Predictors for postoperative delirium after vascular surgery

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Background
Postoperative delirium (POD) is a common and serious problem that is characterized by fluctuating symptoms of inattention, disturbance of consciousness, and disorganized thinking. It is associated with adverse outcomes in a number of settings. POD has a multifactorial pathogenesis, and its incidence ranges from 10 to 46% in the general surgical population.

Aim of the work
The aim of this study was to investigate preoperative, operative, and postoperative factors that predict for POD.

Materials and methods
Between November 2014 and April 2015, 123 consecutive elective vascular surgery patients were evaluated for the diagnosis of POD. Various risk factors such as preoperative, operative, and postoperative were evaluated.

Results
Patients who developed delirium were significantly older (66.93 ± 4.80, $P < 0.001$). Those who developed delirium had a significantly higher frequency of history of diabetes mellitus and renal impairment. The Mini-Mental State Examination indicated that preoperative cognitive functioning was significantly impaired (19.36 ± 1.78, $P < 0.001$) in patients who had POD. Patients who developed POD were also more likely to report a history of moderate levels of depressive symptoms (22.64 ± 7.91, $P < 0.001$). Postoperative C-reactive protein was significantly higher (112.86 ± 12.35, $P < 0.001$) in delirious patients. Tendency for ICU admittance was significantly more frequent [36 (85.7%), $P < 0.001$] in delirious patients. Also, the prolonged hospital stay was significantly related to POD (9.36 ± 2.69, $P < 0.001$).

Conclusion
This study provides evidence that preoperative factors such as age, medical comorbidities (diabetes and renal impairment), cognitive impairment, and presence of depressive symptoms can be used as predictors for an increased risk for POD after vascular surgery. In addition, the type of surgical procedure and other postoperative factors such as high levels of postoperative C-reactive protein, ICU admittance, and prolonged hospital stay can predict POD.

Keywords:
delirium, predictors, vascular surgery

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Introduction

Delirium is an organic brain dysfunction that has multifactorial origin with complex pathophysiology, including inflammatory reaction, hormonal changes, and impairment in neurotransmission and neural network connectivity in the brain (Kiran *et al.*, 2015).

Previously, terms such as ICU psychosis, ICU syndrome, acute confusional state, and acute brain failure were used to describe delirium in critically ill patients. In recent times, the term delirium has been used uniformly to describe this brain dysfunction (Morandi *et al.*, 2012).

The American Psychiatric Association's *Diagnostic and Statistical Manual*, 4th ed., Text Revision (DSM-IV-TR) (American Psychiatric Association, 2002), lists four key features for diagnosis of delirium:

(a) Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention;
(b) A change in cognition (i.e. memory deficits, disorientation, language disturbances, or the presence of a perceptual disturbance, for example, hallucinations) that is not better accounted for by a pre-existing, established, or evolving dementia;
(c) The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day;
(d) There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

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According to the clinical picture, delirium is classified into hyperactive delirium (characterized by increased psychomotor activity with agitation), hypoactive or 'quiet' delirium (with reduced psychomotor behavior), and mixed delirium, which alternates between the two previous types (Robinson *et al.*, 2011).

Delirium is also classified according to its etiology: for example, delirium due to an underlying medical condition (delirium due to a general medical condition), due to medications (substance-induced delirium, substance intoxication delirium), or due to withdrawal from medications (substance withdrawal delirium). Sometimes delirium may be multifactorial (delirium due to multiple etiologies) or of unclear etiology (delirium not otherwise specified) (Steiner, 2011).

Postoperative delirium (POD) can differ in some aspects from delirium that occurs in medical patients; delirium in medical patients occurs because of an acute illness or exacerbation of a chronic one, whereas surgical patients are supposed to have optimal physical condition before surgery. Anesthesia and analgesics are generally absent in medical patients, but may play a role in POD (Chan *et al.*, 2013).

The incidence of POD ranges from 10 to 46% in the general surgical population. Between the second and 10th day after surgery, the incidence is nearly 25%. The incidence then decreases to 10% at 3 months, 5% at 6 months, and 1% at 1 year (Monk and Price, 2011).

POD may represent a diagnostic challenge. Its detection may be missed by medical providers in up to 50% of cases. This may be due to its fluctuating course during the day and the variety of symptoms that may overlap with other disorders such as psychosis, anxiety/depressive disorders, and dementia. However, encephalography or other diagnostic measures have demonstrated no specific findings in delirious patients (Lee *et al.*, 2011).

Delirium in surgical patients has a profound impact on postoperative outcomes. It is usually associated with recurrent falls, fractures, incontinence, and bladder catheterization with higher risk for infections, increased hospital stay, and death (Zhang *et al.*, 2013). Recent studies reported that POD is also associated with an increased incidence of impaired cognitive functions, negatively affecting the whole quality of life of the patient (Banerjee *et al.*, 2011).

