

Delirium in the intensive care unit and long-term cognitive and psychosocial functioning: literature review

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KEY WORDS

intensive care, delirium, sedation, cognitive function, outcomes

ABSTRACT

Objective

This paper reviews existing literature on delirium that arises during mechanical ventilation in the Intensive Care Unit (ICU). It looks at the physiology of delirium, its subtypes and risk factors. It further considers the impact of delirium on cognitive and psychosocial function of patients after their discharge from acute care. The aim of this paper was to increase awareness of ICU delirium, accentuate the potential link between different sedation agents and the development of delirium, and inform practitioners, especially nurses, about this common neurocognitive disorder that appears in the Intensive Care Unit (ICU).

Setting

Intensive Care Unit (of any acute hospital) where is ICU located.

Subjects

Mechanically ventilated patients.

Primary argument

This paper argues for the awareness of delirium in the Intensive Care Unit and examines sedation during mechanical ventilation with its potential role in promoting this disorder.

Conclusion

Delirium is the most common neurobehavioral disorder in patients who are critically ill and mechanically ventilated in ICU. It frequently generates psychiatric and psychological outcomes such as depressed mood, anxiety and/or Post Traumatic Stress Disorder (PTSD). Cognitive and psychological dysfunction following delirium seems to be overlooked, under recognised, and misdiagnosed in the ICU. These impairments are often incorrectly attributed to other processes, such as concurrent psychoactive medication use, substance use, or psychiatric disorders, in particular depression, rather than delirium. Although it is generally accepted that providing sedation for a patient's comfort is an essential part of bedside care for nearly every patient in ICU, an increasing number of researchers hypothesise there is a strong link between sedation practice and long-term patient centred outcomes, such as quality of life (Dimopoulou et al 2004) and cognitive and psychosocial functioning. Increasing nurses' awareness of this potential link is exceptionally important, as they are instrumental in administration and observing subsequent side effects of any medication, including sedatives.

INTRODUCTION

Delirium is a disturbance of consciousness developing over a short period of time, where inattention is accompanied by a change in cognition and/or perceptual disturbance (American Psychiatric Association 2013). It is characterised by an acute confusional state defined by fluctuating mental status, inattention and either disorganised thinking or an altered level of consciousness (Girard et al 2008; Maldonado 2008; Pun and Ely 2007; Stevens and Nyquist 2007). Delirium is one of the most common psychiatric disorders encountered among the medically unwell, yet it very rarely has a psychiatric origin (Gunther et al 2008; Maldonado et al 2009; Jacobson and Schreiber 1997 as cited in Justic 2000; Nicholas and Lindsay 1995 as cited in Justic 2000). It occurs across different health care settings (Levkoff et al 1992 as cited in Jackson et al 2004). Research confirms that delirium affects between 15 to 20% of general hospital patients (Lipowski 1989 as cited in Jackson et al 2004); between 20 to 50% of lower severity ICU patients, and as many as 80% of critically ill ICU patients receiving mechanical ventilation (Girard et al 2008; Pun and Ely 2007; Ely et al 2001a,b,c). In the ICU, delirium is associated with critical illness itself (particularly with multiple co-morbidities and multi-organ failure), as well as management related factors such as mechanical ventilation, sedation, and lack of sleep. It is associated with adverse outcomes including death and long-term cognitive impairments (Cox et al 2009; Pandharipande et al 2008; Quimet et al 2007; Pandharipande et al 2006; Combes et al 2003). Several studies show that ICU delirium risks are cumulative and potentially count towards increased possibilities of cognitive dysfunction and poorer functional status and quality of life (Oeyen et al 2010; Maldonado 2008; Girard et al 2008; Stevens and Nyquist 2007; Pun and Ely 2007; Hopkins and Jackson 2006; Marcantonio et al 2003; McCusker et al 2001). Despite this recognition, cognitive impairments associated with delirium following mechanical ventilation in ICU are not well described and deserve further study. The literature suggests a reduced quality of life for survivors of critical illness and delirium, and this reinforces the relationships between post-ICU cognitive impairment and cognitive morbidity and decreased social interaction (Hopkins and Jackson 2009; Stevens and Nyquist 2007; Jackson et al 2003 as cited in Ely et al 2004a; Hopkins et al 1999). Nonetheless, data to support these relationships are still limited (MacLulich et al 2009; Girard et al 2008; Gunther et al 2008; Stevens and Nyquist 2007).

