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Delirium in intensive care: an under-diagnosed reality

Delirium na unidade de cuidados intensivos: uma realidade subdiagnosticada

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ABSTRACT

Delirium occurs in up to 80% of patients admitted to intensive care units. Although under-diagnosed, delirium is associated with a significant increase in morbidity and mortality in critical patients. Here, we review the main

risk factors, clinical manifestations and preventative and therapeutic approaches (pharmacological and non-pharmacological) for this illness.

Keywords: Delirium; Intensive Care; Sleep; Central nervous system; Antipsychotics agents

INTRODUCTION

Delirium can be defined as an acute cerebral dysfunction characterized by transient and fluctuating alterations in the state of consciousness, accompanied by cognitive impairment. Delirium frequently affects patients admitted to intensive care units (ICUs). The diagnostic criteria for delirium are multidimensional and vary according to source. According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR),⁽¹⁾ which continues to be the gold standard in the diagnosis of delirium, the criteria are the following: (1) disturbance of consciousness (for example, reduced awareness of the environment), with a decrease in the ability to direct, focus, maintain or shift attention; (2) impaired cognition (such as memory deficiency, disorientation or speech perturbation) or development of perception perturbation, which is not well explained by established or developing dementia; (3) the disorder develops over a short period of time (usually hours or days) and as a fluctuating course during the day; and (4) there is evidence from the medical history, physical exams or laboratory findings that the disturbance is due to direct physiological causes originating from a general medical condition. According to DSM-IV-TR, all of these criteria must be present to diagnose delirium. These criteria have been used for the last 10 years, but it is important to remember that the manual will be revised and that the new version (DSM-V) should be published in May 2013. Some key points of this review are the substitution of the term “consciousness” with “awareness”; the inclusion of visual-spatial and executive function impairment as key symptoms of delirium; the duration of the delirium will

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be considered last; and criteria to be added to evaluate the intensity of the delirium. The replacement of the term “consciousness” with “awareness” is important because it allows one to better distinguish delirium from minor and major neurocognitive alterations, as “consciousness” is too nebulous to define the symptoms of delirium and “awareness” better captures the essence of this disturbance.⁽²⁾ With this set of alterations, the primary symptoms of delirium, their characteristics and their subtypes can be described in a more precise manner.

Additionally, DSM-V must include the classification of subsyndromal delirium.

Diagnosed in this manner, delirium is the most common form of acute cerebral dysfunction in the ICU and affects up to 80% of the patients.^(3,4) However, delirium is frequently undervalued and unrecognized, similar to many other cerebral dysfunctions.

The prevalence obtained in multicenter studies varies between 32.3% and 77%, and the incidence can vary between 45% and 87%. These rates depend on the composition of the study group and the scale used for the evaluation^(5,6) (Table 1).

Every year, a growing number of patients are admitted to ICUs and survive the causative critical disease. However, these patients present with acute

and chronic morbidities in the cognitive, functional and emotional domains, which results in a decrease in the global quality of life.^(12,13)

Delirium is also an independent predictor of complications and prognosis, e.g., self-extubation, removal of catheters, prolonged hospitalization,⁽⁷⁾ increased hospital costs,⁽¹⁴⁾ mortality at 6 months and 1 year^(8,15) and long-term cognitive impairment.⁽¹⁶⁻¹⁸⁾

Due to these factors, the interest, investigation and knowledge about this syndrome have grown progressively in recent years.^(19,20)

Classification

The classification of delirium can be subdivided by course over time and motor subtypes. The terminology, according to the course over time, includes a) prevalent (if it is detected at the time of admission); b) incident (if it emerges during the hospital length of stay); and c) persistent (if the symptoms persist over time).⁽¹⁹⁾

Pisani et al.⁽²¹⁾ reported a persistence of delirium of up to 10 days after diagnosis in the ICU, but studies outside the context of the ICU show that symptoms can persist up to 1 month.⁽²²⁻²⁴⁾

The symptoms of delirium can be grouped as either cognitive or behavioral, with broad interpersonal variability. For this reason, some patients

Table 1 - Comparison between different studies on the prevalence of delirium in intensive care units

