Effects of Sublingual and Transdermal Administration of Nitroglycerin for Coronary CT Angiography on Image Quality

NCT#: NCT02961946

Study protocol and statistical analysis plan

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Methods

This study had a prospective, randomized controlled design conducted at a single, academic hospital and was approved by our institution's review board, which required signed consent. The study was HIPAA compliant and registered at the Clinical Trials Registry (#NCT02961946) with the title "Effects of Sublingual and Transdermal Administration of Nitroglycerin for Coronary CT Angiography on Image Quality".

Based on prior literature, we hypothesized that mean coronary artery diameter before and after nitroglycerin application would be 2.86 mm and 3.26 mm, respectively, with 13.8% vasodilation (13). We assumed an equivalence range of 3% and determined a type-I error of (0.05/3=0.017) for a 3-group comparison with 80% power. In total, 198 individuals and 66 individuals per arm were necessary for a 3-group comparison.

Coronary artery vasodilation was the primary outcome. Secondary outcomes included changes in vital signs and frequency of side effects after nitroglycerin application. The dependent variable was the method of nitroglycerin delivery which could be lingual, sublingual, or transdermal.

Patient Selection

We identified potential subjects from our clinical cardiac CT schedule and included those whose study required an ECG-gated non-contrast CT followed by CCTA acquisitions. Subjects with a history of coronary revascularization were included. Exclusion criteria were age under 18 years, known hypersensitivity to nitroglycerin, closed-angle glaucoma, use of phosphodiesterase type 5 inhibitors within 72 hours prior to the study, conditions associated with elevated intracranial pressure, hemodynamic instability, critical aortic

stenosis, systolic blood pressure below 90 mmHg, pregnancy or lactating female, women with a positive urine pregnancy test, and subjects unwilling or unable to consent to participation.

Study Workflow

The physician enrolling the subject to the study was blinded to the method of nitroglycerin administration. After obtaining informed consent, subjects were randomized (block randomization, block size=198) to one of three nitroglycerin delivery methods: (1) sublingual as a tablet (2x0.4 mg, Nitrostat, Pfizer Inc., NY), (2) lingual as a spray (2x0.4 mg, Nitrolingual, Pohl-Boskamp, Hohenlockstedt, Germany), or (3) transdermal as a patch (2x0.4 mg/h, Nitro-Dur, Merck&Co Inc., NJ). After assessing initial vital signs (heart rate, rhythm, and blood pressure), non-contrast CT was acquired. Subsequently, nitroglycerin was administered. Patches were placed on the upper chest, taking care to avoid body hair. The transdermal delivery method required an application time of at least 45 minutes, while lingual and sublingual nitroglycerin required 5 minutes application time before CCTA acquisition (**Figure 1**). After CCTA, the patches were removed, and the location was inspected for skin reaction, while spray and tablets did not require further interaction. Next, we remeasured vital signs and asked for symptoms of allergic-type reactions and if sublingual tablets had completely dissolved. Systolic blood pressure >180 mmHg or a drop of >10 mmHg compared to initial values required observation and follow-up until normalization. Finally, patients filled out a query asking about side effects during the exam.

Image Acquisition

All individuals were scanned on a 128-slice dual-source CT (Somatom Definition Flash, Siemens Healthineers, Forchheim, Germany). Scan length was from carina to diaphragm and was extended if necessary. Scan parameters were as follows: non-contrast CT (prospectively-ECG-triggered at 350ms after the R wave, fixed 120kV, mA adjusted to body size, with a reference of 80 mAs [CareDose4D, Siemens Healthineers], 64x0.6mm collimation), CCTA (prospectively-ECG-triggered for heart rates <85 bpm, ≥85 bpm retrospectively-ECG-gated, with an acquisition window in late systole to early diastole (220-400 msec after the R-wave), 80-120kV with optimal kV [CarekV, Siemens Healthineers] and automatic mA selection based on the scout scan, reference 280 mAs, 64x0.6mm collimation). No beta-blocker was administered, as per our standard site practice.

