



Clinical Efficacy of a Combined Topical Gel of Diltiazem, Papaverine, and Lidocaine on Pain, Spasm, and Hand Function in Patients Undergoing Trans-Radial Coronary Catheterization

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Abstract

Background: Trans-radial coronary catheterization has been known as a routine procedure performed for the patients suffering from coronary artery diseases. Despite the benefits, it would come with many complications. In this regard, this study aims to investigate the clinical efficacy of a combined topical gel containing diltiazem, lidocaine, and papaverine on pain, spasm, and hand function in patients undergoing trans-radial coronary catheterization.

Methods: In this randomized, quadruple-blind clinical trial, the candidates for trans-radial coronary artery interventions were randomly assigned to the intervention (receiving the combined topical gel) and the control (receiving the placebo) groups. The gels were applied around the radial artery 30 to 60 minutes before the catheterization and pain assessment in the forearm was conducted before and two hours after the procedure. Hand function was evaluated before the intervention, after catheter removal, and two hours post-removal, with a focus on the levels of numbness, stiffness, and weakness in the fingers. The occurrence of spasms during the procedure was measured using the clinical spasm scale tailored for the radial artery. Furthermore, sympathetic tone was evaluated through systolic and diastolic blood pressure and heart rate measurements before and after catheterization, as well as two hours post-procedure.

Results: Based on the results, significant alleviations in pain (two hours post-catheterization) and hand numbness were recorded for the intervention group when compared to the control group. Furthermore, the number of attempts required to access the radial artery was significantly lower in the intervention group than in the control group.

Conclusion: The data showed that the current combination can be a candidate to alleviate some of the complications associated with trans-radial coronary catheterization. However, further preclinical and clinical studies may be required in this regard.

Introduction

Coronary artery disease (CAD) is one of the most prevalent diseases nowadays, contributing to the highest mortality rates in both developed and developing countries.¹ In this regard, the common intervention for patients suffering from CAD is coronary catheterization,² which can be performed through various access routes. Among these, transradial coronary interventions (TCI) are gaining popularity due to their ease of access, fewer complications, reduced treatment costs, shorter hospital stays, and

improved quality of life of the patients.³⁻⁵ However, significant limitations have been reported for this approach including radial artery spasm (RAS) and upper limb dysfunction.⁶ A review conducted in 2020 reported that the incidence of access-related complications varies widely, where hematoma (0-16%), spasm (0-16%), pain (0-9%), bleeding (0-4.5%), and occlusion (0-4%) were the leading ones.⁷ Among the contributing factors to the increased incidence of spasm, the small diameter of the radial artery, which can necessitate multiple attempts for cannulation,

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would be very challenging.⁸⁻¹⁰ Additionally, high density of alpha-adrenergic receptors in the inner layers of the radial artery increases the sensitivity to circulating catecholamines, potentially leading to moderate to severe pain and subsequently a higher incidence of spasm.¹¹

Upper extremity dysfunction (UED) may also arise due to serious vascular and neurological deficits incurred during TCI, resulting in a diminished quality of life.¹² Important deficits include thickening of the arterial intima, endothelial dysfunction, and median nerve damage, all of which can contribute to UED,^{6,12} the dysfunction which may manifest as pain and neurological symptoms.⁶

There are various methods to prevent the mentioned complications, among which pharmacotherapy can be noted.¹³ Since injections are always associated with challenges and cause greater discomfort for patients,¹⁴ particularly those who suffer from the relevant phobias,¹⁵ topical administrations have gained attention so that they can facilitate the catheterization process and reduce the invasiveness.^{15,16} The effectiveness of the topical products on one hand, and the role of creativity in the process of manufacturing these products on the other hand,¹⁷ have encouraged the researchers to develop novel formulations.

Recent studies have shown that a topical drug formulation containing nitrates, calcium channel blockers, and lidocaine would be effective in reducing complications associated with TCI.^{10,17,18} As an instance, a study in 2022 demonstrated that the topical formulation of lidocaine, nitroglycerin, and verapamil would lead to a great reduction in pain and an increase in the diameter of the radial artery.¹⁹ Besides, other studies have indicated that injecting the opioids such as papaverine can result in a greater impact on the success rate of TCI compared to injectable nitroglycerin.^{20,21} However, effects of topical papaverine on the complications of the radial artery cannulation have not been adequately studied yet²² and remains a topic for discussion. Despite being considered as a choice to prevent spasms during the procedures by many practitioners,¹⁸ there is limited evidence about the local effects of papaverine in coronary interventions. Thus, the difference between our research and the previous studies would be the involvement of papaverine in the topical drug formulation. Additionally, although complications such as upper limb dysfunction and pain after TCI have recently come to attention,^{6,23} there are few studies conducted on the effects of multi-drug topical gels, containing papaverine. Given the importance of reducing the complications associated with cannulation and also the usefulness of multi-drug formulations, this study was conducted to investigate the effect of using a topical gel composed of diltiazem (a calcium channel blocker), lidocaine (a local anesthetic), and papaverine (a vasodilator and pain reliever) on pain, spasms, and functional impairments of the hand in patients undergoing trans-radial coronary catheterization.

