ORIGINAL ARTICLE

Pain Control and Hemodynamic Changes due to Moderate Sedation during Cardiac Catheterization

Yutthapong Temtanakitpaisan, MD[1,2], Suchaorn Saengnipanthkul, MD[3], Tanyapat Kotana, RN[4], Jittra Boonbuak, RN[4], Panpilai Paipa, RN[4]

[1] Division of Cardiology, Bangkok Hospital Khon Kaen, Bangkok Dusit Medical Services Plc., Thailand; [2] Faculty of Medicine, Mahasarakham University, Maha Sarakham, Thailand; [3] Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [4] Cardiac Catheterization Laboratory, Bangkok Hospital Khon Kaen, Bangkok Dusit Medical Services Plc., Thailand

Background: Moderate sedation is a practice of promoting patient comfort during cardiac catheterization. However, few studies have evaluated the effectiveness of moderate sedation in patients undergoing cardiac catheterization.

Objective: To determine the efficacy of moderate sedation in patients undergoing cardiac catheterization.

Materials and Methods: The authors retrospectively analyzed patients undergoing cardiac catheterization. They were divided into the moderate sedation group, which received midazolam, fentanyl, or combined midazolam and fentanyl, and the control group, which received no sedative medication. The primary endpoint was self-reported pain score during the procedure. The secondary endpoint was a hemodynamic variation during the procedure. Propensity-score matching was used to reduce confounding biases.

Results: One hundred ninety-six patients were included, with 111 patients in the moderate sedation group and 85 patients in the control group. The proportion of patients who experienced any pain was significantly lower in the moderate sedation group than in the control group at 3.6% versus 11.8% (p=0.028). No significant difference was found in the average change in the systolic blood pressure at –9 mmHg versus –4 mmHg (p=0.097) and the heart rate at –1 bpm versus –2 bpm (p=0.289) obtained at baseline and that at the end of the procedure between the moderate sedation group and the control group. However, the change in the diastolic blood pressure (DBP) measured at baseline and at the end of the procedure was significantly lower in the moderate sedation group than in the control group at –4 mmHg versus –1 mmHg (p=0.039).

Conclusion: Moderate sedation by using a low-dose fentanyl, midazolam, or combined fentanyl and midazolam is associated with fewer episodes of pain and better DBP stability during cardiac catheterization.

Keywords: Conscious sedation; Midazolam; Coronary angiography; Percutaneous coronary intervention; Cardiac catheterization

Received 21 August 2023 | Revised 29 August 2023 | Accepted 15 September 2023

J Med Assoc Thai 2023;106(10):988-94

Website: http://www.jmatonline.com

Cardiac catheterization is a well-tolerated procedure. However, anxiety and pain may occur during the procedure, which leads to radial artery spasm (RAS) and vital sign changes. Moderate sedation during cardiac catheterization is a widespread practice in the United States, which aims to promote patient comfort during the procedure. Intravenous administration of midazolam and fentanyl is the mainstay of moderate sedation in the cardiac catheterization laboratory[1]. The usage rates of moderate sedation vary. In the United States, moderate sedation is used in 92% of the cases, whereas in other parts of the world, it was only 38%[2]. Despite the frequent use of moderate sedation, the effectiveness of sedation is not well studied.

Sedation offers a reduction in pain and discomfort, improvement in hemodynamics, and prevention of RAS[3]. However, potential complications of sedation include respiratory and cardiac depression and paradoxical agitation, which require close monitoring.

Data on the specific medication and dosage for sedation during cardiac catheterization are limited. The American College of Cardiology Foundation/Society Cardiovascular Angiography and Interventions Expert Consensus Document on Cardiac Catheterization Laboratory Standards Update[4] provides recommendations for standard

Correspondence to:

Temtanakitpaisan Y.

Division of Cardiology, Bangkok Hospital Khon Kaen, Bangkok Dusit Medical Services Plc., 888 Maliwan Road, Muang, Khon Kaen 40000, Thailand.

