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Depressive Symptoms and Risk of Postoperative Delirium

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Abstract

Objective—Previous studies have shown that elevated depressive symptoms are associated with increased risk of postoperative delirium. However, to our knowledge, no previous studies have examined whether different components of depression are differentially predictive of postoperative delirium.

Methods—One thousand twenty patients were screened for postoperative delirium (n = 1020) using the Confusion Assessment Method as well as through retrospective chart review. Patients underwent cognitive, psychosocial, and medical assessments preoperatively. Depression was assessed using the Geriatric Depression Scale – Short Form (GDS).

Results—Thirty-eight patients developed delirium (3.7%). Using a factor structure previously validated among geriatric medical patients, we examined three components of depression as predictors of postoperative delirium: 1) negative affect, 2) cognitive distress, and 3) behavioral inactivity. In multivariate analyses controlling for age, education, comorbidities, and cognitive function, we found that greater behavioral inactivity was associated with increased risk of delirium (OR = 1.95 [1.11, 3.42]), whereas negative affect (OR = 0.65 [0.31, 1.36]) and cognitive distress (OR = 0.95 [0.63, 1.43]) were not.

Conclusions—Different components of depression are differentially predictive of postoperative delirium among adults undergoing non-cardiac surgery.

Keywords

Delirium; Depression

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INTRODUCTION

The presence of delirium following surgery is independently predictive of increased incidence of adverse medical outcomes, longer hospital stays, and increased rates of cognitive decline(1, 2). Delirium is relatively common among hospitalized older adults and is associated with significant public health expenditures(3), as well as a substantially increased risk of 6-month mortality risk after controlling for disease severity(4). Available evidence suggests that the presence of delirium may also be associated with adverse cerebrovascular outcomes, similar to other surgeries(5, 6). For example, a recent prospective cohort study found that greater duration of delirium in the intensive care unit was associated with greater white matter damage at discharge(7), which persisted over a three-month follow-up period. Recent evidence also has also demonstrated that the presence of delirium is independently associated with long-term cognitive impairment(1).

Although numerous medical factors have been shown to increase the risk of postoperative delirium, recent evidence suggests that the presence of depressive symptoms or a major depressive episode may be associated with elevated risk of delirium. Among cardiac patients, the presence of an ongoing major depressive episode has been associated with a nearly four-fold increased risk of delirium(8) and subclinical depressive symptoms have been associated with graded increases in delirium incidence among individuals undergoing elective non-cardiac surgery(9).

Despite the increased risk of delirium, the mechanisms underlying the depression and delirium relationship have not been studied. Although greater depressive symptoms have been associated with greater incidence of depression across multiple patient samples(9), no past studies, to our knowledge, have examined whether different components of depression are differentially predictive of delirium risk. Different components of depression are known to result from different neurobiological mechanisms(10) and are differentially predictive of adverse events among coronary patients(11). We therefore examined the association between various components of depression and risk of delirium among a large sample of older adults undergoing non-cardiac surgery.

Understanding the risk factors for delirium are important in order to improve patient management and risk stratification prior to surgery(2). Increasing evidence suggests that greater depressive symptoms are associated with an increasing incidence of postoperative delirium.(9, 12, 13) Prior research has shown that elevated preoperative depressive symptoms are associated with increased risk of delirium following coronary artery bypass grafting (CABG)(13) as well as non-cardiac surgery(9, 12), independent of demographic, medical, and cognitive factors. Despite the increased delirium risk associated with depression, no studies to our knowledge, have attempted to better elucidate the nature of this association by examining which components of depression are most predictive of postoperative delirium. We therefore examined the association between components of preoperative depressive symptoms and postoperative delirium in a sample of 1,020 individuals undergoing major, noncardiac surgery.

METHODS

Participants

Participants were enrolled in a previous reported trial examining predictors of postoperative cognitive decline. Potential participants were approached for participation at Shands Hospital (Gainesville, Florida) between February 1, 1999, and January 31, 2002, and gave written informed consent prior to participation. Inclusion criteria included adult age (≥ 18 years) and a scheduled hospital admission as an inpatient for a minimum of 2 days following noncardiac surgery. Patients with a mini mental status exam score < 23, a history of dementia or central nervous system disease, current or past history of psychiatric illness, substance abuse disorders, current or past electroconvulsive therapy, or undergoing active pharmacologic management by a psychiatrist or primary care provider (including tranquilizers and/or antidepressants) were also excluded.

