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High risk of bleeding in elderly patient with coronary artery disease

Alto risco de sangramento em paciente coronariopata idoso

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ABSTRACT - Individuals at high risk of bleeding comprise a significant portion of patients submitted to coronary angioplasty. The optimal duration of dual antiplatelet therapy for these patients remains uncertain, and the use of risk stratification scores for hemorrhagic and ischemic complications, such as PRECISE-DAPT and DAPT, help in the decision-making process. We report the case of an octogenarian patient with known high risk of bleeding (PRECISE-DAPT = 65; DAPT = 0) diagnosed with two chronic subdural hematomas, 4 weeks after angioplasty with placement of drug-eluting stent to treat coronary artery disease. Based on the latest evidence from the literature on the management of antiplatelet agents for this group of patients, the decision was for early discontinuation of clopidogrel on the 31st day after angioplasty. The clinical course was successful over 24-month follow-up.

Keywords: Bleeding; Risk factors; Percutaneous coronary intervention; Platelet aggregation inhibitors; Drug coated stent

RESUMO - Indivíduos com alto risco de sangramento correspondem à parcela significativa de pacientes submetidos à angioplastia coronária. O tempo ideal de terapia antiplaquetária dupla para esses pacientes ainda permanece incerto, podendo ser auxiliado por escores de estratificação de risco para complicações hemorrágicas e isquêmicas, como o PRECISE-DAPT e o DAPT. Relatamos o caso de um paciente octogenário com conhecido elevado risco de sangramento (PRECISE-DAPT = 65; DAPT = 0) diagnosticado com dois hematomas subdurais crônicos 4 semanas após realização de angioplastia com implante de stent farmacológico para tratamento de doença arterial coronariana. A partir de evidências mais recentes da literatura sobre o manejo de agentes antiplaquetários nesse grupo de pacientes, optou-se pela suspensão precoce do clopidogrel no 31^o dia após a angioplastia com evolução clínica favorável ao longo de 24 meses de seguimento.

Descritores: Sangramento; Fatores de risco; Intervenção coronária percutânea; Inibidores da agregação de plaquetas; Stent farmacológico sem polímero

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BACKGROUND

Dual antiplatelet therapy (DAPT) is instrumental to the excellent current results in interventional cardiology, significantly preventing recurrent ischemic events, such as acute myocardial infarction and stent thrombosis. It does, however, present some risks, especially in scenarios more prone to bleeding. It is well known that patients undergoing percutaneous coronary intervention (PCI), either for the treatment of acute coronary syndrome (ACS) or stable coronary artery disease (CAD), tend to have multiple risk factors for both ischemic events and bleeding complications.¹ Determining the duration of DAPT becomes, therefore, more complex, and should be individualized, calculating the risk and benefit of prolonging the therapy, by use of scores considering the possibility of hemorrhagic or ischemic complications (PRECISE-DAPT and DAPT scores, for example).^{1,2} In addition to the management of DAPT, other strategies may be used when dealing with a patient with a clinical profile of high risk of bleeding, such as choosing the appropriate vascular access and using adjunctive intravascular imaging methods, to optimize results or invasive functional assessment that enables a more rational, ischemia-guided intervention.²

The objective of this report was to describe and discuss strategies used in a specific case of high risk of bleeding.

The study was evaluated and approved by the Research Ethics Committee of Faculdade de Medicina da Bahia of the Universidade Federal da Bahia (protocol 3.830.217, CAAE 28187019.7.0000.5577).

CASE REPORT

An 84-year old male patient, former smoker and alcoholic (abstinent for 1 year), hypertensive and insulin-requiring diabetic, diagnosed with malignant prostate cancer under evaluation to decide treatment strategy (surgical or hormone therapy alone), was referred to the cardiologist for recent onset of dyspnea on usual exertion and atypical chest pain. Also presented alcoholic liver disease (Child A), esophageal varices (no history of recent bleeding) and mild anemia (hemoglobin: 10.3g/dL), attributed to liver disease and colonic diverticular disease (also no history of recent bleeding).

Myocardial perfusion scintigraphy demonstrated inferior wall ischemia, associated with a persistent local decreased uptake, and mild reduction in the left ventricular ejection fraction. Elective coronary angiography was thus indicated.

