

Effect of transdermally applied nitroglycerin or lidocaine before transradial coronary angiography on procedure success and complications

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ABSTRACT

Objectives: We investigated the effect of transdermal nitroglycerin or lidocaine application on puncture time, number, and complications in patients who underwent transradial coronary angiography.

Methods: Patients with topical saline applied to the radial artery before the procedure were designated as Group 1 (n=59), those with topical nitrate were designated as Group 2 (n=43), and those with topical lidocaine were designated as Group 3 (n=40). The groups' puncture time, number, and complication rates were compared.

Results: While our average puncture time was 142±122 seconds in all patients, this time was measured as 171±131 seconds in Group 1, 88±48 seconds in Group 2, and 157±146 seconds in Group 3 (P=0.021). During the procedure, radial artery spasm was observed in 15.2% of patients in Group 1, 6.9% in Group 2, and 12.5% in Group 3 (P=0.043). Radial artery occlusion was seen in 8% of patients in Group 1, and 2.5% in Group 3, while it was not observed at all in the nitrate-applied group (P=0.041).

Conclusion: The topical application of nitroglycerin before transradial angiography is a feasible strategy to reduce radial puncture time and number, facilitate trans-radial catheterization, and decrease the incidence of radial artery spasm and occlusion.

Keywords: Transradial coronary angiography, transdermal, nitroglycerin, lidocaine, spasm

New guidelines for myocardial revascularization recommend trans-radial access as the standard approach unless there are procedural drawbacks [1, 2]. For diagnostic angiography and percutaneous coronary procedure (PCI) in coronary artery disease, the transradial approach (TRA) is associated with less bleeding, access site complications, lower mortality, and higher patient comfort compared to the TFA [3].

Due to the smaller vessel size in the trans-radial approach, some interventions are technically difficult.

The possibility of vascular spasm may be considered among its disadvantages [4]. It is reported in the literature that the incidence of radial artery spasm is between 6.8% and 30% [5]. The spasm occurs due to decreased nitric oxide release and increased catecholamine release due to mechanical stimulation and endothelial damage during catheter manipulations. We investigated the effect of transdermal nitroglycerin or lidocaine application on puncture time, number, and complications in patients who underwent transradial angiography.

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METHODS

Study Population

Our study included patients who were examined at the Cardiology outpatient clinic between February 2023 and August 2023 with an indication for angiography. Patients with acute coronary syndromes, severe heart failure, hemodynamic instability, uncontrolled hypertension or diabetes, previous radial access site insufficiency, sensitivity to lidocaine or nitrate, and those with a history of coronary artery bypass surgery were excluded from the study.

Patients were randomly assigned to three groups: topical nitrate, topical lidocaine, and placebo. Medical histories of all patients included in the study were recorded.

Before the procedure, electrocardiography was performed, and blood pressure and pulse rates were noted. Group assignments were documented on a separate data sheet and were not disclosed to the doctors performing the procedure or to the patients. To prevent selection bias in patients undergoing coronary angiography, randomization was conducted by a third party unaware of the patient's clinical information.

The study was approved by the Tekirdağ Namık Kemal University Non-invasive Clinical Research Ethics Committee (Decision date: 28.02.2023 and No: 2023.36.02.14).

Topical Cream Application

Patients were administered topical lidocaine or topical nitrate at least 30 minutes before the procedure on their right wrists. In sequence, 40 mg of lidocaine cream was applied to the topical lidocaine group, 30 mg of nitroglycerin (NTG) ointment (Fougera NY) was applied to the topical nitrate group, and a topical lotion (selected to resemble the appearance of active creams) was applied to the placebo group in the radial artery region. Vital signs were recorded initially, 15 minutes after the procedure, and every 30 minutes before the procedure.

Radial Puncture

Three minutes before radial artery puncture, local subcutaneous anesthesia was applied with a 1 mL injection of 1% lidocaine. Radial artery puncture was performed by an experienced cardiologist using a 20-gauge needle and standard techniques. The working

doctor initiated the puncture duration at the beginning of the procedure using a stopwatch. The puncture duration was defined as the time from the needle touching the forearm at the start of the puncture to the complete insertion of the sheath.

