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REVIEW ARTICLE

Strategies for prevention of postoperative delirium - anesthesiology aspects

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Summary

The occurrence of postoperative delirium is a significant health problem in critically ill elderly patients. The incidence of postoperative delirium varies in different studies and ranges from 10 to 70%. A higher incidence was noted among the elderly population, as well as after major surgical procedures such as vascular, cardiac, and hip fracture operations.

This syndrome is associated with many adverse outcomes that can negatively affect patient hospitalization, prolong mechanical ventilation, increase mortality, and increase treatment costs. Affected patients are at increased risk of readmission and have a low quality of life. The best strategy for reducing the harmful consequences of postoperative delirium is its prevention. It has been shown that simple perioperative interventions can significantly reduce the incidence and severity of this syndrome. These are, above all, an assessment of cognitive function before surgery, avoidance of benzodiazepines, intraoperative monitoring of anesthetic depth, adequate control of postoperative pain, and maintenance of normotension and normothermia.

Keywords: postoperative delirium, postoperative cognitive dysfunction, risk factors, prevention

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INTRODUCTION

Perioperative neurocognitive disorders are one of the most common complications in elderly surgical patients. They have been estimated to occur in up to 65% of cases (1). These disorders include preoperative moderate and severe neurocognitive impairment, postoperative delirium, delayed neurocognitive recovery of up to 30 days, and moderate and severe neurocognitive impairment lasting up to 12 months or longer (2). Postoperative cognitive dysfunction, which often occurs in elderly patients after major surgical procedures, has long been recognized as a significant health problem. It represents a subtle decline in cognition after the patient has recovered from the acute effects of surgery and is now defined as 'delayed neurocognitive recovery' when present within 30 days of surgery (3). However, data from the literature indicate that it is often unrecognized and underdiagnosed (4).

The occurrence of postoperative delirium (POD) is a significant health problem in critically ill elderly patients. Acute and fluctuating disturbances of consciousness, attention, perception, thinking, memory, psychomotor behavior, and the rhythm of wakefulness and sleep are the main characteristics of this syndrome (5). It often occurs within the first 3 days after the procedure and typically lasts 1-3 days. The clinical presentation is variable, and the motoric presentation may range from an agitated, hyperactive form to a hypoactive, reduced-activity form (6,7). The incidence of POD varies across studies, ranging from 10 to 70%. These differences are attributable to differing diagnostic criteria, study populations, and surgical procedures. A higher incidence was noted among the elderly population, as well as after major surgical procedures such as vascular, cardiac, and hip fracture operations (8). This syndrome is associated with many adverse effects that can negatively affect patient hospitalization, prolong mechanical ventilation, increase mortality, and treatment costs (9-11). Even after hospital discharge, these patients remain at increased risk of readmission and may have a low quality of life (4,9). Postoperative delirium is a multifactorial syndrome, and considering its many negative consequences, many studies have examined strategies that can influence the reduction of its occurrence. The most effective approach to reducing the harmful impacts of POD is prevention. It has been shown that simple perioperative interventions can significantly reduce the incidence and severity of this syndrome. About 30-40% of cases can be prevented by influencing the risk factors (12). The following text lists some anesthesia strategies whose use may help prevent POD.

METHODS

Three bibliographic databases, PubMed, WoS, and Scopus, were used in this review for literature search. The literature search was conducted for the period 2000-2025, and the following keywords were used: postoperative cognitive dysfunction, postoperative delirium, risk factors, and preventive strategies. The review presents only the results of studies published in English.

PREOPERATIVE SCREENING

Risk factors

Preoperative assessment aims to identify high-risk patients at risk of developing POD. The risk factors for POD are related to both the patient and the operative procedure. The most researched risk factors are older age, presence of depression, history of previous delirium, and alcohol abuse. Risk factors related to surgery include longer surgical duration, type of anesthesia, anesthesia duration, blood loss, transfusion use, intraoperative hypotension, and severe postoperative pain (13,14). They are most commonly classified in the literature as patient-related or surgical procedure-related factors, or as preoperative, intraoperative, and postoperative factors; importantly, many of them are modifiable **(Table 1).**

