

REVIEW ARTICLE

Recent advances and perspectives of postoperative neurological disorders in the elderly surgical patients

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Abstract

Postoperative neurological disorders, including postoperative delirium (POD), postoperative cognitive dysfunction (POCD), postoperative covert ischemic stroke, and hemorrhagic stroke, are challenging clinical problems in the emerging aged surgical population. These disorders can deteriorate functional outcomes and long-term quality of life after surgery, resulting in a substantial social and financial burden to the family and society. Understanding predisposing and precipitating factors may promote individualized preventive treatment for each disorder, as several risk factors are modifiable. Besides prevention, timely identification and treatment of etiologies and symptoms can contribute to better recovery from postoperative neurological disorders and lower risk of long-term cognitive impairment, disability, and even death. Herein, we summarize the diagnosis, risk factors, prevention, and treatment of these postoperative complications, with emphasis on recent advances and perspectives.

KEYWORDS

cognitive disorders, covert stroke, delirium, hemorrhagic stroke, postoperative neurological disorders, stroke

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1 | INTRODUCTION

Postoperative neurological disorders have been attracting increasing attention in the world, with a vast amount of research conducted on these poorly understood disorders. Postoperative neurological disorders contain postoperative delirium (POD), postoperative cognitive dysfunction (POCD), postoperative covert ischemic stroke, and hemorrhagic stroke, causing cognition decline and poor long-term functional outcome in the elderly. Postoperative neurological disorders increase mortality and cause substantial financial burden on family and society. With a rapid increase in the number of elderly patients undergoing elective surgical procedures, postoperative neurological disorders need more concern and further investigation. This review aims to describe general features and the latest evidence-based knowledge of postoperative neurological disorders.

2 | POSTOPERATIVE NEUROLOGICAL DISORDERS

Postoperative neurological disorders include neurological complications such as delirium, cognitive dysfunction, acute cerebral ischemic stroke, and hemorrhagic stroke that occur after surgery, especially in the elderly. As more elderly patients undergo surgery, the incidence of postoperative neurological disorders is rapidly increased. Although their exact etiology and pathogenesis remain elusive, several risk factors have been recognized.

2.1 | POD

Postoperative delirium is defined as acute emergence of confusion, disorientation, perceptual disturbances, emotional dysregulation, or sleep disturbances, manifesting within a certain period of time. The prevalence of delirium ranged from 5% to 50% when assessed with Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).¹ POD can occur soon after general anesthesia and operation, for example, in the post-anesthesia care unit (PACU). In many cases, POD is frequently linked to anesthesia.² Compared to dementia which chronically deteriorates brain function, POD is usually acute, transient, and presenting common causative factors.³ It contributes to prolonged hospitalization, increased mortality rate, and reduced long-term quality of life, which adds an additional burden to patients and families.

Besides DSM-5 listed in Table 1 and ICD-10 diagnostic criteria which supplements a disturbance in sleep-awake cycle including insomnia, reverse of sleep-awake cycle, various assessment tools have been developed to recognize POD.⁴ The CAM-ICU is a screening tool which consists of the assessment of four characteristics: 1) acute onset and fluctuating course of mental state, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness.⁵ Delirium is diagnosed when both characteristics 1) and 2) are satisfied with 3) or 4) electively satisfied.⁶

2.2 | POCD

Postoperative cognitive dysfunction, also defined as postoperative neurocognitive disorder (pNCD),^{7,8} is characterized by cognitive decline persisting for more than 30 days but less than 12 months following surgery. Unlike POD (Table 2), consciousness, orientation, and attention are not obviously affected in POCD.⁹ However, patients can still manifest impairment in memory, perceptual function, and language.^{9,10} The incidence increases among the elderly, especially those over 60 years old.¹¹ For elderly patients, cognitive decline may result in prolonged hospitalization, reduced quality of life, even increased mortality, which has been neglected in the assessment of patient's prognosis, especially for those undergoing general anesthesia and surgery.¹² The diagnosis criteria for POCD are more complex than for POD, as POCD requires a subjective impression of postoperative cognitive decline in neuropsychological test.¹³

2.3 | Postoperative covert stroke

Cerebrovascular disease, a leading global cause of death and disability with approximately 6.2 million deaths due to stroke, is estimated to become the second leading cause of death by 2030.¹⁴ According to a systemic analysis for the Global Burden of Disease Study, the mortality rates caused by stroke range from 30.6% to 48.3%¹⁵ and are significantly related to operations.¹⁶ Covert stroke has been increasingly recognized over the years. It represents brain infarcts with silent and subtle manifestations that can be detected on brain imaging.^{17,18} Covert stroke may contribute more to poor outcomes and prognosis in elderly patients presenting cognitive decline, as its subtle manifestation can lead to ignorance of cognitive symptoms.¹⁹

