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Review Article

Post-Operative Delirium in the Elderly: Diagnosis, Risk Factors and Prevention

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ABSTRACT

Aim of review: Delirium is a common postoperative complication after major surgery especially in elderly patients. Postoperative delirium (POD) is related to increased perioperative morbidity and mortality. Avoiding risk factors and performing early interventions can decrease the incidence of POD. Aim of this article is to review progresses in diagnosis, risk factors and prevention of POD in old patients.

Methods: We review recent studies on delirium in the past 2 decades. We focus on the diagnosis, risk factors and prevention of POD.

Recent findings: Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are reliable methods for the diagnosis of delirium in critically ill patients. Risk factors for POD can be divided into pre-operative risk factors, operation-related risk factors and anesthesia related risk factors. Old age, preoperative cognitive impairment and current smoking have been proven to be independent risk factors of POD. Multiple non-pharmacological interventions are recommended in high-risk patients of POD. Dexmedetomidine, melatonin, antipsychotics and statins can be used as pharmacological prevention or treatment interventions in POD.

Conclusion: Avoiding risk factors and early interventions can reduce the incidence of POD. Finding early indicators of POD will help to perform early interventions and reduce medical expenses. (Funded by Department of Anesthesiology, Peking Union Medical College Hospital, Beijing, China.)

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Delirium is a sudden onset disturbance of cognition, attention, consciousness and orientation with a transient and fluctuating course (1). Delirium is a common postoperative complication especially in elderly patients, with an occurrence rate of 15% to 50% in adults after surgery according to different researches (2-4). Delirium is related to increased perioperative morbidity and mortality. Martin et. al has proved that delirium is an independent risk factor of all-cause mortality by increasing the mortality rate from 20.2% to 34.5% in 11 years after surgery (5). However, it is reported that more than half of the patients suffering from POD remains undiagnosed (6, 7). Effective prevention interventions have been shown to decrease the number of patients suffering from postoperative delirium (POD) by 40% and improve outcomes of patients (8). Identifying risk factors of postoperative delirium is of great importance to perform preventive strategies. Aim of this article is to review progresses in risk factors, diagnosis and prevention inter-

Table 1. DSM-5 Criteria for Delirium.
1. Disturbance in attention and awareness.
2. The symptoms of delirium are acute onset and tend to fluctuate through the day.
3. Disturbance in cognition (eg. memory, orientation, language, perception).
4. Disturbance in (1) and (3) are not explained by pre-existing neurocognitive disorders.
5. Evidences that delirium is a consequence of another medical condition or multiple etiologies (eg. medication condition, substance intoxication, substance withdrawal, multiple etiologies).

ventions of POD in old patients.

Diagnosis

For the diagnosis of POD, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) listed 5 key features (Table 1): 1) disturbance in attention and awareness; 2) acute and fluctuate; 3) an additional disturbance in cognition such as memory, orientation, language, visuospatial perception; 4) the disturbances cannot be explained by pre-existing neurocognitive disorders; 5) medical history, physical examination or laboratory evidences show that the disturbance is caused by a medical condition, substance intoxication or withdrawal, or side effects of medicine (9). Based on the definition and features of delirium, several methods have been developed to diagnose delirium. Among those diagnostic methods, the Confusion Assessment Method for the ICU (CAM- ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are most widely implied and well validated in critically ill patients (10, 11). A signal-center study conducted in Japan showed that the sensitivity of CAM-ICU is less than the sensitivity of ICDSC (10). While a meta-analysis showed that CAM-ICU and ICDSC had similar sensitivity and specificity in the diagnosis of delirium in critically ill patients (11).

Three subtypes of delirium are defined according to the clinical presentations: 1) hypoactive delirium features somnolent, decreased motor activity and withdrawn; 2) hyperactive delirium features agitation and aggression; 3) mixed delirium presents with a phases alternation between hyperactive delirium and hypoactive delirium. More than half of the clinical delirium cases belong to hypoactive delirium which is usually undiagnosed in clinical practice (12). Hyperactive delirium consists 10 % of the delirium cases, and should be distinguished from inadequate analgesia (13).

