Moderate Procedural Sedation and Opioid Analgesia During Transradial Coronary Interventions to Prevent Spasm

A Prospective Randomized Study

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Objectives The aim of this study was to test the hypothesis that moderate procedural sedation can reduce the incidence of radial artery spasm.

Background Transradial access for left heart catheterization and percutaneous coronary intervention is increasingly used for emergent and elective procedures, in lieu of the femoral approach. However, increased rates of access site crossover have been reported, with radial artery spasm being a major contributor to this effect.

Methods Patients undergoing elective transradial percutaneous coronary intervention were prospectively randomized to receive fentanyl and midazolam during the procedure or no treatment (control subjects). The primary endpoint was angiographically confirmed radial artery spasm. Patient discomfort was quantified with a visual analogue scale.

Results Two thousand thirteen patients (age 64.5 ± 8.4 years) were randomized. Spasm occurred in 2.6% of the treatment group versus 8.3% of control subjects (p < 0.001; odds ratio [OR]: 0.29). The number needed to treat to avoid 1 case of spasm was 18 (95% confidence interval [CI]: 12.9 to 26.6). The access site crossover rate was 34% lower in the treatment group: 9.9% versus 15.0% (OR: 0.62; 95% CI: 0.48 to 0.82). Patient discomfort visual analogue scale score was 18.8 ± 12.5 in the treatment group versus 27.4 ± 17.4 in control subjects (p < 0.001). No significant differences were observed in the 30-day rate of death or repeat hospital stay for any cause: 4.6% versus 4.5% (OR: 1.02; 95% CI: 0.67 to 1.56).

Conclusions Routine administration of relatively low doses of an opioid/benzodiazepine combination during transradial interventional procedures is associated with a substantial reduction in the rate of spasm, the need for access site crossover, and the procedure-related level of patient discomfort. (J Am Coll Cardiol Intv 2013;6:267–73) © 2013 by the American College of Cardiology Foundation
Transradial arterial access for performing diagnostic coronary angiography and percutaneous coronary interventions (PCI) has emerged over the last few years as a preferred catheterization practice, on the basis of evidence that it is associated with less vascular complications and shorter hospital stays (1–4) as well as better outcomes in certain high-risk patient subsets, such as patients with acute coronary syndromes (5,6).

One of the problems with the transradial approach is that access site crossover seems to be more frequent when the initial route is the transradial one (3). The need to transfer to an alternate access route is often the result of severe arterial spasm leading to inability to further advance guidewires and catheters through the radial artery. Access site crossover not only increases the procedure duration and complexity but also seems to be an important predictor of major vascular complications (1). Several preventive measures are being used to prevent radial artery spasm, including nitrates and verapamil. Sedation has been suggested as a means to reduce the incidence of spasm, but there is currently no evidence base for the routine use of sedation or opioid analgesia in transradial PCI. Systematic intravenous sedation and analgesia, although widely applied in some countries, including the United States, is not a universal practice in several parts of the world. In addition, the potential of an intravenous combination of moderate doses of an opioid and a sedative to reduce radial artery spasm has never been tested in the transradial PCI setting (7).

Patients were randomized to either administration of sedation and analgesia (treatment group) or no intra-procedural sedative/analgesic treatment (control subjects). In the treatment group, fentanyl 0.5 μg/kg and midazolam 1 mg slow intravenous push over 2 min were administered at the beginning of the procedure (during preparation of the access site). One additional dose was allowed 45 to 60 min after the first one (additional dosing according to the sedation status of the patient was not allowed, because achieving “conscious sedation” status was not a requisite). The respiration and oxygen saturation of the patient were constantly monitored by a dedicated interventional trained nurse.