POD has a multifactorial pathogenesis; some theories consider that delirium is a manifestation of cortical dysfunction due to neurotransmitter imbalance (dopamine, norepinephrine, acetylcholine, and serotonin) (Peng *et al.*, 2013).

A complex inflammatory response to surgical stress was also suggested to promote delirium, or may act as a direct cause for it; higher levels of C-reactive protein (CRP) and interleukin-6 are associated with this inflammatory reaction, leading to disturbance in the blood–brain barrier and neuronal dysfunction, which may manifest as delirium (Anckarsäter *et al.*, 2014).

As delirium could be considered a leading cause of morbidity and mortality in surgical patients, the aim of this study was to investigate some preoperative, operative, and postoperative factors that may predict for POD. Identifying such predictors may be helpful in the development of delirium prevention strategies, which could influence long-term surgical outcomes.

Materials and methods

This study was conducted in the Department of Vascular Surgery at Mansoura University Hospitals (MUH). All patients were recruited after obtaining written informed consent from either the patient or from their relative.

The study took place during the period from November 2014 to April 2015; 178 vascular surgery patients were asked to join this study, of whom 26 (Koster *et al.*, 2013) refused to participate (not interested, personal causes), nine (Zhang *et al.*, 2013) patients were discharged without surgery, 11 (Peng *et al.*, 2013) patients had a previous history of stroke or cerebral palsy, three (American Psychiatric Association, 2002) patients had severe hearing or visual disabilities, and six (Chan *et al.*, 2013) patients had a history of substance abuse disorders. All of them were excluded because delirium cannot be reliably diagnosed in them.

Finally, 123 patients participated in this study. All patients were assessed both preoperatively and postoperatively. The following predictors were investigated:

(a) Preoperative predictors such as age, sex, medical comorbidities (diabetes, hypertension, cardiac disease, and renal impairment), cognitive impairment, and depressive symptoms, which were assessed 1 day before surgery;
(b) Intraoperative predictor, which was the type of surgical procedure;
(c) Postoperative predictors such as postoperative CRP levels, ICU admittance, and hospital stay.

Instruments

Beck Depression Inventory

Depressive symptoms were assessed using the Beck Depression Inventory (BDI) (Beck *et al.*, 1996). The

BDI is a standardized 21-item self-report questionnaire consisting of symptoms and attitudes related to depression, including items such as self-dislike, suicidal ideation, insomnia, and sadness. The items are summed with total scores ranging from 0 to 63, with higher scores indicating higher levels of depression.

The Mini-Mental State Examination

Preoperative cognitive functioning was assessed with the Mini-Mental State Examination scale (MMSE) on a scale of 0 to 30, with scores lower than 24 indicating cognitive impairment (Folstein *et al.*, 1975).

All patients were screened for diagnosis of delirium; they were observed postoperatively by qualified nurses by using the Delirium Observation Screening scale during three shifts.

When delirium was present or suspected, the psychiatrist was consulted and the diagnosis was confirmed on the basis of the DSM-IV-TR criteria.

The Delirium Observation Screening scale

The Delirium Observation Screening scale consists of 13 items that can be rated during three shifts as absent or present and describes typical behavioral patterns related to delirium. Three or more points were considered indicative of delirium (Scheffer *et al.*, 2011).

All patients were recruited after obtaining written informed consent from either the patient or from their relative.

Results

A total of 123 patients [90 (73.2%) men and 33 (26.8%) women] participated in this study; their mean age was 53.61 ± 13.54 years. With respect to medical comorbidities, 45 patients (36.6%) had diabetes, 54 (43.9%) were hypertensive, 18 (14.6%) had cardiac disease, and 21 (17.1%) were suffering from renal impairment (Table 1).

Preoperative cognitive functioning was assessed with the MMSE scale; the mean score was 24.41 ± 4.45.

Patients in our sample had moderate levels of depressive symptoms (mean BDI = 18.59 ± 8.93). An overall 7.3% of the patients had minimal symptoms, 36.6% had mild symptoms, 41.5% had moderate symptoms, and 14.8% had severe symptoms of depression.

The mean postoperative CRP level was 75.85 ± 36.44; the mean of ICU admittance was 12 (9.89%); and the mean duration of hospital stay was 7.02 ± 2.81 days.

