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RISK FACTORS FOR DELIRIUM IN ICU

(a double-centre trial)

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Indice

ABSTRACT

Background

Delirium is a syndrome characterized by acute brain dysfunction. This syndrome is under-recognized in the intensive care unit (ICU) with not fully elucidated causing mechanisms. The identification of risk factors associated with delirium may prevent the onset of delirium and help in the management. Aim of this study is to estimate the incidence of delirium in ICU and to identify related risk factors in two different ICUs.

Methods

This study was carried out in collaboration with the Intensive Care Unit of Santa Chiara Hospital, Pisa University, Italy, and the Intensive Care Unit of South Egypt Cancer Institute, Assiut University, Egypt. During a 3 months research period patients admitted to the referred ICU were enrolled. The Confusion Assessment Method for ICU was used as methodology for diagnosing delirium. Patients were assessed twice a day. Haemodynamic parameters, arterial blood gas values, electrolytes, presence of sepsis, type of ventilation and type of sedation were assessed at the same intervals. We also recorded daily laboratory investigations, age, diagnosis, length of ICU stay, incidence of complications and general condition at discharge. Data were statistically analyzed with Mann-Whitney test, Wilcoxon test and the Chi-square test.

Results

111 patients in the first ICU and 51 patients in the second ICU were enrolled. ICU delirium was found to be significantly related to sepsis, mechanical ventilation and sedation (*P*-value <0,05).

Conclusion

We believe that the early identification of risk factors that may lead to the occurrence of delirium in ICU, associated with the appropriate treatment, may reduce the incidence of delirium in ICU and delirium related complications.

Key words: delirium, intensive care unit, sepsis, mechanical ventilation, sedation.

Introduction

Recent advances in critical care medicine have improved survival in most of patients, and in doing that they revealed a major public health concern that previously had been under-appreciated. Critical care clinicians have historically been attuned to pulmonary, cardiac, and renal dysfunction as a source of morbidity and mortality in ICU patients but have underestimated the impact of brain dysfunction [1].

Delirium is defined according to the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [2] as a disturbance of consciousness and cognition for which a pre-existing or evolving dementia cannot better account, that develops over a short period of time (hours to days) and fluctuates over time. Many different terms have been used to describe this syndrome of cognitive impairment in critically ill patients, including ICU psychosis, ICU syndrome, acute confusional state, encephalopathy, and acute brain failure [1].

The exact mechanisms causing brain dysfunctions in ICU patients have not been fully characterized; however several hypotheses were actively discussed. The role of abnormalities at the level of the central neurotransmission process, characterized by a reduction of cholinergic activity and an excess of dopaminergic activity is still debated [3,4,5]. Other central neurotransmitters have been thought to play a role in delirium, such as serotonin [6], or gamma-aminobutyric acid (GABA) [7].

Moreover a role of potential organic cerebral lesions not detectable by currently available technology (computed tomography (CT) scan, magnetic resonance imaging, and so on) may explain the mental dysfunction observed in the ICU advocated by some authors [8].

Despite its high prevalence in ICU, delirium is often unrecognized by clinicians or symptoms are attributed to dementia, depression, or ICU syndrome (considered an expected, inconsequential complication of critical illness) [9]. Under-recognition may also attributed to diagnostic methodology as only the CAM-ICU test and the Delirium Screening Checklist are validated for use in mechanically ventilated and sedated patients in ICU. It was reported that as many as 32 to 66% of cases remain unrecognized by the managing physicians and nurses [10].

Delirium can be categorized into subtypes according to psychomotor behavior, and the high prevalence of hypoactive delirium in critically ill patients, characterized by a depressed level of consciousness and abnormal cognition, probably contributes to the clinicians' lack of recognition as often clinicians focus on only hyperactive delirium, that is characterized by agitation, restlessness, and emotional lability; mixed delirium is characterized by fluctuation between hypoactive and hyperactive states [11].

Both the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) may be used as

reliable daily diagnostic instruments for the detection of delirium [12]. Where the CAM-ICU screens for four features at a single point in time and the ICDSC uses a screening checklist of eight features over the period of a nursing shift.

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [13] is widely accepted as the standard tool to asses delirium in intensive care.

In the CAM-ICU, the patient is initially assessed for altered or fluctuating mental status, as well as inattention using a sequence of 10 letters where the patient is required to squeeze the clinician's hand only when a specific letter is stated. Disorganized thinking is assessed through the ability to answer four simple yes/no questions, reduced level of consciousness is assessed at the end of the test. Patients are defined as delirious if altered mental status and inattention are present with disorganized thinking and/or reduced level of consciousness. This test can be performed on any patient who will open their eyes and keep their eyes open to a verbal stimulus [14].

