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Postoperative delirium

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Delirium can be defined as an 'acute brain dysfunction.' Compared to dementia, which is a disease that deteriorates the brain function chronically, delirium shows very similar symptoms but is mostly ameliorated when the causative factors are normalized. Due to the heterogeneity in etiologies and symptoms, people including health care workers often mistake delirium for dementia or other psychiatric disorders. Delirium has attracted global interest increasingly and a vast amount of research on its management has been conducted. Experts in the field have constantly suggested that systematic intervention should be implemented through a team-based multicomponent approach aimed to reduce the incidence and duration of delirium. Surgery involves many health care workers with different expertise who are not familiar with delirium. For a team-based approach on the management of delirium, it is vital that all medical personnel concerned have a common understanding of delirium and keep in constant communication. Postoperative delirium is a common complication and exerts an enormous burden on patients, their families, hospitals, and public resources. To alleviate this burden, this article aimed to review general features and the latest evidence-based knowledge of delirium with a focus on postoperative delirium.

Keywords: Cognitive decline; Current practice; Delirium; Postoperative complication; Prevention; Prognosis; Risk factor.

Introduction

Delirium has attracted global interest increasingly and a vast amount of research on its management has been conducted. Experts in the field have constantly suggested that systematic intervention should be implemented through a team-based multicomponent approach aimed to reduce the incidence and duration of delirium [1,2]. Surgery involves many health care workers with different expertise who are not familiar with delirium. For a team-based approach on the management of delirium, it is vital that all medical personnel concerned have a common understanding of delirium and keep in constant communication. This article aimed to review general features and the latest evidence-based knowledge of delirium with a focus on postoperative delirium.

Concept of Delirium

Acute brain dysfunction

Delirium can be defined as an 'acute brain dysfunction.' Compared to dementia, which is a disease that deteriorates the brain function chronically, delirium shows very similar symptoms but is mostly ameliorated when the causative factors are normalized. While the reversibility of delirium is expressed as 'acute,' the words 'brain dysfunction' connote the diversity of symptoms. Any possible symptom related to the brain such as disorientation, perceptual disturbances, emotional dysregulation, or sleep disturbances could appear in delirium.

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Definition of delirium

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines the key feature of delirium as a disturbance in attention and awareness [3]. As described among the full diagnostic criteria by DSM-5 listed in Table 1, another important factor of delirium is an acute and fluctuating course of mental state. Postoperative delirium usually happens in the recovery room and appears up to 5 days after surgery [4,5]. One study discovered that many patients who showed postoperative delirium on the peripheral ward had delirium in the recovery room [5]. Emergence delirium refers to the delirium in the immediate post-anesthesia period [6,7].

Subtypes of delirium

Clinical subtyping of delirium according to motor activity is widely used [8,9]. Hypoactive delirium is characterized by decreased activity, reduced alertness, withdrawal, unawareness, and decreased speech while hyperactive delirium shows agitation, wandering, irritability, and hallucination [10]. Mixed delirium shows both hyperactive and hypoactive features in short time frames.

Some evidence suggested that certain risk factors such as preexisting cognitive impairment, older age, frailty, and severity of physical illness are more associated with hypoactive delirium [11,12]. More systematic research is required to elucidate the relationship between predisposing factors and motor profile. Due to the absence of overt distress or disturbance in hypoactive delirium, hypoactive delirium is more likely to be overlooked than hyperactive delirium. Worse prognosis has been reported in hypoactive delirium possibly due to the difficulty of detection and subsequent delayed treatment [9].

Assessment Tools

To use a reference standard such as the DSM-5, users must undergo extensive training. To detect and evaluate delirium easily and quickly, many assessment tools have been developed. The Confusion Assessment Method (CAM) [13] is a screening tool that consists of 4 features: (a) an acute onset and fluctuating course of mental state, (b) inattention, (c) disorganized thinking, and (d) altered level of consciousness. Delirium is diagnosed when features (a) and (b) are satisfied essentially and (c) or (d) selectively. The CAM for the intensive care unit (ICU; CAM-ICU) is a two-minute version of the CAM to be administered easily in the ICU with an accuracy of over 93% [14,15]. Skilled personnel with proper education on the tool should be able to apply the CAM with high sensitivity [16].

