Beneficial effects of perioperative statins for major pulmonary resection

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Objectives: Statins improve overall outcomes after noncardiac surgery. The primary aim of the study was to determine whether use of perioperative atorvastatin reduced the rate of postoperative complications in patients undergoing pulmonary resection.

Methods: This was a prospective, randomized, placebo-controlled, double-blind trial of patients undergoing elective pulmonary resection who received atorvastatin (40 mg daily) or placebo beginning 1 week before surgery and continued for 1 week postoperatively. Patient characteristics and postoperative complications were recorded. Plasma inflammatory markers were sampled at baseline, in the post-anesthesia care unit, and on postoperative day 3. Because of difficulty enrolling statin-naive patients, the study was stopped at the interim analysis.

Results: Postoperative complications occurred in 16 of 72 patients (22%) receiving placebo and in 8 of 65 patients (12%) receiving atorvastatin ($P = .13$). For patients undergoing major anatomic resection, there were 24 complications in 15 of 45 placebo-treated patients and 8 complications in 7 of 43 atorvastatin-treated patients ($P = .04$). Plasma levels of C-reactive protein, tumor necrosis factor-α, and myeloperoxidase did not differ between the 2 treatment arms during the study.

Conclusions: After a 2-week perioperative course of atorvastatin (40 mg) in statin-naïve patients undergoing major pulmonary resection, we found evidence of a reduction in the number of clinically important cardiovascular and pulmonary complications compared with placebo. These promising results merit evaluation in a larger, perhaps multicenter study. (J Thorac Cardiovasc Surg 2015;149:1532-8)

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Inflammatory and oxidative changes have been implicated as etiologic mechanisms for a variety of postoperative complications after thoracic surgery, such as atrial fibrillation/flutter, acute coronary syndromes, stroke, and respiratory failure.[1-3] Postoperative atrial fibrillation (POAF) is a common complication, occurring in approximately 16% of all patients, with increasing frequency in elderly patients.[4,5] The rate of postoperative pulmonary complications (pneumonia and respiratory failure) is approximately 10%, with severe lung injury resulting in mortality rates of up to 30%.[6] Because these complications result in prolonged hospital stay, resource use, and long-term sequelae, prevention is essential.

Preoperative use of statins in patients with cardiovascular disease has been shown to reduce perioperative cardiovascular morbidity, but its impact in patients undergoing pulmonary resection is unknown.[3,7] The presumed mechanism of the benefit of statins is through inhibition of inflammation.[3,7,8] Some sequelae of lung injury after thoracic surgery include increased inflammation (C-reactive protein [CRP]), leukocyte activation (myeloperoxidase [MPO]), and other acute-phase inflammatory markers, such as tumor necrosis factor alpha (TNFα).[1,2,9] MPO and CRP levels, which are also increased in patients with acute cardiovascular disease, may be reduced by statins.[10-12]

On the basis of promising experimental[13-15] and observational studies from our institution[9] and others,[16] we hypothesized that compared with placebo, the use of moderate-potency atorvastatin would be associated with a decreased composite rate of clinically significant cardiovascular and pulmonary complications after lung resection. A secondary aim was to compare perioperative changes in levels of CRP, TNFα, and MPO between the 2 treatment arms.

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W.S. and H.T.T. are partly supported by a National Institutes of Health Core Grant P30 CA008748.

Disclosures: David Amar reports consulting fees from ETView. Bernard Park reports lecture fees from Intuitive Surgical. All other authors have nothing to disclose with regard to commercial support.

ClinicalTrial.gov identifier: #NCT00375518.

Received for publication June 26, 2014; revisions received Dec 5, 2014; accepted for publication Dec 7, 2014; available ahead of print Jan 23, 2015.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2014.12.016

Abbreviations and Acronyms
CRP = C-reactive protein
MPO = myeloperoxidase
PCU = post-anesthesia care unit
POAF = postoperative atrial fibrillation
TNFα = tumor necrosis factor alpha

MATERIALS AND METHODS

Patient Population

This was a single-center prospective, double-blind, randomized, controlled trial of perioperative moderate-dose atorvastatin versus placebo for patients undergoing elective pulmonary resection. Inclusion criteria included patients (1) undergoing elective pulmonary resection, (2) aged more than 18 years, and (3) with no active statin use. Patients were excluded if they (1) had a history of chronic atrial fibrillation, (2) were taking class I or III antiarrhythmic drugs or corticosteroids, (3) were not in sinus rhythm at the time of the screening, or (4) had abnormal liver function test results or renal insufficiency. A negative pregnancy test was required for women of childbearing age. Beta-blocker and calcium channel blocker use were continued postoperatively to avoid withdrawal. The study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center, and all patients provided written, informed consent.