Delirium status was determined by chart review and/or the Confusion Assessment Measure (CAM)(14). The Confusion Assessment Method diagnostic algorithm was used to define the presence or absence of delirium, monitored up to eight days after surgery. Delirium was defined as the presence of both 1) acute onset and fluctuating course, and 2) inattention, as well as either 3) disorganized thinking, or 4) altered level of consciousness.

Preoperative assessments were conducted by interview within 14 days of surgery to obtain demographic information, medical history, and background information. Medical comorbidities were indexed using the Charlson comorbidity index (CCI)(15).

Depression was assessed using the 15-item short form of the Geriatric Depression Scale (GDS) (Appendix 1)(16). The GDS assesses several dimensions of depression, including negative affect (NA), cognitive distress (CD), and behavioral/social inactivity (BI) with higher scores indicating greater severity of depressive symptoms. The GDS-NA subscale included items assessing life satisfaction and general mood (e.g. “Are you basically satisfied with your life?”; “Are you in good spirits most of the time?”). The GDS-CD subscale included items assessing negative thoughts about one’s life (e.g. “Do you feel your life is empty?”; “Do you think that most people are better off than you are?”). The GDS-BI subscale included items assessing behavioral changes commonly observed among individuals with depressive symptoms (e.g. “Have you dropped many of your activities and interests?”; “Do you feel full of energy?”).

Control Variables

Executive Functioning was operationalized using a composite of three subtests: the Concept Shifting Task, the Letter-Digit Coding task, and a modified version of the Stroop Interference task. Because evidence exists for the independent contribution of depression and executive function in predicting delirium, in this analysis we control for executive skill to eliminate the effects of this potential confounder in the depression and delirium relationship(17).

Charlson Comorbidity Index The CCI was used to assess the cumulative burden of medical comorbidity. The presence of each of 20 medical conditions was determined from

patient report. The index assigns a weight to each condition, with the weighting coefficients derived from the approximate 1-year adjusted relative risk of mortality associated with that condition in a general medical population. Because greater medical comorbidities have previously been associated with a higher incidence of delirium, the Charlson Comorbidity Index was used to provide a global measure of chronic comorbidities.

Statistical Analyses

In order to examine the relationship between preoperative depression and postoperative delirium we conducted three separate logistic regression models due to high collinearity between depression components ($r^2 > .60$). The presence of postoperative delirium served as the binary outcome within each model. The three GDS subscales were used as our predictors of interest, controlling for age, type of surgery (major = 2, orthopedic = 1, minor = 0), the Charlson Comorbidity Index [CCI], and our composite measure of executive function. Age was scaled in decades and both executive function and depression were scaled using the sample interquartile range. In order to determine if the three GDS subscales were significantly different from one another, we conducted two secondary, explanatory models in which the GDS-NA and GDS-CD subscales were added to the GDS-BI model in order to facilitate a direct comparison of slopes within PROC LOGISTIC (SAS 9.2; Cary, NC).

RESULTS

As previously reported, complete patient data were available for 998 subjects.⁽⁹⁾ Participants in the final sample ranged in age from 18 to 90 (mean age = 51.0 years, SD = 17.0), reported 13.5 years of education (SD = 2.6), and the majority of participants were female (63.4%) and Caucasian (89.3%). Thirty-three participants developed delirium postoperatively (3.7%). Background characteristics are reported in Table 1. As shown, participants who developed postoperative delirium tended to be older, male, had greater medical comorbidities, and exhibited lower executive function.

GDS Subscales: Principal axis factor analysis using a Promax rotation and a minimum loading of 0.5 revealed a 3-factor solution (eigenvalues 4.50, 1.37, and 1.06), corresponding the GDSCD, GDS-BI, and GDS-NA. Specifically, GDS-NA was comprised of items 1, 5, 7, and 11, GDS-CD was comprised of items 3, 8, 12, 15, and 14, and GDS-BI was comprised of items 2, 4, 9 and 13.

Psychosocial Predictors of Delirium: Examination of independent predictors of postoperative delirium showed that older age, higher Charlson comorbidity index scores, and poorer executive function were associated with greater incidence of postoperative delirium (Table 1). Multivariate modeling was used to examine the independent relationship between these predictors and postoperative delirium. Greater age (OR = 1.53 [95% CI 1.15, 2.06], $P = .003$, Wald chi-square = 8.61, $df = 1$) was associated with a greater incidence of delirium, whereas surgery type, the CCI, executive function, and gender were not. Examination of depression indices demonstrated that neither GDS-NA (OR = 0.65 [0.31, 1.36], $P = .250$, Wald chi-square = 1.32, $df = 1$) nor GDSCD (OR = 0.95 [0.63, 1.43], $P = .803$, $df = 1$), Wald chi-square = 0.062, $df = 1$) were significantly associated with postoperative delirium. In contrast, higher levels of GDS-BI was significantly associated

with increased incidence of delirium (OR = 1.95 [1.11, 3.42], $P = .020$, Wald chi-square = 5.41, $df = 1$) (Table 2). Comparison of slopes demonstrated that GDS-BI was a stronger predictor than GDS-NA (Wald chi-square = 8.14, $P = .004$, $df = 1$) and GDS-CD (Wald chi-square = 5.53, $P = .019$, $df = 1$).

