Patients prone for postoperative delirium: preoperative assessment, perioperative prophylaxis, postoperative treatment

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Purpose of review

The aim of this study was to review current literature on identification of patients at risk for postoperative delirium (POD) and to summarize recent findings on prophylaxis and treatment.

Recent findings

Age and preoperative cognitive impairment are among the most important risk factors of POD. POD is the result of a complex interplay of predisposing and precipitating factors. Thus, both prophylaxis and treatment require multicomponent intervention programs. No single medication to prevent or treat POD is available. Avoiding too deep anesthesia, avoiding additional psychoactive substances including benzodiazepines and intravenous opioids, and effective pain management as well as early mobilization are essential.

Summary

An increase of the proportion of elderly patients undergoing surgery will lead to a higher incidence of POD. Preoperative assessment should facilitate identification of patients at high risk. Perioperative management should include monitoring depth of anesthesia, preference for nonopioid pain therapy, early regular delirium monitoring starting in the recovery room, avoiding ICU-sedation, early mobilization and exercise, and cognitive training.

Keywords

cognition, delirium, frailty, mobilization, pain management

INTRODUCTION

Postoperative delirium (POD) is a frequent complication after major surgery and contributes to increased mortality, prolonged duration of ventilation, longer length of stay in ICU as well as in hospital [1▪], a higher rate of tracheostomy [2], and higher treatment costs [3]. In elderly patients with hip fracture followed up for as long as 13.6 years, univariate analysis demonstrated a strong association between POD and survival, but a multivariate analysis identified only age at the time of surgery, illness severity, and duration of ICU stay after surgery as factors contributing to mortality [4]. As much as prophylaxis and treatment of POD definitely make sense from a cost and even more so from an ethical perspective, it is therefore questionable whether it will improve long-term outcome, and POD is just a marker of the fragile patient.

Emergence from anesthesia is often accompanied by signs of delirium, mostly in its hypoactive form. Among 400 patients evaluated for delirium signs during PACU stay, delirium signs were present in up to 31%, and in 4% at discharge from PACU [5]. Of note, positive delirium signs (without full delirium diagnosis) were independent predictors for POD within the next 7 postoperative days [6]. POD was also a risk factor for post-traumatic stress disorder (PTSD) in elderly patients, as has been confirmed in a large prospective observational study in 1707 patients, in which 12% were identified with PTSD 3 months after surgery [7].

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Curr Opin Anesthesiol 2016, 29:384–390

DOI:10.1097/ACO.0000000000000327

KEY POINTS

- Higher age and cognitive impairment are the most significant risk factors of POD.
- The tendency of aging populations will make POD an even more important complication.
- Best-practice statements emphasize the role of early recognition of POD.
- Prevention and treatment of POD include monitoring depth of anesthesia, opoid-sparing pain management, and early mobilization.

Healthcare utilization and higher resource use were reported to be associated with POD [1■,3], but effects on hospital finances are difficult to interpret, as national healthcare reimbursement systems are very different. A German analysis found that even when ICU revenues were increased by POD patients because of longer ICU stay, their higher costs were not covered by the German DRG-based reimbursement scheme [8].

HOW IS DELIRIUM DIAGNOSED?

The newly published fifth edition of the Diagnostic and Statistical Manual (DSM-5) has revised the diagnostic criteria of delirium, putting a focus on 'reduced awareness' and 'inattention' [9■,10]. Key features are as follows:

(1) Impairment of attention and lack of awareness to the environment.
(2) Rapid development and fluctuating course.
(3) Change in at least one cognitive domain (recent memory, orientation, language, or perceptual disturbance). Associated features include change in sleep-wake cycle, changing emotional states, and worsening of behavioral problems in the evening.
(4) The disturbance is not explained by another neurocognitive disorder.
(5) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or is because of multiple causes [11■].

For intubated ICU patient, delirium assessment tools are, among others, the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). Based on the Confusion Assessment Method (CAM) for nonintubated patients, the 3D-CAM was developed as a diagnostic algorithm using operationalized features to quicker diagnose or exclude POD in patients [12]. Other new tools, such as the FAM-CAM, help in identifying delirium by interviewing family members [13], the CAM-S serves as a delirium severity measure [14], and the mCAM-ED allows for screening for delirium in emergency departments [15].

New approaches for diagnosing delirium found a significant decrease in the number of blinks and vertical eye movements per minute during 'eyes-open' registrations, but an increase in the average duration of blinks in patients with POD [16]. Electroencephalography (EEG) recordings after cardiac surgery found disturbed connectivity particularly in frontal regions during phases of delirium [17■]. In nonsedated patients after cardiothoracic surgery, the relative delta power from eyes-closed EEG recordings with only 2 electrodes in a frontal-parietal derivation was shown to distinguish between patients who had delirium and those who did not [18].

