REVIEW ARTICLE

Risk Factors, Pathophysiology, and Management of ICU Delirium: A Literature Review

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Abstract

Background: Delirium is an acute change in mental status with an unpredictable course of diminished attention and incoherent thinking, which is common among ICU patients. Various evidence implies a correlation between delirium and many fatal outcomes in intensive care unit (ICU) patients, such as higher 6-month mortality rate, longer hospital stays, longer post-ICU hospital stays, a higher occurrence of cognitive impairment, and long-term cognitive impairment after a critical illness.

Aim: To identify the risk factors, pathophysiology, and management of ICU delirium among critically ill patients.

Method: Using literature review, this study thoroughly examined the results of studies from different journals investigating ICU delirium.

Findings: The identified risk factors were age, cigarette smoking, alcohol abuse, steroids, sedatives, total number of medications, sodium level, hypoalbuminemia, hypertension, sepsis, chronic renal failure, trauma, immobility, and pain. Moreover, underlying mechanisms in the development of ICU delirium were cholinergic deficiency, neuropathologic lesion, direct brain insults, aberrant stress re-

الملخص

الخلفية: الهذيان هوالتغيرالحاد في الحالة العقلية مع وجود حالة لا يمكن التنؤ بها من تضاءل في الاهتمام والتفكير السليم،وهوأمرشائع بين المرضى في العنايات المركزة. هنالك أدلة متعددة لوجود علاقة بين الهذيان والعديد من النتائج القاتلة لمرضى وحدة العناية المركزة مثل ارتفاع معدل الوفيات خلال ٦ أشهر، والبقاء في المستشفى لفترات طويلة، والبقاء في المستشفى لفترة طويلة بعد فترة وحدة العناية المركزة ،وحدوث ضعف متزايد للإدراك المعرفي وضعف طويل المدى للإدراك المعرفي.

الهدف: تحديد عوامل الخطر، والفيزيولوجيا المرضية، والعناية بالمرضى الذين يصابون بالهذيانفي وحدة العناية المركزة.

الطريقة: مراجعة أدبية لنتائج الدراسات العلمية المحكمة من مجلاتمختلفةتناقش موضوع الهذيان في العنايات المركزة.

النتائج: تمثلت عوامل الخطرللإصابة بالهذيان في: السن والتدخين،وتعاطي الكحول ،والمنشطات والمهدئات،استعمال بعض الأدوية ، ومستوى الصوديوم في الدم،ونقص ألبومين الدم،وارتفاع ضغط الدم ،وتعفن الدم ،والفشل الكلوي المزمن ،والصدمات النفسية ،وعدم القدرة على الحركة ، والألم. وعلاوة على ذلك كانت الآليات الكامنة في تطوير الهذيان في وحدة العناية المركزة متمثلة في نقص الكولينيوالباثولوجيا العصبية، والضغط النفسي. وهنالك العديد من الطرق الفعالة لعلاج الهذيان سوا

sponse and inflammatory process, and alteration of plasma melatonin. Numerous effective non-pharmacologic and pharmacologic treatments are available to manage delirium.

Conclusion: Delirium is a form of acute brain dysfunction that is not well-recognized inICU. The identification of the risk factors and the possible underlying mechanisms for the development of delirium continues to be the first step in its management; then, the next step is often pharmacologic and non-pharmacologic treatments. The choice of these treatments should be understood as part of a greater multicomponent approach inmanagementof critically ill patients.

Keywords: ICU delirium, Risk factors, Pathophysiology, Pharmacologic treatments, Non-pharmacologic treatments

دوائية او غيردوائية.

الخلاصة: الهذيان في وحدة العناية المركزة يعتبر شكل من أشكال الخلل الوظيفي في الدماغ والذي لم يتم التعرف عليه بشكل جيد في وحدة العناية المركزة. يعتبر التعرف على عوامل الخطروالأسباب المحتملة الخطوة الأولى في العلاج. والخطوة التالية هي في العلاجات الدوائية وغيرالدوائية. وينبغي أن يكون مفهوم أأن اختيارهذه العلاجات يعتبر جزء من طريقة مرضى العنايات المركزة.