Expanding investigations on long-term psychosocial functioning following mechanical ventilation-related delirium will facilitate better understanding of this neurocognitive sequelae and its impact on cognitive outcomes. These outcomes seem to be significant markers of a decline in cognitive function, basic daily functioning, quality of life and ability to return to work (de Miranda et al 2011; Oeyen et al 2010).

This article reviews the literature in this area of investigation, with a particular focus on the depressed mood, anxiety, and Post Traumatic Stress Disorder (PTSD) subsequent to mechanical ventilation and ICU delirium. Improving knowledge and awareness in this area of the evidence-based practice in intensive care, will open up insights into this common neurocognitive disorder, its development, consequences and management.

METHODS

Articles were identified through a computerised search of the Medline (1996-2011) and Google Scholar (2000-2011). This was done by combining subject headings and keywords, and the terms were merged with search filters for retrieving articles.

RESULTS

The literature search produced 128 references published between 1996 and 2011. Out of these, 72 articles were excluded based on abstracts or titles, leaving 56 articles for the full text review. The articles were then

tabulated into subgroups such as ICU delirium, post-operative delirium, pathophysiology of delirium, mental health and delirium, and cognition and delirium. During this review, 56 articles were evaluated and included in this review.

DISCUSSION

Delirium was until recently considered to be a relatively benign medical problem in ICU (McGuire et al 2000), and of no importance to survival or long-term quality of life (Girard et al 2008; Ely et al 2004a, b). The prevalence of delirium reported in both medical and surgical ICU cohort studies has varied from 20% to 80%, depending upon severity of illness observed and diagnostic methods used (Thomason 2005 as cited in Patharipande 2008; Bergeron et al 2001 as cited in Pun and Ely 2007; Ely et al 2004b). Nevertheless, despite high prevalence rates in the ICU, delirium often goes unrecognised by clinicians, with symptoms incorrectly attributed to dementia, depression, or 'ICU syndrome', which was considered an expected, inconsequential complication of critical illness (Girard et al 2008; Ely et al 2004b; Justic 2000). For that reason, ICU physicians mostly overlooked delirium, as their main focus was to successfully assess, prevent and reverse multi-organ dysfunction (Pae et al 2008). The above approach resulted in a lack of attention to delirium and obstructed correct diagnosis and subsequent treatment of this condition (Pae et al 2008; Armstrong et al 1997). Ely et al (2004, as cited in Pae 2008) in their exploratory study of the current opinions and perceptions of health care professionals reported that although 92% considered delirium to be a significant or very serious problem, 78% of them reported delirium to be under diagnosed.

Delirium Subtypes

Delirium has been described as a multifactorial syndrome with different mechanisms interacting to produce the typical clinical manifestations. Most of these mechanisms are related to imbalances in the neurotransmitters that modulate cognition, behaviour and mood, thus generating different subcategories of delirium according to the psychomotor symptoms experienced, such as 'hyperactive', 'hypoactive' and 'mixed' delirium (Miller and Ely 2006 as cited in Girard et al 2010; Girard et al 2008; Maldonado 2008; Pun and Ely 2007; Ely et al 2001a,b; Justic 2000).

Hyperactive delirium is reportedly associated with extreme levels of agitation, emotional lability and disruptive behaviours such as shouting, hitting, biting and pulling out indwelling catheters and lines (Pun and Ely 2007; Justic 2000). This delirium subtype was in the past referred to as 'ICU psychosis' and is rare in its pure form. Peterson et al (2006) examined 614 consecutive medical ICU patients for delirium over one year, and reported that hyperactive-only delirium was present in less than 2% of all cases. Kabayashi et al (1992 as cited in Meagher et al 2000) reported that patients with hyperactive delirium had a higher rate of full recovery in comparison to patients with either hypoactive or mixed subtypes. Several studies pointed out that patients with hyperactive phenomenology had shorter hospital stays and better outcomes than either those with mixed or hypoactive subtypes of delirium (Girard et al 2008; Pae 2008; Pun and Ely 2007; Meagher and Trezepacz, 2000 as cited in Pun and Ely 2007; Stevens and Nyquist 2007; Ely et al 2004a,b;

Meagher et al 2000; Olofsson et al 1996 as cited in Meagher et al 2000; Liptzin and Levkoff 1992 as cited in Meagher et al 2000).

Hypoactive delirium alone is also relatively rare and is characterised by withdrawal, lethargy, apathy and a lack of responsiveness (Pun and Ely 2007; Justic 2000). Hypoactive delirium is associated with a worse prognosis than hyperactive delirium.