Atorvastatin Prophylaxis

Once enrolled, patients were randomized between atorvastatin and placebo in permuted blocks between the Department of Epidemiology and Biostatistics and the Department of Pharmacy, in accordance with good medical practice requirements. Blinding of atorvastatin and placebo pills was performed by the Department of Pharmacy, Division of Research. Atorvastatin (40 mg oral daily) or placebo was started 1 week before surgery and continued for 1 week after surgery. In-hospital administration of the study drug or placebo was done by the patient's nurse unless the patient was instructed to take nothing by mouth. Each patient was asked to fill out 2 questionnaires (preoperatively and at conclusion of drug treatment) regarding any untoward effects of the study medication, as well as a diary to record intake of the medication.

Inflammatory Marker Analysis

Venous blood specimens for measurement of high-sensitivity CRP, TNFα, and MPO were obtained 7 to 10 days before surgery, on arrival at the post-anesthesia care unit (PACU), and on the morning of postoperative day 3. Serum was separated by centrifugation and stored at -70°C until analysis. The high-sensitivity CRP assay was performed on the Siemens (Washington, DC) Advia 1800, which uses uniform polystyrene latex particles coated with anti-CRP antibody. The analytic range of the assay was 0.16 to 10.0 mg/L. The MPO assay uses a 2-site "sandwich" enzyme-linked immunosorbent assay method, with 2 polyclonal antibodies that specifically bind to human MPO. The analytic range of MPO, using human MPO as a standard, was 1.9 to 30.0 ng/mL. The TNFα assay uses a quantitative enzyme-linked immunosorbent assay method, with a capture monoclonal antibody specific for TNFα that has been precoated onto a microplate well. The analytic range of this assay, using recombinant human TNFα as a standard, was 0.5 to 32 pg/mL.

Anesthesia, Operation, and Postoperative Care

All patients received premedication with midazolam and standard anesthetic management consisting of isoflurane or sevoflurane in oxygen supplemented with intravenous fentanyl and hydromorphone as needed. Intentional crystalloid restriction (<25 mL/kg) during surgery was attempted in all patients. The operations were performed using minimally invasive video-assisted thoracic surgery or thoracotomy approaches designed to completely remove all neoplastic disease, along with ipsilateral mediastinal lymph node sampling or dissection. Postoperative pain relief was provided by continuous administration of epidural hydromorphone and bupivacaine 0.05% (n = 121) or patient-controlled intravenous hydromorphone analgesia (n = 16; nonanatomic lung resection). After an overnight stay in the PACU, patients were transferred to the thoracic surgical floor on the first postoperative day. Major postoperative cardiac or pulmonary complications were recorded throughout the hospital stay. A research assistant monitored patients for cardiac or pulmonary complications as outpatients and queried patients about intercurrent hospitalizations or emergency department visits. An investigator reviewed these medical records. Continuous dual-lead electrocardiogram telemetry tracings (72-96 hours) after surgery were reviewed by an experienced technician and a cardiologist.

Statistical Analysis

We had originally planned a larger study (n = 480) using a composite of cardiovascular outcomes as the primary end point in patients aged more than 55 years scheduled for anatomic resections. Soon after the start of the trial, new data were published on the greater efficacy of atorvastatin to reduce POAF,[17] and it became clear that a significant number of preoperative patients were already taking statin mediation. We recalculated and estimated that a sample size of 276 patients (138 patients per arm) undergoing lung resection would provide an 80% chance of observing a significant difference ($P < .05$) in the proportion of patients experiencing a major postoperative cardiovascular or pulmonary complication of 27% versus 13%. Because of the difficulty of enrolling patients, the study was stopped at the interim analysis (Figure 1). Among patients who had an anatomic resection (n = 88), a subgroup analysis was performed to assess the difference in overall complication rates for all hypothetical random assignments (permutations) of the treatment arm labels (45 "atorvastatin" + 43 "placebo") to the collection of 88 numbers, each representing the actually observed count of major complications (0, 1, 2, 3, or 4) in the original, combined sample. The 2-sided P value is the proportion of such permutations yielding an absolute difference in overall complication rates at least as large as what was calculated for the actual treatment assignment. SAS version 9.2 (SAS Institute Inc, Cary, NC) was used to determine differences in patient and operative characteristics between the 2 arms and between patients with and without complications. Data are presented as mean ± standard deviation, median (quartiles) for skewed data, or n (%).

RESULTS

From October 2006 to May 2010, a total of 3326 patients were evaluated and 164 patients met the inclusion criteria and were enrolled (Figure 1). Twenty-seven patients were excluded after enrollment, and 137 patients (88 anatomic resections and 49 wedge resections) received atorvastatin or placebo. The 2 treatment groups did not differ in terms of patient characteristics or surgical data, both for the entire study population (Table 1) and for the subset of patients who underwent anatomic lung resection (Table 2). Postoperative complications occurred in 16 of 72 patients (22%) receiving placebo and in 8 of 65 patients (12%) receiving atorvastatin ($P = .13$). The rate of complications was higher after anatomic lung resection compared with wedge resection (22/88, 25% vs 2/49, 4%, $P = .002$). In the wedge resection group, POAF developed in 1 patient and pneumonia developed in 1 patient. The rates of major complications for those who underwent anatomic lung resection by treatment arm are shown in Table 3. Patients treated with atorvastatin had a trend toward decreased