Phone: +66-63-6326359, **Fax**: +66-43-042800

Email: yutt.tem@gmail.com, ktongkn@hotmail.com

How to cite this article:

Temtanakitpaisan Y, Saengnipanthkul S, Kotana T, Boonbuak J, Paipa P. Pain Control and Hemodynamic Changes due to Moderate Sedation during Cardiac Catheterization. J Med Assoc Thai 2023;106:988-94.

DOI: 10.35755/jmedassocthai.2023.10.13904

on drug administration and monitoring of sedation. However, the guideline does not give specific recommendations regarding a specific medication regimen.

Thus, in the present retrospective study, the authors aimed to compare pain perception and hemodynamic changes during cardiac catheterization in patients who received moderate sedation and controls.

Materials and Methods

Study design and setting

The present study was a retrospective study that included all adult patients undergoing coronary angiography (CAG) with or without percutaneous coronary intervention (PCI) at Bangkok Hospital Khon Kaen, Khon Kaen, Thailand between January 1, 2020 and January 31, 2022. Patients with clinical instability, hemodynamic or respiratory compromise, altered sensorium, or inability to monitor side effects were excluded.

In the moderate sedation group, midazolam 0.05 mg/kg, with a maximum dose of 4 mg, fentanyl 0.5 mcg/kg, with a maximum dose of 100 mcg, or combined midazolam and fentanyl were given intravenously before the procedure based on the decision of the interventional cardiologists. Additional doses may be required if the patient remained agitated. Patients' consciousness level, ventilation, oxygenation, and hemodynamics were monitored during the procedure by a dedicated interventional trained nursing staff. Patients who did not receive midazolam, fentanyl, or other sedative medications were assigned to the control group. CAG with or without PCI was performed by interventional cardiologists who decided on the arterial access such as radial or femoral artery. Local anesthesia was administered using subcutaneous lidocaine. Moreover, 6-Fr hydrophilic sheaths were used. The operators selected the guidewires and catheters. Post-procedure hemostasis was applied using a radial compression device (TR Band, Terumo Medical Corporation, Somerset, New Jersey) for 180 to 240 minutes for radial artery access. For femoral artery access, manual compression was performed for 30 to 35 minutes until achieving hemostasis.

The primary endpoints were pain prevalence and patient-perceived pain score, which were assessed by nursing staff in the cardiac catheterization laboratory before, during, and after the procedure. If patients experienced pain, they were asked to rate this pain using a Likert scale, whereby the discomfort was rated on a scale of 1 to 10, with 1 corresponding to "mild pain" and 10 to "worse pain possible". The secondary endpoint was hemodynamic variation. Blood pressure and heart rate (HR) were monitored during the procedure, at the arrival in the cardiac catheterization laboratory, and at the end of the procedure. Blood pressure measurements were obtained at 5-minute intervals using the cuff around the left lower leg. Continuous HR monitoring was performed using an automatic defibrillator machine.

Statistical analysis

Data analyses were performed using Stata, version 10.1 (StataCorp LP, College Station, TX, USA). Descriptive statistics were reported for continuous data using median and interquartile range (Q1 to Q3). Categorical data were presented using frequencies and percentages. The Fisher's exact test was used to compare the incidence of pain during the procedure between the treatment and the control groups, whereas, the Mann-Whitney test was applied to compare pain severity and changes in hemodynamic parameters between the two groups. Statistical significance was set at 0.05. Due to differences in baseline characteristics between patients in two groups, propensity-score matching with the nearest-neighbor, was used to reduce to effect of confounding.

Ethical approval

The study was approved by the Bangkok Hospital Institutional Review Board on June 8, 2023 (BHQ-IRB 2022-03-12).