Item-level Analysis: Exploratory item-level analyses of items comprising the GDS-BI component were conducted to better understand the relationship between individual items and risk of delirium. Results revealed that although the items ‘Have you dropped many of your activities and interests?’ (OR = 1.49 [0.71, 3.13], Wald chi-square = 1.11, $df = 1$, $P = .293$) and ‘Do you often get bored?’ (OR = 1.38 [0.60, 3.19], Wald chi-square = 0.58, $df = 1$, $P = .448$) were not different between delirious and non-delirious participants, we found that ‘Do you prefer to stay at home, rather than going out and doing new things?’ (OR 2.28 [95% CI 1.11, 4.71], Wald chi-square = 4.99, $df = 1$, $P = .026$) and ‘Do you feel full of energy?’ (OR 2.28 [95% CI 1.05, 4.99], Wald chi-square = 4.29, $df = 1$, $P = .038$) were significantly associated with delirium risk (Table 3).

DISCUSSION

Results from the present study demonstrate that various components of depression are differentially predictive of postoperative delirium among adults undergoing noncardiac surgery. We found that for every 2-point increase in behavioral/social inactivity, the odds of delirium approximately doubled after accounting for background characteristics, type of surgery, medical comorbidities, and cognitive function. Although the standardized effect size for the association between behavioral/social inactivity and delirium was modest ($d = 0.16$), the observed association is comparable to the association observed between increasing age and delirium risk in other geriatric samples (OR = 1.95 vs. 2.0)(18) and depressive symptoms were a stronger predictor of delirium than medical comorbidities in the present sample. In contrast, negative affect and cognitive distress were not associated with increased delirium risk.

Depression has been associated with increased risk of delirium across multiple patient populations, including both cardiac(19) and non-cardiac samples.(9) Despite the consistency of this association, no studies have examined whether different components of depression are predictive of delirium. Examination of depression components may be important, as previous work has suggested that different depressive symptoms are predictive of mortality following cardiac surgery(20). In addition, anhedonia, which often contributes to behavioral inactivity and limited engagement in pastimes, has been associated with increased risk of adverse events among patient with acute coronary syndrome after accounting for medical risk factors(11). It is also possible that some dimensions of depression may overlap with somatic symptoms associated with chronic medical conditions, such as malaise, sleep disturbance, and fatigue(21),

The observed relationship between behavioral inactivity and delirium may have resulted from several underlying mechanisms. First, different components of depression have been shown to have differing underlying neurotransmitter correlates, suggesting that certain depression dimensions may have distinct neurobiological correlates(22). Second, anhedonia,

a component of behavioral inactivity, has been shown to increase in inflammatory states(23), which is known to increase the risk of delirium(24). Therefore, self-reported anhedonia may be associated with underlying elevations in basal levels of inflammation. Finally, it is possible that variations in aerobic fitness may explain part of the association between depression and delirium. Multiple intervention studies have demonstrated that aerobic activity is beneficial for depression among both healthy(25) and cardiac populations(26), and greater levels of physical inactivity have been associated with the development of depression in some samples(27).

Limitations. The present study must be viewed with several limitations in mind. We relied on self-reported depressive symptoms in the present analyses. Although the large sample size of the present study made comprehensive interviews for psychological function infeasible, future studies may benefit from utilizing clinician-diagnosed depressive symptoms as a predictor of perioperative outcomes. In addition, the rate of delirium reported in the current sample was low relative to other samples, which may have resulted from a large number of relatively young patients in our cohort. The fact that we were able to observe an association between different components of depression and delirium may underscore the strength of this relationship, given that we were underpowered to detect it. Future studies would benefit from prospective, comprehensive delirium assessment among an older population to better understand the depression and delirium relationship. It is also unclear to what extent underlying anhedonia and/or apathy influenced the current pattern of findings. Indeed, because individuals actively taking psychotropic medications were excluded from participation, we likely excluded many individuals with higher levels of negative affect and cognitive distress, thereby restricting the levels of these commonly observed depressive symptoms. Future studies conducting clinician-interviews for depression may be beneficial in elucidating the mechanisms underlying this relationship, as well as examining depression components among individuals actively being treated for major depression. Finally, it is possible that the observed pattern of relationships was influenced by differences in measurement characteristics and reliability across GDS factors. Future psychometric studies would be helpful in understanding differences in reliability, sensitivity, and specificity across GDS factors.