The exam via radial artery demonstrated 50% to 70% segmental lesion in the mid-third of the dominant right coronary artery (RCA); 50% lesion in the mid-third of the left circumflex artery (LCx); and 90% eccentric lesion in the mid-third of the left anterior descending artery (LAD), involving the second diagonal branch (Dg2), of great anatomical importance, which had no obstructive lesions. Since the symptoms persisted despite drug therapy and there was a discrepancy between the results of the noninvasive test and the coronary angiography, after multidisciplinary discussion, it was decided for functional assessment with fractional flow reserve (FFR) and probable PCI.

The antecubital vein of the right upper limb was catheterized and a 5F pigtail catheter was placed in the superior vena cava for systemic infusion of adenosine (Figure 1). Selective catheterization of the RCA was carried out using a 6F JR 4.0 guiding catheter (LAUNCHER Medtronic) via right radial artery, and a PressureWire™ Certus™ (St. Jude®) was deployed in the distal bed (Figure 2).

FFR was measured after adenosine-induced maximal hyperemia at 140 to 180mcg/kg/minute, with a result of 0.84. The left coronary was then catheterized with the guidewire placed in the distal bed of the LCx artery, with a FFR of 0.83 (Figure 3). Guidewires were passed through the distal bed of the LAD artery (BHW, Abbott Vascular) and into the distal bed of the Dg2 branch (BMW, Abbott Vascular).

An EMERGE 2.5x15mm semi-compliant balloon catheter (Boston Scientific®) was used to pre dilate the lesion,

and a biolimus-eluting A9 polymer-free 2.5x24mm stent Biofreedom® (Biosensors®) was successfully implanted.

The finalization was carried out with kissing balloon technique using non-compliant 2.75x12mm balloon catheter EUPHORA (Medtronic®), with excellent angiographic results, not compromising the lateral branch (Figure 4 and Figure 5). The patient was discharged one day after the procedure, asymptomatic from the cardiovascular perspective, using DAPT with acetylsalicylic acid 100mg daily associated with clopidogrel 75mg daily.

Approximately four weeks after the procedure, the patient was evaluated by the neurology team, as part of the investigation of a long-term dizziness and “forgetfulness” (according to family members). Cranial computed tomography (CT) showed a chronic frontoparietal subdural hematoma on the right, and chronic frontoparietal occipital subdural hematoma on the left, with signs of exacerbation (Figure 6).

Clopidogrel was discontinued on the 31st day after the angioplasty (day the team was notified of the CT result), and acetylsalicylic acid was maintained (which had been used prior to the joint evaluation by the neurology and neurosurgery teams) and intense clinical surveillance was recommended, besides neurosurgical conservative strategy.

Figure 1. Induction of maximum coronary hyperemia with systemic adenosine in superior vena cava to evaluate the fractional flow reserve.

After almost 24-month follow-up, the patient remained with no cardiovascular symptoms and no neurological deficits. The patient has an indwelling bladder catheter, due to

the development of urinary retention secondary to prostatic cancer, with episodes of recurrent gross hematuria; adjuvant palliative urologic surgical treatment is planned.

Figure 2. Assessment of fractional flow reserve in right coronary artery.

Figure 3. Assessment of fractional flow reserve in the left circumflex artery.

Figure 4. Selective left coronary angiogram documenting sub occlusive lesion in the middle segment of the left anterior descending artery.

Figure 5. Selective left coronary angiogram documenting excellent final angiographic result in the left anterior descending artery angioplasty.

Figure 6. Elective cranial computed tomography after 4 weeks of coronary angioplasty, with documentation of bilateral chronic subdural hematoma.