PSYCHOMOTORIC SUBTYPES OF DELIRIUM

Delirium may present either with agitation or drowsiness, whereas other patients may as well seem calm and alert. Three psychomotor subtypes of delirium can be distinguished by assessing the psychomotoric state with the Richmond Agitation-Sedation scale (RASS) or the Riker Sedation-Agitation Scale [2,5]:

(1) Hyperactive delirium: The patient is agitated and possibly aggressive.
(2) Hypoactive delirium: The patient outwardly seems calm or somnolent.
(3) Mixed type: hyperactive and hypoactive phases alternate.

Hyperactive delirium is the easiest subtype to be detected, but constitutes only the minority (ca. 10%) of positive delirium ratings. Hypoactive delirium is far more often (>50%), but it is also the subtype most likely to go undiagnosed [19]. Thus, the RASS or Riker scale alone is not sufficient to determine or exclude POD [8]. Agitation, for instance, might be because of POD, but might as well indicate inadequate analgesia [20■■].

PATHOPHYSIOLOGY AND RISK FACTORS OF DELIRIUM

POD is the result of a complex interplay of predisposing and precipitating factors, making it unlikely to identify a single cause of POD.

Predisposing risk factors in surgery are, among many others, advanced age (≥75 years), preoperative cognitive impairment, multiple comorbidities and severity of illness, hypertension, abnormal BMI and albumin, a history of delirium or stroke, and functional impairment [21▪▪,22,23]. The E-PRE-DELIRIC, one of the few validated models, consists of nine predictors, including age, history of cognitive impairment, history of alcohol abuse, blood urea nitrogen, admission category, urgent admission, mean arterial blood pressure, use of corticosteroids, and respiratory failure, reached only a moderate accuracy, indicated by an area under the receiver-operating characteristic curve of 0.75 (95% CI 0.71–0.79) in the validation dataset. A systematic review of the reports on POD risk prediction models (PODRPMs) concluded,that it 'may be too early to implement a particular PODRPM in clinical practice' [24].

Mild cognitive impairment is not only associated with inflammatory and cortisol alterations but also associated with a higher risk of POD [25]. Preoperative cognitive impairment and severity of surgery were independent risk factors for POD [26]. Cognitive impairment as one of the significant major risk factors is mostly referred to as a binary variable (i.e., 'cognitively impaired' versus 'normal'). A human population-based cohort with graded severity of existing cognitive impairment and a mouse model with progressing neurodegeneration both indicated that the risk of delirium increases with greater severity of pre-existing cognitive impairment and neuropathology [27].

Other clinically important factors identified in prospective studies were depression [28,29], preoperative pain [29], and the complex of sleep disordered breathing, including, among others, snoring, obstructive sleep apnea syndrome, and the upper airway resistance syndrome [30]. ApoE4, a marker of Alzheimer's disease, was no risk factor in surgical patients [31,32]. One study group found brain atrophy not to be associated with incidence of POD [33], whereas others identified decreased grey matter volume or cerebral atrophy contributing to POD [34,35].

Poor mobility is a risk factor of POD [36]. Also, prefracture disability was an independent predictor of increased mortality in an observational prospective cohort study with 6-month follow-up [37]. Frailty, a state of decreased age-associated functional reserve [20▪▪] resulted in a three- to eight-fold higher risk of POD in a prospective observational study in elective cardiac surgery patients [38]. Comprehensive geriatric assessment therefore may be a useful predictive tool for POD in old adults [39].

Precipitating risk factors include acute admissions, electrolyte disturbances, renal insufficiency, aortic aneurysm and noncardiac thoracic surgery, emergency surgery, trauma, higher Acute Physiology and Chronic Health Evaluation II score (APACHE 2), mechanical ventilation, metabolic acidosis, and coma [23,40]. Sevoflurane, but not isoflurane, was found to increase blood-brain barrier permeability in old rats, promoting extravasation of immunoglobulin G with a selective affinity for pyramidal neurons [41]. The clinical utility remains debatable; long-term sedation with isoflurane was well tolerated in a retrospective analysis and associated with a higher 365-d survival (not delirium) compared with propofol/midazolam sedation [42].