The PCI was performed by experienced operators (at least 100 transradial PCI procedures/year), who use the transradial route as default arterial access for coronary catheterization. The right radial artery was cannulated as default, except in cases with previous bypass surgery with use of the left internal thoracic artery, where the left radial artery was catheterized. Local anesthesia (subcutaneous lidocaine solution) was administered. Six-French hydrophilic sheaths (Terumo, Inc., Tokyo, Japan) were used, and all patients received 100 μg of nitroglycerin and 2.5 mg of verapamil through the radial sheath immediately after insertion as well as heparin bolus 40 U/kg intravenously. The choice of guidewires and catheters was made by the operators. To avoid placing 7-F sheaths for more complex procedures requiring larger bore catheters, sheathless guides were employed (ASAHI Sheath-less Eaucath PTCA Guiding Catheter, Vascular Perspectives, Ltd., Cheadle, United Kingdom) when needed. Additional devices and intracoronary modalities, including intravascular ultrasound and pressure wire, were used freely by the operators, according to their judgment. Post-procedural hemostasis was applied by placing a wrist clamp device (TR Band, Terumo Medical Corporation, Somerset, New Jersey) for approximately 180 min.

Patient-perceived discomfort was assessed in the morning after the procedure, with a visual analogue scale (VAS), whereby the patient graded the discomfort on a scale of 0 to 100 (0 corresponding to “no discomfort” and 100 to “extreme pain and discomfort”). The patients were followed during their hospital stay and interviewed by phone contact or on a clinic visit at 30 days from the index procedure.

The primary endpoint of this study was the incidence of spasm during the procedure. It was identified by appearance of marked resistance to the movement of or inability to further advance catheters, with or without accompanying forearm pain reported by the patient, and was confirmed arteriographically as severe constriction of the radial artery lumen. Secondary endpoints were Thrombolysis In Myocardial Infarction major bleeding during hospital stay, patient-reported procedure-related discomfort (VAS score), and a 30-day safety composite of all-cause mortality or repeat hospital stay for any cause.

**Abbreviations and Acronyms**

- CI = confidence interval
- OR = odds ratio
- PCI = percutaneous coronary intervention
- VAS = visual analogue scale

**Methods**

This was a prospective randomized open-label study conducted from January 2010 to February 2012 in 3 referral hospitals in Greece. All subjects provided informed consent, and the study was approved by the institutional review boards. The study population consisted of prospectively recruited patients undergoing PCI with transradial access. Patients with an acute coronary syndrome within the previous 2 weeks, cardiogenic shock, end-stage renal disease, severe hepatic impairment (Child-Pugh class C), chronic opioid or benzodiazepine use, known peripheral artery disease of the upper limbs, or a history of coronary artery bypass grafting with both internal thoracic arteries were excluded. Subjects with known hypersensitivity or history of adverse reactions to benzodiazepines or opioids were also excluded.
All events and complications were studied and adjudicated by a 3-member committee who were blinded as to patient randomization and were not involved in patient care. The same committee reviewed the arteriograms of radial arteries in the cases of spasm to ensure adequate angiographic documentation of spasm.

**Statistical analysis.** Assuming a 10% rate of spasm in control subjects, to detect a decrease of 40%, with a probability of 90%, 965 patients were needed/randomization group (in a 1:1 allocation ratio) at an alpha level of 0.05. Continuous variables are expressed as mean ± SD. Student *t* test was used for comparisons of continuous variables. Categorical variables were expressed as percentages and counts and compared with the chi-square test. Binary logistic regression analysis was applied to test independent associations between various parameters and the occurrence of spasm. The SPSS software package was used (version 16, SPSS, Inc., Chicago, Illinois). Two-sided *p* values <0.05 were considered as indicative of statistical significance.

**Results**

The study included 2,013 patients (29.1% female; age 64.5 ± 8.4 years), randomized into 2 groups (1,007 in the treatment group and 1,006 control subjects) (Fig. 1). Baseline population characteristics, by randomization group and overall, are presented in Table 1. The 2 study arms were well balanced, without significant differences with regard to demographic data and procedural parameters. Periprocedural mortality was low and similar in the 2 groups (3 cases in the treatment group, and 4 in the control group; overall 0.35%). No cases of respiratory depression requiring mechanical respiratory support were recorded. Mild allergic reactions (skin rash and pruritus) shortly after fentanyl and midazolam infusion (before contrast medium was injected) were observed in 11 patients of the treatment group (1.1%). Eight patients of the treatment group (0.8%) had a paradoxical reaction to midazolam (agitation, restlessness). An opioid and/or midazolam had to be administered in 41 patients of the control group (4.1%) during the procedure.

