

Different Spasmolytic Regimens (Nitroglycerin vs Verapamil) and the Incidence of Radial Artery Occlusion After Transradial Catheterization

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Different Spasmolytic Regimens (Nitroglycerin vs Verapamil) and the Incidence of Radial Artery Occlusion After Transradial Catheterization

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ABSTRACT: Objective. This study evaluated whether use of different spasmolytic regimens (nitroglycerin or verapamil) administered soon after sheath insertion affects postprocedural radial artery occlusion (RAO) in patients who underwent transradial catheterization. **Methods and Results.** We performed a *post hoc* analysis of a randomized trial evaluating the use of 500 µg intra-arterial nitroglycerin just before sheath removal in 1706 patients undergoing transradial catheterization. Patients who received 200 µg or 300 µg nitroglycerin after sheath placement (group A; n = 688) were compared with patients who received 5 mg verapamil after sheath placement (group B; n = 1018). The primary endpoint was RAO diagnosed by Doppler ultrasound examination at 1 calendar day after the procedure. Logistic regression was used to determine predictors of RAO. RAO occurred in 16.0% of group A and 5.4% of group B. After adjustment for potential confounders, neither the use of verapamil nor nitroglycerin was associated with RAO [odds ratio (OR), 1.24; 95% confidence interval (CI), 0.51-3.02; *P* = .62]. Radial artery compression >4 hours was the strongest predictor of RAO (OR, 5.41; 95% CI, 2.31-12.65; *P* < .001). **Conclusions.** In this study, the use of verapamil or nitroglycerin as a spasmolytic regimen was not associated with RAO. Given the strong association between duration of radial compression and RAO, further studies are needed to determine the interaction between vasodilator agents and compression protocols on RAO.

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KEY WORDS: radial artery occlusion, spasmolytic regimen, transradial catheterization

Radial artery occlusion (RAO) after transradial catheterization is a major limitation of transradial access¹⁻³ that limits the future use of the occluded radial artery for further transradial catheterization, dialysis shunt, or bypass graft conduit. Postprocedural/prehemostasis intra-arterial nitroglycerin has been shown to reduce RAO after transradial catheterization.⁴ Whether the administration of different spasmolytic regimens soon after sheath insertion may affect the incidence of RAO is not known. We evaluated the use of different spasmolytic regimens (nitroglycerin or verapamil) and their association with the incidence of RAO in patients undergoing transradial catheterization at three experienced radial centers.

Methods

This study is a *post hoc* analysis from a randomized trial (n = 1706) conducted at three experienced radial centers in Indonesia, India, and Macedonia that compared the efficacy of 500 µg intra-arterial nitroglycerin against saline placebo prior to sheath removal on RAO.⁴ In the current analysis, patients were divided based on the type of preprocedural spasmolytic regimen administered immediately after sheath insertion: group A (n = 688) received 200 µg or 300 µg nitroglycerin and group B (n = 1018) received 5 mg verapamil. The incidence of RAO was compared between two groups. The study flow chart is displayed in Figure 1. The study was approved by the local institutional review board at each participating hospital.

Spasmolytic regimen administration. The choice of regimen was left to the discretion of the individual operators and was not blinded. Group A patients received 200 µg or 300 µg nitroglycerin diluted in 1-2 mL saline through the radial introducer sheath, while group B patients received 5 mg verapamil diluted in 10 mL of saline mixed with blood administered through the radial sheath, both immediately after sheath insertion.

Postprocedural/prehemostasis intra-arterial nitroglycerin and hemostasis. Postprocedural/prehemostasis nitroglycerin was given after the sheath was partially removed, leaving 2-3 cm in the radial artery in order to deliver the nitroglycerin in the intended area (puncture site). The saline placebo solution was delivered with a similar technique and identical syringe as the nitroglycerin group.⁴ The hemostatic compression device was applied immediately after sheath removal and patent hemostasis was applied in all patients soon after the compression.

