Study of the utility of lorazepam in the prevention of radial spasm associated with coronary procedures

Estudio de la utilidad del lorazepam en la prevención del espasmo radial asociado a procedimientos coronarios

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ABSTRACT

Introduction. The radial route is the access of choice in most parts of the world to perform coronary diagnostic and therapeutic procedures thanks to its better safety profile compared to the femoral access, lower in-hospital costs, and greater comfort for the patient.
Its use has not quite been imposed in certain regions of the world. Its main disadvantage is vasospasm. Sometimes, this phenomenon negatively conditions the use of this access and the femoral access ends up being the option here. This prospective, randomized, and double-blind study included a primary endpoint where we intended to assess the efficacy and safety profile of sublingual lorazepam to reduce the rate of radial spasm in coronary diagnostic and therapeutic procedures compared to placebo. The secondary endpoint was given by the rate of complications seen between the two groups.
Results. Appearance of clinical spasm: 31.03% vs. 28.73% (OR=1.11 (0.58-2.13) p=0.74); technical spasm: 13.79% vs. 13.79%, (OR=1 (0.42-2.36) p=1); angiographic spasm: 56.32% vs. 47.12%, (OR=1.44 (0.79-2.62) p: 0.22) for groups A and B, respectively. Conversion to the femoral access: group A: 3.44% vs. group B: 6.89% (OR=0.48 (0.11-1.99) p=30). No differences were seen in the rate of complications between the two groups.
Conclusion. The administration of sublingual lorazepam prior to admission to the cath lab does not reduce radial spasm compared to placebo when this access is used to perform coronary diagnostic and/or therapeutic procedures. No significant differences were seen either in the rate of complications between the two groups.

Keywords: *lorazepam, spasm, radial artery.*

RESUMEN

Introducción. El acceso radial es la vía de elección en la mayor parte del mundo para la realización de procedimientos diagnósticos y terapéuticos coronarios debido a un mejor perfil de seguridad comparado con el femoral, disminución de los costos intrahospitalarios y mayor comodidad para el paciente. Su uso no ha terminado de imponerse en ciertas regiones del mundo. Su principal desventaja es el vasoespasmo. En ocasiones, este fenómeno condiciona el abandono dicha vía, utilizando el acceso femoral como alternativa.
Material y métodos. En este estudio prospectivo, aleatorizado y doble ciego nos propusimos, como punto final primario, evaluar la eficacia y seguridad del lorazepam sublingual para disminuir la tasa de espasmo radial en procedimientos coronarios diagnósticos y terapéuticos comparado contra placebo. El punto final secundario estuvo dado por la tasa de complicaciones entre los dos grupos.
Resultados. Aparición de: espasmo clínico en 31,03% vs. 28,73% (odds ratio [OR]=1,11 [0,58-2,13]; p=0,74), espasmo técnico en 13,79% vs. 13,79% (OR=1 [0,42-2,36]; p=1) y espasmo angiográfico en 56,32% vs. 47,12%, (OR=1,44 [0,79-2,62]; p=0,22) para los grupos A y B, respectivamente. Conversión a la vía femoral: grupo A 3.44% vs. grupo B 6,89% (OR=0,48 [0,11-1,99]; p=30). No hubo diferencias en las tasas de complicaciones entre los dos grupos.
Conclusión: La administración de lorazepam sublingual previo al ingreso a la Sala de Hemodinamia no reduce el espasmo radial comparado con placebo cuando este acceso se emplea para la realización de procedimieantos diagnósticos y/o terapéuticos coronarios. Tampoco hubo diferencias significativas en las complicaciones entre los grupos.

Palabras claves: *lorazepam, espasmo, arteria radial.*

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INTRODUCTION

The use of the radial artery as the access route to perform diagnostic cardiac catheterization was initially described by Campeau back in 1989. Afterwards, in 1993, Kiemeneij and Laarman performed the first angioplasty with stenting using this access route (1,2). Since then, its use has gone up steadily for the performance of diagnostic or therapeutic coronary procedures (3). Its main advantage is a lower rate of vascular complications compared to femoral access (3-5). Also, it has proven to be more comfortable for the patient, improve walking, and shorten the hospital stay (3,6).

