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# Effectiveness of sublingual nitroglycerin before puncture compared with conventional intra-arterial nitroglycerin in transradial procedures: a randomized trial☆,☆☆

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ABSTRACT

*Aim:* Sublingual (SL) nitroglycerin administered before radial artery puncture can improve cannulation success and decrease the incidence of radial artery spasm (RAS) compared with intra-arterial (IA) nitroglycerin in transradial procedures.

*Methods:* Patients undergoing diagnostic transradial angiography were randomized to IA (200 mcg) or SL (400 mcg) nitroglycerin. Primary endpoints were puncture time and puncture attempts. Secondary endpoint was the incidence of RAS.

*Results:* Total of 101 participants (mean age 60 ± 11 years, 53% male) were randomized (51 in IA and 50 in SL groups). Puncture time (50 [36–75] vs 50 [35–90] sec), puncture attempts (1.18 ± 0.48 vs 1.20 ± 0.49), multiple punctures (13.7 vs 16.0%) and RAS (19.6 vs 24.0%) were not statistically different between IA vs SL groups respectively. A composite endpoint of all adverse events related to transradial angiography (multiple punctures, RAS, access site crossover, hypotension/bradycardia associated with nitroglycerin and radial artery occlusion) was very similar in IA vs SL groups (39 vs 40%, respectively). However puncture time was significantly longer with SL nitroglycerin in patients <1.65 m height (47 [36–66] vs 63 [41–110] sec, p = 0.042). Multiple punctures seemed higher with SL nitroglycerin in patients with diabetes (0 vs 30%, p = 0.028) or in patients <1.65 m height (7.4 vs 25%, p = 0.085). Likewise, RAS with SL nitroglycerin seemed more frequent in smokers compared to IA nitroglycerin (0 vs 27%, p = 0.089).

*Conclusions:* SL nitroglycerin was not different from IA nitroglycerin in terms of efficiency and safety in overall study population. However it may be inferior to IA nitroglycerin in certain subgroups (shorter individuals, diabetics and smokers).



## 1. Introduction

Radial artery spasm (RAS) is one of few disadvantages of transradial coronary angiography (TRA) that causes patient discomfort, increased procedure times and access site changes [1]. RAS is an important reason for slow adoption of TRA technique among interventional cardiologists because it remains the most common cause of procedural failures [2,3]. When developed it neutralizes the benefits of TRA. Better puncture technique with increasing experience, use of spasmolytic cocktails and hydrophilic-coated and smaller sheaths are mainstays of RAS prevention [4]. Intra-arterial (IA) nitroglycerin and verapamil proved beneficial in the prevention and treatment of RAS [5–9]. However application of spasmolytic agents after the insertion of a foreign body (sheath) into an artery may be suboptimal in terms of RAS prevention. Preparing radial artery (RA) with a vasodilating agent prior to puncture may have better spasm control, and predilated RA can be punctured more easily decreasing puncture time and puncture attempts. Similar approaches have been put forward before. Topical application of nitroglycerin and lidocaine was shown to increase cross sectional area of RA compared to placebo, however the treatment did not reduce the incidence of RAS [10]. In another study, subcutaneous administration of lidocaine plus dinitrate isosorbide reduced the puncture time and puncture attempts compared to lidocaine only [11]. Alternatively, administration of short-acting nitroglycerin sublingually before arterial puncture may have the same vasodilatory properties along entire length of RA. In this pilot study, we aimed to investigate the effectiveness of short-acting SL nitroglycerin administered before arterial puncture on the success of arterial cannulation and the incidence of RAS compared with conventional IA nitroglycerin.

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## 2. Methods

### 2.1. Study design and randomization

The study was designed as single center, parallel group, open-label, randomized clinical trial. Patients over 18 years old undergoing diagnostic TRA with appropriate clinical indication were prospectively enrolled. Exclusion criteria were 1) patients with acute coronary syndromes or requiring emergency intervention, 2) patients with low blood pressure (systolic blood pressure < 100 mmHg) and/or bradycardia (heart rate < 50 beat per minute) before procedure and 3) patients unwilling to participate. All patients participating in the study gave written informed consent. The study was approved by Ethics Committee on Human Research, Faculty of Medicine, Kocaeli University, Turkey.

### 2.2. TRA procedure

Eligible patients were allocated to short-acting SL and IA nitroglycerin groups by computer-generated random numbers before the procedure. SL nitroglycerin was administered prior to RA puncture in commercially available spray form which contains 400-mcg nitroglycerin per application. RA puncture was attempted between 3 to 5 minutes of SL nitroglycerin administration. If more than one attempt was necessary and puncture was not completed within 2 minutes, additional SL nitroglycerin was administered at the discretion of the operator. IA nitroglycerin was administered through the arterial sheath at the dose of 200 mcg.

