Epidural Anesthesia in Elderly Patients Undergoing Coronary Artery Bypass Graft Surgery

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The use of thoracic epidural anesthesia (TEA) in patients undergoing coronary artery bypass graft (CABG) surgery has recently gained popularity because of its potential beneficial effects on the perioperative stress response, analgesia, and postoperative pulmonary function.1-4 The potential advantage of TEA may become evident in high-risk patients who have a higher complication rate. Previous reports showed that TEA significantly attenuates the stress response in patients undergoing cardiac surgical procedures,1,4 significantly decreasing blood levels of norepinephrine, epinephrine, and cortisol. These hormones increase the hemodynamic stress on the ventricular wall and stimulate B-natriuretic peptide (BNP) release from cardiac myocytes directly.5 BNP recently has emerged in the context of cardiac surgery because of its prognostic value in clinical outcomes such as mortality and prolonged intensive care unit (ICU) and hospital stay.6,7

The authors’ working hypothesis was that TEA would modulate the release of BNP after surgery due to its ability to reduce the neurohormonal stress response to surgery trauma.2,3 For this reason, the authors hypothesized that combined TEA and general anesthesia in patients undergoing CABG surgery would lower the release of BNP compared with general anesthesia alone. To do so, a case-matched study was performed in elderly patients with or without an epidural catheter.

METHODS

After ethical committee approval and patients’ written informed consent, 46 consecutive patients undergoing CABG surgery with TEA added to general anesthesia during a 6-month period at the authors’ center were compared with 46 matched controls selected from the comprehensive group of subjects undergoing standard general anesthesia (GA) during the same time period. Because off-pump and on-pump CABG surgery presented no differences in terms of postoperative NT-proBNP release in the authors’ experience,8 the 2 surgical procedures were lumped together. Matching criteria were identical preoperative medical treatment (including use of angiotensin-converting enzyme inhibitors, β-blockers or calcium channel antagonists, and diuretics), left ventricular ejection fraction (stratified as <40%, between 41% and 50%, and >50%), identical comorbidities (including chronic renal failure, chronic obstructive pulmonary disease, and re-intervention), sex, and age.

Patients undergoing elective full-sternotomy CABG with or without cardiopulmonary bypass (CPB) were considered eligible for the study (both epidural and GA group) if the following criteria were met: age more than 65 years, no history of cerebrovascular disease, and normal coagulation profile (prothrombin time and partial thromboplastin time in the normal range, platelet count >100,000/mL). Antiplatelet medications were withdrawn at least a week earlier in all patients of both groups. Heparin infusion, if present, was discontinued 6 hours before performing epidural catheterization. Low–molecular-weight heparin was stopped 12 hours before epidural catheterization.

An 18-G epidural catheter was inserted on the day of the operation at the most prominent intervertebral space between T2 and T5. With the patients in the sitting position and using a midline approach, the epidural space was identified by a loss of resistance to air. The catheter was advanced 4 to 5 cm cephalad into the epidural space. After aspiration for blood or cerebrospinal fluid, a 2-mL test dose of 2% lidocaine was injected to rule out subarachnoid placement of the catheter. The authors abandoned the regional technique after 3 unsuc-
cessful puncture attempts. In case of a bloody tap, the authors’ protocol was to postpone surgery by 24 hours.

The induction of TEA was achieved with a loading dose of 0.1 to 0.2 mL/kg of lidocaine 2%. The level of the block was tested by the loss of sensation to cold. An extension from T1 to T8 was considered satisfactory. Failed epidural anesthesia was defined as the absence of an adequate level of analgesia 15 to 30 minutes after the injection of a loading dose in the epidural space. Regional anesthesia was maintained by a continuous epidural infusion of 0.2% ropivacaine and 1 µg/mL of sufentanil and continued postoperative day 3, when the epidural catheter was removed. Catheter removal was performed with normal coagulation profile (prothrombin time and partial thromboplastin time in the normal range, platelet count >100,000/mL). Heparin infusion, if present, was discontinued 6 hours before catheter removal. Low-molecular-weight heparin was stopped 12 hours before epidural catheter removal. Aspirin was not considered as a contraindication to epidural catheter removal.

The induction of GA was achieved in all patients with propofol, 1 to 2 mg/kg; fentanyl, 2 to 3 µg/kg; and vecuronium, 0.1 mg/kg, to facilitate tracheal intubation. The lungs were ventilated in normocapnia with an air-oxygen mixture. GA was maintained by the continuous infusion of propofol, 50 to 100 µg/kg/min, and the inhalation of desflurane in all patients. Additional boluses of vecuronium and fentanyl were injected if necessary. Monitoring included arterial and central venous blood pressure, electrocardiogram (leads II and V5), pulse oximeter, and end-tidal carbon dioxide. The depth of anesthesia was monitored by Bispectral Index (BIS A2000 Monitor; Aspect Medical System Inc, Newton, MA) in both groups and maintained between 40 and 50.