Despite all these advantages its use has not become popularized in certain parts of the world (3). Its main disadvantage is the development of radial artery vasospasm as reported in up to 30% of the cases (7). There are times that this phenomenon makes it impossible to maneuver the catheters properly. This may lead to abandoning such access route using the femoral access as the option. These maneuvers generate discomfort in the patient, extend the duration of the procedure, and are associated with a higher the rate of vascular complications (8,9). Different types of drugs like IV calcium blockers, diazepam, midazolam, and fentanyl were studied to reduce the incidence rate of this phenomenon (6,10-12). Although benzodiazepines and opioids are often used intravenously, they should be administered with caution due to their potential adverse events (13).
The objective of this study was to assess whether the routine use of sublingual lorazepam prior to cardiac catheterization via radial access reduces the incidence rate of arterial spasm.

Hypothesis

The administration of 2 mg of sublingual lorazepam 60 min before starting the coronary angiography/angioplasty coronaria reduces the incidence rate of radial spasm.

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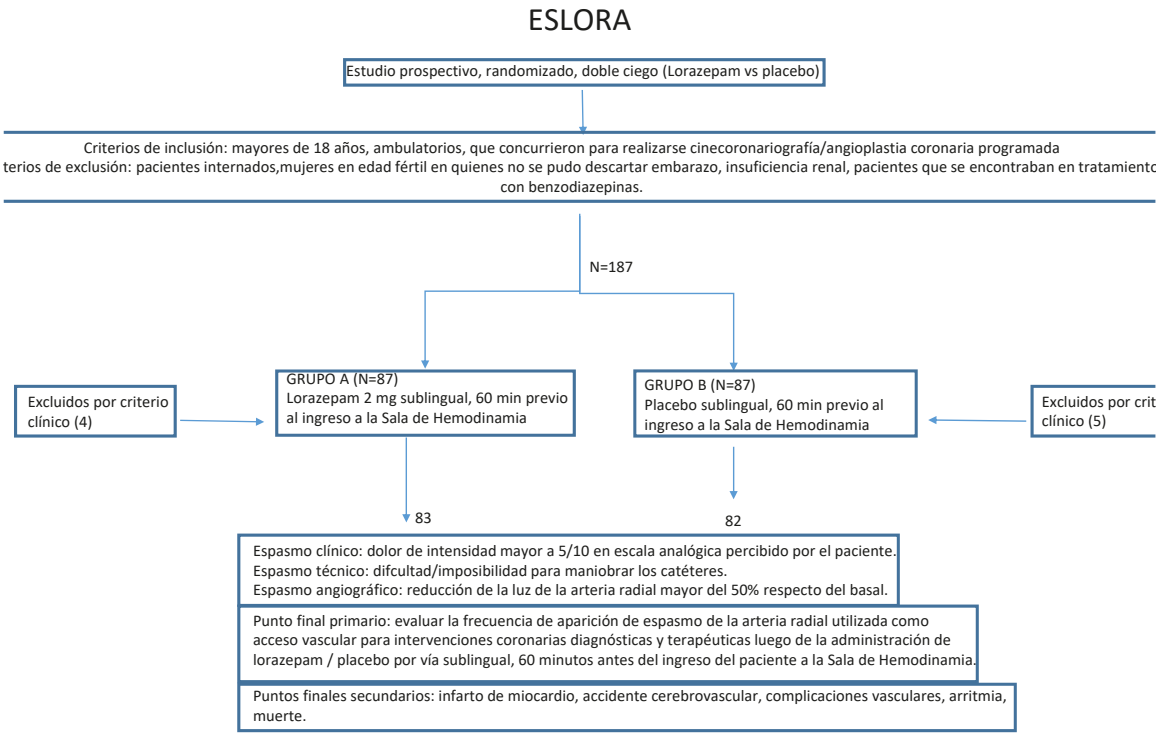


