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Timing of Pre-Operative Beta-Blocker Treatment in Vascular Surgery Patients

Influence on Post-Operative Outcome

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Objectives This study evaluated timing of β-blocker initiation before surgery and its relationship with: 1) pre-operative heart rate and high-sensitivity C-reactive-protein (hs-CRP) levels; and 2) post-operative outcome.

Background Perioperative guidelines recommend β-blocker initiation days to weeks before surgery, on the basis of expert opinions.

Methods In 940 vascular surgery patients, pre-operative heart rate and hs-CRP levels were recorded, next to timing of β-blocker initiation before surgery (0 to 1, >1 to 4, >4 weeks). Pre- and post-operative troponin-T measurements and electrocardiograms were performed routinely. End points were 30-day cardiac events (composite of myocardial infarction and cardiac mortality) and long-term mortality. Multivariate regression analyses, adjusted for cardiac risk factors, evaluated the relation between duration of β-blocker treatment and outcome.

Results The β-blockers were initiated 0 to 1, >1 to 4, and >4 weeks before surgery in 158 (17%), 393 (42%), and 389 (41%) patients, respectively. Median heart rate at baseline was 74 (±17) beats/min, 70 (±16) beats/min, and 66 (±15) beats/min ($p < 0.001$; comparing treatment initiation >1 with <1 week pre-operatively), and hs-CRP was 4.9 (±7.5) mg/l, 4.1 (±.6.0) mg/l, and 4.5 (±6.3) mg/l ($p = 0.782$), respectively. Treatment initiated >1 to 4 or >4 weeks before surgery was associated with a lower incidence of 30-day cardiac events (odds ratio: 0.46, 95% confidence interval [CI]: 0.27 to 0.76, odds ratio: 0.48, 95% CI: 0.29 to 0.79) and long-term mortality (hazard ratio: 0.52, 95% CI: 0.21 to 0.67, hazard ratio: 0.50, 95% CI: 0.25 to 0.71) compared with treatment initiated <1 week pre-operatively.

Conclusions Our results indicate that β-blocker treatment initiated >1 week before surgery is associated with lower pre-operative heart rate and improved outcome, compared with treatment initiated <1 week pre-operatively. No reduction of median hs-CRP levels was observed in patients receiving β-blocker treatment >1 week compared with patients in whom treatment was initiated between 0 and 1 week before surgery. (J Am Coll Cardiol 2010; 56:1922–9) © 2010 by the American College of Cardiology Foundation

Beta-blockers are established therapeutic agents for patients with hypertension (1), heart failure (2), and coronary artery disease (3). In the nonsurgical setting, β-blockers are widely used for the prevention and treatment of coronary heart disease and heart failure, both important determinants of perioperative cardiovascular complications. Over the years multiple observational studies and randomized, controlled trials have been performed to evaluate the effect of perioperative β-blocker treatment in patients undergoing noncardiac surgery (4–15). The majority of these studies have demonstrated cardioprotection derived from perioperative β-blocker treatment.

Proposed mechanisms by which β-blockers exert intraoperative cardioprotective effects include heart rate control, reduction of systolic pressure and ventricular contractile force and its anti-arrhythmic properties. For the long-term, β-blockers reduce mechanical stress imposed on coronary plaques preventing plaque rupture (16). Patients receiving β-blockers tend to have lower plasma concentrations of C-reactive protein (CRP) than those not receiving β-blockers, and the anti-inflammatory properties of β-blockers are thought to stabilize coronary plaques (17–19). In addition, β-blockers are known to lessen adverse

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cardiac remodelling in patients with impaired left ventricular function, which is highly prevalent in the vascular surgery population, by inhibiting the sympathetic nervous system and hormone activation (A-type and B-type natriuretic peptides and norepinephrine) (20–22). Potential side effects associated with β-blocker treatment are bradycardia, hypotension, and stroke. Factors that might relate to the effectiveness of β-blocker therapy and the occurrence of side effects are variations in treatment protocols, such as β-blocker type, β-blocker dose, and timing of β-blocker initiation before surgery. However, the duration of β-blocker treatment before surgery and its effect on cardiovascular outcome has not been evaluated yet in a cohort of vascular surgery patients. The present study was conducted to evaluate timing of β-blocker initiation and its influence on pre-operative heart rate, pre-operative high-sensitivity CRP (hs-CRP) levels, and post-operative outcome in vascular surgery patients.

