Journal of Critical Care 42 (2017) 268–274

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Delirium and exposure to psychoactive medications in critically ill adults: A multi-centre observational study

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ARTICLE INFO

Keywords:
Delirium
Anticholinergic
Benzodiazepine
Opioid
Intensive care

ABSTRACT

Purpose: Investigate the relationship between psychoactive drugs and delirium.
Materials and methods: Prospective observational study of 520 critically ill adult patients admitted ≥24 h to 6 intensive care units (ICUs). Data were collected on psychoactive drug exposure, use of sedation administration strategies, and incident delirium (Intensive Care Delirium Screening Checklist score ≥ 4).
Results: Delirium was detected in 260 (50%) patients, median (IQR) duration 2 (1–5) days, and time to onset 3 (2–5) days. Delirious patients received more low-potency anticholinergic ($P < 0.0001$), antipsychotic ($P < 0.0001$), benzodiazepine ($P < 0.0001$) and non-benzodiazepine sedative ($P < 0.0001$), and opioid ($P = 0.0008$) drugs. Primary regression (24-hours preceding drug exposure) revealed no association between any psychoactive drug and delirium. Post-hoc analysis (extended 48-hour exposure) revealed an association between delirium and high-potency anticholinergic (HR 2.45, 95% CI 1.08–5.54) and benzodiazepine (HR 1.08 per 5 mg midazolam-equivalent increment, 95% CI 1.04–1.12) drugs. Delirious patients had longer ICU ($P < 0.0001$) and hospital ($P < 0.0001$) length of stay, and higher ICU and hospital mortality ($P = 0.003$ and $P = 0.007$, respectively).
Conclusions: The identification of psychoactive drugs as modifiable delirium risk factors plays an important role in the management of critically ill patients. This is particularly important given the burden of exposure and combinations of drugs used in this vulnerable patient population.

1. Introduction

Delirium, an acute confusional syndrome, has been associated with adverse short- and long-term clinical outcomes in critically ill patients, including prolonged duration of mechanical ventilation, ICU and hospital length of stay, functional and cognitive decline, and increased mortality [1-4]. Given these negative sequelae, delirium is considered a substantial burden to patients, their families, and the health care system [5-7]. Numerous pharmacological and non-pharmacological strategies have been investigated for delirium treatment in both ICU and non-ICU settings, yet none consistently demonstrates improved outcomes in clinical trials [8]. As a result, delirium prevention strategies, such as the evaluation and modification of risk factors, are prioritized by current critical care practice guidelines [8]. In line with an emphasis on prevention, a recent systematic review identified 11 delirium risk factors, supported by moderate or strong evidence [9]. However, only two of these risk factors, those related to drug therapy (i.e. sedative-associated coma,

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http://dx.doi.org/10.1016/j.jcrc.2017.08.003
0883-9441/

increased risk, and dexmedetomidine, decreased risk), are potentially modifiable [9].

Psychoactive drugs such as benzodiazepines, non-benzodiazepine sedatives (e.g., propofol), opioids, and compounds with anticholinergic activity can directly or indirectly affect numerous neurotransmitter systems (e.g., cholinergic, dopaminergic, serotonergic, and gamma-amino butyric acid) implicated in the development of delirium [7]. It is therefore plausible psychoactive drugs can influence delirium and its trajectory. At this time, however, studies have not shown a consistent association between any psychoactive drug class and the development of delirium [10-19]. Conflicting evidence is likely due to methodological heterogeneity of available studies such as patient population, small sample sizes, and insufficient methods confirming exposure and outcomes (for example, most studies do not confirm timing of drug exposure prior to delirium). Because psychoactive drugs are commonly used in the ICU [8,20], further clarification of this potential relationship is imperative to optimize prescribing practice. To this end, we conducted a multicentre prospective, observational study of critically ill adults with the primary objective of investigating the relationship between exposure (24 h prior) to psychoactive drugs and the development of delirium. Our secondary objectives were to report the outcomes for the cohort (e.g., length of stay, mortality).

2. Methods

2.1. Design and setting

We conducted a prospective observational study in six mixed adult ICUs between June 2011 and September 2012. These ICUs admitted medical, surgical, cardiac, neurologic and trauma patients. The research ethics board at each participating institution approved the study and waived the need for informed consent because of the non-interventional study design.

Patient management was left to the discretion of each site's respective ICU clinical teams, including the selection and titration of all drugs and strategies for sedation, analgesia, and delirium prevention and treatment. Sedation assessment at all six sites was performed every 1 to 4 h using the Sedation-Agitation Scale (SAS) by bedside nursing staff as standard practice [21]; delirium was assessed daily using the Intensive Care Delirium Screening Checklist (ICDSC) by research staff with the assistance of bedside nursing staff [22]. Delirium was scored once daily in the afternoon considering the day shift and previous night shift.