1. INTRODUCTION

Delirium is a critical change in mental status with an unpredictable course of diminished attention and incoherent thinking [1], which is common in patients such as the elderly, those who abuse alcohol, and patients in intensive care unit (ICU) [2]. It is remarkable that the incidence of delirium in the ICU varies vastly throughout study populations and institutions, ranging from 20% to 40% [3-6]. One reason for the disparity in incidence rates in different setting is that delirium often disregarded, since it is anticipated to occur in patients with severe illness, and medical resources are favorably devoted to managing the life-threatening problems [7]. In addition, an identified limitation of studies which evaluated the incidence rates of delirium in ICU is that the screening instruments [3,8], and only quite a few studies that the diagnosis was confirmed by a psychiatrist [9].

طرق

In comparison to other end-organ injuries, delirium is considered an organ failure of the brain [10]. Evidence implies delirium is substantially related to different harmful outcomes in ICU patients. Some of these adverse effects include: higher 6-month mortality rate, longer hospital stays, longer post-ICU hospital stays, a higher occurrence of cognitive impairment [11], and long-term cognitive impairment after a critical illness [12].

Despite of its significant impact on patients, the mechanisms that explain the occurrence of delirium in critically ill patients are not completely understood[13]. Some hypothesized

mechanisms comprise neurotransmitters, inflammation, physiological stressors, metabolic imbalances, and electrolyte disorders [14]. On the other hand, even though many studies have examined the risk factors for delirium, results are diverging forseveral commonly studied factors include intake of alcohol, smoking, age, hypertension, and mechanical ventilation [13]. Knowledge of the risk factors, pathophysiology, and management of delirium would permit early detection of ICU patients with a high possibility of developing delirium and would be beneficial for effective prevention and development of intervention strategies. Therefore, the aim of this study was to identify the risk factors, pathophysiology, and management of ICU delirium among critically ill patients by thoroughly examining theresults of studies from different journals.

2. METHOD

There were many electronic sources available utilized by the author such as ProQuest and Science Direct between 2001 and 2015 to ascertain potentially pertinent articles. The search was carried out using the following keywords: ICU delirium,risk factors, pathophysiology, pharmacologic management, and nursing management. The reference lists of all related articles were manually inspected to identify additional studies significant to the review. The citations were delimited to those published in English language. Studies were included if they met the following inclusion criteria: (1) minimum of one risk factor associated with ICU delirium, (2) used a validated delirium assessment tool, (3) minimum of one pathophysiology associated with ICU delirium, (4) pharmacologic management of ICU delirium, and (5) nursing management of ICU delirium. Studies were eliminated if they were conducted in a non-ICU setting andthe full text is not available.

The following data were extracted from each study: first author's last name, publication year, purpose, study design, sample size, method, key findings, and study limitations. This article provides significant information regarding risk factors, pathophysiology, and management of ICU delirium among critically ill patients.

3. FINDINGS

3.1 SEARCH RESULTS AND STUDY CHARACTERISTICS

The initial literature search retrieved 4010 citations, and 3893 were excluded on the basis of the title and/or abstract because they were duplicates and other irrelevant articles. Full text of the remaining 117 articles were considered for detailed evaluation. Forty-two articles were subsequently excluded from this review: 57 were not conducted in ICU setting, 29 reported another irrelevant risk factor(s), 15 studies have no full-text available, 11 did not specify the study setting, and 5 did not involve pharmacologic management. Thus, 28 articles were included in the final analysis.

The characteristics of the 28 studies are summarized in table 1-3. All the researches were conducted in an ICU setting. The number of

studies for each design were as follows: Seven studies for prospective cohort design [2, 6, 15-19]; five studies for prospective observational design [7, 8, 20-22], two descriptive correlational [23, 24]; two randomized controlled trial [25, 26]; one retrospective cohort [27], one focused review [10], one literature review [28]; one exploratory and case series[29]; one exploratory[30]; one prospective pre- or post-intervention cohort study [31]; one case study [32]; one prospective, pre-post protocol implementation evaluation [33];one prospective before and after quality improvement project [34]; one quasi-experimental [35];one comparative study [36]; and one prospective, double-blind, randomized trial [37]. The sample size of each study ranged from 5 to 4,450 patients. All the studies included for risk factors and management used a validated delirium assessment tool.