Results

The present study included 196 patients with 30.6% female (61.7±10.9 years). They were divided into two groups with 111 patients in the moderate sedation group and 85 patients in the control group. Baseline characteristics by treatment groups are presented in Table 1. The prevalence of hypertension was significantly higher in the moderate sedation group than in the control group at 64.0% versus 49.4% (p=0.041). The procedure took longer time in the moderate sedation group than in the control group at 35 minutes versus 23 minutes (p=0.002). This difference occurred because the rate of CAG with PCI, which typically takes longer than CAG alone, was higher in the moderate sedation group than in the control group at 42.3% versus 29.4%. The majority of the patients (97.4%) went through the procedure via the right radial access. Among

Table 1. Baseline characteristics by group

Variables	Unmatched patients			Propensity-scored-matched patients		
	Moderate sedation (n=111)	Control (n=85)	p-value	Moderate sedation (n=84)	Control (n=84)	p-value
Age (years); mean±SD	62.3±10.5	61.2±11.4	0.217	61.7±10.4	61.5±10.8	0.745
Sex (male); n (%)	75 (67.6)	61 (71.8)	0.527	58 (69.1)	60 (71.4)	0.736
BMI; mean±SD	24.7±4.9	24.9±4.6	0.391	25.3±4.9	24.9±4.6	0.651
Underlying disease; n (%)						
Hypertension	71 (64.0)	42 (49.4)	0.041	49 (58.3)	42 (50.0)	0.278
Diabetes mellitus	51 (45.9)	35 (41.2)	0.505	46 (54.8)	35 (41.7)	0.089
Dyslipidemia	75 (67.6)	68 (80.0)	0.052	68 (81.0)	68 (81.0)	1.000
Smoking status; n (%)			0.065			0.208
Nonsmoker	57 (51.4)	55 (64.7)		43 (51.2)	54 (64.3)	
Ex-smoker	20 (18.0)	16 (18.8)		17 (20.2)	16 (19.1)	
Smoker	34 (30.6)	14 (16.5)		24 (28.6)	14 (16.7)	
Prior CAG/PCI (yes); n (%)	11 (9.9)	11 (12.9)	0.505	8 (9.5)	11 (13.1)	0.465
Procedure; n (%)			0.166			0.712
CAG	64 (57.7)	60 (70.6)		54 (64.3)	59 (70.2)	
CAG with PCI	47 (42.3)	25 (29.4)		30 (35.7)	25 (29.8)	
Catheter access site; n (%)			0.154			0.106
Radial	87 (78.4)	59 (69.4)		68 (81.0)	59 (70.2)	
Femoral	24 (21.6)	26 (30.6)		16 (19.1)	25 (29.8)	
Contrast volume (mL); median (Q1-Q3)	40 (30 to 80)	40 (30 to 75)	0.220	40 (30 to 70)	40 (30 to 75)	0.399
Access site crossover; n (%)	4 (3.6)	4 (4.7)	0.699	1 (1.2)	4 (4.8)	0.173
Procedure duration (minutes); median (Q1-Q3)	35 (19 to 58)	23 (15 to 39)	0.002	31 (17 to 45)	23 (15 to 42)	0.021
Baseline systolic BP (mmHg); median (Q1-Q3)	145 (134 to 168)	155 (137 to 172)	0.045	146 (131 to 162)	156 (137 to 172)	0.016
Baseline diastolic BP (mmHg); median (Q1-Q3)	78 (71 to 86)	84 (75 to 93)	0.099	79 (72 to 84)	83 (75 to 93)	0.015

BMI=body mass index; BP=blood pressure; CAG=cardiac angiography; PCI=percutaneous coronary intervention; SD=standard deviation

patients in the moderate sedation group, 52 received midazolam alone with a median dose of 1 mg (1 to 1.5), nine received fentanyl alone with a median dose of 25 mcg (25 to 25), and 50 received both midazolam and fentanyl with a median dose of midazolam and fentanyl of 1 mg (1 to 1.5) and 25 mcg (25 to 43.75), respectively.

