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Deferred stent implantation in patients with acute coronary syndromes and thrombus-containing lesion. New indication for direct oral anticoagulants?

Adiamento de implante de stent em pacientes com síndromes coronárias agudas e lesão com presença de trombo. Nova indicação para anticoagulantes orais diretos?

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ABSTRACT – Background: When stents are implanted in the thrombotic environment, they may cause coronary emboli, with increased risk of no-reflow and clinical complications. The aim of this study is to evaluate the impact of delayed stenting in patients with acute coronary syndromes and thrombus-laden coronary arteries using the direct oral anticoagulant apixaban in combination to dual antiplatelet therapy. **Methods:** We included 11 consecutive patients. After first coronariography, patients received treatment with aspirin, clopidogrel and apixaban for 7 days. Another angiography/intervention was planned and stent implantation performed in cases with a residual stenosis diameter >30%. **Results:** Most participants were male (80%). All were diabetic. Multivessel disease was present in 20% of cases. All patients remained clinically stable between the first and second procedure. Stent implantation was not required in two patients. In the remaining nine, the mean residual stenosis and the median thrombus burden was visually smaller, and a drug eluting stent was implanted. There was no phenomenon of no-reflow/slow-flow after stent deployment, with blush grade 3 in all of them. **Conclusion:** Apixaban in association with dual antiplatelet therapy has shown to be effective to reduce thrombus burden and mechanical complications of stent deployment, when coronary thrombus is angiographically identifiable.

Keywords: Coronary thrombosis; Dilatation, pathologic; Apixaban

RESUMO – Introdução: Quando os stents são implantados em ambiente trombótico, podem provocar embolia coronária, aumentando o risco de *no-reflow* e complicações clínicas. O objetivo deste estudo foi avaliar o impacto de adiar o implante do stent em pacientes com síndromes coronárias agudas e artérias coronárias com alta carga de trombos, usando o anticoagulante oral direto apixabana em combinação com a terapia antiplaquetária dupla. **Métodos:** Foram incluídos 11 pacientes consecutivos. Após a primeira coronariografia, os pacientes receberam tratamento com aspirina, clopidogrel e apixabana por 7 dias. Outra angiografia/intervenção foi planejada, e o stent foi implantado em casos com diâmetro de estenose residual >30%. **Resultados:** A maioria dos participantes era do sexo masculino (80%). Todos eram diabéticos. Doença multiarterial foi detectada em 20% dos casos. Todos os pacientes permaneceram clinicamente estáveis entre o primeiro e o segundo procedimento. Não foi necessário implantar stent em dois pacientes. Nos nove restantes, a estenose residual média e a carga de trombo foram visualmente menores, tendo sido implantado stent farmacológico. Não houve fenômeno de *no-reflow* ou *slow-flow* após a implantação do stent, com *blush* miocárdico grau 3 em todos eles. **Conclusão:** A apixabana associada à terapia antiplaquetária dupla mostrou-se eficaz na redução da carga de trombo e das complicações mecânicas do implante de stent, quando grande carga de trombo coronário é identificável na angiografia.

Descritores: Trombose coronária; Dilatação patológica; Apixabana

INTRODUCTION

Current guidelines recommend an early invasive strategy for patients with acute coronary syndrome (ACS).¹⁻³ Coronary thrombus is angiographically identifiable in 6%

to 30% of patients undergoing coronary catheterization.⁴ When stents are implanted in the thrombotic environment, they may cause microvascular obstruction due to coronary emboli, with increased risk of no-reflow, distal embolization, acute closure, stent thrombosis and subsequent clinical complications.⁵ In this setting, stent implantation may be deferred until adjunctive anticoagulation and antiplatelet therapy has allowed thrombus burden to decrease.⁶ On the other hand, postponing percutaneous coronary intervention (PCI) too long can increase spontaneous cardiac events.

We decided to evaluate the impact of delayed stenting in patients with ACS and patent, yet thrombus-laden coronary arteries, with normal epicardial flow, using the direct oral anticoagulant apixaban, in combination to dual antiplatelet therapy.

