



## Intensive Care Unit Delirium

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Delirium is described as a manifestation of acute brain injury and recognized as one of the most common complications in intensive care unit (ICU) patients. Although the causes of delirium vary widely among patients, delirium increases the risk of longer ICU and hospital length of stay, death, cost of care, and post-ICU cognitive impairment. Prevention and early detection are therefore crucial. However, the clinical approach toward delirium is not sufficiently aggressive, despite the condition's high incidence and prevalence in the ICU setting. While the underlying pathophysiology of delirium is not fully understood, many risk factors have been suggested. As a way to improve delirium-related clinical outcome, high-risk patients can be identified. A valid and reliable bedside screening tool is also needed to detect the symptoms of delirium early. Delirium is commonly treated with medications, and haloperidol and atypical antipsychotics are commonly used as standard treatment options for ICU patients although their efficacy and safety have not been established. The approaches for the treatment of delirium should focus on identifying the underlying causes and reducing modifiable risk factors to promote early mobilization.

**Key Words:** critical care; delirium; intensive care units.

### Introduction

Critically ill patients commonly experience anxiety disorder as a result of pain, invasive procedure, unfamiliar environment and fear of death. It is therefore important to distinguish delirium from anxiety before using anxiolytics because this medicine can worsen delirium/confusion status. Delirium is referred to by various terms, including acute confusion state, ICU psychosis, acute brain dysfunction and encephalopathy and characterized by disturbances of attention, orientation, memory and language, which are caused by a medical condition. In other words, delirium represents acute, fluctuating changes in mental status characterized by inattention, disorganized thinking and perceptual disturbance, whereas agitation is defined as extreme arousal, irritability and motor restlessness caused by discomfort and tension.

Although emphasis is being placed on prevention and early detection of delirium, the effort to identify and recognize delirium quickly is far from enough, and many cases of delirium are considered iatrogenic as a result. Given that delirium is a strong predictor of longer ICU and hospital stay, delirium is likely to increase spending for hospital care and risk of death,

when it is overlooked in the hospital setting.[1,2] Critical care providers need to consider delirium an organic brain dysfunction and take more aggressive approach to delirium care because it can be serious as much as an organ system failure.[3]

The aim of the present article was to investigate the incidences of delirium in the ICU in Korea by reviewing related literature and the database of the 2013 American College of

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Critical Care Medicine (ACCM) 's clinical practice guidelines.[1]

## Definition

Delirium is defined as an acute onset and fluctuating course, inattention, impaired consciousness and disordered cognition, according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM).[4] Hallucination or delusion is also observed in delirious patients, they are not required for diagnosis. The abovementioned symptoms are often accompanied by sleep disturbances, abnormal psychomotor activity and emotional disturbances.

Delirium is categorized into 3 subtypes: hyperactive, hypoactive and mixed type.[1] Patients with hyperactive delirium are aggressive, agitated, hallucinating and deluded, showing increased psychomotor activity. Although agitation can occur with other brain and mental health such as dementia, schizophrenia and depression, agitated symptoms of delirious patients include acute onset, fluctuating course and early impaired consciousness. Patients with hypoactive delirium show reduced alertness, lethargy, decreased responsiveness, and slowed motor skills. Patients with mixed type delirium fluctuate between hyperactive and hypoactive delirium.[5] Hypoactive delirium occurred more frequently showing the prevalence of 43-64%, whereas pure hyperactive delirium showed a prevalence of below 2%.[6,7] The prevalence of hypoactive delirium was reported as high as 92% in the cardiac ICU.[8] However, hypoactive delirium can be easily missed; more than 76% of total cases of hypoactive delirium were overlooked in the absence of a routine delirium screening. Because it usually occurs in the elderly patients, diagnosis is not feasible and prognosis is not favorable, calling for more aggressive approach for both diagnosis and treatment.[9]

## Incidence

Delirium incidence varies, depending on patients and the types of screening tool used. McNicoll et al reported 31% of ICU patients had delirium, and 70% of them developed

delirium during hospital stay.[10] The incidence and prevalence of delirium in patients intubated or ventilated ranged 54-82%.[2,11,12] Pisani et al asserted that 70.4% of ICU patients developed delirium within 48 hours after admission.[13]

Thus, the impact of delirium on ICU and hospital stay, duration of mechanical ventilation and mortality has been well documented.[14-18] In particular, the duration of delirium was associated with an increase in mortality in a dose dependent fashion.[16] Specifically, each day of delirium increases the likelihood of death by 10%.[15] The duration of delirium is also considered an independent predictor of cognitive impairment after ICU admission.[19,20] Because even one day of delirium can lead to poor clinical outcomes, preventive measures are critical, and early detection and aggressive symptom management are also important to reduce duration of delirium.