Author	Local	Type of ICU	Scale used	Prevalence (%)	Length of stay (days)* (D versus ND)		Mortality (%) (D versus ND)
					ICU	Hospital	
Salluh et al. ⁽⁵⁾	North and South America (11 countries); Spain	104 UCI (DECCA Study)	CAM-ICU	32.2	22 (11-40) versus 7 (4-18) (p<0.0001)	-	20 versus 5.7 (p=0.002) - ICU 24 versus 8.3 (p=0.0017) - Hospital
Dubois et al. ⁽⁷⁾	Montreal, Canada	Medical-surgical	ICDSC	19	9.3±12 versus 7±7.9 (p=0.14)	-	15 versus 13.6 (p=0.82) - ICU
Ely et al. ⁽⁸⁾	Tennessee, United States	Medical and coronary	CAM-ICU	87	7 (4-15.5) versus 5 (2-7) (p=0.009)	21 (12-25) versus 11 (7-14) (p<0.001)	34 versus 15 (p=0.008) Mortality at 6 months
Quimet et al. ⁽⁹⁾	Montreal, Canada	Medical-surgical	ICDSC	35.2	10.8±11.3 versus 2.5±2.1 (p<0.0001)	36.4±28.9 versus 31.6±46.5 (p=0.0001)	15.9 versus 2.4 (p<0.0001) - ICU 41.6 versus 20.8 (p<0.0001) - Hospital
Quimet et al. ⁽¹⁰⁾	Montreal, Canada	Medical-surgical	ICDSC	31.8	11.5±11.5 versus 4.4±3.9 (p≤0.005)	18.2±15.7 versus 13.2±19 (p≤0.005)	20 versus 10 (p<0.005) - ICU 31 versus 24 (p<0.005) - Hospital
van den Boogaard et al. ⁽¹¹⁾	Nijmegen, Low Countries	Polyvalent	CAM-ICU	26	6 (2-13) versus 1 (1-2) (p<0.0001)	20 (10-20) versus 7 (5-14) (p<0.0001)	18 versus 3 (p<0.0001) - Hospital

D - delirium; ND - no delirium; ICU - intensive care unit; * 95% confidence interval.

predominantly manifest psychomotor slowing or even coma, and some present as anxious, disruptive or combative.

The terminology according to motor subtypes includes a) hyperactive delirium (in which there is an increase in the psychomotor activity and agitation, with attempts to remove invasive devices); b) hypoactive delirium (characterized by psychomotor slowing, apathy, lethargy and a decrease in response to external stimuli); and c) mixed delirium (with unpredictable fluctuation of symptoms between the first two subtypes).^(25,26)

Additional definitions are described, which include subsyndromal delirium and delirium superimposed on dementia.

In subsyndromal delirium, patients have one or more of the symptoms, but this does not lead to a clinical diagnosis of delirium according to the criteria of the DSM-IV-TR. This subtype is mainly described outside the context of the ICU, but Ouimet et al. (2007) defined its presence, using the *Intensive Care Delirium Screening Checklist* (ICDSC), in a population from an ICU. The ICDSC assigns a score from 0 to 8 points, with a score ≥ 4 indicating the presence of delirium and a score between 1 and 3 considered subsyndromal delirium. According to these criteria, 33.3% of the patients in the sample studied showed this subtype of delirium. This group of patients had worse prognosis than those without any form of delirium. More specifically, the presence of subsyndromal delirium, compared to the absence of delirium, showed a significant association with time spent in the ICU and in the hospital, as well as a greater dependence after discharge. A statistically significant effect related to mortality was not observed after adjusting for age, APACHE II score or sedation. Therefore, the presence of subsyndromal delirium could be a marker of the seriousness of the illness and not an independent risk factor in this population.⁽¹⁰⁾

Delirium superimposed on dementia is defined as an acute alteration in mental state (fluctuating course, inattention, disorganized thought or alteration of the state of awareness) in a patient with a diagnosis of dementia. This definition is obvious but raises some interpretation and diagnosis issues, which explains the large variability in the reported prevalence and reflects the risk of aggravating delirium when neuroleptic drugs are administered.⁽²⁷⁾

Risk factors

The attention paid to delirium in the intensive care environment is recent, and therefore, data are still scarce. These patients present many risk factors, which must be taken into consideration for a multifactor approach.

Although they do not have a strong association or definitive causality, many risk factors have been described for the development of delirium, especially from populations outside of the ICU, and they can be divided into a) preexisting condition of the patient; b) acute condition of the patient; and c) iatrogenic or environmental factors^(2,28) (Table 2).