The decision to perform CABG off pump or with CPB was related to the surgeon’s preferences depending on the location and adequacy of target vessels. In the off-pump CABG group, single aortic side-clamping was performed to minimize the risk of aortic trauma in the case of multiple proximal anastomoses. Lesions of the left anterior descending artery were bypassed with a left internal mammary artery pedicle graft when feasible. Routine intracoronary shunting was performed. An initial dose of heparin, 150 U/kg, was given intravenously and the activated coagulation time (ACT) measured. Additional doses of heparin were administered to maintain ACTs greater than 300 seconds. Protamine reversal was performed at the end of surgery. Target artery immobilization and regional myocardial motion control were achieved through a commercially available mechanical stabilization system. Coronary stabilization changeovers and reconfiguration of the stabilizer were required during multivessel surgery. In the CPB group, mild hypothermia (33°C) and myocardial protection were performed by intermittent anterograde cold blood cardioplegia and a warm reperfusion just before the removal of the aortic cross-clamp. An initial dose of heparin, 300 U/kg, was given to reach an ACT greater than 480 seconds. The extracorporeal device consisted of a roller pump, a reservoir, and a membrane oxygenator. The pump flows were adjusted to maintain a cardiac index greater than 2.4 L/min/m². Protamine reversal was performed at the end of the operation.

At the end of the procedure, all patients were transferred intubated to the ICU. Weaning from the ventilator was started when the following criteria were achieved: hemodynamic stability, no significant arrhythmias, no major bleeding, temperature >36°C, adequate level of consciousness and no signs of neurologic injury, adequate pain control, pH and blood gases within normal values with an FIO₂ <60%, and a positive end-expiratory pressure <6 cmH₂O. The patients were eligible for transfer from the ICU when the following criteria were met: SpO₂ >90% at an FIO₂ ≤50% by a facemask, adequate cardiovascular stability with no hemodynamically significant arrhythmias, chest tube drainage <50 mL/h, urine output >0.5 mL/kg, no intravenous inotropic or vasopressor therapy, and no seizures. Criteria for hospital discharge were as follows: stable hemodynamics without arrhythmias, clean and dry incisions, normal body temperature, normal bowel movement, and independent ambulation and feeding.

All data were prospectively collected by a blinded research nurse who interviewed the on-duty physician daily. The preoperative patients’ data were collected as described in Table 1. The most frequent comorbidities included diabetes (currently treated with oral medications or insulin), peripheral vascular disease (lower-extremity disease including claudication, amputation, and prior lower-extremity bypass), and chronic obstructive pulmonary disease (treated with bronchodilators or steroids).

Acute renal failure was defined as serum creatinine doubling when compared with preoperative values. Changes indicative of myocardial ischemia were defined when one or more of the following criteria occurred: the presence of horizontal or downsloping ST-segment depression of 0.1 mV or greater, an elevation of 0.2 mV or greater, 50 millisecondes measured after the J point, and new symmetric inverted T-waves. Myocardial infarction was defined on cardion troponin (cTnI), echocardiographic, and electrocardiographic findings with new Q-waves defined as the appearance of a Q-wave >50 milliseconds in at least 2 adjacent leads; the loss of R-wave amplitude in precordial leads was considered Q-wave equivalent when greater than 50%.

The primary outcome measure was postoperative N-terminal proBNP (NT-proBNP). The secondary outcome was the rate of prolonged ICU stay (>4 days). This cutoff was chosen because patients with an ICU stay longer than 4 days showed, at day 1, significantly higher plasma NT-proBNP levels than patients with ICU stay <4 days as described in a previous cohort of patients. Data on acute renal failure, serum peak creatinine and cTnI values, myocardial ischemia and infarction, time on mechanical ventilation, ICU and hospital stay, and mortality adverse events were collected.

The authors determined the plasma concentrations of NT-proBNP just before anesthesia induction (day 0, baseline values) and 24 hours after the end of the surgery (day 1, postoperative values) because Berendes et al showed that the BNP concentration peak is 24 hours after surgery. Blood was collected in plastic tubes with a clot activator (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ) and was centrifuged (2500g for 15 minutes) before analysis. NT-proBNP was assayed with Dimension RxL (Dade-Behring, now Siemens, Newark, NJ) according to the manufacturer’s instructions. The NT-proBNP method is a 1-step enzyme immunoassay based on the “sandwich” principle. Functional sensitivity of the assay is 3.0 pg/mL. Clinicians were blinded to BNP pre- and postoperative values until the end of the study.