3.2 DEFINITION

Over the past years, the researchers and clinicians used 30 or more synonyms for labelingintensive care unit (ICU) delirium, and these are 'ICU psychosis', 'acute confusion' and 'ICU syndrome' [38, 39]. The introduction of the Diagnostic and StatisticalManual of Mental Disorders, third edition (DSM-III) in 1980 and consequently the fourth revised edition (DSM-IV-R) conveyed consistency to the terms defining delirium. Delirium is defined as a disruption of consciousness and an alteration in cognition that progresses over a short period of time and tends to fluctuate during the day [38-40].Attention is the most affected under the cognitive domain [40, 41]. Presently, delirium is considered as a disease with a variety of severity rather than a binary phenomenon. Subsyndromal delirium has been described as patients with one or more symptoms that never advance to meet full DSM-IV-R delirium diagnosis [9].

3.3 RISK FACTORS

Table 1 summarizes the identified risk factors of ICU delirium. Several risk factors suggested that contribute to the development of ICU delirium include age, lifestyle, medications, laboratory chemistry abnormalities, medical history, immobility and pain.

Age

Age is one of the greatest risk factors for the incidence of delirium in ICU patients [42]. This association was confirmed by some studies [6, 7, 10, 15, 16]. It is noteworthy that Sharma and colleagues [6] found the mean age of their whole sample was 45 years old, which was similar to the findings of Agarwal and co-researchers [43]. However, a substantially greater percentage of elderly patients (>65 years old) experienced delirium if compared to younger patients [6], which corroborates that prevalence and incidence of delirium are higher in the elderly, and old age is one of the main predisposing risk factors for delirium [15, 42, 44].

Lifestyle

Cigarettes contain toxic agents that induce atherosclerotic and microvascular transformations, which form gradually with time and persist even years after quitting [45]. These significant changes are associated with cognitive deterioration and dementia, most especially among older smokers [46] which intensifies the risk of developing delirium [46]. These findings were confirmed by several studies [2, 6, 10, 15, 16, 18,47]. It is noteworthy that smokers have a three-fold higher risk of delirium than nonsmokers [45].

Additionally, alcohol abuse is believed to be another common factor correlated with delirium [2], supported by different studies [2, 10, 15, 18].

Medications

Steroid medications [12] sedative medications [12, 9, 10], insulin, and multiple prescribed medications [12] are identified risk factors for delirium related to drug use.

Studies claim the use of steroids can lead to various psychiatric symptoms like psychosis, depression, mania and cognitive disturbances. Consequently, the development of cognitive disorders and psychosis and the development of delirium may have a similar mechanism [12].

Another identified serious risk factor for the development of delirium among ICU patients is the use of sedatives [12] — also responsible for the longer ICU stays [12]. Specifically, Simons and his co-researchers [9] claim the use of midazolam and propofol were individually correlated with a heightened risk of delirium, which was enhanced when a combination of midazolam and propofol was prescribed. On the other hand, benzodiazepines also were seen to be linked with delirium within diverse ICU populations, and have shown a dose-dependent correlation [18].

Moreover, the intake of multiple medications was also an essential factor for the development of delirium. This finding implies that clinicians should administer medications carefully in ICU patients [12].

Laboratory chemistry abnormalities

It is remarkable that certain laboratory chemistry results were identified as significantly associated with the development of delirium. Some of these laboratory results were hyperuricemia, hypoalbuminemia, deranged ALT, acidosis [6] elevated sodium levels, and elevated bilirubin levels[2].

An abnormal level of sodium has been associated with encephalopathy which may initiate the development of delirium. Certain drugs and heart failure are the common causes of unprecedented levels of sodium. On the other hand, the irregularity in bilirubin has a recognized relationship with hepatic dysfunction and delirium [2].

Hypoalbuminemia causes a decline in the osmotic force which fails to sustain a sufficient amount of intravascular volume. In turn, this

could diminish brain perfusion which makes the patient vulnerable to delirium [1].