The Richmond Agitation-Sedation Scale (RASS) is a tool to assess the level of sedation/agitation [17]. As the DSM-5 guidance notes stated that a severely reduced level of arousal (of acute onset) above the level of coma should be considered as having 'severe inattention' and hence as having delirium [3,18], the RASS can be useful in diagnosing delirium.

The Memorial Delirium Assessment Scale (MDAS) [19] and the Delirium Rating Scale-Revised-98 (DRS-R98) [20,21] are also useful in evaluating the presence and severity of delirium but are more time-consuming than the CAM. The MDAS focuses on the assessment of disturbances in consciousness and cognitive function (10 items with a total score ranging from 0 to 30). The DRS-R98 includes a relatively wider scope of symptoms, containing 3 diagnostic items and 13 severity items (total score ranging from 0 to 46, with higher score indicating more severe delirium). The original validation study suggested that 15 points or more on the severity scale would indicate dementia or other psychiatric disorders [20].

For the routine implementation of assessment tools for delirium, it is essential to train personnel on the basic features of delirium as well as the features and characteristics of the scales. This is not merely because tools such as the CAM require education, but also because the personnel should have a common understanding of delirium and keep in constant communication on the results of the tools [22,23].

Table 1. Definition of Delirium by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [3]

Diagnostic criteria	
A.	A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B.	The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C.	An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D.	The disturbances in criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E.	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 (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Apart from clinical diagnostic tools, previous studies have shown evidence of biomarkers for the detection and monitoring of postoperative delirium in both ICU [24,25] and non-ICU settings [26,27]. However, further research is required to apply them in practice. Electroencephalography (EEG) can also be used as a relatively objective diagnostic tool for delirium. It is widely known that patients show a slowing of background activity as detected by EEG during delirium [28]. The routine use of EEG monitoring for delirium screening would be time-consuming and inefficient because of issues with the interpretation of the results. A recent EEG study using 2 electrodes and automatic processing showed a large difference between delirium and non-delirium in a homogenous population of non-sedated patients [29]. With specific protocols and proper automatic processing, EEG may provide consistent and objective diagnosis of delirium in the future.

Causes and Progression of Postoperative Delirium

Pathophysiology

The pathophysiology of delirium is poorly understood. In spite of many studies to find a common mechanism that explains all aspects of delirium, there may not be a single mechanism that could explain the whole syndrome with its heterogeneous etiologies and presentations. There are 2 leading hypotheses that has helped us to understand the complex nature of delirium [30]. The first emphasizes the role of inflammation, particularly the action of cytokines on the blood-brain barrier and the impact of chronic stress on cytokine and cortisol levels. The second highlights the neurochemical imbalances that affect neurotransmission. Neurochemical changes are found in the acetylcholine, dopamine, glutamate, gamma-aminobutyric acid, and serotonin systems. A recent neuroimaging study investigated the strength of resting-state functional connectivity between regions producing or utilizing acetylcholine and dopamine during and after an episode of delirium using functional magnetic resonance imaging (fMRI) [31]. When compared to the group without delirium, patients with delirium showed disruption in reciprocity of the dorsolateral prefrontal cortex with the posterior cingulate cortex and reversible reduction of functional connectivity of the subcortical regions [31]. Another fMRI study focused on the sleep-wake disturbance in delirium and showed a dysregulation of the default mode network and mental coordination processing areas by the suprachiasmatic nucleus of the hypothalamus [32].