The incidence of postoperative covert stroke has gradually increased due to the aging population. So far, only a few studies have examined its mechanisms.²⁰ Little is known about perioperative covert stroke except its association with substantially increased mortality.²¹ One multicenter prospective cohort study reported that postoperative covert stroke was found in 7% among 1114 participants over 65 years old who underwent inpatient, elective, noncardiac surgery, which were assessed with brain magnetic resonance imaging (MRI) after surgery and Montreal Cognitive Assessment (MoCA) on preoperative baseline and 1-year follow-up.²² Among the patients with a complete 1-year follow-up, cognitive decline after surgery occurred in 42% of participants who had postoperative covert stroke and 29% of participants who did not have postoperative covert stroke.²² In addition, another study suggested that covert stroke can increase the risk of POD, overt stroke, or transient ischemic attack (TIA) during one-year follow-up.²²

2.4 | Hemorrhagic stroke

Although hemorrhagic stroke comprises only 20% of all strokes, the perioperative hemorrhagic stroke could detrimentally deteriorate

patients' recovery and prognosis.²³ According to the American Heart Association (AHA) and the American Stroke Association (ASA),^{24,25} hemorrhagic stroke is divided into the following conditions: 1) focal bleeding in brain parenchyma and 2) in subarachnoid space or ventricular space due to rupture of blood vessel other than trauma. Perioperative hemorrhagic stroke may occur after cerebral hyper-perfusion due to a sudden surge of blood pressure (BP) for a certain amount of time.²⁶ Hypertension is the most common risk factor for hemorrhagic stroke.²⁷ Most anesthetics induce hypotension, so they are unlikely to provoke hemorrhagic stroke while under anesthesia.²⁸ However, if postoperative hypertension persists for several hours, it can lead to certain condition linked to a sudden surge of cerebral perfusion.²⁹

What discussed above is a brief introduction of four major types of postoperative neurological disorders with current understanding, which present disorientation, memory deficit, changes in awareness and attention from the baseline. Cognitive decline and poor prognosis of elderly patients after surgery have been an increasing concern around the world. With few studies on postoperative neurological disorders, the mechanisms and pathophysiology remain unknown,^{30,31} especially for POD, POCD, and covert stroke. Besides, various manifestations of postoperative neurological disorders add

more difficulties for research. As postoperative complications become increasing concerns, the mechanisms, prevention, and management are focus points that still need further research.

3 | RISK FACTORS OF ACUTE POSTOPERATIVE NEUROLOGICAL DISORDERS

The exact mechanisms and pathophysiology of POD, POCD, and postoperative stroke are unclear. In the following paragraphs, we discuss potential risk factors of postoperative neurological disorders.

3.1 | Risk factors of POD and POCD

It is commonly accepted that interactions between predisposing factors and precipitating factors play an important role in the occurrence of postoperative neurological disorders.³² The smaller vulnerability a patient has, the less occurrence of neurological disorders.³² For example, as advanced age is a predisposing factor, patients over 65 years old may present POD or POCD when exposed to only a few precipitating factors.³³ On the contrary, younger patients exposed to the same precipitating factors may not experience POD or POCD. The recent evidence-based risk factors including some novel candidates for POD as listed in Table 3.³² POD and POCD share almost the same risk factors based on current limited researches.³⁴ Moreover, SARS-CoV-2 (COVID-19) infection, a new uprising disease, has been found to be a potential novel risk factor of POD and POCD during the pandemic in the past two years, which is related to an accelerated onset with neurological manifestations³⁵ and deterioration of cognitive decline.³⁶

3.2 | Risk factors of postoperative stroke

Postoperative stroke remains one of the most serious complications after surgery. As for both ischemic stroke and hemorrhagic stroke, risk factors include conventional vascular risk factors, the type of surgery, and other perioperative events (Table 4). Vascular factors and nutritional state are important preoperative risk factors for stroke and postoperative stroke. Postoperative stroke happens more often

TABLE 1 DSM-5 Diagnostic criteria for delirium

DSM-5 Diagnostic criteria for delirium

- A disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- A disturbance that develops over a short period (usually hours to a few days) represents a change from baseline attention and awareness and fluctuates in severity during the day.
- An additional disturbance in cognition (memory deficit, disorientation, language, visuospatial ability, or perception).
- The disturbances in Criteria 1 and 3 are not better explained by another pre-existing established or evolving neurocognitive disorder and do not occur in a severely reduced level of arousal, such as coma.
- There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Abbreviation: DSM-5, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

TABLE 2 Differential diagnosis of POD and POCD

	POD	POCD
Epidemiology	In all ages but more common in older people over 60	In all ages but more common in older people over 60
Manifestation	Disturbance in attention and awareness, emotion, cognition, and fluctuating severity of consciousness.	Cognitive deficits (impairment of memory, perceptual function, language, ability to combine tasks)
Diagnostic tools	Various delirium scale, for example, CAM-ICU	Pre- and postoperative psychometric testing
Timing	Days to weeks	Persisting for months
Prognosis	Reversible if underlying causative factors are treatable	Reversible but with long-time impairment

