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Original Article

Effects of Verapamil on the Reduction of Radial Artery Thrombosis after Coronary Angiography: A Randomized Clinical Trial

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Abstract

Background: *The trans-radial approach significantly reduces access bleeding and underlying vascular complications and is associated with lower health care costs than the transfemoral approach. One of the most common complications, however, is radial artery occlusion (RAO).*

Methods: *This study investigates the effects of verapamil on radial artery thrombosis in patients referred to Taleghani Hospital in Tehran between 2020 and 2021. Patients were randomized into 2 groups: the first group received verapamil, nitroglycerin, and heparin and the second group nitroglycerin and heparin. To randomly assign 100 cases to the 2 experimental and control groups, we first formed a framework for sampling 100 people (from 1 to 100); then, based on the table of random numbers, we assigned the first 50 numbers to the experimental group and the remainder to the control group. The 2 groups were compared for radial artery thrombosis.*

Results: *This study evaluated 100 candidates for coronary angiography in 2 groups of 50 with and without verapamil. The mean age was 58.6±11.2 years in the group with verapamil and 58.1±12.7 years in the group without verapamil (P=0.84). The difference between the 2 groups in terms of heart failure was statistically significant (P<0.028). The prevalence of clinical thrombosis was 2.0% in the group with verapamil and 22.0% in the group without verapamil (P<0.004). The prevalence of ultrasound-confirmed thrombosis was 4.0% in the group with verapamil and 36.0% in the group without verapamil (P<0.001).*

Conclusion: *Intra-arterial injection of verapamil added to heparin and nitroglycerine during trans-radial angiography could significantly reduce RAO.*

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Keywords: *Transradial approach; Verapamil; Radial artery thrombosis*

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Introduction

Nowadays, the trans-radial pathway is increasingly used for diagnostic and interventional cardiovascular interventions,[1] largely due to the evidence of an obvious reduction in accessibility complications of the transradial approach (TRA) compared with transfemoral access[2] and a reduction in costs. Observational and randomized studies have shown that the radial method significantly reduces access site bleeding and major vascular complications and is associated with lower healthcare costs than the transfemoral method.[3-6] Despite the numerous benefits of TRA, there are potential complications that can include local bleeding complications (eg, forearm hematoma), vascular complications (eg, false aneurysms), and in rare cases, radial artery perforation.[7]

Radial artery occlusion (RAO) is the most common complication after trans-radial catheterization, with a prevalence of 1% to 10%. Although RAO is rarely associated with the ischemia of the hand, it is a significant complication due to the prohibition of the future use of the trans-radial method and the prohibition of the use of radial artery bypass or venous arterial fistulae in dialysis patients.[8] This complication is the result of acute thrombosis due to wear of the inner lining and endothelial damage associated with decreased blood flow after the placement of the sheet and the catheter.[9] A significant proportion of these patients experience permanent destruction of the radial artery lumen.[10] RAO often does not cause ischemic symptoms due to extensive parallel blood flow through the palmar arch collaterals and forearm arterioles, preventing the early detection of this complication. Although the immediate effect of this condition may not be clinically apparent, RAO increases the challenges of cross-radial access in potential TRA cases in the future. Several pharmacological and non-pharmacological strategies, including the ratio of the sheath size to the lower artery,[11] intraoperative heparin use, and keeping the radial artery open during homeostasis after TRA,[12] have been shown to reduce the risk of RAO, and these are known as the best practices.[13] Despite these recommendations, the true prevalence of acute RAO is as high as, 10% according to reports from institutions specializing in TRA.[14] What should be considered, however, is the low likelihood of success, the difficulty for physicians and treatment staff, and the limited use of equipment (the hand artery diameter is about 3 mm in men and about 2 mm in women) compared with the femoral artery diameter (usually about 6 mm).[15] Calcium channel blockers can prevent the occurrence of RAO following TRA.

