Journal of Clinical Neuroscience 21 (2014) 1133–1140

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Renin-angiotensin system inhibitors and troponin elevation in spinal surgery

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ARTICLE INFO

Article history:
Received 26 October 2013
Accepted 30 October 2013

Keywords:
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Hospitalization stay
Myocardial infarction
Spinal fusion
Troponin elevation

ABSTRACT

Renin-angiotensin system (RAS) inhibition by angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) has been shown to reduce cardiovascular mortality and non-fatal myocardial infarction (MI) in high-risk surgical patients. However, their effect in spinal surgery has not been explored. Our objective was to determine the effect of RAS inhibitors on postoperative troponin elevation in spinal fusions, and to examine their correlation with hospital stay. We retrospectively analyzed 208 consecutive patients receiving spinal fusions $\geqslant$5 levels between 2007–2010 with a mean follow-up of 1.7 years. Inclusion criteria were age $\geqslant$18 years, elective fusions for kyphoscoliosis, and semi-elective fusions for tumor or infection. Exclusion criteria were trauma and follow-up <1 year. Descriptives, frequencies, and logistic and linear regression were used to analyze troponin elevation ($\geqslant$0.04 ng/mL), peak troponin level, and hospital stay. The results featured 208 patients with a mean body mass index (BMI) 28.5 kg/m^2 who underwent 345 spinal fusions. ACEI/ARB were withheld the day prior to surgery in 121 patients with 11 patients noteworthy for intra-operative electrocardiogram changes, 126 patients with troponin elevation, and 14 MI identified prior to discharge. Multivariate logistic regression identified BMI (p = 0.04), estimated blood loss (p = 0.015), and preoperative ACEI/ARB (p = 0.015, odds ratio = 2.7) as significant independent predictors for postoperative troponin elevation. Multivariate linear regression showed preoperative Oswestry Disability Index (p = 0.002), unplanned return to operating room (p = 0.007), pneumonia prior to hospital discharge (p < 0.01), and preoperative ACEI/ARB to be associated with hospital stay. In patients with spinal fusions $\geqslant$5 levels, ACEI/ARB are independently associated with postoperative troponin elevation and increased hospital stay.

1. Introduction

The renin-angiotensin system (RAS) represents a pharmacologic target whereby blockage of angiotensin II using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) aids in the management of cardiovascular disease [1–3]. ACEI possess direct cardiovascular protective effects through angiotensin II reduction and increased bradykinin availability [4–13]. Cardiovascular disease remains a major cause of mortality in the world [1]. The National Heart, Lung, and Blood Institute estimated that cardiovascular disease was responsible for 870,000 deaths in 2004 in the USA, representing 36% of all death [1]. Hypertension affects almost 50 million people in the USA and increases the risk for cardiovascular diseases [14–16]. Hypertension directly predisposes several atherosclerotic cardiovascular disease outcomes including coronary artery disease, myocardial infarction (MI), stroke, ischemic cardiomyopathy, and peripheral artery disease [17].

Perioperative MI is the most common cause of morbidity and mortality in patients who undergo non-cardiac surgery [18–20]. Vascular and spinal surgery patients with perioperative MI have increased morbidity and mortality during hospitalization, and increased hospital length of stay (LOS) [18]. It has been shown that RAS inhibitors reduce peak troponin in patients experiencing ST elevation MI [21]. Cardiac troponin I is a very sensitive marker for myocardial injury [18,22,23]. It detects and quantifies myocardial cellular damage [22]. There is a direct relationship between peak troponin level and the extent of myocardial damage [24–26]. The relationship of RAS inhibitors and troponin elevation

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http://dx.doi.org/10.1016/j.jocn.2013.10.019

in spinal fusions has not been explored. To our knowledge, our manuscript is the first to explore ACEI/ARB and their relationship with troponin elevation in spinal fusions $\geqslant 5$ levels.

2. Methods

2.1. Patient cohort

Two hundred eight consecutive adult patients from 2007–2010 were retrospectively analyzed. A detailed review of the inpatient and outpatient medical records was completed after Institutional Review Board approval. All elective and semi-elective fusions $\geqslant 5$ levels for kyphoscoliosis, tumor, and infection with $\geqslant 1$ year follow-up were evaluated. All patients must have had at least one fusion $\geqslant 5$ levels. One hundred ten patients had more than one spinal fusion procedure. Ninety-eight patients had a single surgery, 89 patients had two, staged surgeries, 16 patients had three fusion surgeries, four patients had four surgeries, and one patient had five surgeries. Trauma patients, those <18 years of age, and patients without follow-up for at least 1 year were excluded.

2.2. Preoperative evaluation

Preoperative cardiovascular medications were categorized based on sex. Patients were instructed to withhold their ACEI/ARB the day of surgery, and these medications were restarted the day after surgery unless the patient was hemodynamically unstable. In accordance with the most recent American College of Cardiology and American Heart Association guidelines, beta-blockers (BB) were continued on the day of surgery, but the dose was not escalated [27]. The administration of calcium channel blockers (CCB), diuretics, or other anti-hypertensive medications was performed at the discretion of the patient's internist or primary care physician.

2.3. Statistics

Demographics were collected on all patients. Frequencies of preoperative, intraoperative, and immediate perioperative data were sorted based on sex. Outcome variables recorded included troponin elevation ($\geqslant 0.04$ ng/mL), peak troponin level, hospitalization length, and incidence of acute MI or death at discharge, wound check (2 weeks), early follow-up (6 weeks to 4 months), 1 year follow-up, and 2 year follow-up. Electrophysiological changes pre and postoperatively were evaluated. The Oswestry Disability Index (ODI) was reviewed at each follow-up visit.

