Trauma Surgery & Acute Care Open

Incidence and risk factors of delirium in surgical intensive care unit

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Received 23 July 2020
Revised 12 October 2020
Accepted 9 November 2020

To cite: Ali MA, Hashmi M, Ahmed W, *et al*. *Trauma Surg Acute Care Open* 2021;**6**:e000564.

ABSTRACT

Background To evaluate the incidence and modifiable risk factors of delirium in surgical intensive care unit (SICU) of tertiary care hospital in a low-income and middle-income country.

Methods We conducted a single cohort observational study in patients over 18 years of age who were admitted to the SICU for >24 hours in Aga Khan University Hospital from January to December 2016. Patients who had pre-existing cognitive dysfunction were excluded. Intensive Care Delirium Screening Checklist was used to assess delirium. Incidence of delirium was computed, and univariate and multivariable analyses were performed to observe the relationship between outcome and associated factors.

Results The average patient age was 43.29±17.38 and body mass index was 26.25±3.57 kg/m^2. Delirium was observed in 19 of 87 patients with an incidence rate of 21.8%. Multivariable analysis showed chronic obstructive pulmonary disease, pain score >4 and hypernatremia were strong predictors of delirium. Midazolam (adjusted OR (aOR)=7.37; 95% CI 2.04 to 26.61) and propofol exposure (aOR=7.02; 95% CI 1.92 to 25.76) were the strongest independent predictors of delirium while analgesic exposures were not statistically significant to predict delirium in multivariable analysis.

Conclusion Delirium is a significant risk factor of poor outcome in SICU. There was an independent association between pain, sedation, COPD, hypernatremia and fever in developing delirium.

Level of evidence IV.

INTRODUCTION

Delirium in critically ill patients is common and distressing.[1] The incidence of delirium in intensive care unit (ICU) ranges from 45% to 87%.[2 3] Despite its high incidence in literature, the data are scarce in the low-income and middle-income world, especially in surgical patients. One of the reasons may be less sensitization and training of ICU staff, which can delay in prompt diagnosis and management.[3] It is mostly labeled as dementia, depression or ICU syndrome in literature.[4]

Arguably, delirium is a well-recognized cause of morbidity and mortality among ICU patients. It causes longer hospital stay, lower 6-month survival and cognitive impairment persisting even years after discharge.[5] Therefore, it is recommended that all ICU patients are assessed for delirium using a validated tool, which is not very common in most ICUs.[5] In a study, published in 2008, the risk was observed 73% in surgical and trauma patients.[6]

The cause of delirium is almost always multifactorial, dependent on certain predisposing and precipitating factors. Some of the predisposing factors are not modifiable, for example, age, gender, addiction, pre-existing cognitive impairment, pre-existing cardiac and pulmonary disease. Modifiable factors can be environmental and acute illness such as no visible daylight, no clock, no visits, sedation, increase in length of stay, fever, pain, tubes and catheters. It is important to find out the risk factors associated with our patients and introduce guidelines to minimize the modifiable factors therefore preventing delirium in ICU. Moreover, the data and incidence of delirium are scarce in surgical cohort.

The purpose of this study was to evaluate the incidence and associated risk factors of delirium in surgical ICU (SICU) of tertiary care hospital.

METHODS

A single cohort prospective observational study was conducted in SICU of a teaching hospital. Our inclusion criteria included all those patients aged >18 years and had an ICU stay of >24 hours. Patients, who expired within 24 hours of admission, history of cognitive impairment, on any type of antipsychotic medications or patients with do not resuscitate status were excluded from the study because of the difficulty to assess delirium in this group. Patient's eligibility in this study was evaluated by one of the trained investigators. A predesigned proforma was filled. The proforma included age, gender, comorbid conditions like cardiac, respiratory and renal impairment (hypertension, ischemic heart disease (IHD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD)), reason of ICU admission, acute physiology and chronic health evaluation II (APACHE II) score, Glasgow Coma Scale and daily use of sedatives, opioids, steroids or antipsychotics drugs. The sedation level was assessed by using Riker Sedation-Agitation Scale (SAS). Patients were daily evaluated until their SAS score was ≥4, so they could be assessed for delirium using the 8-item Intensive Care Delirium Screening Checklist (ICDSC) every 8 hours until day 5 of ICU admission. Patient with an ICDSC score of 4 or higher was considered delirious. Analysis of whole blood count, arterial blood gases, biochemistry, culture and radiological examinations, such as chest X-ray, were performed as routine ICU measure as per physician discretion. We followed all clinical, laboratory findings and disease status, for instance, hypertension, respiratory diseases and DM as

