Perioperative Risk Factors for Postoperative Delirium in Patients Undergoing Esophagectomy

Running Head: Risk Factors for Postoperative Delirium

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Abstract

Background: Postoperative delirium affects up to 50% of patients undergoing esophagectomy and is associated with negative outcomes. The perioperative risk factors for delirium in this population are not well understood. We conducted this study to assess perioperative risk factors for postoperative delirium among esophagectomy patients.

Methods: We performed a secondary data analysis of patients enrolled in a randomized controlled trial evaluating the efficacy of haloperidol prophylaxis postoperatively in reducing delirium among esophagectomy patients. Postoperative delirium was assessed twice daily using the Confusion Assessment Method for the ICU. Univariate and logistic regression analyses were performed to examine the association between perioperative variables and development of postoperative delirium.

Results: Of 84 consecutive esophagectomy patients, 27 (32%) developed postoperative delirium. Patients who developed postoperative delirium had higher APACHE II scores [22.1 (6.5) versus 17.4 (6.8); p=0.003], longer mechanical ventilation days [1.7 (1.4) versus 1.0 (1.1); p=0.001], and longer ICU days [5.1 (2.6) versus 2.6 (1.6); p<0.001]. In a logistic regression model, only ICU length of stay was found to have significant association with postoperative delirium [OR 1.65; 95% CI 1.21-2.25].

***Conclusions*:** ICU length of stay was significantly associated with postoperative delirium. Other perioperative factors including duration of surgery, blood loss, and hemoglobin levels were not significantly associated with postoperative delirium.

Abstract: 207 words

Postoperative delirium is a common surgical complication associated with negative outcomes such as increased risk of death, institutionalization, and cognitive impairment [1]. Patients undergoing esophagectomy are particularly at risk, with delirium incidence rates as high as 50% [2]. Predisposing factors include advanced age, preexisting cognitive impairment, history of alcohol abuse, vision and hearing impairment, and frailty [3-6]. Furthermore, longer duration of surgery [7], increased blood loss [8], lower postoperative hemoglobin [9], increased number of transfusions [9, 10], intraoperative hypotension [9, 11], and deeper plane of anesthesia [7,12] have been identified as risk factors for postoperative delirium in previous retrospective studies of heterogeneous surgical populations.

Current clinical practice guidelines' recommendations include avoidance of benzodiazepines, adequate pain control, consideration of antipsychotic agents [4, 13], dexmedetomidine infusion for sedation [14], and multicomponent, non-pharmacological interventions to prevent and manage delirium [6, 15, 16]. The focus remains on postoperative management, however, as prospective studies on intraoperative risk factors and management techniques are still limited.

Despite the increased risk of delirium in esophagectomy patients, perioperative risk factors in this population are not well studied. We conducted this analysis to examine the association between perioperative factors, specifically intraoperative factors, and the development of postoperative delirium in esophagectomy patients.

Patients and Methods

Participants were enrolled in PEPOD, a randomized, double-blind, placebo-controlled single center clinical trial comparing scheduled low dose haloperidol versus placebo for delirium prevention in postoperative non-cardiac thoracic surgery patients. The study was conducted from September 2013 until December 2015 at Indiana University Health University Hospital, a tertiary care center. The study was approved by the Institutional Review Board of Indiana University. All patients provided the informed consent prior to enrollment.

Eligible patients were English-speaking, aged 18 years or older, undergoing elective thoracic surgery. Patients were excluded from the study if they had a history of severe dementia, alcohol abuse, schizophrenia, Parkinson's disease, or neuroleptic malignant syndrome. Patients were also excluded if they were pregnant or nursing, on cholinesterase inhibitors or levodopa, or if they had a corrected QT interval > 500 milliseconds. For our analysis, we only included patients undergoing esophagectomy.