One strategy to prevent or diminish the occurrence of delirium is to identify and modify risk factors. Interventions include repeated reorientation of patients, repetitive provision of cognitively stimulating activities for the patients, non-pharmacologic sleep protocol to restore sleep/wake cycles, early mobilization, range-of-motion exercises, timely removal of catheters and physical restraints, use of eye glasses and magnifying lenses, hearing

aids and earwax disimpaction, adequate hydration, use of scheduled pain protocol, and minimization of unnecessary noise/stimuli [15].

This study was carried out in collaboration between 2 centers: the first is the Intensive Care Unit of Santa Chiara Hospital (SCH-ICU), Pisa University, Pisa, Italy; the second is the Intensive Care Unit of South Egypt Cancer Institute (SECI-ICU), Assiut University, Assiut, Egypt. Our study's objective was to estimate the incidence and possible risk factors of delirium in these different ICU centers and to compare results from both centers.

Materials and methods

The SCH-ICU is a 8 bed polyvalent ICU with 4 more beds for reduced intensity of care. The SECI-ICU is a 4 bed ICU with 4 more beds for reduced intensity of care.

Table I General features of the 2 centers

	Santa Chiara Hospital (SCH)	South Egypt Cancer Institute (SECI)
Reference number of surgeries/year	12000	700
Number of ICU admissions/year	680	300
Average days in ICU	3	3
Surgical/non-surgical ratio	70%-30%	85%-15%

Table II Doctors and nurses daily work schedules in the 2 centers

	Morning shift		Afternoon shift		Night shift	
	SCH	SECI	SCH	SECI	SCH	SECI
Time	7am-2pm	8am-2pm	2pm-9pm	2pm-8pm	9pm-7am	8pm-8am
N.of nurses	4 + morning-nurse + high-nurse	10-12 + high-nurse	4	4	4	4
N.of doctors	1 attender, 1 resident, 2 specialized doctors	at least 1 resident + 1 assistant lecturer	1 attender, 1 resident, 1 specialized doctor	1 resident, 1 assistant lecturer	1 resident, 1 specialized doctor	1 resident, 1 assistant lecturer
			2 specialized doctors on call	1 lecturer on call	2 specialized doctors on call	1 lecturer on call
	all activities are under the supervision of the director of the department					

During the 3 months research period 323 patients were observed in the 2 ICUs. From SCH-ICU the enrolled patients were 111 on 220; from SECI-

ICU the enrolled patients were 51 on 103. The inclusion criteria included: general ICU patients, with a RASS (Richmond Agitation Sedation Score) of more than -4, a minimum age of 18 years, and a length of stay in the ICU of at least 24 hours. Patients with pre-existing neurocognitive dysfunction, documented signs of dementia after psychiatric or geriatric evaluation, language barriers or deafness, an active psychiatric disorder like psychosis, and severe neurological disorders like stroke or meningitis were excluded.

In SCH- ICU, a group of attending doctors collected the data; they were trained for one month on the practical use of CAM-ICU scale to provide them with the basic knowledge and proper method of using CAM-ICU. While in SECI-ICU, a group of bed-side nurses collected the data; they too were trained for the same session on the practical use of CAM-ICU scale.

Patients included in the study was assessed twice a day; at 8am and 8pm with the CAM-ICU scale. Haemodynamic parameters (heart rate, blood pressure), arterial blood gas values, electrolytes, presence of sepsis, type of ventilation and mode of sedation were also recorded at the same intervals.
Age, diagnosis, laboratory investigations (complete blood picture, coagulation, serum creatinine, urea nitrogen, liver enzymes, bilirubin,

electrolytes), length of ICU stay, incidence of complications and condition on discharge were also recorded.

In SCH-ICU, at the time of the study, the official visiting hours was from 18 to 19:30 every evening, on Sunday from 12 to 13:30 too; however relatives visits were allowed during the whole day for a maximum of 2 people at a time. In SECI-ICU relatives visits are allowed twice a day: once in the morning and another time in the early evening, each for 30 minutes maximum. Visiting is sometimes limited to complicated and critical cases: if relatives give negative feedback to the patient (as when crying, dealing with him as if he is about to die), the visits have been reduced.

All data were analyzed using MEDCALC 10. Data were compared with Mann-Whitney test for independent samples, Wilcoxon test for paired samples, and the Chi-square test for categorical data. *P*-value of <0,05 was considered as significant.

Results

During the 3 months research period 111 patients in SCH-ICU and 51 patients in SECI-ICU were eligible for participation in the study. Incidence of delirium was 29,7% in SCH-ICU, while it was 53% in SECI-ICU.