## Risk Factors

The major risk factors for delirium include preexisting dementia, history of hypertension, alcoholism and high severity of illness at admission.[1] Additional baseline risk factors can be smoking, living alone at home, the use of drains, tubes and catheters, the use of psychoactive medication, a preceding period of sedation, coma or mechanical ventilation. Environmental variables, including isolation, the absence of visit, the absence of visible daylight, a transfer from another ward, immobility, and the use of physical restraints, also increase the risk of developing delirium,[21,22] not to mention ICU-specific risk factors: underlying psychological stressors, mechanical ventilation, noise, light, patient care interactions and drug-induced sleep disruption and deprivation.[1,23,24] Most of these environmental factors can be modified to reduce the risk of delirium. Age is also one of the significant risk factors not related to ICU, some studies included age as one of the ICU-related risk factors.[17,25]

Exposures to sedative medications pose a risk to develop delirium in ICU patients, and benzodiazepines and dexmedetomidine have been identified as independent risk factors,[22,25,26] although the latter showed a less significant association with delirium.[27,28] To date, the evidence for the relationship between opioid and the development of de-

lirium remains conflicting.[1] Delirium was found to be associated with high perioperative plasma cortisol level in patients undergoing coronary artery bypass graft surgery and systemic corticosteroids in patients with acute lung injury.[29,30] In addition, antihistamine and furosemide were also found to be responsible for causing delirium among medications used in the ICU due to central anticholinergic effects.[31]

Perioperative risk factors of delirium include intraoperative blood loss, transfusion, low hematocrit and pain.[32-36] Preoperative atrial fibrillation, longer surgery duration are also suggested as risk factors in a study involving patients who underwent coronary artery bypass grafting surgery.[37] It is therefore important to identify high-risk patients as part of the preventive measures and early detection of delirium.

## Pathophysiology

The pathophysiology of delirium is not fully understood. However, delirium is considered the neuron network dysfunction in the brain resulting from an interaction of multiple factors.[38] Alertness and attention are mediated by the ascending reticular activating system (RAS) and its bilateral thalamic projection, neocortical and limbic system. Because fluctuation in alertness is one of common signs of delirium, the pathway dysfunction is assumed to be the cause of the symptom. The level of acetylcholine, one of major neurotransmitters involved in RAS function, declines with age, triggering the occurrence of delirium in the elderly, and anticholinergic agents tend to worsen the symptoms of delirium. Acetylcholine levels can change in response to the insults to the brain by ischemia and immunological stressors and disturb the balance of other neurotransmitters, leading to delirium.[39]

The role of dopamine is closely linked to the development of delirium because disorders of oxidative metabolism increase dopamine release from dopaminergic neuron, which promotes glutamate release, causing agitation. The incidence of delirium is also explained by an imbalance of other neurotransmitters, including GABA, serotonin, endorphin and norepinephrine.[40]

Elevated levels of inflammatory mediators in the central nervous system (CNS) resulted from activation of inflam-

matory cascade with acute release of inflammatory mediators cause synaptic dysfunction and subsequent cognitive decline.[41] Neurodegenerative disease in elderly patients causes further inflammation in the central nervous system despite the pre-existing systemic inflammatory reaction, causing a decline in brain function or delirium.[42] Pro-inflammatory cytokines tumor necrosis factors- $\alpha$ , interleukin-1 family cytokines and chemokines are associated with endothelial damage to the CNS, thrombin formation, microvascular dysfunction, leading to delirium. Cerebral atherosclerosis is recognized as a cause of cognitive decline in old age, and severe white matter hyperintensity identified with MRI resulted in increased incidences of delirium in patients who underwent cardiac surgery.[43,44]

## Diagnosis

High prevalence of delirium (70% of patients) on admission signifies the need for the assessment of the presence of delirium and its severity.[45] According to the 2013 ACCM guidelines, the Confusion Assessment Method (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools.[1,46,47]