Abbreviations: POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

TABLE 3 Risk factors of POD and POCD in perioperative patients

	Risk factors	Reference
Preoperative factors	Advanced age	32
	Comorbidities (eg, cerebrovascular including stroke, cardiovascular, peripheral vascular diseases, diabetes, anemia, Parkinson's disease, depression, chronic pain, anxiety disorders, renal failure, and alcohol use disorders)	126-130,131,132,133
	Preoperative fluid fasting and dehydration	32,131
	Preoperative blood transfusion	130
	Hyponatremia and hypernatremia	128
	Drugs with anticholinergic effects	32
	Quinolone	130
	Urine albumin to creatinine ratio (UACR)	134
Intraoperative factors	Site of surgery (abdominal and cardiothoracic)	126,135
	Hybrid procedure	130
	Intraoperative bleeding	136
	Duration of surgery	126
	Bispectral index (too low or too high)	127
	Intraoperative electrolyte disturbance	128
	Hyperthermia or hypothermia	137,138
The rate of decline in intraoperative hemoglobin concentration	136	
Postoperative factors	Pain	139
	Use of bed sensors	140
	Nursing home residency	141
	Delayed ambulation	129

Abbreviations: POD, postoperative delirium; POCD, postoperative cognitive dysfunction

in cardiovascular, general thoracic, and neurosurgery.^{37,38} Among factors below, the BP and coagulation state are specific modifiable risk factors for postoperative stroke according to large-scale database studies, which will be further discussed.

3.2.1 | BP and stroke

Blood pressure fluctuation is an important risk factor for postoperative stroke.³⁹ Emergency surgeries raise the incidence of neurological disorders and even affect long-term cognitive functions.⁴⁰ As mentioned before, older patients are usually complicated with underlying diseases including hypertension, coronary artery disease, and arrhythmia, and thus, they have a greater risk of suffering from postoperative neurological disorders.^{37,41,42} It has been reported that patients developing postoperative stroke (ischemic or hemorrhagic) have higher average mean arterial blood pressure (MAP >80 mmHg).³⁷ Moreover, a previous study suggests a strong relationship between elevated pulse pressure and stroke, which increases cerebral vulnerability to ischemic stroke.⁴² Additionally, evidence showed that intraoperative hypotension (IOH) is associated with the risk of major postoperative cardiac or cerebrovascular events.⁴³ The short exposure to MAP of 55–65 mmHg is significantly associated with postoperative adverse cerebrovascular events, while maintaining systolic blood pressure (SBP) within 10% of the reference value may prevent postoperative adverse events

compared with standard care (only treating if SBP <80 mmHg or <40% of the reference value).^{44,45}

3.2.2 | Coagulation and stroke

For elderly patients, oral anticoagulants, including vitamin K antagonist (VKA) and non-vitamin K oral antagonists (NOACs),⁴⁶ are common and effective therapies for the prevention of thromboembolism and stroke. However, they may lead to an inherent risk of bleeding. For elective and urgent surgery, reversal of anticoagulants is a necessary process for perioperative management.⁴⁷ Traditional broader anticoagulants VKAs, such as warfarin, while effective, had multiple dietary and drug interactions and a great risk for intracranial hemorrhage, where 4-factor (II, VII, IX, and X) prothrombin complex concentrate (4F-PCC) should be used for VKAs reversal.⁴⁸ Recently new types of anticoagulants targeted specific clotting factors (factors IIa and Xa), including dabigatran and rivaroxaban, have been approved for anticoagulation use with less adverse effect and less risk of hemorrhage.⁴⁹ In addition, it is recommended to monitor the coagulation state of patients during the perioperative period.⁵⁰

Postoperative neurological disorders occur by the interaction of predisposing factors and precipitating factors. Risk factors of POD, POCD, and perioperative stroke are listed above, and there may be other underlying risk factors unknown. Therefore, more researches are

Risk factors	Reference	
Preoperative factors	Vascular factors (eg, age, sex, history of stroke or TIA, arrhythmia, coagulopathy)	37,41,42,142-144
	Anemia	42
	Malnutrition	
	Preoperative central nervous system malperfusion	145
	Cerebral diffusion-weighted imaging lesions	146
	Renal dysfunction	147,148
Intraoperative factors	Type of surgery (cardiovascular, neurosurgery, left pneumonectomy other types of surgery)	37,42,38
	Specific intraoperative events (arrhythmia, hypertension, hypotension)	44
Postoperative factors	Adverse events (cardiac arrest, severe arrhythmia)	149
	New-onset atrial fibrillation	150,151

TABLE 4 Risk factors of perioperative stroke

Abbreviation: TIA, transient ischemic attack

needed to understand possible risk factors and pathophysiology related to postoperative neurological disorders. The preventive strategies and protocols need to be established for known risk factors as well.

4 | PREVENTION

4.1 | Perioperative prevention of POD

Prevention strategies should be designed based on predisposing factors and parts of precipitating factors, which are the most effective measures against delirium.⁵¹ The Hospital Elder Life Program (HELP) released a multicomponent intervention guideline to prevent delirium⁵² (Figure 1).

