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CASE REPORT

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Intravascular Ultrasound-Guided Percutaneous Coronary Intervention Using Gadolinium Contrast Medium

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ABSTRACT

Introduction: The iodinated contrast media used in coronary angiography have a very low incidence of adverse effects. In cases in which adverse effects occur, other contrast media are necessary as an alternative. Gadolinium is one of these alternatives, as its safety has been demonstrated in patients with renal failure. However, gadolinium has important limitations, such as low radiopacity for the characterization of the coronary arteries and the need to administer low doses (<0.4 mg/kg) to reduce serious complications, such as nephrogenic systemic fibrosis.

Materials and Methods: We present the first case series of patients undergoing percutaneous coronary intervention in which gadolinium was used as contrast medium and the procedure was guided by IVUS

Results: We report the experience of our center, based on three patients with contraindication to iodinated contrasts who underwent IVUS-guided percutaneous transluminal coronary angioplasty using gadolinium and did not present with significant complications.

Discussion and Conclusions: In cases where percutaneous coronary angioplasty is performed, high contrast doses are usually required. Intracoronary diagnostic techniques such as intravascular ultrasound (IVUS) can help reduce the contrast dose and provide great advantages during the intervention, improving the results.

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Introduction

Iodinated contrast media (ICM) are used during angiography for the characterization and identification of stenosis in the coronary arteries. The molecular characteristics of ICM have evolved substantially in recent years to reduce complications and/or adverse effects that occur after their administration, using for this purpose more hypo-osmolar ionic compounds such as ioxaglate (*Hexabrix®*) [1]. Some case series attribute to ICM an adverse effect incidence of 0.34%, of which only 0.01% are considered severe effects [2]. Uncomplicated allergic reaction is the most frequent adverse effect, characterized by the presence of wheals and/or other skin eruptions that appear almost immediately after the first injection, accompanied by intense itching, which are resolved with corticosteroid and antihistamine treatment. Other times, the reaction is late, and does not have the same response to this treatment. In turn, more infrequent complications that are considered severe, such as thrombocytopenia, angioedema or severe anaphylactic reaction, can lead to shock and death.

Given these cases, it is important to identify other contrast media to be used as alternatives to iodinated agents, such as gadolinium-based media (gadobutrol [3] and gadopentetate dimeglumine [4]). However, the low radiopacity of these media limits the adequate assessment of angiographic lesions, so they are not routinely used for coronary angiography. Despite being a safe compound with a reduced number of allergic reactions (0.7%) similar to ICM [5], gadolinium may sometimes cause renal failure in patients with creatinine >3 mg/dl or if doses >0.4 mmol/kg are used [6], with the most serious complication being nephrogenic systemic fibrosis (NSF) [7]. This entity consists of a fibrosing disorder that affects the skin and other organs, such as the heart, joints, testicles and kidneys. It develops more frequently in patients with severe kidney disease or on hemodialysis, and its onset can take months to years after exposure to gadolinium contrast medium.

Intracoronary diagnostic techniques, such as intravascular ultrasound (IVUS), play an important role in complementing coronary intervention, solving the limitations of gadolinium. Our group presented the first published case of IVUS-guided percutaneous coronary intervention (PCI) using gadolinium as a contrast medium [8].

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After performing coronary angiography with gadolinium contrast medium, we evaluated the coronary segments where the significance of the lesions was not well visualized with IVUS, and the lesion length, vessel diameter and atheroma plaque characteristics were quantified to predict possible complications in cases of complex anatomies such as calcified lesions. The use of IVUS aids in determining the strategy to be followed during the steps of the angioplasty, helping to correctly choose the material and therefore minimize costs [9]. Once the device is implanted, assessment with IVUS is essential to verify stent apposition and expansion. Therefore, with IVUS, we were able to use lower gadolinium contrast doses during coronary angiography, which is directly related to a reduction in the risk of associated complications.

Materials and Methods

We present the first case series of patients undergoing percutaneous coronary intervention in which gadolinium was used as contrast medium and the procedure was guided by IVUS. Three cases are presented in which the role of this combined revascularization strategy in coronary intervention can be seen. This strategy could be reserved for patients who previously had a severe reaction to ICM and therefore their administration is an absolute contraindication. All patients were informed of the risks of the procedure and signed an informed consent form.