Methods

Methodology

This study is a randomized, quadruple-blinded, placebo-controlled clinical trial conducted in the Cath. Lab. of Imam Khomeini Hospital (Amol, Iran) for patients eligible for trans-radial coronary catheterization in 2024. The sample size was estimated using G.Power software with a significance level of 0.05, and a power of 80%, leading to a minimum of 27 patients in each group, totaling 54 patients. Considering a drop-out rate of 10%, 60 patients were enrolled in the study (30 in the intervention group and 30 in the control group).

Inclusion criteria for the study included the patients with at least 18 years old who were candidates for cardiac catheterization via the radial artery, capable of understanding Persian, and with no previous history of right hand injury. Patients with medical emergencies, systolic blood pressure below 90 mmHg, and presence of atrial and ventricular arrhythmias were excluded from the study. Other exclusion criteria included non-palpable radial pulse, pregnancy and breastfeeding, history of allergy to local anesthetics, presence of arteriovenous fistula, history of coronary artery bypass grafting (CABG), and responses classified as C or D on the Barbeau test.

To prepare the topical gel, methylparaben and propylparaben were initially dissolved in a portion of deionized water at concentrations of 1.8 and 0.2 mg per milliliter, respectively. A 1.5% (w/v) solution of hydroxy propyl methyl cellulose (HPMC) was prepared by vigorous stirring at 60°C in water. After that, the solution containing parabens were added to HPMC solution. Meanwhile, while homogenizing this mixture, lidocaine (Darou Pakhsh Pharma Chem Co., Iran), diltiazem (Darou Pakhsh Pharma Chem Co., Iran), and papaverine (Faran Shimi Pharmaceutical Co., Iran), each at a concentration of 20 mg per milliliter, were dissolved in a portion of the formulation's water in a separate container. The resulting solution was then gradually added to the solution containing HPMC and the preservatives, and was mixed to obtain a uniform consistency. The placebo was a colorless, odorless gel that had a similar appearance to the therapeutic gel.

Intervention

Patients were enrolled in the study based on the entry criteria and after obtaining the informed consent. Using a block randomization method, patients were assigned to two groups: the intervention group receiving a topical gel containing diltiazem, papaverine, and lidocaine (A) and the control group receiving a placebo (B). For all patients, the assessment of blood supply in the radial and ulnar arteries was conducted using the Barbeau test by a nurse. A specific amount (fingertip) of the combination gel was applied to the right wrist area, about one centimeter above the styloid process of the radius, over the pulse of the radial artery and additionally within a two-inch radius around the pulse of the artery, 30 to 60 minutes before catheterization in the intervention group. In the control

group, the same amount and method were applied using the placebo. The site of gel application in both groups was covered with a transparent dressing. After the patients were admitted to the catheterization laboratory, the dressing was removed, and the catheterization was performed by the physician. Before catheterization, according to the hospital's standard protocol, all patients received mild sedation with intravenous midazolam and 1% lidocaine subcutaneously for local anesthesia. To catheterize the radial artery, a 0.018-inch guidewire was initially inserted, followed by a 6-French hydrophilic sheath (Prelude Ease, Merit Medical, South Jordan, UT) into the artery. After placing the sheath in the artery, 50 to 70 units of heparin (per kilogram of body weight) were injected to all patients. Catheterization for all patients was performed by the same physician. After the procedure, patients were monitored for complications (such as hematoma and bleeding). Data collection was also performed by a particular nurse. In this study, the participants, the physician, the nurse, and the researcher responsible for data analysis were all unaware of the patients' allocation to either the intervention or control group. In fact, this study was quadruple-blinded.

Pain assessment

Pain was evaluated before and two hours after catheterization of the artery. The pain in the forearm was assessed using the Visual Analog Scale 0-10 (VAS). The VAS consists of a 10-centimeter line, with the word "no pain" at the far left end and "worst pain" at the far right end. The patient indicates the intensity of their pain by marking a point on the line.²⁴

Hand function assessment

Hand function was assessed before and after catheter removal as well as two hours after catheter removal using the HAKIR Questionnaire (HQ-8). The HQ-8 includes seven questions regarding perceived symptoms in the affected hand and one question about the ability to perform activities of daily living. In this study, we used part of this checklist, which includes stiffness of the fingers, weakness of the fingers, and numbness, measured on a scale from zero to 100.²⁵

