Australian Critical Care xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc

Long-term cognitive impairment and delirium in intensive care: A prospective cohort study☆

Marion L. Mitchell PhD, Centaur Fellow[a,b,c,d,*]
David H.K. Shum PhD, FAPS[b,e]
Gabor Mihala GCert Biostat[b,f,g]
Jenny E. Murfield BSc (Hons)[b,c]
Leanne M. Aitken PhD, FAAN, FACN, FACCCN[a,b,c,d,h]

[a] NHMRC Centre for Research Excellence in Nursing, Griffith University, Nathan Campus, Brisbane, Queensland, Australia
[b] Menzies Health Institute Queensland, Griffith University, Nathan Campus, Brisbane, Queensland, Australia
[c] School of Nursing and Midwifery, Griffith University, Nathan Campus, Brisbane, Queensland, Australia
[d] Princess Alexandra Hospital Intensive Care Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia
[e] School of Applied Psychology, Griffith University, Mt. Gravatt Campus, Brisbane, Queensland, Australia
[f] School of Medicine, Griffith University, Logan Campus, Meadowbrook, Queensland, Australia
[g] Centre for Applied Health Economics, Griffith University, Logan Campus, Meadowbrook, Queensland, Australia
[h] School of Health Sciences, City University London, London, UK

ARTICLE INFORMATION

Article history:
Received 6 February 2017
Received in revised form 6 July 2017
Accepted 9 July 2017

Keywords:
Cognition
Critical illness
Delirium
Intensive care units
Long-term effects
Patient outcome assessment

ABSTRACT

Background: Whilst there is a growing body of research exploring the effect of delirium in intensive care unit (ICU) patients, the relationship between patient delirium and long-term cognitive impairment has not been investigated in settings where low rates of delirium have been reported.
Objectives: To assess the association between the incidence of delirium, duration of mechanical ventilation and long term cognitive impairment in general ICU patients.
Methods: Prospective cohort study conducted in a tertiary level ICU in Queensland, Australia. Adult medical and surgical ICU patients receiving ≥12 h mechanical ventilation were assessed for delirium on at least one day. Cognitive impairment was assessed at three and/or six-months using the: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Trail Making Test (TMT) Part A and B; and Mini-Mental State Examination (MMSE).
Results: Of 148 enrollees, 91 (61%) completed assessment at three and/or six months. Incidence of delirium was 19%, with 41% cognitively impaired at three months and 24% remaining impaired at six months. Delirium was associated with impaired cognition at six-months: mean TMT Part A scores (information processing speed) were 7.86 s longer than those with no delirium ($p = 0.03$), and mean TMT Part B scores (executive functioning) 24.0 s longer ($p = 0.04$).
Conclusions: ICU delirium was positively associated with impaired information processing speed and executive functioning at six-months post-discharge for this cohort. Testing for cognitive impairment with RBANS and TMT should be considered due to its greater sensitivity in comparison to the MMSE.

1. Introduction

Delirium is a common neuropsychiatric syndrome that, although occurring in a range of healthcare settings, is particularly prevalent in hospitalised intensive care unit (ICU) patients. However, the incidence of ICU delirium varies widely worldwide—23–84% in North America[1–4]; 15%–39% in Europe[5,6]; 63% in Asia[6]; and 12%–45% in Australia.[6,7] Reasons for these disparities include differences in the severity of illness of ICU patients

☆ Where the work was performed: The work was carried out at Griffith University (School of Nursing and Midwifery, Nathan Campus) and the Princess Alexandra Hospital Intensive Care Unit, Brisbane, Queensland, Australia.

* Corresponding author at: School of Nursing and Midwifery, Health Sciences Building (N48), 170 Kessels Road, Nathan, Queensland 4111, Australia.
E-mail address: marion.mitchell@griffith.edu.au (M.L. Mitchell).

http://dx.doi.org/10.1016/j.aucc.2017.07.002
1036-7314/

between countries,[3] methodological differences in research, the fluctuating nature of delirium and the inability of clinicians to detect delirium.[8] Models of care differ in relation to sedation and mobilisation practices which affect rates of delirium in ICU patients.[1]

Delirium in the ICU patient has been associated with various risk factors including patient age[6]; excessive alcohol consumption[6]; psychoactive medications including benzodiazepines and opioids[9]; mechanical ventilation[10]; coma; infection; metabolic acidosis and severity of illness.[6] Adverse patient outcomes, both during hospitalisation and in the longer-term, post-discharge are also reported.[11–18] These include prolonged mechanical ventilation[15]; increased ICU and hospital length of stay (LOS)[15]; increased risk of in-hospital falls[16]; increased risk of post-traumatic stress symptoms[12]; reduced quality of life post-discharge[11]; increased risk of newly acquired functional disability in activities of daily living post-discharge[2]; and increased mortality rates.[11] In addition, patients are also at an increased risk of cognitive impairments months to years after ICU.[19] Whilst improvements in cognitive function typically occur in the first year post ICU discharge,[20] between a quarter and half of ICU survivors report persistent impairment at one,[3,4] two,[21] and six years.[22] Both longer duration of delirium[4,5] and, more recently, greater severity of delirium,[23] have been identified as risk factors of cognitive impairment. Analgesics and sedative medications have also been posited as possible mechanisms through which both delirium and cognitive impairment develops,[19] although findings to date remain mixed.[4,24]

