Detailed Insight Into the Impact of Postoperative Neuropsychiatric Complications on Mortality in a Cohort of Cardiac Surgery Subjects: A 23,000-Patient-Year Analysis

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Objectives: **This study sought to evaluate the impact of postoperative delirium with/without cerebral ischemia on short- and long-term mortality in a large cohort of cardiac surgery patients.**

Design: **The study constituted a prospective cohort observation of patients following various cardiac surgery procedures.**

Setting: **The investigation was conducted in a single high-volume tertiary cardiac surgery center.**

Participants: **Consecutive candidates for cardiac surgery (n = 8,792) from 2003 to 2008 were subjected to the following exclusion criteria: History of any psychiatric disorders, alcohol abuse and intake of psychoactive drugs and incomplete data.**

Interventions: **No additional interventions were performed, except for standard perioperative management.**

Measurements and Main Results: **5,781 patients finally were assigned to cohorts depending on the presence of postoperative delirium with/without cerebral ischemia and then prospectively followed up over the median time of 46 months. Overall 30-day mortality in patients with delirium was 15.25%, including 6.43% of patients without and 38.46% of subjects with cerebral ischemia. After adjustment for more than 100 perioperative variables, short-term mortality was associated independently with delirium (OR = 3.735), stroke (OR = 5.698), hypertension (OR = 0.333), urgency of surgery (OR = 13.018), baseline plasma glucose and protein concentrations and blood transfusions (AUROC for the model 0.94). Long-term mortality in patients who developed delirium was 23.31%, including 15.2% of patients without and 44.62% of those with postoperative stroke. Long-term mortality independently corresponded with stroke (HR = 3.968), urgent surgery (HR = 27.643), baseline plasma glucose and protein concentrations, chronic obstructive pulmonary disease and blood transfusions. Impact of postoperative delirium was insignificant (p = 0.2). Compared to subjects with cerebral ischemia, death in patients only with delirium was less frequently of cardiovascular cause (p < 0.01).**

Conclusions: **Delirium with/without cerebral ischemia significantly worsened the short-term prognosis. Stroke, yet not delirium, considerably increased the long-term mortality, especially of cardiovascular origin.**

KEY WORDS: delirium, mortality, postoperative complication, determinants, survival analysis, cardiac surgery

DELIRIUM COMMONLY IS DESIGNATED as a transient brain dysfunction and is believed to be a consequence of reduced cerebral blood flow, hypoxia, and metabolic imbalance[1] in genetically[2,3] and structurally[4] vulnerable individuals in the aftermath of cardiac surgery. It has been documented that the rate of postoperative delirium is difficult to assess and often underestimated,[5] reaching up to 70% of cardiac intensive care patients.[6–11] Both functional and structural neuropsychiatric complications account for postoperative morbidity manifested by increased risk of surgical site and pulmonary infections,[6,12–15] the need for extended mechanical ventilation,[14] multiorgan failure,[6,12,14,16] and prolonged time of hospitalization.[9,12,14,17,18] Delirium, regardless of cerebral ischemia, is associated with a decline in health-related quality of life,[17] which can be attributed largely to permanent impairment of cognitive function after cardiac surgery.[19]

Delirium also was found to be related with the outcome, including increased morbidity and mortality, but available data for this association are incoherent.[6,9,11,20] Some data also imply that delirium are predictive of early mortality in the ICU yet does not improve the risk estimation by the APACHE-II model.[21]

Delirium following cardiac surgery has been demonstrated to be related with increased long-term mortality;[8,11,17] however, none of the reports entailed heterogenous (other than coronary) cardiac surgery procedures, assessed a crucial confounding variable in the form of postoperative cerebral ischemia and differentiated between cardiovascular and other-cause mortality. Thus, the authors sought to investigate the effect of delirium with/without cerebral ischemia (ie, transient ischemic attack or stroke) on short- and long-term mortality in a large cohort of cardiac surgery patients. In this study, the authors hypothesized that delirium worsened the outcome, both in short- and long-term perspectives, regardless of cerebral ischemia.

