IJC Heart & Vasculature 32 (2021) 100689

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Novel combined topical gel of lidocaine–verapamil–nitroglycerin can dilate the radial artery and reduce radial pain during trans-radial angioplasty

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ARTICLE INFO

Article history:
Received 5 August 2020
Received in revised form 2 November 2020
Accepted 26 November 2020

Keywords:
Cardiac catheterization
Radial artery
Vasodilation
Radial artery spasm

ABSTRACT

Introduction: Radial approach for coronary angioplasty is accepted by many specialists in medical centers around the world. The use of radial access is associated with fewer vascular complications and the same success rate in comparison with traditional femoral access. Radial artery spasm is one of the main concerns in this method. The small size of the radial artery and high density of alpha-1 adrenergic receptors in this artery can accelerate the spasm. The objects of this study were to evaluate whether the combined topical gel of lidocaine–verapamil–nitroglycerin could dilate the radial artery and reduce patient pain and sympathetic response during radial puncture.

Methods: Patients undergoing elective trans-radial angioplasty were randomized to either placebo or therapeutic gel group in single-center, double-blind study. Placebo or therapeutic gel applied 1 cm proximal to the radial styloid process. Radial artery size was measured by ultrasound. Radial pain was reported by the visual analog scale (VAS) and the sympathetic response was assessed by changes in systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR). The incidence of spasm was defined by the radial artery spasm score.

Results: 60 patients (30 patients in each group) participated in this study. A significant increase in the size of the radial artery was observed in the group receiving therapeutic gel compared to the placebo group (mean diameter, mm: 2.95 ± 0.48 vs. 2.54 ± 0.43, p = 0.001; area, cm^2: 0.07 vs. 0.05, p = 0.001). During radial puncture, the radial pain intensity was significantly decreased in patients receiving therapeutic gel (4 (1–5) vs. 2 (1–2), p = 0.003). Radial artery spasm didn't happen in any group.

Conclusion: Based on our results, Pre-procedural administration of combined topical gel of verapamil-n itroglycerin-lidocaine significantly increases the size of the radial artery and effectively reduces the radial pain during radial puncture in patients undergoing trans-radial angioplasty.

1. Introduction

Trans-radial access has been established as the preferred approach for diagnostic or interventional coronary procedures in both elective and emergency settings. Femoral artery cannulation, despite its relative feasibility, is associated with more complications such as bleeding, hematoma, pseudoaneurysms, and nerve damage. In comparison with femoral access, radial access is safer and reduces vascular complications along with more patient acceptance [1–3].

One of the main challenges during trans-radial interventions is radial artery spasm (RAS), which can decrease the success rate of the procedure [4,5]. The small diameter of the radial artery can make the procedure difficult, and multiple attempts for cannulation may increase the risk of RAS [6–8]. On the other hand, the predominance of alpha-1 adrenergic receptor in the medial layer can lead to an excessive response to circulating catecholamines, thereby increasing the susceptibility to spasm [9]. Hence, moderate-to-severe pain during radial artery cannulation can accelerate RAS incidence.

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https://doi.org/10.1016/j.ijcha.2020.100689
2352-9067/

The application of a topical formulation that can dilate the radial artery and alleviate patient pain may effectively prevent RAS. We formulated a new topical gel with 3 known agents: lidocaine, verapamil, and nitroglycerin. We combined lidocaine 5% as an anesthetic agent, verapamil 15%, and nitroglycerin 2% as vasodilator agents into a topical gel. In the previous study by Beyer et al., a topical mixture of nitroglycerin and lidocaine administration was effective in increasing the size of the radial artery in patients undergoing transradial cardiac catheterization [10].

In this study, we assessed whether our lidocaine–verapamil–nitroglycerin combination gel could dilate the radial artery and whether it could reduce the sympathetic response by lowering pain during radial puncture. As a secondary purpose, we evaluated the incidence of the RAS during the procedure in the study subjects.

2. Methods

2.1. Study design

The present single-center randomized double-blind and placebo-controlled study registered in the Ethics Committee of Tehran University of Medical Sciences. In order to observe the significant difference in the pain intensity during radial puncture with a power of 0.8 and an alpha of 0.05, we needed 30 patients in each group.