Sample-size calculation was based on a 2-sided alpha error of 0.05 and 80% power. Based on the authors’ previous experience, they anticipated a postoperative NT-proBNP release of 4,000 ± 2,500 pg/mL and assumed a 1,500 pg/mL difference between patients with or without TEA being significant. The authors calculated that they would need a sample size of 46 patients per group. Therefore, the total study population was 2 × 46 = 92 patients. Data were analyzed by the use of Epi Info 2002 software (CDC, Atlanta, GA) and SPSS software 16 (SPSS Inc, Chicago, IL). Patients were case matched by preoperative medications, ejection fraction, and comorbidities with patients who did not receive TEA. Preoperative patient characteristics and individual risk factors, intraoperative course, and operative outcomes were compared by univariate analysis. Data are reported as percentage or as mean ± standard deviation or, for variables not normally distributed, as median and 25th to 75th percentiles. All data analysis was performed according to a pre-established analysis plan. Dichotomous data were compared by using the chi-square test with the Yates correction or Fisher exact test when appropriate. Continuous measures were compared by an analysis of variance or the Mann-Whitney U test when appropriate. Two-sided significance tests were used throughout the
analysis. A multiple, forward, stepwise logistic regression was performed to determine which preoperative or intraoperative variables were significantly associated with an ICU length of stay longer than 4 days. The Spearman coefficient matrix correlation was applied to identify significant colinearity between variables. The odds ratio with 95% confidence intervals for the variables selected by the logistic model was calculated. The discrimination power of the logistic equation was evaluated by the C statistic. The Hosmer and Lemeshow chi-square test was used to calibrate the model.

RESULTS

The degree of sensory blockade in the TEA group was adequate in all but 2 patients: one of them had a prolonged ICU stay, and both of them were included in the TEA group. The dura was never punctured. The authors observed no bloody tap. There was no complication related to the positioning or removal of the epidural catheter. In 2 patients, it was not possible to identify the epidural space and insert the epidural catheter: they had an uneventful postoperative course and were included in the GA group.

Patients were well matched for all preoperative and intraoperative variables (Table 1) with a slightly higher number of redo patients and EuroSCORE values in the TEA group and a trend toward a higher number of diabetic patients and number of grafted vessels in the GA group. NT-proBNP preoperative levels were similar in the 2 groups: 402 (115-887 pg/mL) in the TEA group versus 508 (228-1,285 pg/mL) in the GA group (p = 0.9). The number of patients on β-blockers was similar as well, 26 (57%) in the TEA group versus 23 (50%) in the GA group. NT-proBNP increased after surgery in all patients. Patients in the TEA group had significantly (p = 0.001) lower median (interquartile range) NT-proBNP values at day 1, 1,846 (1,135-3,687 pg/mL) versus 5,005 (2,220-11,377 pg/mL) of the GA group (Fig 1), with the lowest 6 values in the TEA group and the highest 6 values in the GA group. Patients operated off pump or with CPB had a similar release of NT-proBNP, 2,175 (1,026-5,925 pg/mL) versus 2,781 (1,664-6,363 pg/mL) (p = 0.4).

Postoperatively, there were no statistically significant differences in the incidence of perioperative ischemia, perioperative myocardial infarction, postoperative renal failure, and postoperative cTnI peak (Table 1). There were 4 in-hospital deaths, 3 in the GA group (6.5%) and 1 in the TEA group (2.2%), without a significant statistical difference (p = 0.39). Two
patients (one in each group, 78 and 79 years old) died of perioperative myocardial infarction. The other 2 patients (both in the control group) died of multiple-organ failure and sepsis after a prolonged ICU stay: one after low-cardiac-output syndrome and acute renal failure and the other after excessive bleeding and multiple transfusions. Notably, there were more patients in the GA group (9 patients) than in the TEA group (4 patients) who experienced prolonged ICU stay (>4 days, \( p = 0.043, 8.8\% \, v \, 19.5\%\)), with the 5 patients with the longest ICU stay all belonging to the GA group.