**Primary outcome measure.** Spasm occurred in 26 patients of the treatment group (2.6%) versus 83 in the control group (8.3%; *p* < 0.001; odds ratio [OR]: 0.29, 95% confidence interval [CI]: 0.18 to 0.47). The relative risk reduction was 68.7%, and the number needed to treat to avoid 1 incidence of spasm was 18 (17.6; 95% CI: 12.9 to 26.6).

As a result, the access site crossover rate was 34 lower in the treatment group: 9.9% versus 15.0% (OR: 0.62, 95% CI: 0.48 to 0.82; *p* = 0.001). Patients with spasm had an OR of 47.9 (95% CI: 28.7 to 79.8) for access crossover compared with those without spasm (*p* < 0.001). In 81.7% of patients with radial artery spasm the operator had to forgo the transradial route. Accordingly, spasm was the most frequent cause for access site crossover, being responsible for 35.5% of crossovers, followed by (in decreasing order of frequency): excessively acute angulation between the innominate artery and the aortic arch, severe tortuosity and/or anatomic variations of the upper limb arteries (including high takeoff of the radial artery and arteria lusoria), poor guide support, radial artery complication (e.g., radial artery perforation or dissection).

Overall, the incidence of spasm was 5.4%. Patients with shorter stature and lower body mass index were more prone to spasm. Female sex and smoking were also predisposing factors. Spasm was more frequent in patients undergoing combined coronary angiography and PCI procedures (as opposed to PCI only) and was positively associated with the number of catheters used/procedure, the duration of the procedure, and the administered contrast volume (Table 2).
Secondary analyses. Self-reported patient discomfort was significantly lower in the treatment group: 18.8 ± 12.5 points (of the 100-point maximum VAS score) versus 27.4 ± 17.4 points in the control group. Spasm was, expectedly, strongly associated with higher patient discomfort, with patients reporting almost double VAS scores if spasm occurred (55.7 ± 13.8 vs. 21.2 ± 13.6; p < 0.001).

By contrast, no significant differences were observed with regard to the secondary composite safety endpoint (30-day death or repeat hospital stay for any cause), which was reached in 46 patients of the treatment group (30-day death or repeat hospital stay for any cause), with regard to the secondary composite safety endpoint occurred (55.7 vs. 21.2). Spasm was, expectedly, strongly associated with higher patient discomfort, with patients reporting almost double VAS scores if spasm occurred (55.7 ± 13.8 vs. 21.2 ± 13.6; p < 0.001).