Inflammatory effects are linked with cholinergic deficiency; these two mechanisms are presumed to play major roles in the pathophysiology of POD [43]. Stimulation of the cholinergic anti-inflammatory pathway may therefore prevent POD [44]. Neuroinflammation owing to endotoxemia in mice, evoked by tibia fracture, produced acute cognitive dysfunction, which was blocked by stimulation of the alpha7 nicotinic acetylcholine receptor [45]. Bone marrow-derived macrophages, engaged by high mobility group box 1 proteins (HMGB1), seem to be involved in these inflammatory processes and could be blocked by an anti-HMGB1 monoclonal antibody before experimental surgery, so that neither systemic nor hippocampal inflammatory responses occurred [46]. Anti-inflammatory therapeutics might therefore be promising candidates to prevent delirium (see also 'pharmacological treatment').

With higher age and cognitive impairment being some of the most significant risk factors of POD, the demographic development of aging populations will also drive the incidence of POD. Considering that nearly half of the elderly will require surgery after the age of 65 years [47], and almost half of hip fracture patients are occurring among the 'oldest old' with an increasing trend [37], POD will be a more frequent devastating complication in the future [48]. Consequently, monitoring of POD has already become a quality marker in some health care policies [49].

DEPTH OF ANESTHESIA

Intraoperative depth of anesthesia and burst suppression as measured by processed EEG were associated with POD in several randomized controlled trials (RCT) and retrospective analyses [50–53]. There is even a link between mortality and depth of sedation during regional anesthesia [54]. Intraoperative processed electroencephalographic monitors of anesthetic depth during intravenous sedation or general anesthesia in older patients may therefore be used to reduce postoperative delirium [20▪▪,55].

PATIENT BLOOD AND HEMODYNAMIC MANAGEMENT

Low postoperative hemoglobin was associated with the development of delirium after hepatectomy [56]. Length of red-cell unit storage of less than 14 days was not associated with increased rate of delirium in cardiac surgery [57], but a storage time of more than 14 days was associated not only with significantly increased inflammatory plasma parameters such as interleukin-8 and interleukin-1ß, but also with increased length (but not incidence) of POD in elderly patients undergoing hip fracture surgery [58]. Patient blood management can therefore be part of delirium prevention strategies. Surprisingly, intraoperative hypotension had only a nonsignificant tendency to increase the risk of POD in cardiac surgery in one study [59]. In other studies, arterial pressure above cerebral autoregulation limit during cardiopulmonary bypass [60], as well as both very high and very low intraoperative blood pressure, was associated with POD [61]. Others found that not absolute or relative hypotension, but increased fluctuations in blood pressure to be predictive of POD [62]. In conclusion, maintaining blood pressure at a stable level, based on preoperative values, appears to help preventing POD.

PHARMACOLOGICAL TREATMENT

Given the multifactorial pathogenesis, no single medical treatment has been shown to be effective to prevent POD [20▪▪,55,63▪▪].

Sedation in ICU is a major risk factor of delirium [64▪▪]. Benzodiazepines were identified to carry a high delirogenic potential [63▪▪]. The odds of transitioning to delirium upon benzodiazepines were higher with continuous administration of benzodiazepines, compared with bolus injections in a large prospective cohort study [65▪]. In a randomized placebo-controlled trial with lorazepam as a sedative premedication before surgery, no effect on patient experience and anxiety was found, but time to extubation and the rate of early cognitive recovery were significantly lower in the lorazepam group [66▪]. Perioperative opioids were associated with delirium signs during PACU stay [5]. Fentanyl intraoperatively (compared to remifentanil) was shown to be associated with an increased risk of delirium not only in the recovery room, but also on the first postoperative day [67].

If sedation is inevitable because of special indications, the 'Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit' (PAD-Guideline 2013) suggests the use of a continuous infusion of dexmedetomidine or propofol instead of benzodiazepines [63▪▪]. ICU sedation with dexmedetomidine versus propofol reduced incidence, delayed onset, and shortened duration of POD after cardiac surgery [68▪]. Deep sedation (versus light sedation) in ICU was associated with higher 180 days' mortality [69]. In the ICU, it is recommended to regularly monitor depth of sedation by clinical tools such as RASS or the Riker scale, and to maintain ICU patients at light or no sedation, or to perform daily interruption of sedation (DIS) [63▪▪,70▪].

There has been some debate, as to whether ICU sedation confounds diagnosis of POD, as sedation might be mistaken for delirium, so that studies overestimated the incidence [10]. In a prospective cohort study, delirium assessment was performed before and after DIS. Positive delirium rating was 10.5 times more likely before than after DIS [70▪]. The authors coined this 'rapidly reversible, sedation-related delirium,' which was associated with fewer ventilator days, shorter ICU length of stay and less hospital days than persistent delirium and suggested to coordinate delirium assessments with DIS [70▪].