Preoperative neurocognitive assessment

Almost all anesthetics and analgesics used during surgery act on receptors in the central nervous system (CNS). Its impaired functioning before surgery represents a significant risk factor for the occurrence of POD. Preoperative evaluation of cognitive function enables the identification of patients at increased risk of developing this complex syndrome and the timely implementation of preventive strategies. One recommendation of the Fifth International Perioperative Neurotoxicity Working Group is that patients be preoperatively informed about the possibility of perioperative cognitive deficits, within the framework of informed consent for surgery and anesthesia. Thus, they and their families would have clear information about the possible occurrence of these complications, as well as about their possible duration of several days, weeks, or months after the operation (16).

Today, numerous simple cognitive screening tests are available and can be administered in a few minutes. The Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Mini-Cog test, and others are commonly used **(Table 2).** According to the recommendations of this working group, preoperative cognitive status should be assessed using a brief screening test as part of the preoperative evaluation in all patients older than 65 years, as well as in any other patient at risk for POD development (16). Despite the growing body of evidence on the importance of POD development, the literature suggests that screening for preoperative cognitive deficits, informing patients about the risks, and implementing preventive measures have not become routine in anesthesiology practice (16,17).

Table 1. Risk factors for development of postoperative delirium (15)

Modifiable risk factors	Non-modifiable risk factors
Preoperative predisposing factors	**Preoperative**
Immobilization or limited mobility	Age >65 years
Hearing or vision impairment	Male gender
Presence of infection or shock	ASA physical status ≥III
Inadequately controlled pain	History of delirium, stroke, neurological disease, falls, or gait disorder
Depression	Current hip fracture
Alcohol abuse or smoking	Dementia or cognitive impairment
Anemia and hypoalbuminemia	Functional impairment
Decreased oral intake and malnutrition	Renal or hepatic insufficiency
Intraoperative precipitating factors	
Hypoxia or hypercarbia	**Intraoperative**
Dehydration-oliguria	Aortic procedures
Use of psychotropic medications (antipsychotics, benzodiazepines, anticholinergics, antihistamines, meperidine)	Multiple co-morbidities burden
Electrolyte abnormalities (hyper- or hypo-natremia)	Surgery: Emergency surgery, vascular surgery, orthopedic
Polypharmacy: More than five drugs at a time	Surgery
Postoperative precipitating factors	**Postoperative**
Risk of urinary retention or constipation	Environment (e.g., admission to ICU)
Presence of a urinary catheter	Prolonged hospital stay (chronic illness)
Pain, emotional distress	Advanced oncological disease
Sustained sleep deprivation	

ASA = American Society of Anesthesiologists, ICU = Intensive Care Unit

Table 2. Most used preoperative cognitive screening tools (18)

Instrument	Cognitive domain assessment	Neurologic condition	Approximate time (min)
MMSE (Mini-Mental State Examination)	Memory, language, orientation, praxis, attention, and visuospatial ability	Dementia	10
MoCA (Montreal Cognitive Assessment)	Memory, language, orientation, executive function, praxia, attention, visuospatial ability	Mild neurocognitive disorder Dementia	10
Mini-Cog	Memory, visuospatial ability	Dementia	3-5

ANESTHESIA-RELATED FACTORS

The results of studies comparing the effects of regional anesthesia techniques and general anesthesia on the incidence of POD remain controversial. There are no recommendations to support the use of regional instead of general anesthesia in an attempt to prevent POD. A systematic review of the literature investigated the risk factors and prevalence of POD in surgical patients, excluding cardiac surgery. The results have shown that POD occurs about 3 times more often after surgical procedures under general anesthesia compared to those under regional anesthesia (19). A randomized multicenter study included 950 patients aged 65 years or older scheduled for hip fracture surgery. The researchers compared the effects of general anesthesia (intravenous and inhalational) and regional anesthesia (epidural, spinal, and combined spinal-epidural). The results showed that, compared with general anesthesia, regional anesthesia without sedation did not significantly reduce the incidence of POD (20). In contrast, a meta-analysis by Zhao et al. showed that the patients undergoing total knee or hip arthroplasty under general anesthesia have an increased risk of POD. This risk can be reduced by using spinal anesthesia (21).

