are one of the most common causes and one of the most treatable. The risk of drug-induced delirium is high in hospitalized elders in whom polypharmacy, altered pharmacokinetics and pharmacokinetics, and underlying pathology all interact to cause delirium.[14] Many drugs have been implicated, but central nervous system active drugs, all commonly used in the perioperative period, are most often implicated.

Although the mechanisms of drug-induced delirium are not well defined, imbalances in major cortical and subcortical neurotransmitter systems are probably important. Disturbances in multiple neurotransmitters have been implicated in delirium, but the neurochemical basis of delirium is most often explained by a deficit in cholinergic transmission ("cholinergic hypothesis").[35] Acetylcholine plays important roles in attention, consciousness, and memory, and it is critically affected in dementia. Alterations in cholinergic system function are supported by the observations that anticholinergic intoxication produces a delirium that can be reversed by cholinesterase inhibitors and by the propensity of antimuscarinic drugs to induce delirium. Indeed, a number of drugs associated with delirium have marked antimuscarinic side effects. Serum anticholinergic activity can be used to indicate a patient's net anticholinergic load from drugs and endogenous sources and has been positively correlated with delirium symptoms.[36] Anticholinergic effects have also been implicated in postoperative cognitive impairment.[37] But the pathophysiology is clearly more complicated because cholinesterase inhibitors do not typically treat or prevent postoperative delirium. Nonpharmacologic factors, such as ischemia or inflammation, can also contribute to postoperative delirium (fig. 2).

Alterations in neurotransmission involving the γ-aminobutyric acid, glutamate, and the monoamines (serotonin, norepinephrine, and dopamine) have also been linked to the pathogenesis of delirium, which is not that surprising, given the multiple interactions between these systems. A number of sedative/hypnotics including inhaled anesthetics, propofol, and benzodiazepines potentiate γ-aminobutyric acid-mediated transmission through γ-aminobutyric acid type A receptors in the central nervous system. The monoamine transmitters have prominent neuromodulatory roles in regulating cognitive function, arousal, sleep, and mood, and they are modulated by cholinergic pathways. An excess of dopaminergic transmission has been implicated in hyperactive delirium, which can respond to antipsychotic dopamine receptor antagonists such as haloperidol. There seems to be an inverse relationship between acetylcholine and dopamine system activity in delirium, and the terminal fields of these transmitters overlap extensively in the brain. Antiparkinsonian drugs such as levodopa can induce delirium, and dopamine antagonists can treat its symptoms. Both increases and decreases in serotonin signaling have been associated with delirium, which can be induced by selective serotonin reuptake inhibitors. Excessive norepinephrine has also been associated with hyperactive delirium.

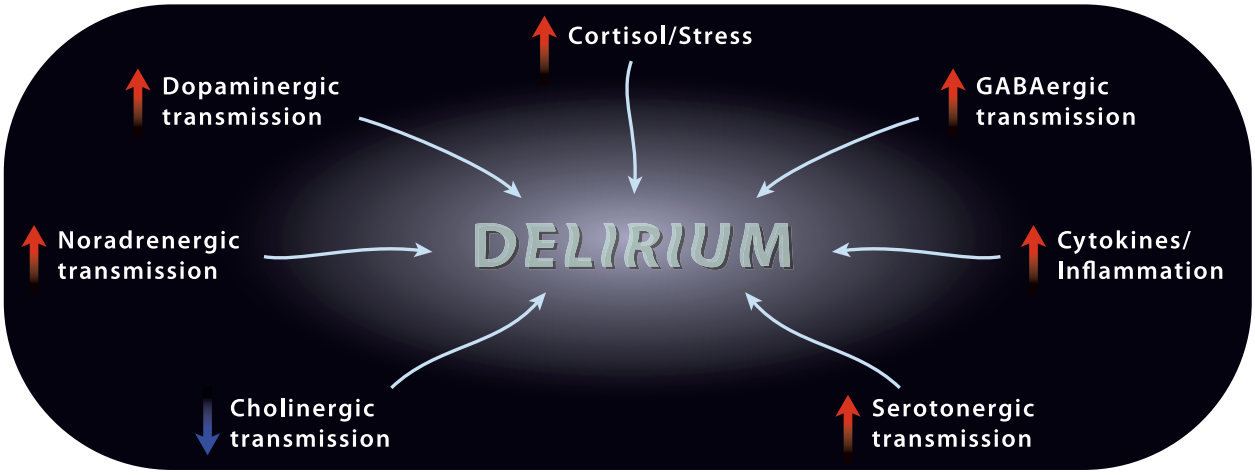

Fig. 2. Hypotheses for neuropathogenesis of delirium in elderly surgical patients. Activation (*ascending arrows*) or inhibition (*descending arrows*) of neurotransmitters, cytokines, and hormones by various factors (medications, withdrawal syndrome, sleep disorders, organ failure, inflammation, sepsis, and so on) can contribute to postoperative delirium in elder patients undergoing anesthesia and surgery. GABA = γ-aminobutyric acid.

Approach to Postoperative Delirium in the Elderly: The View of the Geriatrician and Current Concepts

For elderly patients, a surgical procedure is an acute event with potential life- and autonomy-threatening adverse outcomes. Prevention of cardiovascular events and stroke, postoperative delirium, poor nutrition, and loss of autonomy represent associated challenges for frail elderly patients in the perioperative period.