Table 1. Population Characteristics

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Overall (n = 2,013)</th>
<th>Treatment Group (n = 1,007)</th>
<th>Control Group (n = 1,006)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.9 ± 8.3</td>
<td>64.5 ± 8.2</td>
<td>65.2 ± 8.3</td>
<td>0.081</td>
</tr>
<tr>
<td>Female sex</td>
<td>606 (30.1%)</td>
<td>315 (31.3%)</td>
<td>291 (28.9%)</td>
<td>0.250</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 3.3</td>
<td>26.9 ± 3.0</td>
<td>27.0 ± 3.4</td>
<td>0.667</td>
</tr>
<tr>
<td>Diabetes</td>
<td>652 (32.4%)</td>
<td>310 (30.8%)</td>
<td>342 (34.0%)</td>
<td>0.124</td>
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<tr>
<td>Hypertension</td>
<td>819 (40.7%)</td>
<td>406 (40.3%)</td>
<td>413 (41.1%)</td>
<td>0.737</td>
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<tr>
<td>Smoking</td>
<td>692 (34.4%)</td>
<td>365 (36.2%)</td>
<td>327 (32.5%)</td>
<td>0.077</td>
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<td>Dyslipidemia</td>
<td>1,063 (52.8%)</td>
<td>531 (52.7%)</td>
<td>532 (52.9%)</td>
<td>0.946</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>329 (16.3%)</td>
<td>162 (16.1)</td>
<td>167 (16.6%)</td>
<td>0.756</td>
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<td>Renal dysfunction</td>
<td>459 (22.8%)</td>
<td>240 (23.8%)</td>
<td>219 (21.8%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Previous radial artery catheterization</td>
<td>211 (10.5%)</td>
<td>96 (9.5%)</td>
<td>115 (11.4%)</td>
<td>0.164</td>
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<tr>
<td>Procedural parameters</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CAA and ad hoc PCI</td>
<td>965 (47.9%)</td>
<td>468 (46.5%)</td>
<td>497 (49.4%)</td>
<td>0.188</td>
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<td>Additional modalities</td>
<td></td>
<td></td>
<td></td>
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<td>FFR</td>
<td>302 (15.0%)</td>
<td>156 (15.5%)</td>
<td>146 (14.5%)</td>
<td>0.209</td>
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<tr>
<td>IVUS</td>
<td>217 (10.8%)</td>
<td>108 (10.7%)</td>
<td>109 (10.8%)</td>
<td>0.904</td>
</tr>
</tbody>
</table>

Values are mean ± SD, or n(%).

*As opposed to PCI alone.

**BMI = body mass index; CAA = coronary artery angiography; FFR = fractional flow reserve; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

Table 2. Potential Univariate Spasm Correlates

<table>
<thead>
<tr>
<th></th>
<th>No Spasm (n = 1,904)</th>
<th>Spasm (n = 109)</th>
<th>Univariate p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.8 ± 8.1</td>
<td>66.2 ± 10.8</td>
<td>0.175</td>
</tr>
<tr>
<td>Female sex</td>
<td>533 (28.0%)</td>
<td>73 (67.0%)</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.1 ± 3.3</td>
<td>25.6 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.3 ± 6.6</td>
<td>162.7 ± 6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of catheters</td>
<td>2.4 ± 0.9</td>
<td>3.7 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedure duration (min)</td>
<td>63.5 ± 15.1</td>
<td>80.7 ± 23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
<td>367.7 ± 110.0</td>
<td>471.9 ± 130.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedure type (CAA and ad hoc PCI)</td>
<td>875 (46.0%)</td>
<td>90 (82.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active smoking status</td>
<td>634 (33.3%)</td>
<td>59 (54.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal dysfunction*</td>
<td>441 (23.2%)</td>
<td>18 (16.5%)</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Values are mean ± SD, or n(%).

*Estimated (Cockcroft-Gault) glomerular filtration rate <60 ml/min/1.73 m².

Abbreviations as in Table 1.

**Discussion**

The principal finding of this prospective randomized study is the reduction in the incidence of radial artery spasm by administration of opioid analgesia combined with sedation during transradial PCI procedures. This resulted in significant decrease in access site crossover rate and less patient discomfort. Moderate doses of the 2 drugs were used, without titration according to the level of sedation of the patient.

Transradial arterial access for left heart catheterization and PCI is increasingly being used in Europe and the...
United States for emergent and elective procedures, in lieu of the femoral approach (1,8). Lower rates of access-related complications, more timely patient mobilization, shorter hospital stays, and less patient discomfort are some of the advantages of the transradial access route (1,4,5,9). However, increased rate of access site crossover has been reported when the transradial access is used (1,5), with radial artery spasm being a major contributor to this effect. The reported frequency of spasm in transradial procedures shows considerable variation in the published data, ranging from as low as 4% to higher than 20% (7,9–13). The manifestation of spasm during a procedure is a troublesome complication; as a result, preventive measures have been devised, most commonly including administration of a “vasodilator cocktail” after insertion of the radial artery sheath. This cocktail usually includes verapamil and/or a nitrate derivative (10,11,14,15), whereas a number of other agents have also been tried with varying results (16,17).