METHODS

This is a prospective, descriptive, observational registry, which assessed the effects of delayed stenting for seven days in patients with ACS, patent yet thrombus-laden coronary arteries, and treatment with apixaban in combination to dual antiplatelet therapy. We included patients (≥ 21 years) who presented with ACS (unstable angina – UA – and non-ST segment elevation myocardial infarction – NSTEMI)⁷ low to moderate risk,⁸ thrombus-containing lesion at diagnostic angiography and normal epicardial flow.⁹

Exclusion criteria included patients with ST-segment elevation myocardial infarction (STEMI), high risk patients,⁸ total occlusion at coronariography, chest pain suspected not to be caused by coronary artery disease, intolerance to contrast media or anticoagulant/antithrombotic medication, age ≥ 75 years, creatinine > 1.8 mg/dL,¹⁰ stent thrombosis and increased risk of bleeding, according to Mehran score.¹¹

All patients signed the Informed Consent Form before proceeding to the catheterization laboratory. The study protocol for the present work was approved by the Ethics Committee of the Angel Cruz Padilla Hospital, Tucumán, Argentina.

In-hospital medication

Prior to initial diagnostic angiography, all patients were treated with aspirin (300mg loading dose followed by 100mg orally once daily), and clopidogrel (300mg loading dose followed by 75mg orally once daily). All patients received unfractionated heparin (80UI/kg, maximum 10,000UI, followed by infusion at a rate of 16UI/kg/hour, maximum 1,000UI/hour) for 2 days previously to coronariography. Apixaban therapy was started immediately after initial diagnostic angiography and was administered in a dose of 10mg daily (5mg twice a day) for 7 days.¹²⁻¹⁴

Coronariography

Intracoronary thrombi were angiographically defined as the presence of an intracoronary filling defect, non-calcified,

round, irregular or spheroid, surrounded by contrast material, seen in various orthogonal projections. Only patients with a thrombus-containing lesion grade 4 at diagnostic angiography were included. Thrombus burden grade 4 was defined, according to Gibson et al., when a thrombus with the largest diameter equivalent to at least twice the diameter of the vessel was observed.¹⁵ When a thrombus-containing lesion grade 4 with TIMI 3 flow was seen in angiography, the procedure was interrupted, with no other intervention (neither balloon angioplasty nor mechanical aspiration) and patients were immediately transferred to the coronary care unit, where treatment with aspirin, clopidogrel and apixaban was administered together with beta-blockers, rosuvastatin, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers for seven days, according to previous studies.¹⁶ During the hospital stay, total creatine kinase, creatine kinase MB, and cardiac troponin (cTn) levels were routinely checked once daily.

Repeated angiography/intervention

Another angiography/intervention (second procedure) was planned seven days after the primary procedure, and stent implantation was performed in the culprit lesion. If the lesion was deemed stable at the second examination ($< 30\%$ residual stenosis,^{17,18} no significant thrombus burden and no visible dissection) stent implantation could be waived.

Events

Evaluation of results was divided into primary and secondary objectives. The primary objective was procedural success, defined as final diameter stenosis $< 20\%$, TIMI 3 flow and no occurrence of slow-flow, no-reflow or distal embolization. The secondary objectives were the presence of in-hospital major adverse cardiac events (MACE) defined as death, myocardial infarction (MI) during hospitalization (type 1), MI related to post PCI procedure (type 4), stroke, recurrent ischemia, target lesion revascularization (TLR) or bleeding.

Slow-flow was defined as a decrease in TIMI flow from 3 to 2 during the procedure; no-reflow was defined as TIMI flow decreasing from 3 to either 0 or 1 during the procedure.