All procedures were performed using 6F radial sheaths. To assess forearm pain, a verbal pain scale was utilized by a catheter laboratory nurse. The nurse, unaware of the patient's group assignment, queried and reported it. All patients received intra-arterial spasmolytic treatment with heparin and 200 µg nitroglycerin.

Procedure time, puncture time (Time from subcutaneous lidocaine infiltration to puncture), number of puncture attempts, and all complications were recorded. Pre-discharge examinations were conducted, and any developed complications were noted. Before discharge, patients were examined by the doctor for local complications and clinically assessed. Blood pressure and pulse measurements were taken and recorded. One week after discharge, patients were called for a follow-up, examinations were repeated, and procedure-related complications were noted. The primary objective of this study was to evaluate the effect of topical lidocaine or nitrate application on puncture duration and frequency. The secondary objectives were to investigate the effect on pain during puncture and evaluate its impact on complications during discharge and at 1-week follow-up examinations.

Statistical Analysis

Descriptive statistics for baseline parameters of continuous variables with normal distribution were presented as mean \pm standard deviation, while those without normal distribution were presented as median (minimum-maximum). Qualitative variables were presented as numbers and percentages. The significance of differences in means of continuous variables was evaluated using the Student's t-test when the number of independent groups was two and the ANOVA test when the number of groups was three. To compare the group medians of continuous variables that did not adhere to the normal distribution, the Mann-Whitney U test was employed for the presence of two independent groups, and the Kruskal-Wallis test was used for the presence of three independent groups. If the Kruskal Wallis test statistics indicate significance, post-hoc Tukey or non-parametric multiple comparison tests were utilized to identify the conditions causing the dif-

ference. P-value below 0.05 was considered statistically significant. All tests were performed using the SPSS 22.0 (SPSS Inc., Chicago, IL) software version.

RESULTS

Patients participating in our study were divided into three groups: group 1, the control group (n=59), group 2, with nitrate-containing cream applied (n=43), and group 3, with lidocaine-containing cream (n=40) (Table 1). Successful puncture was achieved in 85 patients (59.9%) on the first attempt, while 57 patients (40.1%) required 2 or more punctures. TRA was successfully performed in 131 patients (92.3%), while in 11 patients (7.7%), the procedure was continued via the femoral artery due to puncture failure or spasm. The average number of punctures for all patients undergoing TRA during the study was 1.7±1. 1, and the

average radial puncture duration was 142.2±122 seconds (Table 2). The most frequently observed complication was spasm during the procedure (12%), followed by hematoma in 12 patients (8. 5%) during follow-up after the procedure. During outpatient clinic controls, the arterial ultrasound revealed occlusion in the radial artery in 6 patients (4.2%). No pseudoaneurysm, radial artery dissection, or rupture was observed in any patient throughout the study. Puncture time was significantly lower in Group 2. (Group 1; 171±131 seconds, Group 2; 88±48 seconds and Group 3; 157±146 seconds) (P=0.002) (Table 2).

When comparing the three groups based on the number of punctures, a significant difference was observed (P<0.018). This difference was found to be between the group with nitrate application (Group 2) and the group without cream application (Group 1) (P=0.014), while no significant difference was observed between the lidocaine group (Group 3) and the