Table 1 Baseline clinical and demographic characteristics of the patients

N	123
Delirium [*n* (%)]	42 (34.1)
Age	53.61 ± 13.54
Sex [*n* (%)]	
Male	90 (73.2)
Female	33 (26.8)
Diabetes [*n* (%)]	45 (36.6)
HTN	54 (43.9)
Cardiac disease [*n* (%)]	18 (14.6)
Renal impairment [*n* (%)]	21 (17.1)
Mini-Mental State Examination	24.41 ± 4.45
Beck Depression Inventory	18.59 ± 8.93
Beck Depression Inventory [*n* (%)]	
Minimal	9 (7.3)
Mild	45 (36.6)
Moderate	51 (41.5)
Severe	18 (14.8)
Postoperative CRP	75.85 ± 36.44
ICU admittance [*n* (%)]	12 (9.89)
Hospital stay	7.02 ± 2.81

CRP, C-reactive protein; HTN, hypertension.

Forty-two patients (34.1%) were diagnosed with POD.

Table 2 highlights the preoperative and postoperative factors that may predict for POD; patients who developed delirium were significantly older (66.93 ± 4.80 years; $P < 0.001$).

An overall 64.3% of delirious patients were male, whereas 35.7% were female, but the difference was not significant. Those who developed delirium had significantly higher frequency of history of diabetes mellitus and renal impairment, whereas hypertension and cardiac disease were nonsignificant.

The MMSE scale indicated that preoperative cognitive functioning was significantly impaired (19.36 ± 1.78, $P < 0.001$) in patients who had POD.

Patients who developed POD were also more likely to report a history of moderate levels of depressive symptoms (22.64 ± 7.91, $P < 0.001$).

Postoperative CRP levels were significantly higher (112.86 ± 12.35 mg/l; $P < 0.001$) in delirious patients.

Tendency for ICU admittance was significantly more frequent [9 (21.5%); $P < 0.001$] in delirious patients.

Also, prolonged hospital stay was significantly related to POD (9.36 ± 2.69, $P < 0.001$).

The incidence of delirium in relation to type of surgical procedures is presented in Table 3: the highest incidence was seen in endovascular procedures [17 patients (40.5%)], followed by shunt surgery for chronic renal failure

Table 2 Predictors for postoperative delirium

Variables	Nondelirious (*n* = 81)	Delirious (*n* = 42)	Test	*P*
Age	46.70 ± 11.25	66.93 ± 4.80	*t* = 13.922	<0.001*
Sex [*n* (%)]				
Male	63 (77.8)	27 (64.3)	χ^2 = 2.565	0.109
Female	18 (22.2)	15 (35.7)		
Diabetes [*n* (%)]	15 (18.5)	30 (71.4)	χ^2 = 33.374	<0.001*
HTN [*n* (%)]	33 (40.7)	21 (50)	χ^2 = 0.963	0.326
Cardiac disease [*n* (%)]	12 (14.8)	6 (14.3)	χ^2 = 0.006	0.937
Renal impairment [*n* (%)]	3 (3.7)	18 (42.9)	χ^2 = 29.947	<0.001*
Mini-Mental exam	27.04 ± 2.85	19.36 ± 1.78	*t* = 18.320	<0.001*
Beck Depression Inventory	16.48 ± 8.75	22.64 ± 7.91	*t* = 3.824	<0.001*
Beck Depression Inventory [*n* (%)]				
Minimal	9 (11.1)	0 (0)	14.465	0.002*
Mild	36 (44.4)	9 (21.4)		
Moderate	27 (33.3)	24 (57.1)		
Severe	9 (11.1)	9 (21.4)		
Postoperative CRP (mg/l)	56.67 ± 29.24	112.86 ± 12.35	*t* = 14.917	<0.001*
ICU admittance [*n* (%)]	3 (3.7)	9 (21.5)	χ^2 = 30.373	<0.001*
Hospital stay (days)	5.81 ± 1.99	9.36 ± 2.69	*t* = 7.519	<0.001*

CRP, C-reactive protein; HTN, hypertension; *$P < 0.05$, significant.

Table 3 Incidence of delirium in relation to the type of surgical procedure

Types of surgical procedures	Number of patients (*N* = 123) [*n* (%)]	Delirium present % (*N* = 42) [*n* (%)]
Endovascular procedure	38 (31)	17 (40.5)
Bypass surgery	9 (7.3)	3 (7.2)
Carotid surgery	2 (1.6)	0
Aortic surgery	3 (2.4)	2 (4.8)
Varicose vein surgery	30 (24)	0
Shunt surgery for chronic renal failure	32 (26.4)	15 (35.6)
Amputation surgery	7 (5.7)	4 (9.5)
Lymphatic surgery	2 (1.6)	1 (2.4)
Total	123	42

[15 patients (35.6%)], amputation surgery [four (9.5%)], bypass surgery [three (7.2%)], aortic surgery [two (4.8%)], and finally carotid surgery and varicose vein surgery.

Discussion

The primary aim of this study was to investigate some preoperative, operative, and postoperative factors that may predict for POD.