Assessment of radial artery spasm

To assess spasm, the Radial Artery Spasm Scale was

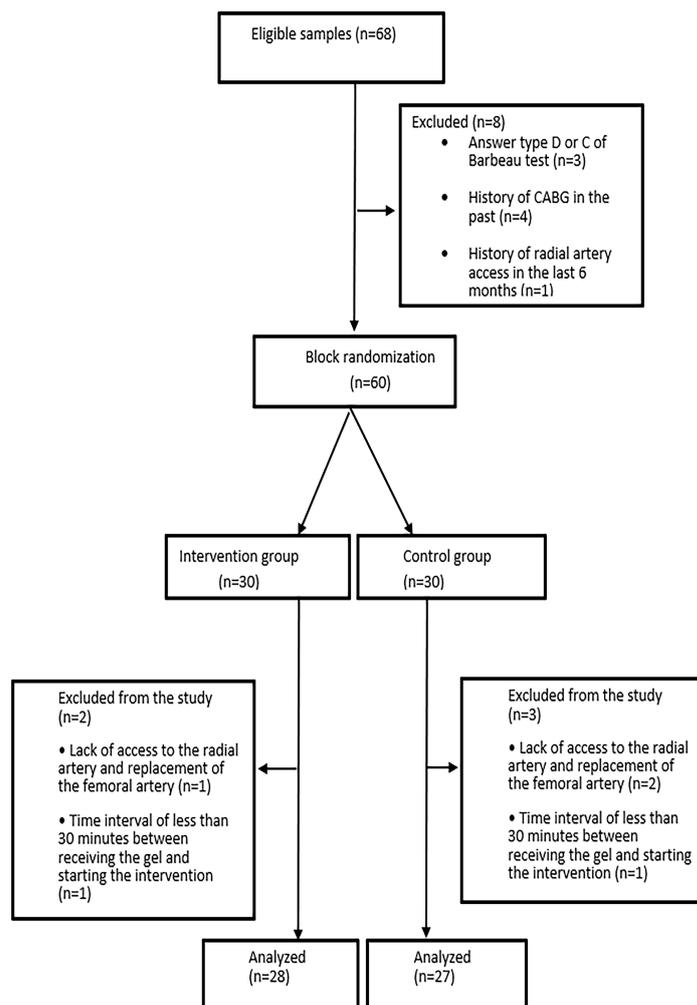


Figure 1. Consort diagram of the present study.

employed. This tool was developed by Mirak *et al.*²⁶ in 2020. According to this scale, the occurrence of any of the following four items scores one point, and a score of one or more from the total points indicates radial artery spasm. The items include pain in the forearm that the patient feels during the procedure and worsens with catheter/sheath movement; difficulty in moving the catheter that limits its advancement; difficulty in removing the sheath at the end of the procedure; and additional injection of a vasodilator cocktail during the procedure.

Assessment of sympathetic response

To assess sympathetic tone, systolic and diastolic blood pressure and heart rate were measured using pulseoximetry and hemodynamic monitoring equipment before, during, and after transradial coronary catheterization.

Statistical analysis

In this study, the Shapiro-Wilk test was used to examine normal distribution; additionally, the Chi-square test was employed to determine the homogeneity of groups regarding nominal variables. Quantitative data were expressed as mean and standard deviation. Qualitative data were presented as frequency and percentage. To investigate the relationship between qualitative variables in two groups, the Chi-square test was used. Furthermore, the comparison of quantitative variables between the two groups was analyzed using the t-test. To compare variables at different times (before, during, and after the procedure), repeated measures ANOVA was utilized. For measuring changes in pain levels two hours after the intervention, while adjusting and controlling for pre-intervention scores, analysis of covariance (ANCOVA) was utilized. The significance level for all tests was set at $P < 0.05$. Statistical analyses were conducted using SPSS software (version 26, IBM Corporation, Armonk, NY, USA).

Ethical notes

This study was registered in Iranian Clinical Trials Center (IRCT20231018059760N1). Additionally, the ethical code was obtained from Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1402.521). During this

research, No pain, no costs, and no additional procedures were imposed on the patients. The participants entered the study with informed consent.

Results

In this study, 68 patients were evaluated for eligibility to enter the study, of which 8 were excluded due to not meeting the entry criteria. From the 60 patients included, 30 were assigned to the control group through block randomization, and 30 entered the intervention group. Three patients in the control group and two patients in the intervention group were excluded due to replacement of the radial artery with the femoral artery or inability to adhere to the 30 minute time interval between receiving the gel and the start of the intervention. Ultimately, 27 patients in the control group and 28 patients in the intervention group were analyzed, and the results were evaluated. Figure 1 shows the flowchart of the study.

Homogeneity assessment

The results of the Chi-square test indicated that there was no statistically significant difference between the intervention and control groups regarding the history of tobacco use, diabetes, body mass index, and gender ($P > 0.05$). Additionally, in advance of the intervention, pain and hand dysfunction were not present in either group, and the level of sympathetic system function did not show a statistically significant difference between the two groups ($P > 0.05$) (Table 1).

Assessment of pain intensity

Controlling for pre-catheterization pain intensity scores, the ANCOVA results indicated a significant difference in pain intensity (after two hours), with the intervention group (3.51 ± 2.17) showing lower pain levels compared to the control group (3.94 ± 4.29) ($P < 0.05$, $F = 0.07$) (Table 2).