Risk factors

It is widely accepted that delirium occurs by the cumulative interactions between predisposing and precipitating factors [2]. Predisposing factors are generally considered potent predictors of delirium. The smaller the vulnerability a patient has at baseline, the more resistance to delirium he/she shows even under stressful conditions. On the contrary, with high vulnerability, a patient may easily develop delirium under little insult [30]. For example, considering that old age is a strong predictor of delirium, a patient aged more than 65 would experience delirium when exposed to just 1 or 2 precipitants [33]. With the same precipitating factors, younger patients may not have delirium or may stay in the subthreshold state. In younger patients, compared to elderly patients, delirium would develop under much more complex and varied interactions among the causative factors. The European Society of Anesthesiology presented the evidence-based and consensus statements for preoperative, intraoperative, and postoperative risk factors for postoperative delirium as listed in Table 2 [2]. Among the risk factors, pain is shown to be significantly correlated with anxiety and the dose of opioids administered in a recent study [34]. Since patients in the ICU commonly display anxiety [35] and prolonged administration of sedatives and analgesics to reduce anxiety may cause delirium [36], accurate evaluation and comprehensive management of both pain and anxiety is necessary to prevent delirium.

Additionally, emergency surgery [37,38] and postoperative complications raise the incidence and duration of postoperative delirium as well as the risk of long-term cognitive impairment [39]. To investigate these risk factors and to introduce strategies for risk reduction (e.g., fast track surgery) [23,40], a well-devised protocol needs to be developed. A report stated that hypothermia in the recovery room may be a risk factor for hypoactive emergence [41]. Also, the incidence of delirium after cardiac surgery was associated with preoperative fasting glucose concentrations [42,43].

Table 2. Risk Factors of Postoperative Delirium [2]

Preoperative factors	Advanced age
	Comorbidities (e.g., cerebrovascular including stroke, cardiovascular, peripheral vascular diseases, diabetes, anemia, Parkinson's disease, depression, chronic pain, anxiety disorders, and alcohol use disorder)
	Preoperative fluid fasting and dehydration
	Hyponatremia or hypernatremia
	Drugs with anticholinergic effects
Intraoperative factors	Site of surgery (abdominal and cardiothoracic)
	Intraoperative bleeding
Postoperative factor	Pain

Effect of sedatives on delirium

As mentioned earlier in this article, clinical scoring tools such as the CAM and MDAS are based on the evaluation of the level of consciousness and changes in cognition. Sedative drugs are almost always used in patients who undergo surgery, but their interference with the assessment of delirium has not received much attention. One study showed that the apparent prevalence of delirium is dependent on how the level of consciousness is interpreted (persisting sedation despite the discontinuation of sedatives versus delirium) [44]. Another study reported that patients with rapidly reversible, sedation-related delirium did not differ from patients with no delirium in prognostic outcomes such as ventilator days, length of stay in the ICU, length of stay in the hospital, or hospital or 1-year mortality, whereas patients with persistent delirium showed worse outcomes [45]. It is not clear whether the effect of sedative drugs should be considered otherwise in diagnosing delirium since the diagnostic criteria according to the DSM-5 (criterion E) acknowledged multiple etiologies that affect attention and awareness. Setting aside diagnostic issues, the effect of sedative drugs should be closely monitored in delirium assessment.

Psychological factors

Strong correlation between subjective emotional factors (e.g., pain and anxiety) and delirium is generally acknowledged [46]. Subjective emotional factors are mostly manifested on the basis of personality. Although various physical and medical risk factors for delirium have been identified, the effect of psychological factors has not been clearly studied so far. A recent study investigated the psychological risk factors for postoperative delirium to identify hidden subgroups of delirium. Phenotypic subgroups of delirium were assessed using Topological Data Analysis (TDA), and the results showed 4 predictive risk factors: the Mini-Mental State Examination score, neuroticism, conscientiousness, and regional anesthesia (Fig. 1) [47]. TDA is a clustering technique to discover the pattern or grouping in data while allowing overlaps among clusters [48]. Among the 5 personality factors proposed by Goldberg (extraversion, agreeableness, neuroticism, conscientiousness, and openness) [49], only 2 were shown to have an effect on the occurrence of delirium in the study by Shin et al. [47]; neuroticism and conscientiousness. Neuroticism is frequently used in affect studies and is generally considered to be related to negative affect [50]. People with high neuroticism tend to become miserable or to create unhappy situations. They are vulnerable to stress [51] and have poor emotional control [52]. Conscientiousness reflects self-control and people with high conscientiousness have a strong ability to control emotions [53]. The study using TDA mentioned above showed that patients with less self-control were more vulnerable to delirium [47]. It is an interesting and understandable result, but more research is necessary to elucidate the relationship between personality and delirium.