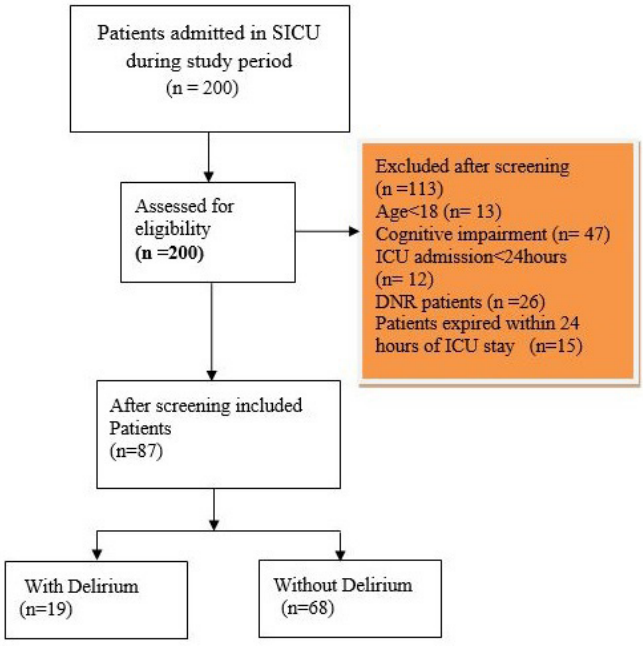

Figure 1 Flow diagram of patient in the study. DNR, do not resuscitate; ICU, intensive care unit; SICU, surgical intensive care unit.

potential risk factor for delirium. Patients were followed until hospital discharge.

Statistical analysis

All statistical analyses were performed with the software SPSS V.19 (SPSS, Chicago, Illinois, USA). Incidence of delirium was computed by ICDSC and it was outcome variable. Age, body mass index (BMI), APACHE, hospital stay and ICU stay were estimated as mean±SD or median (25th–75th percentile) and analyzed by independent sample t-test or Mann-whiny U test between patients with and without delirium. Frequency and percentages were computed for all categorical variables and analyzed by χ^2 test or Fisher's exact test. P values ≤0.05 were considered as statistically significant. In univariate analysis, those variables which had p value ≤0.20 were included in multivariable analysis. Multivariable logistic regression with forwarding Wald test was used to observe the factors associated with delirium. The goodness of fit of the models was examined by using Hosmer-Lemeshow goodness-of-fit tests.

RESULTS

From January to December 2016, we screened prospectively 200 patients who were admitted to SICU. A total of 87 patients were included who followed the inclusion criteria (figure 1). The average age of the patient was 43.29±17.38 and BMI was 26.25±3.57 kg/m^2. There were 62 (78.2%) male and 19 (21.8%) female patients. Comorbidities were observed in 57.7% (50/87) cases and a total of 26 patients had more than one comorbidity. Hypertension was found in 30 (34.5%), DM 17 (19.5%), COPD 13 (14.9%), IHD 7 (8%) and 19 (31.3%) had other comorbidities. Neurosurgical and general surgery procedure were commonly performed as presented in table 1.

Median APACHE II score, ICU stay and a hospital stay of the patients is also reported in table 1.

Delirium was assessed in five consecutive days in three time points on each day, there were 9.2% (8/87) patients who had

Table 1 Characteristics of the patients according to incidence of delirium

Variables	Delirium (n=19)	Non-delirium (n=68)
Age (years)	41.47±18.84	43.79±17.07
Weight (kg)	72.63±12.28	72.68±11.77
Height (cm)	167.16±8.17	165.88±6.54
BMI (kg/m^2)	25.91±3.36	26.36±3.63
Gender		
Male	14 (73.7%)	54 (79.4%)
Female	5 (26.3%)	14 (20.6%)
Comorbid	14 (73.7%)	36 (52.9%)
Hypertension	4 (21.1%)	26 (38.2%)
Diabetic mellitus	3 (15.8%)	14 (20.6%)
IHD	3 (15.8%)	4 (5.9%)
COPD	10 (52.6%)	3 (4.4%)
Others	3 (15.8%)	16 (23.5%)
Surgical procedure		
Neurosurgical	5 (17.2%)	24 (82.8%)
Gynecological	0 (0%)	4 (100%)
General	13 (28.3%)	33 (71.7%)
Others	1 (12.5%)	7 (87.5%)
APACHE II*	18 (15–22)	18 (16–20)
Length of ICU stay (days)*	8 (5–12)	5 (3–8)
Length of hospital stay (days)*	21 (11–26)	13 (8–21)

