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Original Article

Effects of Adding Papaverine for the Local Anesthesia of the Access Site in the Transradial Approach for Cardiac Catheterization

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ABSTRACT

Background: Transradial coronary arteriography has been developed as the first method of choice for interventional procedures in many centers, and its feasibility and safety contribute to its popularity. Gaining access is the main step in radial artery arteriography. We sought to evaluate the efficacy of the preprocedural administration of papaverine in diminishing arteriography complications.

Methods: A total of 120 patients were enrolled in the present study. The study population was divided into 2 equal groups of 60 patients. One group was catheterized with the preprocedural administration of papaverine, and the other group was administered traditional TNG. The groups were thereafter compared in terms of the administration of papaverine versus traditional TNG.

Results: No significant difference was observed between the 2 groups concerning failure to gain radial access. There was a significant difference in the time to gain access (P=0.016) and in the number of tries to gain access (P=0.007) between the study groups, and both of these values were lower in the papaverine group. Subgroup analysis revealed that the time to gain access was significantly lower in the male patients (P=0.035), younger patients (P=0.008), and smokers (P=0.043). There was also a significant difference in favor of the papaverine administration with respect to the operator's experience in the low-volume operators. Additionally, a shorter procedure time was observed in the papaverine group, which was more meaningful in the nondiabetic and nonhypertensive cases.

Conclusions: The preprocedural administration of papaverine in radial artery angiography confers benefits and could, thus, be a suitable substitution for traditional TNG with a view to diminishing the undesirable consequences of radial artery catheterization. ***(Iranian Heart Journal 2019; 20(2): 6-12)***

KEYWORDS: Radial artery catheterization, Papaverine, TNG, Vascular side effects

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The safety and feasibility of the transradial approach for cardiac catheterization and intervention have been well established.[1] Successful access to the radial artery needs experienced operators, and the traditional method of obtaining access by palpation is widely deemed a trial and error process. An unsuccessful attempt at accessing the radial artery can cause radial artery spasm.[2] The range of successful first-attempt radial access with palpation guidance differs from 13.8% to 68.6%, which can even be further complicated in some patients such as female patients, hypotensive patients, and obese patients. These cases often necessitate multiple tries, thereby causing more vascular complications.[3]

If there are spasm and hematoma in the radial artery, femoral access may be preferred; the latter, however, fails to deliver the benefits of the transradial approach. Crossover to femoral access and the transradial approach failure most often occur due to insufficient puncture in 57% and radial spasm in 17% of cases.[4]

Previous research suggests that any intervention capable of improving the palpation and localization of the radial puncture site may reduce the failure rate by more than 70%. Accordingly, we hypothesized that the use of a vasodilator agent could augment the accuracy of identifying the radial pulse access site and, thus, improve the success rate. We chose papaverine because of its unique features inasmuch as it is a non-selective phosphodiesterase inhibitor obtained from opium "poppy". It has been previously demonstrated that papaverine can increase cGMP and cAMP in smooth muscles.[5] Intraluminal papaverine is frequently used for the prevention of spasm before coronary revascularization via the radial artery approach.[6]

A comparative study of the vasodilatory reactions of the radial artery to different agents showed that papaverine was as effective as nitroglycerine.[7] It has also been previously reported that papaverine administration can relieve severe radial artery spasm induced by a trapped intraluminal guide-wire whenever intra-arterial verapamil and nitrates fail.[8]

Catecholamine release due to stress or a reduced cardiac function can intensify the radial artery spasm. Nitroglycerin in an anti-spasmolytic cocktail has a short half-life, and other agents such as calcium-channel blockers are not safe in many cardiac conditions. In contrast, papaverine has a longer half-life (about 100 min), and an in vitro study showed its effectiveness in vasoconstriction prevention mediated by intrinsic epinephrine or dopamine.[9] Since the majority of coronary angiographies and interventions end before 100 minutes, papaverine can be used to lessen the radial artery spasm during the whole procedure.

Papaverine is used via the subcutaneous route before the evaluation of microangiopathy in diabetic patients and increasing vascular transmural pressure in generalized scleroderma.[10,11]

No interaction has been reported for the combination of papaverine and lidocaine, and it is used (up to 300 mg) in intra-arterial infusions in cerebral vasospasm with no adverse effects.[12,13,14]

METHODS

This study was a randomized double-blinded parallel-group clinical trial. The study protocol was approved by the Research Department and the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran.

Patients were enrolled from among those who were clinically indicated for diagnostic or interventional coronary artery catheterization in Rajae Cardiovascular, Medical, and Research Center; and they were selected based on our inclusion/exclusion criteria (Table 1). Written informed consent was obtained from the entire study population. The inclusion criteria were comprised of clinical candidacy for the transradial access and provision of written

informed consent; and the exclusion criteria consisted of atrioventricular blocks, any QRS prolongation >120 ms, Parkinson's disease (using levodopa), prolonged QT intervals, breastfeeding, pregnancy, known hepatic dysfunction, type C or D response in the Barbeau test, and anatomical anomalies of the radial or brachial arteries necessitating crossover to femoral access.