Patients above 18 years of age who were candidates for elective trans-radial angioplasty were included in this study.

Patients with cardiogenic shock, Hemodynamic instability and emergency admission were excluded from the study. The other exclusion criteria were the inability to receive nitroglycerin, verapamil, or lidocaine due to allergy; absence of radial artery flow; the presence of arterio-venous fistulae; and pregnant or nursing mothers.

Demographic data on age, sex, smoking history, hypertension, diabetes mellitus (DM), coronary catheterization history, procedure time, and the number of radial artery punctures were collected for every participant.

2.2. Topical gel preparation

The topical gel was formulated by dispersing hydroxylpropyl methylcellulose (HPMC) as the gelling agent in water with continuous stirring. For therapeutic gel preparation, proper amounts of verapamil (15%), lidocaine (5%), and nitroglycerin (2%) were added to the aqueous phase. The placebo was an odorless and colorless gel with the same appearance as the therapeutic gel.

2.3. Primary skin irritation test for the topical gel

Three adult albino rabbits, weighing between 2.5 kg and 3.5 kg, were taken for the experiment. The animals were acclimatized a minimum of 5 days before the test. Each rabbit was inserted in a private cage with 20–25 °C temperature and 50–60% humidity.

24 h before the test, the hair on the dorsal areas of each rabbit was shaved in two test areas (one on the right side and one on the left side), each measuring 6 cm^2. 0.5 g of the therapeutic gel on the right side and 0.5 g of the placebo gel on the left side were applied and covered with a gauze pad for 4 h. After 4 h of the exposure period, the degree of irritation was read and scored at 0, 24, 48, 72 h after the patch removal. The scores for erythema and edema were evaluated according to the tests for irritation and skin sensitization ISO 10993-10 (Tables 1 and 2) [11].

Table 1
Primary skin irritation scoring.

Skin reaction	Value
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to eschar formation)	4
Edema formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well raised)	2
Moderate edema (raised approx.1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

Table 2
Primary skin irritation index.

Evaluations	Score
Non-Irritant	0.0
Negligible Irritant	0.1–0.4
Slight Irritant	0.41–1.9
Moderate Irritant	2.0–4.9
Severe Irritant	5.0–8.0

2.4. Radial artery diameter measurement and study gel application

After randomization, patients were assigned to placebo and intervention group|. Baseline diameter of the right radial artery was measured for both groups using a high frequency (13 MHz) linear array transducer from Esaote® (MyLab™Alpha). All ultrasound measurements were made 1 cm proximal to the radial styloid process. Either the therapeutic gel (2 g) or the placebo (2 g) was applied to the right wrist overlying the radial pulse and covered with a transparent dressing, 30 min to 3 h before arterial puncture. After patient admission to the catheterization laboratory, the topical gel was removed and the radial artery diameter was again measured by ultrasound, using the same method applied at baseline. Before cannulation, all the patients received mild sedation with intravenous midazolam and subcutaneous 1% lidocaine for local anesthesia. After sheath insertion into the artery, 50–70 units/kg of unfractionated heparin and 100 μg of nitroglycerin were administered.

2.5. Pain assessment during radial puncture

When the introducer sheath was inserted into the radial artery, pain intensity was evaluated in each patient using the visual analog scale (VAS). The VAS is a 10 cm line with verbal descriptions at each end. The patient determines the severity of the pain by choosing a point on the line [12].

2.6. Measurement of the sympathetic response

Sympathetic tone, including systolic blood pressure (SBP), diastolic blood pressure (DBP), and the heart rate (HR), was measured as baseline value before lidocaine infiltration via noninvasive blood pressure and digital pulse oximeter monitoring. Thereafter, these parameters were measured again after sheath insertion.

2.7. Clinical definition of radial artery spasm

The assessment of the occurrence of radial artery spasm was in accordance with the scoring system used in the TNT-RASP trial

[13]. The score of 1 or more of the total scores indicates radial artery spasm. These scores are:

1. Pain in the forearm that patient feels during the procedure and worsens with the movement of the catheter/sheath: absent: 0; present: 1.
2. Difficulty in catheter movement that restricts its progress: absent: 0; present: 1.
3. Problem with sheath removal at the end of the procedure: absent: 0; present: 1.
4. Additional injection of vasodilator cocktail during the procedure: No: 0; Yes: 1.