Table 2 - Risk factors for delirium

Preexisting conditions
Age >70 years
Transfer from a nursing home
Visual or hearing impairment
History of depression, dementia, cardiac insufficiency, stroke, epilepsy
Renal or liver disease
HIV infection
Alcohol abuse in previous month
Use of psychotropic drugs (anticholinergics, benzodiazepines, opiates)
Malnutrition
Acute conditions
Higher severity of illness score
Illicit drug use
Metabolic alterations (glycemia, natremia, thyroid dysfunction)
Hypothermia or fever
Sepsis
Hypoxemia
Urea:creatinine ratio >18
Iatrogenic/environmental factors
Medications: anticholinergics, sedatives, analgesics
Physical restriction
Tube feeding
Urinary or rectal catheter
Central venous catheters

In general, these risk factors can be divided into non-modifiable and modifiable. Considering the potential for intervention, the focus must be on the group of modifiable risk factors, especially in patients at high risk for the development of delirium. The typical environment of an ICU represents a risk factor in and of itself, due to the absence of natural

illumination, the absence of clocks, perturbation of the patterns of sleep and wakefulness and the isolation of the patient.

Delirium is common in the state of systemic inflammation. C-reactive protein (CRP) has been widely used to evaluate the degree of inflammation. An association between the level of serum CRP and delirium has been demonstrated in various studies.^(29,30)

Tsuruta et al.⁽³¹⁾ demonstrated that mechanical ventilation, the maximum value of CRP and ICU length of stay are independent factors for the development of delirium.

Despite the identification of all of these risk factors, the underlying mechanism of delirium is not entirely clear. This knowledge would substantially contribute to the care of the critical patient, through preventive interventions and specific treatments.

Impact and consequences

Delirium has short- and long-term consequences, including emotional consequences. Ringdal et al.⁽³²⁾ observed that during hospitalization in the ICU, delirium was associated with delusional memories; Roberts et al.⁽³³⁾ reported that ICU patients with delirium had less factual recall than the group without delirium. However, the emotional impact of delirium is not easy to evaluate. Other clinical consequences, namely those related to mortality, ICU length of stay, hospital length of stay, number of days of mechanical ventilation and incidence of complications related to delirium, are measurable and have been studied extensively. These results are more relevant because they are directly related to the use of limited resources in ICUs.

Zhang et al.,⁽³⁴⁾ in a 2012 meta-analysis, compared 16 studies involving 6,410 patients. The results analyzed in the studies were time in the ICU and in the hospital, destination after discharge, duration of mechanical ventilation, mortality, complications and functional capacity. It was observed that delirium was associated with a higher rate of mortality, longer ICU stay (average difference of 7.32 days), longer hospital stay (average difference of 6.53 days), a greater time on mechanical ventilation (average difference of 7.22 days) and a higher probability to be transferred to a support unit after discharge.

van den Boogaard et al.⁽¹¹⁾ studied the short-term consequences of delirium, including an analysis of each subtype of delirium. One-fourth of the study sample with a time of hospitalization >1 day and half of the patients with hospitalization >2 days developed delirium. This group had a greater probability of developing short-term complications and a six-fold greater probability of dying, independent of the seriousness of the disease. The mixed subtype was the most common (53%), followed by hypoactive (36%) and hyperactive (11%). Short-term complications, defined by days of mechanical ventilation, rate of reintubation, accidental removal of tubes and catheters, time in the ICU and time in the hospital, were more frequent in the group of patients with delirium, with the highest rate being observed in the patients with the mixed subtype.

Survivors of the ICU have long-term cognitive consequences.⁽²⁰⁾ The duration of delirium during hospitalization in the ICU is independently associated with cognitive impairment after adjustment for various covariables.⁽³⁵⁾ A questionnaire regarding quality of life was sent to a sample of 1,291 survivors 18 months after ICU discharge. Despite the lack of statistical significance in the quality of life between patients who presented delirium and those who did not, a more pronounced cognitive impairment was found in the first group after adjustment for covariables.⁽³⁶⁾ The neurocognitive impairment in delirious ICU patients is heterogeneous and frequently involves memory, executive function and attention. This problem also affects the family and the caregivers, as it compromises the capacity of the survivor to return to work, reduces their quality of life and increases medical costs.⁽³⁷⁾