In a large randomized trial involving 1600 patients undergoing hip fracture surgery, the incidence of POD was compared between those receiving general or spinal anesthesia. The results showed a similar percentage of POD cases in both groups (22). However, in a study that included 1720 older age patients who underwent complex abdominal or thoracic procedures, excluding cardiac surgery, the incidence of POD was significantly lower in those who received combined epidural and general anesthesia than in those who received only general anesthesia (23).

There is no clear evidence that any volatile anesthetic causes POD. However, it is well known that sensitivity to these agents increases with age; therefore, it is advisable to avoid excessive use by monitoring the minimum alveolar concentration adjusted for the patient's age. This strategy can help reduce the side effects of volatile anesthetics and the development of POD (24). In a systematic literature review, the effects of total intravenous and inhalation anesthesia on the development of postoperative cognitive deficits were compared. The research included 28 randomized controlled trials involving 4507 elderly

patients scheduled for non-cardiac surgery. This review found no significant difference between the two general anesthetic techniques in reducing the incidence of POD. Additionally, the use of different inhaled anesthetics, such as isoflurane, desflurane, and sevoflurane, did not show a significant difference in POD incidence (25).

Intraoperative EEG monitoring and anesthetic titration

Many randomized controlled trials investigated the effects of anesthesia depth on the occurrence of POD. Excessive levels of anesthesia depth can cause a number of adverse effects, such as depression of the cardiovascular system, respiratory problems, prolonged emergence time, anxiety, and delirium. Therefore, the use of anesthesia depth monitoring can potentially reduce the risks of anesthetic overdose, improve recovery time from anesthesia, and reduce perioperative opioid requirements (26).

The amount of anesthetic delivered to the patient and, consequently, the risk of postoperative cognitive dysfunction can be reduced by titrating anesthetics using bispectral index (BIS) monitoring and auditory evoked potentials (27). Many studies have examined the impact of intraoperative continuous electroencephalography (EEG) monitoring on the development of POD. In response to higher concentrations of anesthetics at the site of action in the brain, patients exhibit EEG suppression. Patients with increased low-frequency EEG activity during surgery are at increased risk of POD. Likewise, higher concentrations of volatile anesthetics are a risk factor for EEG suppression. A study involving 727 patients who were administered general anesthesia and had continuous intraoperative EEG monitoring showed that patients with a longer duration of EEG suppression had more frequent occurrence of POD (28).

A multicenter randomized clinical study followed the development of POD five days after major surgery. The study included 655 patients and showed that the risk of POD was reduced when patients had shallower anesthesia during surgery. One group of patients had intraoperatively BIS values of 50 (they received "shallow anesthesia"), and the second group of patients had BIS values of 35 (they received "deeper anesthesia"). The incidence of POD differed significantly between the two groups: 19% in the first group and 28% in the second. After 1 year of follow-up, patients in the first group showed significantly better cognitive function (29). Despite numerous studies, the relationship between the depth of anesthesia and the development of POD remains controversial. The extensive ENGAGES study did not demonstrate the importance of this type of monitoring in preventing delirium (30). However, the European Association of Anesthesiologists guidelines for POD in adults recommend monitoring anesthesia depth using EEG to reduce POD incidence (31).

Avoiding hypotension

Intraoperative hypotension is one factor that may influence POD development. Its occurrence is common, even during short-duration surgery with minimal bleeding (32). Maintaining normotension during surgery to preserve organ perfusion also applies to cerebral perfusion. Elderly patients usually have chronic arterial hypertension and altered cerebral autoregulation, so maintenance of normotension should be individualized for each patient in relation to their baseline blood pressure. In elderly patients, intraoperative hypotension should be avoided due to the risk of cerebral hypoperfusion and reduction of cerebral blood flow. Research results on its influence on POD development are conflicting. While some studies have shown an association with increased incidence of POD or other cognitive changes (33, 34), others have not (35, 36).

To avoid fluid overload, goal-directed fluid therapy should be used. It is well established that this overload is associated with poor healing of intestinal anastomoses, prolonged ileus, and pulmonary and peripheral edema. Hypotension caused by central neuraxial blockade should be treated with vasoconstrictors rather than excessive fluid administration (4).