The baseline systolic blood pressure (SBP) was lower in the moderate sedation group than in the control group at 145 mmHg versus 155 mmHg (p=0.045), but no significant difference in baseline diastolic blood pressure (DBP) was observed.

Due to major imbalances between the moderate sedation and control groups with respect to baseline characteristics, propensity-score method was used to balance the biases. Eighty-four patients in each group were successfully matched. The differences between moderate sedation and control variables were attenuated in the propensity-match samples compared to the unmatched samples (Table 1).

Primary outcome measures: The percentage of patients who experienced any pain was significantly lower in the moderate sedation group than in the control group at 3.6% versus 11.8% (p=0.028). Among those who reported pain, the average pain score was 7 (6.5 to 7.5) in the moderate sedation group compared with 8 (7 to 9) in the control group, which were not significantly different (Table 2). The benefit of moderate sedation in decrease episodes of pain remained evident in the propensity-score-matched analysis.

Secondary outcome measures: No significant difference in average changes in SBP and HR obtained at the baseline and the end of procedure was found between the moderate sedation group and the control group with SBP of –9 mmHg versus –4 mmHg (p=0.097) and HR of –1 bpm versus –2 bpm (p=0.289). However, the change in DBP obtained at baseline and the end of the procedure was significantly lower in the moderate sedation group than in the control group with –4 mmHg versus –1 mmHg (p=0.039) (Table 2). In the propensity-score-matched analysis, the benefit of DBP stability was similar to unmatched analysis.

Table 2. Comparison of primary and secondary endpoints

Outcomes	Unmatched Patients			Propensity-scored-matched patients		
	Moderate sedation (n=111)	Control (n=85)	p-value	Moderate sedation (n=84)	Control (n=84)	p-value
Pain during procedure; n (%)	4 (3.6)	10 (11.8)	0.028	3 (3.6)	10 (11.9)	0.043
Pain severity (1-10); median (Q1-Q3)	7 (6.5 to 7.5)	8 (7 to 9)	0.263	7 (6 to 7)	8 (7 to 9)	0.156
Hemodynamic parameters; median (Q1-Q3)						
Change in systolic BP (mmHg)	–9 (–20 to –1)	–4 (–14 to 6)	0.097	–8.5 (–19.5 to –1)	–4 (–14 to 6)	0.054
Change in diastolic BP (mmHg)	–4 (–12 to 1)	–1 (–7 to 5)	0.039	–3.5 (–11.5 to –1)	–1 (–7 to 5)	0.033
Change in pulse rate (beat per minute)	–1 (–7 to 3)	–2 (–6 to 5)	0.289	–1 (–6 to 3.5)	–2 (–6 to 4.5)	0.818

BP=blood pressure

Discussion

Adequate sedation during cardiac catheterization is desirable to ensure patient comfort[5]. However, data regarding optimal sedation during cardiac catheterization are limited, and previous studies yielded conflicting results[6-8]. The authors' retrospective study was conducted to determine the benefits of moderate sedation during cardiac catheterization. Most of the present study patients undergoing elective cardiac catheterization did not experience pain at any point during the procedure. Only four patients (3.6%) in the moderate sedation group and ten patients (11.8%) in the control group reported pain or discomfort. Among those who experienced pain or discomfort, the average pain scores were 7 (6.5 to 7.5) and 8 (7 to 9) in the moderate sedation and control groups, respectively. Based on the present study data, significantly less incidence of patient-perceived pain was noted in the moderate sedation group. The benefits of patient comfort during the procedure were similar to that reported by Deftereos et al., who measured patient discomfort using a visual analog scale[9].