RAO evaluation. RAO was evaluated by Doppler ultrasound examination of the accessed forearm at 1 calendar day after the transradial catheterization. The absence or presence of antegrade flow in the radial artery was examined while compressing the ulnar artery, as previously described.⁴

Study outcome and definition. The primary study outcome was the incidence of RAO at 1 day post procedure, as confirmed by the absence of antegrade flow of the radial artery by Doppler evaluation. Secondary outcomes were severe radial artery

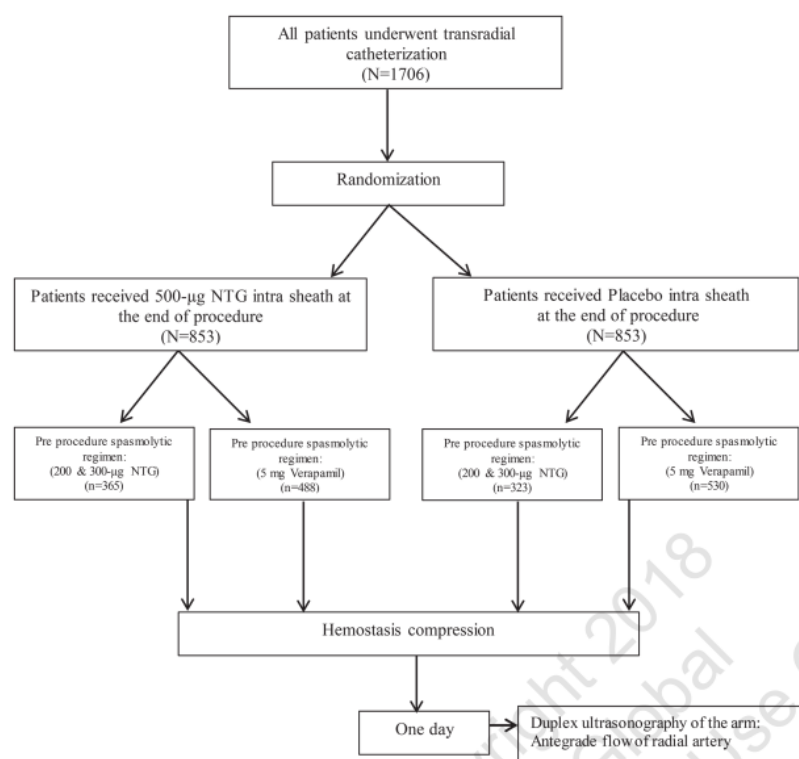


FIGURE 1. Study flow chart. NTG = nitroglycerin.

spasm (RAS) during the procedure and radial artery diameter examined by Doppler evaluation at 1 day post procedure.

Demographic and procedural data were recorded from the database. Multiple puncture attempts were defined as >1 attempt at puncturing the radial artery.⁴ Severe RAS was defined as severe local pain and discomfort during catheter movement compelling the operator to stop the procedure and cross over to another route.⁵

Statistical analysis. Patients were divided into two groups based on the spasmolytic regimen used (nitroglycerin or verapamil). The differences between the groups were compared. Continuous data were presented as mean \pm standard deviation or median (interquartile range) and compared by t-test or Mann-Whitney U-test, as appropriate. Categorical data were presented as percentages and differences were compared by chi-square test or Fischer's exact test, as appropriate. Logistic regression analyses were used to find the predictors of RAO. Covariates included in the model were use of verapamil as an indicator variable ('yes' indicating the use of verapamil, 'no' indicating the use of nitroglycerin), use of >6 Fr sheath, diabetes mellitus, body mass index <25 kg/m², male gender, age >65 years, duration of hemostasis, multiple puncture attempts, and RAS. A P-value <.05 was considered statistically significant. Statistical analyses were performed using SPSS 17.0.

Results

Baseline and procedural characteristics. Patients in the verapamil group were older, less often male, more likely to have had a prior percutaneous coronary intervention, had a sheath >6 Fr, had longer procedural times, and were less likely to have a TR Band used. A smaller proportion of verapamil patients had hemostasis compression time >4 hours than the nitroglycerin group. Body mass index was higher in the verapamil group than the nitroglycerin group. Other baseline and procedural characteristics are displayed in Table 1.