Most patients demonstrate a mixed hyperactive and hypoactive delirium after mechanical ventilation in ICU, and this subtype is associated with the worst outcomes and the highest mortality of the three subtypes

(Girard et al 2008; Pun and Ely 2007; Miller and Ely 2006; Ely et al 2004a; Misra and Ganzini 2003; Ely et al 2001a,b; Justic 2000; Meagher et al 2000).

Pathophysiology

Delirium is thought to be a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of neurotransmitters that normally control cognitive function, behaviour, and mood (Trzepacz 1999 as cited in Girard et al 2008; Maldonado 2008). Maldonado (2008) argues that derangements of these multiple neurotransmitter systems have been implicated in the pathophysiology of delirium. Trzepacz (1999 as cited in Girard et al 2008) reported that these neurotransmitters work in opposition, with dopamine increasing and acetylcholine decreasing neuronal excitability. Any such imbalance results in neuronal instability, unpredictable neurotransmission and delirium. Similarly, research shows that other neurotransmitters may equally play a role in the pathogenesis of delirium, including aminobutyric acid (GABA) serotonin, endorphins, and glutamate (Girard et al 2008; Maldonado 2008; Marcantoni et al 2003).

ICU Delirium Risks

Risk factors for delirium can be divided into predisposing factors (host factors), and precipitating factors (Girard et al 2008; Pun and Ely 2007; Inoye and Charpentier 1996). Predisposing factors are present before ICU admission and are difficult to alter, while precipitating factors occur during the course of critical illness and may be alterable. More recently Miller and Ely (2006) proposed three categories of risk factors for the development of delirium: a) predisposing or baseline vulnerability; b) intrinsic risk factors such as the features of the acute illness and c) hospital related or iatrogenic factors (table 1).

Table 1. Risk factors for delirium

Baseline characteristics	Intrinsic / Disease factors	Iatrogenic / environmental factors
Cognitive Impairment	Sepsis	Sedative medications
Comorbidities	Hypoxemia	Analgesic medications
Age	Metabolic derangements	Use of bladder catheter
	Severity of illness score	Anticholinergic medications
		Sleep quality / quantity

Miller et al 2006, p56.

There is an ongoing debate on the relative contribution of intrinsic versus iatrogenic risk factors in the development of delirium (Meyer and Hall 2006). Pandharipande et al (2006) reported that although delirium may result from patients' specific underlying illness, it was often an outcome of different iatrogenic and thus preventable sources.

Gunther et al (2008) argued that sedatives and analgesics represent the leading modifiable iatrogenic risk factor for transiting to delirium. Similarly, an increasing number of researchers suggest the use of ICU sedative, analgesic and anticholinergic medication may be contributing to the development of delirium (Shehabi 2010; Riker et al 2009; Maldonado 2008; Shehabi et al 2008; Pandharipande et al 2006; Pandharipande and Ely 2006). Several studies (Riker et al 2009 Maldonado et al 2009; Gunther et al 2008; Maldonado 2008; Gaudreau et al 2005) imply that there is a link between the use of pharmacologic agents with known psychoactive activity, such as opiates, corticosteroids, benzodiazepines, non-steroidal anti-inflammatory agents and chemotherapeutic agents, and the increasing occurrence of ICU delirium.

Esteban et al (2002 as cited in Maldonado 2008) suggest about 90% of ventilated patients in ICU who develop delirium receive benzodiazepines, opioids, or both, to facilitate management and ease the discomfort

associated with intubation. Maldonado (2008) argues there is a strong body of evidence, gathered through past experimental studies and clinical observations, which clearly demonstrates the link between the use of drugs with anti-cholinergic properties and a physical and mental impairment (Tune 2000 as cited in Maldonado 2008; Tune and Egeli 1999 as cited in Maldonado 2008; Flacker et al 1998 as cited in Maldonado 2008; Tune et al 1993 as cited in Maldonado 2008; Golinger et al 1987 as cited in Hopkins et al 1999; Innoye and Charpentier 1996 as cited in Innoye et al 1998). Similarly, Maldonado (2008) reports an exposure to anticholinergic agents alone is an independent risk factor for the development of delirium and an increase in delirium symptom severity. This research is in line with previous studies (Plaschke et al 2007 as cited in Pandharipande et al 2008; Marcantonio et al 1994 as cited in Pandharipande et al 2006; Pandharipande and Ely 2006), which have already suggested the possible association between the use of sedation, such as γ -aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines) and the increased occurrence of delirium.