Clinical course and impact

Delirium is often considered a transient brain dysfunction, and most patients achieve full remission. However, the results of previous studies strongly suggest that delirium is associated with long term cognitive [54] and non-cognitive morbidity [55], including a low quality of life [56].

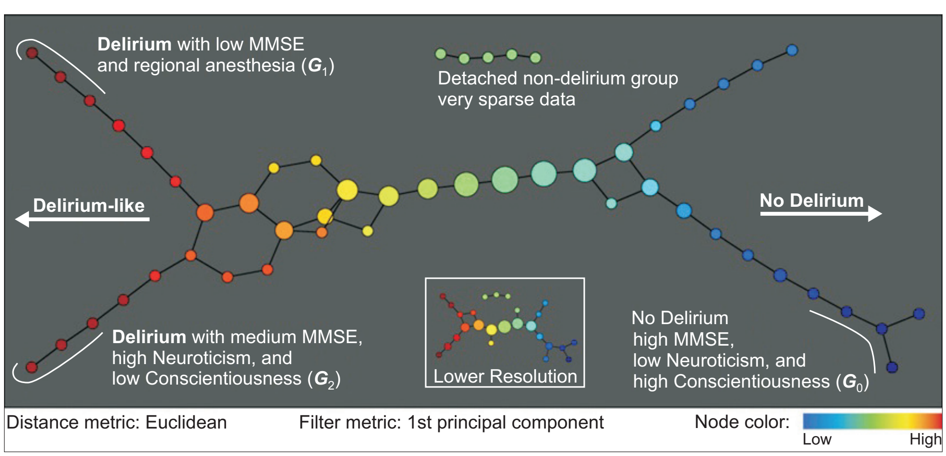

Fig. 1. Topological data analysis of patient-patient networks for psychological risk factors in postoperative delirium. Filter metric was subdivided into 8 intervals with 80% overlap. Several nodes were disconnected from the main graph. An inset graph in the bottom right represents a lower resolution topology with 4 intervals and 60% overlap. Subgroup G_1 includes 7 delirious patients with low Mini-Mental State Examination (MMSE) scores and regional anesthesia and G_2 includes 4 delirious patients with medium MMSE scores, high neuroticism, and low conscientiousness scores. G_0 includes 6 patients with high MMSE, low neuroticism, and high conscientiousness scores. Adapted from Shin et al. [47] with permission.

Studies have shown that delirium in ICU patients was independently associated with worse prognosis [57,58]. In ICU patients, the prolonged duration of delirium was a strong indicator for a longer length of stay in the hospital and more days in the ICU [59]. Also, multiple studies have reported that the presence of delirium in ICU patients was associated with a reduced 6-month survival rate and cognitive decline on discharge [60,61]. Postoperative delirium, regardless of ICU admission, extends the total length of stay in the hospital [62–64]. Various studies have also reported the association between postoperative delirium and increased mortality [65–67].

Evidence has shown that postoperative delirium is associated with both short and long term cognitive impairment [54,68,69]. The trajectory of cognitive impairment following postoperative delirium is characterized by an initial decline and prolonged deterioration [54]. One study even suggested the association between postoperative delirium and dementia up to 5 years after delirium [70].

