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Emergence from general anaesthesia and evolution of delirium signs in the post-anaesthesia care unit

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Editor's key points

- Limited evidence suggests that early postoperative delirium is associated with worse outcome.
- The authors determined the incidence of emergence agitation and delirium among 400 adult patients.
- On post-anaesthesia care unit admission, 31% of patient had signs of delirium.
- Further studies are needed to confirm an association with adverse outcomes.

Background. Emergence from anaesthesia is often accompanied by signs of delirium, including fluctuating mental status and inattention. The evolution of these signs of delirium requires investigation since delirium in the post-anaesthesia care unit (PACU) may be associated with worse outcomes.

Methods. Adult patients emerging from anaesthesia were assessed for agitated emergence in the operating room using the Richmond Agitation-Sedation Scale (RASS). The Confusion Assessment Method for the Intensive Care Unit was then used to evaluate delirium signs at PACU admission and during PACU stay at 30 min, 1 h, and discharge. Signs consistent with delirium were classified as hyperactive *vs* hypoactive based upon a positive CAM-ICU assessment and the concomitant RASS score. Multivariable logistic regression was utilized to assess potential risk factors for delirium during PACU stay including age, American Society of Anesthesiologists classification, and opioid and benzodiazepine exposure.

Results. Among 400 patients enrolled, 19% had agitated emergence. Delirium signs were present at PACU admission, 30 min, 1 h, and PACU discharge in 124 (31%), 59 (15%), 32 (8%), and 15 (4%) patients, respectively. In patients with delirium signs, hypoactive signs were present in 56% at PACU admission and in 92% during PACU stay. Perioperative opioids were associated with delirium signs during PACU stay (P=0.02).

Conclusions. A significant proportion of patients develop delirium signs in the immediate postoperative period, primarily manifesting with a hypoactive subtype. These signs often persist to PACU discharge, suggesting the need for structured delirium monitoring in the PACU to identify patients potentially at risk for worse outcomes in the postoperative period.

Keywords: anaesthesia; complications; delirium

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Delirium is an acute brain organ dysfunction characterized by changes in level of consciousness, inattention, and disorganized thinking. Delirium can manifest with hyperactive signs (i.e. hyperactive subtype with agitation and restlessness) or with hypoactive signs (i.e. hypoactive subtype with lethargy and inattentiveness). It is extremely common throughout the hospital, with 60–80% of mechanically ventilated patients and 20–50% of patients with a lower severity of illness developing delirium at some point during their hospital course.[1–3] Studies in surgical patients focusing on delirium in the first few postoperative days[4–14] have found that this brain organ dysfunction is independently associated with increased length of stay, higher cost of care, prolonged cognitive impairment, and increased mortality, similar to that reported in general hospital patients.[4 15–18] The course of this brain dysfunction in the immediate postoperative period, however, is not well characterized.

Recent data suggest that even early postoperative delirium – at post-anaesthesia care unit (PACU) discharge – may be associated with worse outcomes[14] and that delirium in the PACU is likely predictive of further delirium in the postoperative course.[13] Unfortunately, delirium diagnosis in this period is confounded by the fact that emergence from general anaesthesia often presents with signs similar to delirium with alterations in mental status, inattentiveness, and disorganized thinking. We hypothesized that delirium signs would be most common immediately after general anaesthesia and decrease over time, that signs would persist in a significant number of patients at PACU discharge, that hypoactive features (often underdiagnosed in this setting)

would be frequent, and that certain patient and anaesthetic characteristics (e.g. age, drug exposure) would predict increased probability of delirium signs. We, therefore, performed a prospective cohort study of patients undergoing general anaesthesia and assessed them for level of arousal using the Richmond Agitation-Sedation Scale (RASS)[19] and for delirium signs using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[1] at multiple time points immediately after general anaesthesia.

Methods

Study design and patient population

This prospective observational study was approved by the Vanderbilt University Institutional Review Board with waiver of consent due to the non-interventional nature of the study. The principle investigator (EC), experienced in CAM-ICU[1] delirium assessments, first trained five PACU nurse investigators in delirium assessment. We included non-cardiac surgery patients admitted to the PACU at Vanderbilt University Medical Center after general anaesthesia with volatile anaesthetics. These patients were assigned by the charge nurse (in the usual round-robin, rotation fashion) to the PACU nurse investigators, as is standard PACU practice of assigning patients to PACU nurses/beds. Thus, this was a prospective convenience sample study of patients assigned randomly to our five nurse investigators. Exclusion criteria included non-English speaking or deaf patients and those with a history of severe dementia, anoxic brain injury, or neuromuscular disorders as documented in the patient's medical record by his/her treating physicians.