Bivariate analysis (*t*-tests, analysis of variance [ANOVA], crosstabulation, frequency analysis, χ^2) evaluated troponin elevation and peak troponin level with preoperative ACEI/ARB. Logistic regression analysis evaluated troponin elevation and ACEI/ARB. Linear regression models assessed hospital LOS and peak troponin. If missing data points were identified for a variable, the sum total of the potential events did not include the missing variable population. All analyses were carried out using the Statistical Package for Social Science software version.20 (SPSS, Chicago, IL, USA). A p value of <0.05 was considered significant.

3. Results

There were 208 patients (79 men, 129 women) who received 345 surgeries. The average age at surgery was 58.9 years and mean body mass index (BMI) was 28.5 kg/m^2, (range 17.6–55.8 kg/m^2). Preoperative predictors of cardiovascular morbidity were reviewed and are listed in Table 1. Seventy patients required smoking cessation with 31 receiving a urine nicotine test prior to surgery.

Antihypertensive medications were categorized as follows: 121 patients had their ACEI/ARB withheld the day of surgery; 119 surgeries involved patients continuing on a BB; 69 patients had a CCB withheld prior to surgery; there were 125 surgeries where a diuretic was withheld; and 106 surgeries featured a statin, preoperatively. Aspirin was withheld for 7 days prior to surgery, and clopidogrel (Plavix, Bristol-Myers Squibb, New York, NY, USA) was withheld 14 days prior to surgery in 94 (27%) and 16 (5%) patients, respectively. Of the patients who had their aspirin and Plavix withheld, 57/94 aspirin-withheld patients and 11/16 Plavix-withheld patients had an ACEI/ARB in their medication profile. Coumadin (Bristol-Myers Squibb) was withheld for 21 (6.1%) surgeries.

Three hundred forty-one surgeries had a preoperative electrocardiogram (ECG) with 169 (49.6%) being normal and 146 (42.8%) having one change. The mean Charlson Comorbidity Index Score and mean American Association of Anesthesiology Score was 3.46 and 2.6, respectively. The mean preoperative ODI was 49.1.

Mean preoperative cardiovascular laboratory investigations were as follows: HbA1c was 5.80 (standard deviation [SD] = 1.5, normal 0.0–6.5), creatinine was 0.79 (SD = 0.30), high density lipoprotein (HDL) was 39.0 (SD = 23.5, normal >40), low density lipoprotein (LDL) was 77.7 (SD = 45.8, normal 0–100), and triglycerides were 113.3 (SD = 67.5, normal 50–150). Six surgeries (1.7%) had HbAIc >7.0, 40 surgeries (11.6%) had abnormal creatinine (males >1.2, females >1.0), 45 surgeries (13.0%) had abnormal HDL (males <40, females <50), 21 surgeries (6.1%) had LDL >100, and 13 surgeries (3.8%) had triglycerides >150. The mean number of abnormal cardiovascular laboratory values was 1.7 (SD = 0.8). Nine patients (2.6%) had documented valvular disease and 15 patients (4.3%) had a cardiac coronary artery stent. Means were reviewed and categorized based on abnormal values for sex; none were significant on bivariate analysis.

Intraoperative and postoperative data is listed in Table 2. The mean number of surgical levels was 8.2 with a mean estimated blood loss of 2773 cc. Mean length of surgery was 427 minutes. There were 46 (13.3%) pedicle subtraction osteotomies performed and 24 (7.0%) vertebral column resections completed. There were 11 (3.2%) patients notable for intraoperative ECG changes. The mean troponin elevation was 0.28 ng/mL. There were 126 surgeries with postoperative troponin level $\geqslant 0.04$ ng/mL. A total of 271 ECG were performed postoperatively. The sum of ECG changes are as follows: no change in 109 (40.2%), one change in 120 (44.3%), two changes in 34 (12.5%), three changes in seven (2.6%), and four changes in one (0.4%). An ECG change was defined as any sinus tachycardia, ST elevation, ST depression, supraventricular tachycardia/atrioventricular re-entrant tachycardia, atrial fibrillation, atrial flutter, bundle branch block or T-wave inversion. No statistically significant differences in the pre and postoperative transthoracic ECG were identified. There was one (0.3%) postoperative coronary catheterization. The mean intensive care unit stay was 3.55 days, and the mean hospital LOS was 14.2 days.

MI were defined as troponin $\geqslant 0.50$ ng/mL and ECG change. These were confirmed with a cardiology service evaluation. There were 39 (11.3%) postoperative cardiology consultations. There were 14 MI (4.1%) and three deaths (0.9%) prior to hospital discharge. There were no MI and nine deaths (2.9%) at the time of the wound check at 2 weeks. One hundred twenty-five inpatient rehabilitation (36.2%) discharges were required. The most frequent complications at the time of discharge or at the time of the wound check were infection and deep vein thrombosis (DVT).

The mid- and long-term follow-up information is listed in Table 3. The most frequent complications at these intervals remained infection and DVT. There were 4 MI (1.3%) at early follow-up and no MI at 1 year or 2 year follow-up. At both 1 and 2 year follow-up there were 10 infections (4.1% and 7.4%,