2.8. Statistical analysis

The qualitative variables were expressed as the median with the interquartile range, and the quantitative variables were expressed as the mean ± the standard deviation. The categorical data were presented as percentages. The χ^2 test was employed to compare these categorical variables. The statistical analyses were performed with the SPSS software, version 26. The values were compared using the unpaired *t*-test for the normally distributed variables and the Mann–Whitney *U* test for the nonparametric variables. A *P* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Primary skin irritation test for topical gel

Primary skin irritation was scored from 0 to 4 for erythema and edema effects. The macroscopic observation is shown in Figs. 1 and 2. Table 3 shows the skin scores for therapeutic gel and placebo gel sites. At 24, 48, and 72 h after observation, the scores were equal for therapeutic gel and placebo gel sites and includes 0.0 ± 0.0, 0.16 ± 0.4, and 0.16 ± 0.4, respectively. These results show that both topical gels is negligible irritant (Table 2).

3.2. Patient characteristics

From a total of 113 patients, 103 were randomized in double blind fashion, and the final analysis was conducted on 30 patients in the placebo group and 30 patients in the therapeutic group (Fig. 3).

The clinical characteristics and medications of the patients in the 2 groups are depicted in Tables 4 and 5. The 2 groups were well balanced for age, gender, medical history, smoking, prior interventions and their access and medications use. The body mass index in the group receiving gel therapy was higher than that in the placebo group (27.6 ± 4.7 vs. 24.5 ± 4.1; $P = 0.009$).

For all the patients in both groups, the radial artery was successfully accessed at the first puncture and the sheath was inserted in the first attempt. All the trans-radial angioplasties were performed through the right radial artery. The duration of the procedure in the group receiving the therapeutic gel was longer than that in the placebo group (50 min vs. 35.5 min), but this difference was not statistically significant ($P = 0.07$).

3.3. Radial artery size

In this study, radial artery size was reported as the mean diameter (mm) and area (cm^2) (Fig. 4). The diameter and area of the radial artery were increased significantly in the therapeutic group (mean diameter, mm: 2.95 ± 0.48 vs. 2.54 ± 0.43, p = 0.001; area, cm^2: 0.07 vs. 0.05, p = 0.001) (Table 6).

3.4. Sympathetic system response

Sympathetic tone, including SBP, DBP, and HR, was similar in the 2 groups, and there was no significant difference between the groups (Table 7).

