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Delirium in the critically ill: risk factors, diagnosis, management and prevention

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Abstract

Delirium is an acute illness and is a frequent condition in the intensive care unit (ICU) setting. It is characterized by an altered state of consciousness, impaired perception, cognition and attention, alongside with the patients' ability to receive, process, store and recall information. Hallucinations, circadian rhythm and emotional dysregulation might also be present. There are three subtypes of delirium – hyperactive, hypoactive and mixed. Elderly patients and those with many underlying diseases are most at risk for developing delirium. Persistent monitoring for ICU delirium should be performed as early detection and treatment could result in better outcome. Delirium is diagnosed clinically, using diagnostic tools such as Richmond Agitation Sedation Scale (RASS), Confusion Assessment Method (CAM)-ICU or Intensive Care Delirium Screening Checklist (ICDSC). The diagnostic criteria for delirium are described in the DSM-5 classification. While treating delirium, it is important to treat any predisposing conditions or diseases. Typical and atypical antipsychotics, although frequently used to treat this syndrome, are not proven to shorten the duration of delirium, mechanical ventilation or lower mortality rates. Dexmedetomidine is recommended for mechanically ventilated patients who cannot be extubated due to agitation.

Keywords: ICU delirium, delirium in the critically ill, delirium risk factors, delirium management, delirium prevention, CAM-ICU, critical care.

Introduction

Delirium is a quite common condition in the ICU. American Psychiatric Association Diagnostic and statistical manual of mental disorders, fifth edition, defines delirium as an acute disturbance in attention and awareness with changes in cognition and is not explained by a pre-existing neurocognitive disorder and caused by another medical condition [1]. Patients who have a high risk for developing delirium in the ICU include elderly people and those with a history of preexisting dementia, hypertension, alcoholism and a higher APACHE II score [2,3]. ICU delirium could also be associated with long term consequences such as cognitive impairment, dementia [3,4]. It has also been linked to higher mortality rates and longer duration of hospitalization, resulting in higher health care costs [5,6]. The identification, prevention and treatment of delirium is crucial in the intensive care setting as it can improve outcome, therefore a routine assessment using a validated screening tool is necessary [3].

The aim of this review was to evaluate the risk factors, clinical presentation, diagnosis, management, prevention and prognosis of delirium in critically ill patients.

Methodology

Data search was conducted in electronic scientific databases PubMed, ScienceDirect, UpToDate, Wiley etc. using search words included: ICU delirium, delirium in the critically ill, delirium risk factors, delirium outcomes. We reviewed and examined the most relevant sources on this topic.

Risk factors and pathogenesis

In order to improve our understanding of ICU delirium, it is necessary to recognize the most important risk factors. The knowledege of these risk factors could also be of use to the development of prevention strategies. 2018 Society of Critical Care Medicine Pain, Agitation and Delirium guidelines acknowledge a few risk factors that are significantly associated with ICU delirium, including preexisting dementia, history of hypertension, alcoholism and a higher Acute Physiology and Chronic Health Evaluation (APACHE) II score [3]. Strong evidence suggests that age is a risk factor for ICU delirium [2]. Other important risk factors include mechanical ventilation, (poly)trauma, delirium previous day, coma, use of physical restraints [2,7,8]. Some cases indicate that the use of sedatives such as benzodiazepines or propofol could be a risk factor for delirium [7,9] though it is lacking evidence [2]. Environmental factors should also be considered, as lack of daylight, ICU sound level and interruptions could increase the risk of delirium [10].

The pathophysiology of delirium is a complex process and is yet to be understood. There are several hypotheses described, including a focus on neuroinflammation, an aberrant stress response, neurotransmitter imbalances and neuronal network alterations [10]. The most common changes in neurotransmitter systems inlcude deficiencies in acetylcholine and/or melatonin availability, excess in dopamine, norepinephrine and/or glutamate release and variable alterations in serotonin, histamine and/or gamma-amino butyric acid. With aging the activity acetylcholine, melatonin, serotonin, histamine and gamma-amino butyric acid is likely to be decreased. Trauma, surgery and medical illness are associated with acetylcholine, melatonin deficiency, excess in dopamine, norepinephrine and glutamate release. Alcohol, sleep deprivation and infection can also affect these neurotransmitters [4]. The treatment and prevention of delirium is based on targeting these systems. Oxidative stress and a disturbance of circadian integrity may also contribute to the pathogenesis of delirium. It is thought that delirium could not be

explained based solely on one hypothesis and they complement each other [10].