Figura 1. *Diagrama de flujo del estudio.*

Endpoints

Primary endpoints

To assess the incidence rate of radial artery spasm used as vascular access to perform diagnostic and therapeutic coronary procedures after the administration of sublingual lorazepam/placebo for 60 min prior to the arrival of the patient to the cath lab. This incidence rate will be determined as follows:

Radial artery spasm is defined by, at least, one of the following criteria:

- **Clinical**. Moderate-intense pain at forearm level while advancing or removing material through the radial artery. A scale from 1 to 10 will be used to assess pain. Scores from 5 to 7 will be indicative of moderate pain. Scores > 8 will be indicative of severe pain. Such scale will be established by a nurse from the recovery room who did not participate in the procedure.
- **Technical**. Difficulty/impossibility advancing or removing the catheter through the introducer sheath as perceived by the interventional cardiology.
- **Angiographic**. Radial artery angiography performed through collateral artery using an introducer sheath before and after the procedure. Spasm is defined as a > 50% reduction of the radial artery baseline diameter. The angiography should be performed with the table placed at 90 cm of height. Distance from the x-ray image intensifier tube should be 100 cm.

Secondary endpoints

To assess the appearance of procedural complications defined as:

- Myocardial infarction: defined according to the third universal definition of myocardial infarction (14).
- Stent thrombosis:
  - Definitive: symptoms suggestive of acute coronary syndrome and angiographic or anatomopathological confirmation of in-stent thrombosis.
  - Probable: unexplained death within 30 days or myocardial infarction associated with the revascularized coronary artery.
  - Possible: unexplained death after 30 days.
- Vascular complications:
  - Dissection: double-lumen image compromising the arterial wall.
  - Vascular rupture: contrast extravasation in site adjacent to the blood vessel.
- Coronary spasm: transient reduction >50% of the arterial lumen.
- Stroke: neurological deficit confirmed on the nuclear magnetic resonance imaging or brain CT scan showing signs of cerebral ischemia.
- Arrhythmia: changes in the baseline heart rhythm as seen on the monitoring performed at the cath lab.

MATERIAL AND METHODS

During the period from July 2018 through March 2020, a total of 174 patients were included.

This was a double-blind, prospective, randomized clinical trial. Data were analyzed based on an "intention-to-treat" model. Patients were divided into 2 groups: group A received sublingual lorazepan 2 mg (87 patients), and group B received sublingual placebo (87 patients) 1 hour before being admitted to the cath lab to perform a scheduled cine coronary arteriography and/or coronary angioplasty via radial vascular access.

The study was conducted at the *Hospital de Alta Complejidad en Red "Néstor Kirchner"* (HEC) in Florencio Varela, Argentina. The protocol was approved by the center ethics commi-

TABLE 1. Demographiccharacteristics of thepopulation.

Variable	Group A (n: 87)	Group B (n: 87)	p
Age (years)	55,16±6,87	55,36±7,18	0,70
Body surface	1,90±0,26	1,92±0,18	0,55
Males	75 (86,20%)	75 (86,20%)	0,95
Smoking	29 (29,80%)	24 (27,58%)	0,73
Arterial hypertension	57 (65,51%)	60 (68,96%)	0,63
Dyslipidemia	23 (26,43%)	35 (40,22%)	0,04
Diabetes	27 (31,03%)	34 (39,08%)	0,26
Evolving acute myocardial infarction	14 (12,64%)	15 (17,24%)	0,39
Hypertrophic cardiomyopathy	0 (0%)	1 (1,14%)	0,31
NSTEACS	9 (10,34%)	6 (6,89%)	0,41
Dilated cardiomyopathy	12 (13,79%)	12 (13,79%)	0,95
Valvular heart disease	10 (11,49%)	13 (14,94%)	0,50
Silent ischemia	0 (0%)	2 (2,29%)	0,14
Stable chronic angina	39 (44,82%)	38 (43,67%)	0,85
Post cardiac transplant	1 (1,14%)	0 (0%)	0,31
Calcium channel blockers	3 (3,44%)	3 (3,44%)	0,95
Beta-blockers	69 (79,31%)	65 (74,71%)	0,47
Ace I	53 (60,91%)	57 (65,51%)	0,53
Ara II	7 (8,04%)	8 (9,19%)	0,77
Isosorbide mononitrate	5 (5,74%)	5 (5,74%)	0,95
Acetylsalicylic acid	70 (80,45%)	71 (81,60%)	0,82
Clopidogrel	22 (25,28%)	20 (22,98%)	0,72
Statins	67 (77,01%)	62 (71,26%)	0,38