Table 1. Demographic data for each group

Variable	Group 1 (Control) (n=59)	Group 2 (Nitrate) (n=43)	Group 3 (Lidocaine) (n=40)	P value
Male, n (%)	32 (54. 2)	29 (67. 4)	26 (65)	0.132
Age (years)	61±10	59±12	61±11	0.422
BMI _{kg/m²}	31.87±6.2	28.47±4.7	27.97±4.9	0.001
Smoking, n (%)	22 (37.3)	19 (44.1)	11 (27.5)	0.081
Alcohol, n (%)	13 (22)	8 (18.6)	5 (12.5)	0.093
HT, n (%)	38 (64.4)	29 (67.4)	25 (62.5)	0.101
DM, n (%)	20 (33.8)	11 (25.5)	17 (42.5)	0.232
CAD, n (%)	17 (28.9)	12 (27.9)	12 (30)	0.979
HL, n (%)	22 (37.2)	16 (37.2)	16 (40)	0.652
Medication, n (%)				
Antiplatelet	31 (52.5)	21 (48.8)	23 (57.5)	0.322
OAC	5 (8.4)	3 (6.9)	5 (12.5)	0.231
BB	23 (38.9)	15 (34.8)	23 (57.5)	0.546
CCB	7 (11.8)	7 (16.2)	2 (5)	0.433
Statin	20 (33.8)	13 (30.2)	16(40)	0.578
ECG, n (%)				
Sinus	52 (88.1)	41 (95.3)	35 (87.5)	0.492
AF	7 (11.9)	2 (4.7)	5 (12.5)	

Data are shown as mean±standard deviation or n (%). HT=Hypertension, DM=Diabetes Mellitus, CAD=Coronary Artery Disease, HL=Hyperlipidemia, OAC=Oral Anticoagulant, BB=Beta-blocker, CCB=Calcium Channel Blocker, ECG=Electrocardiography, AF=Atrial Fibrillation, BMI=Body Mass Index

Table 2. Comparison of puncture characteristics and complications between groups

Variable	Group 1 (Control) (n=59)	Group 2 (Nitrate) (n=43)	Group 3 (Lidocaine) (n=40)	P value
Single puncture n (%)	29 (49.1)	33(76.7)	23 (57.5)	0.018
>2 puncture n (%)	30 (50.9)	10(23.3)	17 (42.5)	0.018
Femoral puncture n (%)	7 (11.8)	1(2.3)	3 (7.5)	0.045
Complications	24 (40.6)	4(9.3)	9 (22.5)	0.010
Spasm	9 (15.2)	3(6.9)	5 (12.5)	0.043
Hematoma	9 (15.2)	1(2.3)	3 (7.5)	0.022
Occlusion	5 (8.47)	0(0)	1 (2.5)	0.041
Pseudoaneurysm	0 (0)	0(0)	0 (0)	1.000
Dissection/rupture	0 (0)	0(0)	0 (0)	1.000
Compartment syndrome	0 (0)	0(0)	0 (0)	1.000
Puncture durations (seconds)	171±131	88±48	157±146	0.002
Puncture Count	2 (1-8)	1 (1-4)	1 (1-6)	<0.001

Data are shown as mean±standard deviation or n (%) or median (minimum-maximum).

group without cream application (Group 1) (P=0.675). Additionally, it was observed that there was a significantly lower number of punctures in group 2 as well (p<0.001). It was observed that the need for femoral procedure in group 2 significantly decreased compared to group 1 (P=0.045). In Group 1, the spasm was

observed in 9 patients (15.2%), and hematoma in 9 patients (15.2%). Radial artery occlusion was observed in five patients (8.4%) in group 1. Complications developed in a total of 24 patients (40.6%) in Group 1, 4 patients (9.3%) in Group 2, and 9 patients (22.5%) in Group 3 (P=0.010). When comparing the