At the same time, little is known about the relationship between the duration of sedative administration and the risk of delirium following operative procedures and both general and regional anaesthesia. The majority of studies suggest short periods of exposure to these agents are not associated with similar risks to those of longer term administration in the ICU setting (Bryson and Wood 2006).

ICU Delirium and Cognitive Functioning

Evidence is also emerging in support of an association between the experience of delirium and either a poor functional and cognitive recovery, or long term cognitive impairment following hospital discharge (Girard et al 2010; Jackson et al 2010; Pun and Ely 2007; Stevens and Nyquist 2007; Hopkins et al 2006; Hopkins and Jackson 2006, Jackson et al 2004; Ely et al 2004b; McCusker et al 2001; O'Keeffe and Lavan 1997). Several longitudinal studies report approximately one third of ICU patients receiving mechanical ventilation have long term neurocognitive impairments, and this is documented up to six years after hospital discharge (Girard et al 2010; Pun and Ely 2007; Jackson et al 2007; Hopkins and Jackson 2006; Hopkins et al 2006; Ely et al 2001a,b).

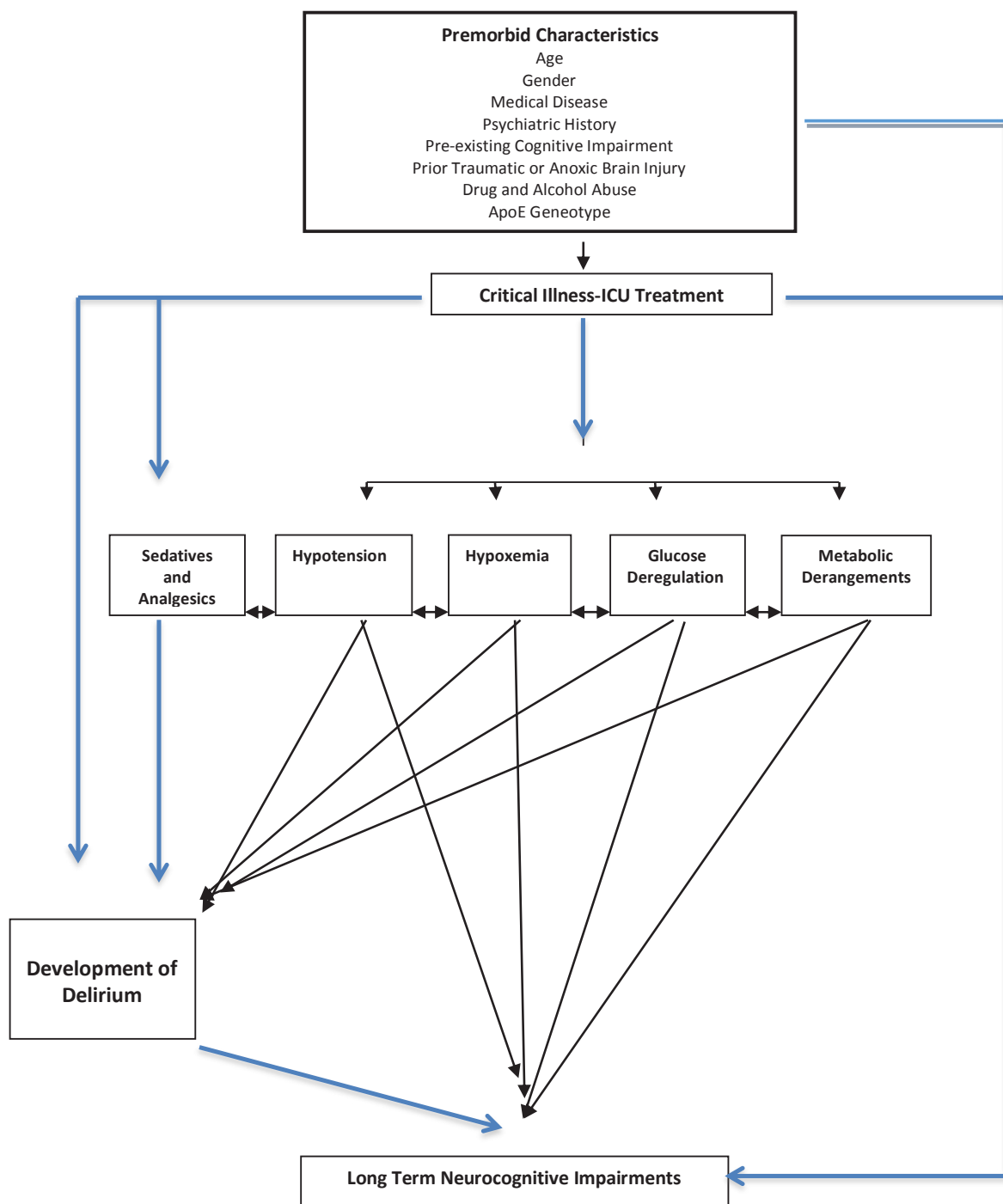
Although the relationship between the management of critical illness in the ICU (including mechanical ventilation, sedation and multiple medications) and illness-factors such as metabolic derangements, underlying infections, multiple organ failure, and the development of delirium is under ongoing investigation (Hopkins and Jackson 2009), evidence is emerging that this has the potential to promote delirium, exacerbate existing and/or introduce new cognitive impairments (figure 1).

