Artículo de Opinión

Es tiempo de repensar la indicación de terapia antiplaquetaria dual en la cirugía de revascularización

It is time to rethink the dual antiplatelet therapy indication in revascularization surgery

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RESUMEN

La doble terapia antiagregante plaquetaria (DAP) en la cirugía de revascularización miocárdica (CABG) en el contexto de la cardiopatía isquémica estable está en creciente desarrollo, aunque la ACC/AHA y las guías Europeas no la recomiendan enfáticamente y tienen criterios diferentes. La falla del injerto de vena safena en el primer mes en el postoperatorio de la cirugía no solo es frecuente sino grave. El equilibrio entre el riesgo trombótico y hemorrágico debe obtenerse en estos pacientes con el objetivo de identificar quiénes se beneficiarán con DAP y quiénes no. En este artículo de opinión se muestra la evidencia más reciente para considerar DAP para el postoperatorio en CABG.

Keywords:
Coronary artery bypass grafting, dual antiplatelet therapy, saphenous vein graft failure

It is time to rethink the dual antiplatelet therapy indication in revascularization surgery?

ABSTRACT

Dual antiplatelet therapy (DAP) in coronary artery bypass grafting (CABG) surgery in the context of stable ischemic heart disease is in increasing development, although ACC/AHA and European guidelines do not strongly recommend it and have different criteria. Saphenous vein graft failure in the first month in the postoperative period of surgery is not only frequent but serious. The balance between thrombotic and hemorrhagic risk must be obtained in these patients with the objective of identifying those who will benefit with DAP and those who will not. In this opinion paper the newest evidence is shown for considering DAP for the postoperative period in CABG.

The American and European guidelines recommend double antiplatelet therapy (DAP) in Coronary Artery Bypass Grafting (CABG) surgery in the context of acute coronary syndromes (ACS), while in stable ischemic heart disease both societies do not have the same criteria. In this clinical context, they maintain the same criteria regarding antiplatelet therapy with aspirin, but not with DAP[1,2]. The ACC/AHA recommends considering DAP in some scenarios based on patient risk/benefit. In contrast, the European Society of Cardiology does not give any recommendation for DAP[3]. Consequently, and given the lack of coherence between both societies, it was decided to write this document.

Despite optimal medical therapy after revascularization, some patients have recurrent ischemic events due to both progression of underlying coronary artery disease and graft failure, particularly saphenous vein graft (SVG) failure. One year after surgery, up to 25% of venous graft failure has been reported and, because several patients have multiple grafts, up to 40% of patients have an occluded graft[4]. The clinical implication of graft closure is not only that it leaves the revascularized area ischemic, but also that many of these graft closures are clinically silent, and ischemia continues, generating necrosis and deteriorating ventricular function[5].

The question that we should ask is whether the indication of DAP in the postoperative period of the CABG has a rationale that supports it. To answer this question, we should observed two variables: the first, in which clinical context the surgery is performed and the second, the pathophysiology of the graft obstruction and its relationship with the elapsed time of the CABG.

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Saphenous vein grafts have a higher failure rate than arterial grafts; 3 to 12% fail before hospital discharge, 8 to 25% fail at one year, and 40 to 50% % fail after 10 years[6,7]. The risk factors for the occurrence of early SVG occlusion are largely related to the procedure technique, such as trauma to the vein during its extraction or a misalignment of the caliber between the vein and the coronary artery to be revascularized. Besides, anastomotic stenosis, graft kinking or overstretching, and postoperative graft spasm can occur[7]. These mechanical aspects can cause turbulent flow and lead to thrombus formation.

The goal of DAP after ACS is to treat the underlying atherothrombosis and prevent future events of plaque rupture, as occurs in myocardial infarction, regardless of the revascularization strategy. In the framework of a stable patient with angina needing CABG, for example, DAP has not a strong indication; for this, guidance must be done considering the occlusion mechanisms of the SVG. As it had already seen, SVG failure is a multifactorial process that involves acute thrombosis, intimal hyperplasia, inflammation, and atherosclerosis[7]. These events can occur between surgery and even after the first year. The pathophysiological mechanism that occurs earliest is thrombosis, followed by intimal hyperplasia that occurs within a few months and atherosclerosis that begins within the first year[8].

