Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Subcutaneous Injection of Nitroglycerin at the Radial Artery Puncture Site Reduces the Risk of Early Radial Artery Occlusion After Transradial Coronary Catheterization

A Randomized, Placebo-Controlled Clinical Trial

See Editorial by Dharma and Gilchrist

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BACKGROUND: Transradial coronary catheterization is widely used as a diagnostic or interventional procedure for coronary disease. However, it can lead to adverse complications, such as radial artery occlusion. We sought to determine whether preprocedural injection of nitroglycerin at the radial artery puncture site reduces radial artery occlusion.

METHODS AND RESULTS: A total of 188 patients undergoing transradial coronary catheterization were randomized in a single-blind fashion to receive subcutaneous injection of 0.5 mL 0.1% nitroglycerin or a placebo at the radial artery puncture site. The participants underwent ultrasound examinations of the radial artery before and at 24 hours after the procedure. Of the 188 patients enrolled, 182 completed the study, as the procedure failed in 2 participants in the nitroglycerin-treated group and 4 in the placebo group. Baseline demographic and clinical characteristics were similar between 2 groups. Comparing the radial artery diameters before and after the operation, there was a statistically significant increase in the nitroglycerin-treated group (2.48±0.45 versus 2.45±0.46 mm; P=0.003) but a decrease in the placebo control group (2.41±0.50 versus 2.46±0.49 mm; P<0.001). Importantly, the incidence of radial arterial occlusion was substantially lower in the nitroglycerin-treated group than in the placebo control group (5.4% versus 14.4%; P=0.04). There was not significant difference in other complications (forearm hematoma and radial artery pseudoaneurysm, respectively), and there was no incidence of cause hypotension or an intolerable headache.

CONCLUSIONS: Subcutaneous injection of nitroglycerin at the radial artery puncture site dilates the radial artery and reduces the incidence of early radial artery occlusion post-catheterization.

CLINICAL TRIAL REGISTRATION: URL: https://www.chictr.org.cn. Unique identifier: ChiCTR-IPR-15006559.

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Key Words: injections, subcutaneous ■ nitroglycerin ■ puncture ■ radial artery ■ risk

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WHAT IS KNOWN

- Transradial coronary catheterization can cause radial artery occlusion.
- It is beneficial to prevent this complication as the radial artery provides an important source of blood vessel for coronary artery bypass grafting and a puncture site for future coronary catheterization.
- New methods for preventing radial artery occlusion are required.

WHAT THE STUDY ADDS

- Subcutaneous injection of nitroglycerin at the radial artery puncture site dilates the radial artery and reduces the incidence of early radial artery occlusion.
- This is a safe, economical and effective approach to reduce the incidence of radial artery occlusion post transradial coronary catheterization.

Transradial coronary catheterization is widely used as a diagnostic or interventional coronary procedure. In comparison with transfemoral cardiac catheterization, the transradial approach causes less access site bleeding, has lower vascular complication rates, and requires shorter hospital stays.[1] However, it can cause radial artery occlusion (RAO). RAO is secondary to thrombosis, initially occurring at the puncture site. It has been reported that 2.8% to 11.7% of all patients undergoing transradial coronary catheterization develop RAO shortly after the procedure, which persists for >1 month in ≈60% of these patients.[2–4]

Although RAO does not cause hand ischemia because of the fact that the hand does not rely solely on the radial artery for blood supply, it is desirable to prevent RAO as the radial artery provides an important source of blood vessel for coronary artery bypass grafting and a puncture site for future coronary catheterization.

It has been reported that local injection of nitroglycerin at the puncture site in patients undergoing transradial coronary catheterization can dilate the radial artery without affecting blood pressure.[5] Pertinent to this finding, nitroglycerin has been shown to deter radial artery spasm[6] and act as a nitric oxide (NO)-donor,[7] whereas NO has been demonstrated to inhibit vascular thrombosis and inflammation induced by transradial catheterization in a pig model.[8]

However, whether or not local administration of nitroglycerin can prevent RAO remains unclear. In this study, we investigated whether periradial subcutaneous administration of nitroglycerin would reduce the occurrence of early RAO in patients undergoing transradial coronary catheterization.

METHODS

This was a randomized, placebo-controlled clinical study. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Participants

Patients scheduled to undergo clinically indicated diagnostic or therapeutic coronary catheterization via the transradial approach at the First Affiliated Hospital of Shantou University Medical College during the period from March 2015 to January 2016 were invited to participate in this study. Patients with inadequate dual blood supply to the hand determined by a negative Allen test, or with a history of serious renal failure, or being hemodynamically unstable were excluded. A total of 188 patients were enrolled in this study and randomized into either the nitroglycerin-treated group or the placebo group (Figure 1). The cardiologists performing the procedure, but not the participants, knew which participants received subcutaneous injection of nitroglycerin or placebo. The study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College, and all participants provided written informed consent. All subjects in this study were Chinese.

