Effect of Vasodilatory Medications on Blood Pressure in Patients Undergoing Transradial Coronary Angiography: A Comparative Study

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ABSTRACT

Background: In patients undergoing coronary intervention, different vasodilators are used to prevent the radial artery spasm (RAS). To date, no studies investigated the effect of these vasodilators in blood pressure (BP) reduction.

Aim: The study aimed to investigate and compare the effect of vasodilatory medications on BP reduction in patients undergoing transradial coronary angiography procedure.

Methods: We consecutively included 300 patients undergoing transradial coronary angiography procedures and randomly assigned them into three equal groups to compare the effect of verapamil (2.5 mg), nitroglycerin (200 µg), and combination (verapamil 2.5 mg with nitroglycerin 200 (µg) was diluted in 5 ml of normal saline and given through radial sheath. Changes in the BP, heart rate (HR), and other clinical parameters were assessed and presented as standardized mean differences (SMD) with 95% confidence intervals (CIs). ANOVA test was performed to analyze the differences in the BP and other clinical parameters between the three groups.

Results: Overall, the mean age of the study population was 53.26 years (standard deviation: 9.27), male patients (84%), with dyslipidemia (62.6%), and diabetes (45%). At baseline, the mean systolic BP (SBP) was 150.91 ± 31.66 mmHg, HR (72.34 ± 12.71 beats/min). After the administration of vasodilators, the combination group reduced SBP significantly (SMD: −33.35 [95% CI]: −40.27--−26.42, \( P < 0.001 \)). There was a statistically significant difference between groups for the SBP (\( F[2,296] =3.38, P= 0.035 \)). Verapamil alone showed a significant decrease in the SBP by −27.23 mmHg and diastolic BP by −4.980 mmHg.

Conclusion: Intra-arterial administration of verapamil alone showed lower BP reduction compared to the combination of vasodilators. Verapamil could be a safer and effective alternative to prevent RAS with no deleterious effect on BP and HR in patients undergoing transradial coronary angiography.

Key words: Cocktail, nitrates, radial artery spasm, radial coronary angiogram, vasodilators, verapamil

INTRODUCTION

Percutaneous coronary angiography or angioplasty is a standard procedure to evaluate coronary artery disease.¹,² Transradial access (TRA) approach has significantly reduced local vascular complications...
from 2.8% (femoral approach) to 0.3%\textsuperscript{[3,4]} and may reduce mortality among patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.\textsuperscript{[5]} Furthermore, faster postprocedural ambulation times for patients, reduce cost, increase patient satisfaction, and decrease mortality, particularly.\textsuperscript{[6,7]}

Despite the benefits associated with TRA, radial artery spasm (RAS) occurs in around 4%–20% of cases and is one of the significant causes of access failure.\textsuperscript{[5,6]} Access failure can lead to considerable pain and may require switching to the other side or shifting to femoral access. It is well known that the radial artery has a higher sensitivity to spasm compared with other arteries.\textsuperscript{[8]} RAS can be caused by the circulating catecholamines stimulating the alpha-1 adrenoreceptors that contract smooth muscle cells of the radial artery.\textsuperscript{[9]}

The administration of various intra-arterial and intravenous medications such as nitrates and calcium channel blockers (CCBs) are used to reduce RAS.\textsuperscript{[11-13]} Nitrates relax smooth muscles, and CCBs reduce the influx of calcium into vascular and arterial smooth muscles resulting in vasodilation. Studies demonstrated mixed results using nitrates and CCBs either alone or in combination as a cocktail.\textsuperscript{[11-16]}

Vasodilators in transradial catheterization offer greater satisfaction and increased comfort; however, these medications may cause a set of complications and although infrequent. For instance, some patients may experience precipitous episodes of hypotension and bradycardia during the procedure and ultimately hemodynamic deterioration of patient conditions and required fluids or vasopressor support. These inexplicable conditions may present a challenge to catheterization laboratory staff to manage these issues as they appear. This may significantly influence procedural volume, increased overtime costs, and deteriorate satisfaction among staff. However, to explore these incidences, clinical evaluation of the vasodilatory effect on preventing RAS and overall treatment outcomes is essential.

**Aim**

The aim of the study was to investigate and compare the effect of vasodilatory medications on blood pressure (BP) reduction in patients undergoing transradial coronary angiography procedure.