Medical history

One review article identifies studies that discuss the neuropsychological effects of chronic hypertension where hypertensive patients show poor performance on memory, attention and abstract reasoning when compared to normotensives [2]. Further, when hypertensive patients are subjected to significant physical or psychological stresses in the ICU, they may be more susceptible to developing delirium [2]. Specifically, vascular problems brought about by hypertension places patients at a greater risk for cerebral hypoperfusion and possibly for cerebral hypoxia, which is significantly related to the development of delirium [48].

Notably, sepsis increased the risk of developing delirium which is consistent with the findings of previous studies [49]. Sepsis causes acute brain dysfunction and delirium by the stimulation of inflammatory cytokine and endothelial damage, which aggregates the permeability of the blood-brain barrier initiating damage to the capillary blood flow [50].

Encephalopathy is common among patients with renal failure possibly caused by uremia, thiamine deficiency, dialysis, hypertension, fluid and electrolyte imbalances or drug toxicity [51]. Encephalopathy exhibits complex symptoms which advance from mild sensorial clouding to delirium and coma [51]. This is supported by a study conducted by Pipanmekaporn and colleagues [16] wherein they found that chronic renal failure increased the risk of delirium.

Also, delirium has been acknowledged as a severe and frequent clinical problem in trauma victims [52, 53], evident in some studies [9, 54, 55]. Moreover, Naidech and colleagues [56] found that after focal neurologic injury among the patients in their study, delirium symptoms were present and considered to be a cause of successive poorer functional outcomes.

Immobility and pain

ICU delirium and neuromuscular function have been hypothesized to be strongly interconnected [57]. Observational and clinical trial data indicate that one of the risk factors for delirium among ICU patients is immobility [57-59].

On the other hand, several studies reported that untreated pain is a risk factor for the development of delirium [33, 60]. Specifically, Pisani and co-researchers [61] claim that pain within 24 hours of ICU discharge among their patients had a significant relationship with persistent delirium.

3.4 PATHOPHYSIOLOGY

Numerous hypotheses have been posited to explain the underlying pathophysiology of ICU delirium. Table 2 summarizes the underlying mechanisms of pathophysiology of ICU delirium which include:

Cholinergic deficiency

The origin of the cholinergic deficiency hypothesis came from observations that delirium occurred with the intake of drugs that injure cholinergic function [28]. Specifically, there was a strong correlation between the proliferation of serum anticholinergic activity (SAA) levels and the development of delirium, while the reduction in the level of SAA was related to the resolution of delirium. Moreover, a possible mechanism for cholinergic insufficiency includes the damage of presynaptic, synaptic or postsynaptic functions of acetylcholine [28] which could lead to hallucinations and cognitive inadequacies [62].

Monoamine activity stabilizes the cholinergic system where the dysfunction has also been connected with delirium. Particularly, dopamine, norepinephrine, and serotonin have functions in arousal and the sleep-wake cycle which facilitates physiological responses to stimuli. Extreme levels of dopamine may cause hyperactive delirium which has been related to a concurrent decline in acetylcholine. Thus, acetylcholine and dopamine may have an inverse relationship in the pathogenesis of delirium [28].

Serotonin has a direct and indirect relationship to the cholinergic deficiency hypothesis. Specifically, excess levels of serotonin have been observed in concurrence with reduced levels of acetylcholine [28]; thus, it may be associated with cholinergic deficiency [63]. On the other hand, norepinephrine has a vital role in regulating attention, anxiety, and mood; like dopamine, an overload in the noradrenergic activity has been linked with hyperactive delirium [64].

Neuropathologic lesion

A study by Janz and colleagues [29] claim diminished cerebral blood flow, cerebral hypoxia, and cerebrovascular disease may contribute to the development of delirium in ICU patients. They conducted brain autopsies and found that 86% exhibited hypoperfusion and gross and microscopic cerebrovascular disease. Specifically, in most of the autopsied brains, hippocampal lesions were the only specific neuroanatomical structures that were impaired [29]. This damage of the hippocampus postulates a neuroanatomical explanation for long-term cognitive impairment because its normal function is to transfer information into long-term memory [4].

Direct brain insults

Direct brain insults include acute processes that impair brain function by initiating energy deficiency, metabolic abnormalities, trauma, hemorrhage, or direct alterations in neurotransmitter levels by drugs. In patients with delirium, severe brain dysfunction was distinct in multiple regions which were triggered by hypoxemia and systemic hypoglycemia. This could lead to deficiencies in attention and cognition which meet the criteria for delirium [30].