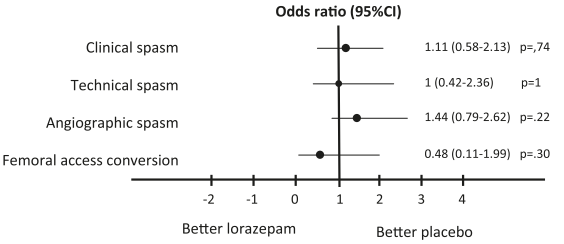
ttee. All patients signed an informed consent form specifically designed for the purposes of the study.

Inclusion criteria:

All outpatients over 18 were treated with a percutaneous coronary intervention (whether diagnostic or therapeutic) at the cath lab of *Hospital El Cruce* were included in the study. Patients excluded from the study: patients hospitalized, fertile women in whom pregnancy could not be ruled out, patients with a negative modified Allen's test, previous myocardial revascularization surgery with left internal mammary artery bridge, kidney disease with a glomerular filtration rate < 30 mL/min (http://www.renal.org.ar/utilitarios_filtrado3.php), CHILD C and D severe liver disease, patients on benzodiazepines and/or who may have received benzodiazepines within the last 48 hours.

Procedure

Patients were randomly divided through an electronic randomization system. One hour after receiving the active drug/placebo, the patients were transferred to the cath lab.
In all the cases, the patient's right arm was extended and laid on the armrest with his hand in the supine position, with hyperextension of his wrist and hand over the pad. The hand was fixed to the armrest using an adhesive cloth and the patient was administered antisepsis with povidone-iodine. The surgical field was covered with sterile sheet. Radial pulse was checked on such artery 2 fingerbreaths above the fold of the wrist. A total of 2 to 5 cc of lidocaine at 2% were administered using a 25-G 5/8 in needle. After finding the site with the greatest amplitude of radial pulse, a 20-G needle was used or a 20-G Abbocath catheter in a 45° angle was inserted using Seldinger technique. After obtaining pulsatile flow, a 0.018 in guidewire (*ad-hoc* wire) was advanced smoothly. After removing the Abbocath catheter needle or Teflon and performing a small incision with a scalpel blade no. 11, the introducer sheath was advanced while keeping a steady point over the guidewire and holding the proximal edge. Once in position, the dilator and the guidewire were removed. A 6-Fr dedicated arterial introducer sheath for radial access without hydrophilic covering (Radiofocus, Terumo Tokyo, Japan) was used in all the cases. Saline solution was used as a purging liquid and heparin was administered in doses of up to 5000 IU for diagnostic procedures and 100 IU/kg for therapeutic procedures via lateral access site. After connecting the lateral access site to the manifold and measuring the arterial blood pressure at the start of the procedure, 100 µg to 200 µg of nitroglycerin were administered via lateral access site to all patients with systolic arterial pressures > 100 mmHg. Afterwards, a baseline radial arteriography was performed through the collateral of the introducer sheath in the anteroposterior projection while keeping the angiographic table 90 cm away from the floor and a distance between the intensifier and the x-ray tube of 100 cm. (18) Then, preformed catheters were advanced towards the aortic root while mounted over a 0.035 in J-shaped tip guidewire with floppy distal end. 6-Fr JL 3.5 and JR 4 catheters (Impulse, Boston Scientific, Baja California, Mexico) were used to perform the diagnostic angiography of the left and right coronary arteries, respectively, and/or 6-Fr EBU 3.5 and JR 4 guide catheters (Convey, Boston Scientific, Leek, The Netherlands) to perform the therapeutic procedures. Measures and/or alternative curves were used in patients with smaller or larger aortic root diameters and anatomical variants that would not allow correct cannulations with these catheters. Once the procedure had been completed, the catheter was removed under the protection of the 0.035 in J-shaped tip guidewire with floppy distal end. Before removing the introducer sheath, the angiography of the radial artery was repeated using the same technique described above. The time it took to perform the procedure since the obtention of the first angiography of the radial artery until the angiography performed after completion was recorded.
After removing the introducer sheath, the radial artery was wrapped up in a compression bandage. Forty minutes later and in the absence of bleeding or swelling at the puncture site, the bandage was removed and replaced for a non-compressive bandage that was carried for 12 hours.