These data are important to clinical practice because they highlight the need to take preventative measures. The high incidence of delirium and the serious associated complications should be sufficient to alert healthcare professionals to the need for regular evaluation of delirium in ICU patients.

van den Boogaard et al.⁽³⁸⁾ developed the first predictive model of delirium in ICU patients, known as PRE-DELIRIC (PREdiction of DELIRium in ICU patients). This model predicts the development of delirium during the entire ICU stay, based on 10 risk factors (age, APACHE-II score, coma, admission

category, infection, metabolic acidosis, morphine dose, sedation, urea, urgent admission) in the first 24 hours of admission. The patients are classified according to risk: low risk 0-20%; moderate risk >20 to 40%; high risk >40 to 60%; and very high risk >60%. The stratification of risk in these patients permits the implementation of preventative measures in high-risk or very high-risk patients and the use of available resources in an efficient manner. However, the low-risk classification does not exclude the possibility of developing delirium, especially when dealing with a static model rather than a dynamic model. The development of a dynamic model, using parameters of the Sequential Organ Failure Assessment (SOFA), could improve its predictive value, especially in the low-risk group.

Importance of monitoring

It is important to monitor delirium because it is frequently under-diagnosed (3 to 66% of the cases of delirium are not diagnosed)⁽³⁹⁾ and has important prognostic implications for the patient. Given the high prevalence of delirium in the intensive care environment, current guidelines recommend the daily evaluation of delirium and a multidisciplinary approach.⁽⁴⁰⁾

The monitoring of delirium during hospitalization in the ICU is important not only as an indicator of organ dysfunction but also for the prevention of accidental injuries. Thus, delirium monitoring promotes reduction of adverse effects and allows implementation of preventative and therapeutic measures to provide adequate rehabilitation and potentially diminish losses related to quality of life.⁽⁴¹⁾

The capacity to evaluate delirium in a precise manner is a key component of any systematic strategy adopted to prevent or treat it. Importantly, despite evidence that a multifactor intervention reduces the duration of delirium, the hospitalization time and mortality, no scientific evidence indicates that a systematic evaluation of delirium alone improves the results.⁽⁴²⁾

Thus, delirium poses an important question with respect to the safety of the critical patient. The reduction of the incidence of delirium in the ICU must be considered an indicator of quality and a target to be pursued, representing an improvement in the process of providing care to the patient.

Various tools to evaluate delirium have been validated for use in environments outside of the ICU. However, a number of characteristics of the intensive care population restrict the use of these tools, including the difficulty of participation and verbal communication of intubated patients, the reduced or fluctuating level of awareness that impedes response to complex questions, clinical instability and the frequent lack of availability of psychiatric professionals. For these reasons, the scale used in this environment must a) have the capacity to evaluate the primary components of delirium (for example, awareness, inattention, disorganized thought and fluctuation course); b) must have proven validity and reliability in ICU populations; c) must involve a fast and easy evaluation; and d) should not necessitate the presence of psychiatric professionals.⁽⁴³⁾