Brain injury markers identified include serum brain-derived neurotrophic factor (BDNF) and

neuron-specific enolase (NSE) [65], which were substantially increased in ICU patients with delirium [24]. It is remarkable that every 2-fold increase in plasma NSE concentration was accompanied by a 5.2% increased risk of delirium [66]. This finding corroborates that neuronal damage arises in the pre-ICU setting or soon after admission, which is a secondary factorin patients who experienced delirium later during an ICU stay. It is more likely that serum BDNF and NSE levels may indicate predisposition to early development of delirium among critically ill patients [24].

Aberrant stress response and inflammatory process

Acute stress is well-known to affect attention, cognition, motivation, mood, perception, and other facets of mental function [67]. Similarly, systemic inflammation brings fatigue, diminished activity, anhedonia, and diminished appetite [30], adaptive mechanisms of the body. However, dysfunction of the stress response and intensified inflammatory states are common with aging and neurodegeneration [68]. It is evident that prior pathology and systemic problems such as stress, infection, injury, and surgery repeatedly act together to induce delirium [30].

Prolactin is a stress hormone comparable to cortisol that can disturb behavioral or cognitive function and also participates in the regulation of the immune system further than sexual reproductive and lactogenesis properties [69]. It is notable that hyperprolactinemia has repeatedly been reported in neuropsychiatric disorders, including schizophrenia, bipolar disorder, and altered mood [70]. A study conducted by Nguyen and colleagues [20] claimed patients with delirium had elevated prolactin levels. Prolactin affects behavior or cognitive function by acting on the brain limbic system and the prefrontal cortex [69]. An elevated prolactin level stimulates brain dopamine hyperactivity which could bring cognitive dysfunction or delirium [71]. Further, prolactin augments sleep deprivation, which is one of the contributing factors for ICU delirium [72].

In critical illness, systemic inflammation and disrupted coagulation are vital factors in the development and persistence of delirium [73]. Girard and co-investigators [12] found three plasma markers of inflammation and coagulation such as metalloproteinase-9 (MMP- 9), soluble tumor necrosis factor receptor-1 (sTNFR1), and protein C are correlated with delirium in the ICU. These results validate the hypothesis that inflammation and disrupted coagulation are essential mechanisms of delirium during critical illness.

On the other hand, tryptophan and tyrosine, amino acid precursors for neurotransmitters, are linked to the development of delirium in patients [74]. A potential mechanism for tryptophan-related delirium is through the release of neurotoxic metabolites which form after activation of the immune and inflammatory response systems seen in critical illness [74]. A high tryptophan concentration may lead to high production of melatonin, thereby

initiating the somnolent symptoms of hypoactive delirium; while a low tryptophan ratio could be responsible for a decline in melatonin, sleep dysregulation, and the development of hyperactive delirium [75]. On the other hand, patients with elevated levels of tyrosine are more likely to have a dopamine overload or its downstream neurotransmitter, norepinephrine, both of which have been connected to the pathogenesis of delirium [76].

Alteration of plasma melatonin

Melatonin is a hormone originated from the pineal gland whose concentration reportedly diminishes during the postoperative period [77]. A declining level of melatonin may be a sign of the severity of illness [21] which can be a precipitating risk factor for postoperative delirium [78]. Further, less amount of melatonin concentration might also be a sign of the aging process [21], which is most repeatedly cited as one of the predisposing factors for postoperative delirium [78]. Also, diminished melatonin secretion in the postoperative period may initiate sleep disturbances and subsequent interruption of the sleep-wake cycle, which in turn can promote the development of delirium [79].

3.5 MANAGEMENT

Similar to the multiple hypotheses and risk factors suggested to explain the pathophysiology and contributing factors of ICU delirium, several nonpharmacologic and pharmacologic treatments have been examined in critically ill patients with delirium. Haloperidol isthe identified drug of choice useful in the majority of patients; however, due to its recognized adverse effects, there are continuous clinical trials to seek more drug options to treat delirium. However, in addition to the pharmacologic regimen, there are nonpharmacologic treatments to help reduce the adverse effects of delirium. Available treatments published in articles between 2009 and 2017 are discussed in Table 3.