Graphic 1. *Final primary endpoint and need for femoral access conversion.*

STATISTICAL ANALYSIS

Based on the rate of radial spasm reported in the medical literature (20%) and estimating a 6% reduction, an N of 87 patients is estimated in each branch. The estimates of the sample were established with an alpha error of 0.05 and a beta error of 0.2.

The block randomization model was used (website http://www.randomizer.org/).

The data obtained were expressed as mean, median, 95% confidence interval, standard deviation or range, where applicable. The incidence rate of radial artery spasm was estimated in patients treated with a scheduled cine coronary arteriography/angioplasty.

The statistical analysis of the results obtained was conducted using the statistical software SPSS, version 20. Categorical variables were compared using the chi-square test or Fisher's exact test depending on the case. Quantitative variables were compared using the Student *t* test or the Mann-Whitney test depending on whether variable distribution was normal or non-parametric, respectively. *P* values < .05 were considered statistically significant.

RESULTS

Table 1 shows the patients' clinical characteristics. In group A, the rate of patients with dyslipidemia was higher compared to group B (26.43% vs 40.22%, *P* = .04). No statistically significant differences were seen in the remaining variables studied.

No significant differences were seen in the variables associated with the procedure: duration (20.65 ± 12.71 min vs 21.69 ± 19.28 min, *P* = .67), radiation dose (841.46 ± 609.18 mGy vs 879.43 ± 715,84 mGy, *P* = .70), and volume of contrast used (95.36 ± 36.01 mL vs 95 ± 34.48 mL, *P* = .94) for groups A and B, respectively.

Regarding the primary endpoint **(Graphic 1)**, the appearance of clinical spasm was reported in 31.03% vs 28,73% [OR, 1.11 (0.58-2.13) *P* = .74], technical spasm in 13.79% vs 13.79%, [OR, 1 (0.42-2.36) *P* = .1], and angiographic spasm in 56.32% vs 47.12%, [OR, 1.44 (0.79-2.62) *P* = .22] for groups A and B, respectively.

Although the need for conversion to femoral access was numerically lower in group A (3.44% vs 6.89%), this difference was not statistically significant [OR, 0.48 (0.11-1.99) *P* = .30].

In group B, 1 patient showed hyperacute stent thrombosis (1.14%) and another patient suffered from an arterial rupture (1.14%) that resolved using a compressive bandage without consequences. In group A, 1 patient showed radial artery dissection (1.14%) without compromise of antegrade flow. A total of 3 patients (3.44%) from group A and 1 patient (1.14%) from group B had catheter-induced coronary spasm. None of the patients developed strokes, arrhythmias or death. No statistically significant differences were reported in the rate of complications between both groups.

After being included in the study, the radial procedure could not be performed in 4 patients from group A and 5 patients from group B.

DISCUSSION

In this study we assessed the efficacy and safety profile of sublingual lorazepam prior to admission to the cath lab to reduce radial artery spasm when such artery is used as the access route to perform diagnostic and therapeutic coronary procedures.