DISCUSSION

This case illustrates an increasingly frequent situation in the routine of catheterization laboratories, which comes along with the increased life expectancy of the population: progressively more complex patients with multiple comorbidities. The expansion of possibilities of percutaneous treatment of coronary artery disease and the improved results are accompanied by problems related to the adjuvant drug therapy used and the clinical complexity of patients treated. Patients at high risk for bleeding account for about 20% of patients undergoing coronary angioplasty; however, they are generally excluded from clinical trials that test new devices and antithrombotic drug regimens.³

Many studies have already pointed to an association between shorter DAPT duration and reduced risk of bleeding. A large meta-analysis including the RESET, OPTIMIZE, EXCELLENT, and PRODIGY clinical trials compared bleeding complications in patients receiving short-term (3 and 6 months) and long-term (≥ 12 months) DAPT. The reduction in bleeding events was important with shorter DAPT, with no significant differences over other types of cardiovascular adverse events over the same period.⁴ The old recommendations for patients with high-risk of bleeding when treating CAD were 1 month of DAPT after placement of a bare-metal stent (class I recommendation) - or 6-month regimen (could be shortened to 3 months) after drug-eluting stent (class I recommendation). In the case of ACS, the minimum predicted DAPT duration was 12 months (class I recommendation), regardless of the type of stent

implanted.^{1,2} Bare-metal stents until not long ago were preferred to drug-eluting stents in patients at high risk of bleeding, especially in the elderly, since they enabled shorter duration of DAPT.

The LEADERS FREE trial and its sub-studies, however, suggested that DAPT could be “shortened” to 1 month with the Biofreedom® stent, since it proved to be superior in clinical efficacy and safety outcomes as compared to the bare-metal stent tested.³ The comprehensiveness of these data, including the scenario of ACS and oral anticoagulation, combined with 2-year follow-up data, led to a review in the guidelines, with new recommendations on the duration of DAPT and the choice of stent according to the patient’s risk of bleeding.^{3,5} The new guidelines therefore include the possibility of 1-month DAPT in patients at high risk of bleeding after percutaneous treatment of stable CAD with specific drug-eluting stent (class IIb recommendation) and DAPT reduced to 6 months after percutaneous treatment of ACS with this same type of stent (class IIa recommendation).^{2,5} Similar result was found in the SENIOR study, which demonstrated the superiority of another specific drug-eluting stent over the bare-metal stent in the treatment of stable CAD using one-month DAPT, specifically in elderly patients. The group treated with drug-eluting stents had a reduction in the occurrence of the combined outcome of all-cause mortality, infarction, stroke, and need for revascularization of the target lesion, with no differences in bleeding as compared to the bare-metal stent.⁶

Risk stratification for hemorrhagic and ischemic events was crucial for deciding the intervention strategy, the choice of access route and type of stent, enabling shorter DAPT after the identification of an adverse hemorrhagic event in our patient. Anemia, hypertension, renal impairment due to age, advanced age, and history of previous bleeding were variables that directly increased the chance of bleeding complications after implantation of drug-eluting stent (PRECISE-DAPT = 65). Hypertension, advanced age, renal impairment, diabetes, stable CAD and stent implantation in bifurcation were variables that increased the ischemic risk after implantation of the drug-eluting stent.⁵ The risk of bleeding, on the other hand, was higher than the risk of ischemic events after risk stratification by validated scores (DAPT = 0). The current guidelines emphasize individualized treatment for patients at high risk of bleeding (DAPT < 2 or PRECISE-DAPT ≥ 25), and it is the responsibility of the medical team to weigh the risk and benefit of shortening DAPT, which supported our decision to interrupt DAPT after the bleeding event (31st day after angioplasty).^{2,5}

The patient had other comorbidities, some not directly considered in DAPT and PRECISE-DAPT, which however represent traditional risk factors for bleeding: chronic alcohol abuse, alcoholic liver disease (Child-Pugh stage A), and esophageal varices. It is worth emphasizing that alcoholic liver disease is an important cause of anemia and, when associated with a significant reduction in liver function, further increases the risk of bleeding and may even lead