For every participant, we collected demographic data on age, sex, smoking history, hypertension, diabetes mellitus, coronary catheterization history, carotid plaque, medications, unfractionated heparin dose, procedural time, number of radial artery puncture, radial artery inner diameter/sheath outer diameter ratio, hemostatic time, and complications (incidence of RAO, forearm hematoma, radial artery pseudoaneurysm, hypotension, intolerable headache, and osteofascial compartment syndrome, respectively).

Transradial Coronary Catheterization

Coronary catheterization via the right radial artery was performed by experienced interventional cardiologists. The right arm was positioned beside the patient's body, and the wrist was hyperextended. After local subcutaneous anesthesia with 2% lidocaine at the wrist 1 to 2 cm proximal to the styloid process of the radial bone, subjects of the nitroglycerin-treated

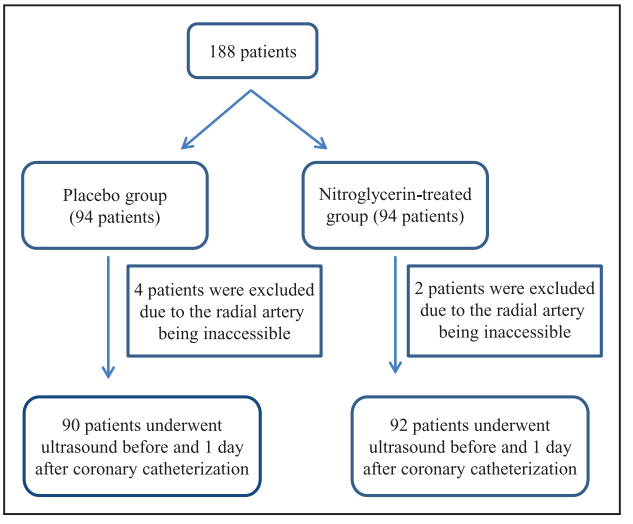

Figure 1. Study flow chart

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group were injected subcutaneously with 500 μg nitroglycerin in 0.5 mL saline solution, whereas subjects of the placebo control group were injected subcutaneously with 0.5 mL saline solution without nitroglycerin. Subsequently, the right radial artery was cannulated with the use of a 21-gauge needle (TERUMO, Japan) through which a 0.018-inch guide (TERUMO Japan) wire was then advanced, followed by the introduction of a 6F hydrophilic sheath (TERUMO, Japan). After sheath insertion, the subjects received an intra-arterial injection of 200 μg nitroglycerin and 3000 IU unfractionated heparin and then underwent coronary angiography. If a subsequent coronary fractional flow reserve measurement or a coronary intervention is required, the subjects received a bolus of 100 IU unfractionated heparin per kilogram of body weight. At the completion of the procedure, a TR-Band inflated by 15 mL of air was applied at the puncture site, and the radial sheath was removed. Two hours later, the TR-Band was gradually deflated at the rate of 2 mL of air every 2 hours until hemostasis was achieved and then the TR-Band was removed. During this period of time, the radial artery puncture site was frequently checked for any signs of bleeding or hematoma and for distal flow. If bleeding or poor distal flow was observed, the TR-Band was reinflated or deflated by 1 to 2 mL of air.

Ultrasound Measure of Radial Artery

All participants underwent ultrasound measurements of the radial artery before and 1 day after the transradial coronary