The CAM-ICU is designed to assess four features: 1) acute change or fluctuating course of mental status; 2) inattention; 3) altered level of consciousness and 4) disorganized thinking. The manifestation of features 1 and 2 plus either feature 3 or 4 is deemed CAM-ICU positive. Because the CAM-ICU was developed for ICU patients undergoing mechanical ventilation, this assessment tool is not useful for patients who are unable to communicate due to tracheal intubation and deep sedation.[46,48] The CAM-ICU is easy to use and only takes a little time to perform on a patient. Its results show a high sensitivity and specificity of more than 90%, respectively.[49] However, the sensitivity of the CAM-ICU falls when the tool is used for non-critically patients and patients in the postanesthesia care unit. Therefore, caution is required for the assessment.[50,51]

ICDSC can be used for patients who fail to appropriately communicate and assesses 8 features: 1) altered level of consciousness; 2) inattention; 3) disorientation; 4) hallucination or delusion; 5) psychomotor agitation or retardation; 6)

inappropriate mood or speech; 7) sleep/wake cycle disturbance and 8) symptom fluctuation based on DSM criteria. The presence of more than four items is considered delirium positive. The ICDSC shows a sensitivity of 99% and specificity of 64%.[47]

However, the actual use of ICU delirium screening tools appears to be low. A study reported that 53% of total ICU nurses performed delirium assessment.[52] The skill of assessors is an important factor because assessment results showed a low sensitivity when assessors were not properly trained.[53,54] If delirium remains undetected without delirium monitoring, treatment will be delayed, allowing the progression of cognitive impairment. Routine monitoring of delirium should therefore be performed in the ICU, and ICU health providers should be trained to use delirium assessment tools professionally.[55,56]

Electroencephalography (EEG) shows the overall slowing and recovery from delirium after treatment. EEG can detect delirium tremens (alcohol withdrawal syndrome), non convulsive status epilepticus and cerebral lesion using different signals. Once indicators of delirium are identified by a screening tool, consultation with a psychiatrist can be sought to confirm the diagnosis. The first step in treating delirium is to identify underlying cause.

## Treatment

Delirium can be described a disease-induced syndrome. Treatment of the underlying cause is therefore a key to reducing incidence, severity, duration of delirium. Related risk factors can be modified, and adjunctive therapy is provided, if necessary. Because most sedatives, analgesics and hypnotics are likely to be associated with iatrogenic delirium, caution should be exercised when administering these drugs to ICU patients.

Medications are used to increase acetylcholine levels and decrease dopamine levels. Although the effectiveness and safety of antipsychotic agents in treatment of delirium are not fully established, haloperidol and atypical antipsychotics are widely used as standard treatment options in the ICU.

Haloperidol, as a first generation antipsychotic medication, blocks opaminergic D2 receptors and disinhibits

acetylcholine.[57] Haloperidol can be administered intravenously at a dose level ranging from 0.5 to 10 mg, depending on the severity of agitation, medical status of patient and age. Clinical responses are then monitored every 30 minutes before additional dose. When the desired effects are not achieved after the starting dose, the next dose can be doubled. The combination of haloperidol and low-dose lorazepam will provide a rapid onset of sedation, lower total dose and reduce side effects of haloperidol, which include extrapyramidal symptoms, neuroleptic malignant syndrome, dystonia and QT prolongation. Since QT prolongation is a potentially fatal condition, proper monitoring of QT interval on the ECG is needed: A corrected QT interval >500 msec or a greater than 25% increase over baseline is considered dangerous. In such a case, serum K, mg and Ca level should be checked before reducing the dose of haloperidol.[58,59] The fact that all atypical antipsychotics can cause QT prolongation should be heeded.[60]

Atypical or second-generation neuroleptic agents, including risperidone, olanzepine, quetiapine, ziprasidone and aripiprazole, are known to be safe and effective to use in place of haloperidol because these medications have lower affinity for dopaminergic D2 receptors and variable affinities for serotonin, adrenergic and muscarinic receptors and because they reduce the risk of trapyramidal symptoms. Although these medications have fewer and less severe side effects than haloperidol, they can cause QT prolongation, movement disorders, seizures, hyperglycemia and even neuroleptic malignant syndrome in rare cases.[1,61] Neuroleptics tends to be used in a more discreet manner for the treatment of delirium due to its side effects. Because the treatment of underlying causes of delirium is a key component of managing delirium, the use of neuroleptics cannot be enough to eliminate delirium, but it will help reduce symptoms and prevent serious complications.