Right RA was used as the first choice throughout the study. Left RA was used in patients with negative modified Allen's test or previous coronary artery bypass graft operation or previous TRA from right RA. Verapamil was not included in spasmolytic cocktail. After subcutaneous injection of prilocaine, arterial puncture was made by using 21G needle with 0,018 guidewire. An 11 cm 6 F hydrophilic-coated sheath was introduced into RA. Diagnostic angiography was performed using 5 F standard diagnostic catheters. Brachiocephalic tortuosity was defined as clinically important tortuosity or anatomic variation of upper limb arteries making catheter manipulation difficult. Fixed-dose unfractionated heparin (5000 IU) was administered through the diagnostic catheter into the ascending aorta. Number of angiographic views necessary for satisfactory reporting was left to the operator. If additional nitroglycerin was required during procedure for clinically severe spasm, the operator was allowed to give nitroglycerin through the diagnostic catheter. Ad-hoc percutaneous coronary intervention for a suitable lesion was not allowed in study participants. After sheath removal, hemostasis was achieved with gauze and compression for 4 hours (gradual release of compression pressure after 2 hours) without use of any special equipment (inflatable wristband, etc). All TRAs were undertaken by single interventional cardiologist who performs more than 500 transradial procedures per year and who use RA as default arterial access site for coronary procedures.

### 2.3. Outcome measures

Primary endpoints of the study were puncture time and number of puncture attempts. Puncture time was measured from the onset of puncture to sheath placement. Multiple puncture was defined as the need for more than one puncture attempt to cannulate artery. Secondary endpoint was the incidence of RAS. RAS was defined as marked forearm pain plus resistance to catheter manipulation or sheath withdrawal reported by the operator. Routine arteriography to confirm RAS was not performed, as it could provoke pain or discomfort to asymptomatic patient.

Procedure time was measured from the onset of puncture to securing hemostasis after sheath removal. Other recorded parameters were development of hypotension and/or bradycardia related to nitroglycerin administration (arterial blood pressure dipping below 90 mmHg and/or heart rate dipping below 50 beat per minute with accompanying symptoms), access site crossover and the incidence of radial artery occlusion (RAO). RAO was evaluated at 1 week follow-up with Doppler ultrasonography. In addition, a composite endpoint of all adverse events related to TRA (incidence of multiple punctures, RAS, access site crossover, hypotension/bradycardia associated with nitroglycerin and RAO) was calculated to compare two nitroglycerin routes.

### 2.4. Statistical analysis

Based on our daily practice, we expected a mean puncture time around 90 seconds (estimated standard deviation around 45 seconds) with IA nitroglycerin. Considering 20% reduction in puncture time as clinically significant, we estimated that 50 participants in each nitroglycerin group were needed to detect statistically significant difference with 0.80 power and 0.05 type I error. Mean of 1.5 puncture attempts were expected in IA nitroglycerin group based on the study of Ouadhour et al. [11] Forty nine patients in each nitroglycerin group were needed to detect 40% reduction in puncture attempts (that means 1.3 puncture attempts or less), again with 0.80 power and 0.05 type I error. Therefore we decided to include 50 participants in each group.

Continuous data that showed symmetrical distribution were presented as means ± standard deviations and compared with student t-test. Data that did not distribute symmetrically were presented as medians (interquartile ranges) and compared with Mann–Whitney U test. Categorical variables were presented as numbers (percentages) and compared with chi square or Fisher's exact test. Two-sided p value <0.05 was considered significant. Data collection and analysis were performed using Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL).

## 3. Results

Two hundred and four patients were assessed for eligibility, and 101 of those patients were randomized (Fig. 1). Study participants were 60 ± 11 years old, 53% male, 67% hypertensive, 24% diabetic, 26% hyperlipidemic and 21% current smoker. Known coronary artery disease (CAD) was present in 27%. Demographic characteristics were similar between two groups (Table 1). RA was cannulated in all patients. Left RA was used in 9 patients (8.9%). One procedure had to be completed from femoral artery in IA group because of severe RAS. Brachiocephalic tortuosity was present in 14 patients (14%).

Of primary endpoints, puncture time, number of puncture attempts and incidence of multiple punctures were not statistically different between IA vs SL groups (Table 2). Overall, RAS developed in 22 participants (22%) according to the definition, and there was no statistical difference between two groups. Total procedure time together with fluoroscopy time and contrast volume was not different between two groups. Nitroglycerin-related hypotension/bradycardia episodes were rare in both groups. Limited number of participants required additional nitroglycerin during the procedure. No complication related to coronary angiography itself was observed. Wrist ecchymosis developed in 11 (11%) patients while hematoma was not observed. At 1 week follow-up, incidence of RAO were 8.9% (n = 9) in all patients; there was no difference between two groups. All RAOs were asymptomatic and without clinical sequelae. Equal number of adverse events related to TRA procedure was observed in each group.

Analyses of subgroups according to age, sex, body weight, height, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), smoking status and presence of coronary artery disease (CAD) were presented in Figs. 2 and 3. Incidence of multiple punctures was higher with SL nitroglycerin in patients with diabetes (0/14, 0% vs 3/10, 30%) or in patients <1.65 m height (2/27, 7.4% vs 6/24, 25%), although the latter had borderline statistical significance (Fig. 2). Likewise, RAS was more frequent in smokers with SL nitroglycerin compared to IA nitroglycerin (0/9, 0% vs 3/11, 27%) which had borderline statistical significance as well. In parallel with these findings, puncture time was significantly longer with SL nitroglycerin in patients <1.65 m height