Results

Cases series

The patients' demographic characteristics, personal history and intervention data are shown in Table 1.

Case 1

A 47-year-old male who underwent kidney transplantation in 1993 with resumption of hemodialysis in 1999 due to relapse of focal and segmental glomerulonephritis. In 2007, coronary angiography was performed for typical chest pain, administering acetylsalicylic acid (ASA) 100 mg and a loading dose of clopidogrel 300 mg; no significant coronary lesions were identified. At 24 hours after the procedure, the patient presented with severe thrombocytopenia (7,000 x 10e9/L) that was attributed to the pretreatment with clopidogrel. In 2014, a new coronary angiography was performed, dispensing with clopidogrel and administering ASA as pretreatment and unfractionated heparin. Multivessel disease was evident. After 24 hours, a decrease in platelets was detected at 25,000 x 10e9/L, ASA was suspended, and it was confirmed that it was not pseudothrombocytopenia. The heparin-induced thrombocytopenia test was negative, and the coagulation parameters and times were normal. The platelet counts were normalized on the 4th day after the procedure, at which time prasugrel was started for 3 days without affecting the platelet count. Percutaneous intervention was performed, implanting a total of 7 zotarolimus-eluting stents (*Resolute Onyx®)* (Figure 1A), using 213 cc of the iodinated ionic contrast agent ioxaglate sodium and ioxaglate meglumine (*Hexabrix®*) and bivalirudin as anticoagulant. At 6 hours, an analyte was obtained that showed zero platelets, with the platelet count progressively recovering thereafter. A diagnosis of severe thrombopenia after ICM administration was established.

Six months after revascularization, the patient underwent a new coronary angiography for persistent angina with minimal effort, despite optimal medical treatment, using gadolinium (*Gadoteridol®*) as a contrast medium. 36 cc was used, showing evidence by IVUS of severe multisegmental restenosis of the previously implanted stents at the level of the first obtuse marginal artery (OM1) and right coronary artery (RCA) (Figure 2A). There was no reduction in platelet counts after the procedure. The findings were presented to the Heart Team, which rejected surgical revascularization, instead deciding to perform two-stage percutaneous coronary intervention (Figure 2B). 42 cc of *Gadoteridol®* was used in each procedure, and hemodialysis was performed 4 hours after the procedure to reduce the risk of NSF. The platelet count did not decrease in the hours following either procedure.

Case 2

A 70-year-old male who underwent right hemicolectomy in 2012 for colon adenocarcinoma without subsequent recurrence.

Table 1: Patients' demographic characteristics, personal history and intervention data.

	Case 1	Case 2	Case 3
Sex	Male	Male	Male
Age	47	70	69
Hypertension	Yes	Yes	Yes
Dyslipidemia	Yes	Yes	Yes
Diabetes	Yes	Non	Yes
Smoke	Ex-smoked	Ex-smoked	Ex-smoked
Chronic renal disease	Hemodialysis	Non	Non
Previous ischemic cardiac disease	Yes	Non	Yes
Contraindication to iodinated contrast	Thrombocytopenia	Allergy	Allergy
Previous allergy test	Negative	Late reaction	Negative
Ischemia detection test	Stress test (ergometry)	Stress echocardiography	Nuclear Medicine
Indication for catheterization	NSTEMI	Stable angina	Unstable angina
Coronary disease	Multi-vessel	Left coronary artery	Multi-vessel
Previous plasmatic creatinine	6mg/dl	0.89mg/dl	1,14mg/dl
Post-PCI plasmatic creatinine	4,5mg/dl	0,71mg/dl	1,02mg/dl
Ejection Fraction left ventricle	52%	55%	64%
Amount of gadolinium contrast	42cc	55cc	66cc