**METHODS**

This was a prospective, cross-sectional pilot study conducted over 6 months from June to November 2016 among the patients undergoing coronary angiography procedure with or without PCI via radial artery at Al Ain Hospital and Mediclinic Hospital, Al Ain, United Arab Emirates (UAE). Patients who received intra-arterial injection bolus of nitrates (200 µg), verapamil 2.5 mg, or a cocktail (combination of both nitrates and verapamil) are randomly assigned (using computer-generated random numbers) into three groups (Group 1: Nitroglycerin 200 mcg, Group 2: Verapamil 2.5 mg, and Group 3: Nitroglycerin 200 mcg + verapamil 2.5 mg). All procedures were planned as diagnostic coronary angiography or angioplasty. Patients with the absence of a palpable radial pulse and access site failure were excluded from the study.

The coronary angiography procedure was performed by puncturing the right radial artery (using an 18G needle entry at 1–2 cm proximal to the styloid process after) following the administration of 2% lidocaine (local anesthesia). After puncturing the radial artery, a 10-cm long 5F sheath was inserted over a hydrophilic guidewire (0.035") into the radial artery. All the patients in the three groups received 5000 international units of unfractionated heparin. Vasodilatory medications such as nitroglycerin (200 µg) or verapamil (2.5 mg) or a cocktail (a combination of nitroglycerin 200 µg and 2.5 mg of verapamil) were diluted in 5 ml of normal saline and were given through the sheath slowly. Pre- and post-coronary catheterization, systolic BP (SBP) and diastolic BP (DBP), heart rate (HR), serum creatinine, platelet count, and hemoglobin levels were recorded.

**Statistical analysis**

All the statistics were performed using SPSS software (IBM Corp., Armonk, New York, USA). Categorical data were presented as absolute values and percentages. Continuous variables were presented as a mean ± standard deviation (SD), and changes in the clinical parameters were presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs). ANOVA test was performed to analyze the difference in the rate of radial spasm between the three groups. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

Three hundred patients were recruited and categorized equally in each group. Baseline characteristics categorized by groups are presented in Table 1. The mean age of the study population was 53.26 years (SD): 9.27. A higher percentage of male patients (84%) were identified and received nitrates (88%). Nearly two-thirds of the patients who received verapamil alone underwent coronary artery grafting. Most of them have diabetes (50 patients in nitrates), dyslipidemia (both verapamil[66] and cocktail [66]), and a comparable number of patients in each group had hypertension. The mean SBP and DBP was 150.91 ± 31.66 mmHg and 68.44 ± 15.09 mmHg, and HR (72.34 ± 12.71 beats/min).

Pre- and post-administration of vasodilators among three groups are presented in Table 2. The
three groups differed in baseline SBP and DBP. Compared to baseline, the mean SBP after a vasodilator administration was 117.01 ± 23.72 mmHg in nitrates group, 125.62 ± 23.10 mmHg in verapamil group, and 120 ± 14.35 mmHg in the cocktail group.

The three groups showed significant differences in the clinical parameters after vasodilator administration [Table3]. Briefly, a significant SMD in SBP after a vasodilator administration was reduced by −33.35 (95% CI: −40.27–−26.42), $P < 0.001$, and DBP −6.13 (−10.19–−2.06), $P < 0.001$ in the cocktail group following nitrates group (SBP: −29.51 [−36.91–22.1]; DBP: −2.54 [−7.90–3.86]) and verapamil group (SBP: −27.23 [−35.25–19.20] and DBP: −4.98 [−8.62–1.33], $P < 0.001$). There was a statistically significant difference between groups for the SBP as determined by one-way ANOVA ($P = 0.035$). Similarly, a significant difference was also seen in ANOVA ($P = 0.030$) between patients on verapamil and cocktail groups in HR. On the other hand, Tukey post hoc analysis failed to show any statistically significant difference in other parameters between any of the three groups [Table 4].

