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Impact of different nitrate therapies on long-term clinical outcomes of patients with vasospastic angina: A propensity score-matched analysis

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ABSTRACT

Background: Despite the short-term vasodilatory effects of nitrates, the prognostic effects of long-term nitrate therapy in patients with vasospastic angina (VSA) remains unclear. We investigated the prognostic impact of chronic nitrate therapy in VSA patients.

Methods: Between January 2003 and December 2014, a total of 1154 VSA patients proven by ergonovine provocation tests were classified into nitrate (n = 676) and non-nitrate (n = 478) groups according to prescriptions for oral nitrates, including isosorbide mononitrate (ISMN) and nicorandil. The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of cardiac death, myocardial infarction, any revascularization, or rehospitalization due to recurrent angina.

Results: The nitrate group was found to have a higher risk of MACE (22.9% vs. 17.6%, hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.01–1.73, p = 0.043) than the non-nitrate group. After propensity score matching, the nitrate group had greater risks of MACE (HR 1.32, 95%CI 1.01–1.73, p = 0.049). Patients who received the immediate-release formula of ISMN (HR 1.80, 95%CI 1.35–2.39, p < 0.001) or were administered any forms of ISMN other than at bedtime (HR 1.90, 95%CI 1.41–2.57, p < 0.001) had a significantly higher risk of MACE compared with the non-nitrate group. Nicorandil was shown to have a neutral effect on VSA patients (HR 1.11, 95%CI 0.73–1.69, p = 0.62).

Conclusions: The long-term use of nitrate therapy was associated with increased risk of adverse cardiac events in VSA patients. The use of immediate-release ISMN or the administration of ISMN other than at bedtime was related with poor outcomes of VSA patients.

1. Introduction

Vasospastic angina (VSA) is one of the important functional ischemic heart diseases and is triggered by the abrupt and rigorous vasoconstriction of epicardial coronary arteries, resulting in transient myocardial ischemia [1,2]. The prognosis of patients with VSA is generally favorable when treated with calcium channel blockers (CCB). However, VSA may be associated with more serious cardiac conditions, including myocardial infarction [3,4] or lethal ventricular arrhythmias, which may lead to sudden cardiac death [5]. For this reason, an intensive treatment regimen for VSA is essential to prevent such serious situations.

Along with CCBs, conventional nitrates are widely used as concomitant agents for the treatment of VSA [6]. Furthermore, the introduction of nicorandil, a hybrid of nitrate and K^+_{ATP} channel agonists, has expanded the range of choices for concomitant therapy for VSA [6]. Although the short-term use of long-acting nitrates such as isosorbide mononitrate (ISMN) may decrease symptoms, their chronic use has not been proven to improve prognosis. Indeed, a recent study suggested that long-term therapy with nitrates may actually worsen prognosis [7]. Therefore, we sought to investigate the clinical implications of different nitrate regimen for VSA patients.

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2. Methods

2.1. Study population

Between January 2003 and December 2014, an intracoronary ergonovine provocation test was performed in 3595 patients from Samsung Medical center. A total of 1198 consecutive patients showed the positive result of intracoronary ergonovine provocation test, and we enrolled those patients in a Samsung Medical Center VSA registry (online Fig. 1). Among these, patients who refused to follow-up after diagnosis with VSA (n = 44) were excluded. The remaining 1154 subjects were divided into nitrate and non-nitrate groups according to prescription of oral nitrates at discharge. The choices of type (ISMN, nicorandil, or both), dosage formulas (immediate-release or extended-release), or administration timing (at bedtime or not) of nitrates were at the discretion of the patients' attending physicians. The Samsung Medical Center Institutional Review Board approved this study and waived the requirement for written informed consent for access to an institutional registry.

2.2. Provocation test

A spasm provocation test was performed with intracoronary ergonovine injection after baseline angiography. Incremental doses of 20, 40, and 80 μg were injected into the left coronary artery. If coronary spasm was not provoked in the left coronary artery, 10, and then 20 μg were injected into the right coronary artery. Once coronary spasm was induced, intracoronary nitrate was injected. Vasoactive drugs including nitrates, nicorandil, and CCBs were discontinued at least 48 h before coronary angiography.

The definition of VSA was total or subtotal occlusion (>90% diameter stenosis) of the coronary arteries after intracoronary ergonovine injection in addition to ischemic symptoms and/or electrocardiographic changes. Patients who showed spontaneous total or subtotal coronary spasm on baseline angiography that was relieved after intracoronary nitrate injection were also diagnosed with VSA. An electrocardiographic change was defined as ST-segment elevation, depression (≥1 mm), or T-wave inversion in at least two consecutive leads. Multi-vessel spasm was defined as coronary artery spasm in more than two major (≥2.5 mm) epicardial coronary arteries. The types of spasm were classified into focal (vasoconstriction observed within the confines of one isolated coronary segment) or diffuse (in ≥2 adjacent coronary segments) [8]. Organic coronary stenosis was assessed as no stenosis, non-significant stenosis (0% to 50% luminal narrowing), or significant stenosis (>50% luminal narrowing) by baseline angiography.