This study aimed to evaluate the use of verapamil to reduce the incidence of RAO induced by transradial angiography.

Methods

The study proposal was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (the code of ethics: IR.SBMU.MSP.REC.1399.570). The study was performed as a double-blind and randomized clinical trial. The study population was composed of candidates for radial angiography. Through the selection of a 95% confidence interval (CI), an 80% power, and a 30% effect size (average effect size in the Cohen equation) and the use of the G * Power software (version 3.1.9.2), the number of samples in each group was determined to be 44. Considering the probability of falling, 50 cases in each group were studied.[16] To randomly assign 100 cases to the 2 experimental and control groups, we first formed a framework for sampling 100 individuals (from 1 to 100). Subsequently, based on the table of random numbers, we assigned the first 50 numbers to the experimental group and the remainder to the control group. By referring to the study site, we placed eligible patients in the desired groups, according to the order of admission.

This study investigated the use of 2.5 mg verapamil on top of heparin (5000 IU) and nitroglycerine (100 µg) to reduce the incidence of RAO due to the transradial angiography of patients referred to Taleghani Hospital between 2020 and 2021. All the participants were informed about the research objectives, the research protocol, and the treatment options involved in the present study before they signed informed consent to participate.

The Allen test was performed at baseline in all the patients to confirm the existence of double circulation and the open palmar arch. The exclusion criteria included abnormal Allen tests and verapamil contraindications, such as a systolic blood pressure of less than 90 mmHg, a heart rate below 60 beats per minute, heart block, and heart failure (the ejection fraction <35%).

After filling out a designed questionnaire on patient characteristics, diagnosis, and medications, we divided the patients into 2 groups. In one group, after the insertion of a 6-F radial sheath, 5000 units of heparin and 100 µg of nitroglycerin were administered through the radial artery. The other group received 5000 units of heparin, 100 µg of nitroglycerin, and 2.5 mg of verapamil after the insertion of a 6-F radial sheath.[17] The characteristics of the sheaths and catheters used, the number of punctures, the puncture sites (the right or left radial artery), vital signs during the procedure, complications during the procedure, and the failure of the procedure (the femoral change rate) were recorded in a pre-designed questionnaire. Complications after angiography through the radial artery included bleeding, radial artery thrombosis, venous arterial fistulae, hematoma (grade I: 5 cm above the wrist, grade II: 10 cm above the wrist, grade III: forearm involvement, and grade IV: arm involvement), and compartment syndrome. The 2 groups

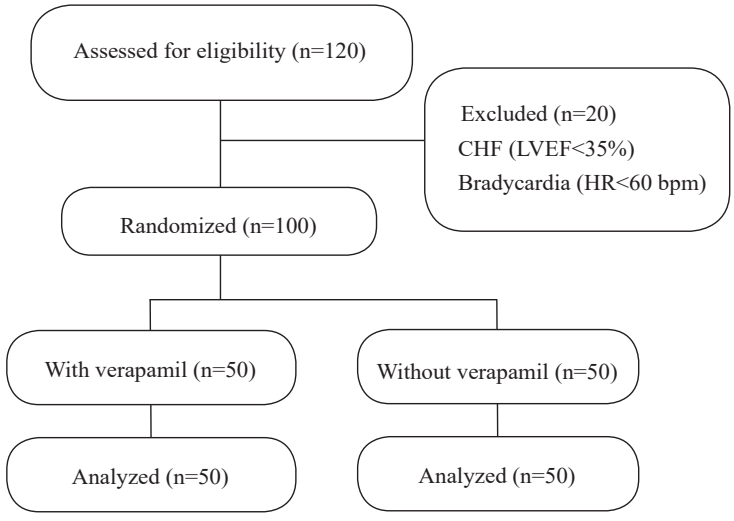

Figure 1. The image depicts the CONSORT flow diagram of the study.
CHF, Congestive heart failure; HR, Heart rate; LVEF, Left ventricular ejection fraction

were also evaluated for lack of pulse on examination and ultrasound-confirmed thrombosis.