METHODS

The study was performed in a single high-volume tertiary cardiac surgery center and covered consecutively admitted patients between January 2003 and December 2008. The following exclusion criteria were applied for a cohort of 8,792 subjects: History of any psychiatric disorders, use of psychoactive drugs, and history of alcohol abuse. Patients with incomplete data, missing more than 5 of more than 100 preoperative, intraoperative, and postoperative non-psychiatric variables (Appendix) also were excluded from the final analysis. As a result, 5,781 people (1,750; 30.3% women and 4,031; 69.7% men) underwent

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prospective observation until June 2010. The median follow-up period was 46 (range 18-90) months, covering 23,127 patient-years.

The survival analysis took into account the time of death (short- and long-term mortality) and the cause of death (cardiovascular or other cause). Short-term death was defined as demise during index hospitalization (in-hospital) or within 30 days following the procedure if the patient was discharged before the end of this period. Statistics concerning the death, together with its cause and exact time, were obtained from the official database of national healthcare provider and the National Cardiac Surgery Registry. The data on mortality were complete regarding all the participants.

The study complied with the Declaration of Helsinki and was approved by the local ethics committee. All the participants gave their written consent to personal medical data processing for the purpose of this study.

Delirium was diagnosed predominantly by the attending physician (a cardiac surgeon or intensive care specialist trained and experienced in perioperative care) according to the Diagnostic and Statistical Manual of Mental Disorders IV edition (DSM-IV),[22] which is assumed to constitute the most complete definition of delirium.[23] The criteria covered: (1) Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, (2) a change in cognition or the development of a perceptual disturbance that could not be explained by a preexisting, established, or evolving dementia, (3) a disturbance developing over a short period of time (usually hours to days) with the tendency for fluctuation during the course of the day, and (4) evidence from past medical history, physical examination, or laboratory findings that the disturbance resulted from direct physiologic consequences of a general medical condition. All the patients were screened for delirium twice a day during a ward round except for acute hyperactive cases that were diagnosed on the basis of psychotic symptoms (ie, hyperactive, aggressive and/or uncooperative patient with cognitive deficits). Every case subsequently was verified by a consulting psychiatrist. Should neurologic deficits be suspected, a meticulous neurologic examination was conducted by a consulting neurologist. The term, "cerebral ischemia," encapsulated TIA or stroke, which means "rapidly developing clinical signs of focal (or global) disturbance of cerebral function with neurological symptoms leading to death or not with no apparent cause other than of vascular origin, regardless of duration of symptoms," according to the World Health Organization criteria.[24] If not gathered primarily on admission or during current hospitalization, the data on comorbidities were collected using referral letters and discharge summaries enclosed by patients, which required retrospective investigation of medical documents.

All the patients were assessed routinely with 2D-echocardiography so as to obtain left ventricular ejection fraction (LVEF) and identify possible valvular heart disease. Heart function was classified into the following categories: Good (LVEF $>50\%$), moderate (LVEF $= 30\%$-50%), and poor (LVEF $< 30\%$). The extent of carotid artery stenosis was evaluated preoperatively with Doppler ultrasonography. Preoperative risk assessment was based on Additive EuroSCORE (in points) and Logistic EuroSCORE (in %). Patients' operative risk was stratified into: Low (0-2 points), moderate (3-5 points), or high (6+ points).[25] Moreover, physical status by the American Society of Anesthesiologists (ASA) classification was obtained.[26] Laboratory tests were performed in the time frame 24 hours before and after the procedure. Samples for arterial blood gas analysis were collected from the radial artery in the operating room. All measurements complied with ISO 9001:2008 certificate, which is the internationally recognized quality standard for the management of businesses. It is used for establishing and maintaining sufficient control over the quality of products and services provided by certain organizations so that the needs and expectations of customers are met. Evaluation of hemodynamic variables directly preceded the induction of anesthesia (continuous electrocardiographic monitoring, invasive arterial blood pressure monitoring, central venous pressure measured through jugular or subclavian access).