4.1.1 | Nonpharmacological interventions

Based on the studies of HELP, the multicomponent nonpharmacological intervention significantly reduces the incidence of delirium, including reorientation (using orientation calendar, clocks), early mobilization, promotion of sleep cycle, adequate hydration, visual and hearing aids, and increased supervision in hospital.⁵³ If implemented by a skilled interdisciplinary team, these measures are effective against POD.⁵⁴ Apart from common contents of HELP, a recent clinical trial has found that tailored, family-involved HELP could be beneficial for reducing POD, maintaining, or improving cognitive function, which may increase the implementation of this program.⁵⁵ During the operation, however, the EEG (electroencephalography)-guided anesthetic administration, compared with usual care, failed to decrease the incidence of POD.⁵⁶

4.1.2 | Pharmacological interventions

Although several clinical trials have run various pharmacologic measures, there is a lack of strong evidence for effective prevention.

One network meta-analysis demonstrated that haloperidol plus lorazepam might be the best treatment, while ramelteon may be the best preventive medicine for POD.⁵⁷ Besides, a recent randomized clinical trial has evaluated the effectiveness of tropisetron and found that tropisetron could decrease the incidence of delirium after non-cardiac procedures in adults.⁵⁸ Another trial has found that postoperative scheduled intravenous (IV) acetaminophen, combined with IV propofol or dexmedetomidine, could reduce the incidence of POD in hospital versus placebo group, while patients receiving one single intravenous anesthetic had no significant improvement for POD.⁵⁹ According to a Cochrane review that examined antipsychotic medications for preventing delirium in hospitalized, non-ICU patients, medications such as cholinesterase inhibitors, melatonin, and melatonin-receptor agonists have no clear effect in preventing delirium.⁶⁰

Besides, measures against precipitating factors are mainly adopted in the perioperative period, including limiting fasting time, reducing the use of preoperative medications such as benzodiazepines, opioids, and anticholinergic medications. For elderly patients with risk factors, preoperative neurological assessment is essential for predicting and preventing of POD.⁶¹

4.2 | Prevention of POCD

4.2.1 | Preoperative interventions

The evaluation of patients' baseline is important for the identification and prevention of POCD. Neuropsychological tests should be used before and after operations.⁶² Also, cognitive training and exercise⁶³ have been proven to be beneficial for preventing POCD occurrence.⁶⁴ Besides, Lu et al. found that pretreatment of parecoxib sodium combined with dexmedetomidine can decrease the incidence of POCD in patients undergoing arthroscopy by over 10%.⁶⁵ These interventions should be particularly considered in high-risk patients.