Different factors were identified as predisposing factors for radial artery spasm: use of phentolamine during the procedure, smaller baseline arterial diameter, radial artery anatomical abnormalities, feminine sex, body surface < 1.938, age > 66 years, and introducer sheaths < 10 cm in length (7) (15). Since sympathomimetic drugs can induce vasospasm (16) and given the predominance of alpha-1 adrenoceptors in the radial artery vascular endothelium (17), it is possible that states of great adrenergic discharge like the stress suffered by the patients before entering the cath lab also favor the occurrence of vasospasm. On the other hand, the state of anxiety, defined as a feeling of apprehension associated with the activation of the autonomous nervous system in response to a situation seen as a threat, is a phenomenon documented prior to entering the cath lab through different scales designed for this purpose. This state affects the patient during the entire procedure and is associated with long-term cardiovascular adverse events (18).

Lorazepam belongs to the family of benzodiazepines and has the capacity to stimulate the binding of gamma-aminobutyric acid (GAMA), the primary inhibitory neurotransmitter, to the GABAA subunit of GABA receptors. It has anxiolytic, sedative-hypnotic, and amnesic effects and is still used as a preanesthetic medication. It is used via sublingual administration, reaches its plasma peak after 60 min, and its mean half-life is 12 h (19,20).

Our study analysis showed that although the rate of appearance of angiographic spasm was high (62.02% and 54.66% for groups A and B, respectively), these data were similar to those reported by the medical literature and their association with the appearance of technical vasospasm determined by the difficulty/impossibility maneuvering the catheters was low (14% in both groups) (21). Regarding the pain scale, approximately 30% of the patients experienced pain intensity in their forearm > 5/10 when the procedure was performed in both groups. This was the cut-off value used to define clinical spasm, which is consistent with the rate of spasm published in other studies (7). The need to administer fentanyl as the anesthetic agent was similar in both groups.

The need to use another vascular access to finish the procedure dropped 50% among the patients who received lorazepam. Although not statistically significant, this difference may have shown a greater tolerance to the discomfort caused by the procedure. This finding will need to be confirmed by further studies.

Our results are different from those published by Rodriguez Blanco et al. (22) These authors studied the use of IV midazolam to reduce radial artery spasm in patients treated with cardiac catheterization and found a statistically significant difference in their final primary endpoint; 5-Fr introducer sheaths were used in half of these patients, a factor known to reduce the rate of spasm; also, drug administration was intravenous. Astarcioglu et al. (23) also assessed midazolam and nitroglycerin or midazolam alone to reduce radial spasm and found no statistically significant differences between the 2 courses of treatment.

Although, like we did, the aforementioned studies used benzodiazepines to reduce radial artery spasm, in both cases the agent used was midazolam. This drug widely used as an anesthetic inducer was administered intravenously. It is a short-acting drug with a different safety profile. Therefore, we should be cautious about the dose administered because of the risk of causing respiratory distress (24). In our study we tried to assess the sublingual use of a benzodiazepine that has a superior safety profile.

It is obvious that in the medical literature available results are varied when benzodiazepines are assessed in this clinical context, which is why we tried to conduct the very first double-blind, randomized clinical trial with oral benzodiazepines to assess their efficacy and safety profile reducing radial artery spasm.

Some of the limitations of this study are that only outpatients were assessed and that protocol applicability is for stable patients since 1 hour of wait is required after the administration of the drug before starting the procedure.

In conclusion, we can say that based on the results obtained, the administration of sublingual lorazepam prior to being admitted to the cath lab does not reduce radial spasm compared to placebo when this access route is used to perform diagnostic and/or therapeutic coronary procedures. No significant differences were reported in the complications seen between the groups.