Delirium occurs more frequently with advancing age, but the underlying mechanisms are not clearly understood. Patients with increased postoperative delirium risk require specific attention. Numerous conditions are associated with postoperative delirium, which require specific attention as well.[34] A validated model of delirium prediction has been reported based on four criteria evaluated using specific scales, including illness severity (Acute Physiology and Chronic Health Evaluation Score),[38] visual impairment (Snellen test),[39] cognitive impairment (Mini Mental State Evaluation Score),[40] and serum urea/creatinine ratio.[41] For hip fracture surgery, postoperative delirium was reported in 37% of patients in the high-risk group compared with 3.8% in the low-risk group.[42]

In addition to these factors, cognitive impairment is the strongest factor associated with postoperative delirium; dementia and delirium are closely related. First, their symptoms strongly overlap, and time is required to get a valuable neuropsychological evaluation far from the acute episode. Second, patients with dementia are highly prone to delirium.[43] Third, half the patients undergoing delirium will develop dementia.[44] Finally, dementia can sometimes be difficult to diagnose, because elderly patients with a starting dementia can erroneously be considered normal because of compensatory mechanisms. Delirium was reported as a sign of undetected dementia with a 55% incidence 2 yr later in a small study[44] and might accelerate the trajectory of cognitive decline in patients with Alzheimer disease.[45]

Preoperative depression increases the risk for postoperative delirium.[46] In vascular surgery, patients with postoperative delirium had higher preoperative scores of depressive symptoms, using the Hamilton Depression Scale.[47] In younger patients, delirium was associated with depression using the preoperative Geriatric Depression Scale—Short Form Score[48] or the Beck Depression Inventory.[49] Recently, patients with an overlap syndrome of delirium and depressive symptoms had a particularly poor outcome prognosis including nursing home placement, 1 yr death, and 1 month functional decline.[50] Simple questions about memory complaints, activities of daily living, depressive symptoms, excessive familial or professional help, as well as previous postoperative delirium or drug-induced delirium provide crucial information for anesthesiologists. Some scales give clear information about global cognitive function (Mini Mental State Evaluation),[40] depression (Geriatric Depression Scale-short form),[51] and autonomy (Activity of Daily Living and Instrumental Activity of Daily Living Scales).[52,53] They are the cornerstones of most geriatric assessments, but physicians must be trained in their use.

A focus about assessment of autonomy in elderly patients is crucial for global and cognitive evaluation. First, a loss of physical or cognitive autonomy is always a disease-associated condition. Ageing people without any disease do not need help for reading (look for the glasses and search for cataract or macular degeneration), hearing (look for hearing aids and search for ear wax), feeding (search for depression or underlying disease or treatment), or thinking (search for dementia and depression) for example. Second, dementia criteria require loss of autonomy, and attention of physician to dementia is frequently drawn by loss of autonomy. Finally, use of validated scales (Activity of Daily Living or Instrumental Activity of Daily Living) highlights points frequently consid-

ered as nonsignificant by family or caregivers. However, evaluation of autonomy depends on the sociocultural level and requires specific questions depending on individual past activities or hobbies. Most importantly, a loss of autonomy is never an age-related normality but always a disease-associated symptom. For example, in this case, a cognitive assessment could have been discussed in the presence of difficulties for financial or medication management, looking for possible cognitive dysfunction related to vascular disease or age-related neurodegenerative disease. Whether a diagnosis of dementia should be made before surgery remains unclear because there is no evidence that preoperative treatment of dementia prevents postoperative delirium. This issue is a challenge for future research.

Medication use is another important concern. The role of anesthetics has been discussed previously. Preoperative benzodiazepines are associated with postoperative delirium.[11] Such prescriptions should always be questioned during preoperative assessment, because they are associated with falls or memory complaints. If preoperative medication is chosen, hydroxyzine or small doses of mianserine may be considered. Sudden withdrawal of benzodiazepines is a classic cause of delirium and must be avoided.

Numerous perioperative complications can trigger postoperative delirium. A randomized study reported a reduction of postoperative delirium in patients with hip fracture using a geriatric assessment and care plan (relative risk 0.64, 95% confidence interval 0.37–0.98).[54] This assessment included all parameters considered essential in the perioperative period: central nervous system oxygen delivery, fluid and electrolyte balance, treatment of severe pain, elimination of unnecessary medications, regulation of bowel and bladder function, nutritional intake, early mobilization and rehabilitation, management of postoperative complications, and appropriate environmental stimuli. A recent study in a large cohort confirmed and extended these findings.[55] Those patients could require cognitive assessment at regular intervals after surgery by geriatricians or neurologists.

Knowledge Gap

Although the pathophysiological mechanisms underlying delirium are poorly understood and clearly multifactorial, drugs acting on the cholinergic, γ-aminobutyric acid-mediated, and monaminergic neurotransmitter pathways are frequently involved. Future efforts to clarify these mechanisms and their relationship to other patient factors such as dementia should enhance diagnosis, treatment, and prevention. Collaborative approaches, including anesthesiologists, surgeons, and geriatricians, are essential for optimal management. The link between the perioperative period, postoperative delirium, and long-term postoperative cognitive dysfunction in elderly surgical patients represents an important research area. Finally, data suggest that assessment and early intervention can predict and avoid postoperative delirium in elderly patients. Future directions for preventing postoperative delirium in elderly patients should encourage combined anesthetic/geriatric approaches. The impact of such strategies as the use of pharmacologic agents, the evaluation of preoperative memory and executive functions, or the control of environmental factors on postoperative delirium in elderly surgical patients represent important challenges for future investigations.

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