Anxiety is common among patients undergoing CAG, which can activate the sympathetic nervous system, leading to hypertension and tachycardia[10]. These hemodynamic changes could be detrimental and cause myocardial ischemic and heart failure[11]. Raza et al. reported that midazolam caused a significant reduction in systemic vascular resistance, DBP, and left ventricular stroke work index among patients with severe coronary occlusion[12]. Moderate sedation was also studied in other procedures. Prabhudev et al. showed better patient-reported tolerance and satisfaction composite scores with the intake of midazolam alone or combined fentanyl and midazolam than placebo in patients undergoing flexible bronchoscopy[13]. However, no differences in HR, SBP, and DBP were observed[13]. Regarding hemodynamic parameters in the present study, moderate sedation showed better DBP stability during the procedure than did the control group. Nevertheless, no significant difference in SBP and HR was observed between the moderate sedation and the control groups.

Transradial arterial access becomes a preferred practice for CAG and PCI because of the comparable procedural success rate with less vascular complications and shorter hospital stay[14,15]. However, access-site crossover from the radial to the femoral access could occur and become problematic, as it may increase the procedure time and major vascular complications[14,16]. RAS is one of the major contributors for access-site crossover[9] and it is caused by pain and anxiety[14,17]. Therefore, RAS must be prevented to avoid vascular injury, procedural failure, and patient discomfort.

Benzodiazepine has dose-dependent vasodilatory effects[18]. At a low dose, midazolam induces vasodilation via an endothelium-dependent mechanism, whereas at a high dose, it occurs mostly via an endothelium-independent mechanism. Gursoy et al. reported the dose-dependent vasorelaxant effects of opioids on the human radial artery[19]. Among each opioid analgesic, fentanyl and meperidine were more potent relaxant agents than morphine and remifentanil[19]. Therefore, the use of benzodiazepine and opioid analgesics during cardiac catheterization may offer the benefits of both anxiolytics, such as pain control and vasodilation, which can prevent RAS. Deftereos et al. demonstrated that procedural sedation with midazolam and fentanyl in patients undergoing elective PCI can reduce RAS compared with the control intervention for 2.6% versus 8.3% ($p<0.001$)[9]. The access-site crossover rate was also lower in patients who received procedural sedation with 9.9% versus 15% ($p=0.001$). On the contrary, Astarcioglu et al. failed to demonstrate the effect

of midazolam in preventing RAS[17]. As the present study had a small sample size with a low incidence of access-site crossover, the benefit of moderate sedation in the prevention of RAS and access-site conversion cannot be entirely assessed.

Morphine may activate platelet aggregation by binding to the alpha2-adrenoreceptors in platelets, resulting in the increased formation of thromboxane A and eventually induced platelet aggregation[20,21]. According to the IMPRESSION trial, morphine altered the pharmacokinetics of ticagrelor by reducing the total exposure to its active metabolite by 36%. Moreover, data demonstrated a delay in the maximal plasma concentration of ticagrelor of four hours versus two hours (p=0.004) in patients with acute myocardial infarction who received morphine[22]. Regarding other opioid derivatives, McEvoy et al. reported that fentanyl lowers the concentration of ticagrelor and delays its antiplatelet effects[23]. Iglesias et al. conducted a randomized controlled study to determine different effects of fentanyl compared to morphine on platelet inhibition induced by ticagrelor in patients with acute ST-elevation myocardial infarction. The results showed that fentanyl did not improve platelet inhibition two hours after the administration of the loading dose of ticagrelor in comparison with morphine. Nevertheless, fentanyl may increase platelet inhibition at four hours compared to morphine[24].

As morphine and its derivatives blunt the antiplatelet effects of P2Y12 receptor antagonists along with a concern of opioid dependence, midazolam monotherapy is another strategy for procedural sedation. Black et al. reported that midazolam alone can control pain as effectively as combined therapy of midazolam and fentanyl[25]. In addition, studies have supported the sole use of midazolam[6,26,27]. Therefore, morphine and its synthetic derivatives should be cautiously used, especially in patients with high thrombotic risks such as acute myocardial infarction.