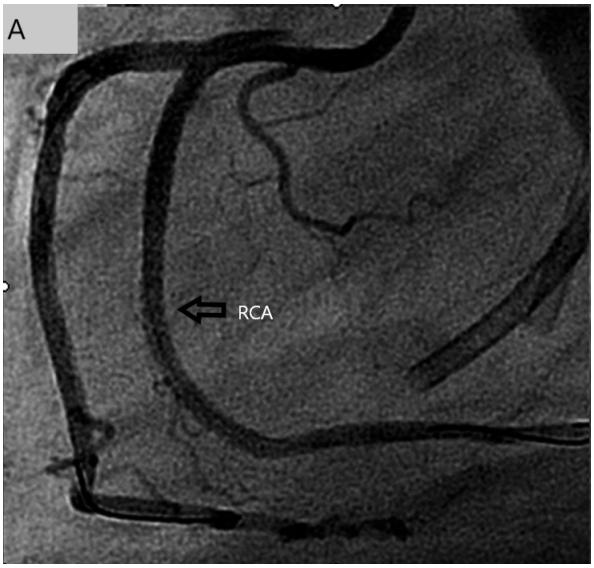

Figure 1: Percutaneous intervention of the right coronary artery (RCA) using iodinated contrast medium. Four zotarolimus-eluting stents were implanted.

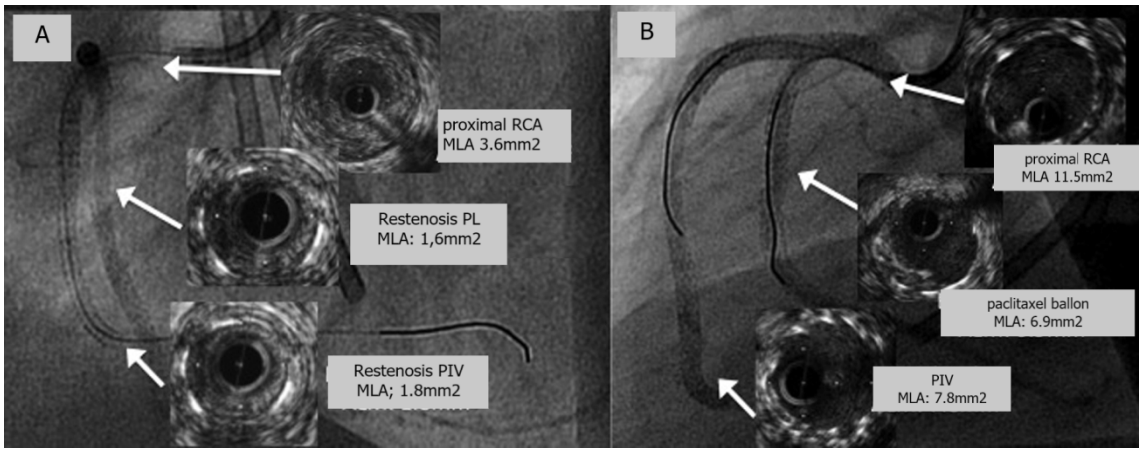

Figure 2: Percutaneous coronary intervention using gadolinium contrast medium and intravascular ultrasound (IVUS) guided to procedural. (A) Showing evidence by IVUS of severe multisegmental restenosis of the previously implanted stents at the level of the right coronary artery (RCA). Minimal luminal area (MLA) by IVUS showed several restenosis in proximal segment, posterolateral (PL) artery and posterior interventricular (PIV) artery. (B) Final result after ballon angioplasty on PL artery and stent angioplasty on proximal RCA and PIV. MLA by IVUS showed an improvement.

During a cancer extension study, the patient developed a delayed allergic reaction after administration of ICM (iodixanol, *Visipaque®*) with respiratory failure that required adrenaline without orotracheal intubation. In 2014, a cardiological study was performed for stress angina, with clinically positive ergometry and stress echocardiogram showing reversible ischemia in the territory of the anterior descending artery (ADA). The study of allergy to ICM and ASA showed that there was a delayed reaction to ICM that decreases the possibility of prevention with glucocorticoids and antihistamines and therefore absolutely contraindicates their use.

Coronary angiography was performed using *Gadoteridol®* and IVUS. In the diagnostic study, a faint ostial lesion in the circumflex artery (CxA) (minimal luminal area (MLA) of 7.2 mm^2 assessed by IVUS) and severe stenosis of 85% in the mid ADA (MLA of 3.2 mm^2 by IVUS) were evident. Percutaneous transluminal coronary interventional (PCI) was performed on this lesion by implanting a zotarolimus- eluting stent (*Resolute Onyx®*, 2.75 x 22 mm), post-dilating with a 3-mm noncompliant balloon and verifying the result with IVUS (MLA of 6.6 mm^2), concluding the procedure. A total of 55 cc of gadolinium was used, and the patient presented no immediate or delayed complications. At the one year of follow-up, the patient was asymptomatic, successfully completing the cardiac rehabilitation program.