Demographic and clinical data were collected from the electronic medical record. Consented patients underwent a thorough preoperative evaluation and baseline data collection including neuropsychological testing, medication history, chronic co-morbidities, acute physiology and chronic health evaluation II (APACHE II) score, and other demographic characteristics. The anesthesia record was reviewed for intraoperative data. Type of procedure, duration of surgery, intraoperative medications given, amount of blood loss, amount of fluid administration, and number of blood units transfused were recorded. Depth of anesthesia such as bispectral index (BIS) was not monitored in most cases.

Postoperative data were collected through the electronic medical record and included immediate postoperative hemoglobin, lowest postoperative hemoglobin, number of blood units transfused, daily sedatives and analgesics exposure, use of epidural analgesia, duration of mechanical ventilation in the intensive care unit (ICU), length of ICU stay, and length of hospital stay. Labs were drawn daily or more frequently depending on clinical situation, and lowest postoperative hemoglobin was defined as the lowest hemoglobin value recorded during the hospital stay following surgery. The timing of the lowest postoperative hemoglobin was also recorded in postoperative days.

We used the Confusion Assessment Method for the ICU (CAM-ICU) to detect delirium among patients during their ICU and hospital stay [17]. As delirium is a fluctuating disorder, we conducted two delirium assessments performed by trained research assistants each day at different time points to maximize delirium identification. Prior to applying CAM-ICU, Richmond Agitation Sedation Scale (RASS) was used to assess patient's eligibility for delirium assessment [18]. Patients with a RASS score of -4 and -5 with lack of response to verbal or physical stimuli were characterized as comatose and were not eligible for CAM-ICU assessments.

Any patients who had at least one CAM-ICU positive episode during their hospital stay were categorized as delirium positive. We used the Fisher's exact test for categorical variables and the Wilcoxon Rank Sum test for continuous variables to compare demographics and surgery related factors across delirium status. Logistic regression analyses were performed to examine the association between perioperative variables and development of postoperative delirium. To avoid overfitting, each potential risk factor was examined by univariate analysis. In the final logistic regression model, variables showing univariate significance as well as intervention status were included. All analyses were conducted using SAS v9.4.

Results

In the parent trial, 132 esophagectomy patients were screened, and 84 were randomized. Forty-two of these patients (50%) were allocated to intervention (haloperidol) and the remaining 42 (50%) to placebo. Among the 84 esophagectomy patients, 27 (32%) developed postoperative delirium (Table 1). Patients who developed postoperative delirium (postoperative delirium positive group) had a mean age of 64.5 (SD: 9.4) while patients in the postoperative delirium negative group had a mean age of 60.5 years (SD: 10.8) (p=0.127). The mean preoperative APACHE II score was higher in the postoperative delirium positive group compared to the postoperative delirium negative group [22.1 (6.5) versus 17.4 (6.8); p=0.003]. Almost all patients in the study (98.8%) were categorized as American Society of Anesthesiology physical status classification Class III. Other baseline characteristics did not differ significantly between the two groups.

No difference in intraoperative factors (Table 2) was observed between the two groups including duration of surgery [postoperative delirium positive group 4.9 (1.0) hours versus postoperative delirium negative group 4.9 (1.1) hours; p=0.785], estimated blood loss [postoperative delirium positive group 277 (162) ml versus postoperative delirium negative group 245 (161) ml; p=0.409], or transfusion rate [postoperative delirium positive group 11.1% versus postoperative delirium negative group 3.5%; p=0.322]. Mean doses of intraoperative benzodiazepines [postoperative delirium positive group 34.2 (24.5) mg versus postoperative delirium negative group 29.0 (24.2) mg, p=0.423] and opioids [postoperative delirium positive group 33.2 (13.8) mg versus postoperative delirium negative 36.5 (14.3) mg, p=0.192] were not significantly different. Immediate postoperative hemoglobin values were similar between the groups [postoperative delirium positive group 11.5 (1.7) g/dL versus postoperative delirium negative group 11.6 (1.6) g/dL; p=0.443] (Supplemental Table 1). Patients who developed postoperative delirium had longer duration of mechanical ventilation [1.7 (1.4) days versus 1.0 (1.1) days; p=0.001], longer ICU days [5.1 (2.6) days versus 2.6 (1.6) days; p<0.001] and longer length of hospital stay [13.1 (4.0) days versus 11.2 (3.0); p=0.038] (Table 3).