The primary outcome was radial artery thrombosis the day after angiography confirmed by Doppler ultrasound. The data collection method was based on questionnaire filling, trans-radial angiography, and color and Doppler ultrasound performed during the course. The data obtained were entered into the SPSS 16 software. After the information was summarized, descriptive statistics were presented with the help of the mean and the standard deviation for quantitative data and frequencies and percentages for qualitative data. For the examination of the relationship between drug use and thrombosis, analytical statistics, including the t-test and the χ^2 test, were used. Descriptive statistical methods, such as percentage calculations, the mean, and the standard deviation, were employed to describe the data. The significance level in the tests was considered 0.05.

Results

The mean age was 58.6±11.2 years in the group with verapamil and 58.1±12.7 years in the group without verapamil (P=0.840). A comparison of the 2 groups in terms of qualitative variables is shown in Table 1. The difference between the 2 groups concerning heart failure was statistically significant (P<0.028).

The complication rates are presented in Table 2. The difference between the 2 groups was significant regarding the composite complications of hematoma and pain (P<0.026), lack of pulse on examination (P<0.004), and ultrasound-confirmed thrombosis (P<0.001).

Significant complications of verapamil injection, including permanent hypotension and heart rates below 60 beats per minute, were not observed in the patients. The procedure was successful in all the cases. (There was no change in the femoral method.)

RAO occurred in 10 patients (50.0%) with 1 radial puncture attempt and 10 patients (50.0%) patients with more than 1 radial puncture attempt. RAO occurred in none of the patients with the use of a special radial catheter (the Tiger type) and in 20 patients with the use of right and left catheters. Ten patients (50.0%) with RAO were first punctured, and 61 patients (76.0%) without RAO were first punctured (P=0.031).

The intra-arterial injection of verapamil added to heparin and nitroglycerine during trans-radial angiography significantly decreased RAO.

Discussion

The main finding of the present study vis-à-vis the RAO rate was that it occurred in 20.0% of the entire study population, 4.0% of patients with verapamil, and 36.0% of patients without verapamil. The use of verapamil was associated with a significant reduction in radial artery thrombosis and complications such as hematoma and pain. Significant complications of verapamil injection, including permanent hypotension and heart rates below 60 beats per minute, were not observed in the studied patients, and the procedure was successful (there was no change in the femoral method) in all the cases.

In the 2018 VERMUT study by Tebaldi et al,[17] comparing verapamil and heparin as adjunctive therapy for trans-radial

Table 1. Clinical characteristics of the group received verapamil and control group

Variables	With Verapamil (n=50)	Without Verapamil (n=50)	P
Sex			0.881
Male	32 (64.0)	32 (64.0)	
Female	18 (36.0)	18 (36.0)	
HTN	24 (48.0)	26 (52.0)	0.842
Diabetes	18 (36.0)	10 (20.0)	0.118
HLP	13 (26.0)	11 (22.0)	0.815
HF	2 (4.0)	10 (20.0)	0.028
Smoking	22 (44.0)	13 (26.0)	0.093
History of MI	3 (6.0)	4 (8.0)	0.662
History of radial angiography	5 (10.0)	5 (10.0)	0.672
Diagnosis			0.620
SIHD	37 (74.0)	33 (66.0)	
UA	9 (18.0)	13 (26.0)	
MI	4 (8.0)	4 (8.0)	
Medicines			
Concomitant CCB use	3 (6.0)	2 (4.0)	0.580
Concomitant BB use	12 (24.0)	15 (30.0)	0.650
Concomitant NG use	7 (14.0)	4 (8.0)	0.520
Concomitant ACE-I use	21 (42.0)	20 (40.0)	0.828
Concomitant ASA use	29 (58.0)	25 (50.0)	0.552
Concomitant statin use	30 (60.0)	26 (52.0)	0.550
Type of Catheter			0.012
TIG	12 (24.0)	3 (6.0)	
Left and right	38 (76.0)	44 (88.0)	
Guiding	0 (0)	3 (6.0)	
Right Catheter Size			0.552
5 F	29 (76.3)	35 (79.5)	
6 F	9 (23.7)	9 (20.5)	
left Catheter Size			0.822
5 F	23 (60.5)	28 (63.6)	
6 F	15 (39.5)	16 (36.4)	
Number of Punctures			0.786
1	35 (70.0)	36 (72.0)	
>1	15 (30.0)	14 (28.0)	
Location of Punctures			0.929
Right radial	49 (98.0)	50 (100)	
Left radial	1 (2.0)	0 (0)	
Type of Procedures			0.206
CAG	44 (88.0)	38 (76.0)	
CAG + angioplasty	4 (8.0)	8 (16.0)	
Angioplasty	1 (2.0)	4 (8.0)	
CAG + FFR	1 (2.0)	0 (0)	