Table. Characteristics of Study Subjects

	Nitroglycerin-Treated Group (n=92)	Placebo Control Group (n=90)	*P* Value
Clinical characteristics			
Age, y	61.5±8.4	62.9±9.1	0.30
Male/female	57/35 (62.0%/38.0%)	56/34 (62.2%/37.8%)	0.88
Cigarette smoking	37 (40.7%)	37 (41.1%)	0.90
Hypertension	60 (65.2%)	54 (60.0%)	0.47
Diabetes mellitus	30 (30.2%)	25 (27.8%)	0.48
History of transradial coronary catheterization	19 (19.6%)	15 (16.7%)	0.61
Presence of carotid plaque	15 (18.1%)	18 (20.0%)	0.52
Creatinine, mmol/L	105±23	102±10	0.31
Medications			
Aspirin	92 (100%)	90 (100%)	1.00
Clopidogrel/ticagrelor	28 (30.4%)	23 (25.6%)	0.45
β-blockers	33 (35.9%)	44 (48.9%)	0.75
Calcium channel blockers	29 (28.4%)	18 (20.0%)	0.18
Nitrates	9 (9.8%)	10 (11.1%)	0.77
Statin	62 (65.4%)	57 (63.3%)	0.57
Procedure			
Coronary angiography	58 (63.0%)	61 (67.8%)	0.50
FFR or PCI	34 (37.0%)	29 (32.2%)	0.50
Unfractionated heparin dose for coronary angiography, IU	3000	3000	0.67
Unfractionated heparin dose for FFR or PCI, IU	6103.5±760.4	6176.47±824.6	0.72
Mean procedural time, min	31.5±19.8	28.5±18.3	0.30
No of radial artery puncture	26 (28.9%)	36 (39.1%)	0.55
Radial artery inner diameter/sheath outer diameter ratio	1.23±0.23	1.24±0.24	0.72
Mean hemostatic time, h	6.5±1.3	6.4±1.3	0.87
Complications			
Incidence of radial artery occlusion	5 (5.4%)	13 (14.4%)	0.04
Forearm hematoma	1 (1.0%)	1 (1.1%)	1.00
Radial artery pseudoaneurysm	0	0	1.00
Hypotension	0	0	1.00
Intolerable headache	0	0	1.00
Osteofascial compartment syndrome	0	0	1.00

Mean±SD values are shown for continuous variables; numbers (percentages) are shown for categorical variables. FFR indicates fractional flow reserve; IU, for international unit; and PCI, percutaneous coronary intervention.

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catheterization procedure. The ultrasound measurements were conducted by an experienced operator who was blinded to the study groups, using an Acuson SC2000 ultrasound system (Siemens, Germany) with 7 to 14 MHz linear array transducers. The participant had a supine rest for 10 minutes before measurement, and then right radial artery parameters were measured at the site 2 cm proximal to the radial styloid process of the radial bone. Radial artery course and measure, radial artery intima, atherosclerotic plaque, thrombus, and diastolic radial artery diameter were determined and recorded by 2-dimensional ultrasound and Doppler ultrasound. RAO was determined by a visible obstruction on 2-dimensional ultrasound and the absence of Doppler flow signal at the original entry site.

Statistical Analysis

Data were analyzed using the statistical analysis package SPSS version 19. The χ^2 test was used to ascertain differences in categorical variables, including RAO incidence between the nitroglycerin-treated and placebo groups. The unpaired Student *t* test was performed to test differences in continuous variables and in radial artery diameter change between the groups. The paired Student *t* test was used to compare radial artery diameter before and after operation in the nitroglycerin-treated group and in the placebo group, respectively. A *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 188 patients were enrolled in this study, among whom 94 were randomized to the nitroglycerin-treated group and 94 to the placebo group in a single-blind fashion. Two participants in the nitroglycerin-treated group and 4 in the placebo group were excluded from the analysis because the transradial procedure was unsuccessful and hence replaced by a transfemoral procedure in these 6 patients.

There was no significant difference between the 2 groups in age, sex, transradial artery intervention history, presence of carotid plaque, hypertension, diabetes mellitus, cigarette smoking history, creatinine level, medications used, or procedure indication (Table).

Local administration of nitroglycerin resulted in a statistically significant increase (by 0.03±0.10 mm) in radial artery diameter post operation as compared to the baseline (2.48±0.45 versus 2.45±0.46 mm; *P*=0.003), whereas, interestingly, there was a decrease (by 0.05±0.09 mm) in radial artery diameter in the placebo group (2.46±0.49 mm before operation and 2.41±0.50 mm after operation; *P*<0.001; Figure 2). The difference in radial artery diameter change between the 2 groups was 0.08 mm (95% confidence interval, 0.05–0.11 mm; *P*<0.001).

Importantly, the incidence of early RAO (within 24 hours) was substantially lower in the nitroglycerin-treated group than in the placebo group (5.4% versus 14.4%; *P*=0.04; Table). The relation risk for early RAO was 0.34 (95% confidence interval, 0.116–0.998) in the nitroglycerin-treated group as compared to the placebo group.