POD, postoperative cognitive dysfunction (POCD), mild cognitive impairment (MCI), dementia and alcohol withdrawal syndrome are different conditions. POCD is a decline of cognitive flexibility, attention and working memory arising after anesthesia and surgery (14). It may last weeks, months or even years. While POD usually has a short course of disease, the disturbance in attention and awareness usually develops hours to a few days after surgery (15). The diagnosis of POCD based on formal neuropsychological testing such as mini-mental state examination (MMSE) and montreal cognitive assessment (MoCA) before and after surgery (16). Although MMSE is one of the most widely used neuropsychological testing on the diagnosis of POCD (17, 18), it has been criticized for its less sensitivity. Limited sensitivity of MMSE may be caused by ceiling effect and learning effect. Detection of POCD is affected by the number of neuropsychological tests in the assessment battery (19). Neuropsychological test battery is recommended by the international study of postoperative cognitive dysfunction (ISPOCD) on the detection of POCD. The battery is applicable in low schooling level population and in patients undergoing different types of surgery and anesthetic techniques (20).

MCI is an intermediate condition between healthy aging to dementia (21). MCI features mild decline in cognition especially in memory impairment. Cognitive decline can be found by neuropsychological testing (22). Dementia is associated with progressive decline of cognitive disturbance. Despite memory impairment, aphasia, apraxia, agnosia and altered executive func-

tioning are usually occurred during dementia (23). Alcohol withdrawal syndrome (AWS) occurs in patients with a history of alcohol use disorder. The onset of AWS usually develops within 24 hours after the last consumption of alcohol and lasted for 7 days (24).

Risk factors

Many possible risk factors of POD have been found and reported. These risk factors can be categorized as pre-operative risk factors, operation related risk factors and anesthesia related risk factors (Table 2).

Pre-operative risk factors

Age

Advanced age has been identified as an independent risk factor for delirium after surgery (25, 26). In patients more than 72 years old, the risk of developing POD is 5.5 times higher than patients under 72 years old (25). In patients more than 80 years old, age is associated with a 32% increase in the occurrence of POD (27).

Pre-operative cognitive impairment and psychiatric disorders

Despite different diagnostic tools are used, studies have proved that pre-operative cognitive impairment is another independent risk factor for delirium after surgery (27-29). Surgery and anesthesia may deteriorate psychiatric disorders and neurodegenerative disorders, which may result in increased rate of POD in patients with cognitive impairment. Pre-operative cognitive impairment is associated with an odds ratio of 16.4 for POD (28- 31). Besides neurodegenerative disorders such as MCI and dementia caused cognitive impairment, depression is another important risk factors of POD. Schneider et al. have found that patients developing POD after surgery have higher pre-operative depression score (31).

Comorbidity

There are many studies focused on the relationship between pre- operative comorbidity and POD. Comorbidities which may influence the cerebral blood flow, cerebral energy metabolism and brain oxygenation may increase the risk of POD (32).

Table 2. Risk Factors of POD.

Risk factors	Odds ratio or % of POD	References
Pre-operative risk factors		
-Age		
⩾ 72 years vs 60~71 years	5.5 (2.8~10.7)	(25)
⩾ 80 years vs 65~79 years	66 % vs 34 %	(27)
-Pre-operative cognitive impairment	16.4 (4.7~57.0)	(28)
-Comorbidity		
Diabetes mellitus	6.23 (11.1~52.2)	(27)
SNAQ-RC ⩾ 3	5.55 (1.07~42.0)	(27)
Renal failure	5.0 (1.9~13.0)	(25)
Atrial fibrillation	2.74 (1.17~6.37)	(34)
ASA score ⩾ 3	4.1 (0.8~20.5)	(41)
Current smoking	3.99 (1.25~12.8)	(34)
Alcohol abuse	3.24 (1.88~5.60)	(43)
Fluid fasting time (solid fasting ⩾ 12 h, fluid fasting ⩾ 6 h)	2.69 (1.4~5.2)	(45)
Operation-related risk factors		
-Emergency surgery vs elective surgery	59 % vs 14 %	(41)
-Transcortical access vs non-transcortical access (transcatheter aortic value replacement)	7.74 (3.26~18.1)	(34)
Anesthesia related risk facotrs		
-BIS < 20	1.027	(52)
-Benzodiazepines	0.57 (0.03~1.10)	(54)

POD: postoperative delirium; SNAQ-RC: Short Nutritional Assessment Questionnaire for Residential Care.