3.5.1 Nonpharmacologic treatments

Prevention and management of delirium are fundamental to the reduction of its adverse effects [25]. Various nonpharmacologic strategies have been recommended in the ICU, including: standard nonpharmacologic prevention, plus early and intensive occupational therapy (OT) [25]; sleep enhancement and relaxation protocols [31]; electroconvulsive therapy (ECT) ([32]; pain assessment on day 2 of ICU stay [19]; Music, Opening/closing of blinds, Reorientation/cognitive stimulation, and Eye/ear care (M.O.R.E.) [33]; multidisciplinary team focused on the reduction of heavy sedation and the increase of staffing in the ICU [34]; and sleep care guidelines for noise and light reduction [35].

Occupational therapy

Alvarez and co-researchers [25]initiated a standard nPP plus early and intensive OT beginning in the first 24 hours of admission of patients to the ICU. This intervention was delivered twice a day, 40 minutes each session, one in the morning and one in the evening for

five consecutive days. OT intervention had a positive impact evidenced when patients had notably fewer hours of delirium when matched with the control group that used proven interventions in hospitalized elderly patients.

Further, patients who received the intervention had a significantly lower risk of developing delirium, significantly lower incidence of delirium, and higher independence level. Upon discharge, the enhanced functionality of patients influences the recovery process as well as reduces the use of resources in the long term and prevents rehospitalization [80].

Sleep enhancement and relaxation

Sleep enhancement and relaxation protocols were proposed to promote sleep and eradicate factors that restrict the normal sleep-wake cycle. At night, nursing assistants were prohibited from regular bathing of patients. Lights and televisions were turned off, and monitors and machinery were put to night mode. Light therapy lamps were turned on during daytime hours. Twice a day, afternoons and evenings, patients were programmed to have 90-minute periods of quiet time where compact disc players were made accessible with soothing music [31]. Patients who experienced this intervention had a significant decrease in the duration of delirium, less time being delirious, and less time being mechanically ventilated [31].

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is a well-established and successful standard management of protracted refractory psychiatric conditions which includes delirium [81] as well as delirious mania [82]. Nielsen and co-investigators [32] conducted ECT in six ICU patients in collaboration with psychiatrists experienced in treating delirium. ECT yielded a notably positive effect in these five cases. Specifically, long-standing agitation and discomfort were controlled in all patients after the unsuccessful use of the usual pharmacologic therapy. ECT was successful for four patients in managing delirium in 6 to 19 days. The last patient became relaxed and free from stress but continued in a state of posttraumatic amnesia following a head injury [32]. It is remarkable that ECT appears to be the most effective and rapidly active treatment modality in certain mental disorders despite ever-increasing psychopharmacologic alternatives [83].

Pain assessment

Certain studies indicate that pain may be a risk factor for the development of delirium [42,84]. Pain itself triggers deleterious cognitive effects as well as agitation in the ICU, which if not recognized can lead to unsuitable sedative administration [10].Payen and co-researchers [19] conducted a prospective cohort study of mechanically ventilated patients receiving analgesia on day 2 of their stay in the ICU. They found that patients evaluated for pain on day 2 were more likely

to obtain sedation level assessment, non-opioids, and analgesia during painful procedures than patients whose pain was not measured. Patients also acquired fewer hypnotics, had a shorter duration of mechanical ventilation, and a reduced length of stay in the ICU [19].

M.O.R.E. nonpharmacologic strategies

Most literature that supports the effectiveness of nonpharmacologic interventions has taken a multifaceted approach, and many of these protocols included the implementation of a sedation and mobilization protocol [65]. A study by Rivosecchi and co-researchers [33] supports the use of M.O.R.E. (Music, Opening/closing of blinds, Reorientation/cognitive stimulation, and Eye/ear care) nonpharmacologic strategies to the ICU patients with delirium, to lessen their time of being delirious if a mobilization procedure and a sedation algorithm already exist in the institution. It is noteworthy that this intervention diminished the amount of time Medical Intensive Care Unit (MICU) patients experienced delirium as well as lessened the risk of developing delirium while regulating the predisposing risk factors for delirium [33].