**DISCUSSION**

Cardiac catheterizations using a radial approach utilize a variety of intra-arterial vasodilators to prevent RAS. Currently, a cocktail of intra-arterial verapamil and nitrates was widely used for this approach. Evaluating the efficacy of these medications in reducing the BP and other cardiac parameters either alone or in combination in radial artery angiography is essential. Although no

### Table 1: Baseline characteristics ($n = 300$)

| Characteristics | Nitrates ($n=100$) | Verapamil ($n=100$) | Nitrates + verapamil ($n=100$) | Overall |
|-----------------|--------------------|--------------------|-------------------------------|---------|
| Age $^1$        | 52.74±9.395        | 53.01±8.64         | 54.05±9.79                    | 53.26±9.27 |
| Gender (male)   | 88                 | 83                 | 80                            | 251     |
| CABG            | 55                 | 65                 | 48                            | 168     |
| CABG + PCI      | 45                 | 35                 | 52                            | 132     |
| Diabetes mellitus | 50               | 47                 | 38                            | 135     |
| Dyslipidemia    | 56                 | 66                 | 66                            | 188     |
| Hypertension    | 52                 | 53                 | 51                            | 156     |
| NSTEMI          | 24                 | 15                 | 20                            | 59      |
| SBP $^1$        | 146.52±29.08       | 152.85±33.53       | 153.35±32.06                  | 150.91±31.66 |
| DBP $^1$        | 67.40±16.59        | 66.86±13.55        | 71.05±14.78                   | 68.44±15.09 |
| Mean BP $^1$    | 89.38±17.63        | 90.05±17.05        | 92.52±20.45                   | 90.65±18.43 |
| HR              | 73.24±13.42        | 70.40±12.65        | 73.39±11.91                   | 72.34±12.71 |
| Serum creatinine $^1$ | 0.95±0.26  | 0.89±0.21          | 0.97±0.27                     | 0.94±0.25 |
| Platelets $^1$  | 273,067±71,253.15  | 250,292.55±62,698.19 | 251,484.95±67,172.21  | 258,461.62±67,765.63 |
| Hemoglobin $^1$ | 14.56±1.60         | 14.76±1.62         | 14.48±1.95                    | 14.60±1.73 |

$^1$Mean±SD. SD: Standard deviation, NSTEMI: Non-ST segment elevated myocardial infarction, CABG: Coronary artery bypass graft, PCI: Percutaneous coronary intervention, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BP: Blood pressure, HR: Heart rate

### Table 2: Mean changes at pre- and post-administration of vasodilators, throughout the study

|                      | Nitrates | Verapamil | Cocktail | Overall |
|----------------------|----------|-----------|----------|---------|
| Prior procedure      | 146.52±29.08 | 152.85±33.53 | 153.35±32.06 | 150.91±31.66 |
| DBP                  | 67.40±16.59  | 66.86±13.55  | 71.05±14.78  | 68.44±15.09  |
| Mean BP              | 89.38±17.63  | 90.05±17.05  | 92.52±20.45  | 90.65±18.43  |
| Heart rate           | 73.24±13.42  | 70.40±12.65  | 73.39±11.91  | 72.34±12.71  |
| Serum creatinine $^1$| 0.95±0.26    | 0.89±0.21    | 0.97±0.27    | 0.94±0.25    |
| Platelets $^1$       | 273,067±71,253.15 | 250,292.55±62,698.19 | 251,484.95±67,172.21 | 258,461.62±67,765.63 |
| Hemoglobin $^1$      | 14.56±1.60   | 14.76±1.62   | 14.48±1.95   | 14.60±1.73   |

SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Cocktail: Nitrates+verapamil, BP: Blood pressure, HR: Heart rate
Table 3: Mean differences in clinical parameters from baseline after vasodilator administration

|                | Nitrates (mmHg) | Verapamil (mmHg) | Cocktail (mmHg) |
|----------------|-----------------|------------------|-----------------|
| SBP            | −29.51 (−36.91–−22.10)** | −27.23 (−35.25–−19.20)** | −33.35 (−40.27–−26.42)** |
| DBP            | −3.57 (−7.90–0.76) | −4.98 (−8.62–−1.33)** | −6.13 (−10.19–−2.06)** |
| Mean BP        | −6.27 (−10.92–−1.61)** | −4.89 (−9.48–−0.29)* | −7.29 (−12.55–−2.02)** |
| HR (bpm)       | 1.33 (−2.36–5.602) | 0.80 (−2.53–4.13) | 2.250 (−1.14–5.64) |
| Serum creatinine (µmol/L) | −0.11 (0.19–−0.02)** | −0.04 (−3.16–3.08) | −0.01 (−0.08–0.06) |
| Platelets (/µL) | −6946.17 (−29,015.47–15,123.13) | −3790.33 (−22,812–15,232.03) | −8554.30 (−26,738.05–9629.45) |
| Hemoglobin (g/dl) | −0.05 (−0.49–0.39) | −0.24 (−0.72–0.24) | −0.50 (−1.07–0.07) |