Whilst there is a growing body of research exploring the effect of delirium in ICU patients, the relationship between patient delirium and cognitive impairment has limited reports of investigation in settings where low rates of delirium have been reported.[6,11,17,18] Consequently, the current study sought to explore the association between the incidence of delirium, duration of mechanical ventilation and patients' cognition at three and six-months post ICU discharge. To aid international comparison, the study design was based on that conducted in the USA by Girard et al.,[3] which was the first prospective cohort study to identify delirium as a predictor of long-term cognitive impairment at three and 12-months post-discharge All risk factors, covariates and outcomes were determined a priori and based on Girard et al.'s work.[3] However, limitations of Girard et al.'s study included the exclusion of surgical patients, and the study being nested within a sedation and weaning protocol clinical trial[3] which may have had some inadvertent impact on the results.

2. Methods

2.1. Study design, sample, and setting

This prospective cohort study was conducted in the ICU at a tertiary referral teaching hospital in Australia. The 750-bed hospital has a 25-bed ICU with approximately 2200 adult surgical, medical and trauma patients admitted yearly.

ICU nurses with advanced knowledge and previous training in all aspects of research including screening, data collection and data entry worked as research nurses for the project. They screened ICU patients daily for inclusion, with those aged ≥18 years and mechanically ventilated for ≥12 h eligible. Patients were excluded if they: were not receiving active ICU treatment as determined in discussion with the ICU consultant (i.e., palliative care); were unable to communicate in English; were likely to be inaccessible in-person (i.e., geographically) for follow-up; had a pre-existing neurological deficit that prevented independent living[3]; or had a traumatic brain injury with a Glasgow Coma Scale[24] score <14.

Ethical approval for the study was granted by the relevant Human Research Ethics Committees (HREC/11/QPAH/230; NRS 34/11/HREC). Ethical principles stated in the Declaration of Helsinki and the National Statement on Ethical Conduct in Research Involving Humans were adhered to. Patient's next of kin provided written informed consent at study enrolment, with subsequent written consent obtained from the patient prior to discharge and confirmed before subsequent assessments.

2.2. Risk factors, covariates, and outcomes

2.2.1. Risk factors

The primary predictor was the number of delirium days the patient experienced in the ICU. Duration of delirium was defined as the number of days, to a maximum of 28, participants were assessed as positive using the Confusion Assessment Method for the ICU (CAM-ICU)[25] at least once each day. Participants assessed as having a Richmond Agitation-Sedation Scale (RASS)[26] score of −4 or −5 (i.e. deeply sedated) were not assessed for delirium in line with instructions for use of the CAM-ICU.[25] Both the RASS and CAM-ICU are routinely used in the study ICU.

A secondary predictor variable was the duration of mechanical ventilation (defined as the time from endotracheal intubation to successful extubation and unassisted ventilation). In keeping with Girard et al.,[3] duration of mechanical ventilation was included to explore the possibility that it was a predictor of cognitive impairment.[12,27]

2.2.2. Covariates

Covariates included: age; sex; highest level of education; admission diagnosis; severity of illness (Acute Physiology and Chronic Health Evaluation II and III scores [APACHE II & III])[28,29]; ICU LOS; hospital LOS; total doses administered in ICU of propofol, benzodiazepines (milligram [mg] of lorazepam equivalent using the following conversion formulas: 1 mg of lorazepam equals: 0.5 mg of alprazolam; 5 mg of diazepam; 2.5 mg of midazolam; 15 mg of oxazepam; and 15 mg of temazepam [personal email correspondence with Girard TD, 11th September 2014]), and opioids (mg of fentanyl equivalent using the following conversion formulas: 1 mg of fentanyl equals 70 mg of methadone; 66.7 mg of morphine; 10 mg of oxycodone; and 0.83 mg of remifentanyl).

2.2.3. Outcomes

The primary outcome was participants' cognitive status at three and six-months post ICU discharge. Cognitive assessment was conducted by trained psychologists blinded to the details of each participant's critical illness and number of delirium days. Assessment was undertaken face-to-face at the participant's home, the hospital, or the university's Psychology Clinic. Three validated measures were used to assess participant's cognition:

1) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[30] profiles cognitive impairment across five domains that are each comprised of sub-tests that provide raw scores, adjusted for age, to give a standardized index score for domain and an overall score (mean 100; *SD* = 15). Lower scores indicate worse cognitive functioning. RBANS has demonstrated reliability and validity in various contexts and countries,[30,31] and Australian normative data are available.[31] In this study, participant's scores were categorized as: no cognitive impairment; mild-moderate cognitive impairment; severe cognitive impairment based on their standardized index scores using the procedures found in Girard et al.'s study.[3] That is, participants were classified as mildly to moderately impaired if they scored 1.5 *SD* below the mean on two of the index scores or 2 *SD* below the mean on one of the index scores. They were classified as

Please cite this article in press as: Mitchell ML, et al. Long-term cognitive impairment and delirium in intensive care: A prospective cohort study. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.07.002