Deaths were classified as cardiac-related unless they could be clearly attributed to another cause, as determined by the clinical events committee. A myocardial infarction was defined as typical chest pain, accompanied by a rise of more than two times the upper reference limit of cardiac cTn, development of new ischemic or Q waves on the electrocardiogram, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, identification of a coronary thrombus by angiography or autopsy.¹⁹ Myocardial infarction related to PCI requires a five-fold increase of cTn values in patients with normal baseline values, or 20% in patients with elevated pre-pro-

cedure cTn, in whom the cTn levels are stable or falling. In addition, there should be evidence of new myocardial ischemia, either from electrocardiogram changes, imaging evidence, or from procedure-related complications associated with reduced coronary blood flow, such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, slow-flow or no-reflow, or distal embolization.¹⁹

Stroke was defined as neurological deficiencies that developed within 24 hours of the procedure, and that lasted for, at least, 12 hours. Bleeding was classified according to the TIMI criteria.²⁰ Major bleeding was defined as the need for transfusion of >2 units of whole blood or packed red blood cells, intracranial or retroperitoneal hemorrhage, a fall in hemoglobin 2.5mg/dL (or 12% of hematocrit), without an identifiable bleeding site, spontaneous or non-spontaneous blood loss associated with 2mg/dL decline of hemoglobin (or 10% of hematocrit) and vascular surgery for bleeding complications.

Statistical analysis

Descriptive statistics and patient data listings were used to summarize the data collected on the case report form. Categorical variables were described using frequencies and percentages.

RESULTS

In total, 11 consecutive patients were included in the study. The demographic characteristics of the study patients are outlined in table 1. Most participants were males (80%) with age range from 58 to 65 years. All patients were diabetic.

Table 1. Baseline characteristics of patients and lesions

Age, years	58-65
Male, %	80
Diabetes mellitus, %	100
Hypertension, %	75
Hyperlipidemia, %	45
Current or previous smoker, %	80
Family history of CAD, %	54
Previous myocardial infarction, %	18
History of angina, %	60
Number of diseased vessels 1/2/3, %	80/10/10
Previous PCI, %	10
Previous Coronary artery bypass grafting, %	0
Peripheral artery disease, %	40
Culprit artery LAD/LCX/RCA, %	0/30/70
Ectasia (type 1/2), %	100 (70/30)
Mehran score	8-12

CAD: coronary artery disease; PCI: percutaneous coronary intervention; LAD: left anterior descending artery; LCX: left circumflex coronary artery; RCA: right coronary artery.

We use right femoral access in all cases. The same access site was used in the first and the second procedure in all patients. As mentioned in the inclusion criteria, only patients with a thrombus-containing lesion grade 4 with TIMI 3 flow were included (Figures 1 and 2). Multivessel disease was present in 20% of patients, with the right coronary

Figure 1. Ectasia and thrombus. The image shows stenosis in the circumflex artery (A, dotted arrow). In addition, ectasia is observed in the proximal portion of the vessel, with thrombus grade 4 (A and B, solid arrow). After 7 days of apixaban and dual antiplatelet therapy (C) the thrombus disappeared (solid arrow), and one stent was implanted in the lesion (dotted arrow).

Figure 2. High risk of stroke. The image shows stenosis in the right coronary artery (A, dotted arrow). In addition, ectasia is observed in the proximal portion of the vessel, with a thrombus grade 4 (solid arrow). Considering the proximity to the ostium, there is a high risk of stroke due to retrograde movement of the thrombus when passing through the stent. After seven days of apixaban and dual antiplatelet therapy (B), the thrombus disappeared (solid arrow) and one stent was implanted in the lesion (C, dotted arrow).

artery or circumflex artery being the most frequently reported culprit artery. It is noteworthy that ectasia was present in all cases, type 1 in seven patients and type 2 in the rest. All patients remained clinically stable after the index procedure and no MACE occurred in any of the patients between the first and second procedure. No patients experienced a rise in creatine kinase, creatine kinase MB and cTn levels during hospital stay. There was also no change in electrocardiogram compared to that of admission.

Second procedure

The culprit artery was patent in all cases. Of the eleven patients, stent implantation was deemed unnecessary in two, due to residual stenosis <30% with no residual thrombus at the second examination (Figures 3 and 4). In the remaining nine patients, the mean residual stenosis was

considerably reduced from the index to the second procedure. Compared with the results at the end of the first procedure, the median thrombus burden was visually smaller at the beginning of the second procedure.

In 100% of cases, the stent was successfully implanted. We used drug eluting stent, as per protocol in our organization. There was no phenomenon of no-reflow/slow-flow after stent deployment. Blush grade was 3 in all patients. In none of the cases thrombus aspiration or distal protection devices were used. Complete revascularization was performed in case of multivessel disease.