Hand function measurement

According to Table 2, the results of the Repeated Measures ANOVA with Greenhouse-Geisser correction (considering the violation of Mauchly's test of sphericity) showed no significant differences between the intervention and

Table 1. Characteristics of patients participating in the study.

Variable			Intervention group	Control group	P value
Gender	[N (%)]	Male	16 (57.1%)	13 (48.1%)	0.504
		Female	12(42.9%)	14 (51.9%)	
Smoking (yes)	[N (%)]		8(28.6%)	5 (18.5%)	0.380
Diabetes (Yes)	[N (%)]		11(39.3%)	8 (29.6%)	0.452
Body mass index (kg/m ²)	[N (%)]	Thin	0	1 (3.1%)	0.571
		Normal	11(39.3%)	7 (25.9%)	
		Overweight	14(50%)	16(59.3%)	
		Fat	3(10.7%)	3 (11.1%)	
Age (y)	[mean \pm SD]		58.30 \pm 9.85	61.20 \pm 10.03	0.296
Systolic blood pressure	[mean \pm SD]		131.80 \pm 1.61	132.80 \pm 2.20	0.726
Diastolic blood pressure	[mean \pm SD]		77.50 \pm 1.45	76.70 \pm 1.57	0.699
Heart rate	[mean \pm SD]		74.20 \pm 1.70	67.60 \pm 3.03	0.066

Table 2. Mean and standard deviation of pain, hand function, and sympathetic tone in the intervention and control groups.

Variable	Measurement round	Intervention group	Control group	P value*	P-value (effect size)*		
		Mean \pm SD			Time-Group	Group	Time
Pain	Before	0	0	P<0.05			
	After two hours	2.1 \pm 3.5	4.29 \pm 3.9				
Stiffness	Before	0	0	P>0.05 (0.027)			
	After	6.6 \pm 19.6	10.3 \pm 25.4				
	After two hours	7.8 \pm 23.3	19.2 \pm 33.7				
Weakness	Before	0	0	P>0.05 (0.018)			
	After	11.7 \pm 25.8	2.9 \pm 15.3				
	After two hours	18.9 \pm 33.8	21.1 \pm 36.5				
Numbness	Before	0	0	P<0.05 (0.100)	P<0.05 (0.156)	p<0.001 (0.230)	
	After	0	11.8 \pm 25.4				
	After two hours	7.5 \pm 22.5	32.5 \pm 40.3				
Systolic blood pressure (mmhg)	Before	131.8 \pm 8.5	132.8 \pm 11.4	P>0.05 (0.023)			
	During	133 \pm 12.9	130.8 \pm 14.2				
	After	129 \pm 9.6	126.3 \pm 9.4				
	After two hours	128.8 \pm 9	124.2 \pm 8.6				
Diastolic blood pressure (mmhg)	Before	77.5 \pm 7.6	76.7 \pm 8.1	P>0.05 (0.007)			
	During	75.5 \pm 6.3	73.1 \pm 6.72				
	After	75.35 \pm 5.12	83 \pm 8.3				
	After two hours	76.2 \pm 5.6	73.5 \pm 5.7				
Heart rate (n/ min)	Before	74.2 \pm 9.4	67.6 \pm 5.7	P>0.05 (0.017)			
	During	73.4 \pm 10.1	70.7 \pm 8.3				
	After	72.6 \pm 6	72 \pm 9.9				
	After two hours	68.5 \pm 20.3	67.7 \pm 15.7				

* Based on the Repeated Measures ANOVA

Based on the ANCOVA

control groups regarding changes in finger stiffness and weakness at three time points: before, immediately after, and two hours post-operation ($P>0.05$). However, changes in finger numbness measured at the three time points were significantly less in the intervention group compared to the control group ($P<0.05$). Additionally, when the trend over time was not considered, the groups exhibited a significant difference ($P<0.05$, $\eta = 0.156$). Lastly, examining the effect of time on finger numbness revealed that the level of numbness in the two measurement occasions after catheterization and two hours post-procedure was lower in the intervention group than in the control group. This difference was statistically significant ($P<0.001$, $\eta=0.230$). (Table 2).

Evaluation of radial artery spasm

The incidence of spasm in the control group was 25.9%,

while in the intervention group it was 1.7%. However, this difference was not statistically significant ($P>0.05$).

Sympathetic system response

According to Table 2, changes in the sympathetic system response, which included systolic blood pressure, diastolic blood pressure, and heart rate, were assessed at four time points: before, during, after, and two hours after the procedure. The two groups did not show a significant difference in sympathetic tone changes.

Both groups were studied concerning the occurrence of hematomas, but there was no statistical difference between them ($P>0.05$) in this regard. However, the frequency of patients who required more than one attempt to access the radial artery was 1.7% in the intervention group and 29.6% in the control group. This difference was statistically significant ($P<0.05$).