In a logistic regression model adjusting for APACHE II score, duration of mechanical ventilation, ICU length of stay, and intervention group, only ICU length of stay was significantly associated with postoperative delirium [OR 1.62; 95% CI 1.18-2.22]. The haloperidol intervention did not have a significant effect on postoperative delirium [OR=0.58; 95% CI: 0.19-1.77].

Comment

Postoperative delirium is a leading complication and is associated with poor health outcomes. While best practice guidelines from the American Geriatrics Society have laid out evidence-based recommendations for postoperative care, there is insufficient data to guide certain areas of patient care such as choices of anesthetic agents and techniques, optimal use of intraoperative blood transfusion, and prophylactic administration of antipsychotics [6]. We conducted this study to address the knowledge gap in perioperative risk factors.

In our study of 84 esophagectomy patients, postoperative delirium was associated with higher APACHE II scores, longer duration of mechanical ventilation, and longer ICU and hospital stays. Although these findings are consistent with prior studies in the non-esophagectomy population [19-21], we are uncertain whether greater duration of ventilation and ICU stay was the cause or an effect of delirium.

While severity of illness was associated with delirium in our analysis, age was not. In contrast to a prior study in which depression was suggested as an independent predictor of postoperative delirium in spine surgery [22], we did not find psychiatric conditions associated with delirium. There were no significant associations between baseline depression, anxiety, or post-traumatic stress disorder symptoms and postoperative delirium.

Our study did not find any significant differences in intraoperative variables, including duration of surgery, blood loss, and transfusion rate in patients with or without delirium. This differs from retrospective studies that demonstrated a lower incidence of postoperative delirium with postoperative hemoglobin values greater than 10 g/dL [23-27]. However, patients in our analysis had higher postoperative hemoglobin values [9, 23-27], with only 14 patients (16.7%) in our study having immediate postoperative hemoglobin lower than 10 g/dL. It is possible that the subgroup with low hemoglobin was insufficient in size to reproduce the previously shown association with postoperative delirium.

The absence of significant differences in intraoperative factors between groups may suggest that the impact of the intraoperative variables we measured on delirium is limited. However, much still remains unknown regarding optimal intraoperative care to reduce the incidence of postoperative delirium, and more studies on other risk factors are needed. In our study, for example, intraoperative blood pressure [9, 11] and depth of anesthesia monitoring [7, 12, 28-30], which have previously shown to affect delirium development, were not recorded.

Recently published guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU (PADIS guidelines) [16] highlight the importance of pain control, mobilization and sleep during the postoperative period. For patients admitted to the ICU, adherence to the bundled care protocol is associated with lower delirium and coma [31]. Our institution did not have a protocol dedicated to delirium management during the study period, and therefore, these factors were not evaluated. Since delirium is a multifactorial phenomenon, future studies are encouraged to include a wide range of variables such as pain control, use of sedatives, mobility, sleep hygiene, and family support.

The strengths of our study are the predetermined protocol for twice daily delirium screening and rigorous perioperative clinical data collection. The blinded nature of the parent trial reduced investigator bias. Our study also has certain limitations. First of all, the study was a single-center study design and therefore limits the generalizability of the study. The center's patient population, surgical techniques, anesthetic management, and postoperative care may have limited our ability to identify other variables associated with delirium. Secondly, our study was a secondary analysis (rather than a pre-specified a priori analysis) utilizing haloperidol intervention study data. We adjusted for the intervention effect in our final model but an observational study would be cleaner. Lastly, our results are limited by a relatively small sample size. The statistical power may not have been adequate to yield statistical differences in some of the variables evaluated.