2.2. Participants

We included all patients ≥18 years of age admitted for ≥24 h to one of the six participating ICUs. Patients were ineligible if unable to communicate in English or French (Quebec sites only), had acute severe head trauma (Glasgow Coma Scale < 9) [23], or were comatose at the time of screening. A comatose state was defined as either a score of A (no response) or B (the need for vigorous stimulation (e.g., pain) to obtain any response) on item 1 of the ICDSC, which also precluded delirium assessment [22]. Patients initially presenting as comatose were subsequently eligible for study enrolment if coma resolved. No other inclusion or exclusion criteria were applied.

2.3. Measurements and outcomes

Research staff collected data pertaining to delirium and drug exposure daily until the patient was discharged from the ICU. The primary outcome of interest was delirium, defined as an ICDSC score ≥ 4. Delirium status was categorized each day as *comatose* (i.e., score of A or B on item 1 of ICDSC), *delirious* (i.e., score of C, D or E on item 1, and a total score ≥ 4), or *not delirious* (i.e., score of C, D or E on item 1, and a total score < 4). We quantified all psychoactive drugs exposure to benzodiazepines, non-benzodiazepine sedatives (i.e. propofol, dexmedetomidine, and ketamine), opioids, antipsychotics, and drugs with anticholinergic activity [24]. Secondary outcomes were to report duration of invasive mechanical ventilation, ICU and hospital length of stay, ICU and hospital mortality, and disposition at hospital discharge.

We developed a standardized case report form to collect relevant data including drug type, dose, route, and time of administration, and use of sedation administration strategies (e.g., sedation protocol, daily interruption of continuous sedative or analgesic infusions). Research staff reviewed electronic pharmacy and written medication administration records to ascertain patients' psychoactive drug exposure each day of their ICU admission. We recorded in-hospital drug exposure in the 24 h preceding ICU admission and prior to hospital admission (i.e. Best Possible Medication History) [25].

We collected data pertaining to variables potentially associated with delirium [9,13,15,17,26], including: age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score [27], ICU admission type (surgical, medical, trauma), location prior to ICU admission, comorbidities (e.g., hypertension), visual and auditory impairment, smoking history (and use of nicotine replacement therapy), and significant alcohol consumption (i.e. ≥ 2 drinks daily or ≥26 oz of 40% alcohol weekly) [13,26]. We collected the following data on a daily basis: total number of administered medications (as a marker of polypharmacy), use of corticosteroids, beta blockers, epidural catheters, chest tubes, urinary catheters, and physical restraints, total number of intravenous catheters, use of isolation precautions, presence of visible window(s), media access (e.g., television, computer, radio), visibility of a functional clock, and mobilization (e.g., dangling, ambulation).

2.4. Statistical analysis

Based on published data and our own sedation research program [1,4,20,26,28-30], we assumed at least 30% of ICU patients would screen positive for delirium at least once during their ICU stay, and 70% would be prescribed at least one psychotropic drug (range of 50–90%). Therefore, using an expected hazard ratio of 2.0 (alpha 0.05, beta 0.20) and a conservative correlation of 0.5 for covariate adjustment, we required a sample size of 520 patients.

We used descriptive statistics to report baseline demographic and clinical variables for patients with and without delirium. We compared continuous data using Student t or Mann Whitney tests, and categorical data using χ^2 or Fisher Exact test, as appropriate. We determined the total daily and cumulative (i.e., over entire ICU admission) dose of propofol, fentanyl and midazolam equivalents, and the number of drugs with low or high anticholinergic potency, received in each 24-hour period. We converted opioids to fentanyl equivalents (e.g., 0.1 mg fentanyl = 10 mg morphine = 2 mg hydromorphone) and benzodiazepines to midazolam equivalents (e.g., 1 mg midazolam = 0.5 mg lorazepam) [29], We categorized anticholinergic activity based on a systematic review by Duran and colleagues that used a quantitative grading tool to classify the potency of 225 drugs as either low or high [24]. Examples of drugs categorized as high anticholinergic activity were diphenhydramine, dimenhydrinate, ipratropium, atropine, scopolamine; examples of drugs categorized as low anticholinergic activity were ranitidine, trazodone, olanzapine, risperidone, and haloperidol.

We used Cox regression modeling to evaluate the association between delirium and delirium risk factors in the preceding 24 h selected a priori based on previous studies and investigator consensus [9,13,15,17,26]. Fixed factors considered in the model were age, APACHE II score on admission, smoking, history of significant alcohol consumption, history of hypertension, presence of pre-existing neurologic condition (e.g., dementia, stroke, neuromuscular disease, seizure disorder), ICU admission type (e.g., surgery), and mechanical ventilation. Time-varying factors (i.e., exposure or presence may vary each day) considered in the model were benzodiazepines, non-benzodiazepine sedatives, opioids, low- and high-potency anticholinergic drugs, β-blockers, corticosteroids, pH < 7.2, and physical restraint. We conducted a post hoc analysis using a