Data are presented as n (%), mean±SD.
*Median (25th–75th percentile).
APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IHD, ischemic heart disease.

delirium on day 1, 8.6% (6/79) on day 2, 2.7% (2/73) on day 3, 1.4% (1/71) on day 4 and 2.9% (2/70) on day 5. Cumulative incidence of delirium was observed in 21.8% (19/87) during the ICU stay. The onset of delirium commonly occurring on second day was 73.6% (14/19). In univariate analysis, COPD, fever, pain score >4 on visual analog scale, agitation, sedation, hypernatremia (Na >145), length of ICU stay ≥7 days and mortality were significantly high in those patients who developed delirium (table 2).

Midazolam and propofol were 4 times more likely to develop delirium as well as analgesic medication pethidine was also more likely to develop delirium in univariate analysis (table 3).

The stepwise multivariable logistic regression showed that increasing OR of COPD, inadequate pain relief (pain score >4) and hypernatremia were strong predictors of delirium (table 4) and in another model regarding the medication of sedation, midazolam (adjusted OR (aOR)=7.37; 95% CI 2.04 to 26.61) and propofol exposure (aOR=7.02; 95% CI 1.92 to 25.76) were the strongest independent predictors of delirium. Analgesic medications were not significant to predict delirium in multivariable analysis (table 5).

DISCUSSION

The overall incidence of delirium in our study is 21.8% in SICU, which is in the range, reported in the literature.[7 8] However, higher incidence was found in many other studies which is explained by differences in definitions of delirium, ICU population (medical or surgical), the severity of illness and the diagnostic tool used.[7 9 10] It is observed in our study that inadequate

Table 2 Factors associated with delirium in univariate analysis

Variables	N=87	With delirium (n=19)	Without delirium (n=68)	OR (95% CI)	P value
Age (years)					
≤40	42	12 (28.6%)	30 (71.4%)	2.17 (0.76 to 6.19)	0.142
>40	45	7 (15.6%)	38 (84.4%)	Ref	
Gender		14 (20.6%)			0.593
Male	68	5 (26.3%)	54 (79.4%)	0.726 (0.22 to 2.36)	
Female	19		14 (73.7%)	Ref	
BMI (kg/m^2)					
≥25	47	9 (19.1%)	38 (80.9%)	0.71 (0.26 to 1.97)	0.51
<25	40	10 (25%)	30 (75%)	Ref	
COPD					0.0005*
Yes	13	10 (76.9%)	3 (23.1%)	24.07 (5.55 to 104.33)	
No	74	9 (12.2%)	65 (87.8%)	Ref	
Intubation					0.677
Yes	78	18 (23.1%)	60 (76.9%)	2.4 (0.28 to 20.49)	
No	9	1 (11.1%)	8 (88.9%)	Ref	
Fever					0.009*
Yes	25	10 (40%)	15 (60%)	3.92 (1.35 to 11.42)	
No	62	9 (14.5%)	53 (85.5%)	Ref	
Infection				0.85 (0.27 to 2.69)	0.792
Yes	25	5 (20%)	20 (80%)	Ref	
No	62	14 (22.6%)	48 (77.4%)		
Pain ≥4					0.0005*
Yes	19	11 (57.9%)	8 (42.1%)	10.31 (3.19 to 33.29)	
No	68	8 (11.8%)	60 (88.2%)	Ref	
Agitation					0.0005*
Yes	40	17 (42.5%)	23 (57.5%)	16.63 (3.53 to 78.26)	
No	47	2 (4.3%)	45 (95.7%)	Ref	
Sedation					0.024*
Yes	54	16 (29.6%)	38 (70.4%)	4.21 (1.12 to 15.80)	
No	33	3 (9.1%)	30 (90.9%)	Ref	
Hypernatremia (serum sodium ≥145)					0.0005*
Yes	42	16 (38.1%)	26 (61.9%)	8.61 (2.28 to 32.46)	
No	45	3 (6.7%)	42 (93.3%)	Ref	
Serum creatinine ≥1.2					0.142
Yes	45	7 (15.6%)	38 (84.4%)	0.46 (0.16 to 1.31)	
No	42	12 (28.6%)	30 (71.4%)	Ref	
Length of ICU stay (days)					
<7 days	56	8 (14.3%)	48 (85.7%)	Ref	0.022*
≥7 days	31	11 (35.5%)	20 (64.5%)	3.3 (1.16 to 9.43)	
Length of hospital stay					0.291
≤10	32	4 (12.5%)	28 (87.5%)	Ref	
11–30	44	12 (27.3%)	32 (72.7%)	2.63 (0.76 to 9.07)	
>30	11	3 (27.3%)	8 (72.7%)	2.63 (0.48 to 14.23)	
Mortality					0.0005*
Yes	21	11 (52.4%)	10 (47.6%)	7.97 (2.57 to 24.72)	
No	66	8 (12.1%)	58 (87.9%)	Ref	

