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Peripheral artery disease is associated with poor clinical outcome in patients with abdominal aortic aneurysm after endovascular aneurysm repair☆

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ABSTRACT

Background: We investigated the effects of coronary artery disease (CAD) or peripheral artery disease (PAD) on clinical outcomes of patients with abdominal aortic aneurysm (AAA) treated with endovascular aortic aneurysm repair (EVAR).

Methods: We retrospectively evaluated a total of 475 patients with AAA treated with EVAR at a single center. Patients were divided into three groups: group A ($n = 166$), patients without CAD or PAD; group B ($n = 196$), patients with CAD but without PAD; and group C ($n = 113$), patients with PAD regardless of CAD. The primary endpoint was the accumulated rate of major adverse cardiovascular and cerebrovascular event (MACCE), a composite of all-cause death, myocardial infarction (MI), or stroke.

Results: The prevalence of CAD and PAD in patients with AAA was 55.8 and 23.8%, respectively. Patients were followed for 40.2 ± 35.3 months. Baseline characteristics were similar among the groups except for current smoking (A, 27.4%; B, 20.8%; C, 50.5%; $p = 0.001$). Three years after EVAR, the incidences of MACCE (A, 5.6%; B, 9.5%; C, 16.7%; $p = 0.021$) and stroke (A, 0%; B, 2.2%; C, 5.2%; $p = 0.025$) were highest in group C. All-cause death and aneurysm death did not differ among the groups. PAD [hazard ratio (HR) 2.88, 95% confidence interval (CI) 1.32–6.29, $p = 0.008$] and previous stroke (HR 4.39, 95% CI 1.94–9.93, $p < 0.001$) were independent predictors of MACCE.

Conclusions: PAD was an independent risk factor of increased MACCE and stroke for patients with AAA undergoing EVAR. More intensive secondary prevention may be needed to reduce adverse cardiovascular events in AAA patients with PAD.

1. Introduction

The mechanisms that initiate and stimulate the progression of abdominal aortic aneurysm (AAA) are poorly understood. Previous studies suggest that atherosclerosis may play an important role in AAA pathogenesis. AAA and atherosclerosis share multiple risk factors such as smoking, hypertension, obesity, and family history [1]. However, it is unclear whether the association between atherosclerosis and AAA is causal or due to common risk factors. Registry studies report a high prevalence of atherosclerotic disease in patients with AAA, including coronary artery disease (CAD, 34.2–43%) and peripheral artery disease (PAD, 19–43.6%) [2–5].

Current guidelines recommended both open and endovascular repair as standard treatments for infrarenal AAA with suitable anatomy [6,7]. However, treatment of AAA has largely shifted to endovascular repair due to shorter hospital length stay, faster recovery to daily life activity, lower short-term morbidity and mortality rates compared to open surgery [8,9].

Several large randomized control trials reported favorable long-term mortality and low aneurysm-related mortality (0–2.3%) after endovascular aortic aneurysm repair (EVAR) [10–12]. Gooney et al. [13] reported that cardiovascular disease was the leading cause of late mortality after endovascular and open surgical repair of infra-renal AAA. However, there is paucity of data regarding clinical outcomes after

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endovascular repair of AAA when the patient also has atherosclerotic diseases. This study investigates clinical outcomes for patients with AAA treated with EVAR who also have CAD or PAD.

2. Materials and methods

2.1. Study population

This retrospective study included all 475 consecutive patients treated with EVAR in Severance Cardiovascular Hospital from January 2005 to May 2016, without specific exclusion criteria. Patients were divided into three groups according to the presence of concomitant CAD or PAD: group A ($n = 166$, 34.9%), group B ($n = 196$, 41.3%), and group C ($n = 113$, 23.8%). Group A included patients without CAD or PAD, group B included patients with CAD but without PAD, and group C included patients with PAD regardless of the presence of CAD. The study protocol conformed to the 1975 Declaration of Helsinki. The Institutional Review Board of Severance Hospital approved this study and waived the requirement for informed consent for this retrospective analysis.

2.2. Data collection

Baseline clinical information was collected for the patients, including age, gender, risk factors, past medical history, and clinical presentation. We obtained the anatomical parameters of AAA using pre- and post-procedural computed tomography (CT), angiographic data, and procedural and outcome data. Follow-up involved outpatient clinic examinations at 30 days and 3 months after the procedure, and then every 6 to 12 months thereafter. Patients lost from regular clinical follow-up were contacted by telephone and asked about their clinical status. CAD was defined as at least one major epicardial artery with at least 50% stenosis, or a previous history of myocardial infarction (MI), coronary artery bypass surgery, or percutaneous coronary intervention. CAD was routinely screened before EVAR or at the same session using coronary angiography. However, in patients with moderate to severe renal failure independent of dialysis, we primarily performed non-invasive assessment of CAD such as echocardiography, an exercise stress test, or nuclear myocardial perfusion imaging. In those patients, CAD was considered present if a regional myocardial wall abnormality or thinning corresponding to a specific coronary artery territory was found on echocardiography, or a positive finding suggestive of myocardial ischemia was detected on a stress testing. PAD was defined as the presence of any one of the following parameters: ankle-brachial index (ABI) ≤ 0.90 in either leg, significant stenosis of ≥50% in the upper or lower extremity arteries, or history of previous vascular bypass or angioplasty. PAD was evaluated using CT angiography, which routinely included subclavian, iliac, and proximal femoral arteries. ABI measurements and additional imaging studies were performed for cases of suspicious symptomatic PAD. We utilized the following definitions: hostile neck, the presence of a short neck (distance between the lower renal artery and the aneurysm sac < 15 mm); angle neck, the angle between the longitudinal axis of the proximal neck and the longitudinal axis of the aneurysm sac > 60°; and diameter of the aneurysmal neck >28 mm. Obesity is defined as body mass index (BMI) ≥ 25 kg/m^2 in Korea [14].