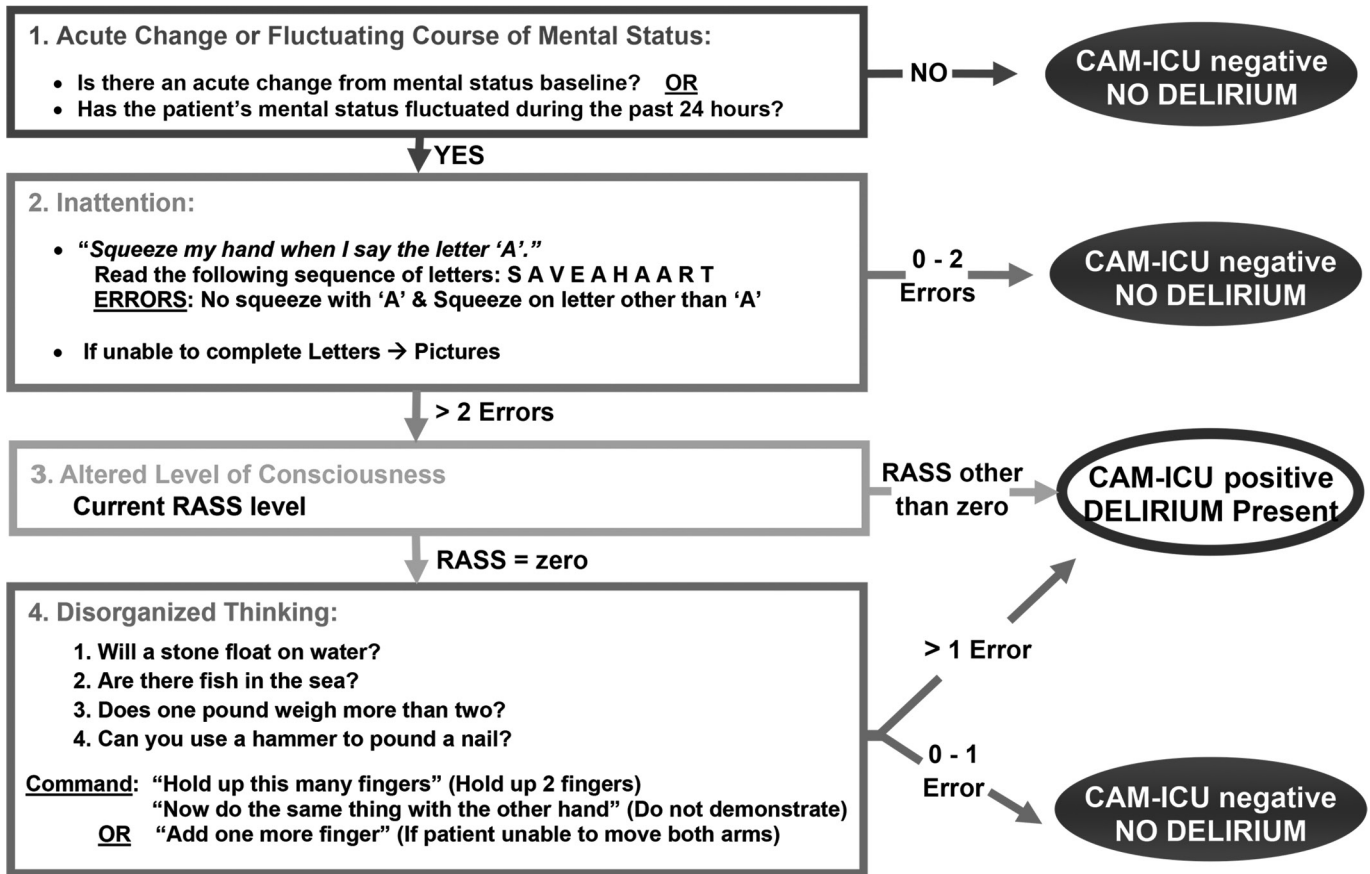
The tools validated for evaluation of delirium in an intensive care environment are the Confusion Assessment Method-ICU (CAM-ICU)⁽⁵⁾ (Figure 1) and ICDSC.⁽⁴⁾ Both scales were translated to Portuguese (Brazil) by Salluh and Dal-Pizzol and validated by Gusmao-Flores et al.⁽⁴⁴⁾

The Richmond Agitation- Sedation Scale (RASS), which integrates the CAM-ICU evaluation, also has a validated Portuguese version.⁽⁴⁵⁾ The Portuguese and English versions of CAM-ICU are available at http://www.mc.vanderbilt.edu/icudelirium/docs/CAM_ICU_flowsheet_Portugese_B.pdf and http://www.mc.vanderbilt.edu/icudelirium/docs/CAM_ICU_flowsheet.pdf, respectively; but the Portuguese version of ICDSC has not been published (Figure 1 and Table 3).

Plaschke et al.⁽⁴⁶⁾ compared CAM-ICU with ICDSC and found good agreement between the two tools.

Neto et al. conducted a systematic review and meta-analysis to evaluate the precision of the tools for screening delirium in critical patients. Sixteen studies published between 1966 and 2011 were included. It was found that sensitivity to evaluation of delirium is greater in ICDSC (80.1%) than CAM-ICU (75.5%). In contrast, CAM-ICU had greater specificity (95.8% versus 74.6%). The authors detected high heterogeneity, which could be explained by the type of patients (neurological versus non-neurological) and by context (routine evaluation versus in-depth investigation).⁽⁴⁷⁾

Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet



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Figure 1 - Method of evaluating mental confusion in the ICU (Confusion Assessment in the ICU - CAM-ICU). Available at: http://www.mc.vanderbilt.edu/icudelirium/docs/CAM_ICU_flowsheet.pdf. ICU - intensive care unit.

