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Critical review

ICU Delirium: Is prevention better than cure?

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Abstract

Introduction

Delirium is a form of acute brain dysfunction that commonly develops in the intensive care unit (ICU) setting. Multiple risk factors have been identified but it is often underdiagnosed without the use of standardised assessment tools. Preventing ICU delirium is crucial as it is associated with significant mortality and morbidity. Pharmacological as well as non-pharmacological strategies have shown promise in reducing the risk of ICU delirium whereas there is comparatively less evidence to guide physicians on the management of critically ill patients with established delirium. This review aims to discuss both preventive and treatment strategies for managing ICU delirium and provides a summary on the current evidence.

Conclusion

The emphasis on ICU delirium management should be on prevention and a multi-component strategy encompassing sound sedation practices, early mobilisation and pharmacological therapy in high-risk groups have been shown to be beneficial.

Introduction

Delirium is a form of acute brain dysfunction and is defined according to the DSM IV criteria[1]as having the following 4 features a) disturbance of consciousness b) change in cognition or development of perceptual disturbance not accounted for by pre-existing dementia c) development over a short period of time d) clinical evidence that the disturbance is due to a medical condition, substance intoxication or medication side effect. It can manifest as hyperactive, hypoactive or mixed motoric subtypes[2].

Delirium is common in ICU and has been found to be present in 22% to 81% of critically ill patients depending on the population studied, definition used, frequency of assessmentand duration of observation[3,4,5]. The onset of delirium is usually within 72h of ICU admission[6]and the median duration of delirium ranges from 2 to 3 days[4,5].

However, the duration of delirium can be much longer in certain subgroups of patients. In a group of chronically critically ill patients who had elective tracheostomy performed for weaning failure and admitted to the respiratory care unit (RCU), 14.8% were delirious at admission to ICU even though they had spent a mean of 16days in ICU prior to RCU admission[7]. This group of chronically ventilated patients spent a mean duration 17.9 days in delirium or coma, suggesting that acute brain dysfunction persisted for a much longer period of time in chronically critically ill patients. Delirium is often under-recognised in the 'real world setting' and especially so in patients with hypoactive delirium[8].

The American College of Critical Care Medicine recommends routine monitoring of delirium in ICU using the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Both assessment tools have shown good validity and reliability, and can be used in ventilated or non-ventilated patients[9].

Without the use of standardised assessment tools, ICU physicians were found to miss up to 75% of ICU delirium[10]. Our experience from a national point prevalence study showed that delirium assessment tools were very much under-utilised in ICUs and 72% of the patients did not have any form of delirium assessment performed at all[11].

Multiple risk factors for ICU delirium have been identified and they can be largely grouped according to patient characteristics, chronic medical pathology, acute illness and environmental factors[11]. These include hypertension, alcoholism, smoking, pre-existing dementia, APACHE II score and benzodiazepine use[6,12,13,14,15].

Rompaey also found that isolation of the patient with no visible daylight was a risk factor for delirium[12] although this factor was not found to be significant in another study by Dubois[6]. It is important for critical care physicians to recognize patients with predisposing risk factors and start preventive strategies early (see discussion below) and to minimize aggravating factors.

ICU delirium should not be thought of as an innocuous entity and accepted as a corollary of critical illness as it has significant impact on the morbidity and mortality of ICU patients. Studies have shown that delirious patients had longer duration of mechanical ventilation[3], higher ICU mortality[4] and longer hospital length of stay[5]. They were also more likely to have cognitive impairment when tested at hospital discharge as well as higher mortality at 6 months. The BRAIN-ICU study demonstrated that patients with a longer duration of delirium in ICU had worse cognition scores at 3 and 12 months after discharge and some had cognitive impairment which was as severe as that seen in patients with moderate traumatic brain injury and mild Alzheimer's disease[16]. The effect of delirium is also cumulative with each additional day of delirium associated with a 10% and 20% increase in death and hospital length of stay respectively[5].

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Given the serious repercussions of delirium on critically ill patients, there is impetus for physicians to prevent the onset of delirium as best as possible. At the same time, as there is suggestion that each day of delirium is associated with increased morbidity and mortality, there is also a need to treat and shorten the duration of delirium when it does occur. In this clinical review we will examine strategies for the prevention of, as well as treatment options available for delirium in the critically ill.

We will not be discussing the management of withdrawal delirium from substance dependence in this review.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Preventive strategies

Strategies for the prevention of ICU delirium encompass both pharmacological methods such as sedative agents, use of antipsychotics and other treatment agents, as well as non-pharmacological methods. We will be focusing on each of the above modalities in turn.