* p value<0.05
*p value <0.05
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

pain control, use of sedatives, hypernatremia and COPD are strongly related to development of delirium.

The relationship between opioid analgesics and delirium in critical care patients appear complex especially when examining the literature, given the seemingly conflicting results of observational studies. In ICU population, where opioids are used most often to treat pain (eg, in trauma and burn ICU populations), treatment with opioid analgesics has been associated with a

Table 3 Sedative and analgesic medication as risk factor of delirium in univariate analysis

Variables	N=87	Delirium (n=19)	OR (95% CI)	P value
Sedative medications				
Midazolam				
Yes	27	11 (40.7%)	4.46 (1.53 to 13.02)	0.004*
No	60	8 (13.3%)		
Propofol				
Yes	36	13 (36.1%)	4.24 (1.42 to 12.60)	0.007*
No	51	6 (11.8%)	Ref	
Analgesic medications				
Tramadol				0.199
Yes	29	4 (13.8%)	0.46 (0.14 to 1.53)	
No	58	15 (25.9$)	Ref	
Nalbuphine				
Yes	18	5 (27.8%)	1.51 (0.46 to 4.95)	0.493
No	89	14 (20.3%)		
Pethedine				
Yes	6	5 (83.3%)	23.93 (2.59 to 220.96)	
No	81	14 (17.3%)		
Morphine				0.502
Yes	8	1 (12.5%)	0.48 (0.05 to 4.19)	
No	79	18 (22.8%)	Ref	
Fentanyl				0.105
Yes	20	7 (35%)	2.46 (0.81 to 7.49)	
No	67	12 (17.9%)	Ref	
Steroid				
Yes	14	4 (28.6%)	1.55 (0.42 to 5.63)	0.506
No	73	15 (20.5%)	Ref	

reduced risk of delirium.[11] Conversely, in general medical and SICU populations, where opioids are frequently used for sedation (either alone or in conjunction with other sedating medications, particularly benzodiazepines), treatment with opioid analgesics has been associated with an increased risk of delirium, particularly when their use induces a coma.[11–13] However, there is significant reduction in delirium with good pain control.[14]

Apart from acute illness, delirium can be precipitated by administration of certain medications. These are antihistamines, anticholinergics, antibiotics, corticosteroids, benzodiazepines and metoclopramide.[15] Investigators have reported the use of lorazepam and midazolam are the independent risk factors for the development of ICU delirium, which is consistent with our findings. The absence of sedation protocol explains this result; but sedation, especially benzodiazepine, was implicated in delirium several times. In a study, including trauma and postoperative patients, midazolam increased the risk of delirium by

Table 4 Factors associated with delirium in multivariable logistic regression

Variables	P value	aOR	95% CI
COPD	0.003	55.02	4.60 to 745.67
Pain ≥4	0.003	56.55	3.93 to 816.19
Hypernatremia (serum sodium ≥145)	0.007	40.73	2.80 to 592.27
Sedation	0.072	8.71	0.82 to 91.89

Model accuracy=90.8%. Nagelkerke R^2=69.4%.
aOR, adjusted OR; COPD, chronic obstructive pulmonary disease.