Study outcome. The unadjusted incidence of RAO was 16.0% in the nitroglycerin group and 5.4% in the verapamil group (Table 2). Multivariable modeling for predictors of RAO showed that the type of spasmolytic regimen was not associated with RAO (odds ratio [OR], 1.24; 95% confidence interval [CI], 0.51–3.02; $P=.62$). Hemostatic compression >4 hours was strongly associated with RAO (OR, 5.41; 95% CI, 2.31–12.65; $P<.001$) (Table 3). With respect to secondary outcomes, the

incidence of severe RAS during the procedure was lower in the verapamil group. The median radial artery diameter measured at 1 day post procedure was larger in the nitroglycerin group than the verapamil group (Table 2).

Discussion

Our previous study showed that the administration of 500 µg intra-arterial nitroglycerin at the end of the radial procedure reduced the incidence of RAO by 38%.⁴ The main finding of the present study showed that the use of different spasmolytic regimens (nitroglycerin or verapamil) at the initiation of the procedure did not affect the incidence of RAO after transradial catheterization. This suggests that the administration of spasmolytic regimens at the beginning of the radial procedure has no association with RAO of the accessed radial artery.

In a common radial practice, an intra-arterial spasmolytic regimen is frequently administered prophylactically to prevent RAS. A spasmolytic regimen (eg, verapamil) inhibits the calcium ion influx through slow channels into conductile and contractile vascular smooth muscle cells.⁸ In humans, intra-arterial infusion of verapamil is eliminated bi-exponentially, with a rapid early distribution phase (half-life, ~4 minutes) and a slower terminal elimination phase (half-life, 2–5 hours).

Table 1. Baseline characteristics based on spasmolytic regimen (n = 1706).

Variables	Nitroglycerin Group (n = 688)	Verapamil Group (n = 1018)	P-Value
Baseline characteristics			
Male gender	521 [76%]	646 [63%]	<.001
Age [years]	56 ± 10.8	61 ± 9.5	<.001
Body mass index [kg/m ²]	25.5 [23.4-28.3]	25.9 [24.1-28.4]	.01
Diabetes mellitus	208 [30%]	205 [20%]	<.001
Procedure			
Coronary angiography	497 [72%]	528 [51%]	<.001
PCI	190 [27%]	487 [48%]	<.001
Others	1 [0.1%]	3 [0.3%]	.65
Procedural characteristics			
Right radial access	675 [98%]	1009 [99%]	.07
Multiple puncture attempts	96 [14%]	111 [11%]	.05
Sheath size			
5 Fr	438 [63%]	58 [5%]	<.001
6 Fr	250 [36%]	957 [94%]	<.001
7 Fr	0 [0%]	2 [0.1%]	.51
8 Fr	0 [0%]	1 [0.09%]	>.99
Procedural time (min)	9 [5-23]	25 [15-40]	<.001
Hemostatic compression >4 hours	551 [80%]	2 [0.2%]	<.001
Use of TR band	568 [82%]	741 [73%]	<.001

Data provided as mean ± standard deviation, number (percentage), or median (range).

PCI = percutaneous coronary intervention; IU = international unit.

The peak therapeutic effect of verapamil occurs within 3–5 minutes after a bolus injection.⁸ Other spasmolytic regimens, such as nitroglycerin, also have an immediate effect after intravenous infusion and a rapid plasma half-life (~3 minutes).⁹ It produces vasodilation by directly relaxing vascular smooth muscle cells in the arterial walls by activation of cyclic guanosine monophosphate.¹⁰ The short half-life of nitroglycerin and the relatively low systemic dose of verapamil may be related to why initial spasmolytic regimens did not affect the patency of the radial artery during hemostasis.

Similar with our previous findings, severe RAS was not associated with the incidence of RAO (Table 3), although we found that patients who received verapamil had lower incidence of severe RAS (Table 2). These results emphasize that RAS may not play a major role in the development of RAO. This study also found that patients in the nitroglycerin group had larger median radial artery diameters than the verapamil

Table 2. Study outcomes.

