Importance of recognizing and managing delirium in intensive care unit

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Delirium is an acute and fluctuating change in mental status, with inattention and altered levels of consciousness. It is a common comorbidity in intensive care units (ICU), resulting in delayed withdrawal of mechanical ventilation, prolonged length of stay in ICU, increased ICU mortality and impaired long-term cognitive function of the survivors. Narcotic or psychoactive medication is one of the major risk factors that contribute to ICU delirium. Surveys conducted in several countries indicated that delirium in ICU was inadequately monitored, underdiagnosed and lacked standardized treatment. In order to improve the prevention and treatment of ICU delirium, it is imperative that the ICU professionals should enrich their knowledge about this comorbidity, familiarize themselves with its screening and management, as well as standardize the administration of narcotic and psychoactive medications.

Key words: Intensive care units; Critical care; Delirium

With advances in the diagnostic technologies and life-supporting systems in critical care medicine, an increasing population of severely ill patients has survived in the intensive care units (ICU). Monitoring patients’ organs and systems and supporting or reversing their failure organs are routine tasks of ICU professionals. However, brain is usually less centered than other major organs (e.g. the heart, the lungs, etc.) in ICU. As a form of acute brain dysfunction, delirium has not got extensive attention from physicians, nurses and therapists in ICU until this decade.

Delirium is an acute and fluctuating change in mental status, with inattention and altered levels of consciousness.\(^1,2\) It is a common syndrome that mostly affects geriatric patients or patients with critical illness. Unfortunately, delirium along with critical illness, or ICU delirium, has been grossly under-recognized by ICU clinicians in the past, and has been referred to by various terms in literature, such as “ICU psychosis”, “acute brain dysfunction”, “encephalopathy of critical illness”, and so on. Some practitioners believed that ICU delirium is a transient, non-organic, inconsequential and totally reversible neuropsychological syndrome without any need of specific intervention.\(^3\) In recent years, as objective approaches of detecting delirium have been proposed and validated by a series of investigations, a number of studies indicated that ICU delirium is associated not only with high incidence but also with worse ICU outcome and long-term cognitive impairment.\(^4-13\) Therefore, investigating the pathophysiological process of ICU delirium as well as its preventing and treating strategies may help improve both the ICU outcome and the long-term cognitive function in critical illness.

Epidemiology of ICU delirium

Several epidemiological studies conducted in multiple countries found that delirium develops in 20%-50% of lower-severity ICU patients or those receiving no mechanical ventilation, and 60%-80% of ICU patients with mechanical ventilation.\(^4,9\) Most of time delirium develop unobtrusively in ICU, for it is usually considered as “dementia”, “depression” or even expected as “part of the scenery” in the critically ill patients.\(^14,15\) Many ICU clinicians expect delirium to present with agitation or hallucination, therefore, patients with “hypoactive delirium”, which is characterized with decreased mental and physical activities and inattention, have been severely under-diagnosed.\(^16,17\) Peterson et al\(^18\) had found in a cohort study of 613 ICU patients within one year that among the patients experiencing delirium, pure hyperactive delirium was rare (1.6%), whereas hypoactive
and mixed subtypes of deliria accounted for the vast majority. In China, though no multi-centered epidemiological investigations on ICU delirium are available by now, some studies have reported that approximately 11.8%-16.3% of the geriatric patients developed delirium postoperatively.\(^{18,20}\)

**Pathophysiological mechanisms of ICU delirium**

The brain has its own inflammatory reactions, including production and release of cytokines, cell infiltration and tissue damage in response to systemic infections or other harmful stimulations (hypoxia, cerebral hypo-perfusion, etc).\(^{21,22}\) These inflammatory responses of brain are thought to alter the patterns of local neuronal activities, therefore resulting in delirium. Though the detailed mechanisms and pathways of delirium are still not well understood, experts of neuroscience thought that they are related to the imbalances of neurotransmitters involved in the modulation of cognitive function, behavior and mood.\(^{23-27}\) Dopamine, acetylcholine and γ -aminobutyric acid (GABA) are the three major neurotransmitters considered to be related with delirium. In general, excess of dopamine and depletion of acetylcholine are two main changes of the neurotransmitter system in the development of delirium. In addition, imbalance or dysfunction of other neurotransmitters, such as serotonin, endorphin and noradrenalin, is also reported to induce delirium.\(^{24,27}\)