No femoral bleeding was registered. One patient had a hematoma at the access site after the second procedure, with no requirement of blood transfusion. Patients were discharged with aspirin, statins, clopidogrel (12 months), beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and treatment for diabetes.

Figure 3. Thrombus and branch occlusion. Image A shows ectasia of the proximal segments of the right coronary artery. Image B shows stenosis in distal portion with thrombotic content (dotted arrow) and absence of flow to the posterior descending branch. A grade 4 thrombus is also observed in the posterolateral trunk (solid arrow).

Figure 4. Branch patency: after 7 days of apixaban and dual antiplatelet therapy, normal distal flow is observed in the artery, the thrombus disappeared in posterolateral trunk, and there is normal flow in the posterior descending branch. The remarkable improvement of the distal lesion was also observed, which did not require stent implantation due to stenosis <30%.

Six-month clinical follow-up data were available for the eleven patients. All patients remained uneventful.

DISCUSSION

Our data suggest that in patients presenting with ACS and patent thrombus-containing lesion, PCI can safely be deferred for seven days, when patients are given dual antiplatelet therapy and apixaban. This strategy allows the thrombus burden to decrease before stent implantation, optimizing its apposition, with the expectation of reducing mechanical complications.⁶ As specified per protocol, in all cases a normal blood flow of the related artery was present at first angiography. Angiographically visible coronary thrombus is considered an independent predictor of adverse outcomes during and after PCI.^{21,22} Tang et al. compared immediate *versus* delayed stent implantation after 7 days of adjunctive anticoagulation and antiplatelet therapy, in patients with a first MI successfully reperfused by thrombectomy. Delayed stenting was associated with a significant reduction in post-stenting coronary emboli and no-reflow phenomena. At the same time, the extent of myocardial damage was significantly lower.¹⁶ In a systematic review assessing the impact of immediate *versus* delayed stenting in patients admitted for STEMI and NSTEMI, Freixa et al. found that delayed stenting (up to seven days) was associated with a significant reduction in procedure-related angiographic events and possibly with a reduction in adverse cardiovascular events.²³ In the DEFER-STEMI (Deferred Stent Trial in STEMI), delayed stenting significantly reduced the occurrence of no-reflow and intraprocedural thrombotic events compared with conventional stenting.²⁴ On the contrary, in the MIMI (Minimalist Immediate Mechanical Intervention) trial, delayed stenting was associated with a deterioration in microvascular obstruction expressed as percentage of left ventricular mass using magnetic re-

sonance imaging.²⁵ Such events were linked to an obvious coronary dissection or an inappropriate use of anticoagulation.²⁵ The third Danish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction (DANAMI-3) compared a strategy of delayed with conventional stenting in 1,215 patients with an acute myocardial ischemia. The strategy of delayed stenting was associated with a nonsignificant reduction in all-cause death and hospitalization for congestive heart failure.¹⁷ However, no adjunctive anticoagulation was required in the interval between the index reperfusion and the DS implantation. Postponement of stent implantation for hours or days may potentially allow the thrombus material of the culprit lesion to resolve considerably and thereby limit the risk of embolization.^{23,26} Pascal et al. showed that delayed stenting allows time to select the proper revascularization strategy tailored to each patient by decreasing the number of stents implanted (30% had no stent).²⁷ In addition, residual thrombus after PCI contributes to the higher rate of restenosis observed in thrombotic lesions. Thrombus compression or displacement by the stent struts may cause stent malapposition, thus increasing the risk of late stent thrombosis.¹⁸ In our patients, the residual stenosis and thrombus burden was considerably reduced during the antithrombotic regimen between the index and secondary procedure. In fact, in two patients was unnecessary to implant a stent in the related lesion at the second examination. In these cases, the artery was found patent with no significant stenosis.