HTN, Hypertension; HLP, Hyperlipidemia; HF, Heart failure; MI, Myocardial infarction; SIHD, Stable ischemic heart disease; UA, Unstable angina; BB, β-blocker; CCB, Calcium channel blocker; NG, Nitroglycerin; ACE-I, Angiotensin-converting enzyme inhibitors; TIG, Tiger; CAG, Coronary angiography; FFR, Flow fraction ratio

Table 2. Complication rates in group received verapamil vs. control group

Variables	With Verapamil (n=50)	Without Verapamil (n=50)	P
Complications			0.026
Hematoma	0 (0)	3 (6.0)	
Pain	1 (2.0)	6 (12.0)	
None	49 (98.0)	41 (82.0)	
Lack of pulse	1 (2.0)	11 (22.0)	0.004
Thrombosis on sonography	2 (4.0)	18 (36.0)	0.001
Type of Thrombosis			0.447
Complete	1 (50.0)	14 (77.8)	
Partial	1 (50.0)	4 (22.2)	

coronary procedures, 418 patients underwent trans-radial coronary artery bypass grafting 1: 1 to receive intra-radial verapamil (5 mg) or heparin (5000 IU) after 6-F sheath insertion. The primary outcome was defined as a 24-hour occurrence of RAO (ultrasound confirmation), site access complications, and radial artery spasm requiring vasodilator rescue. Local administration of verapamil versus heparin reduced radial artery spasm without increasing RAO, strictly related to the radial artery diameter and the hemostasis time. In our study, although we examined fewer samples, verapamil reduced RAO. Additionally, we did not evaluate the effects of the radial artery diameter and the homeostasis time.

In 2019, Sadaka et al[18] assessed the incidence and prognosis of RAO after transradial coronary catheterization on 164 patients. They performed Doppler ultrasound evaluations of the radial artery on the first day and 6 months after surgery. On day 1, the Doppler examination showed RAO in 54 patients (32.9%), while after 6 months, RAO was diagnosed in 49 patients (29.9%). Interestingly, only 1 new case (0.9%) of RAO was observed, and 6 patients (11.1%) regained their radial artery opening. Based on their multivariate analysis, the female sex, age, manual compression, and radial artery diameter were independent predictors of RAO. The use of the transradial band for homeostasis for only 2 hours was recognized as a strong independent predictor. The authors concluded that although RAO was a clinically silent issue, it was a major complication after TRA; moreover, patients with a high RAO prognosis required careful management and follow-up to ensure long-term radial artery opening. In our study, we evaluated fewer samples, and RAO was a significant complication observed in 20% of the studied patients. Nonetheless, in our study, age and sex did not play a role in RAO.