Diabetes mellitus, which can cause abnormal glucose metabolism, has been proven to increase the risk of POD by 6.2 times higher than patients without diabetes mellitus by Van et al (27). However, a study from Sasajima et al. finds that there is no difference between patients with diabetes mellitus and without diabetes mellitus on the occurrence of POD (25).

Nutritional status has also been suggested to be one of the risk factors of POD (33). Willem et al. have found that patients with a score of 3 or more in the Short Nutritional Assessment Questionnaire for Residential Care (SNAQ-RC) have a higher risk of developing POD (27).

Renal failure which may cause stack of metabolite and affect cerebral metabolism can increase the occurrence of POD. Sasajima et al. have

shown that end stage renal failure can increase the incidence of POD from 47% to 53% (P= 0.029) (25).

As is suggested by a retrospective observational cohort study published recently, atrial fibrillation which may influence the cerebral blood flow is associated with an OR of 2.74 for POD (34).

Studies show that chronic obstructive pulmonary disease (COPD) (35- 37) and obstructive sleep apnea syndrome (OSAS) (38) are risk factors of POD. Lack of effective oxygenation may underlie the pathogenic mechanisms that patients with COPD or OSAS have higher risks of POD.

Other risk factors include critical limb ischemia, diabetic foot ulcers, multiple occlusive lesions and abdominal aortic aneurysm (25, 39, 40).

ASA score

ASA ⩾ III has been suggested to be one of the risk factors of POD (29, 41). Koebrugge et al. have shown that ASA ⩾ III is associated with an OR of 8.7 for POD.

Smoking

Current smoking is among potential risk factors for delirium (40). Benoit et al. have suggested that smoking is an independent risk factor for POD (43). Visser et al. have shown that current smoking can increase the incidence of POD by 10 folds (28). A meta-analysis published recently also find that current smoking can increase the incidence of POD (40).

Alcohol abuse

Shah et al. have reported that heavy drinking (more than 2 drinks daily) can increase the risk of POD by 3.24 times higher than those patients without heavy drinking (44). A meta-analysis also indicate that alcohol abuse is one of the risk factors of POD (40, 45).

Fluid fasting time

A cohort study performed by Radtke et al. suggests that longer fluid fasting time (> 6 h) increased the incidence of POD from 5% to 12.9 % in comparison with shorter fluid fasting time (2 - 6 h) (46).

Laboratory abnormalities

Biochemical abnormalities are related to increased risk of POD (46). Sasajima et al find that patients with BUN > 20 mg/dl or A/G < 1.31 have increased risk of developing POD (25). Preoperative IL-6 levels in blood (47), aromatic amino acid in CSF (48), C-reactive protein levels in blood (28) and apolipoprotein E (49) are also associated with the increased risk of POD.

Operation-related risk factors

Surgery

Surgery may influence POD by promoting neuroinflammation. Severity of surgery is associated with increased risk of POD (46). Patients after aortic aneurysm surgery, critical limb ischemia surgery, cardiac surgery, hip replacement surgery and thoracic surgery have higher risk of POD than other elective surgeries (40, 50). In comparison with open repair surgery for abdominal aortic aneurysm, endovascular surgery can decrease the risk of POD (39). Masien et al. report that transcatheter aortic valve replacement have lower risk than nontransfemoral access (34).

In comparison with elective surgery, the emergency surgery has higher risk of POD. Koebrugge reports that emergency surgery increased the incidence of delirium from 14% to 59% in aortoiliac surgery (41).