Preoperative risk factors

Patient age (66.93 ± 4.80 years) is an important demography-related preoperative risk factor. This finding is consistent with those of Jodati *et al.* (2013) and Lahariya *et al.* (2014), who found that higher age is a predictor of delirium. Advanced age is usually associated with neurodegeneration and formation of microglia to increasing the release of inflammatory cytokines within the brain in response to any mild systemic inflammatory process (DeCrane *et al.*, 2011).

With regard to medical comorbidities, those who developed delirium had significantly higher frequency of history of diabetes mellitus and renal impairment, supporting the results of other previous studies (Cebeci and Güven, 2012; Scott *et al.*, 2014).

Our finding that preoperative cognitive impairment (19.36 ± 1.78, $P < 0.001$) was associated with increased likelihood of POD is consistent with recent studies (Slor, 2013; Tognoni *et al.*, 2011; Grover *et al.*, 2014) that reported that pre-existing cognitive impairment might not only increase the chance of developing delirium but also prolong it.

Our results also confirm the findings of other recent studies (Cardoso *et al.*, 2010; Kazmierski *et al.*, 2010; Grover *et al.*, 2014) that report that higher levels of depressive symptoms are associated with an increased incidence of POD.

Although the pathophysiology of delirium is multifactorial (Koster *et al.*, 2013), the aminobutyric acid, acetylcholine, and serotonin neurotransmitters seems to be involved. Recent theories suggest that impairment in the homeostasis of tryptophan, a precursor to serotonin, may have a role in the pathogenesis of POD (Steiner, 2011), as dysregulation of serotonin has been always associated with depression. This may explain the relation between depression and delirium (Hohman *et al.*, 2011).

Another hypothesis is that white matter damage in the frontal–striatal areas in the brain predisposes for POD. Mild white matter damage may manifest preoperatively as cognitive impairment and/or higher levels of depression (Ji *et al.*, 2013). Recent coronary artery bypass grafting research reported that the

relation between cognitive dysfunction and delirium may be explained by the severity of atherosclerosis (Krenk *et al.*, 2010).

Postoperative CRP was significantly higher (112.86 ± 12.35 mg/l, $P < 0.001$) in delirious patients. Normal level is usually lower than 10 mg/l; higher levels (40–200 mg/l) are seen in active inflammation, burns, and in severe viral and bacterial infections (Hohman *et al.*, 2011; Anckarsäter *et al.*, 2014). Higher levels of CRP and interleukin-6 and procalcitonin (inflammatory mediators) are associated with inflammatory reaction (Hudetz *et al.*, 2011). Animal studies reported that inflammatory mediators cross the blood–brain barrier, increase vascular permeability, and reveal electroencephalography changes similar to those of delirious patients (McGrane *et al.*, 2011), suggesting that this inflammatory process produces a cascade of endothelial damage, thrombin formation, and cerebral vasoconstriction leading to brain dysfunction (Kalb *et al.*, 2013).

Tendency for ICU admittance was significantly more frequent (9.36 ± 2.69, $P < 0.001$) in delirious patients.

Further, the prolonged hospital stay was significantly related to POD (9.36 ± 2.69, $P < 0.001$), agreeing with the results of another recent study (Jodati *et al.*, 2013; Veiga *et al.*, 2012).

The highest incidence of POD was observed in patients undergoing aortic surgery (4.8%). Two out of three patients developed POD.

Patients undergoing an endovascular procedure [17 of 38 patients (40.5%)] and shunt surgery for chronic renal failure [15 of 35 patients (35.6%)] were also at high risk for POD. These results are consistent with those of Kalb *et al.* (2013); Pol *et al.* (2014) suggested that delirium tends to occur more in patients undergoing more complicated intraoperative procedures.

Conclusion

This study provides evidence that preoperative factors such as age, medical comorbidities (diabetes and renal impairment), cognitive impairment, and presence of depressive symptoms can be used as predictors for an increased risk for POD after vascular surgery. In addition, the type of surgical procedure and other postoperative factors such as high levels of postoperative CRP, ICU admittance, and prolonged hospital stay can predict for POD.

Recommendations

It may be beneficial in future studies to elucidate the risk factors for delirium, which can be used to develop strategies for accurate prevention and diagnosis of delirium.

In contrast, the systematized use of accurate diagnostic tools for delirium will prevent overdiagnosis and facilitate treatment based on subjective individual evaluation of the patient's mental status. Careful screening for preoperative, operative, and postoperative predictors for POD is recommended, which may help in improving short-term and long-term outcomes in surgical patients.

Limitations

One of the limitations of the study was the nonstandardization of neuropsychological tests utilized at different times of the day. Other limitations are lack of a control group, the relatively small size of the sample, and loss of many patients during the study. In addition, administration of different drugs preoperatively may affect the patients' cognitive functions.

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Conflicts of interest

There are no conflicts of interest.

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