Table III Delirium and underlying desease

Underlying diseases and/or surgical treatment	**Delirium percentage (%) in SCH-ICU**	**Delirium percentage (%) in SECI-ICU**
Respiratory disease	19	70
Cardiovascular disease	21	53
Renal disease	23	100
Hepatic disease	20	50
Cancer	30	53
Diabetes	50	60
Abdominal surgery	27	37
Neck surgery	5	0
Urogenital surgery	14	61
Orthopedic surgery	14	

Age was not significantly related to delirium in SCH-ICU (P=0,3), while it was a significant risk factor for development of delirium in SECI-ICU group (P=0,005). Delirium was significantly related in both groups to sepsis, defined according to the ACCP/SCCM criteria (SCH-ICU P=0,0001 & SECI-ICU P=0,0069) and mechanical ventilation of more than 24 hours (SCH-ICU P=0,0000006 & SECI-ICU P=0,0338). Delirium was significantly related to the use of sedatives (sedoanalgesia with propofol or midazolam and morphine or remifentanil) in SCH-ICU (P=0,01) and in

SECI-ICU (P=<0,0001). It was also found that delirium was significantly related to changes in both Base Excess and Sodium levels in SCH-ICU (P=0,000003 & 0,0193 respectively) but not in SECI-ICU (P=0,7467 & near to be significant 0,0912). Delirium was significantly related in both groups to the increase in heart rate (SCH-ICU P=0,0001 & SECI-ICU P=0,002); in both groups delirium was significantly related to changes in systolic blood pressure but in SCH-ICU it was related to the increase in systolic blood pressure (P=0,0001), while in SECI-ICU it was related to the decrease in systolic blood pressure (P=0,001). Delirium was not significantly related to mortality in SCH-ICU (P=0,3443), while it was significantly related to mortality in SECI-ICU (P=0,0008).

Table IV Analyzed variables and their level of statistical significance

	Pisa	Egypt
Number of patients	111	51
Delirium onset	29,7%	53%
Correlation age-delirium	p=0,3	p= 0,005
Correlation sepsis-delirium	p=0,0001	p=0,0069
Correlation MV > 24h-delirium	p=0,0000006	p=0,0338
Correlation sedation-delirium	p=0,01	p=<0,0001
Correlation Base Excess values-delirium	p=0,000003	p=0,7467
Correlation Sodium values	p=0,0193	p=0,0912
Correlation heart rate (increase)-delirium	p=0,0001	p= 0,002
Correlation systolic blood pressure-delirium	p=0,0001	p=0,001
Correlation mortality-delirium	p=0,3443	p=0.0008

Discussion

This study investigated the incidence and possible risk factors of delirium in 2 different ICU centers, at Santa Chiara Hospital (SCH), Pisa University, Pisa, Italy, and at South Egypt Cancer Institute (SECI), Assiut University, Assiut, Egypt.

In both units the majority of admissions are related to postoperative cases (70% in SCH and 90% in SECI). In SCH: some surgical patients undergo different laparoscopic surgeries (as laparoscopic cholecystectomy, intestinal resection-anastomosis, sleeve gastrectomy or gastric bypass in bariatric surgery, etc). While in SECI: most of patients undergo major surgical interventions with radical tumor excisions, or amputations and re-constructive procedures in most of cases.

We found that the incidence in delirium was higher in SECI-ICU (53%) than in SCH-ICU (29,7%), but still both within the reported ranges for delirium in ICU [16,17]: delirium is reported to occur in 20% to 50% of non-intubated ICU patients and in 60% to 80% of patients receiving mechanical ventilation [18]. The different incidence in the 2 centers may be related to the different types of patients dealt with in both units as previously described. It was found by researches outside the ICU that delirium is possibly related to chronic pathological conditions (cancer in this case) [19,20].

Age was not significantly related to delirium in SCH-ICU patients (P=0,3), while it was significantly related to delirium in SECI-ICU group (P=0,005) This could be explained by the old age of most of the patients in SCH-ICU where average age is 65 years old; while in SECI-ICU group average age is 55 years old with a wider variability of age in the sample that probably makes it more statistically significant. Age was accepted as an important risk factor for development of delirium expecially in postoperative patients. Indeed delirium was found to be the most common complication of hospital admission for older people [21] and it develops in up to a half of older patients postoperatively [22, 23]. In elderly a preexisting structural brain damage, the reduced homeostatic capacity, changes in vision and alterations of hearing, age-related changes in pharmacokinetics and pharmacodynamics, psychosocial stressor like widowhood are factors that predispose to the onset of delirium [24].