Thorough evaluation of patients before surgery for the presence of delirium and cognitive impairment is necessary because any cognitive impairment prior to hospital admission is an independent risk factor for long term cognitive impairment [71] and preoperative evaluation has shown prevalence rates of preexisting delirium up to 29.7% [72].

The progress and time course of delirium varies greatly due to its heterogeneous etiologies. According to the latest study, postoperative delirium developing as a secondary complication following surgery showed longer duration and length of hospitalization compared with postoperative delirium attributable to surgery and delirium in medical patients [73]. In the same study, as in Fig. 2 that shows the delirium recovery rate according to the time course, patients with delirium in medical wards showed lower delirium recovery rates at discharge than patients in surgical wards [73]. Along with the complex etiological nature of delirium, the findings above suggest that targeted screening and intervention are necessary.

Management of Postoperative Delirium

The management of postoperative delirium is not so different from that of general delirium. Immediate treatment of both precipitating factors and symptoms is important in reducing the duration of postoperative delirium [65,74]. Current management approaches to delirium are mainly focused on the precipitants. However, if the precipitating factor is the surgery, which is inevitable, other approaches should also be considered. As for prevention, managing the predisposing factors of delirium is vital and would decrease the morbidity/mortality associated with delirium.

Non-pharmacological/supportive measures

Non-pharmacological interventions are useful in both the prevention and management of delirium. They modify the patient's surroundings to maximize the safety and calmness of the environment and to provide reassurance and decrease fear and agitation associated with delirium. Evidence-based approaches target 6 risk factors for multicomponent non-pharmacological intervention: cognition/orientation, early mobility, hearing, sleep-wake cycle preservation, vision, and hydration [75]. Orienting communication, minimization of immobilizing equipment, hearing aids, visual aids, environmental cues for normal sleep-wake cycles, and adequate nutrition are typical examples of non-pharmacological interventions. In addition to the care provided by the staff, family or close friends can be extremely important in the management of the patient's symptoms. If regularly informed of the situation, family members can reassure the patient, provide reorientation, and reduce anxiety and agitation. Familiar items from home may be useful for selected patients. A recent meta-analysis study showed that multicomponent non-pharmacological delirium intervention is effective in reducing delirium incidence and preventing falls, with a trend toward decreasing the length of stay in hospitals and avoiding institutionalization [76].

Pharmacological guidelines for symptomatic treatment

The pharmacological management of delirium is not sup-

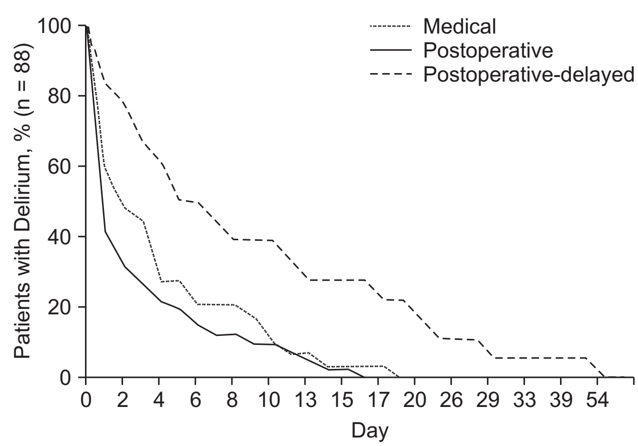

Fig. 2. Delirium recovery rate according to the time course. The graph shows the time course of delirium recovery among 88 patients whose delirium was resolved during hospitalization (72%). The proportion of patients with delirium decreased with increasing length of delirium duration. A total of 39 days were required for medical patients to recover, versus 16 days and 77 days for postoperative and postoperative-delayed patients who recovered during hospitalization, respectively. Adapted from Kim et al. [73] with permission.

ported by strong evidence. It should be reserved for the management of behaviors associated with delirium that involves a safety risk for the patient and delirium due to drug or alcohol withdrawal. Two classes of medications are most frequently used: antipsychotics and benzodiazepines.