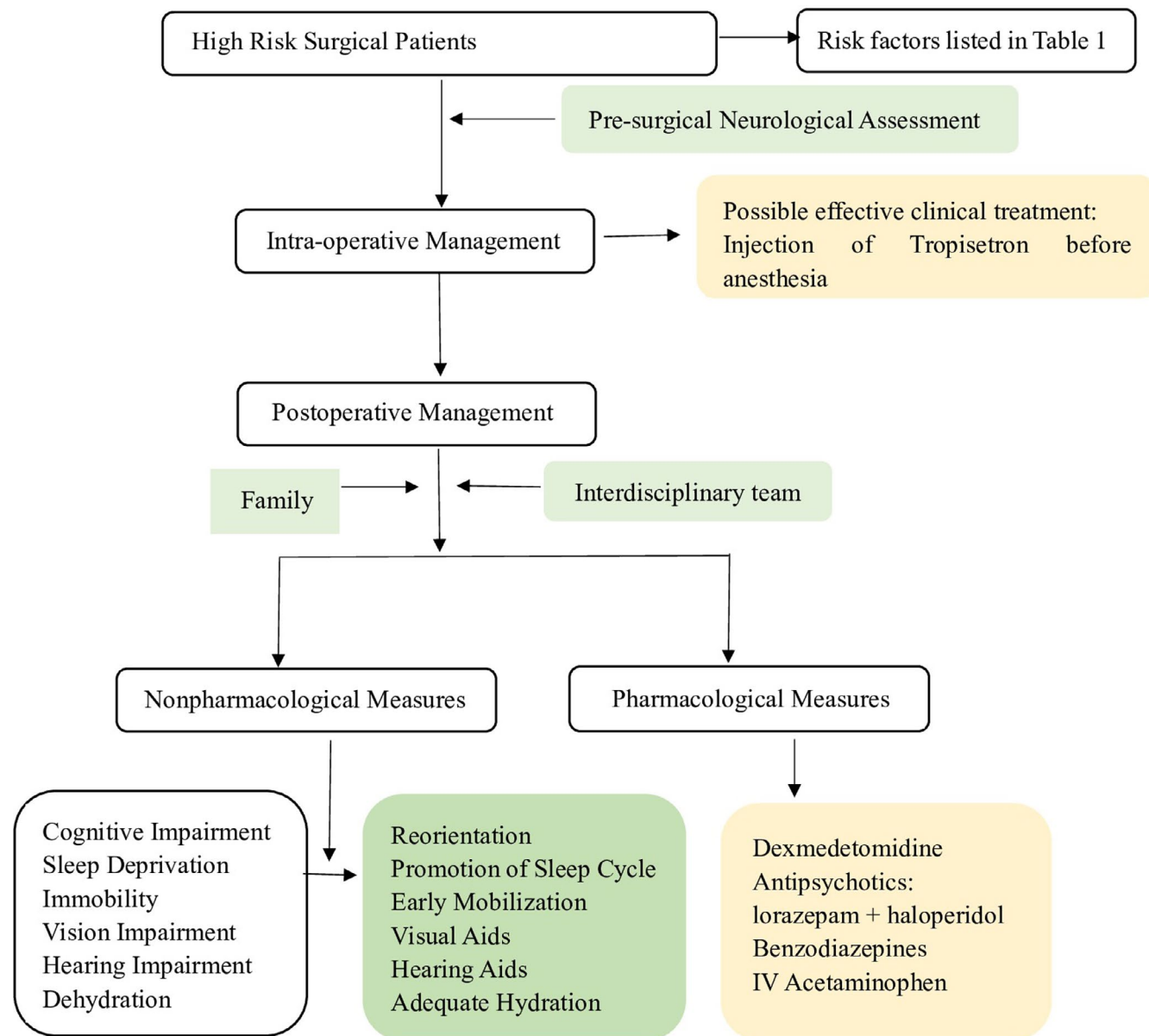


FIGURE 1 Nonpharmacological and pharmacological interventions during preventive process of POD recommended in HELP and latest evidence-based advance research on prevention of POD, including interventions throughout the whole process of surgery and possible medications for treatment that needed further research. POD, postoperative delirium; HELP, Hospital Elder Life Program

4.2.2 | Intraoperative interventions

In addition to preoperative interventions, there are several intraoperative measures to consider, including minimal exposure to anesthetics with careful monitoring. Regarding the anesthetic choice, Chen et al. found that the use of inhaled anesthetics⁶⁶ in cardiac surgery generated higher postoperative scores in the Mini Mental State Exam (MMSE) compared with total intravenous anesthetics.⁶⁷ Also, propofol may have a significant advantage in reducing POCD incidence compared with dexmedetomidine and midazolam sedation in elderly patients, in which midazolam has the highest inhibitory effects on cognitive functions.⁶⁸

As for monitoring measures, one trial has shown a decreased incidence of short-term POCD with bispectral index (BIS)-guided deep

anesthesia during the operation.⁶⁹ Lastly, it has been suggested that postoperative management, including early identification and treatment of postoperative complications, may decrease the risk of POCD, which will be discussed in the treatment section. All interventions discussed above are listed in Figure 2.

4.3 | Prevention of stroke

As for perioperative ischemic (covert) stroke and hemorrhagic stroke, the control of modifiable risk factors is the most effective preventive strategy. These identified modifiable risk factors include hypertension, diabetes mellitus, hyperlipidemia, obesity, and smoking.⁷⁰

4.3.1 | Modifiable risk factor—hypertension

Hypertension is the most important modifiable factor for stroke,⁷¹ attributing to more than half of all stroke events worldwide.⁷² Antihypertensive medications are recommended for patients with BP over 140/90 mmHg.⁷³ The most common medications include β -adrenergic agonists (β -blockers), calcium channel blockers (CCB), diuretics, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptors blockers (ARB), and the choice of therapy depends on individual comorbidities.⁷³ Adequate BP control is important, while the goal adjustment should also be considered for older patients to avoid complications such as hypotension and dizziness. Although perioperative use of β -blockers might be beneficial in reducing heart rate and sympathetic activity and controlling BP, there is no association between β -blockers and perioperative outcomes.^{74,75}

4.3.2 | Modifiable risk factor—hyperlipidemia

Hyperlipidemia is another remarkable risk factor, as several clinical trials and meta-analyses have reported decreased vascular events and mortality rates in patients with treatment for hyperlipidemia, especially lowering LDL-C (low-density lipoprotein-cholesterol).⁷² A randomized trial evaluated the benefits of statin as secondary prevention of stroke and found that atorvastatin can reduce the incidence of stroke in patients with recent stroke or TIA.⁷⁶

Treatments of hypertension and hyperlipidemia have been proven to prevent stroke. However, the effectiveness of other factors such as weight and blood glucose control, or smoking cessation may warrant further trials. Besides these control measures against risk factors, there are some other strategies proved to prevent postoperative stroke. Researchers have found that