Table 3 - Richmond Agitation-Sedation Scale

Points	Term	Description
+ 4	Combative	Overtly combative, violent, immediate danger to staff
+ 3	Very agitated	Pulls or removes tube(s) or catheter(s); verbally aggressive
+ 2	Agitated	Frequent non-purposeful movements; fights ventilator
+ 1	Restless	Anxious, but movements are not aggressive or vigorous
0	Alert and calm	
- 1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
- 2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
- 3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
- 4	Intense sedation	No response to voice, but movement or eye opening to physical stimulation
- 5	Does not wake	No response to verbal or physical stimulation

Translated by Nassar Junior AP, Pires Neto RC, de Figueiredo WB, Park M. Validity, reliability and applicability of Portuguese versions of sedation-agitation scales among critically ill patients. Sao Paulo Med J. 2008;126(4):215-9.⁽⁴⁵⁾

In pediatric patients, Smith et al. demonstrated that the Pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU) has validity and reliability in

terms of identifying delirium in children when compared to the DSM-IV criteria employed by psychiatrists (sensitivity of 83% and specificity of 99%).⁽⁴⁸⁾

Is the implementation of a delirium screening tool in an ICU practicable and sustainable? A number of studies including more than 2,000 patients confirm that it is. However, it is important to emphasize that the sustainability of this screening in clinical practice for 3 years was possible because it was accompanied by education strategies (didactic and at the patient bedside) for health care professionals, frequent reminders, quality evaluations and the participation of a multidisciplinary team that valued the role of the evaluation of delirium in daily clinical decisions.⁽³⁰⁾

The evidence demonstrates that only when the screening of delirium is integrated into a well-defined protocol with strategies of action are clinical and economic benefits observed.^(49,50)

Prevention

Prevention involves understanding the predisposing and precipitating risk factors and is considered to be the most effective form of reducing the incidence of delirium. Many risk factors are modifiable by relatively easy and inexpensive interventions, such as sedation-limiting benzodiazepines, early mobilization, correction of hydroelectrolytic disturbances, prevention of hypoxia, early suspension of mechanical ventilation and removal of invasive devices. These interventions, although they reduce the risk of delirium, are not widely used in ICUs around the world.⁽⁵¹⁾

In this context, a new concept emerges: “liberation and animation.” The pillars of this approach are comfort and control of pain, the use of the least amount of sedation as possible, proactive strategies of weaning off of mechanical ventilation and the early initiation of occupational therapy. A proposed implementation of this approach is labeled “ABCDE” and consists of **A**wakening and **B**reathing coordination of daily sedation and ventilator removal trials; **C**hoice of analgesic and, if needed, sedatives; **D**elirium monitoring and management; **E**arly mobility and exercise.⁽⁵²⁾

Scientific evidence supporting these measures was provided by Schweickert et al., who demonstrated that early exercise and mobilization, through daily physical and occupational therapy, reduce the duration of delirium (median of 2 days versus 4 days in patients who did not undergo such exercise and mobilization).⁽⁵³⁾

With regard to sedation and analgesia, the use of drugs associated with the development of delirium, such

as benzodiazepines (midazolam and lorazepam), must be avoided, in favor of drugs that are associated with a reduction of the prevalence of delirium, such as α_2 -agonists (for example, dexmedetomidine). Various randomized, controlled clinical trials have compared sedation approaches that used benzodiazepines or propofol with those that used dexmedetomidine. In the MENDS study by Pandharipande et al.,⁽⁵⁴⁾ dexmedetomidine was compared to lorazepam. The group of patients treated with dexmedetomidine had more days free of delirium (7 versus 3). When they compared various subgroups, the patients with sepsis had a 70% reduction of daily risk of delirium.⁽⁵⁵⁾ Riker et al.⁽⁵⁶⁾ observed a reduction of the prevalence of delirium in a group sedated with dexmedetomidine compared to the group on midazolam (54% versus 76.6%). Strom et al. compared two groups: sedation with daily waking (propofol and a morphine bolus, with daily interruption of sedation) versus only analgesia without sedation (morphine bolus). In the intervention group, decreased mechanical ventilation time was observed during the stay in the ICU and in the hospital. However, hyperactive delirium was greater in patients who only received morphine (20% versus 7%). Additionally, that study did not use any of the scales validated for the ICU, and it did not identify patients with mixed or hypoactive delirium, which are the more common forms in the ICU.⁽⁵⁷⁾