Discussion

The present study was conducted to evaluate the clinical efficacy of topical co-administration of papaverine, lidocaine and diltiazem on radial artery spasm, pain, sympathetic tone and hand function in patients undergoing TCI. Based on the literature, pain have been found among the underlying factors for spasms of arteries, so that the radial artery would be more sensitive to pain compared to the femoral artery due to the unique anatomical features.²⁷ In the current study, the results showed that the recorded values for pain in the intervention group were significantly lower when compared to the control group. In this regard, Latsios and colleagues in 2017 reported that the values recorded for pain were not statistically different between the groups treated by a topical gel consisted of lidocaine and prilocaine and the group receiving lidocaine injection.¹⁵ This shows that, topical products can exert a clinical efficacy comparable to injections. The present study also indicated that topical products have significant potential particularly when administered in combination. Another research in 2021 claimed that topical administration of lidocaine, glyceryl trinitrate and verapamil would reduce pain during catheterization.²⁶ Notably, in the mentioned research, the time of administration was 0.5 to 3 hours earlier than administration while in the present study, the time period was 0.5 to 1 hour. Besides, in addition to its vasodilatory action, papaverine, which was one of the drugs used in the current study, is an opioid with notable analgesic effects²⁸ that can help improve the efficacy of the current co-administration. In spite of the differences in the settings, both indicated the ability in reducing the pain. It is important to note that, administration of topical drugs to reduce pain has a very long history. In this regard, the available literature has expressed higher efficacy and safety for topically applied drugs. Furthermore, this route of administration can exert a localized effect with a greater concentration at the site of action²⁹ which can be very useful during the procedure focused in this research.

Besides, neurological injuries that lead to hand dysfunction are a rare but important complication that should be considered during catheterization.²⁷ The results of our study showed that there was no significant difference between the intervention group and the control group in terms of changes related to the stiffness and weakness of the fingers before, after and two hours after the operation, so that the trend of the changes was not different. However, the process of changes in the numbness of the fingers in the 3 times of measurement was significantly different in the intervention group than the control group ($P < 0.05$). So that the numbness of the fingers in the two checkpoints (immediately following the procedure and two hours later respectively) was significantly less in the intervention group. Although few studies are available in this regard, according to a study in 2015, almost 20% of the patients would suffer from complications such as numbness, tingling and stiffness after TCI, so that almost 50% of them would last for 30 days.³⁰ Based on this fact, the present research

was formed to find a solution for alleviating the mentioned complications through possible pharmacological interventions. The novelty, the availability and cost-effectiveness of papaverine, lidocaine and diltiazem on one hand, and the reported pharmaceutical stability of these compounds together on the other hand,^{31,32} led this study to be focused on this topical co-administration. Papaverine, the natural alkaloid found in the biological structure of *Papaver somniferum* is popular for exerting effects against vasoconstriction and pain.²⁸ Interestingly, systemic absorption of this alkaloid has reported to be negligible when administered topically,³³ besides, local anesthesia (particularly using lidocaine) has been found as a standard solution in various types of catheterization.^{34,35} Furthermore, blocking calcium channels is a well-known mechanism which can potentiate vasodilation.³⁶ Therefore, considering the mentioned points, focusing on papaverine, lidocaine and diltiazem in this research seem to be justifiable.

The mentioned combination was also tested concerning the spasms in the radial artery. Based on our results, the incidence of spasm during the procedure was reported as 7.1% and 25.9% in the intervention and control groups, respectively. Although this difference was not statistically significant, the incidence of spasm was 18.8% less than the control group. In terms of spasm occurrence rate, our results were almost consistent with other studies. As an example, a research in 2012 reported the incidence of radial artery spasm from 4 to 20%.³⁷ Also, a systematic review has reported the prevalence of spasm in this artery during TCI to be about 15%. Although, reviewing the available literature indicates that many pharmacological interventions were unable to exert significant changes,^{17,38} some other studies reported statistically meaningful improvements in this regard.^{39,40} Apart from the nature of the studied compounds, the reason for this inconsistency can be the differences in the sample sizes or the incoherence of the clinical and angiographic factors. So that, the study population was different between the present setting and an earlier research conducted in 2023.³⁹ Furthermore, the agents and the administration routes employed in the earlier research were not completely consistent with those used in the current project. On the other hand, in a study by Tatlı and colleagues⁴⁰, using angiography which is more accurate for measuring spasm may be the cause for obtaining more significant results. Altogether, it seems that the variations in the experimental designs were strongly determinative in this regard.

Another finding of the present study was about sympathetic tone. Since radial artery compliance would be affected by sympathetic stimulation through different mechanisms, controlling the response of the sympathetic system can influence the success rate of TCI.⁴¹ Considering that stimulation of the sympathetic system can affect heart rate and blood pressure,^{42,43} in this study, by measuring heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), we investigated the response

of the sympathetic system. The results of our study showed that the changes in HR, SBP, and DBP were not significantly different in the intervention and control groups. Interestingly, the results reported by Michaili and colleagues, who used the topical gel containing lidocaine, verapamil (another calcium channel blocker) and nitroglycerin (the well-known vasodilator), were consistent with our study in this regard.²⁶