For agitation with perceptual disturbances associated with sleep-wake cycle abnormalities and uncontrolled behavior problems, antipsychotic agents can be useful. Haloperidol, a typical antipsychotic, is commonly used to manage delirium in spite of weak evidence to support its efficacy and lack of U.S. Food and Drug Administration approval for this indication. It is preferred over other antipsychotics because of fewer anticholinergic and hypotensive side effects. However, the high potency of haloperidol is related to increased frequency of extrapyramidal side effects such as dystonic reactions, akathisia, tardive dyskinesia, and malignant catatonia [30]. Close observation of the patient is indispensable not only for effectiveness but also for the monitoring of adverse events. Haloperidol is also associated with increased risk of corrected Q-T interval prolongation, and electrocardiography monitoring is recommended after administration [30].

Due to the lower incidence of extrapyramidal side effects, atypical antipsychotics such as risperidone, olanzapine, and quetiapine have been more frequently used to manage delirium. Several recent studies have shown some promising results in both their efficacy and safety [77–79]. Studies have shown that there was no significant difference in the efficacy between haloperidol and atypical antipsychotics in the treatment of delirium [80,81].

In the treatment of delirium with antipsychotic medication, advanced age may be a predictor of poor response [81–84]. Compared with other antipsychotics, olanzapine may show poor response in patients of older age because of its high affinity for muscarinic receptors (Fig. 3) [81].

Benzodiazepines have also been used historically to sedate agitated patients with delirium. In light of evidence to suggest that benzodiazepines can increase both the risk and duration of delirium [85], particularly in the elderly, benzodiazepines should mainly be used for the management of agitation associated with sedative-hypnotic withdrawal (e.g., alcohol, benzodiazepines, barbiturates).

Recent studies suggest that dexmedetomidine (Precedex) may be effective in preventing and treating delirium in critically ill patients [86,87]. However, larger well-designed trials are warranted to elucidate the therapeutic role of dexmedetomidine in the treatment of delirium.

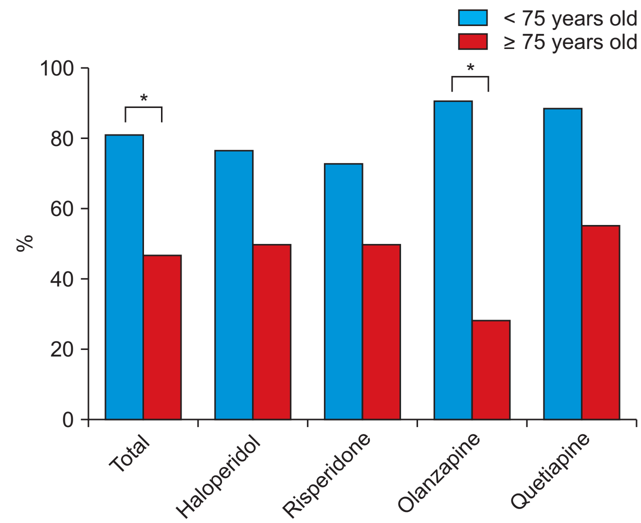

Fig. 3. Treatment response rate between young-old and old-old groups in the 4 antipsychotic groups. *P < 0.05 by Chi-square test or Fisher's exact test. Treatment response was defined as a ≥ 50% reduction from the baseline score on the Korean version of the Delirium Rating Scale-Revised-98 (DRS-R98-K) [21]. DRS-R98-K is evaluates the presence and severity of delirium. This figure is adapted from Yoon et al. [81] with permission.

Conclusions

Postoperative delirium is a common complication and exerts an enormous burden on patients, their families, hospitals, and public resources. Its management should be maintained throughout all stages of surgery with regards to the following 3 aspects: prevention, assessment, and treatment. Systematic intervention should be implemented through a team-based multicomponent approach aimed to reduce the incidence and duration of delirium.

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