The effect of relatively low doses of an opioid and a benzodiazepine on the appearance of radial artery spasm seen in the present study has a sound pharmacobiological basis. Their sedative and analgesic action—along with the accompanying dissociative effect—could, in their own right, explain their impact on spasm incidence, but it is also true that they have direct vasoactive effects. Gursoy et al. (18) studied the vasodilatory effect of several opioids on the isolated radial artery and reported that all the tested agents produced concentration-dependent and endothelium-independent relaxation in human radial artery rings, with meperidine and fentanyl being more potent relaxant agents than morphine and remifentanil. The vasodilatory effects of fentanyl have also been demonstrated in human vein experimental models (19). Benzodiazepine-induced vasodilation is also a well-documented effect. Colussi et al. (20) showed that low concentrations of midazolam induce vasodilation via an endothelium-dependent mechanism that does not involve nitric oxide production, whereas high concentrations of midazolam induce vasodilation via an endothelium-independent mechanism. Midazolam has been shown to lead to hyperpolarization of human smooth muscle cells, probably through activation of potassium channels, resulting in vasorelaxation (21), while it attenuates the vasoconstrictive response to adrenergic stimuli (22), which might be a particularly relevant action in the setting of adrenergic
overactivation circumstances, such as the stress-inducing situation of a PCI procedure.

By contrast, although the routine administration of opioid analgesia and sedation in patients undergoing elective PCI led to a significant reduction in spasm occurrence, the effect of this practice on safety endpoints, including major bleeding and 30-day death or repeat hospital stay, was neutral. This is reassuring as far as the safety of the studied treatment is concerned but also indicates that the reduction of spasm is not translated into better outcomes. However, this was to be expected, because the population of the study was a generally low-risk population (elective procedures) with low expected in-hospital and short-term adverse outcome rates. As a result, an intervention such as that described in the present report would not be expected to—and indeed was not found to—have a significant impact on hard endpoints. Consequently, the main merit of the proposed strategy lies in the prevention of radial artery spasm, which in itself is a valid target, because when it happens, it complicates and usually prolongs the procedure, frustrates the interventionalist, increases the possibility of subsequent radial artery closure (23), aggravates patient discomfort, and essentially nullifies the advantages of the transradial approach. Of note, in this large series of patients no serious adverse events related to the administration of fentanyl and midazolam were observed.

Study limitations. Spasm cannot always be defined with objectivity, and different definitions have been proposed in the past (12,13). The definition used in the present study is quite restrictive, because it requires angiographic confirmation, but it has the advantage of objectivity. Furthermore, because there is no reason to believe that spasm was reported in a different way between the 2 treatment arms, the issue of definition of spasm should not be of import for the conclusions of this study. In addition, it should be noted that some patient subgroups were excluded (see Methods), and as a result, the study findings might not be applicable in these patient subsets (although some of these patient subgroups might not be candidates for sedation anyway). The use of a specific sedation protocol implies that these findings might not necessarily apply to other sedative medications. However, the studied drugs are widely used throughout the world in catheterization laboratories. Finally, it should be taken into account that operators in this trial were all very experienced in transradial procedures, and the need for patient sedation might be greater among novice or less experienced operators.

Conclusions

Routine administration of moderate doses of fentanyl and midazolam during transradial interventional procedures is associated with a substantial reduction in the rate of spasm, the need for access site crossover, and the level of patient discomfort. No differences were found as far as secondary safety endpoints were concerned. These results suggest that routine administration of moderate procedural sedation during transradial procedures could be useful in everyday practice. By contrast, although the relative risk reduction was substantial, the number needed to treat was relatively high, obviously due to the relatively low overall incidence of spasm. These observations indicate that a focused use of this option in catheterization laboratories where conscious sedation is not routinely administered (i.e., administration of fentanyl-midazolam only in cases of anticipated increased complexity of a procedure or in patients with risk factors for spasm) might also be a reasonable recommendation.

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REFERENCES


Key Words: fentanyl ■ midazolam ■ percutaneous coronary intervention ■ radial artery ■ spasm.