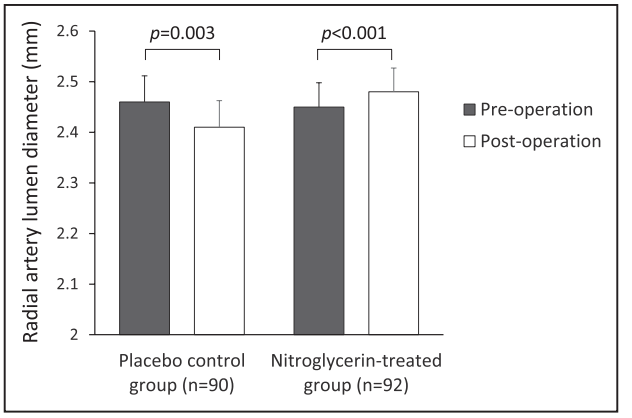

Figure 2. Radial artery lumen diameters before and after operation. Data shown are mean, SE of mean, and *P* values from paired *t* tests.

There was no significant difference between the 2 groups in other local complications (forearm hematoma and radial artery pseudoaneurysm, respectively; Table). Noteworthily, nitroglycerin treatment did not cause hypotension, intolerable headache, or osteofascial compartment syndrome (Table).

DISCUSSION

This randomized, controlled study shows that local subcutaneous injection of nitroglycerin dilates the radial artery and, importantly, it demonstrates that nitroglycerin injection at the radial artery puncture site reduces the risk of early RAO after transradial coronary catheterization.

We found that the radial artery diameter was decreased post-operation in the control group, which is in agreement with findings of previous studies.[4,5,9] It has been reported that after transradial coronary catheterization, the radial artery luminal diameter is continuously decreased for 6 months.[10] This may be an acute inflammatory response caused by radial artery puncture and mechanical friction between the sheath and the intima, leading to endothelial dysfunction, reduced release of the vasodilator NO, local edema, and radial artery contraction. The finding of our study that nitroglycerin injection at radial artery puncture site increases radial artery diameter is consistent with the notion that nitroglycerin acts as an NO donor,[7] therefore, counteracting the reduction of NO release induced by radial artery puncture and mechanical friction between the sheath and the intima.

Because of the lower vascular complication rate, shorter hospital stay, and increased patients comfort, the transradial catheterization approach, rather than via femoral access, is recommended for interventional coronary procedures.[11] However, RAO affects

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the availability of radial access for subsequent coronary catheterization and increases the risk of palmar necrosis. The use of NO-coated sheath for transradial coronary intervention has been shown to dilate vessel diameter at the access site immediately after percutaneous coronary intervention, decrease inflammation, reduce the risk of thrombosis, and inhibit intimal hyperplasia.[8] Because nitroglycerin acts as a NO donor, local injection of nitroglycerin may have a similar effect to the use of NO-coated sheath. The finding of our study that subcutaneous injection of nitroglycerin at the radial artery puncture site reduces early RAO is consistent with this notion and offers a cheaper method for reducing RAO incidence.

It is noteworthy that a recent study by Dharma et al[3] showed that intra-arterial injection of nitroglycerin (500 μg) at the end of transradial catheterization reduced the incidence of early RAO. However, injection of a high dose of nitroglycerin injection can potentially cause hypotension and headache because of vasodilatation.[12] In comparison with intra-arterial nitroglycerin injection, local subcutaneous administration of nitroglycerin, as conducted in our study, provides nitroglycerin more directly and locally to the radial artery, which will likely have less side effects. Notably, there was no incidence of hypotension or an intolerable headache in our study.

Apart from nitroglycerin, it has been reported that infusion (via sheath) of the calcium channel blocker diltiazem reduces the incidence of RAO in patients undergoing coronary angiography via the transradial approach.[13]

Our study has some limitations. First, this was a single center study, and all participants were Chinese. Further studies in other populations would be warranted. Second, we did not measure the activated clotting time in the study participants. However, a recent study found no association between activated clotting time and RAO.[14] Third, our study focused only on early RAO. Further investigations to assess the effect of local nitroglycerin injection on late RAO would be interesting, as spontaneous recanalization occurs in many RAO patients after 1 month.

In conclusion, our study suggests that subcutaneous injection of nitroglycerin at the radial artery puncture site can be a safe, economical, and effective approach to reduce the incidence of RAO post transradial coronary catheterization.

ARTICLE INFORMATION

Received February 14, 2018; accepted June 8, 2018.

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Sources of Funding

This work was supported by the National Natural Science Foundation of China (No. 81473063 and 81370202) and the GuangDong Provision Natural Science Foundation (No. 2015A030310040). Dr Ye thanks the support of the British Heart Foundation (PG/16/9/31995, RG/16/13/32609). The work falls under the portfolio of research conducted within the National Institute for Health Research Leicester Biomedical Research Centre.

Disclosures

None.

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Circ Cardiovasc Interv. 2018;11:
doi: 10.1161/CIRCINTERVENTIONS.118.006571
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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