In a neuroimaging study, Koponen et al\(^{28}\) found significant ventricular enlargement and generalized atrophy in the brain of delirious patients compared with the controls. Suchyta et al\(^{29}\) also reported that among critically ill patients who underwent brain CT scan for altered levels of consciousness, impaired cognitive function or prolonged delirium, 61% had abnormal findings, including atrophy, ventricular enlargement, white matter lesions and cortical/subcortical lesions. These structural changes in the central nervous system may be the pathological ground of the long-term cognitive impairment in the ICU survivors, especially in those with experience of ICU delirium.

**Risk factors for ICU delirium**

Besides traditional risk factors of delirium, including age, previous neurocognitive disorder, comorbidity, severity of illness, sepsis, hypoxia and metabolic derangements, narcotic or psychoactive medication is the predominant and characteristic risk factor in ICU. Inouye et al\(^{30}\) summarized in a review that benzodiazepines, opioids and several psychoactive drugs were associated with a 3-11-fold increase in relative risk of delirium. Marcantonio et al\(^{31}\) found that diazepam and pethidine were closely correlated with ICU delirium. In another study, Pandharipande et al\(^{32}\) concluded that the use of lorazepam was an independent risk factor of ICU delirium. The same group also found that the administration of midazolam was a strong predictor of delirium in surgical and trauma ICU patients.\(^{33}\) In addition, sleep deprivation or loss of circadian rhythm is also thought to be a potential risk factor of ICU delirium, whereas the mechanism involved still needs to be illuminated by further studies.\(^{33}\)

**ICU delirium and prognosis**

ICU delirium is a neither benign nor self-limited disease. In fact, it is associated with a series of adverse outcomes. In two prospective cohort studies on mechanical ventilated patients, Ely et al\(^{10}\) and Lin et al\(^{8}\) found that ICU delirium was an independent predictor of mortality, which inflicted patients a 3-fold increase in the risk of death. Other studies indicated that ICU delirium was also related with an increased risk of reintubation, prolonged length of stay in ICU and hospital, as well as higher medical expenditures.\(^{34-36}\) Delirium risks are thought to be cumulative: each additional day spent with delirium is associated with a 20% increased risk of prolonged length of stay in hospital and a 10% increased risk of death. And 10%-24% of patients with persistent delirium would have long-term cognitive disorders.\(^{4,10,39}\) However, whether ICU delirium is the direct cause of these adverse consequences or merely a clinical manifestation of the real cause is still unknown, which needs to be explored in well-designed and prospective cohort studies in the future.

**Monitoring ICU delirium**

The “2002 guidelines of the Society of Critical Care Medicine (SCCM) for sedation and analgesia” underlined the importance of monitoring the levels of sedation and delirium simultaneously of critical illness.\(^{40}\) In daily practice, ICU physicians and nurses should first assess a patient’s level of consciousness/sedation with specific tools, mainly including Ramsay scale, sedation agitation scale and Richmond agitation sedation scale.\(^{40-42}\) Evaluation of the sedation level would not only avoid over-sedation and help the patients liberate from the ventilators earlier, but also tell the clinicians which
patients should be screened for delirium. All patients (neither in over-sedation nor in coma) who are responsive to verbal stimuli should be assessed for delirium. Currently, there are two major assessment tools for ICU delirium, including the intensive care delirium screening checklist and the confusion assessment method for the ICU (CAM-ICU). The latter has been welcomed by the critical care clinicians and widely used in ICU in these years, for its high sensitivity and specificity (both around 95%), as well as its simplicity, which makes it feasible for non-psychiatric clinicians to perform routine bedside screening.