In a 2013 study by Filho et al,[19] patients were randomly assigned to receive a placebo (G1) or diltiazem (GII) through a catheter inserted into a radial artery. Ultrasound examination was performed before the test and 30 minutes and 7 days after the test to evaluate the flow, diameter, and outlet of the artery. Complications, including spasm, obstruction, and partial obstruction, occurred in 4 patients in the GI group and none of the patients in the GII group (P=0.04). In conclusion, the authors stated that their study showed a reduction in vascular complications through trans-radial access for coronary angiography using the antispasmodic drug diltiazem, which significantly increased the diameter of the radial artery and its outlet. The results of our study are consistent with theirs insofar as verapamil had fewer side effects.

In 2015, Tian et al[20] examined the risk factors for radial artery pulse weakness and its predictive value for RAO after trans-radial angiography. Additionally, they sought to determine what could effectively maintain the radial artery flow. Their results revealed that after the intervention using transradial coronary intervention, a weaker radial artery pulse was an imminent indicator of RAO. Furthermore, continuous compression of the ipsilateral radial artery was an effective approach to maintaining radial artery opening. The results of our study are consistent with theirs insofar as the lack of the radial artery pulse was an imminent indicator of RAO.

In 2010, Zankl et al[21] evaluated 488 patients for the effects of anticoagulant therapy the day after trans-radial coronary angiography on RAO (the radial artery opening rate). RAO was seen in 51 patients (10.5%) 1 day after angiography. In addition, symptoms were seen at the angiographic site in 30 patients (58.8%), while 21 patients (41.2%) had no symptoms. The symptomatic patients were treated with low-molecular-weight heparin for 4 weeks. After 4 weeks of treatment, 26 patients (86.7%) in the symptomatic group showed partial or complete recanalization of the radial artery compared with 4 patients (19.1%) in the asymptomatic group not treated with anticoagulants. In conclusion, the authors stated that RAO was a common complication after transradial coronary angiography. The prevalence of RAO was underestimated due to the presence of asymptomatic patients. In our study, RAO was a common complication: it occurred in 20 patients (20%) 1 day after angiography, which is higher than the rate in the investigation by Zankl and colleagues.

The salient limitation of the present study is its relatively small number of patients (because of the significant impact of COVID-19 on the number of patients referred for elective angiography). Two other noteworthy limitations are the lack of a long-term follow-up of patients and the non-exclusion of the effect of the catheter type (1 vs 2 catheters) used for radial angiography.

Conclusion

The intra-arterial injection of verapamil added to heparin and nitroglycerine during trans-radial angiography was associated with a significant reduction in RAO.

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References

1. Feldman DN, Swaminathan RV, Kaltenbach LA, Baklanov DV, Kim LK, Wong SC, Minutello RM, Messenger JC, Moussa I, Garratt KN, Piana RN, Hillegass WB, Cohen MG, Gilchrist IC,