to spontaneous intracerebral hemorrhage.⁷ The history of previous fall is also a very important factor to be evaluated in order to define medical management when individualizing the treatment, considering that the main risk factor for new falls in the elderly is a recent past of falls. Added to the patient history of chronic alcoholism, the risk of intracranial or non-intracranial bleeding due to trauma, especially falls, is quite high.^{8,9} Another important comorbidity that drew attention of the team was moderate anemia (hemoglobin: 10.3g/dL). Moderate or severe anemia (hemoglobin <10.9g/dL) in patients with ACS undergoing PCI or diagnostic angiography is associated with a significant increased risk of bleeding in the first 6 months after the procedure, which in turn may be associated with concomitant ischemic events.¹⁰ It is important to emphasize that the discontinuation of DAPT was due to documented bleeding, and was not part of the initial treatment plan after PCI. Current guidelines even recommend considering prolonging DAPT, regardless of the type of stent implanted, if the patient does not present hemorrhagic complications throughout the treatment follow-up, which was not the case for this patient.^{2,5} Some strategies used during the percutaneous procedure were key for preventing hemorrhagic events: choosing the radial access and FFR-guided percutaneous treatment. If there are no contraindications, the radial access is associated with a reduction in hemorrhagic vascular complications at the puncture site as compared to the femoral access.¹ The scope of these results, well described in the RIVAL, RIFLE-STEACS and MATRIX trials, is beyond the context of ACS, even though greater benefit is described in these circumstances. Despite the advantages described, factors related to the convenience of the operator and the learning curve related to the use of this access, both for complex coronary interventions and for combined use of coronary adjunctive methods, such as intravascular ultrasound (IVUS) and FFR, even today limit its widespread use in some places. Nevertheless, in recent years, there has been a considerable increase in the teaching and incorporation of the radial technique for PCI in Brazil, even in cases of greater complexity.¹¹ Regarding the measurement of FFR, the gold standard method for the definition of stress-induced myocardial ischemia, the DEFER study showed that stent placement in coronary arteries with stenoses that are functionally non-significant did not have significant benefits in clinical outcomes, nor did it improve cardiovascular outcomes at 5-year follow-up, when compared with the group not undergoing PCI (drug-optimized treatment).¹² The relevance of these results, along with knowledge derived from studies, such as FAME and FAME 2, was essential to guide a more selective, ischemia-guided coronary intervention, without addressing the RCA and LCx of our patient.¹²⁻¹⁴

Based on the results of several prospective randomized clinical trials that tested the decision to conduct FFR-based revascularization, the method has high clinical relevance.

In the absence of noninvasive evidence of ischemia, FFR, conducted in stenosis with 50% to 90% diameter reduction, receives class I recommendation and level of evidence A in the main coronary revascularization guidelines, such as those published by the European Society of Cardiology, in 2014.¹⁵ On the other hand, it is worth mentioning FFR also reflects the myocardial area at risk, *i.e.*, a 90% stenosis in a minor marginal branch will have a result of FFR ≥ 0.8 , while a 90% stenosis in the proximal segment of the left anterior descending artery most likely will have a very ischemic FFR result. Evan Shlofmitz and Allen Jeremias, in a recent editorial, pointed to a similar management, not recommending FFR in stenosis $\geq 90\%$.¹⁶ Based on these data, and considering that we were dealing with $\geq 90\%$ stenosis in the LAD artery (large area potentially at risk) we decided jointly for percutaneous intervention, regardless of the invasive functional assessment of the vessel, although some studies also pointed to a favorable initial clinical progress in patients maintained only with optimized drug treatment, especially considering the risk of bleeding and the presentation as stable CAD.¹⁷

Although no specific scores were used for the initial stratification of the patient's level of frailty, invasive diagnostic procedure and subsequent intervention were considered relevant by the multidisciplinary assessment, considering the mid-term prognosis of comorbidities presented by the patient, and his autonomy for most basic activities of daily living. Pimentel et al. studied specifically nonagenarians, and found a complication and mortality rate (6.4%) comparable to literature data on percutaneous revascularization in elderly patients (>80 years), in which the overall mortality rate was 2.2% to 3.5% in elective cases, and 14.1% in acute coronary syndromes. The main factors found to increase mortality were multivessel coronary disease, depressed left ventricular function, insulin-dependent diabetes, renal failure, and need for emergency intervention,¹⁸ which does not apply to our patient. Percutaneous coronary intervention with stent implantation, less invasive and traumatic, and presenting good results in selected cases, is an important option in the treatment of very elderly patients.

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None.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: CVES, YG and VA; data collection: CVES, YG and VA; data interpretation: CVES; writing of the text and approval of the final version to be published: CVES, YG, VA, AMO, LER and ED.

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