Sedative agents

There have been a few observational studies which found a positive association between the use of benzodiazepines (BZD) and the risk of ICU delirium. The question has always been whether BZDs were administered for treatment of delirium or were they the cause of it. Pandharipande studied a cohort of 198 mechanically ventilated patients who were admitted to the medical or coronary ICU. He used a time-dependent multivariable analysis to factor in the temporal relation between BZD use and transitioning to delirium[14].The study showed that lorazepam was an independent risk factor for delirium with a trend towards significance for midazolam as well. The same author also studied a group of surgical and trauma patients using the same statistical method and found midazolam to be an independent risk factor for developing delirium. Lorazepam was not found to be a risk factor but the number of patients on lorazepam was small in this study[15].

In contrast to the above-mentioned, other observational studies failed to find similar association between BZD use and delirium[6,13]. More recently, an interesting study looked at the use of midazolam, cytochrome P450 inhibitors, blood brain barrier transporter inhibitors (P-gp), and inflammatory cytokines like IL-6[17]. The study demonstrated that the use of midazolam was not associated with increased incidence or duration of delirium, although it was a risk factor for coma.

However, the use of P-gp inhibitors and an increase in inflammatory cytokine IL-6 were risk factors. This suggests that the reported link between BZD and delirium may be confounded by pharmacokinetic interactions with other co-administered drugs as well as the inflammatory state of the patient affecting the blood brain barrier permeability.

A few randomized controlled trials have compared the use of BZD versus non-BZD sedation (Table 1). The MENDS trial[18] randomized 106 mechanically ventilated medical and surgical ICU patients to lorazepam or dexmedetomidine for up to 120 hours.

The dexmedetomidine group had more days alive without delirium or coma. However this difference was largely due to the dexmedetomidine group having more coma-free days. There was no significant difference between the 2 groups in terms of delirium-free days.

The dexmedetomidine group also had greater percentage of time spent at target sedation level although more open-label sedation boluses were required to achieve deeper levels of sedation targets. There were no differences in 28 day mortality or ventilator-free days. In the SEDCOM trial[19] 375 mechanically ventilated medical and surgical ICU patients received midazolam or dexmedetomidine.

The dexmedetomidine group had less delirium and shorter duration of mechanical ventilation but also required more open-label midazolam boluses.

Other studies have looked at the use of dexmedetomidine as compared to other sedatives. In a pilot study by Ruokonen[20], 85 patients were sedated with midazolam, propofol or dexmedetomidine.

There were no differences between the 3 groups in proportion of CAM-ICU positive patients. The MIDEX and PRODEX trials[21] randomized patients to dexmedetomidine versus midazolam or propofol respectively. One of the secondary end-points was the rate of neurocognitive adverse events which included agitation, anxiety and delirium.

Patients in the propofol, but not the midazolam group had more neurocognitive adverse events compared to the dexmedetomidine group. The dexmedetomidine group also needed less concomitant treatment for agitation, anxiety and delirium. Shehabi[22] compared dexmedetomidine to morphine in a group of elderly post cardiac surgery patients and found that there was no difference in the incidence of delirium between the 2 groups. However in the subgroup of patients requiring intra-aortic balloon pump the use of dexmedetomidine resulted in less delirium. Patients who were on dexmedetomidine also had a shorter duration of delirium and earlier time to extubation.

One meta-analysis evaluating the use of BZD versus non-BZD sedation looked at 6 randomised studies of which 3

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incorporated daily delirium assessment[23].

The authors concluded that the data on delirium prevalence was insufficient to draw definitive conclusions although it appeared that the use of non-BZD sedation was associated with a shorter length of ICU stay and mechanical ventilation. Another meta-analysis looked specifically at dexmedetomidine as a sedative and analgesic agent[24], including a total of 24 trials with 2419 patients. Dexmedetomidine was not found to be associated with a reduction in the risk of delirium but there was significant heterogeneity in the studies and the various studies reported risk of delirium differently and not all studies had mandatory daily sedation breaks.

It appears that there are conflicting observations regarding the risk of BZD use and delirium. Other factors like pharmacokinetics and drug-drug interactions will probably need to be considered before attributing delirium solely to BZD use. The use of non-BZD sedation such as dexmedetomidine may lead to less risk of over sedation with resultant shorter duration of ICU stay but studies so far have not conclusively demonstrated superiority of one sedative agent over another in terms of reducing the risk of ICU delirium per se.

Antipsychotics for delirium prevention

The use of antipsychotics as delirium prophylaxis appears to be beneficial in certain patient groups. 457 elderly patients who underwent non-cardiac surgery were allocated to low dose intravenous haloperidol or placebo for 12 hours post surgery[25]. Most of the patients had intra-abdominal surgery. The study found the incidence of delirium within the first 7 days after surgery to be reduced in the haloperidol group compared to placebo group. The haloperidol group also had longer delirium-free days and shorter ICU stay.