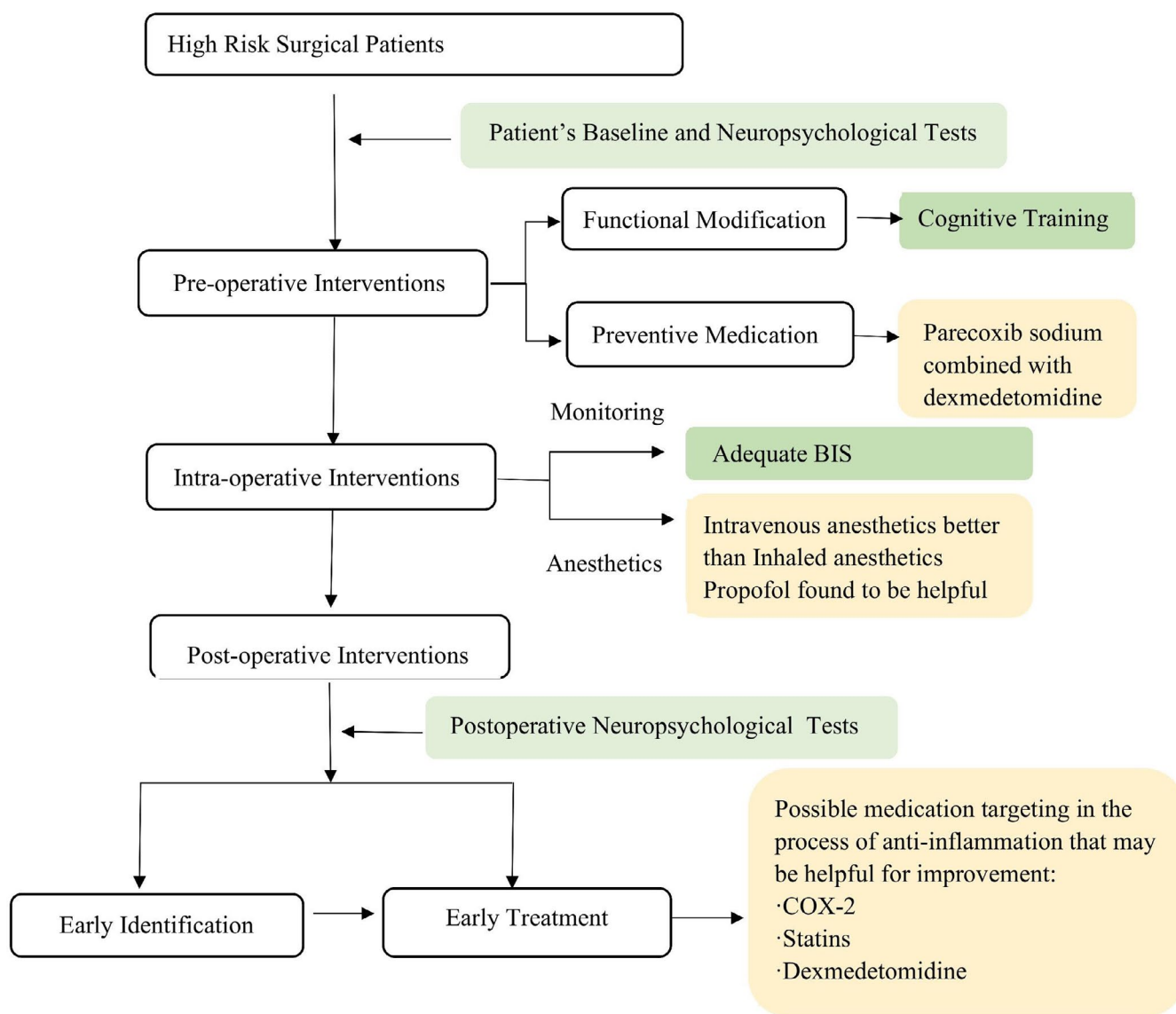


FIGURE 2 Preventive measures of POCD based on latest research on it during preoperative, intraoperative, and postoperative process and possible effective medications that may contribute to the prevention. POCD, postoperative cognitive dysfunction. BIS, bispectral index. COX-2, cyclooxygenase-2

perioperative use of dexmedetomidine reduced the incidence of postoperative stroke and delirium in elderly patients following cardiac surgery.⁷⁷ And in another clinical trial, left atrial appendage (LAA) surgical exclusion is effective on prevention of stroke, particularly in patients with atrial fibrillation after mitral valve replacement (MVR).⁵⁵

5 | CLINICAL MANAGEMENT AND PRECLINICAL STRATEGIES

Immediate treatment of etiologies and symptoms can contribute to a shorter duration of postoperative neurological disorders and lower risk of long-term cognitive impairment, disability, and even death.^{78,79} The clinical treatments and preclinical studies of POD, POCD, postoperative ischemic stroke, and postoperative hemorrhagic stroke are discussed below.

5.1 | Treatment of POD

5.1.1 | Nonpharmacological measures

Nonpharmacological measures are beneficial for both preventing and treating POD,⁸⁰ including reorientation, early mobilization, promotion of sleep cycle, adequate hydration, and visual and hearing aids. They can modify and create a safe and calm environment for patients.