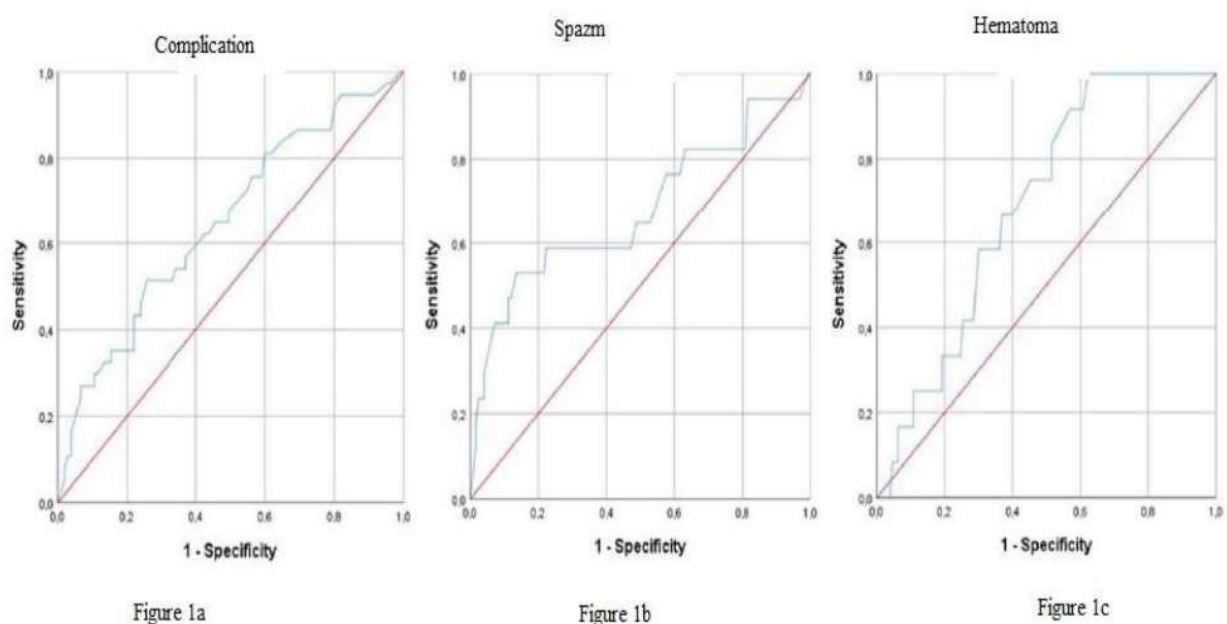


Fig. 1. Determination of puncture duration cut-off value on the development of complication.

complication rates among the three groups, it was found that spasm, hematoma, occlusion, and total complications were significantly less common in Group 2 ($P < 0.05$). While the puncture time of 70 patients (49.3%) in the study group was 100 seconds or less, the puncture time of 72 patients (50.7%) was over 100 seconds.

When examining complications, in the group with puncture time exceeding 100 seconds, radial artery spasm occurred in 11 patients (15.3%), local hematoma in 9 patients (12.5%), and radial artery occlusion in 2 patients. In the group with a puncture time of 100 seconds or less, radial artery spasm occurred in 6 patients (8.6%), local hematoma in 3 patients (4.3%), and radial occlusion in 4 patients (5.7%). Although the rates of spasm and hematoma were higher in the group with puncture time over 100 seconds, and the occlusion rate was higher in the first group, these differences were statistically insignificant ($P = 0.218$, 0.079 , and 0.384 , respectively). When considering total complications, in the group with longer puncture time (> 100 seconds), complications were observed in 24 patients (33.3%), while in the group with puncture time ≤ 100 seconds, complications were observed in 13 patients (18.6%), and this difference is statistically significant ($P = 0.045$).

When the puncture time exceeds 104 seconds, it increases the risk of complications with a sensitivity of 62.2% and specificity of 57.1% ($AUC = 0.649$; $p = 0.053$). Looking at the subcategories of complications, when the puncture time exceeds 106 seconds, it also increases the likelihood of spasm with a sensitivity of 58.8% and specificity of 60% ($AUC = 0.678$; $p = 0.082$). Puncture time over 114 seconds increases the risk of regional hematoma with a sensitivity of 66.7% and specificity of 63.3% ($AUC = 0.691$; $P = 0.060$) (Figs. 1a, 1b and 1c). There was no significant difference between puncture time and radial occlusion.

DISCUSSION

According to the results of our study, topical nitroglycerin application is a feasible strategy to reduce radial puncture duration and number, facilitate trans-radial catheterization, and decrease the incidence of radial artery spasm and subsequent occlusion. Topical nitro-

glycerin effectively reduces both the number of radial artery punctures and the procedure duration.