Jackson et al (2007) followed 98 patients who were mechanically ventilated for acute respiratory failure in medical ICUs and found prolonged periods of ICU delirium were associated with an increased risk for long-term cognitive impairment at three months post-discharge. Girard et al (2010) in their study of mechanically ventilated medical ICU patients reported the duration of delirium was independently associated with long-term cognitive impairment, such as memory issues and the decline in basic life skills and functioning. This, in some patients, promotes development of mental health problems, such as post-traumatic stress disorder (PTSD), anxiety and depression.

PTSD is characterised by the development and persistence of intrusive recollections, avoidance symptoms, and hyper-vigilance. In addition to the strain the disorder itself places upon psychosocial functioning and psychological health, PTSD is implicated in increased rates of depression, substance abuse, and suicide attempts (Strauss et al 2006). Anxiety demonstrates itself as a diffuse sensation of fear, which is not related to an actual external danger (Sareen et al 2005). This sensation could be due to the numerous stressful situations that take place in the critical care setting such as pain, noise and loss of body control. Although a

certain degree of anxiety seems to be 'normal' in the ICU environment, a literature describes a 'pathological' anxiety when this sensation appears to be disproportionately high considering its cause, and when it is associated with other severe signs, such as severe dysautonomia, and loss of self-control which cannot be appropriately treated due to a complete lack of patient cooperation (Chevrolet and Joliet 2007).

Figure 1: A possible explanatory model of neurocognitive impairments among ICU survivors (Hopkins and Jackson 2006; p876). ApoE = apolipoprotein E



CONCLUSION

While most of the literature supports an association between delirium following mechanical ventilation in ICU and subsequent cognitive dysfunction in the short and long term, the functional correlates of cognitive impairments seem to be under-studied (Pae et al 2008). These functional correlates reflect patients' ability to return to work or to work at previously established levels, as well as function effectively in emotional and interpersonal domains (Oeyen et al 2010; Hopkins and Jackson 2009; Schweickert et al 2009). In addition, more research is needed in observing the development of depression, anxiety and PTSD following ICU delirium, as they are the markers of a psychological function that significantly shapes one's quality of life.

The ability of nursing staff to observe and report delirium has not received the attention it deserves. The presence and attention given to each patient in ICU as a consequence of one-to-one nursing gives an opportunity for nurses to identify early signs of delirium, and work with the rest of the medical team to implement strategies designed to reduce the incidence and severity of delirium occurrence. Therefore, educating nurses to understand delirium, its subtypes, risks and pathophysiology, is an important step in dealing with this neurobehavioral disorder. Using this knowledge, nursing staff will be empowered to act to increase the patients' cognitive status by enhancing their sense of security, safety, and comfort.

RECOMMENDATIONS

An increasing number of researchers call for an individualised, balanced approach to analgesia and sedation in order to minimise side effects and iatrogenic risks of ICU delirium and consequent poor cognitive and psychosocial outcomes (Shehabi et al 2010; Riker and Fraser 2005). Recognising and treating delirium in the ICU should become an avenue more thoroughly explored if we are to offer good, all-inclusive care in the ICU. In doing so, we need to recognise nurses' presence with the ICU patient and their ability to identify delirium. Therefore, equipping nurses with the best practice strategies to manage patients who are experiencing delirium in the ICU is of the utmost importance (Justic 2000; Webb et al 2000).

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