All patients were anesthetized in accordance with the unified protocol involving oral premedication with midazolam (7.5 mg-15 mg, 1/2 h-1 h before the surgery) and induction with intravenous etomidate (0.15-0.2 mg/kg) or propofol (1.0-2.5 mg/kg), fentanyl (7.0-10.0 μg/kg) and the use of nondepolarizing muscle relaxant (pancuronium 1.0-2.0 mg/kg or cisatracurium 0.15-0.2 mg/kg). The anesthesia was sustained with the technique of total intravenous anesthesia (TIVA; midazolam 1.5-2.0 μg/kg/min or propofol 0.05-0.25 mg/kg/min or fentanyl 0.15 μg/kg/min) or in selected cases with combined intravenous and inhalation anesthesia (sevoflurane, isoflurane or desflurane). Muscle relaxation was sustained with the repeated doses of muscle relaxant every 20-40 minutes. Intubation was performed using 6.5-9 mm single- or double-lumen endotracheal tubes (MIDCAB procedures). The authors used pressure-control or volume-control mechanical ventilation with 100% oxygen, simultaneously monitoring respiratory rate and volume, airway pressure, end-tidal CO2 and blood oxygen saturation. Patients were hemodynamically monitored in a continuous fashion (electrocardiography: II and V5 leads, invasive intra-arterial blood pressure monitoring, central venous pressure measurement with the use of a triple-lumen catheter introduced via Seldinger technique). Body temperature was measured using a thermistor-based esophageal temperature probe. A Foley catheter was inserted and urine output was assessed continuously. Antibiotic prophylaxis in the form of 1st generation cephalosporin was administered to every operated patient for at least 72 h after induction. Intravenous fluids were supplemented at the rate of 80-150 mL/h, depending on hydration status (preferably crystalloid solutions).

Surgical management varied depending on the type of procedure and surgeon's preference. Median sternotomy was the predominant approach with the exception of minimally invasive surgeries that involved lateral thoracotomy. On-pump cardiac surgery involved administration of full-dose low-molecular-weight heparin (3 mg/kg), along with the insertion of a cannula into the ascending aorta and right atrium. High-potassium (20-30 mmol/L) cardioplegic solution (4:1) was injected reversely into the coronary arteries (initially 800-1000 mL, subsequently, repeated doses of 200-300 mL). The majority of surgeries were conducted in moderate hypothermia (32°C), except for the aortic dissection surgery requiring deep hypothermia. Rewarming rate was 0.5-1.0°C/5 minutes.

Statistical analysis was performed using SAS 9.2 (SAS Institute, Gary, NC) and Statistica 8.0 (StatSoft Inc, Tulsa, OK) software. Continuous variables are expressed as mean and standard deviation (normally distributed) or as median and interquartile range (IQR) (non-normally distributed). Distribution was verified using the Shapiro-Wilk test. Qualitative variables are expressed as crude values and percents. Between-group differences for normally distributed quantitative variables were assessed using Student t-test or analysis of variance, and Mann-Whitney U-test or Kruskal-Wallis test were used for those non-normally distributed. As far as qualitative variables are concerned, Mantel-Haenszel chi-square or Fisher's exact test were applied. The association between patient- and procedure-related perioperative parameters and short-term mortality was evaluated initially by means of bivariate analysis. Variables with $p < 0.1$ were subjected consecutively to a multivariate stepwise logistic regression model. Logistic ORs with 95% CIs subsequently were estimated. Survival analysis was based on the Kaplan-Meier method. Death was treated as a primary endpoint and survival time was the period between the day of surgery and the date of death (completed) or the date of January 6, 2010 (censored). Nonparametric log-rank test was applied to compare Kaplan-Meier plots. The impact of the above-mentioned perioperative variables, including delirium and cerebral ischemia on