In conclusion, different components of depression are differentially predictive of delirium following non-cardiac surgery. Future studies should examine whether underlying differences in inflammatory response or other biological markers may mediate the observed relationships. Examination of neuroimaging correlates of depression and delirium, such as white matter burden, may be beneficial to better understand possible mechanisms underlying the delirium and depression relationship. If confirmed, these findings may suggest that interventions designed to improve these specific depressive symptoms prior to surgery may reduce the incidence and impact of delirium during hospitalization, which could have potential implications for the mitigation of long-term cognitive impairment(1) and possibly poor clinical outcomes (28).

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Appendix 1. Geriatric Depression Scale Short Form and corresponding subscale

Question / Item	Subscale
Are you basically satisfied with your life?	Negative Affect
Have you dropped many of your activities and interests?	Behavioral Activation
Do you feel that your life is empty?	Cognitive Distress
Do you often get bored?	Behavioral Activation
Are you in good spirits most of the time?	Negative Affect
Are you afraid that something bad is going to happen to you?	-----
Do you feel happy most of the time?	Negative Affect
Do you often feel helpless?	Negative Affect
Do you prefer to stay at home, rather than going out and doing new things?	Behavioral Activation
Do you feel you have more problems with memory than most people?	-----
Do you think it is wonderful to be alive?	Negative Affect
Do you feel pretty worthless the way you are now?	Cognitive Distress

Question / Item	Subscale
Do you feel full of energy?	Behavioral Activation
Do you feel that your situation is hopeless?	Cognitive Distress
Do you think that most people are better off than you are?	Cognitive Distress

Table 1

Background characteristics of entire sample.

Variable	Delirium	No Delirium
Age, years (SD)	63.9 (15.5)	50.5 (16.8)**
Female, %	14 (40%)	617 (64%)**
Education, years (SD)	13.0 (3.1)	13.5 (2.6)
Charlson, mean (SD)	3.0 (2.0)	1.5 (1.9)**
Executive Function, z-score (SD)	-2.5 (3.4)	-0.1 (2.6)**
Type of Surgery		
Major	23 (70%)	551 (58%)
Orthopedic	6 (18%)	2656 (27%)
Minor	4 (12%)	144 (15%)
GDS-CD, mean (SD)	0.22 (0.5)	0.27 (0.6)
GDS-BI, mean (SD)	1.6 (1.0)	1.2 (1.0)*
GDS-NA, mean (SD)	0.21 (0.5)	0.37 (0.8)

GDS = Geriatric Depression Scale; NA = Negative Affect; BSI = Behavioral and Social Inactivity; CD = Cognitive Distress.

* P-value < .05 for t-test;

** P-value < .01.

Group differences were compared using a chi-squared test for categorical variables and t-test for continuous variables (df = 995).

Major surgery includes abdominal, gynecologic, thoracic, urologic, or vascular surgeries. Orthopedic includes knee, hip, spine, shoulder, thigh, or other orthopedic surgery. Minor surgery included breast, minor ear/nose/throat, or other less invasive surgeries.

Table 2

Logistical regression analyses examining GDS Behavioral / Social Inactivity and postoperative delirium.

Variable	Odds Ratio	95 % CI	df	P-value
Age	1.53	1.15, 2.02	1	.003
Surgery Type (0=minor, 1 =orthopedic, 2 =major)	1.19	0.68, 2.08	1	.552
Charlson	1.16	0.99, 1.36	1	.066
Executive Function	0.78	0.53, 1.14	1	.191
Female, %	0.50	0.24, 1.04	1	.063
GDS-BI	1.95	1.11, 3.42	1	.020

Table 3

Exploratory logistic regression analyses of GDS Behavioral / Social Inactivity items and postoperative delirium controlling for age, type of surgery, Charlson comorbidity index, executive function, and gender.

GDS-BI Item	Odds Ratio	95 % CI	df	P-value
Have you dropped many of your activities and interests?	1.49	0.71, 3.13	1	.293
Do you prefer to stay at home, rather than going out and doing new things?	2.28	1.11, 4.71	1	.026
Do you feel full of energy?	2.28	1.05, 4.99	1	.038
Do you often get bored?	1.38	0.60, 3.19	1	.448