Images were reconstructed using iterative reconstruction algorithm (strength level 3/5, Admire, Siemens Healthineers) with 0.6 mm slice thickness at 350ms for non-contrast images and 220-440ms (20ms intervals) for CCTA images. All studies were blinded as to the nitroglycerin delivery method. Coronary calcium scores (Agatston method) and severity of any coronary artery disease were assessed from the radiology reports.

Quantitative Analysis

A cardiovascular imaging-trained radiologist with six years of experience (X.X.)(anonymized) measured coronary diameters at seven locations (**Figure 2**) using a 3D-workstation (Aquarius v.4.4.12, Terarecon Inc., Foster City, CA). These locations were predetermined as: (1) proximal right coronary artery (RCA) 1.5 cm distal from the ostium; (2) mid RCA 1.0 cm proximal of the acute marginal branch; (3) distal RCA 1.0 cm

proximal of the bifurcation into posterior descending artery and right postero-lateral branch; (4) middle of the left main (LM); (5) proximal left anterior descending artery (LAD) 1.0 cm after LM bifurcation or, if less distance to the 1st diagonal branch, in the middle of the proximal LAD; (6) mid LAD 2.0 cm distal of 1st diagonal branch or if less distance to the 2nd diagonal branch, in the middle of mid LAD; and (7) left circumflex coronary artery 2.0 cm distal of the LM bifurcation. Positions were located in the non-contrast images and reaffirmed on CCTA images using a corresponding phase of the cardiac cycle. Locations with non-calcified or calcified plaques or unclear depiction of the coronary artery due to adjacent structures such as veins were avoided, and in those segments, the location of measurement was moved distally up to 1.0 cm from the original position while staying in the same coronary segment and avoiding bifurcations. If coronary diameters could not be measured at any of these positions, the location was excluded. We excluded stented or bypassed locations from measurements. All coronary diameters were measured twice at each location using short-axis views in an enlarged field-of-view and averaged using window width and level of 350 HU and 50 HU for non-contrast and 800 HU and 200 HU for CCTA images (**Figure 2**). Window settings were set based on preliminary measurements in 20 patients who underwent CCTA without nitroglycerin and therefore no diameter differences in non-contrast and CCTA images. Locations #1, #4, and #5 were defined as proximal-, locations #2 #6, and #7 as mid-, and location #3 as distal coronary segments.

Safety

By query, side effects were evaluated, including headache, dizziness, and nausea during the exam. The severity of headache was quantified on a 10-point scale ranging from 1 minimal- to 10 maximal-intensity.

Statistical Analysis

Demographic and scan parameter summaries were calculated for the entire subject cohort and by nitroglycerin administration method. Categorical variables were summarized using frequencies and percentages, while continuous variables were summarized as means and standard deviations, or as median and interquartile range (25^{th} and 75^{th} percentiles) if the distribution of the variables were skewed. Differences in continuous variables by treatment were assessed using the Kruskal-Wallis test, and differences in categorical variables were assessed using either the Pearson χ^2 test, or Fisher's exact test. Changes of vital parameters pre- and posttreatment were compared using paired t-test.

A linear quantile (median) mixed-effects model was constructed to quantify the unadjusted association between treatment and vasodilation (contrast diameter/non-contrast diameter x 100) while accounting for dependencies within the data set due to multiple observations per subject. This modeling approach permitted the estimation of the median vasodilation as a function of covariates while avoiding the parametric modeling assumptions that are typically associated with linear mixed models. Estimates of fixed-effects, and their 95% Wald-type confidence intervals, were computed for all model

parameters. Linear combinations of these parameters were used to estimate overall effects, and effects by treatment.

Two additional models were constructed where we hierarchically accounted for patient demographics (i.e., age, gender, BMI and height) and then by patient demographics and disease severity measure (i.e., CA score). A subgroup analysis was performed where model parameters were estimated by proximal, mid and distal regions. Due to the explorative nature of this subgroup analysis, p-values were not adjusted for multiple comparisons.

All analyses were performed using R 3.4.3 (R-Core Team, 2017, Vienna, Austria) (20) and the lqmm R library (21).