REFERENCES

1. *Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions. Am Heart J 1995;129:146-72.*
2. *Elgharib NZ, Shah UH, Coppola JT. Transradial cardiac catheterization and percutaneous coronary intervention: a review. Coron Artery Disease 2009;20:487-93.*
3. *Shilpa Sachdev, Sibu Saha. Transradial Approach to Cardiovascular Interventions: An Update. International Journal of Angiology 2014;23:77-83.*
4. *Jolly SS, Yusuf S, Cairns J, 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.*
5. *Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS study. Journal American College of Cardiololy 2012;60:2481-9.*
6. *Deftereos S, Giannopoulos G, Raisakis K, et al. Moderate Procedural Sedation and Opioid Analgesia During Transradial Coronary Interventions to Prevent Spasm. JACC: Cardiovascular Interventions 2013;6:267-73.*
7. *Ruiz-Salmerón R. J, Mora R, Vélez-Gimón M, et al. Radial Artery Spasm in Transradial Cardiac Catheterization. Assessment of Factors Related to Its Occurrence, and of Its Consequences During Follow-up. Revista Española de Cardiología 2005;58:504-11.*
8. *Hetherington SL, Adam Z, Morley R, 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.*
9. *Jolly S, Amlani S, Hamon M, Yusuf S, Phil D, Mehta S. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: A systematic review and meta-analysis of randomized trials. American Heart Journal 2009;157(1):132-40.*
10. *Hwa Ho H, Haider Jafary F, Jau Ong P. Radial artery spasm during transradial cardiac catheterization and percutaneous coronary intervention: incidence, predisposing factors, prevention, and management. Cardiovascular Revascularization Medicine 2012;13:193-5.*
11. *Kiemeneij F, Vajifdar B, Eccleshall S, Laarman G, Slagboom T, van der Wieken R. Evaluation of a Spasmolytic Cocktail to Prevent Radial Artery Spasm During Coronary Procedures. Cathet Cardiovasc Intervent 2003;58:281-4.*
12. *Rosencher J, Chaıb A, Barbou F, et al. How to Limit Radial Artery Spasm During Percutaneous Coronary Interventions: The Spasmolytic Agents to Avoid Spasm During Transradial Percutaneous Coronary Interventions (SPASM3) Study. Catheterization and Cardiovascular Interventions 2014;84:766-71.*
13. *Bailey P, Pace N, Ashburn M, Moll J, et al. Frecuent Hypoxemia and Apnea After Sedation with Midazolam and Fentanyl; Anesthesiology 1990;73:826-30.*
14. *Thygese K, Alpert J, Jaffe A, et al. Tercera Definición Universal del Infarto de Miocardio. Rev Esp Cardiol 2013;66:132.e1-132.e15.*
15. *Carvalho M, Calé R, de Araújo Gonçalves P, et al. Predictors of Conversion from Radial Into Femoral Access in Cardiac Catheterization. Arq Bras Cardiol 2015;104:401-8.*
16. *Guo-Wei H. Arterial grafts for coronary surgery: Vasospasm and patency rate. J Thorac Cardiovasc Surg 2003;125:S68-70.*
17. *Guo-Wei H, Cheng-Qin Y. Characteristics of adrenoceptors in the human radial artery: clinical implications. J Thorac Cardiovasc Surg 1998;115:1136-41.*
18. *Delewi R, Rohling W, Wagenaar T, et al. Anxiety levels of patients undergoing coronary procedures in the catheterization Laboratory. International Journal of Cardiology 2017;228:926-30.*
19. *Brunton L. (2006). Goodman & Gilman: Las Bases Farmacológicas de la Terapéutica. Undécima edición. Colombia. McGraw-Hill Americana.*
20. *Whitehead N, Clark A, Williams T, Collins N, Boyle A. Sedation and Analgesia for Cardiac Catheterisation and Coronary Intervention. Heart, Lung and Circulation 2020;29:169-77.*
21. *Fukuda N, Iwahara S, Harada A, et al. Vasospasms of the Radial Artery After the Transradial Approach for Coronary Angiography and Angioplasty. Jpn Heart J 2004;45:723-31.*
22. *Rodríguez Blanco S, Leyva Quert A, Mendoza Ortiz JL, et al. Midazolam in the prevention of spasm of the radial artery. Randomized double blind clinical trial. Revista Argentina de Cardioangiología Intervencionista 2018;9:39-46.*
23. *Astarcioglu MA, Sen T, Kilit C, et al. Procedural sedation during transradial coronary angiography to prevent spasm. Herz 2016;41:435-8.*
24. *González Castro L, Mehta J, Brayanov J, Mullen G. Quantification of respiratory depression during pre-operative administration of midazolam using a non-invasive respiratory volume monitor. PLoS ONE 2017; 12: e0172750.*