In conclusion, our analysis of perioperative risk factors for postoperative delirium in esophagectomy patients found length of ICU stay significantly associated with postoperative delirium. Intraoperative factors, including duration of surgery, blood loss, and hemoglobin levels were not significantly associated with postoperative delirium.

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Table 1. Baseline Characteristics of Patients

	Total (N=84)	Post-operative delirium positive (N=27)	Post-operative delirium negative (N=57)	P-value
Age in years mean (SD)	61.7 (10.5)	64.5 (9.4)	60.5 (10.8)	0.127
African-American n (%)	3 (3.6)	1 (3.7)	2 (3.6)	1.000
Female n (%)	18 (21.4)	7 (25.9)	11 (19.3)	0.572
Body Mass Index (SD)	28.7 (7.6)	27.4 (7.7)	29.3 (7.6)	0.143
Prior Chemotherapy n (%)	58 (75.3)	19 (76.0)	39 (75.0)	1.000
Smoking History				0.712
Current (%)	13 (16.7)	5 (19.2)	8 (15.4)	
Former (%)	45 (57.7)	16 (61.5)	29 (55.8)	
Never (%)	20 (25.6)	5 (19.2)	15 (28.8)	
Reason for esophagectomy				0.830
Cancer (%)	69 (82.1)	22 (81.5)	47 (82.5)	
Achalasia (%)	5 (6.0)	1 (3.7)	4 (7.0)	
Esophogeal stricture/fistula/diverticulum (%)	4 (4.8)	2 (7.4)	2 (3.5)	
Other (%)	6 (7.1)	2 (7.4)	4 (7.0)	
Depression (PHQ-9[a] 5+) (%)	30 (38.5)	7 (26.9)	23 (44.2)	0.217
Anxiety (GAD-7[b] 5+) (%)	25 (32.0)	6 (23.1)	19 (36.5)	0.306
Post-traumatic stress disorder (PTSS-10[c] 35+) (%)	2 (2.6)	0 (0.0)	2 (3.8)	0.550
Mean PHQ-9[a] (SD)	4.1 (3.9)	3.2 (3.3)	4.5 (4.1)	0.182
Mean GAD-7[b] (SD)	3.4 (3.7)	2.4 (2.7)	3.9 (4.1)	0.202
Mean PTSS-10[c] (SD)	17.2 (7.4)	15.3 (5.3)	18.1 (8.1)	0.201
Mean Katz Activity of Daily Living (SD)	6.0 (0.2)	6.0 (0.2)	6.0 (0.1)	0.605
Mean Lawton Instrumental Activity of Daily Living (SD)	7.3 (1.0)	7.1 (1.3)	7.4 (0.8)	0.510
Mean Charlson Comorbidity Index (SD)	3.0 (2.2)	3.5 (2.5)	2.8 (1.9)	0.208
Mean APACHE[d] II (SD)	18.9 (7.0)	22.1 (6.5)	17.4 (6.8)	0.003
ASA[e] physical status classification				1.000
Class II n (%)	1 (1.2)	0 (0.0)	1 (1.8)	
Class III n (%)	83 (98.8)	27 (100.0)	56 (98.2)	
Home Medications				
Any antipsychotic (%)	2 (2.4)	2 (7.4)	0 (0.0)	0.101
Any selective serotonin reuptake inhibitor (%)	9 (10.7)	1(3.7)	8 (14.0)	0.260
Any serotonin and norepinephrine reuptake inhibitor (%)	3 (3.6)	0 (0.0)	3 (5.3)	0.548
Any tricyclic antidepressant (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Any Anticholinergic (1,2,3) (%)	26 (31.0)	10 (37.0)	16 (28.1)	0.454
Any Anticholinergic (2,3) (%)	5 (6.0)	2 (7.4)	3 (5.3)	0.655
Randomization				
Intervention Group	42 (50.0)	10 (37.0)	32 (56.1)	0.160