2.3. Study outcomes

The primary outcome was major adverse cardiovascular events (MACE), a composite of cardiac death, myocardial infarction, any revascularization, or rehospitalization due to recurrent angina. All deaths were considered to be of cardiac causes unless definite non-cardiac causes could be established. Myocardial infarction was defined as recurrent symptoms with new electrocardiographic changes compatible with myocardial infarction or cardiac marker level at least twice the upper limit of normal [9]. Revascularization was defined as any revascularization of an epicardial coronary artery treated with percutaneous coronary intervention or bypass graft surgery. Rehospitalization was defined as any hospitalization or emergency department visits due to recurrent angina. All-cause death was analyzed as a secondary outcome. All outcomes were identified by the attending physicians, and reviewed by 7 authors (A.Y.L., S.W.C, M.S.O., D.H.L., C.S.S., H.B.G., and T.K.P.) who had full access to the patient's clinical and laboratory records, and adjudicated with 2 other authors (J.H.Y. and S.-H.C).

2.4. Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables as numbers and percentages. Group comparisons were performed using the *t*-test or Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher's exact test for categorical data as appropriate. Survival curves were constructed using Kaplan–Meier estimates and compared with the log-rank test. The Cox proportional hazards model was used to compare the risks of adverse cardiac events between the nitrate and non-nitrate groups. Covariates that were either statistically significant on univariate analysis or clinically relevant were included in multivariate models. Among them, variables with a p value ≤ 0.2 in univariate analyses were included in multivariable Cox regression models. Furthermore, we used propensity score matching to balance intergroup differences. Upon matching propensity scores, we created 672 patients in the nitrate group and 455 patients in the non-nitrate group. The propensity matching method was determined to be adequate when overall balance was achieved, indicated by having a standardized mean difference < 0.1. All the clinical variables in Table 1 were applied in this analysis. When balance was achieved, the matched data set was analyzed using a Cox regression model for each clinical outcome. To compare more than two treatment conditions, variables with p-values ≤ 0.2 in univariate analyses were included in multivariable Cox regression model, and inverse probability of treatment weighting (IPTW) method based on the propensity score was used [10]. All tests were 2-tailed, and p-values < 0.05 were considered to be statistically significant. All analyses were performed using R 3.3.1 (R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics and treatments

A total of 1154 patients were included in the final analysis. Of these, 676 patients (58.6%) were treated with chronic nitrate therapy, while 478 patients (41.4%) were not. The baseline clinical and angiographic characteristics of the two groups are summarized in Table 1. Patients with nitrates had a higher prevalence of diabetes mellitus (26.0% vs. 20.7%, p = 0.037), whereas the patients without nitrates had a higher prevalence of family history of coronary artery disease (10.0% vs. 6.2%, p = 0.017) and significant organic coronary stenosis (17.2% vs. 22.4%, p = 0.039). There was no significant difference in the prevalence of acute coronary syndrome between the two groups (Nitrate group 13.0% vs. Non-nitrate group 16.0%, p = 0.16). In the nitrate group, CCBs were more often prescribed than the without-nitrate group (96% vs. 92.9%, p = 0.02). However, CCBs were used in >90% of both groups. Other medications, including statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aspirin, were administered similarly between groups. After propensity score matching for the entire population, there were no significant differences in baseline clinical and angiographic characteristics for the propensity score-matched population.

3.2. Clinical outcomes

The median follow-up duration was 54.7 months (interquartile ranges: 26.3 to 87.6 months). Clinical outcomes of the total and propensity score-matched populations are shown in Table 2. In the total population, the nitrate group was found to have significantly higher risks of MACE (22.9% vs. 17.6%, hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.01–1.73, p = 0.043) and rehospitalization due to recurrent angina (20.0% vs. 13.0%, HR 1.49, 95% CI 1.10–2.02, p = 0.010) than the non-nitrate group. There was no statistically significant difference in the risk of all-cause death between the nitrate and non-nitrate groups (4.3% vs. 2.5%, HR 1.98, 95% CI 0.98–4.02, p = 0.057). After propensity score matching, patients with nitrates also had higher risks of MACE (HR 1.32, 95% CI 1.01–1.73, p = 0.049, Fig. 1A) and rehospitalization due to recurrent angina (HR 1.52, 95% CI 1.12–2.06, p = 0.008, Fig. 1B). There were no significant differences in the risks of all-cause death, cardiac death, myocardial infarction, or revascularization between the two groups.

3.3. Types, formulas, and administration timings of nitrates

The relationship among the types, forms, and number of nitrates and patient outcomes was also assessed by univariable and multivariable Cox models, and verified using the IPTW method (online Table 1 and Fig. 2). Among the 676 patients who received long-term nitrate therapy, 441 (65.2%) patients were treated with ISMN, 362 patients (53.6%) with nicorandil, and 127 patients (18.8%) with a combination of ISMN and nicorandil. After IPTW adjustment, compared with the non-nitrates group as a reference, both patient groups treated with single ISMN (HR 1.70, 95% CI 1.24–2.35, p = 0.001) and with combined nitrate (HR 1.80, 95% CI 1.17–2.76, p = 0.008) were found to have significantly higher risks of MACE. In contrast, nicorandil was not shown to have an adverse effect on clinical outcomes. Interestingly, of 441 patients with ISMN therapy, patients who received the immediate-release formula of ISMN (HR 1.80, 95% CI 1.35–2.39, p < 0.001) or were administered any forms of ISMN by early evening (HR 1.90, CI 1.41–2.57, p < 0.001) had a significantly higher risk of MACE compared with the non-nitrate group.