The study by Mehta et al., which compared two sedation protocols, one with daily interruption of sedation and another without daily interruption, in patients on mechanical ventilation did not show a difference in the rate of delirium between the groups (53.3% versus 54.1%).⁽⁵⁸⁾

This approach of sedation and analgesia is integrated in the concept of “conscious sedation target”,⁽⁵⁹⁾ in which the patients must be kept awake whenever possible, even during the critical phases of the illness. However, this strategy has not been widely adopted due to potential risks of removing invasive devices and because healthcare professionals are concerned about the discomfort of the patients and the potential increase in the workload.⁽⁶⁰⁾

The application of “ABCDE” is associated with a shorter mechanical ventilation time, shorter hospitalization time, lesser duration and incidence of delirium, reduction of cognitive impairment and

increase in survival.⁽⁵²⁾

Inouye et al.⁽⁶¹⁾ indicated other factors that can be targets of intervention. They used a sample of patients hospitalized outside of the ICU, which allows us to infer similar results in ICU patients. The interventions that they performed included correcting dehydration and electrolytic disturbances, non-pharmacological measures against sleep deprivation, early mobilization and use of eyeglasses and auditory devices.

Sleep deprivation is a potentially modifiable risk factor. Patients admitted into the ICU have a propensity for a reduced sleep quality, with fragmentation and other sleep disturbances. In healthy people, sleep deprivation causes inattention, fluctuation in mental capacity and cognitive dysfunction, characteristics that are also present in patients with delirium. The ICU environment has abundant and strong risk factors for delirium and sleep disturbances, including medications such as benzodiazepines and propofol that impair slow-wave and rapid eye movement sleep, leading to serious sleep fragmentation. The relationship between sleep deprivation and delirium has been studied for many years, leading to the identification of an association between them, but it has not been possible to establish a clear cause-effect relationship.⁽⁶²⁾

In relation to environmental factors, some strategies have been proposed to prevent delirium in the ICU, such as the reduction of noise, minimizing exposure to artificial light at night, optimization of the ambient temperature, improvement of communication techniques with patients, limitation of social isolation and restriction of mobility.⁽⁶³⁾

Efforts at pharmacological prevention of delirium in ICUs have not yet shown conclusive results. With the development of the previously described PRE-DELIRIC predictive model, the early identification of patients at risk for development of delirium permits the application of preventive measures in these patients. For the high-risk group, this predictive model facilitates specific pharmacological interventions, although the evidence for the benefit of these measures is not strong.

In 2012, Reade et al. conducted a randomized, double-blind trial that studied the effect of intravenous haloperidol on the prevention of delirium in patients admitted into the ICU after non-cardiac surgery. Haloperidol leads to a reduction in the incidence

of delirium in the first 7 days after surgery (15.3% versus 23.2%) and a reduction in ICU length of stay (21.3 hours versus 23 hours). Patients administered haloperidol had lower mortality at 28 days, although this effect lacked statistical significance.⁽⁶⁴⁾

In 2013, van den Boogaard et al. implemented a policy of prevention of delirium in high-risk patients according to the PRE-DELIRIC model and evaluated their impact on the consequences of delirium. Patients with a predicted risk $\geq 50\%$ and with a history of alcohol abuse or dementia were identified and medicated with haloperidol (1 mg iv q8h), according to the designed prophylactic protocol. Prophylaxis with haloperidol resulted in a reduction in the incidence of delirium (65% versus 75%) and an increase in the number of days free of delirium (median of 20 days versus 13 days) in the intervention group compared to the control group. After Cox regression analysis using the presence of sepsis as a covariable, a 20% reduction in relative mortality at 28 days was obtained. The patients in the intervention group had a lower probability of removing tubes and catheters and of being readmitted to the ICU. However, significant differences were not observed in the duration of mechanical ventilation, ICU length of stay, hospital length of stay or incidence of reintubation. Even though this study suggested that the prophylactic treatment of delirium with a low dose of haloperidol had beneficial effects, confirmation of the results is necessary with a randomized, controlled clinical trial.⁽⁶⁵⁾

A randomized, controlled, double-blind clinical trial is underway [Preventing ICU Subsyndromal Delirium Conversion to Delirium With Low Dose IV Haloperidol: A Double-Blind, Placebo-Controlled Pilot Study (ClinicalTrials.gov Identifier:NCT01174290)] with the goal of determining whether haloperidol (1 mg iv q6h) administered to patients with subsyndromal delirium (ICDSC 1-3) prevents the development of clinical delirium (ICDSC ≥ 4).