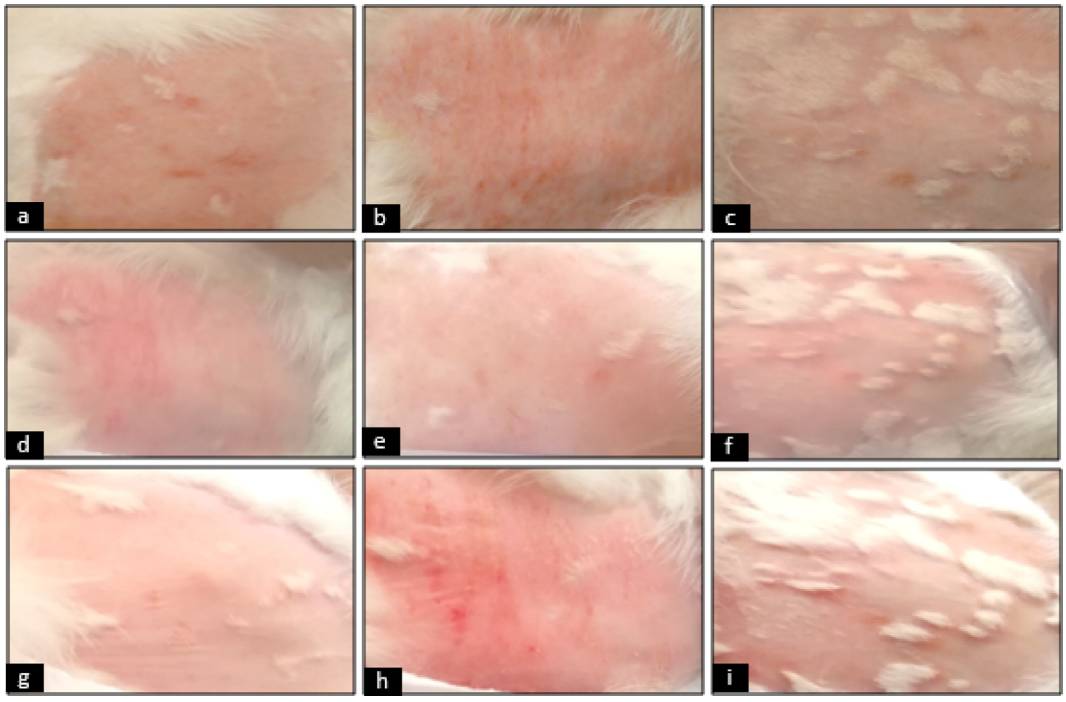

Fig. 1. Macroscopic results of placebo gel. Observation after 24 h (a, d and g); observation after 48 h (b, e and h); observation after 72 h (c, f and i).

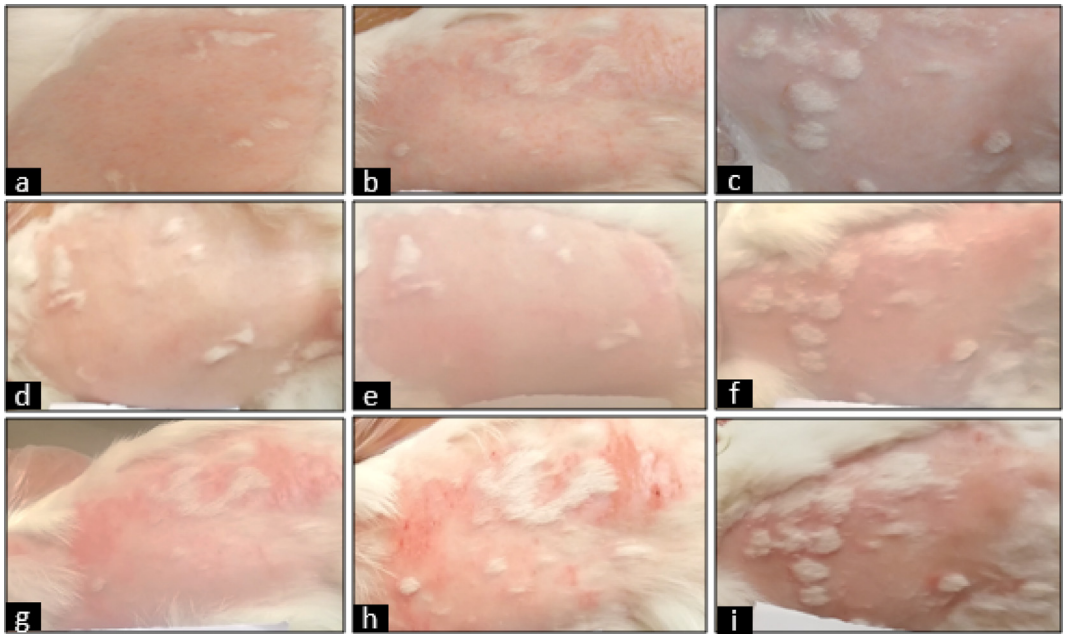

Fig. 2. Macroscopic results of therapeutic gel. Observation after 24 h (a, d and g); observation after 48 h (b, e and h); observation after 72 h (c, f and i).

Table 3
Skin irritation score (mean).

	24 h	48 h	72 h
Placebo gel	0.0 ± 0.0	0.16 ± 0.4	0.16 ± 0.4
Therapeutic gel	0.0 ± 0.0	0.16 ± 0.4	0.16 ± 0.4

3.5. Radial pain score during the procedure

During radial puncture, radial pain measured by VAS was significantly lower in the group receiving the therapeutic gel (4 [1–5] vs. 2 [1–2]; $P = 0.003$) (Table 8).