Multidisciplinary team

Immobility is responsible for neuromuscular weakness [85] which is related to a reduction in ICU survivors'physical function, quality of life, and return to work [86]. Researchers led by Needham [34] developed a multidisciplinary team concentrated on decreasing heavy sedation and increasing MICU staffing which includes full-time physical and occupational therapists. This quality improvement project resulted in reduced use of benzodiazepines with lower median sedative doses; patients had improved sedation and delirium status, and a higher level of functional mobility. Thus, ICU and hospital lengths of stay were decreased [34].

Sleep care

Sleep disruptions can have unfavorable effects on cognition and emotions as well as in the standard functions of cardiovascular, respiratory and immune systems [87]. These adverse consequences put ICU patients at a higher risk of infection, complications, longer hospital stays and mortality [88]. Li and co-researchers [35] conducted a quasi-experimental study among surgical patients from the ICU who were cared for by nurses utilizing the sleep care guidelines for noise and light reduction. Perceived noise and sleep interruptions from care-related activities and noises were significantly lower in patients who experienced the sleep care guidelines. Patients reported having better sleep quality and efficiency [35].

3.5.2 Pharmacologic treatments

Several factors contribute to the development of delirium, and one of these is excessive dopaminergic activity [89]. Antipsychotics have been examined comprehensively as a treatment practice; guidelines support the use of high potency non-sedating antipsychotics for the treatment of severe agitation

when other methods became unsuccessful [90]. Identified effective pharmacologic treatments for delirium in the literature include atypical antipsychotics such as haloperidol, risperidone,olanzapine and aripiprazole [36]; quetiapine [26]; and dexmedetomidine and midazolam [37].

Antipsychotics

Haloperidol, a typical antipsychotic, is the first choice among the pharmacological treatments in various populations [91], noting it has not been approved by the US Food and Drug Administration for delirium [92].

Boettger and co-researchers [36] compared the effectiveness and side-effect profile of the typical antipsychotic haloperidol with the atypical antipsychotics risperidone, olanzapine, and aripiprazole in the treatment of delirium. It is remarkable that the atypical antipsychotics risperidone, aripiprazole, and olanzapine and the typical antipsychotic haloperidol were equally effective in the treatment of delirium symptoms. However, these drugs have distinct side effects. Specifically, haloperidol triggers increased rates of extrapyramidal symptoms, and olanzapine significant sedation [36].

Quetiapine

Quetiapine is an atypical antipsychotic which has numerous benefits that may be especially valuable when managing delirium in the ICU, including a predominate antihistaminic mechanism of action, a short half-life that enables dose titration, and few reports of extrapyramidal symptom effects [93]. Devlin and co-investigators [26] conducted a randomized, placebo-controlled trial to assess the efficacy and safety of quetiapine to intravenous haloperidol in critically ill patients with delirium. It is remarkable that when quetiapine was dose increased, it achieveda faster resolution of delirium, a diminished time of delirium and agitation, and a better disposition upon discharge than patients who received as-necessary intravenous haloperidol therapy alone. Therefore, an increasing dose of quetiapine may assist to avoid adverse effects of haloperidol [26].

Dexmedetomidine

Dexmedetomidine is an alpha-2 adrenoreceptoragonist which has a unique mechanism of action, providing sedation and anxiolysis through the receptors within the locus coeruleus, analgesia through the receptors in the spinal cord, and reduction of the stress response with no substantial respiratory depression [94]. Riker and co-investigators [37] conducted a prospective, double-blind, randomized trial among ICU patients, administering either dexmedetomidine or the usual sedation of midazolam infusions for up to 30 days of mechanical ventilation. A notable finding was: patients managed with dexmedetomidine experienced delirium 20% less often than patients managed with midazolam and were removed from mechanical ventilation almost 2 days earlier. This finding suggests alpha-2 agonists advance many vital aspects of critical care such as less delirium and

shorter periods hooked to mechanical ventilator [37].