Another important variable in our study is the number of attempts to access the radial artery. Since increasing the number significantly raises the complications of TCI,⁴⁴ the findings would be clinically meaningful. According to the results of our study, the number of attempts was statistically lower in the intervention group. Meanwhile, it has been reported that the combined topical gel of lidocaine and prilocaine had no effect on this variable.¹⁵ The reason for this finding can be related to the key agent of the present research, papaverine, which can relax the smooth muscles of the blood vessels through different mechanisms.⁴⁵ Accordingly, a study in 2021 reported that, the radial artery diameter was higher in the group receiving papaverine than in the group receiving nitroglycerin,²⁰ so that the access to the artery would be easier.²¹ So, The main contributor to the distinctive effects of the present combination appears to be papaverine. Unfortunately, the aforementioned potential of this alkaloid has not been completely addressed in the available literature as it should be. Thus, further studies in this regard would be required.

Limitations

The limitations of this study include the small sample size and the inability to perform angiographic assessments of spasm occurrence. Therefore, we recommend that future studies be conducted with a larger sample size and utilizing angiographic factors alongside clinical factors for the diagnosis of spasms. Also, the complications following catheterization can be examined over a longer period post-procedure.

Conclusion

Current clinical trial demonstrated that the topical application of a combined gel containing diltiazem, lidocaine, and papaverine significantly increased the success rate of radial artery access. Additionally, this intervention led to a notable reduction in pain two hours post- catheterization and decreased hand numbness both immediately and two hours after the procedure in patients undergoing transradial coronary catheterization.

Ethical Issues

This study was registered in Iranian Clinical Trials Center (IRCT20231018059760N1). Additionally, the ethical code was obtained from Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1402.521). During this research, No pain, no costs, and no additional procedures were imposed on the patients. The participants entered the study with informed consent.

Data Sharing

The data of this study can be accessed on request from the corresponding author.

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Author Contributions

Amir Akbari Molkabadi: Writing - Original Draft, Investigation. **Kiarash Fekri:** Conceptualization, Supervision, Writing - Review & Editing. **Hamid Sharif-Nia:** Methodology, Formal Analysis. **Shahram Emami:** Resources, Writing - Review & Editing. **Hossein Dabbaghian:** Resources. **Roghieh Nazari:** Conceptualization, Supervision, Writing - Review & Editing.

Conflict of Interest

The authors report no conflicts of interest.

References

1. Ralapanawa U, Sivakanesan R. Epidemiology and the magnitude of coronary artery disease and acute coronary syndrome: A narrative review. *J Epidemiol Glob Health.* 2021;11:169-77. doi:10.2991/jegh.k.201217.001
2. Dehghani A, Roghani Dehkordi F. A comparative review of various interventional methods for coronary angiography and angioplasty. *J Basic Clin Pathophysiol.* 2019;7(2):12-9. doi:10.22070/jbcp.2019.4736.1121
3. Rao SV, Ou FS, Wang TY, Roe MT, Brindis R, Rumsfeld JS, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: A report from the national cardiovascular data registry. *JACC Cardiovasc Interv.* 2008;1(4):379-86. doi:10.1016/j.jcin.2008.05.007
4. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (rival): A randomised, parallel group, multicentre trial. *Lancet.* 2011;377(9775):1409-20. doi:10.1016/S0140-6736(11)60404-2
5. Nasiri M, Rahimian B, Larihani M, Norozi S. Survey the educational needs and quality of life of the patients with chronic myocardial infarction in emam sajjad