5.1.2 | Pharmacological measures

There is no strong evidence for pharmacological management of POD, although the use of dexmedetomidine resulted in more ventilator-free time at 7 days among patients with agitated delirium in the intensive care unit.⁸¹ Medications are generally applied for delirium-associated behaviors. Two types of medications are frequently used, that is, antipsychotics and benzodiazepines.⁸²

For agitation with perceptual disturbance or sleep-wake cycle abnormalities, antipsychotics can be useful.⁸³ Nevertheless, patients with POD, which is more common in advanced age, may respond poorly to antipsychotic medications.⁸⁴ Benzodiazepines are historically used to sedate patients with delirium for decades. However, evidence suggests that benzodiazepines may increase the risk and duration of delirium, especially in elderly patients.⁸⁵ Thus, benzodiazepines should be mainly used in the treatment of agitation associated with sedative withdrawal.⁸² Another randomized trial showed that the addition of lorazepam to haloperidol resulted in a significantly reduction in agitation at 8 hours in hospitalized cancer patients with agitated delirium.⁸⁶ Given the above evidence, pharmacologic treatment is not strongly recommended but can be used to treat severe agitation and life-threatening POD complication.

5.2 | Treatment of POCD

Preventive interventions discussed above can also be used for the treatment of POCD. Several preclinical and clinical studies suggested that targeting postoperative neuro-inflammation⁸⁷⁻⁹¹ may be a potential way to treat POCD. There are some medications used in the clinical trials attempted to block the process of neuroinflammation.

The cyclooxygenase-2 (COX-2), which is responsible for catalyzing the conversion of arachidonic acid to pro-inflammatory prostaglandins⁹² and increasing blood-brain barrier (BBB) permeability,^{93,94} is considered to be an important mediator of neuroinflammation and thus a potential target for POCD treatment. Moreover, a meta-analysis suggested that the administration of parecoxib was effective in treating early POCD within 7 days and reducing interleukin-6 (IL-6) and S100 calcium-binding protein B protein (S100 β) concentrations within 2 days after operations.⁹⁵ Other anti-inflammatory medications, such as minocycline⁹⁶ and dexamethasone,⁹⁷ may also provide possible treatments for POCD. However, no prospective clinical trials investigated the promising effect of antioxidative agents for the prevention of POCD.

Statins are reversible competitive inhibitors of the rate-limiting enzyme in cholesterol synthesis.⁹⁸ They have been widely proven to be beneficial for neurological disorders, including dementia⁹⁹ and delirium.¹⁰⁰ In POCD, a clinical trial showed a significant reduction in memory dysfunction comparing statin to placebo in patients undergoing off-pump coronary artery bypass grafting (CABG).¹⁰¹

Dexmedetomidine has downstream effects on reducing serum pro-inflammatory cytokines in POCD.¹⁰² Dexmedetomidine treatment has been shown to ameliorate neurological dysfunction and decrease the incidence of cognitive impairment following surgical trauma in a hyperlipidemia rat model.¹⁰³

5.3 | Treatment of postoperative ischemic stroke

Postoperative covert stroke, as a type of postoperative ischemic stroke, has been studied little so far, and thus, there is no recommended treatment. Focusing on underlying treatable causes may be helpful but it is still in need of further investigation. Further research developed, treatment protocol may be clearer with more information. There are several clinical treatments for stroke, including intravenous thrombolysis, mechanical thrombectomy, intravenous infusion of unfractionated heparin,¹⁰⁴ which are major treatments for stroke. As for postoperative stroke, some of the treatments may not be suitable for patients undergoing surgeries. For example, intravenous unfractionated heparin is not recommended for postoperative stroke due to the high incidence of bleeding. However, the prolonged therapeutic window and new thrombectomy devices will give more opportunities to treat postoperative ischemic stroke in the future. Several effective treatments of postoperative ischemic stroke are listed below, which may be possible complications of covert stroke.

5.3.1 | Intravenous thrombolysis, injecting intravenous medications to dissolve thrombus

For patients with ischemic stroke up to 4.5 hours after symptom onset,¹⁰⁵ intravenous thrombolysis using tissue-type plasminogen activator (t-PA) can be considered as the first-line treatment. However, undergoing major surgery within 14 days is a contraindication for t-PA administration because of bleeding of surgical sites. Therefore, it is challenging and controversial to use intravenous t-PA even with clear symptoms for patients with postoperative stroke.¹⁰⁶ The use of t-PA should be individualized based on the risk and benefit of the treatment.

5.3.2 | Mechanical thrombectomy, using a guidewire to remove thrombus

Multiple clinical trials have demonstrated that endovascular therapy (EVT) has effective recanalization¹⁰⁷ and better clinical outcomes without the additional complication of hemorrhage in anterior circulation ischemia with large vessel occlusion (mainly of the intracranial internal carotid artery [ICA], middle cerebral artery [MCA] main trunk, or the M2 major branch of the MCA), which is considered as a treatment option for postoperative stroke.¹⁰⁸ Besides, studies have expanded the therapeutic window up to 24 hours after symptom onset for patients with a small core and large penumbra.¹⁰⁹ New devices continue to be developed for reaching distal branches,¹¹⁰ which may provide standard treatment for perioperative stroke.