4. DISCUSSION

Delirium is highly prevalent in the ICU setting across the developing and developed countries. The studies included in this review identified numerous risk factors that could be present to patients who are at risk to develop ICU delirium. Therefore, it is vital to screen and obtain a thorough medical history to all the patients admitted in the ICU for delirium so that the clinician may be aware to cut down on the possible avoidable risk factor and overall incidence of delirium. Moreover, if these cannot be prevented then the health care team should be cautious for the emergence of delirium and manage it properly. It is also important to note that the identification of the risk factors is the initial step of an approach that could lead to earlier diagnosis and intervention which could contribute to a better and more cost-effective management.

There are quite a number of hypotheses established by the studies in this review regarding the pathophysiologic mechanisms of ICU delirium. It is important that the clinicians must be aware of this to provide an effective and appropriate intervention for the patients. There are important directions for future research which include identification of delirium biomarkers and determining genetic contributions. These would allow critical advances in both basic and clinical investigation of delirium.

It was established by the studies in this review that non-pharmacologic strategies of ICU deliriumare effective to control, to decrease the amount of time, as well as to reduce the risk of the development of delirium. It is remarkable that the participation of the nursing unit director and nursing unit clinicians in the educational process will result in better acceptance and involvement to the protocol implementation. Thus, it is encouraged that the nursing unit director and nursing unit clinicians must be involved in training the nurses to the new non-pharmacologic strategies that will be implemented in the hospital. On the other hand, the choice of medication used to provide sedation for ICU patients is essential to deliver safe and effective care. Since Quetiapine added to as-needed Haloperidol resulted in faster delirium resolution and less agitation, future studies should assess its effect on mortality, resource utilization, post-intensive care unit cognition, and dependence after discharge in a larger group of patients. Moreover, Dexmedetomidine appears to provide several advantages compared with Midazolam, thus, future studies must look beyond the quality or quantity of sedation to focus on additional important clinical outcomes including prevalence of delirium and time of mechanical ventilation.

Overall, future studies should be performed prospectively with larger sample sizes, use a control group of patients with similar illness but with the absence of delirium, and randomized controlled trial to further establish the findings mentioned in this review.

5. CONCLUSION

Delirium, an essential form of acute brain dysfunction, is not well-recognized in the ICU. The identification of risk factors and the possible underlying mechanism for the development of delirium continue to be the first step in its management. The next step is often pharmacologic and non-pharmacologic treatments. Identified risk factors were age, cigarette smoking, alcohol abuse, steroids, sedatives, intake of multiple medications, elevated sodium levels, hypoalbuminemia, hypertension, sepsis, chronic renal failure, trauma, immobility, and pain. Underlying mechanisms in the development of ICU delirium are a cholinergic deficiency, neuropathologic lesion, direct brain insults, aberrant stress response and inflammatory process, and alteration of plasma melatonin.

The prevention and management of delirium are vital to decrease its adverse effects. Non-pharmacologic strategies that have been recommended in the ICU include standard non-pharmacologic prevention plus early and intensive OT, sleep enhancement and relaxation protocols, ECT, pain assessment on day 2 of ICU stay, M.O.R.E., a multidisciplinary team focused on the reduction of heavy sedation and an increase of staffing in the ICU, and sleep care guidelines for noise and light reduction.

Antipsychotics have been assessed meticulously as a practice of treatment and guidelines backing the use of high potency non-sedating antipsychotics for the treatment of severe agitation when other methods are ineffective. Effective pharmacologic treatments for delirium in the literature include antipsychotics such as haloperidol, risperidone, olanzapine, aripiprazole, quetiapine, dexmedetomidine, and midazolam. The choice of drugs and other non-pharmacologic treatments should be understood as part of a greater multicomponent approach to the treatment of a critically ill patient. Future evidence-based strategies to minimize the duration and adverse effects of delirium while assuring patient comfort and safety should be based on the greater benefits that it may provide to the patient.

KEYPOINT BOX:

- Several risk factors that contribute to the development of ICU delirium include age, lifestyle, medications, laboratory chemistry abnormalities, medical history, immobility and pain.
- Some of the pathophysiologic basis for the development of delirium are cholinergic deficiency, neuropathologic lesion, aberrant stress response and inflammatory process, direct brain insult, and alteration of plasma melatonin.

- Haloperidol is the drug of choice for the treatment of delirium, however, there are various available non-pharmacologic treatment which could help in decreasing the duration as well as the incidence of delirium.

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