Sepsis frequently presents with delirium and represents perhaps the most common causal factor for ICU delirium [25, 26, 27]. The prevalence of coexistent delirium during sepsis reaches up to 71% depending on diagnostic definitions. In our study, ICU delirium was found to be significantly related (SCH P=0,0001, SECI P=0,0069) to sepsis. Sepsis may be a gateway to acute central nervous system (CNS) dysfunction and

brain damage. A septic inflammatory cascade has the potential to decrease essential oxygen and nutrient delivery to cells by impairing capillary blood flow; elevated level of tumor necrosis factor-alpha, interleulkin-1 and other cytokines and chemokines that are released in response to lipopolisaccharide can result in disseminated intravascular coagulation, promote leukocyte-vascular endothelium adhesion and induce endothelial damage; the prolonged exposure to lipopolysaccharide may impair the synaptic transmission and neuronal excitability of neurons [28]. Sharshar and colleague reported that sepsis-induced encephalopathy may result from degradation of the blood-brain barrier, leading to increased permeability [29].

Delirium was significantly related to the use of sedatives in both SCH-ICU (P=0,01) and SECI-ICU (P=<0,0001). Multiple studies have demonstrated the strong positive relation between the use of sedative medications in ICU and development of delirium [30, 31]. Pandharipande and colleagues reported that the administration of benzodiazepines was an independent risk factor for the development of delirium in surgical and trauma ICU patients [32,33]. Inouye and colleagues concluded that benzodiazepines, opioids and other psychoactive drugs are associated with an increased relative risk for delirium [21]. Most of ventilated patients receives benzodiazepines and opioids to improve oxygenation, alleviate agitation,

and prevent removal of support devices, resulting in a summation of risk factors for delirium. Propofol and benzodiazepines have high affinity for GABAergic receptors in key areas: decreasing global CNS arousal has the potential to cause unpredictable neurotransmission and bring about disruptions in cerebral functional connectivity [28].

Metabolic disturbances and electrolyte imbalance were found to be among the possible precipitating factors of delirium by causing acute imbalance of acetylcholine, dopamine and GABA [1, 34]. Incidence of delirium in SCH-ICU was significantly related to alterations in sodium level (P=0,0193) and to alterations in base excess (P=0,000003), but not in SECI-ICU patients (P=0,0912, and 0,7467 respectively). In our opinion, this may be the result of the chronic nature of metabolic derangements accompanying cancer which develop slowly and gradually over several months with adaptive homeostatic mechanisms maximally stimulated.

Delirium was significantly related to increased heart rate in both SCH-ICU (P= 0,0001) and SECI-ICU (P=0,002), while it was significantly related to hypertension (P=0,0001) in SCH-ICU and to hypotension (P=0,001) in SECI-ICU. This may be attributed to the association of delirium with neuro-endocrine system activation and catecholamine release in the first case, while in the second case by the association of delirium with brain

hypo-perfusion caused by hypotension that exerts a reflex increase in the heart rate. Yokota and colleagues reported that delirious patients experienced, during and after acute delirious states, a 42% reduction in overall cerebral blood flow (CBF) [35]. More recently, Fong and colleagues found wide-spread hypoperfusion during and after acute delirious states [36]. Medical conditions or sedative agents could impact with brain perfusion, causing cognitive processing to fluctuate and manifest as delirium [28].

Finally, we found that occurrence of delirium was not significantly related to mortality rate in SCH-ICU (P=0,3443) with only 15% of deaths in delirious cases after 1 month from admission in ICU, nevertheless that is twice compared with the percentage of deaths in not delirious cases. In SECI-ICU the occurrence of delirium was significantly related to mortality rate (P=0,0008) with 41% of deaths in delirious cases after 1 month from admission in ICU. In the literature we find that ICU delirium predicts an increased risk of death at 6 months [37,38]. We suggest that the difference in the mortality rate between the two groups may be influenced by the different types of patients hospitalized in both ICUs.

Conclusion

From our study we conclude that the differences between results from both centers can be attributed to different ethnic groups and to the nature of the underlying disease. Cancer has a larger psychological burden on the patient, a factor that may play an important role in the higher total percentage of delirious cases in SECI-ICU. Concomitant diseases and metabolic variables may also play a partial role in development of delirium. Finally we compare different types of ICU: in terms of relatives' visits, SCH-ICU is a permissive ICU versus SECI-ICU that is a restrictive ICU.

We believe that a study like this, although patient populations and the ways health care are different, give reasons for attention about this symptomatology which identifies an important field of development and application of the study of morbidity in ICU.

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