Of the mechanisms mentioned, thrombosis is the one that could be avoided in the first month with DAP. This can mainly be caused by: a) technical factors, either due to trauma to the graft during harvesting or due to anastomotic deficiencies, b) related to the conduit due to mismatch in conduit size, c) pre-existing graft pathology, or d) due to hypercoagulability[9]. Deendothelialization leads to exposure of the extracellular matrix and activation of the extrinsic coagulation cascade by tissue factor. The reduced bioavailability of prostacyclin and nitric oxide (NO) results in vasoconstriction and stasis, further promoting fibrin accumulation, adherence of platelets and recruitment of leukocytes to the luminal surface, and thrombus formation[10]. Due to the high prevalence of SVG occlusion in the first stage, the most important mechanism to prevent in this stage is thrombosis.

Due to these prothrombotic mechanisms that occur from the implantation until the first month, it would be rational to indicate DAP over aspirin alone, particularly in the first month, as established by the guidelines[1,2]. These mechanisms have similarities and differences with ACS or after coronary stent implantation in stable ischemic heart disease.

The most recent revascularization guidelines are those of the ACC/AHA in which they refer to antiplatelet therapy in the postoperative period of CABG, they recommend as class 1 recommendation level that aspirin should be started (100-325 mg daily) within 6 hours postoperatively and then continue indefinitely to reduce the occurrence of SVG closure and cardiovascular events[11]. In turn, surgical bleeding continues to be a concern in the perioperative and immediate postoperative periods and, therefore, this risk must be considered in the use of antiplatelet therapy. Pioneering work has shown that aspirin improves vein graft patency and all the evidence supports the early use of aspirin to improve SVG patency and reduce ischemia[12,13,14,15,16,17,18].

Dual antiplatelet therapy should be offered to selected patients with aspirin and clopidogrel or ticagrelor for 1 year, with a recommendation level IIb as reasonable for improving vein graft patency compared to aspirin alone based on small randomized clinical trials, observational data, and a meta-analyses that have shown that DAP (mainly with aspirin and clopidogrel) after CABG improves venous graft patency, mainly in patients undergoing off-pump surgery[17,19,20,21,22]. The DACAB (Different Antiplatelet Therapy Strategy after Coronary Artery Bypass Graft Surgery) trial compared DAP with a single antiplatelet regimen in 500 patients undergoing CABG[22]. Off-pump procedures were performed in 75% of these patients. At 1-year follow-up, the DAP group was found to have higher vein graft patency, when assessed with coronary computed tomography angiography, compared with aspirin alone.

Recently, Sandner et al. published a meta-analysis of four studies conducted with ticagrelor with the aim of comparing the risks of venous graft failure in patients undergoing CABG and treated with DAP with ticagrelor, ticagrelor monotherapy, or aspirin monotherapy[19]. They were evaluated with coronary angiotomography and all events of graft failure and bleeding were analyzed according to the Bleeding Academic Research Consortium (BARC) classification, trying to homogenize the sample of the 4 randomized clinical trials[20,21,22,23]. Over a total of 1,316 patients and 1,668 vein grafts, DAP with ticagrelor compared with aspirin monotherapy was associated with a significantly lower incidence of vein graft failure (11.2% vs. 20.0%) and a significantly higher incidence of BARC type 2, 3, or 5 bleeding events (22.1% vs 8.7%), concluding that adding ticagrelor to aspirin was associated with a significantly lower risk of vein graft failure but was accompanied by a significantly increased risk of clinically important bleeding. Analyzing the bleeding, they were fundamentally significant at the expense of type 2, since type 3 or 5 were not. With respect to the subgroups, all benefited significantly except women, in whom there were no differences[19].

Although this review is based on patients with chronic coronary artery disease, the sub-analysis of the PLATO study, which included, among others, patients with acute coronary syndrome who underwent coronary artery bypass grafting, were randomized to receive ticagrelor or clopidogrel after 7 postoperative days[24]. It showed that ticagrelor reduced total 12-month mortality from 9.7% to 4.7% (HR 0.49; 95% CI 0.32-0.77; p=0.01), CV death from 7, 9% to 4.1% (HR 0.52; 95% CI 0.32-0.85; p=0.01) and non-CV death numerically from 2.0% to 0.7% (p=0.07), without significant difference in major bleeding related to the surgery.

Based on the results of this meta-analysis and the data presented in this paper, and according to the pathophysiology of graft occlusion in the first month of CABG, we

would be warranted in recommending DAP with ticagrelor and aspirin in the first month of postoperative CABG where the cause of graft failure is thrombosis. It could be extended to 3 months in those patients with high ischemic risk criteria applying the Syntax Score and a single month in those with high bleeding risk applying the PRECISE-DAPT score[25,26]. After DAP, monotherapy with ticagrelor could be considered instead of aspirin.

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