One disadvantage of DS is the risk of reocclusion.¹⁸ However, one of the most reassuring findings was the absence of acute coronary occlusion in the interval between the initial coronariography and the second procedure. These results indicate a higher success rate without any risk of intercurrent vessel occlusion in patients with initial TIMI 3 flow, in whom stent implantation is deferred for seven days. In a review of five studies, Freixa et al.²³ found no

cases of acute coronary occlusion occurring in the interval between the initial reperfusion and stent implantation in patients assigned to DS, with an average delay of 3.7 days between procedures. The intensive pharmacologic treatment with dual antiplatelet agents, apixaban, and statin, could have combined to create a safe environment for delayed stenting without ischemic reocclusion related events.

Low molecular weight heparin (LMWH) is a widely used agent in ACS. It has a more predictable dose-effect relation than unfractionated heparin. The most widely used is enoxaparin. Monitoring of anti-activated coagulation factor X (Xa) activity is not necessary.²⁸ Despite the multiple advantages of LMWH, this agent is not available at our hospital. Unfractionated heparin remains a widely used anticoagulant in non-ST segment elevation ACS (NSTEMI-ACS) in the context of short delays to coronary angiography and short hospital stays. However, it has a pharmacokinetic profile with large interindividual variability and a narrow therapeutic window,³ that requires continuous laboratory monitoring, and it is not always possible to be in therapeutic range for a long period of time. Apixaban is an oral, potent, highly selective, reversible and direct inhibitor of Xa, which binds directly to the active site of Xa factor with a very high affinity exerting its anticoagulant and antithrombotic effects. Additionally, it has the capacity to indirectly inhibit thrombin-induced platelet aggregation. Apixaban inhibits not only this clot-bound, but also free Xa and prothrombinase activity. It can exert directly its action without requiring a previous biotransformation and does not need the presence of antithrombin to manifest its anticoagulant action.¹² Maximum plasma concentration of apixaban is achieved in approximately 3 to 4 hours after the administration.¹⁰ There is large data regarding its effectiveness in patients with non-valvular atrial fibrillation.^{13,14,29} Apixaban is as effective as dabigatran and rivaroxaban in reducing the risk of thromboembolic events. Also, it is safer than both, dabigatran and rivaroxaban, in reducing bleeding events.¹⁴

The choice of a 7-day period for anticoagulation was aleatory, considering that most of the previous publications mentioned a period of three to five days.^{4,17,24,30}

A possible complication of delayed stenting with anticoagulation is the increased risk of bleeding. Bleeding events and transfusions have been shown to be independent predictors of mortality in patients with ACS undergoing PCI.²³ Of note was the absence of major and minor bleeding episodes in our study, despite using femoral access. In fact, the same access was used in the second procedure. Tang et al. found similar rates of bleeding comparing immediate *versus* delayed stenting.¹⁶ Similar results were found in DEFER-STEMI, MIMI or DANAMI-3 studies.

Ectasia³¹ was present in all cases. It has been described as a major risk factor of thrombus formation, mainly due to impairment of intracoronary flow in association with shear stress and atherosclerosis. Moreover, patients with coronary artery ectasia without stenosis, had positive results during myocardial perfusion and treadmill exercise tests.

Distal embolization or occlusion of ectatic segment with thrombus were proposed as possible mechanisms.³¹

Finally, it is noteworthy that we had no cases of anterior descendent coronary involvement, which can be attributed to chance, due to the small number of patients included in this report.

Limitations

Delayed stenting has the disadvantage of prolonging hospital stay of a considerable proportion of patients, who are often discharged the day after stent implantation.

Another disadvantage of delayed stenting is the need to perform two procedures, with the associated costs, discomfort for the patient, prolonged hospitalization, and risks related to the repeated invasive procedure.

This is observational study with a small sample size and no control group. Further studies are needed to validate the results obtained in the present study.

CONCLUSION

In the face of significant thrombus burden, stents should be withheld until adjunctive anticoagulation and antiplatelet therapies have been administered. Reducing thrombotic burden before stenting could not only reduce embolic events, but also allow for a better stent selection which might translate into shorter lengths and larger diameters. Apixaban has shown to be an effective anticoagulation therapy in association with clopidogrel, to reduce thrombus burden and mechanical complications of stent deployment when coronary thrombus is angiographically identifiable.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: LAGN e PP; data collection: LAGN, PP, RF e MSE; data interpretation: LAGN, RF e PP; text writing: LAGN; approval of the final version to be published: PP.

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