3.6. Radial artery spasm

The patients in both treatment and placebo groups didn't report pain during procedure that worsen with the catheter/sheath movement, nor was there a report of difficulty in progressing the catheter or removing the sheath in either group. The vasodilator cocktail was not reused in either group. Vis-à-vis the RAS score, the patients did not experience RAS either in the treatment or placebo group.

4. Discussion

Despite the low rate of access site complications and the increasing popularity of trans-radial catheterization, this method is associated with problems that can lead to the failure of the procedure [6]. One of the main concerns in this method is the occurrence of spasms, which can prolong the procedure, impose more pain and discomfort for the patient, and even lead to crossover to femoral access [4,5].

Preventing spasm is more effective than treating it [14]. There are no single guideline for intra-arterial (IA) vasodilator cocktail components to prevent RAS. A comparison of the results of different studies have shown that the best known and effective combination is verapamil plus nitroglycerin [15]. However, according to the SPASM3 trial, the use of IA cocktails could lead to side effects that limit the trans-radial approach in hemodynamically unstable patients [8]. Chen et al. showed that nitroglycerin alone can be as effective as the nitroglycerin plus verapamil, so verapamil can be removed from the IA cocktail [16]. The VITRIOL clinical trial has shown that in medical centers with experienced interventionists in the trans-radial method, verapamil-containing cocktails can be omitted. However, many experts still believe in the need to prescribe vasodilator cocktails [17]. Because of the side effects of verapamil and the possibility of removing this drug from the cocktail, we decided to provide a topical formulation, its main difference with previous formulations is the use of verapamil as a calcium channel blocker along with nitroglycerin and lidocaine. The use of this combined gel and the following removal of verapamil from the IA cocktail resulted in the patient not experiencing any further side effects but also benefiting from the prophylactic effects of verapamil. The main difference between our study and previous types, especially Beyer et al. [10], is the use of verapamil in topical formulation.

The small size of the radial artery is one of the factors contributing to spasm [4,5]. The enlargement of the radial artery can have several benefits: not only is the artery easier to access but also equipment with larger diameters can be used, which might effectively reduce RAS and radial artery occlusion. Statistically, we detected a significant increase in the diameter and area of the radial artery in the group treated with a combined topical gel (Table 2). This finding chimes in with that in a study by Beyer et al, who reported that the preprocedural administration of a topical mixture of nitroglycerin and lidocaine increased the size of the radial artery in healthy adults and patients undergoing transradial cardiac catheterization [10,18].

The high-density of alpha-1 adrenergic receptor in the muscular layer of the radial artery wall with little beta-adrenergic function augment the sensitivity of this artery to catecholamines [9]. Therefore, the pain that the patient experiences during arterial puncture can stimulate the secretion of catecholamines and eventually spasm [16]. Our combined topical gel significantly reduced the intensity of pain in the treatment group (4 [1–5] vs. 2 [1–2]; $P = 0.003$), with 96.7% of the patients in the treatment group experiencing no pain or mild pain. Similar results with EMLA®, as a local anesthetic, were reported by Joly et al and Youn et al. [19,20].