Clinical presentation

Delirium is described as a complex neurocognitive syndrome caused by an organic global brain dysfunction. The prevalence of this syndrome is reported to be up to 50% out of all patients in the ICU [11]. Delirium is a state of disturbed consciousness and has the onset of hours or days. The patients‘ perception, cognition and attention are impaired, alongside with their ability to receive, process, store and recall information. It is important to highlight that these symptoms cannot be attributed to coexisting conditions like dementia, sedation or coma [12]. The severity of delirium is fluctuating and disturbances like disorientation, memory deficit, changes in language or visuospatial ability may appear over time. Other features that may be a part of this syndrome are delusions, dysarthria, dysgraphia, emotional disturbancies (fear, anxiety, anger, apathy, depression, euphoria), abnormal psychomotor activity and sleep-wake cycle disturbancies. The prodromal period is characterized by frequent awakening or difficulty falling asleep, irritability, anxiety and restlessness [11,13]. There are three subtypes of delirium: hyperactive, hypoactive and mixed. A patient with hyperactive delirium will suffer from agitation, anxiety and will make attempts to remove all external devices (drains, catheters, face masks, intravenous lines) [12]. This subtype is also associated with hallucinations and delusions [13]. Hypoactive delirium is diagnosed when a patient is withdrawn, somnolent and has a reduced responsiveness to stimuli. This subtype is often confused with depression or fatigue, however, patients may also experience hallucinations or delusions. The mixed subtype is characterized by fluctuations between hyperactive and hypoactive states [11,12].

Diagnostic criteria and assessment

As there are no laboratory or radiological tests available for the diagnosis of delirium, this syndrome is diagnosed clinically [14]. Ideally, making the diagnosis consists of a clinical interview, collateral history and evaluating the patient’s cognition, which allows to operationalize the DSM-5 diagnostic criteria [11]. The criteria include: a disturbance in attention and awareness, a quick onset and a fluctuating course of illness, an additional disturbance in cognition. The disturbances are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of 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, a substance, a toxin, or is due to multiple etiologies [1]. However, the majority of clinicians find the DSM-5 classification complicated and time-consuming. Therefore, several diagnostic tools are being used in order to allow physicians to diagnose delirium effectively [14].

The first step in diagnosing delirium is assessing the level of consciousness. This can be done using the Richmond Agitation-Sedation Scale (RASS). The score of this scale ranges from -5 (unarousable, has no response to voice or physical stimulation, reacts only to touch) to +4 (aggressive, fights and endangers the staff). If the level of consciousness is deeply altered – RASS score being -5 or -4 – it is recommended to stop monitoring and reassess the score later. When higher levels of consciousness are maintained, the second step of diagnostics can be taken. In this step, the content of consciousness is evaluated using the Confusion Assessment Method

(CAM)-ICU scale, which consists of four features: acute onset of mental status changes or fluctuating course, inattention, altered level of consciousness and disorganized thinking. When the first two features are absent, it is unnecessary to examine the rest [7]. Another monitoring tool for delirium is the Intensive Care Delirium Screening Checklist (ICDSC), which assesses altered level of consciousness, inattention, disorientation, psychosis, altered psychomotor activity, inappropriate speech or mood, sleep disturbances and symptom fluctuation. Both tools can be effectively used by nursing staff, if appropriate training has been provided [15]. Examination for delirium should be conducted every 8-12 hours or when the patients' status changes [12].

Management

The cornerstone in managing delirium is correcting any homeostasis-impairing diseases and medical conditions that may be contributing to the development of delirium. Data on effective pharmacological treatment of delirium is limited as there are no large randomised studies [12,15]. The clinical approach usually consists of typical and atypical antipsychotics, although the evidence of their use is conflicting [15]. Haloperidol has been considered to be the gold standard in treating delirium and is still widely used by many clinicians. However, there is no evidence that haloperidol reduces the duration of delirium in the ICU [3,14]. In the recent years, atypical antipsychotics (such as quetiapine, risperidone and olanzapine) have been used for treating patients who are able to take oral medication [14]. A study on the efficacy of quetiapine has demonstrated a quicker treatment for the first episode of delirium, although it had no effect on the ICU stay and mortality [12]. As there is evidence that suggests that the routine use of haloperidol or atypical antipsychotics is not associated with a shorter duration of delirium, mechanical ventilation or lower mortality rates, it is only recommended to administer these drugs to patients who are experiencing significant anxiety, hallucinations, delusions or agitation [3]. It is important to note that the use of antipsychotics is not recommended in patients who are at risk for *torsades de pointes* [13].

Another drug used for treating delirium is a central receptor alpha-2-adrenoreceptor agonist dexmedetomidine [12]. This drug is recommended for mechanically ventilated patients, when extubation is precluded by agitation [3]. Administering dexmedetomidine is associated with a shorter ICU stay, faster resolution of delirium symptoms and fewer over-sedation episodes, the most common side effect being bradycardia. Although there is evidence that supports the use of dexmedetomidine in the treatment of refractory delirium, further trials are needed to examine its role as a first line therapy [15]. However, if delirium is caused by alcohol withdrawal or benzodiazepine dependence, the usage of benzodiazepines is recommended [12].