	Nitroglycerin Group (n = 688)	Verapamil Group (n = 1018)	P-Value
Presence of RAO	115 [16%]	55 [5.4%]	<.001
Radial artery diameter (mm)	2.95 [2.5-3.5]	2.79 [2.5-3.0]	<.001
Severe RAS	9 [1.3%]	4 [0.4%]	.03

RAO = radial artery occlusion; RAS = radial artery spasm.

Table 3. Multivariate predictors of radial artery occlusion.

	Odds Ratio	95% Confidence Interval	P-Value
Use of verapamil	1.24	0.51-3.02	.62
Use of >6 Fr sheath	0.97	0.64-1.48	.91
Diabetes mellitus	1.15	0.80-1.65	.44
Body mass index <25 kg/m ²	0.80	0.57-1.13	.21
Male gender	1.0	0.69-1.45	.96
Age >65 years	1.17	0.80-1.72	.4
Hemostatic compression >4 hours	5.41	2.31-12.65	<.001
Multiple puncture attempts	0.93	0.54-1.59	.79
Severe RAS	2.34	0.68-8.04	.17

BMI = body mass index; RAS = radial artery spasm.

group, as assessed by Doppler ultrasound examination (2.95 mm vs 2.79 mm, respectively; $P < .001$) (Table 2). However, the effect of spasmolytic regimen on radial artery dilation needs to be further investigated.

The results of this study provide the insight that in experienced radial centers (>90% radial procedures in the lab) with experienced radial operators (performing >300 radial procedures/year), the use of a spasmolytic regimen for spasm prophylaxis needs to be reconsidered. A randomized study found that spasmolytic regimen did not significantly reduce the incidence of RAS as compared with patients who did not receive spasmolytic regimen.¹¹ Furthermore, an international survey across 75 countries showed that nearly 14% of operators do not use a prophylactic vasodilator for transradial procedures.⁷ One possible explanation is that experienced radial operators may need less catheter manipulation, leading to a lower incidence of severe RAS. The routine use of a spasmolytic regimen may be indicated in training centers where residents or fellows are developing their radial techniques, or in centers less experienced with radial techniques. In daily transradial practice, the primary use of a spasmolytic regimen is as a prophylactic measure to prevent RAS when using large-bore catheters (eg, >6 Fr) or after a routine patient complains of arm pain related to RAS.

The multivariate analyses from this study further confirm the previously noted association of hemostasis duration with

RAO.^{4,12,13} Regardless of the type of preprocedure spasmolytic cocktail used, early hemostasis (<4 hours) is strongly associated with less RAO after transradial procedures.^{4,12}

Randomized controlled trials have shown that adequate dose of anticoagulation,^{14,15} early hemostasis,¹² patent hemostasis,¹⁶ ulnar compression during radial hemostasis,¹⁷ and postprocedural/prehemostasis intra-arterial nitroglycerin⁴ are currently the best practices for reducing RAO after a transradial procedure. Whether all the techniques applied to a patient with transradial catheterization will result in a dramatic reduction of RAO needs to be investigated in detail. Meanwhile, future studies focusing on the role of different vasodilator agents administered just before hemostasis or added during hemostasis are potential areas of further research to reduce the incidence of RAO.

Study limitations. This study was a *post hoc* analysis of our previously published study. The administration of spasmolytic regimen (verapamil or nitroglycerin) was not randomized; therefore, any conclusions should be drawn with caution and are hypothesis-generating for future studies. Moreover, the preprocedure regimens were not blinded, and the hemostasis protocols were not uniform. We also could not determine whether radial artery patency was maintained during the hemostasis procedure.

Conclusion

In this study, neither verapamil nor nitroglycerin as a spasmolytic regimen was associated with RAO after transradial catheterization. Given the strong association between duration of radial compression and RAO, further studies are needed to determine the interaction between vasodilator agents and compression protocols on RAO.

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