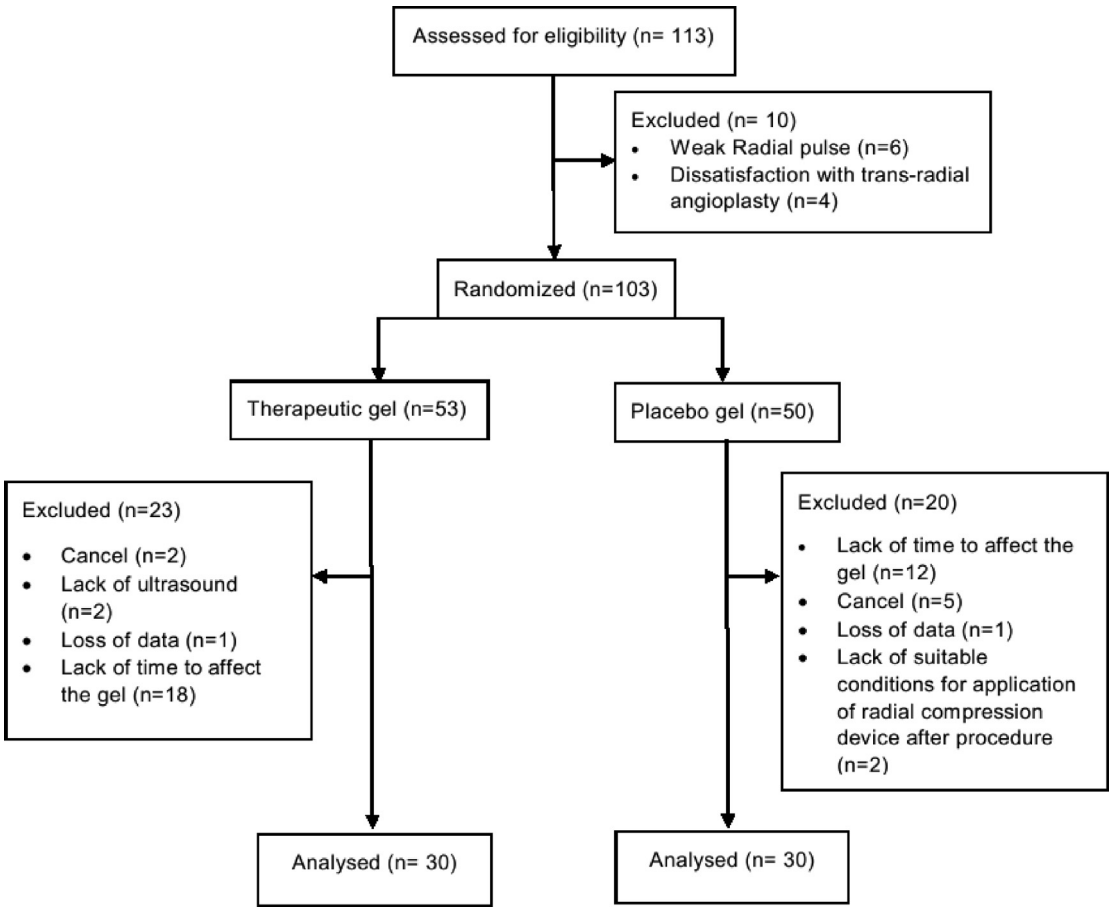

Fig. 3. Study flow chart.

Table 4
Patient characteristics.

Variable	Placebo Gel	Therapeutic Gel	*P* value
Age (y) [mean ± SD]	64.2 ± 8.996	59.967 ± 8.467	0.66
Gender (male) [N (%)]	22 (73.3%)	21 (70%)	0.774
Body mass index (kg/m^2) [mean ± SD]	24.537 ± 4.112	27.617 ± 4.736	0.009
Diabetes (Yes) [N (%)]	4 (13.3%)	6 (20%)	0.488
Hypertension (Yes) [N (%)]	10 (33.3%)	9 (30%)	0.781
Prior myocardial infarction (Yes) [N (%)]	1 (3.3%)	5 (16.7%)	0.195
Smoking (Yes) [N (%)]	1 (3.3%)	4 (13.3%)	0.353
Prior intervention (Yes) [N (%)]	23 (76.7%)	20 (66.7%)	0.39
Access (femoral) [N (%)]	14 (46.7%)	14 (46.7%)	0.569
Procedural duration (median [IQR])	35.50(20–50)	50.00(35–70)	0.076

Table 5
Drugs before Procedure.

Drugs before procedure	Placebo Gel	Therapeutic Gel	*P* value
Aspirin (Yes) [N (%)]	73.34	66.67	0.573
Clopidogrel (Yes) [N (%)]	20	30	0.371
Nitrates (Yes) [N (%)]	50	46.67	0.796
Calcium Channel Blockers (Yes) [N (%)]	23.34	13.34	0.317
Beta blockers (Yes) [N (%)]	90	76.67	0.166

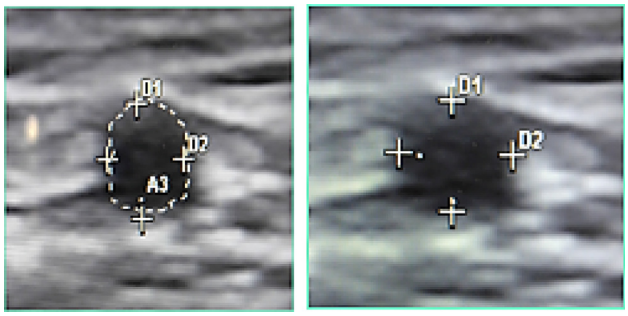

Fig. 4. Representative Example of Radial Artery Size.