5.4 | Treatment of postoperative hemorrhagic stroke

Some clinical trials suggested various effective treatment methods for hemorrhagic stroke, including the control of high BP and intracranial pressure (ICP), and treatment of complications and intracranial hemorrhage,¹¹¹ which are important treatment methods for hemorrhagic stroke. We will discuss the most effective methods below.

5.4.1 | Controlled BP

Patients with hemorrhage usually present high BP. High SBP has been associated with neurological deterioration and death,¹¹² which should be gradually reduced by using antihypertensive drugs such as CCB and ACEI. The ASA recommended that for patients presenting with SBP between 150 and 220 mmHg, an acute and aggressive reduction of SBP is safe and beneficial for functional outcomes.¹¹² However, some clinical trials found no significant relationship between SBP reduction and hematoma expansion or outcome.¹¹³ The goal and effect of BP control in postoperative hemorrhagic stroke need to be elucidated in future studies.

5.4.2 | Interventions to control intracranial pressure (ICP)

The initial treatment should include elevating the head of the bed to 30° and the patients' head facing midline to avoid excessive flexion or rotation of the neck.¹¹⁴ Then, osmotic agents (mannitol and hypertonic saline) are given; for example, 20% mannitol is given at 1.0–1.5 g/kg.¹¹⁵ Next, early intubation and mechanical ventilation should be applied, especially for patients in coma. ASA also recommends ICP monitoring with a ventricular catheter to ensure the cerebral perfusion pressure (CPP) between 50 and 60 mmHg to prevent cerebral ischemia.¹¹²

5.4.3 | Treatment of complications

Researches showed that 3% to 17% of patients have seizures¹¹⁶ in the first two weeks after operation, which should be treated with antiepileptic drugs.¹¹² First-generation antiepileptic drugs negatively affect cognitive function, which should be avoided in patients with postoperative stroke.¹¹⁷ Drugs developed after 2000 are known as third-generation antiepileptic drugs, such as eslicarbazepine acetate, lacosamide, perampanel, brivaracetam, rufinamide, and stiripentol.¹¹⁸ These drugs, characterized with new mechanisms of action and favorable pharmacokinetics, can decrease the occurrence of side effects and drug-drug or hormonal interactions compared with first-generation antiepileptic drugs. These new drugs are also useful therapies in patients with intractable epilepsy.¹¹⁹ However, currently there are no instructions on the use of these drugs for postoperative stroke patients.

5.4.4 | Surgical treatments of hemorrhage

There are different types of surgical treatments of hemorrhagic stroke, including craniotomy for hematoma drainage, decompressive craniectomy with or without hematoma drainage, minimally invasive endoscopic aspiration and catheter aspiration.¹²⁰

Open surgery

Although the approach of open surgery to treat patients with cerebral hemorrhage remains controversial, it is still one of the most common approaches applied for hematoma drainage.¹²¹ The Surgical Trial in Intracerebral Hemorrhage (STICH), which was the first multicenter, multinational, randomized clinical trial that compared the benefits of hematoma drainage with conservative management, found that there was no overall benefit from early hematoma drainage compared with conservative treatment.¹²² Subsequently, another international, multicenter, prospective, randomized trial, which included only patients with superficial hematomas within 1 cm from the brain's cortical surface of the brain, indicated that patients with superficial hematomas could benefit from early intervention of hematoma removal.¹²³

Minimally invasive approach

The practice of open craniotomy is complicated with brain tissue damage and related complications because it requires a large bone flap and exposure of the brain tissue. On the contrary, a minimally invasive approach with thrombolysis is safer, more feasible, and more efficacious.¹²⁴ However, it still showed no significant benefit of long-term functional outcome than conservative treatment based on clinical trials.¹²⁴

In summary, decompressive craniectomy and hematoma evacuation are performed more frequently for hemorrhagic stroke in patients with Glasgow Coma Scale (GCS) scores of 8 or less and large hematomas. These procedures reduce mortality and may improve functional outcomes.¹²⁵

6 | CONCLUSION AND FUTURE REMARKS

Postoperative neurological disorders are common complications without effective treatment that exert an enormous burden on patients, their families, hospitals, public resources, and society. The existing knowledge of risk factors provides certain information to guide possible effective interventions that may need more repeating trials, but further interventional research is urgently needed to improve the outcomes or prognosis for hospitalized patients who experience the condition. Early prevention is likely to be more effective than treatment for prognosis. Thus, further prospective trials should gain deeper insight into uncertain mechanisms and contributing factors underlying these neurological disorders, avoiding simple risk factor evaluation, and validating possible prognostic models for interventional research.

Significantly, dexmedetomidine may be an effective medication for the prevention of POD and POCD as mentioned in multiple trials, which should be considered in future research. As for covert stroke, early identification may be more effective, likely given priority to in further research.

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CONFLICT OF INTEREST

The authors declare to have no potential conflicts of interest. All data included in this study are available upon request by contact with the corresponding author.

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