Case 3

A 69-year-old male with a history of paroxysmal atrial fibrillation anticoagulated with acenocoumarol (*Sintrom®*) and known chronic ischemic heart disease with debut in 2002, when a significant non-revascularized lesion in the OM1 was observed. During catheterization, the patient presented with an uncomplicated allergic reaction that resolved with glucocorticoids and antihistamines. In 2013, a new coronary angiography was performed for angina refractory to medical treatment, showing the same OM1 lesion, moderate disease of the middle segment of the RCA and another moderate calcified and diffuse ADA lesion. It was decided to use a pressure guidewire in both moderate lesions, but the patient suffered an adverse reaction to ICM (*Hexabrix®*) despite premedication with glucocorticoids and antihistamines, so the procedure was terminated. It was decided to assess the extent of myocardial ischemia by performing a cardiac single photon emission

computed tomography (SPECT), which showed severe ischemia in the inferobasal and middle segments and moderate ischemia at the level of the apical segments. The antianginal treatment was optimized, but after 6 months, the patient presented with progression of angina to class III, so coronary angiography with gadolinium (*Gadoteridol®)* was performed.

Disease progression was observed relative to the previous catheterization, presenting severe stenosis of 85% of the RCA ostium, followed by stenosis of 85% in the middle segment, both evaluated with IVUS (MLA of 2.8 mm^2 and 2.5 mm^2, respectively). These were treated by implanting two zotarolimus-eluting stents (*Resolute Onyx®,* 3 x 30 mm), post-dilating with a 3.5-mm noncompliant balloon, after evaluation by IVUS. The ADA was also evaluated by IVUS, showing an MLA of 2.5 mm^2 in its midsegment, and two zotarolimus-eluting stents (*Resolute Onyx®,* 3 x 34 mm and 3 x 12 mm) were implanted, post-dilating the proximal area with a 3.5-mm noncompliant balloon. The subsequent evaluation with IVUS showed infraexpansion of the most proximal stent, so a new post-dilation was performed at a greater atmosphere with a final MLA >7 mm. The CxA lesions were not revascularized because it was a smaller caliber vessel, and the procedure was terminated. A total of 66 cc gadolinium contrast was used during the complete intervention, and there were no subsequent complications related to its use.

Discussion

The serious complications associated with ICM are a real problem in patients diagnosed with ischemic heart disease and stenosis of the epicardial coronary arteries. Percutaneous intervention has an impact on patient prognosis and on anginal symptom improvement, according to the clinical practice guidelines [10]. In the case of absolute contraindication to ICM, surgical revascularization can be considered, such as in case 1. However, on numerous occasions, patients are rejected because they present a high surgical risk, added to the technical difficulties derived from the anastomosis (poor distal beds). The possibility of surgical revascularization in case 2 was not considered since the revascularization of the affected vessel was performed in the same procedure. In the case of patient 3, the surgical option could have been considered; however, the decision was made based on the patient's comorbidity and resolving the process in the same act. We believe that the use of gadolinium can be considered an alternative to ICM, including before bypass surgery, in extreme cases and involving an unacceptable surgical risk. To date, there is little experience with the use of gadolinium as a contrast agent used in coronary angiography, but there are some case series in the literature that show its safety [11]. Sarkis et al. [12] reported the first coronary angiography using gadolinium in 2001, and Bokhari et al. [13] the first percutaneous coronary angioplasty using this contrast agent. In both cases, the patients had underlying renal failure, and no significant complications were observed, thus establishing the indication for gadolinium administration in patients with renal failure and contraindication for ICM. In this sense, Boyden et al. [14] conducted a review of all retrospective and prospective observational studies and randomized studies from 1996 to 2007 in which gadolinium was used. They assessed the safety of gadolinium and the risk of gadolinium-induced nephropathy (GIN) in patients who received this contrast medium during nuclear magnetic resonance imaging or angiography. This was compared with the probability of developing iodinated contrast-induced nephropathy (ICIN), and it was concluded that although in the analyzed observational studies there was no increase in cases of GIN, in the randomized studies, it did not provide a significant benefit in terms of renal protection compared to the use of ICM. Adverse effects on renal function increase significantly when the dose of gadolinium >0.4 mmol/kg, especially in patients with chronic renal failure, due to global and interstitial fibrosis and tubular atrophy [15-16].