The combined use of midazolam and fentanyl may be utilized in some situations. In patients with a history of chronic pain, better pain control can be achieved using combined midazolam and fentanyl compared with midazolam use alone[25]. Furthermore, prolonged procedural time is associated with pain, and in this scenario, the combined use of midazolam and fentanyl may be beneficial[25].

Limitation

First, this is a retrospective, non-randomized, observational study that could suffer from biases despite propensity-score matching. The dosage regimen of moderate sedation is individualized based on the complexity of the procedure and patient response to sedative medication. Additionally, the assessment of patient-perceived pain is subjective, and each patient may have different pain thresholds. Moreover, the authors did not analyze the benefit of moderate sedation in each regimen because of the small sample size. Finally, the average doses of sedative medication were low compared with those in other studies, average doses of midazolam and fentanyl were only 1 mg and 25 mcg, respectively. The actual benefit of moderate sedation in pain control and hemodynamic stability may be more pronounced if a larger dose of a sedative was given.

Conclusion

Combined midazolam and fentanyl have been used for moderate sedation during cardiac catheterization. The present study demonstrated that moderate sedation resulted in less incidence of pain and better DBP stability during cardiac catheterization. Further studies conducted in a larger, randomized multicenter are required to better explore the benefit of moderate sedation and proper regimen during cardiac catheterization.

What is already known on this topic?

Moderate sedation results in reduction of pain and improvement of patient tolerability during cardiac catheterization. However, the effectiveness of sedation is not well studied.

What does this study add?

This study demonstrated that moderate sedation is associated with fewer episodes of pain with better DBP stability during cardiac catheterization. This could facilitate the procedure and improve patient comfort.

Acknowledgement

The authors would like to thank Enago (www.enago.com) for the English language review.

Funding disclosure

This study was financially supported by the BDMS Health Research Center, Bangkok Dusit Medical Services Plc. The research team conducted the trial, managed the database, and performed the analyses independently of the sponsor.

Conflicts of interest

The authors declare no conflict of interest.

