Brief Report

Ranolazine and Microvascular Angina by PET in the Emergency Department: Results From a Pilot Randomized Controlled Trial

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ABSTRACT

Purpose: Coronary microvascular dysfunction (CMD) is a common but underdiagnosed cause of chest pain. Literature is scant regarding effective treatments. We explored the effect of ranolazine on coronary flow reserve (CFR) among symptomatic patients with CMD.

Methods: This pilot double-blinded randomized controlled trial included emergency department patients with chest pain and CMD admitted to an observation unit between June 2014 and November 2015. Participants were assessed by cardiac Rb-82 positron emission tomography and computed tomography imaging at baseline and 30 days. CMD was defined as CFR <2 corrected for rate pressure product or <2.5 uncorrected, with no evidence of obstructive or nonobstructive coronary artery disease or calcification. Patients with infarction, hypertensive urgency, heart failure, or prescribed QTc-prolonging drugs were excluded. Participants were assigned to ranolazine or placebo in a 2:1 ratio. Primary outcome was change in CFR at 30 days.

Findings: We enrolled 31 patients (71% female, mean [SD] age 50 [6] years) with CMD (mean [SD] corrected CFR 1.6 [0.3]). Ranolazine improved CFR at 30 days by 17% ($P = 0.005$) compared with 0% with placebo ($P = 0.67$). However, there was no significant difference in the primary outcome as measured by mean change in CFR (0.27 ranolazine compared with 0.06 placebo; 95% CI, −0.08 to 0.62).

Implications: The emergency department offers a unique venue to diagnose CMD with acute symptoms. In an exploratory randomized controlled trial of symptomatic patients with CMD and no coronary artery disease, promising results were seem with ranolazine and CFR improving at 30 days. Large robust clinical trials are needed to verify improvement of CMD in a sex-specific model. ClinicalTrials.gov identifier NCT02052011. (*Clin Ther*. 2017;39:55–63)

Key words: chest pain, emergency department, microvascular angina, PET, randomized controlled trial, ranolazine.

INTRODUCTION

Each year, there are more than 6 million emergency department (ED) visits due to chest pain, some of which are attributed to causes unrelated to obstructive coronary artery disease (CAD), such as cardiac

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microvascular dysfunction (CMD).[1–3] CMD diagnosis tends to be elusive, as it frequently occurs in women and in younger patients with few Framingham cardiac risk factors—patients who are otherwise considered low-to-intermediate risk for CAD.[4–6] The standard ED evaluation protocols focus on CAD diagnosis and do not routinely measure coronary flow reserve (CFR), which is a surrogate marker for diagnosing CMD.[3] Without treatment, CMD carries a 2.5% annual rate for adverse outcomes, such as myocardial infarction, heart failure, and death.[7–9] In fact, low CFR has an inverse linear relationship with adverse cardiac events.[7] It is also associated with persistent chest pain, repeat health services utilization, and poor patient function, with disease-related costs that mount to $13 billion.[10–12] Thus, early diagnosis and optimal management of symptomatic CMD is critical.

Evidence-based options to improve CFR and outcomes in patients with CMD are limited.[13] Research in this area has greater implications for women, as CMD predominantly affects women. However, effective therapies that improve CFR would help mitigate cardiovascular risk and manage symptoms in both men and women. Ranolazine, a cardiac late sodium channel blocker recently approved by the US Food and Drug Administration holds promise for treating CMD. It is associated with diastolic relaxation and possibly relaxation of the subendocardial microvasculature, thereby improving CFR.[14] However, evidence regarding the effects of ranolazine on coronary microvascular function has been mixed.[15–18]

We sought to clarify and explore the efficacy of ranolazine for improving CFR by studying patients with symptomatic CMD in the absence of CAD. The pilot was not designed to conduct a sex-specific analysis.

METHODS

Study Design and Setting

We conducted a pilot double-blind randomized controlled trial (RCT) at the Yale New Haven Hospital Chest Pain Center, an ED observation unit that treats patients with low-to-moderate cardiac risk. The study was approved by the Institutional Review Board at Yale University.

Selection of Participants

Patients who underwent clinically indicated cardiac Rb-82 positron emission tomography and computed tomography (PET and CT) imaging per the 2013 guidelines of the American College of Nuclear Cardiology were screened for participation.[19] Eligible patients included adults aged 30 years and older with chest pain within 24 hours of ED presentation and reduced CFR (CFR <2 corrected for rate pressure product or <2.5 uncorrected). Exclusion criteria included coronary artery calcification, acute coronary syndrome, hypertensive crisis (blood pressure $>180/110$ mm Hg), known CAD, left ventricular ejection fraction $<35\%$, dialysis, liver cirrhosis, aortic stenosis, active substance abuse, current use of potent CYP3A4-inhibitors, inducers or QTc-prolonging drugs, baseline ECG QTc >580 ms, pregnancy, and inability to consent or communicate in English.

Interventions

Participants were randomly assigned to either ranolazine or placebo in a 2:1 ratio using a computer-generated block sequence. Drugs were identical in appearance, prepacked in bottles and consecutively numbered. Ranolazine was given 500 mg orally twice a day for 1 week, and then 1000 mg twice a day for 3 weeks, as tolerated. No changes were made to patient's current medications, diet, or exercise during the study period. All investigators, staff, and participants were kept blinded throughout the study.

Measurements

Baseline information about demographics, clinical profile including Thrombolysis in Myocardial Infarction (TIMI) score and Duke Activity Score Index (DASI) was collected.

PET and CT Imaging Acquisition and Reconstruction Protocol

All PET and CT imaging was performed on a whole-body 3-dimensional PET and 64-slice CT scanner (Discovery 690, GE Healthcare, Milwaukee, Wisconsin). Patients were imaged after a 4-hour fast and cessation of all caffeine- or methylxanthine-containing substances. A CT transmission scan was acquired for attenuation correction. Beginning with a timed IV administration of 740–925 MBq ^{82}Rb (20–25 mCi) for 30 seconds using a precalibrated infusion system (Bracco, Monroe Township, New Jersey), a 7-minute list mode PET acquisition was acquired. ECG-gated PET images (16 frames per cardiac cycle) were reconstructed. On completion of the rest images,