Rao SV. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007-2012). Circulation 2013;127:2295-2306.
2. Bertrand OF, Bélisle P, Joyal D, Costerousse O, Rao SV, Jolly SS, Meerkin D, Joseph L. Comparison of transradial and femoral approaches for percutaneous coronary interventions: a systematic review and hierarchical Bayesian meta-analysis. Am Heart J 2012;163:632-648.
3. Amin AP, House JA, Safley DM, Chhatriwalla AK, Giersiefen H, Bremer A, Hamon M, Baklanov DV, Aluko A, Wohns D, Mathias DW, Applegate RA, Cohen DJ, Marso SP. Costs of transradial percutaneous coronary intervention. JACC Cardiovasc Interv 2013;6:827-834.
4. Cooper CJ, El-Shiekh RA, Cohen DJ, Blaesing L, Burket MW, Basu A, Moore JA. Effect of transradial access on quality of life and cost of cardiac catheterization: A randomized comparison. Am Heart J 1999;138(3 Pt 1):430-436.
5. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J 2009;157:132-140.
6. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, Budaj A, Niemelä M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S, Mehta SR; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409-1420.
7. Shroff A, Siddiqui S, Burg A, Singla I. Identification and management of complications of transradial procedures. Curr Cardiol Rep 2013;15:350.
8. Avdikos G, Karatasakis A, Tsoumeleas A, Lazaris E, Ziakas A, Koutouzis M. Radial artery occlusion after transradial coronary catheterization. Cardiovasc Diagn Ther 2017;7:305-316.
9. Uhlemann M, Möbius-Winkler S, Mende M, Eitel I, Fuernau G, Sandri M, Adams V, Thiele H, Linke A, Schuler G, Gielen S. The Leipzig prospective vascular ultrasound registry in radial artery catheterization: impact of sheath size on vascular complications. JACC Cardiovasc Interv 2012;5:36-43.
10. Pancholy SB. Transradial access in an occluded radial artery: new technique. J Invasive Cardiol 2007;19:541-544.
11. Saito S, Ikei H, Hosokawa G, Tanaka S. Influence of the ratio between radial artery inner diameter and sheath outer diameter on radial artery flow after transradial coronary intervention. Catheter Cardiovasc Interv 1999;46:173-178.
12. Pancholy S, Coppola J, Patel T, Roke-Thomas M. Prevention of radial artery occlusion-patent hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional versus patency documented hemostasis after transradial catheterization. Catheter Cardiovasc Interv 2008;72:335-340.
13. Rao SV, Tremmel JA, Gilchrist IC, Shah PB, Gulati R, Shroff AR, Crisco V, Woody W, Zoghbi G, Duffy PL, Sanghvi K, Krucoff MW, Pyne CT, Skelding KA, Patel T, Pancholy SB; Society for Cardiovascular Angiography and Intervention's Transradial Working Group. Best practices for transradial angiography and intervention: a consensus statement from the society for cardiovascular angiography and intervention's transradial working group. Catheter Cardiovasc Interv 2014;83:228-236.
14. Sciahbasi A, Rigattieri S, Sarandrea A, Cera M, Di Russo C, Fedele S, Romano S, Penco M, Rocco Pugliese F. Radial artery occlusion and hand strength after percutaneous coronary procedures: Results of the HANGAR study. Catheter Cardiovasc Interv 2016;87:868-874.
15. Ferrante G, Rao SV, Jüni P, Da Costa BR, Reimers B, Condorelli G, Anzuini A, Jolly SS, Bertrand OF, Krucoff MW, Windecker S, Valgimigli M. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. JACC Cardiovasc Interv 2016;9:1419-1434.
16. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-191.
17. Tebaldi M, Biscaglia S, Tumscitz C, Del Franco A, Gallo F, Spitaleri G, Fileti L, Serenelli M, Tonet E, Erriquez A, Campo G, Ferrari R. Comparison of Verapamil versus Heparin as Adjunctive Treatment for Transradial Coronary Procedures: The VERMUT Study. Cardiology 2018;140:74-82.
18. Sadaka MA, Etman W, Ahmed W, Kandil S, Eltahan S. Incidence and predictors of radial artery occlusion after transradial coronary catheterization. Egypt Heart J 2019;71:12.
19. Mont'Alverne Filho JR, Assad JA, Zago Ado C, da Costa RL, Pierre AG, Saleh MH, Barretto R, Braga SL, Feres F, Sousa AG, Sousa JE. Comparative study of the use of diltiazem as an antispasmodic drug in coronary angiography via the transradial approach. Arq Bras Cardiol 2003;81:59-63.
20. Tian J, Chu YS, Sun J, Jiang TM. Ulnar artery compression: a feasible and effective approach to prevent the radial artery occlusion after coronary intervention. Chin Med J (Engl) 2015;128:795-798.
21. Zankl AR, Andrassy M, Volz C, Ivandic B, Krumsdorf U, Katus HA, Blessing E. Radial artery thrombosis following transradial coronary angiography: incidence and rationale for treatment of symptomatic patients with low-molecular-weight heparins. Clin Res Cardiol 2010;99:841-847.