Procedure

A total of 120 patients were randomized (block randomization) to receive 2 mL of lidocaine (2%)+0.5 mL of distilled water as the control group or 2 mL of lidocaine (2%) +0.5 mL (20 mg) of papaverine (40 mg/mL) as the papaverine group.

All the solutions were prepared by an experienced cath-lab operator, and both the operators and the patients were unaware of the local anesthesia allocation. The subcutaneous solutions were injected medial to the radial pulse and 2 cm proximal to the styloid process of the radius; then, the radial artery access was gained using a 6-F Prelude EASE™ Hydrophilic Sheath Introducer (Merit Medical Systems). Depending on the operator's preference, the anterior or posterior wall puncture was selected. Next, 5000 U of intravenous unfractionated heparin was administered. (In the case of percutaneous coronary intervention, the dose was increased.) In addition, depending on the baseline blood pressure, at least 100 µg of intra-radial nitroglycerin was injected.

The operator verified if there was any radial artery spasm, as identified by significant complaints of the patients or noticeable resistance while crossing the catheter. At the end of the catheterization, a TR band (Terumo Company) was used for hemostasis, and persistent hemostasis was rechecked via the reverse Barbeau test.[15]

End Points

The end points consisted of the number of tries to gain access, the time to gain access, failure to gain radial access, vascular adverse effects (eg, hematoma and spasm), and crossover to femoral access.

On the announcement of the operator that the patient was ready for the commencement of the procedure, the time to gain access was measured until a successful wire insertion. The number of tries to gain access was calculated as the number of needle skin passage and observed by an aid technician. Failure to gain radial access was taken to mean that the sheath could not be inserted or no pressure could be detected. Spasm was registered by the operator as any difficulty for the catheter passage or significant pain for the patient. Hematoma was documented after the sheath removal if it was extended >2 cm. Crossover to femoral access due to severe spasm that was refractory to spasmolytic drugs and interventions was considered the second approach.

In the fellowship training program in our center, operators' experience is graded as high-volume (>50 angiography or intervention procedures) or low-volume (<50 angiography or intervention procedures) according to the number of transradial procedures they have performed.

Statistical Analysis

It was calculated that 50 patients were needed in each group to conduct a meaningful statistical analysis. A further 10 patients per group were enrolled to make the statistical power more satisfactory. The categorical variables were compared using the Pearson χ^2 test. The continuous variables are presented as the median, and they were compared using the paired *t*-test or the Mann–Whitney *U*-test. A logistic regression model for binary variables was employed for the analysis of adverse effects, and a linear regression model was used for the continuous variables—including the time to gain access. All the statistical analyses were performed with the SPSS software. A *P* value <0.05 was considered statistically significant.

RESULTS

Totally, 120 patients were recruited and they were equally divided into the papaverine group and the control group. The mean age of the papaverine group was 58.12 years (minimum=38 y and maximum=82 y), and the mean age of the control group was 58.27 years (minimum=40 y and maximum=80 y). The *t*-test showed no significant difference in the mean age between the 2 groups (*P*=0.728) (Table 2).

No significant difference was observed between the study groups in terms of the number of failed attempts to gain radial access (Table 3).

There were significant differences between the groups in the time to gain access (*P*=0.016) and in the number of tries to gain access (*P*=0.007), and both were lower in the papaverine group (Table 4).

Our subgroup analysis demonstrated that the time to gain access was significantly lower in the male patients (*P*=0.035), the younger patients (*P*=0.008), and the smokers (*P*=0.043).

There was also a significant difference in favor of the papaverine group in terms of the operator's experience among the low-volume operators (*P*=0.016) (Table 5).

A significantly shorter procedure time was observed in the papaverine group, which was more meaningful in the nondiabetic and nonhypertensive cases (*P*=0.039 and *P*=0.018). As was expected, the number of tries to gain access was meaningfully lower the in same subgroups (Table 6).

Expected adverse effects were much less frequent in the papaverine group (*P*=0.007), and the subgroup analysis showed significantly beneficial results among the smokers (*P*=0.009) (Table 7).

The rate of crossover to femoral access was lower and on the edge of significance in the papaverine group (1 case in the papaverine group vs 6 patients in the control group [*P*=0.056]), and it was significantly lower in the male gender but not in the other subgroups (*P*=0.034).