Anticholinesterase and physostigmine proved to be effective for the management of delirium, but short duration of action and narrow therapeutic window are deemed downsides. Although the effectiveness of donepezil and rivastigmine against delirium has not proven, donepezil was effective for the treatment delirium caused by anticholinergic toxicity.[62] Rivastigmine is not recommended by the 2013 ACCM guidelines for the purpose of reducing the duration of delirium.[1]

Also, droperidol, which was used as dopaminergic antagonist, was withdrawn from the market after black box warning from FDA in 2001 due to potential risk of QT prolongation, Torsade-de-pointes and death. Pheno-thiazine antipsychotics are not suitable for delirium because of their anticholinergic effect and  $\alpha$ -adrenergic blockade.[63]

The 2013 ACCM guidelines recommend light levels of sedation in ICU patients. The use of dexmedetomidine is also recommended for the treatment of delirium except delirium caused by alcohol or benzodiazepine withdrawal because of better outcome, compared with benzodiazepine.[1] Dexmedetomidine was reportedly more effective in reducing the prevalence of delirium than haloperidol and benzodiazepine. However, this medication was not effective for sedation, although the recent studies showed otherwise.[21,27,28,64-66] A study of cardiac surgery on cardiopulmonary bypass reported lower incidences of delirium in patients administered with dexmedetomidine, compared with those administered with remifentanyl as postoperative sedative agent.[67]

## Prevention/Education

High-risk patients and their families can be informed of the risk of delirium in advance to help them deal with symptoms in healthy ways without feeling humiliated when delirium occurs. To sustain a more favorable ICU environment, regular sleep-wake cycle can be maintained along with reduced noise (monitor, alarm, pumps, pagers, etc), and orientation to time is boosted by asking patients the date and day. Displaying the hospital name for easy recognition, arranging more family visits and placing favorite photo or thing at bedside can be also helpful.[68-72] Some studies claimed early mobilization of patients reduced the incidence and duration of delirium, and the 2013 ACCM guidelines advocate the importance of early mobilization.[1,73,74] A study involving non ICU population stated that early mobilization increased synaptic transmission and neurotransmitter release, promoted neurogenesis, improved cognitive function as part of its neuroprotective effect.[75] If restraints are needed, they can be used in combination with sedation medication because the physical restraint itself can cause agitation.[22,76]

The 2013 ACCM guidelines do not recommend the use of

haloperidol and other atypical antipsychotics for the prevention of delirium.[1] However, haloperidol or risperidone effectively reduced the incidence of delirium when they were used as preventive medications, according to the literature.[77-80]

It is suggested that ABCDE bundle approach successfully reduce the occurrence of incident delirium by focusing on awakening and breathing coordination, delirium management, early mobilization in sequence.[81-83]

## Prognosis

Patients who developed delirium in the ICU are characterized by high 6-month mortality rate, longer hospital stay and high cognitive impairment at discharge.[2] Patients who had prolonged delirium showed poor global cognition and executive function scores at 3 and 12 months after discharge.[84] Patients who suffered from delirium had a high risk of neuropsychiatric sequel after discharge and the occurrence of cognitive impairment was twice as high at 2 years, compared with that in patients who did not develop delirium.[85] Patients who suffered from delirium showed greater risks of dementia and long-term cognitive impairment, regardless of the severity and duration of delirium they had.[86] Post-traumatic stress disorder, which is one of common symptoms in ICU patients, was closely associated with delirium.[87] Thus delirium has an adverse impact on post-discharge life of patients,[88] although Wolters et al asserted that ICU delirium was not related with long term mortality or health related quality of life.[89]

## Conclusion

Delirium frequently occurs in the ICU and increases ICU and hospital length of stay, mortality rate and cost of care because it is an acute subset of organic brain dysfunction. However, the management of delirium has been traditionally neglected. To prevent poor clinical outcomes, preventive interventions are vital for treatment planning. Routine daily assessment is needed to detect delirium early, and aggressive treatment is necessary to improve the quality of life for patients after hospital discharge.



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