- hospital in ramsar. *Nurs Midwifery J.* 2008;6(3):145-50. doi:10.61186/unmf
6. Haq MAU, Rashid M, Gilchrist IC, Bertrand O, Kwok CS, Wong CW, et al. Incidence and clinical course of limb dysfunction post cardiac catheterization-a systematic review. *Circulation J.* 2018;82(11):2736-44. doi:10.1253/circj.CJ-18-0389
 7. Nairoukh Z, Jahangir S, Adjepong D, Malik BH. Distal radial artery access: The future of cardiovascular intervention. *Cureus.* 2020;12(3):e7201. doi:10.7759/cureus.7201
 8. Dandekar VK, Vidovich MI, Shroff AR. Complications of transradial catheterization. *Cardiovasc Revasc Med.* 2012;13(1):39-50. doi:10.1016/j.carrev.2011.08.005
 9. Kanei Y, Kwan T, Nakra NC, Liou M, Huang Y, Vales LL, et al. Transradial cardiac catheterization: A review of access site complications. *Catheter Cardiovasc Interv.* 2011;78(6):840-6. doi:10.1002/ccd.22978
 10. Rosencher J, Chaïb A, Barbou F, Arnould MA, Huber A, Salengro E, et al. How to limit radial artery spasm during percutaneous coronary interventions: The spasmolytic agents to avoid spasm during transradial percutaneous coronary interventions (spasm3) study. *Catheter and Cardiovasc Interv.* 2014;84(5):766-71. doi:10.1002/ccd.25163
 11. He GW, Yang CQ. Characteristics of adrenoceptors in the human radial artery: Clinical implications. *J Thorac Cardiovasc Surg.* 1998;115(5):1136-41. doi:10.1016/S0022-5223(98)70414-3
 12. Amoroso G, Kiemeneij F. Transradial access for primary percutaneous coronary intervention: The next standard of care? *Heart.* 2010;96(17):1341-4. doi:10.1136/hrt.2010.196824
 13. Goldberg SL, Renslo R, Sinow R, French WJ. Learning curve in the use of the radial artery as vascular access in the performance of percutaneous transluminal coronary angioplasty. *Catheter Cardiovasc Diagn.* 1998;44(2):147-52. doi:10.1002/(SICI)1097-0304(199806)44:2<147::AID-CCD5>3.0.CO;2-6
 14. Kwok CS, Rashid M, Fraser D, Nolan J, Mamas M. Intra-arterial vasodilators to prevent radial artery spasm: A systematic review and pooled analysis of clinical studies. *Cardiovasc Revasc Med.* 2015;16(8):484-90. doi:10.1016/j.carrev.2015.08.008
 15. Latsios G, Toutouzas K, Antonopoulos AS, Melidi E, Synetos A, Vogiatzi G, et al. Anesthetic ointment only (lidocaine/prilocaine) instead of injectable local lidocaine in trans-radial catheterization: A viable no-needle alternative. *J Interv Cardiol.* 2017;30(4):382-6. doi:10.1111/joic.12399
 16. Broka SM. Implications anesthésiologiques de l'abord radial en cardiologie interventionnelle. *Ann Cardiol Angeiol (Paris).* 2009;58(6):344-7. doi:10.1016/j.ancard.2009.10.005
 17. Youn YJ, Kim W-T, Lee J-W, Ahn S-G, Ahn M-S, Kim J-Y, et al. Eutectic mixture of local anesthesia cream can reduce both the radial pain and sympathetic response during transradial coronary angiography. *Korean Circ J.* 2011;41(12):726-32. doi:10.4070/kcj.2011.41.12.726
 18. Rinkinen J, Halvorson EG. Topical vasodilators in microsurgery: What is the evidence? *J Reconstr Microsurg.* 2017;33(1):1-7. doi:10.1055/s-0036-1592191
 19. Kumar R, Singh PK. Use of topical nitroglycerin and lidocaine in locally vasodilating the radial artery. *J Cardiovasc Dis Res* 2022;13(08):2970-5. doi:10.31838/jcdr.2022.13.08.386
 20. Said A, Maher M, Fathy W. The effect of peri-radial injection of papaverine versus nitroglycerine on radial artery diameter prior to cannulation. *Egypt J Hosp Med.* 2021;85(2):4344-7. doi:10.21608/ejhm.2021.209964
 21. Yazdi A, Zahed Mehr A, Khalilpur E. Effects of adding papaverine for the local anesthesia of the access site in the transradial approach for cardiac catheterization. *Iran Heart J.* 2019;20(2):6-12.
 22. Portero-Portaz JJ, Córdoba-Soriano JG, Gutiérrez-Díez A, Gallardo-López A, El-Assali DM, Expósito-Calamardo L, et al. Rationale and study design on the effectiveness of vasodilators and topical local anesthetics to prevent radial spasm. The e-radial trial. *REC Interv Cardiol.* 2022;4(3):193-8. doi:10.24875/recive.M22000279
 23. van Leeuwen MA, van der Heijden DJ, Hermie J, Lenzen MJ, Selles RW, Ritt MJ, et al. The long-term effect of transradial coronary catheterisation on upper limb function. *EuroIntervention.* 2017;12(14):1766-72. doi:10.4244/EIJ-D-15-00395
 24. Lazaridou A, Elbaridi N, Edwards RR, Berde CB. Pain assessment. Benzon HT, Raja SN, Liu SS, Fishman SM, Cohen SP, editors. *Essentials of pain medicine.* Amsterdam: Elsevier; 2018. doi:10.1016/B978-0-323-40196-8.00005-X
 25. Carlsson IK, Ekstrand E, Astrom M, Stihl K, Arner M. Construct validity, floor and ceiling effects, data completeness and magnitude of change for the eight-item hakir questionnaire: A patient-reported outcome in the swedish national healthcare quality registry for hand surgery. *Hand Ther.* 2021;26(1):3-16. doi:10.1177/1758998320966018
 26. Mirak SM, Talasaz AH, Jenab Y, Vatanara A, Amini M, Jalali A, et al. Novel combined topical gel of lidocaine-verapamil-nitroglycerin can dilate the radial artery and reduce radial pain during trans-radial angioplasty. *Int J Cardiol Heart Vasc.* 2021;32:100689. doi:10.1016/j.ijcha.2020.100689
 27. Dharma S, Kedev S, Patel T, Gilchrist IC, Rao SV. The predictors of post-procedural arm pain after transradial approach in 1706 patients underwent transradial catheterization. *Cardiovasc Revasc Med.* 2019;20(8):674-7. doi:10.1016/j.carrev.2018.09.006
 28. Ashrafi S, Alam S, Sultana A, Raj A, Emon NU, Richi FT, et al. Papaverine: A miraculous alkaloid from opium and its multimedicinal application. *Molecules*