References

1. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.
2. Lavi S, Jolly SS, Bainbridge D, Manji F, Randhawa V, Lavi R. Sedation, analgesia, and anaesthesia variability in laboratory-based cardiac procedures: an international survey. Can J Cardiol 2014;30:627-33.
3. Whitehead NJ, Clark AL, Williams TD, Collins NJ, Boyle AJ. Sedation and analgesia for cardiac catheterisation and coronary intervention. Heart Lung Circ 2020;29:169-77.
4. Bashore TM, Balter S, Barac A, Byrne JG, Cavendish JJ, Chambers CE, et al. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: A report of the American College of Cardiology Foundation Task Force on Expert Consensus documents developed in collaboration with the Society of Thoracic Surgeons and Society for Vascular Medicine. J Am Coll Cardiol 2012;59:2221-305.
5. Mall A, Girton TA, Yardley K, Rossman P, Ohman EM, Jones WS, et al. Understanding the patient experience of pain and discomfort during cardiac catheterization. Catheter Cardiovasc Interv 2020;95:E196-200.
6. Woodhead J, Harding SA, Simmonds M, Dee S, McBride-Henry K. Premedication for cardiac catheterization and percutaneous coronary intervention: does it increase vascular access site complications? J Cardiovasc Nurs 2007;22:466-71.
7. Alamri H, Almoghairi A, Almasood A, Alotaibi M, Alonazi S. Do we need premedication before coronary angiography? A controlled clinical trial. Cardiol Res 2011;2:224-8.
8. Beddoes L, Botti M, Duke MM. Patients' experiences of cardiology procedures using minimal conscious sedation. Heart Lung 2008;37:196-204.
9. Deftereos S, Giannopoulos G, Raisakis K, Hahalis G, Kaoukis A, Kossyvakis C, et al. Moderate procedural sedation and opioid analgesia during transradial coronary interventions to prevent spasm: a prospective randomized study. JACC Cardiovasc Interv 2013;6:267-73.
10. Nascimento J dos S, Módolo NSP, de Carvalho HG, Dórea EML, Santos KP. Clonidine in cineangiocardiography: sedative effects on blood pressure and heart rate. Arq Bras Cardiol 2006;87:603-8.
11. Chassot PG, Delabays A, Spahn DR. Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery. Br J Anaesth 2002;89:747-59.
12. Raza SM, Masters RW, Zsigmond EK. Comparison of the hemodynamic effects of midazolam and diazepam in patients with coronary occlusion. Int J Clin Pharmacol Ther Toxicol 1989;27:1-6.
13. Prabhudev AM, Chogtu B, Magazine R. Comparison of midazolam with fentanyl-midazolam combination during flexible bronchoscopy: A randomized, double-blind, placebo-controlled study. Indian J Pharmacol 2017;49:304-11.
14. Hetherington SL, Adam Z, Morley R, de Belder MA, Hall JA, Muir DF, et al. Primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: changing patterns of vascular access, radial versus femoral artery. Heart 2009;95:1612-8.
15. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409-20.
16. Le J, Bangalore S, Guo Y, Iqbal SN, Xu J, Miller LH, et al. Predictors of access site crossover in patients who underwent transradial coronary angiography. Am J Cardiol 2015;116:379-83.
17. Astarcioglu MA, Sen T, Kilit C, Durmus HI, Gozubuyuk G, Agus HZ, et al. Procedural sedation during transradial coronary angiography to prevent spasm. Herz 2016;41:435-8.
18. Colussi GL, Di Fabio A, Catena C, Chiuch A, Sechi LA. Involvement of endothelium-dependent and -independent mechanisms in midazolam-induced vasodilation. Hypertens Res 2011;34:929-34.
19. Gursoy S, Bagcivan I, Yildirim MK, Berkan O, Kaya T. Vasorelaxant effect of opioid analgesics on the isolated human radial artery. Eur J Anaesthesiol 2006;23:496-500.
20. Sheu JR, Yeh GC, Fang CL, Lin CH, Hsiao G. Morphine-potentiated agonist-induced platelet aggregation through alpha2-adrenoceptors in human platelets. J Cardiovasc Pharmacol 2002;40:743-50.
21. Hsiao G, Shen MY, Fang CL, Chou DS, Lin CH, Chen TF, et al. Morphine-potentiated platelet aggregation in in vitro and platelet plug formation in in vivo experiments. J Biomed Sci 2003;10:292-301.
22. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J 2016;37:245-52.
23. McEvoy JW, Ibrahim K, Kickler TS, Clarke WA, Hasan RK, Czarny MJ, et al. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: The PACIFY randomized clinical trial (platelet aggregation with ticagrelor

inhibition and fentanyl). Circulation 2018;137:307-9.
24. Iglesias JF, Valgimigli M, Carbone F, Lauriers N, Masci PG, Degrauwe S. Comparative effects of fentanyl versus morphine on platelet inhibition induced by ticagrelor in patients with ST-segment elevation myocardial infarction: Full results of the PERSEUS randomized trial. Cardiol J 2022;29:591-600.
25. Black W, Baljepally R, Shali L, Alsharif O, Warden S, Heidel E, et al. Old is (not) gold: Midazolam monotherapy versus midazolam plus fentanyl for sedation during cardiac catheterization. J Interv Cardiol 2021;2021:9932171.
26. Baris S, Karakaya D, Aykent R, Kirdar K, Sagkan O, Tür A. Comparison of midazolam with or without fentanyl for conscious sedation and hemodynamics in coronary angiography. Can J Cardiol 2001;17:277-81.
27. Conway A, Rolley J, Sutherland JR. Midazolam for sedation before procedures. Cochrane Database Syst Rev 2016;(5):CD009491.