Table 5 Multivariable analysis of sedative medication as risk factor associated with delirium

Variables	P value	aOR	95% CI
Age (years)			
≤40	0.142	2.53	0.74 to 8.7
>40		Ref	
Gender			
Male	0.296	0.46	0.11 to 1.96
Female		Ref	
BMI (kg/m²)			
≥25	0.699	1.27	0.38 to 4.30
<25		Ref	
Midazolam			
Yes	0.002	7.37	2.04 to 26.61
No			
Propofol			
Yes	0.003	7.02	1.92 to 25.76
No			

Model accuracy=83.9%. Nagelkerke R^2=33%.
aOR, adjusted OR; BMI, body mass index.

twofold to threefold[7]; hence, many studies were conducted to find an alternative for midazolam. Dexmedetomidine seems to be the most attractive choice in current literature.

Literature reported the risk of delirium is high in various diseases, for instance, hypertension, DM, myocardial ischemia, atrial fibrillation, peripheral vascular diseases, heart failure and COPD.[16] This study underlined the presence of COPD as significant risk in the development of delirium in SICU. The most possible explanation is the occurrence of psychological disturbances caused by hypoxemia, hypercapnia and tobacco withdrawal. Furthermore, patients with COPD are frequently treated with corticosteroids, which is itself a risk factor for delirium but in this study, steroid association with delirium could not be ascertained. Most of the patients were prescribed intravenous hydrocortisone for the treatment of septic shock.

The presence of electrolyte disorders or an abnormal electrolyte channel is associated with many neuropsychiatric disorders including dementia.[17] Several previous studies have shown that fluid/electrolyte disorders are closely related to delirium.[18 19] In the present study, we found that the risk of postoperative delirium in patients with electrolyte disturbances (hypernatremia; serum sodium >145) was higher than that of individuals with normal electrolytes. The result of this study is comparable to previous paper that described disturbance in sodium level was a very important risk factor for delirium.[20] We believe that an effective balance of fluid and electrolytes is important for the prevention of delirium in ICU.

Fever is also an important risk factor in the development of delirium in ICU. In univariate analysis, we have found a significant correlation between fever and delirium. Elevated body temperature increases brain metabolic activity and the demand for oxygen supply to the brain, which might compromise cerebral cellular metabolism in old patients with pulmonary and cardiovascular diseases. Fever is probably usually a symptom of infections, which could give rise to mental changes as a result of cytokines and/or bacterial toxins and cerebral metabolic changes.[21] In our study, all-cause hospital mortality was higher in patients with delirium, which is consistent with the current data available on delirium.[21 22]

The data from low-income andmiddle-income countries worldwide describing the prevalence of delirium are limited as most of the representation comes from Europe and high-income countries. What is the risk of delirium in low-income andmiddle-income countries? Not very much explicit from published papers. On this subject, these data can be a source of information related to the incidence of delirium to better understand its pattern and outcome. It will also help in designing appropriate future clinical studies.

This study has some shortcomings as it was a single-center study. Follow-up was restricted to 5 days only; therefore, we were not able to address the impact of delirium on long-term morbidity and mortality in our population. Delirium is managed with various ways (ie, physical restraint, sedatives, antipsychotics), and such diverse approaches may have impact on clinical outcomes. Also delirium was measured as a dichotomous variable without taking into consideration the severity and duration. Considering that delirium is a predictor of mortality, prolonged cognitive impairment and higher cost of care, interventional studies should be conducted to determine whether alternative management strategies are associated with reductions in delirium and other short-term and long-term clinical outcomes in the critically ill population.

CONCLUSION

Delirium is a significant entity with poor outcome in SICU. Inadequate pain control, sedative medication, COPD, hypernatremia and fever are important modifiable risk factors, which should be controlled with appropriate management. More studies are warranted to confirm these findings in surgical group of patients distinctively.

Contributors AAA, MH, WA and MH developed the concept of study. AAA and SAR contributed to the study question and design. AAA, MH, WA, FK and BS contributed in literature search data analysis and interpretation; prepared the draft of the report and contributed to subsequent versions. AAA and BS contributed in drafting of the final report. MH, WA, AR and MFK contributed to the data analysis and interpretation, and drafting of the final report. All authors approved the final version. AAA is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by Aga Khan University Ethics Committee (3210-Ana-ERC-14) and participants gave informed consent before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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