- 2023;28(7):3149. doi:10.3390/molecules28073149
29. Choi E, Nahm FS, Han WK, Lee PB, Jo J. Topical agents: A thoughtful choice for multimodal analgesia. *Korean J Anesthesiol.* 2020;73(5):384-93. doi:10.4097/kja.20357
 30. van Leeuwen MA, van Mieghem NM, Lenzen MJ, Selles RW, Hoefkens MF, Zijlstra F, et al. The effect of transradial coronary catheterization on upper limb function. *JACC: Cardiovasc Interv.* 2015;8(4):515-23. doi:10.1016/j.jcin.2014.10.025
 31. Shah M, Kachhiya H, Tandel J, Chhalotiya U, Shah D, Patelia A, et al. A validated HPTLC method for quantification of a new combination containing lidocaine HCl and diltiazem HVL. *Discov Chem.* 2024;1(1):12. doi:10.1007/s44371-024-00014-w
 32. Molaei H, Yavari A, Khorasani G, Sedaghat M, Hosseini ZSS, Masoomzadeh M. Evaluating the effect of compound solution of papaverine, lidocaine, and heparin on vasodilation of vessels for microvascular anastomosis. *Indian J Surg.* 2024;86(4):795-800. doi:10.1007/s12262-023-03954-2
 33. Kim ED, El-Rashidy R, McVary KT. Papaverine topical gel for treatment of erectile dysfunction. *J Urol.* 1995;153(2):361-5.
 34. Burke SD, Vercler SJ, Ra'Net OB, Desmond PC, Rees YW. Local anesthesia before iv catheterization. *Am J Nurs.* 2011;111(2):40-5. doi:10.1097/01.NAJ.0000394291.40330.3c
 35. Halm MA. Effects of local anesthetics on pain with intravenous catheter insertion. *Am J Crit Care.* 2008;17(3):265-8. doi:10.4037/ajcc2008.17.3.265
 36. Ozawa Y, Hayashi K, Kobori H. New generation calcium channel blockers in hypertensive treatment. *Curr Hypertens Rev.* 2006;2(2):103-11. doi:10.2174/157340206776877370
 37. Ho HH, Jafary FH, Ong PJ. Radial artery spasm during transradial cardiac catheterization and percutaneous coronary intervention: Incidence, predisposing factors, prevention, and management. *Cardiovasc Revasc Med.* 2012;13(3):193-5. doi:10.1016/j.carrev.2011.11.003
 38. Beyer AT, Ng R, Singh A, Zimmet J, Shunk K, Yeghiazarians Y, et al. Topical nitroglycerin and lidocaine to dilate the radial artery prior to transradial cardiac catheterization: A randomized, placebo-controlled, double-blind clinical trial: The pre-dilate study. *Int J Cardiol.* 2013;168(3):2575-8. doi:10.1016/j.ijcard.2013.03.048
 39. Elattar MM, NBIomy R, Haseeb WA, Salama MK. Topical lidocaine and or/intravenous midazolam before radial coronary angiography to prevent radial artery spasm. *J Pak Med Assoc.* 2023;73(4):S103-S8. doi:10.47391/jpma.egy-s4-22
 40. Tatlı E, Yilmaztepe MA, Vural MG, Tokatlı A, Aksoy M, Ağaç MT, et al. Cutaneous analgesia before transradial access for coronary intervention to prevent radial artery spasm. *Perfusion.* 2018;33(2):110-4. doi:10.1177/0267659117727823
 41. Grassi G, Giannattasio C, Failla M, Pesenti A, Peretti G, Marinoni E, et al. Sympathetic modulation of radial artery compliance in congestive heart failure. *Hypertension.* 1995;26(2):348-54. doi:10.1161/01.hyp.26.2.348
 42. Narkiewicz K, Somers VK. Interactive effect of heart rate and muscle sympathetic nerve activity on blood pressure. *Circulation.* 1999;100(25):2514-8. doi:10.1161/01.cir.100.25.2514
 43. van Der Ster BJP, Sperna Weiland NH, Westerhof BE, Stok WJ, van Lieshout JJ. Modeling arterial pulse pressure from heart rate during sympathetic activation by progressive central hypovolemia. *Front Physiol.* 2018;9:353. doi:10.3389/fphys.2018.00353
 44. Harvey JA, Kim S, Ireson ME, Gulati R, Bell MR, Moran SL. Acute upper-limb complications following radial artery catheterization for coronary angiography. *J Hand Surg Am* 2020;45(7):655 e1-e5. doi:10.1016/j.jhsa.2019.11.007
 45. Nagaraja PS, Singh NG, Manjunatha N, Desai RC. Effect of periradial administration of papaverine on radial artery diameter. *Anesth Essays Res.* 2017;11(1):228-32. doi:10.4103/0259-1162.194579