It has been attempted to compensate the poor coronary visualization provided by gadolinium with an increase in the quality of the radiation used, resulting in greater exposure for both patients and health workers. With current radiodiagnostic equipment, this problem can be reduced, decreasing radiation dispersion [17]. Specific injection systems have been used in an attempt to improve the poor coronary visualization resulting from the limited radiopacity of gadolinium [18]. However, as indicated by that study, a greater administration flow rate can increase the inherent toxicity of gadolinium and therefore generate complications secondary to its arrhythmic potential (malignant ventricular arrhythmias). Our experience in this regard is clearly conservative because we performed gadolinium contrast injections manually, without using injection pumps, precisely to reduce the risk of ventricular arrhythmias. None of the injections administered caused acute cardiac complications or hemodynamic deterioration.

Intracoronary diagnostic techniques can play an important role in this patient profile. The limitations of gadolinium can be counteracted with the support of morphological techniques such as optical coherence tomography (OCT) and IVUS, as well as functional techniques such as fractional flow reserve (FFR). The experience found in the literature is scarce, and therefore, there is no consensual basis to establish a recommendation in this regard. Casey et al. [19] describe the performance of an IVUS-guided angioplasty of hemodialysis loop graft using gadolinium. More recently, Gupta et al. showed a satisfactory result of an IVUS-guided percutaneous coronary intervention of chronic total coronary occlusion in a patient with allergy to ICM using gadolinium contrast [20].

In our opinion, IVUS offers more advantages than other intracoronary diagnostic techniques to complement the coronary evaluation, in which we use gadolinium as a contrast medium. Once angiography was performed, we performed IVUS evaluation of coronary arteries in which the significance of the lesions was not well visualized, or to assess the true vessel diameter and the lesion length. Likewise, it provides us with information on the characteristics of the plaque, anticipating possible complications in the case of complex anatomies such as highly calcified or tortuous lesions. Therefore, it aids us to determine the strategy to follow during the angioplasty steps, helping us to correctly choose the material. Another utility that IVUS offers in this type of intervention, as shown in Figure 2, is the radiopaque markings of the probe, which serve as a reference when we are ready to implant the stent.

IVUS assessment of the post-implant result offers an assurance of good stent apposition and expansion, greater than that determined by simple angiographic assessment. In our cases, the final result was verified with IVUS in all cases, and in two of them, post-dilation was performed as optimization. Therefore, better results in reducing restenosis and the risk of thrombosis were obtained; however, since there were only three cases, such an assertion cannot be affirmed. All these maneuvers with IVUS allow us to use lower doses of gadolinium during coronary angiography, which, as mentioned above, is directly related to the risk of complications [14].

OCT has a higher spatial resolution than IVUS [21], allowing better visualization of the intima and the first layers of the media, but limited vessel depth penetration. The main handicap that we found with OCT for its use in patients where the contrast medium used is gadolinium is precisely the need to use it for blood "washing" when performing image acquisition, thus requiring higher contrast doses.

Evaluation with FFR would allow a functional assessment of the stenosis of coronary lesions, fundamental in patients for whom there are doubts after angiography [22]. We did not use FFR in any of the three patients, since IVUS allowed us to determine the severity of the lesions and subsequently check the result. Only in case 3 was pressure guidewire proposed; however, the onset of allergic symptoms after the second catheterization led to discarding this option and finally performing SPECT. However, we believe that FFR could be interesting in centers where IVUS is not available.

Conclusions

Patients with contraindication to ICM and the need for PTCA pose a challenge for interventional cardiologists. The available evidence supports the use of gadolinium as an alternative; at reduced doses, complications are significantly reduced. However, its low radiopacity justifies the use of other intracoronary diagnosis methods to optimize coronary intervention. IVUS offers numerous advantages to guide PTCA in this patient profile, showing results comparable to conventional coronary angiography, although when verifying the results with IVUS, we obtain greater certainty and intervention safety, without complications. We present the experience of our center and the first published study in which gadolinium and IVUS are used to guide PTCA in patients with ischemic heart disease.

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