There was no increase in adverse effects in the intervention group. Another randomised controlled study also found reduced incidence of delirium in a group of post cardiac surgery patients given risperidone[26].

One before/after study of a delirium prevention project looked at a mixed group of ICU patients comprising medical, surgical, trauma and neurology/neurosurgical patients[27]. All ICU patients were screened for delirium risk using the PREdiction DELIRium Intensive Care score (PREDELIRIC). Those with high risk for delirium (PREDELIRIC score >50%), diagnosis of dementia or alcohol abuse received prophylacticintravenous haloperidol during the intervention period. The intervention group had lower incidence of delirium, more delirium-free days and lower 28d mortality.

The recently published HOPE-ICU trial[28] randomized 142 patients in the general adult ICU to intravenous haloperidol or placebo irrespective of coma and delirium status at admission. The study found that haloperidol did not reduce duration of delirium-free days. None in the haloperidol group had any severe adverse events. The use of prophylactic haloperidol for delirium prevention has been shown to be safe and it is possible that its efficacy may be more obvious in select subgroups of patients with a higher risk of delirium or specific precipitating factors e.g. post-surgery allowing targeted delirium prevention therapy rather than a general group of critically ill patients who may need control of other risk factors as well for delirium prevention.

Other pharmacological therapies

Neuro-inflammation has been hypothesized to be one of the factors responsible for the development of delirium.

A recent prospective cohort study[29] on a population of medical and ICU patients who were already on statins prior to ICU admission, found a reduction in risk of delirium in patients who were continued on statins compared to those in whom statins were not restarted at all in ICU. This association was postulated to be due to the anti-inflammatory effect of statins as the statin group also had a lower CRP level.

ABCDE bundle

The Awake and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility (ABCDE) bundle has been shown to improve delirium outcomes. Kress demonstrated for the first time that daily sedation interruptions improved ICU outcomes in terms of shorter duration of mechanical ventilation and ICU length of stay although this study did not examine the impact on ICU delirium[30]. The ABC trial[31] showed that daily awakening trials coupled with daily spontaneous breathing reduced the duration of mechanical ventilation, ICU length of stay and improved neurological outcomes in shortening the duration of coma. Of the assessable patients there was no difference in incidence of delirium between the intervention and control group. However the more recent SLEAP study suggested that when a protocolised sedation practice targeting light sedation was in place, daily sedation interruption did not improve ICU outcomes, including delirium outcomes and may instead increase nursing workload[32].

Table 1: Summary of RCT comparing BZD vs non BZD sedation.

Study	Findings
MENDS[18]	Lorazepam vs dexmedetomidine Lorazepam group had fewer days alive without delirium/coma
SEDCOM[19]	Midazolam vs demedetomidine Midazolam group had more delirium and longer duration of mechanical ventilation
MIDEX[20]	Midazolam vs dexmedetomidine No difference in neurocognitive adverse effects (agitation, anxiety, delirium) between both groups

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Critical review

An innovative study which looked at a protocol of no sedation but emphasized instead on analgesia first, found improved outcomes in terms of ventilator-free days, ICU and hospital length of stay in the intervention group receiving no sedation[33]. The control group in this study was found to have less hyperactive delirium but the authors acknowledged that this could be contributed by under-recognition of other motoric forms of delirium in sedated patients using the DSM-IV criteria for screening.

Early physical and occupational therapy in ICU has been shown to not only to shorten the duration of mechanical ventilation, but also decreased the duration of delirium and improved functional status[34].

Combining components of the above trials, Balas carried out a prospective before/after study on the ABCDE bundle[35].There was no difference in the dose of sedatives and opiates received in the intervention and control period.

However patients in the intervention period had a lower risk of developing delirium as well as a reduction in duration of delirium.

It seems that protocolised sedation practices with emphasis on addressing analgesia first and minimizing sedation, coupled with early mobilisation and physical therapy in ICUcan be implemented in the practical real-world setting to help improve delirium as well as other ICU outcomes.

Sleep, reorientation and multi-component therapy

Sleep deprivation and delirium share many clinical similarities. Sleep deprivation has also been shown to affect areas of the brain that are also involved in patients with delirium[36].

One study demonstrated the possible link between sleep deprivation and delirium[37]. Patients with more sleep cycle interruptions were more likely to have mental state changes.

A before/after quality improvement study was performed, incorporating interventions to improve the quality of sleep in ICU[38].

Sleep disruptions were minimized and efforts were made to promote normal circadian rhythms and night time sleep with non-pharmacological and finally pharmacological aids if needed. Patients in the intervention period had lower delirium/coma incidence and longer delirium/coma-freeperiod.