Table 1. Demographic data

		Drug		*P* Value
N (percent)		**Saline** 60(50)	**Papaverine** 60(50)	
Age level	35-50	44.1(15)	55.9(19)	0.028
	50-65	62,7(37)	37,3(22)	
	65-80	30.8(8)	69.2(18)	
	Up to 80	0,0(0)	100(1)	
Gender	Male	31(45.6)	37(54.4)	0.269
	Female	29(56.9)	23(44.2)	
Fellow's experience	Low-volume	49(48.5)	52(51.5)	0.453
	High-volume	8(42.1)	11(57.9)	
Hypertension	Yes	39(54.9)	32(45.1)	0.194
	No	21(42.9)	28(57.1)	
Diabetes mellitus	Yes	20(48.8)	21(51.2)	0.847
	No	40(50.6)	39(49.4)	
Smoking	Yes	20(42.6)	27(57.4)	0.190
	No	40(54.8)	33(45.2)	

Table 2. Time to gain access and the number of tries to gain access in both groups

Time to Gain Access	**N**	**Median(QRT)**	***P* value**
Papaverine	57	38 (29.5-71.5)	**0.016**
TNG	54	62.5 (37.5-109)	
Number of Tries to Gain Access	**N**	**Median(QRT)**	***P* value**
Papaverine	57	1 (1-2)	**0.007**
TNG	54	2 (1-3)	

Table 3. Time to gain access according to the operator's experience

Operator		N	Median(QRT)	*P* value
Low-volume	Papaverine	49	39 (28.5-80.5)	**0.016**
	TNG	43	79 (39-109)	
High-volume	Papaverine	8	36 (30.25-64.75)	**0.545**
	TNG	11	45 (30-98)	

Table 4. Subgroups with a lower number of tries to gain access results

		P value	Median(QRT)	N
Younger (35-50 y)	Papaverine	19	1 (1-2)	0.037
	TNG	13	2 (1. 5-3. 5)	
Male	Papaverine	35	1 (1-2)	0.01
	TNG	28	2 (2-3)	
Nondiabetic	Papaverine	36	1.5 (1-2)	0.02
	TNG	36	2 (1.25-3.75)	
Nonhypertensive	Papaverine	27	2 (1-2)	0.017
	TNG	18	3 (2-4.25)	
Low-volume operator	Papaverine	49	1 (1-2)	0.008
	TNG	43	2 (1-3)	
Smoker	Papaverine	30	1 (1-2)	0.037
	TNG	36	2 (1-3)	

Table 5. Adverse effects

	Adverse Effect	Papaverine	TNG	*P* value
	Total number	50(56.8)	38(43.2)	0.070
	Spasm	5(27.8)	13(72.2)	
	Hematoma	2(40.0)	3(60.0)	
Smoking				
No	No	25(48.1)	27(51.9)	0.625
	Spasm	4(40)	6(60)	
	Hematoma	1(25)	3(75)	
Yes	No	25(69.4)	11(30.6)	0.009
	Spasm	1(12.5)	7(87.5)	
	Hematoma	1(100)	0	
Operator's experience				
Low-volume fellowship	No	42(58.3)	30(41.7)	0.175
	Spasm	5(33.3)	10(66.7)	
	Hematoma	2(40)	3(60)	
Experienced fellowship	No	8(50)	8(50)	0.228
	Spasm	-	3(100)	
	Hematoma	-	-	

DISCUSSION

The use of the radial approach for coronary angiography and intervention is continuously on the rise, with many operators underscoring access gain as the cornerstone of a successful procedure. A lower number of tries to gain access can reduce the rate of complications, whereas multiple attempts increase the time required, patient discomfort, and the risk of arterial spasm.

In this study for the first time we showed a significant reduction in the time to gain access and in the number of tries to gain access after adding papaverine to lidocaine (*P*= 0.016 and *P*=0.007) (Table 4).

The time to gain access was significantly lower in the male patients (*P*=0.035), younger patients (*P*=0.008), and the smokers (*P*=0.043).

Moreover, we observed a significant difference in favor of papaverine administration with respect to the operator's experience among our low-volume operators (P=0.016) (Table 5). Our results revealed a significantly lower time with the use of papaverine in nondiabetic and nonhypertensive cases (P=0.039 and P=0.018).

Previous studies have demonstrated a higher frequency of the radial artery spasm in the female gender.[16] Total NO-dependent vasodilation was lower in the forearm arteries for women in a previous investigation.[17]

Nagaraja et al[18] evaluated the effect of papaverine on the radial artery diameter and reported its efficacy in the palpability of the radial pulse.

We showed a significant reduction in the time to gain access as regards the operator's experience among our low-volume operators. Consequently, papaverine can be practically used in the radial approach in training centers and fellowship programs.

A lower number of tries to gain access reduces vascular complications and alleviates patient discomfort.

In the current study, overall adverse effects were much less frequent in the papaverine group (P=0.007) and our subgroup analysis showed significant results in the smokers (P=0.009) but not according to other variables and the operator's experience (Table 7).

The rate of crossover to femoral access was lower and on the edge of significance in our papaverine group (1 case in the papaverine group vs 6 cases in the control group [P=0.056]).

CONCLUSIONS

The addition of papaverine for subcutaneous anesthesia can reduce the time to gain access, access site adverse effects, severe spasm, and crossover to femoral access. It can, therefore, have a beneficial effect on the procedure length, patient comfort, procedural success, and femoral access-related complications.

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