Treatment

Non-pharmacological measures are important in both the prevention and treatment of delirium and must be strongly encouraged.

In relation to pharmacological measures, haloperidol (a first-generation antipsychotic) has been widely

used in recent years to treat delirium. However, as described in the 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit, there is no published evidence that haloperidol reduces the duration of delirium in adult patients in the ICU. Some studies have sought to clarify the role of atypical antipsychotics in the treatment of delirium. A meta-analysis from 2009 (*The Cochrane Library*)⁽⁶⁶⁾ compared only the results from two studies: one examined the effects on delirium of risperidone versus haloperidol⁽⁶⁷⁾ and the other olanzapine versus haloperidol.⁽⁶⁸⁾ Neither risperidone nor olanzapine had significantly different effects on delirium compared to haloperidol, nor were there differences in the adverse effects of the low dose of haloperidol relative to the atypical antipsychotics studied. In two placebo-controlled studies,^(68,69) patients who received haloperidol or olanzapine showed significant improvement in the scales of delirium.

Another atypical, second-generation antipsychotic studied in the treatment of delirium is quetiapine. Devlin et al. compared quetiapine against a placebo in a double-blind, randomized clinical trial with a sample of 36 patients. These patients were randomized into two branches of pharmacological treatment: quetiapine 50 mg bid versus placebo. All of the patients could receive haloperidol in SOS. In the patients treated with quetiapine, the time until resolution of delirium was less than 3.5 days versus 4.5 days for the placebo group; the need for haloperidol in SOS (3 versus 4 days) and the duration of agitation (6 versus 36 hours) were also lower. The difference in the mortality and complications (QT-long, extrapyramidal symptoms) was not statistically significant.⁽⁷⁰⁾

Along with the above-cited recommendations, it must be emphasized that for the patients with delirium not related to alcoholic abstinence or benzodiazepines, dexmedetomidine must be administered as a sedative, instead of benzodiazepines, to reduce the duration of delirium in these patients.

The scientific evidence in this area is limited, especially because it involves studies with small samples. For this reason, better-designed clinical trials with fewer limitations are needed to define the best first-line treatment for delirium.

CONCLUSIONS

Delirium is common in patients admitted to the ICU, is frequently under-diagnosed and influences the prognosis. The first step to change this paradigm is to seek, evaluate and identify the causes of delirium in the ICU. It is necessary to implement a protocol of systematic evaluation of the presence of delirium, using a scale validated for use in the ICU (CAM-ICU or ICDS-C), with well-defined intervention objectives.

To prevent is better than to treat. For this reason, it is important to identify the risk factors, especially modifiable risk factors, as well as the groups of patients at greater risk of delirium. Prevention consists mainly of non-pharmacological measures, integrating the ABCDE approach without forgetting the unfavorable environment inherent to the ICU and interventions that are inexpensive and easy to perform. Among these non-pharmacological measures, early mobilization has a predominant role and is supported by growing scientific evidence that it helps prevent delirium in the ICU. Sedation with dexmedetomidine instead of benzodiazepines is also associated with a reduction in the prevalence of delirium. In relation to pharmacological prevention, there appears to be a benefit to haloperidol at a low dose, but the scientific evidence is still insufficient for that recommendation to be definitive. The treatment of delirium must be considered a medical emergency. The drug of choice continues to be haloperidol, but some studies suggest that the atypical antipsychotics could play a beneficial role.

Neurological monitoring requires teamwork and awareness on the part of the healthcare professionals of the importance of this subject, whether in daily clinical practice or regarding the long-term impact on patients in intensive care units.

RESUMO

Entidade frequente em medicina intensiva, ocorrendo em até 80% dos doentes internados na unidade de cuidados intensivos, embora muito subdiagnosticado, o *delirium* está associado a aumento significativo da morbidade e da mortalidade no

doente crítico. No presente artigo, foram revistos os principais fatores de risco, manifestações clínicas e abordagens preventivas e terapêuticas (farmacológicas e não farmacológicas) nessa doença.

Descritores: Delírio; Cuidados intensivos; Sono; Sistema nervoso central; Antipsicóticos

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