Table 6
Radial Artery Size at Baseline and after the Topical Gel Application.

Variable	Placebo Gel	Therapeutic Gel	*P* value
Baseline Diameter Mean (mm) [mean ± SD]	2.445 ± 0.432	2.472 ± 0.537	0.833
Final Diameter Mean (mm) [mean ± SD]	2.54 ± 0.43	2.95 ± 0.48	0.001
Baseline Area (cm^2) [median (IQR)]	0.04 (0.04–0.05)	0.05 (0.04–0.06)	0.643
Final Area (cm^2) [median (IQR)]	0.05 (0.04–0.06)	0.07 (0.05–0.09)	0.001

Table 7
Sympathetic System Response at Baseline and after the Sheath Insertion.

Variable	Placebo Gel	Therapeutic Gel	*P* value
Baseline SBP[mean ± SD]	131.533 ± 16.408	131.20 ± 15.904	0.937
Final SBP [mean ± SD]	107.87 ± 25.9	111.93 ± 15.97	0.467
Baseline DBP [mean ± SD]	77.933 ± 9.645	79.2 ± 9.59	0.612
Final DBP [mean ± SD]	65.2 ± 10.55	66.93 ± 13.58	0.583
Baseline HR [mean ± SD]	72.7 ± 9.12	71.5 ± 5.918	0.548
Final HR [mean ± SD]	73.5 ± 9.47	74.03 ± 8.33	0.818

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate.

Table 8
Radial pain score during the procedure.

Variable	Placebo Gel	Therapeutic Gel	*P* value
Patient pain (Median[IQR])	4 (1–5)	2 (1–2)	0.003

Because pain can activate the sympathetic system, we tried to find a relationship between pain intensity and sympathetic system activation by measuring SBP, DBP, and HR before and after sheath insertion in transradial angioplasty. These variables had no marked differences between the 2groups; and although the placebo group reported having experienced severe pain, the sympathetic system did not have more activity. This is contrary to the results of a study by Youn et al, who reported that EMLA® cream was able to reduce the activity of the sympathetic system [20]. Perhaps the reason for the lack of difference between the 2groups is that blood pressure and HR may vary due to different factors.

Young age, female gender, DM and low BMI are the predisposing factors for RAS [5]. In our study, patients had a normal distribution in terms of age, sex, and DM. However, BMI in the patients receiving placebo gel was lower than therapeutic gel group statistically significant (27.6 ± 4.7 vs. 24.5 ± 4.1; $P = 0.009$). Therefore, it was expected that the incidence of spasm in the placebo gel group was higher than therapeutic gel one, but in practice, none of the patients in this two groups experienced spasm during the procedure. The assessment of the incidence of RAS was consistent with the TNT-RASP trial in which clinical factors were used [13]. This result is in contrast to the results of Youn et al [20] and Beyer et al [10] studies that reported the occurrence of spasm but did not reach a significant difference between the placebo and therapeutic groups. Although RAS incudence has been reported to be around 25% in Beyer et al [10] study, in other studies it has been reported to be 7.8% or even less [21]. However One reason we could not detect RAS in our patients may be the small sample size, which is not enough to observe RAS On the other hand, according to Fukuda et al study, angiographic parameters can help diagnose spasm [22]. Another limitation in our study is the impossibility of examining angiographic parameters. Accordingly, we recommend that our experiment be tested in larger-sized trials with concomitant angiographic and clinical examination for RAS incidence.

5. Conclusions

In our randomized double-blind and placebo-controlled study, preprocedural administration of a combined topical gel of verapamil–nitroglycerin–lidocaine significantly increased the size of the radial artery and effectively reduced radial pain during radial puncture in patients undergoing transradial angioplasty.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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