[a] PHQ-9: Patient health Questionnaire
[b] GAD-7: Generalized Anxiety Disorder 7-item Scale
[c] PTSS-10: Post Traumatic Symptom Scale
[d] APACHE: Acute Physiology and Chronic Health Evaluation Score
[e] ASA: American Society of Anesthesiologists

Table 2. Intraoperative Data

	Total (N=84)	Postoperative delirium positive (N=27)	Postoperative delirium negative (N=57)	P-value
Type of surgery				
Ivor-Lewis n (%)	71 (84.5)	23 (85.2)	48 (84.2)	1.000
Other n (%)	13 (15.5)	4 (14.8)	9 (15.8)	
Mean Duration of surgery - hours (SD)	4.9 (1.1)	4.9 (1.0)	4.9 (1.1)	0.785
Mean Duration of anesthesia - hours (SD)	6.4 (1.3)	6.5 (1.0)	6.4 (1.4)	0.250
Mean Amount of intravenous fluid - ml (SD)	3187 (1262)	3210 (845)	3176 (1425)	0.565
Mean Estimated blood loss (SD)	255 (161)	277 (162)	245 (161)	0.409
Intraoperative transfusion rate n (%)	6 (7.1)	4 (14.8)	2 (3.5)	0.081
Intraoperative medications				
Opioids n (%)	84 (100)	27 (100)	57 (100)	
Benzodiazepine n (%)	81 (96.4)	26 (96.3)	55 (96.5)	1.000
Ketamine n (%)	10 (11.9)	3 (11.1)	7 (12.3)	1.000
Ondansetron n (%)	22 (26.2)	4 (14.8)	18 (31.6)	0.119
Atropine/scopolamine n (%)	3 (3.6)	1 (3.7)	2 (3.5)	1.000
Dexamethasone n (%)	7 (8.3)	0 (0.0)	7 (12.3)	0.091
Mean Opioid Dose - mg* (SD)	35.5 (14.1)	33.2 (13.8)	36.5 (14.3)	0.192
Mean Benzodiazepine Dose# - mg (SD)	30.7 (24.3)	34.2 (24.5)	29.0 (24.2)	0.423

*Opioid dose is measured in morphine equivalents
#Benzodiazepine dose is measure in diazepam equivalents

Table 3. Postoperative Data

	Total (N=84)	Post-operative delirium positive (N=27)	Post-operative delirium negative (N=57)	P-value
ICU admission n (%)	81 (96.4)	27 (100.0)	54 (94.7)	0.548
Postoperative mechanical ventilation n (%)	80 (95.2)	25 (92.6)	55 (96.5)	0.591
Postoperative opioid use n (%)	82 (97.6)	26 (96.3)	56 (98.2)	0.542
Use of epidural analgesia n (%)	74 (88.1)	23 (85.2)	51 (89.5)	0.720
Postoperative benzodiazepine use n (%)	31 (36.9)	13 (48.2)	18 (31.6)	0.155
Postoperative propofol use n (%)	40 (47.6)	15 (55.6)	25 (43.9)	0.356
Mean numbers postoperative benzodiazepine days (SD)	1.1 (2.1)	1.3 (2.2)	1.0 (2.1)	0.222
Mean numbers postoperative opioid days (SD)	5.0 (3.3)	4.9 (3.5)	5.0 (3.2)	0.707
Mean ICU length of stay (days) (SD)	3.4 (2.3)	5.1 (2.6)	2.6 (1.6)	<0.001
Mean length of mechanical ventilation (days) (SD)	1.2 (1.2)	1.7 (1.4)	1.0 (1.1)	0.001
Mean hospital length of stay (days) (SD)	11.8 (3.5)	13.1 (4.0)	11.2 (3.0)	0.038

[e] ICU: Intensive Care Unit