Anesthesia related risk factors

A meta- analysis including 21 studies has found that there was no significant difference between general anesthesia and regional anesthesia on the occurrence of POD (51). However, the depth of anesthesia is among the risk factors of POD. Some RCT studies have shown that bilateral bispectral index (BIS)- monitoring can decrease the incidence of POD (52-54). Radtke et al. find that episodes of deep anesthesia (BIS < 20) is independent risk factors of POD (53).

Benzodiazepines and anticholinergic medication are associated with increased risk of POD (50, 55). A research conducted by Card et al. has shown that perioperative opioids consumption is associated with delirium signs in the post-anesthesia care unit (56). In comparison with fentanyl, remifentanil can decrease the incidence of POD (57).

Prevention and treatment

Delirium is preventable in 30% – 40% of all the cases (58). Effective prevention interventions and treatment are recommended by 'American Geriatrics Society Clinical Guideline for Postoperative Delirium in Older Adults' in patients identified as moderated and high-risk for POD. Prevention is the most effective strategy to decrease the incidence of POD. By avoiding exposure to known risk factors in high-risk patients, the incidence of delirium can be reduced (59). Prevention interventions are based on the identifying and addressing risk factors (40). Both prevention and treatment can be categorized as non-pharmacological and pharmacological interventions.

Non-pharmacological interventions

As recommended by AGS, multiple non-pharmacological interventions have been used to prevent and treat delirium including behavioral interventions, rehabilitation, environmental adaptation, psychological and social supports, medication reductions and system and process changes (60). Several programs including various non-pharmacological interventions have been studied (61, 62). Among these programs, the Hospital Elder Life Program (HELP) has been proven to be effective in decrease the incidence of POD (63). Another program named 'Stop Delirium' is ongoing and preliminary suggesting potential improvements on delirium (62, 64).

Non- pharmacological interventions are recommended for their harmless but limited to the medical expenses and resources.

Pharmacological interventions

A meta-analysis including 1491 participants demonstrated that prophylaxis with antipsychotics can reduce the incidence of POD (65). Antipsychotics exert their effects by blocking the dopamine 2 receptor and the serotonin 2A receptor. They also have been used treat agitation and psychotic symptoms of delirium. Antipsychotics may cause extrapyramidal side effects, sedation, anticholinergic side effects and cardiac arrhythmias which should be noticed especially in old adults (8).

Melatonin can regulate the sleep-wake cycle and prevent agitation. A RCT study uses melatonin and placebo have shown that exogenous low dose melatonin administration nightly can decrease the incidence of delirium in the emergency care unit (66). Results from Clayton-Chubb et al. suggest that moderate dose melatonin have positive effect on the treatment of delirium in elderly in comparison with placebo (67). Regulation of sleep-wake cycle.

Dexmedetomidine, a selective α-2 adrenergic agonist, has been proven to decrease the incidence of delirium (68, 69). A RCT study including 700 patients suggest that prophylactic low-dose dexmedetomidine significantly decrease the risk of POD in patients over 65 years old (68).

Statins has also been proved to reduce the incidence of delirium after cardiac surgery (70). The protective effects of statins may be realized by its anti-inflammatory and immunomodulatory properties. Rosuvastatin has been shown to reduce the activation of microglia and decrease the level of interleukin-6 in the brains of mice (71). Pro-inflammatory mediators can induce hyperphosphorylation and aggregation of tau which has been demonstrated to be among the leading cause of Alzheimer's disease (AD) (72).

Conclusions

POD is not uncommon in old patients after major surgery. POD can be diagnosed by DSM-V. According to the clinical manifestations, three subtypes of POD including hypoactive delirium, hyperactive delirium and mixed delirium are defined. Identifying patients with high risks of POD and avoiding risk factors can decrease the incidence of POD. Effective prevention interventions including non- pharmacological interventions and pharmacological interventions help to prevent the occurrence of POD. Prevention interventions based on risk factors of POD may increase medical expenses. Further detection of sensitive early indicators of POD may help apply early interventions and reduce medical expenses.

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