Beyer *et al.* [6] study, which compared the effect of topical nitrate and lidocaine cream before trans-radial angiography in 83 patients, found that the group treated with nitrate + lidocaine cream had a 24% larger radial artery diameter compared to the control group, which was believed to reduce endothelial damage. However, unlike our study, radial artery spasms occurred in 25% of patients in both groups in this study, and no significant difference was observed. Some studies indicate that an increase in puncture attempts, pain at the access site, and spasms are risk factors for radial artery occlusion [7]. When the sheath size is larger than the arterial lumen, it may stretch the radial artery and cause endothelial damage. The rate of radial artery occlusion after arterial access seems to be related to the size of the radial sheath. While intra-arterial vasodilators used in our routine practice are applied after sheathing, endothelial damage begins with sheathing. Although the onset of action of topical nitrates is not as fast as intra-arterial application, topical nitrates are locally effective and have a longer duration of action. As dilation begins before sheathing, it is expected that there will be less endothelial damage.

A meta-analysis incorporating previous randomized controlled trials has shown that nitroglycerin administered subcutaneously reduces radial artery spasm and incidence of radial artery occlusion effectively [8]. Additionally, nitroglycerin has been effective in increasing radial artery diameter. Therefore, the prevention of radial artery spasm may subsequently lead to the prevention of radial artery occlusion. The variability in nitroglycerin dosage may also affect the findings. For example, regarding intra-arterial nitroglycerin dosage: both Dhrama *et al.* [8] and Da Silva *et al.* [9] used 500 μg . On the other hand, except for Coroleu *et al.* [10] who used 200 μg , the subcutaneous nitroglycerin dosage was 500 μg . Similarly, while subcutaneous nitroglycerin was effective in reducing spasms, intra-arterial nitroglycerin was not found to be effective.

In our study, nitroglycerin was effective in reducing radial artery puncture attempts and procedure duration. Multiple puncture attempts are the main cause of radial artery spasms. Our study suggests that the application of topical NTG half an hour before coronary angiography expands the artery diameter, increases

successful access in a single puncture, significantly reduces the number and duration of punctures, facilitates access to the radial artery, and significantly reduces the need for switching to an alternative artery by reducing endothelial damage and increasing the radial artery/sheath diameter to reduce spasm, thus reducing radial artery occlusion and associated complications.

The relationship between gender, age, body mass index, smoking and alcohol use, chronic diseases, and medications used was not shown to be associated with puncture duration. The prolongation of puncture duration has significantly increased complications. Puncture duration has been hypothesized as an important parameter in complications occurring at the sheath insertion site. A cut-off value for puncture duration was investigated, and ROC analyses revealed that a puncture duration exceeding 104 seconds predicted the risk of complications with 62.2% sensitivity and 57.1% specificity. When looking at the subcategories of complications, a puncture duration exceeding 106 seconds also increased the likelihood of spasm with 58.8% sensitivity and 60% specificity. A puncture duration exceeding 114 seconds increased the risk of regional hematoma with 66.7% sensitivity and 63.3% specificity. No significant relationship was found between puncture duration and radial occlusion.

Limitations

Differences in operator experience could potentially affect our results. Variations in puncture techniques and equipment used, especially differences in sheath size in trans-radial catheterization techniques, are reported as indicators of radial artery occlusion and could influence our results. Hemostasis protocols could also impact our findings. Furthermore, age-related atherosclerotic changes are also potentially confounding variables that we could not control for.

CONCLUSION

According to the findings of our study, topical nitroglycerin application emerges as a feasible and straightforward strategy to reduce radial puncture duration and frequency, facilitate trans-radial catheterization, and diminish the incidence of radial artery spasms and subsequent occlusion.

Authors' Contribution Study

Conception: NU, AD; Study Design: NU, AD, ŞA; Supervision: AD, ŞA; Funding: NU, HA; Materials: NU, AD; Data Collection and/or Processing: NU, AD; Statistical Analysis and/or Data Interpretation: CA; Literature Review: CA, ŞA, HA; Manuscript Preparation: AD, CA and Critical Review: CA, HA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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