Since the diagnosis of delirium includes an altered mental state, a patient is considered cured when CAM-ICU stays negative for 24 hours. Therefore, even if the result is negative during one shift, monitoring the patient should be continued up to 24 hours and further pharmacological treatment must be considered, although the dose might be reduced [12].

Prevention

ICU delirium is associated with increased mortality, prolonged hospitalisation and mechanical ventilation, higher healthcare expenses, worse long-term outcomes [10,12], therefore, prevention of this disease is important and certain measures should be taken. Prevention strategies involve both nonpharmacologic and pharmacologic approaches.

First of all, critically ill patients should be regularly evaluated for delirium using a valid tool, for example, the CAM-ICU scale as it is essential for a prompt initiation of treatment and could therefore result in better outcomes [3]. Secondly, risk factors should be identified and modified, if possible. This includes removing physical restraints at the earliest possible moment, correcting any electrolyte abnormalities, improving sleep hygiene [10]. Sleep hygiene could be improved by minimizing sleep disruptions, providing ear plugs to patients, promoting normal circadian rhythms [15]. Patients in the ICU should have access to natural daylight and family visits [4]. Early mobilization of adult ICU patients has been also demonstrated to reduce ICU delirium [10,15].

Benzodiazepines are often linked to delirium in the ICU, therefore minimizing the use of these agents should be considered. Dexmedetomidine expresses sedative and analgesic effects and could be an acceptable alternative for benzodiazepines [10].

Pharmacologic prevention is often discussed in literature but the data surrounding it is insufficient. The use of antipsychotic agents for delirium prevention is a target for many clinical trials and some get positive results, one example is a study of van den Boogaard et al., where it is suggested that prophylaxis with low dose haloperidol in ICU patients with a high risk for delirium could have beneficial effects [16]. However, the overall data supporting this statement is inadequate and the 2018 Society of Critical Care Medicine Pain, Agitation and Delirium guidelines do not suggest using haloperidol or any atypical antipsychotic agent for delirium prevention [3]. Apart from antipsychotics, many other agents are considered for delirium prophylaxis, such as dexmedetomidine, antiglutamatergic and calcium channel blocking agents (e.g. gabapentin, carbamazepine), ketamine, melatonin, statins, acetylcholinesterase inhibitors [4] but the 2018 Society of Critical Care Medicine Pain, Agitation and Delirium guidelines established that the evidence is insufficient and do not recommend using either of these agents to prevent delirium in all critically ill adults [3]. More detailed and extensive clinical trials must be performed in order to establish the validity of pharmacologic prevention.

Outcomes

ICU delirium is often associated with higher mortality rates as well as an increased length of ICU and hospital stay, longer duration of mechanical ventilation [5,6]. Intubated patients that developed delirium also have a reduced chance of successful extubation and are more likely to develop respiratory and neurologic complications [4,6,8]. Some studies have found that the severity of ICU delirium is positively associated with cognitive impairment at the time of hospital discharge and in most cases the cognitive function is regained by the sixth month after discharge but there are cases that report poor long-term cognitive functioning. Patients who had developed delirium in the ICU were also at a higher risk of dementia [4,17]. Some cases report that ICU delirium could be the cause of posttraumatic stess disorder (PTSD) [4]. The 2018 Society of Critical Care Medicine Pain, Agitation and Delirium guidelines point out that delirium in critically ill adults is strongly associated with cognitive impairment at 3 and 12 months after ICU discharge and longer hospital stay and there is no strong evidence for it to be associated with PTSD or post-ICU distress, ICU length of stay, depression, functionality or mortality [3]. Despite that we must recognize ICU delirium as a serious condition that should be predicted and treated effectively to reduce the risks of any negative outcomes.

Conclusion

ICU delirium is a common condition that could result in negative outcomes. It is essential to learn about this condition, its risk factors and clinical presentation and therefore be able to apply prophylaxis and promptly initiate treatment. Early mobilization, proper sleep hygiene and the removal of physical restraints as early as possible are important nonpharmacologic prevention measures. Pharmacologic prevention is not recommended for all adult ICU patients, however some studies show low-dose haloperidol could be effective in high-risk patients. Dexmedetomidine should be considered as an alternative for benzodiazepines as they could be considered a risk factor for ICU delirium. Dexmedetomidine instead of benzodiazepines should also be used in already delirious patients. Antipsychotic agents are useful in treating hallucinations and agitation, but show no significant reduction in the duration of delirium.

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