USE OF MEDICINES

The use of many medications may be associated with an increased risk of developing POD. Drugs that should be avoided in patients over 65 years are shown in **Table 3.**

Table 3. Medications that should be avoided or used with caution in elderly patients (37)

Rationale for Avoiding	Medication or Class of Medication
Central anticholinergic effects	First-generation antihistamines (Diphenhydramine) Antispasmodics/anticholinergics (Atropine, scopolamine) Phenothiazine-type antiemetics (Prochlorperazine, promethazine)
Risk of cognitive impairment, delirium	Benzodiazepines (Midazolam, diazepam) Corticosteroids (Hydrocortisone, methylprednisolone) Antipsychotics (Haloperidol) H2-receptor antagonists (Ranitidine)
Extrapyramidal effects	Metoclopramide
Neurotoxic effects	Meperidine

The medicines with highly anticholinergic effects should be avoided due to their reduced clearance with advanced age, risk of toxicity, risk of confusion, dry mouth, and constipation (37). Antipsychotics, first and second generation, should be avoided due to increased risk for cerebrovascular accident (stroke) and a greater rate of

cognitive decline and mortality, especially in patients with dementia (37). Metoclopramide can cause extrapyramidal effects, including tardive dyskinesia, especially in frail older adults (37). Meperidine is an ineffective oral pain medication in dosages commonly used, but may have a higher risk of neurotoxicity, including delirium, than other opioids (37).

The most substantial evidence for pharmacologic prophylaxis of POD relates to the avoidance of benzodiazepine use. Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. In general, all benzodiazepines increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults (37). Benzodiazepines can cause short-term cognitive deficits, particularly in memory, learning, and attention, and they are also associated with the development of lasting cognitive deficits and dementia (38). The incidence of POD is two to five times higher in patients who received benzodiazepines perioperatively (39,40).

The use of opioids is also often cited as a risk factor for the development of POD. However, the goal of their postoperative use is to relieve severe acute pain, which is also a risk factor for this syndrome. Severe postoperative pain intensity proved to be a significant risk factor for POD in a prospective cohort study that included 581 patients scheduled for major non-cardiac surgery. Also, the administration of high doses of opioids increased the risk of POD in this study (41). The literature emphasizes the importance of avoiding meperidine due to its anticholinergic properties and its metabolism to normeperidine, a neuroexcitatory metabolite associated with central nervous system toxicity (42).

Dexmedetomidine use

Recent studies show that dexmedetomidine reduces the incidence and duration of POD (43). In a randomized study in elderly patients undergoing major laparoscopic surgery, an initial bolus of dexmedetomidine followed by a continuous infusion significantly reduced the incidence of POD compared with a single bolus dose or placebo. At the same time, significantly lower interleukin-6 (IL-6) levels were observed in patients receiving dexmedetomidine, suggesting a reduced inflammatory response as a mechanism by which it reduces the incidence of delirium (44).

However, the European Association of Anesthesiologists guidelines for postoperative delirium do not recommend the prophylactic use of any drug to reduce the incidence of POD (31). Additionally, when dexmedetomidine is used intraoperatively or postoperatively for these purposes, it is recommended that the benefit-to-side-effect ratio (particularly bradycardia and hypotension) be carefully evaluated (31).

TREATMENT OF POSTOPERATIVE PAIN

Inadequate postoperative pain control is a risk factor for the occurrence of numerous postoperative complications, including postoperative cognitive impairment and POD (45). Elderly patients are sensitive to the use of opioids, so their use in higher doses in patients with risk factors for POD can significantly contribute to its occurrence. In postoperative pain control, opioid doses should be carefully titrated to the minimum effective dose to reduce the occurrence of side effects. Meperidine use is not recommended, while morphine, oxycodone, and fentanyl are not significantly associated with POD. Application of multimodal analgesia will optimize postoperative pain control and avoid the side effects of opioid overuse. It includes the use of nonsteroidal anti-inflammatory drugs, paracetamol, regional nerve blocks, and local anesthetic infiltration (46,47). Additionally, preemptive analgesia can improve postoperative pain management (48). The European Association of Anesthesiologists guidelines on postoperative delirium recommend regular assessment of pain intensity and adequate treatment of postoperative pain (31).