*P<0.05, **P<0.001. SMD: Standard mean difference, CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, BP: Blood pressure

Table 4: ANOVA (nitrates, verapamil, and nitrates-verapamil)

|                | F (df) | df | P     |
|----------------|--------|----|-------|
| SBP            | 3.38   | 2, 296 | 0.035 |
| DBP            | 1.24   | 2, 296 | 0.290 |
| Mean BP        | 0.55   | 2, 296 | 0.580 |
| HR             | 3.56   | 2, 295 | 0.030 |
| Serum creatinine | 3.10   | 2, 155 | 0.048 |
| Platelets      | 1.46   | 2, 152 | 0.236 |
| Hemoglobin     | 1.44   | 2, 152 | 0.241 |

F-test post hoc ANOVA test. df: Degree of freedom, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, BP: Blood pressure.

Studies have compared the cocktail combination therapy to each vasodilatory medication in the UAE population, this is the first study to compare the effect of vasodilatory medications on BP and HR in patients undergoing transradial coronary angiography procedure.

RAS is still a significant concern during TRA for coronary catheterization and intervention. To prevent RAS, the administration of vasodilators through intra-arterial route is mandatory. Several studies have demonstrated that the marked muscle mass and high intensity in alpha receptors slight catecholamine release in the radial artery may be the cause of RAS.[8,12,17] Medications such as verapamil alone or in combination with nitroglycerin as a cocktail are administered as a standard vasodilator during the transradial coronary procedure Chen CW et al.[18]

In our study, the administration of nitroglycerin and verapamil (cocktail) associated with a significant fall in SBP by −33.35 (−40.27–−26.42) and DBP − 6.13 (−10.19–−2.06), indicates vasodilators are important for optimal BP reduction. Similar results were noticed in et al.’s study, where this was not seen in the other groups; intra-arterial administration of a cocktail can be useful even in hemodynamically unstable patients.

Our data showed that nitrates are more effective than verapamil (SMD: −29.51) in reducing the SBP levels, but not superior to cocktail (SMD: −33.35). Similar results were noticed in Chen et al.[18] study showed that nitroglycerin alone (100 mcg) is as effective as the combination of nitroglycerin (100 mcg) and verapamil (1.25 mg).[18] Nevertheless, the cocktail was superior in reducing the SBP, DBP, overall BP, and increased HR (2.25 bpm). This indicates that administration nitroglycerin in combination with verapamil as a cocktail may lead to hypotension and bradycardia. Maintaining a stable BP during the TRA procedure is more essential to improve the efficacy and compliance and makes the procedure more comfortable to the patients.

Global evidence suggests that verapamil is the most frequently utilized medication in patients undergoing TRA. However, it is important to note that in patients with left ventricular systolic dysfunction, bradycardia, and hypotension and verapamil is contraindicated due to its negative chronotropic and inotropic effect.[6,11,19] From this study, we identified the effect of verapamil in lowering the SBP is inferior to other vasodilators, this indicates verapamil can be a suitable option to maintain a stable BP without affecting the patient’s hemodynamics during the procedure.

Compared with nitroglycerin, the advantages of verapamil has shown better reduction in BP and RAS by dilating the coronary and systemic arteries. Blocking the reflux of extracellular calcium ion in cardiac and vascular smooth muscles is proven. In SPASM3 study, verapamil 2.5 mg showed as much reduction in RAS as with isosorbide dinitrate, but with verapamil, if RAS develops, the pain was much less than with isosorbide dinitrate.[20] This indicates, verapamil deemed necessary drug to minimize the risk of RAS, reduced systemic vascular resistance and constant HR makes it more favorable.
with net benefits to prevent intra- and post-procedural complications.

Limitation
There are some limitations to this study. First, this is a single-center, cross-sectional study; the results cannot be generalized to other population, different health-care setting and procedures. Due to cross-sectional nature, the follow-up of the patients was not done. Lack of placebo control and operators are not blinded. Second, since this is a pilot study aimed to assess and compare the effect of vasodilatory medication on BP reduction, no sample size calculation was performed, and a small number of patients were included in the study. This warrants future investigation in a large sample randomized controlled trial. Finally, we did not have an objective parameter to assess radial spasm such as Doppler/impedance.

CONCLUSION
Intra-arterial administration of verapamil alone showed lower BP reduction compared to the combination of vasodilators. Verapamil could be a safer and effective alternative to prevent RAS with no deleterious effect on BP and HR in patients undergoing transradial coronary angiography.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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