Preventing and treating strategies of ICU delirium

Firstly, ICU clinicians should have a thorough understanding of delirium and consider it as a severe comorbidity that should be promptly intervened. Several surveys conducted in the western countries indicated that delirium still has not been intensively centered in the daily ICU practice. In 2001, Ely et al questioned 912 ICU physicians, nurses and therapists who were attending critical care meetings or continuing medical education. And they found that 60% of the respondents thought that delirium was common in the ICU (with the incidence >25%), 24% agreed that it was a normal part of ICU hospitalization, and only 29% thought that it could be prevented or partly prevented. Among the 912 surveyed participants, 78% recognized delirium being under-diagnosed in the ICU currently, 40% reported routine screening for delirium, yet only 27% conducted daily screening and 6% reported screening for delirium with specific assessment tools, including the mini mental state examination, the Glasgow coma scale, the sedation scales and the CAM-ICU. Five years later, a paralleled questionnaire was carried out and it found that the ICU clinicians attached significantly more importance to delirium. In this survey, 59% of the respondents reported routine screening for delirium and 20% used specific tools. The significant changes in the ICU professionals’ attitudes and behaviors towards delirium are coincident with the fact that ICU delirium has become a hot spot both in the basic and clinical study of critical care medicine. In addition, another study also reported that only 14% of the Dutch ICU regularly monitored delirium, while half of these ICU used specific assessment tools. In China, a similar survey has been conducted recently in the ICU of two university hospitals and it found that delirium is still severely under-recognized and lacks adequate monitoring and standardized interventions in the Chinese ICU. Of the questioned clinicians in the two hospitals, only 42% and 56% thought that more than 25% of the ICU patients or patients receiving mechanical ventilation experienced delirium, respectively. Fifty-six percent of the respondents agreed that delirium was under-diagnosed, but only 5% had randomly screened patients for delirium. Although 81% of the surveyed clinicians agreed that patients with delirium needed active and prompt interventions, most of them confessed that they had no idea of how to treat this comorbidity, and only 32% mentioned haloperidol or olanzapine. These results indicate a pressing need for the ICU professionals to update their knowledge of delirium and familiarize themselves with theories, guidelines and research advances of delirium, for the prevention and treatment of ICU delirium would not be ultimately improved only after various ignorances, biases and misunderstandings towards delirium are corrected.

Secondly, all potential risk factors that lead to delirium should be minimized in ICU. Sepsis, hypoxia and other situations that have adverse impacts on the brain function should be identified and treated in time. Moreover, objective aims and standardized protocols for sedation and analgesia should be adopted in order to minimize the use of narcotic and psychoactive medications. Also, novel sedatives like dexmedetomidine, a kind of α2-receptor agonist, should be considered as a replacement of the traditional potent GABA-receptor agonists. A recently-conducted randomized, blinded, and multi-centered study showed that patients sedated with dexmedetomidine experienced significantly fewer episodes of delirium compared with those sedated with midazolam, which indicated a promising future of these novel sedatives in ICU. In addition, sleep deprivation should be avoided and plans that can help patients maintain their circadian rhythms should be established.

Thirdly, patients with delirium or high risk of delirium should be promptly intervened. For those at high risks, non-pharmacological approaches are mainly adopted, including helping patients better receive information from the environment via use of eyeglasses and hearing aids, reestablishing their orientation via communication and early mobilization activities, diminishing adverse stimulants via withdrawal of ventilators and removal of various tubes/catheters. For the patients with delirium, pharmacological treatment usually cannot be omitted.
Although haloperidol is the most frequently-used empirical agent in clinical practice, it has not been approved by the United States Food and Drug Administration for treatment of delirium, nor have any other medications. With adverse effects including extrapyramidal symptoms, prolongation of the Q-T interval, torsades de points and neuroleptic malignant syndrome, haloperidol should be administered with great caution in critically ill patients. Olanzapine and other atypical antipsychotics have also been reported for treating delirium, while the extensive use of these agents is still controversial for they may potentially increase death risk.\(^{50,51}\) Therefore, the research and development of new drugs and therapies treating delirium will be central in the near future.

In summary, delirium is a common comorbidity in critically ill patients and is associated with prolonged hospitalization, higher medical expenditures, increased mortality and long-term cognitive impairment of the ICU survivors. It is imperative for ICU professionals to have a thorough understanding of delirium and optimize its monitoring and management, by which, more critically ill patients will survive and have a better quality of life.

**REFERENCES**