SEDATION IN MECHANICALLY VENTILATED PATIENTS

The type of sedation in mechanically ventilated patients in the ICU may also influence the occurrence of POD. In a multicenter study comparing the use of dexmedetomidine and midazolam for sedation of patients in the ICU, it was determined that there were significantly more cases of POD in the group sedated with midazolam (49). A meta-analysis of seven randomized studies that compared dexmedetomidine sedation with midazolam or propofol sedation showed that the risk of delirium occurrence was significantly lower in those sedated with dexmedetomidine (50).

It is believed that POD may be influenced by inadequate mechanical ventilation. Although there is limited clear evidence for this, some studies have shown that using a lung-protective strategy reduces the incidence of POD. In a randomized, double-blind study, a lung-protective strategy has been shown to significantly reduce the incidence of this syndrome . The study included 64 patients undergoing spinal surgery in the prone position, and ventilation was performed with low respiratory volumes, lung recruitment, and a positive end-expiratory pressure of 5 cmH_2O. The assumed mechanism of action is the reduction of inflammation and improvement of cerebral oxygenation. In the group of patients in whom this strategy was applied, the value of IL-6 was significantly lower (51).

AVOIDING PERIOPERATIVE HYPOTHERMIA

Maintenance of normothermia during the perioperative period should be considered as much as adequate pain control or depth of anesthesia. In an extensive study that included 22,548 subjects undergoing non-cardiac surgery, a significant association between unplanned perioperative hypothermia and POD was found (52). Another study showed that intraoperative hypothermia significantly increases the risk of POD developing. The research included 27,674 patients who underwent non-cardiac surgery under general anesthesia lasting more than two hours. Patients were divided into three groups based on their intraoperative mean body temperature. The incidence of POD was significantly lower in the normothermia group compared to those with severe or moderate hypothermia (53).

CONCLUSION

The frequent occurrence of postoperative delirium in elderly patients after major operations represents a significant clinical problem. Many risk factors for its occurrence can be modified during the perioperative period. Therefore, the goal of preoperative assessment should be to identify high-risk patients. By implementing simple prevention measures, we can influence the development of this syndrome. Despite growing evidence of the importance of this clinical entity, the literature indicates that screening for preoperative cognitive deficits, informing patients about the risks, and implementing preventive measures have not become part of routine anesthesiology practice.

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STRATEGIJE ZA PREVENCIJU POSTOPERATIVNOG DELIRIJUMA - ANESTEZIOLOŠKI ASPEKTI

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Sažetak

Pojava postoperativnog delirijuma predstavlja značajan zdravstveni problem kod starijih pacijenata u jedinicama intenzivnog lečenja. Učestalost postoperativnog delirijuma varira u različitim istraživanjima i kreće se od 10% do 70%. Veća incidencija je zabeležena među starijom populacijom, kao i nakon velikih hirurških procedura kao što su vaskularne, srčane i operacije preloma kuka. Ovaj sindrom može biti udružen sa velikim brojem negativnih kliničkih ishoda koji mogu uticati na hospitalizaciju bolesnika. Često je kod pacijenata produžen boravak na mehaničkoj ventilaciji, a povećana je stopa mortaliteta i troškovi lečenja. Ovi pacijenti su takođe u povećanom riziku od ponovne hospitalizacije i imaju lošiji kvalitet života. Najbolja strategija za smanjenje štetnih posledica postoperativnog delirijuma jeste njegova prevencija. Pokazano je da neke jednostavne intervencije tokom perioperativnog perioda značajno mogu smanjiti incidenciju i težinu ovog sindroma. To su pre svega procena kognitivne funkcije pre operacije, izbegavanje upotrebe benzodijazepina, intraoperativni monitoring dubine anestezije, adekvatna kontrola postoperativnog bola, održavanje normotenzije i normotermije.

Ključne reči: postoperativni delirijum, postoperativni kognitivni deficit, faktori rizika, prevencija

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