Data collection

Data collected included de-identified demographics (age, gender, race, American Society of Anesthesiologists [ASA] classification), health history (comorbid diseases, chronic alcohol or illicit drug use, and smoking status), details of anaesthetic course (length of anaesthetic exposure, inhaled agent used, induction agent and dose, and lowest intraoperative vital signs [temperature, oxygen saturation, systolic and diastolic blood pressure]), perioperative medications (benzodiazepines, opioids, ketamine), PACU vital signs (lowest temperature, oxygen saturation, systolic and diastolic blood pressure), blood product administration, Aldrete scores,[20] and verbal pain scores.

Assessments and definitions

A multidisciplinary focus group of anaesthesiologists, intensivists, and nurses (including but not restricted to the authors) determined face valid definitions for agitated emergence and PACU delirium signs based on review of literature and expert opinion. Agitated emergence was defined as agitation after discontinuation of the inhaled anesthetic based on RASS score of $+1$ to $+4$ as reported by in-room anaesthesia providers. Patients were assessed for delirium signs using the CAM-ICU performed by the trained nurse investigators at PACU admission, at 30 min, at 1 h, and at discharge from the PACU. The CAM-ICU has been validated against the *Diagnostic and Statistical Manual of Mental Disorders-IV*[21] in both ventilated and non-ventilated verbal patients[1 22–24] and can be rapidly and accurately performed by bedside nurses. The CAM-ICU has a higher specificity than sensitivity for delirium when used in the PACU[25]; thus, we expected fewer false positives than false negatives, thereby taking a conservative approach to the determination of the incidence of delirium signs in our cohort. Delirium signs were defined as being present if patients were CAM-ICU positive at any time point. Hyperactive delirium signs were defined as a RASS score of $+1$ to $+4$ (i.e. agitated patient) accompanying a positive CAM-ICU. Hypoactive delirium signs were defined as a RASS score of -3 to 0 (i.e. somnolent or calm patient) accompanying a positive CAM-ICU. Postoperative delirium (not assessed in this study) was defined as delirium that continued beyond the PACU or occurred in the hospital ward or the ICU.

Statistical analysis

Descriptive data are presented as medians (with interquartile ranges [IQR]) and percentages where applicable. We used a multivariable logistic regression model to study the associations of perioperative risk factors with the occurrence of delirium signs during PACU stay (dependent variable). For the regression model alone, having PACU delirium signs was classified as a positive CAM-ICU at 30 min, at 1 h, or at PACU discharge (thus excluding the assessment upon arrival to the PACU for this was considered continuation of emergence from general anaesthesia). The following a priori defined risk factors were assessed: age, ASA classification, opioid exposure (fentanyl equivalents), and benzodiazepine exposure (midazolam equivalents). A sensitivity analysis was performed adjusting for anaesthetic duration in addition to these above mentioned risk factors, as a recent study demonstrated surgical duration to be associated with postoperative delirium.[14] In the statistical model, opioid doses were transformed using their cube root to reduce the influence of extreme outliers, and continuous variables were modelled using restricted cubic splines to allow for nonlinear associations. Benzodiazepine exposure was categorized into three categories (0, 0.5–2, and >2 mg) owing to sparseness of data.

Per standard recommendations, each degree of freedom for our multivariable model required 10 cases of delirium in order to reliably fit the model. Thus, a multivariable model with a complexity of 7 degrees of freedom would require at least 70 patients with delirium.[26] We anticipated our PACU delirium signs rate to be approximately 20% in this cohort of general surgical patients, thus our study had a planned enrollment of 400 subjects into the cohort to be able to evaluate the risk factors of interest. Because missing data rarely occur entirely randomly, excluding such patients may have biased our results.[27] Thus, we used multiple imputation to account for missing variables at time of modelling, which occurred in 9 patients (2.3%). We calculated optimization to assess potential overfitting. Smaller optimization is indicative of less overfitting, and optimization <0.20 indicates a model with good predictive ability (lack of overfitting). Optimization in our PACU delirium model was 0.14, confirming that the model was not