Postoperative BNP levels were higher, 6,363 (2,220-17,800 pg/mL), in patients with a prolonged (>4 days) ICU stay than in those with an ICU stay \( \leq 4\) days, 2,695 (1,249-5,047 pg/mL) (\( p = 0.02\)). When the preoperative and intraoperative variables described in Table 1 were entered into a stepwise logistic regression analysis to identify the predictors of a length of the stay longer than 4 days as described in the Methods section, the first variable to enter the model was preoperative \( \beta \)-blockade followed by TEA. None of the other variables were significant predictors of a length of stay >4 days. When the absence of \( \beta \)-blockade (odds ratio [OR] = 3.94; 95% confidence interval [CI], 1.123-13.833; \( p = 0.03\)) and the absence of TEA (OR = 3.951; 95% CI, 1.068-14.619; \( p = 0.04\)) were included in the final model, this was highly significant (Hosmer and Lemeshow chi-square test, \( p = 0.85\)). The model also showed good discrimination power (c-statistic: 0.713; 95% CI, 0.582-0.844; 78.6% of patients being appropriately classified).

DISCUSSION

The most important result of this study is to show that the secretion of NT-proBNP is significantly attenuated in elderly patients when TEA is added to a standard GA for CABG surgery. Furthermore, the authors documented, for the first time, that elderly patients receiving TEA have a reduced incidence of prolonged ICU stay in this setting. Because high postoperative NT-proBNP levels correlate with morbidity and 1-year mortality after cardiac surgery,6,7 its attenuation could already be considered a relevant endpoint.

Only 1 group11 showed that reversible sympathectomy and pain therapy by high TEA significantly improved regional left ventricular function and, as an unexpected finding, attenuated BNP release after CABG surgery. Their study had no sufficient power to document improved hospital clinical outcomes in CABG patients.

BNP is released predominantly from ventricular myocytes and acts as a counter-regulatory hormone increasing sympathoadrenal and neurohormonal activation.12 Wall stretch controls the release of BNP from cardiac myocytes13 by several endocrine factors, such as norepinephrine and angiotensin II.5 The mechanism through which TEA reduced blood levels of BNP is not fully understood; in fact, postoperative myocardial damage and cardiac dysfunction after cardiac surgery are not exhaustive explanations.6,7 The authors’ working hypothesis is that TEA decreases the release of BNP after surgery, improving the neurohormonal stress response to surgery trauma.2,3 The finding that patients operated off-pump or with standard CPB had a similar release of NT-proBNP in the present study, supports this hypothesis. Only 1 author documented that BNP increases postoperatively after major noncardiac surgery and that TEA could lower postoperative BNP.14 Notably, in the study of Suttner et al,14 cTnI concentrations were within normal limits in TEA and GA patients at all times, suggesting that myocardial damage is not the only cause of BNP release.

Other investigators documented that TEA significantly attenuates the stress response in patients undergoing cardiac surgical procedures in terms of decreased blood levels of norepinephrine, epinephrine, and cortisol.1-4 Interestingly, the present results show, for the first time, that TEA reduces ICU stay in elderly patients undergoing CABG surgery (patients not receiving TEA had almost 4 times the chance of a prolonged ICU stay). To date, no randomized controlled studies evidenced improvements in major clinical outcomes15-17 because previous investigations studied low-risk patients, with few adverse events. The potential advantages of TEA became evident in a small cohort of high-risk elderly patients who probably benefited more from the attenuation of the stress response. TEA use did not facilitate tracheal extubation in the authors’ experience. This could be attributed to the absence of a fast-track protocol.
Another important finding of this study is the association between the preoperative use of β-blockers and ICU stay after CABG surgery in elderly patients. Although β-blockers have beneficial effects in the perioperative period in high-risk patients undergoing major noncardiac surgery, to date, there is no evidence in the setting of cardiac surgery. The depression of myocardial contractility and/or the exacerbation of underlying reactive airway disease are major concerns in patients undergoing CABG surgery. Nonetheless, a large multicenter observational study in North America suggested that preoperative β-blockade improves survival in patients undergoing CABG surgery except for those with poor left ventricular function (<30%). It also should be acknowledged that a recent meta-analysis on the use of esmolol in cardiac surgery suggested that the perioperative use of this β-blocker reduces perioperative ischemia and the need for inotropic drugs.

The obvious limitation is the nonrandomized design of the study. The authors also have an insignificant higher number of diabetic patients in the control group. The authors did not collect some important data such as atrial fibrillation, the reason for prolonged ICU stay, and the occurrence of type-II neurologic dysfunction.

CONCLUSIONS

The results of the present case-matched study suggest that elderly patients undergoing CABG surgery with supplementary TEA have a reduced release of NT-proBNP and present less morbidity in the postoperative phase as documented by a reduced incidence of prolonged ICU stay in elderly patients.

REFERENCES