Abbreviations and Acronyms

CI = confidence interval

hs-CRP = high-sensitivity C-reactive protein

MI = myocardial infarction

RAAS = renin-angiotensin-aldosterone system

Methods

Study population. The original study population consisted of 940 vascular surgery patients undergoing (open or endovascular) lower extremity artery, carotid artery, or abdominal aorta repair, receiving pre-operative β-blocker treatment. Open abdominal aortic aneurysm repair and lower extremity revascularization were considered procedures with high cardiac risk. Carotid surgery and endovascular surgery were considered procedures with intermediate-cardiac risk (23). Patients undergoing emergency surgery; randomized for β-blocker treatment in previous randomized, controlled trials; and with pre-operative heart rate <50 beats/min were not included in the present study. The study was performed at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period of 2002 to 2008. The study was approved by the hospital ethics committee and performed with informed consent of all patients.

Baseline characteristics. Before surgery, a detailed history was obtained from every patient. Clinical data included age, sex, ischemic heart disease (defined as a history myocardial infarction [MI], coronary revascularization, or the presence of pathologic Q waves on pre-operative electrocardiogram), heart failure (defined as the presence of heart failure symptoms according the New York Heart Association functional classification or previous hospital admission for decompensated heart failure), and cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke). In addition, kidney dysfunction (serum creatinine >2.0 mg/dl), diabetes mellitus (fasting blood glucose ≥6.1 mmol/l or requirement of antidiabetic medication), hypertension (blood pressure ≥140/90 mm Hg in nondiabetic patients and ≥130/80 mm Hg in diabetic patients or requirement of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol >3.5 mmol/l or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification), and smoking status were recorded as well. Peripheral blood samples for hs-CRP in mg/l, measured by a nephelometric assay on a Beckman-Immage analyzer (Beckman-Coulter, Fullerton, California), were routinely performed 1 day before surgery.

Medication use. The use of the prescription medications was captured at baseline and included β-blockers, statins, aspirin, clopidogrel (at the Erasmus Medical Center antiplatelet therapy is continued during surgery per protocol), oral anticoagulants, inhibitors of the renin-angiotensin-aldosterone system (RAAS) (angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, renin inhibitors, aldosterone antagonists), and diuretics. During the first pre-operative visit at the outpatient clinic, pre-operative β-blocker use was established in patients already receiving β-blockers; and in patients not already receiving β-blockers, pre-operative β-blocker treatment was initiated. Pre-operative β-blocker use was subdivided according to initiation time of treatment: 0 to 1, >1 to 4 or >4 weeks before surgery. All patients returned to the outpatient clinic after 1 week; and β-blocker dosage, if needed, was adjusted and titrated as tolerated to obtain a pre-operative heart rate between 60 and 70 beats/min (24). This protocol could not be followed in patients in which β-blocker treatment was initiated <1 week before surgery.

Study outcomes. Main study end points were 30-day cardiovascular events and long-term mortality. The 30-day cardiovascular events were the composite of myocardial damage (defined as myocardial ischemia or infarction), stroke, and mortality up to 30 days after surgery. Serial electrocardiograms and troponin-T measurements were obtained from all patients before surgery; post-operatively on days 1, 3, and 7; and before discharge. Perioperative myocardial ischemia was defined for patients with normal pre-operative and elevated (>0.03 ng/ml) post-operative troponin-T levels. Elevated troponin-T levels in combination with electrocardiographic changes (new onset ST-T changes and pathological Q waves) or with or without symptoms of angina pectoris defined MI (25). Patients with elevated troponin-T levels before surgery were not included in the study. Long-term mortality was assessed by approaching the municipal civil registries. Mean follow-up was 2.2 ± 1.8 years. Secondary end points were pre-operative heart rate (beats/min) and hs-CRP levels (mg/l). Peripheral blood samples for hs-CRP were routinely performed 1 day before surgery. Optimal specificity and sensitivity of hs-CRP to predict post-operative outcome was calculated with receiver-operating characteristic curve analyses, and a cutoff value ≥6.5 mg/l was used in the analyses.

Statistical analysis. Dichotomous data are described as numbers and percentages, and categorical data are compared with the chi-square test. The continuous variable age is described as mean ± SD and compared with analysis of