2.3. Study outcomes

The primary outcome was the absence of major adverse cardiovascular and cerebrovascular events (MACCEs) at 3 years after the procedure, which was defined as a composite of all-cause death, myocardial infarction (MI), and stroke. Aneurysm-related mortality was defined as death from any cause within 30 days after the primary EVAR procedure, death within 30 days after any secondary intervention or surgical conversion, or any death involving aneurysm rupture or device complication. Secondary interventions included all surgical or endovascular interventions performed after the index procedure to resolve graft-related complications. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type 3 or type 5 [15].

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD and were compared using ANOVA. Categorical variables were expressed as percentages and were compared using chi-squared statistics or Fisher's exact test as indicated. Kaplan-Meier curves and estimates were computed using log-rank tests, and were used to compare clinical outcomes between groups for death, stroke, MI, systemic embolization, and major bleeding. Predictors were analyzed as follows. Each predictor was evaluated by univariate analysis using logistic regression models. Then, predictors with a p value <0.10 in the univariate analysis were included in a multivariate analysis to assess the independent effect of each predictor. Multicolinearity was assessed using linear regression analysis, where a variance inflation factor > 4.0 indicated potential intercorrelation among variables. A two-sided p value <0.05 was considered as statistically significant. Statistical analyses were performed with SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

The baseline demographic and clinical characteristics of the study population are presented in Table 1. Mean patient age was 76.3 ± 9.7 years (range, 45–97 years), and 89.5% (425/475) of patients were male. The prevalence of CAD and PAD among all 475 participants was 55.8% (265/475) and 23.8% (113/475), respectively, whereas 34.9% (166/475) of patients did not have concurrent CAD or PAD (group A). A total of 41.3% (196/475) of patients were diagnosed with only CAD (group B), and 23.8% (113/475) of patients were diagnosed with PAD regardless of concurrent CAD (group C). The baseline characteristics did not differ significantly among the three groups. No differences were observed among groups A, B, and C with respect to the prevalence of symptoms (22.9, 15.8, and 16.8%, respectively; $p = 0.195$); ruptured AAA (3.6, 3.1, and 2.7%, respectively; $p = 0.898$); maximal AAA diameter (60.1 ± 15.6, 60.1 ± 11.0, and 57.1 ± 9.8 mm, respectively; $p = 0.365$); hostile neck (35.5, 43.4, and 38.9%, respectively; $p = 0.316$); and medication at hospital discharge including antiplatelet agents ($p = 0.700$), statin ($p = 0.826$), angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blocker (ARB) ($p = 0.590$), beta-blocker ($p = 0.117$), calcium channel blocker ($p = 0.107$), and diuretics ($p = 0.889$).

3.2. Clinical outcomes

The 3-year clinical outcomes of patients with AAA treated with EVAR and evaluated according to the presence/absence of concurrent CAD or PAD are presented in Table 2. Mean follow-up period was 40.2 ± 35.3 months for all patients, and there were no differences in mean follow-up times among the three groups. Of the 475 patients, 363 patients were available for 1-year follow-up and 240 patients for 3-year follow-up. Overall, there were 36 MACCEs (28 all-cause deaths, 7 aneurysm-related deaths, and 1 MI) and 8 strokes, which represented an event rate of 10.0% during 3 years after EVAR. Aneurysm-related mortality was reported in 1.7% of patients, whereas non-aneurysm-related mortality was reported in 6.4% of patients. The non-aneurysm-related deaths were caused by cardiovascular disease (38.1%, 8/21); malignant disease (23.8%, 5/21); and infectious disease (33.3%, 7/21). The event rates of MACCE (A, 5.6%; B, 9.5%; and C, 16.7%, $p = 0.021$) and stroke (A, 0%; B, 2.2%; and C, 5.2%, $p = 0.025$) significantly differed among the groups, and were highest in group C. Group C had significantly higher MACCE ($p = 0.008$) than group A, and a trend toward higher MACCE ($p = 0.070$) compared with that of group B (Fig. 1A–D). However, the MACCE rate was similar in groups A and B. The stroke rate ($p = 0.008$) also was higher in group C than in group A. However, stroke rate did not significantly differ between groups A and B and between groups B and C. The rates of all-cause mortality (A, 5.6%; B, 7.4%; C, 12.0%; $p = 0.791$), aneurysm-related mortality (A, 2.3%; B, 1.1%; C, 1.8%; $p = 0.791$), cardiovascular death (A, 0.9%; B, 2.6%; C, 5.0%; $p = 0.263$), and major bleeding (A, 0.7%; B, 0.6%; C, 0%; $p = 0.723$) did not significantly differ among the three groups.

3.3. Risk factors for MACCE and all-cause death

Univariate analyses indicated that the following parameters were associated with MACCE: old age ≥ 80 years (HR 2.06, 95% CI 1.07–3.98), obesity defined as BMI ≥ 25 kg/m^2 (HR 0.43, 95% CI 0.18–1.41), concurrent PAD (HR 2.36, 95% CI 1.22–4.55), congestive heart failure (CHF) (HR 3.09, 95% CI 0.95–10.08), previous stroke (HR 3.45, 95% CI 1.66–7.15), maximal AAA diameter ≥ 60 mm (HR 2.10, 95% CI 1.02–4.34), hostile neck (HR 1.95, 95% CI 1.01–3.76), and no use of antiplatelet agents (HR 4.78, 95% CI 1.98–11.51). Multivariate analyses identified the following parameters as independent risk factors for MACCE: concurrent PAD (HR 3.17, 95% CI