Apart from improving sleep in ICU, a frequent reorientation strategy was shown to reduce the risk of developing delirium in ICU[39]. This study was a before/after study and during the intervention period patients were orientated to their surroundings, the time and their names, as well as given environmental, acoustic and visual stimulation. These strategies reduced the risk of delirium by almost 50%.

Inouye demonstrated that a multicomponent intervention was effective in reducing the incidence of delirium in a group of elderly hospitalized patients[40]. Patients with intermediate to high risk of delirium were identified using a predictive model developed by the same author[41].

The patients in the intervention group received targeted interventions for 6 delirium risk factors: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration. Incidence of delirium in the intervention group was 9.9% compared to 15% in the control group. The intervention group also had a shorter duration of delirium. Although this study was performed in the non-ICU setting, the interventions proposed are highly applicable to critically ill patients as well and it would be worthwhile to examine the use of similar multi-component therapy in the ICU.

Treatment strategies

First and foremost, management of a delirious patient would include treatment of the underlying medical illness e.g. sepsis and correction of identifiable metabolic derangements. In addition to these supportive measures, pharmacological therapy may be considered to reduce the duration and severity of delirium.

There are comparatively fewer studies looking at specific pharmacologic treatment for critically ill patients in whom delirium is already established. Most of these studies were on the use of antipsychotics. Haloperidol use in a group of elderly hip surgery patients was found to reduce the severity and duration of delirium, although the study population was not strictly ICU patients[42]. Girard randomized 103 medical and surgical patients on mechanical ventilation with abnormal conscious level or receiving sedative/analgesic medication to haloperidol, ziprasidone or placebo[43].

About 50% of the study population had delirium at enrolment. The use of haloperidol and ziprasidone did not increase the number of delirium-free days in this study. However it did show that the use of antipsychotics in ICU was relatively safe with no increase adverse events e.g. extrapyramidal side effect or QT abnormalities. In another study, 73 patients with delirium in ICU were randomized to haloperidol or olanzapine[44].

There was no placebo group. Both groups showed similar decrease in severity of delirium and the authors concluded that olanzapine was a safe alternative to haloperidol, although without a placebo group it was difficult to ascertain the actual efficacy of antipsychotic use on delirium severity.

In a small pilot study, Devlin enrolled 36 patients with established delirium (ISDSC ≥4) to quetiapine or placebo[45].

Both groups were allowed to have as needed intravenous haloperidol. The quetiapine group had shorter time to resolution of delirium (median of 1 day versus 4.5 days) and also a shorter amount of time spent in delirium (36h versus 120h). There was a trend towards smaller amounts of haloperidol required in the quetiapine group although it was not statistically significant.

There are suggestions that delirium was associated with impaired cholinergic neurotransmission. This led to the postulation that a cholinesterase inhibitor such as rivastigmine, would

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Critical review

potentially reduce the duration of delirium. A multicentre trial randomized critically ill patients with established delirium to rivastigmine or placebo[46]. The study was terminated prior to full enrolment due to increased mortality in the rivastigmine group. The intervention group also had a longer duration of delirium although this did not reach statistical significance. In light of the trial result, rivastigmine is not recommended for treatment of delirium in critically ill patients.

Conclusion

The emphasis on delirium management in ICU should be on prevention rather than cure. Thus far, there is little conclusive evidence of available effective pharmacological treatmentto reduce the duration and severity of delirium. A multi-component strategy (Figure 1) which encompasses sound sedation practices, early physical therapy and cognitive engagement appears to be effective in preventing delirium.

In addition, identification of patients at higher risk for developing delirium and instituting prophylactic antipsychotic agents may be beneficial although further studies will be needed to further confirm this observation.

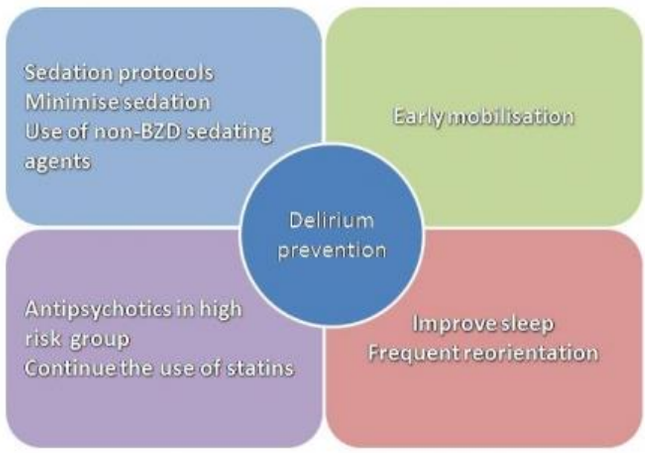

Figure 1: Strategies for delirium prevention.

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