Haloperidol, given as a low-dose prophylaxis, was suggested by the American Geriatric Society in geriatric patients at high risk of delirium [55]. Recent randomized, prospective trials, however, could not confirm the effectiveness of haloperidol prophylaxis to reduce incidence or length of delirium [71–73]. Ketamine was reported to reduce the incidence of POD in a single-center prospective study in cardiac surgery, whereas no effect was found upon a single dose of 0.5 mg/kg ketamine in a study involving 56 elderly orthopedic patients under general anesthesia [74]. Though lower plasma GABA level had a significant independent association with POD [75], a perioperative course of gabapentin produced only a clinically insignificant improvement in analgesia, but was associated with a higher incidence of sedation [76]. Pregabalin had no beneficial effects after total knee arthroplasty, either, but increased drowsiness and confusion [77]. Steroids (methylprednisolon or dexamethasone) did not affect the risk of POD in two large RCTs in cardiac surgery [78,79].

Melatonin is part of the regulation of the sleep-wake cycle and prevents agitation in patients with dementia. Melatonin is also disturbed after surgery, but did not reduce the incidence of POD in an older hip fracture population [80]. According to a meta-analysis, melatonin supplementation decreased the incidence of delirium in medical wards, but not in elderly surgical patients [81]. Statins were shown to have anti-inflammatory effects and may therefore prevent delirium. Among 470 prospectively studied patients, 151 patients received statins at the time of ICU admission and had lower rates of delirium in

ICU [82]. A large multicenter RCT is currently conducted to verify this observation [83].

SURGERY

Trauma and surgery trigger proinflammatory cytokines and promote neuroinflammation [45]. Severity of surgery was identified as an independent risk factor for POD [26]. It was sought whether minimally invasive surgery reduces POD, but no impact of the surgical approach (laparascopic versus open gastrectomy) on POD incidence was found in a prospective trial [84]. In emergency hip fracture patients, delirium was already present in 57.6% of patients before surgery. Not all patients with preoperative delirium continued to present with delirium postoperatively; the rate of POD was 41.7% [85]. This emphasizes that trauma is a part of the pathophysiology, and that surgical repair is part of POD treatment.

MULTICOMPONENT INTERVENTION PROGRAMS

Multicomponent intervention programs, possibly involving geriatric assessment, screening for delirogenic co-medication, avoiding too deep anesthesia, early mobilization, nonopioid pain therapy and many more, have been introduced to prevent and treat delirium [21▪▪,86]. Proofs of efficacy are difficult, as intervention programs can hardly be blinded, and controls are difficult to standardize and heterogeneous between studies. Outcomes and differences therefore are difficult to interpret. For instance, in a single-center, prospective RCT randomizing 329 patients with hip fracture to treatment on an acute geriatric ward (including daily interdisciplinary meetings) or on a standard orthopedic ward, no effect in the orthogeriatric group on the incidence of POD, but a positive effect on mobility in those patients not admitted from nursing homes was found [87]. A meta-analysis concluded that duration of delirium was shorter upon multiple interventions, but found no intervention to have an effect on short-term mortality [88]. Another meta-analysis confirmed multicomponent nonpharmacological delirium prevention to be effective in reducing delirium incidence, but sought more subtle outcome parameters, such as preventing falls and a trend toward decreasing length of stay and avoiding institutionalization [89▪].

EARLY MOBILITY AND EXERCISE

Poor mobility and frailty were mentioned earlier to be risk factors of POD [36]. Early mobilization is one of the priorities to prevent and treat delirium and ideally should be carried out three times a day [21▪▪,90]. Mobilizing intubated patients is personnel-intensive, requires special skills and is therefore costly. In a 1-day point-prevalence study conducted across Germany, only 24% of all mechanically ventilated patients and only 8% of patients with an endotracheal tube were mobilized out of bed as part of routine care [91]. In the ICU, the combination of light sedation, spontaneous breathing trials, delirium monitoring and management and early mobility and exercise (ABCDE-bundle) led to significantly higher rate of patients being out of bed, and resulted in almost 3 more days free from mechanical ventilation and reduced the risk of delirium by almost 50% [92].

CONCLUSION

Higher age and cognitive impairment are the most significant risk factors of POD; the demographic development of aging populations will make POD an even more important complication in the nearby future. Best-practice statements on the perioperative management of elderly people particularly emphasize the role of early recognition of POD, and the importance of cognitive training, monitoring depth of anesthesia, sufficient, nonopioid postoperative pain management techniques, and early mobilization and exercise.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

U.G. and F.R. received honoraria and lecture fees from Orion Pharma, Germany. L.R. has no conflicts of interest.

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