Can we think of a TAT, that is a "tailored antiplatelet therapy"?

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Abstract

What can be seen from the case report by Verzelloni et al. has a double value, beyond the case itself. First of all, the use of platelet aggregation assessment tests, such as TEG-PM, allows clinicians to verify the exact timing between the suspension of thienopyridines and the possibility of surgery without further temporal delays and is also able to favor the evolution of ischemic problems or hemodynamic instability not easily treatable. It therefore allows clinicians to optimize the bleeding / thrombosis matching. Secondly, the use of point of care methodologies for the evaluation of platelet aggregation allows us to evaluate the adequacy of the anti-aggregation, facilitating, where resistance or percentages of anti-aggregation are lower than expected, modification of the therapeutic regimen.

Can we think of a TAT, that is a "tailored antiplatelet therapy"?

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Dual antiplatelet therapy (DAPT) is a key part of the medical management of patients with coronary artery disease (CAD), particularly those with recent acute coronary syndrome (ACS) events. DAPT includes aspirin plus a P2Y12 receptor inhibitor (thienopyridines, such as clopidogrel, prasugrel, and ticagrelor) and should be based on the patient's degree of heart disease, type of stent, and proximity to stent placement. It lasts from 1 month to 1 year [1]. Numerous studies have shown that DAPT can reduce the risk of thrombosis in the stent. Depending on the time since stent insertion, stopping treatment may increase this risk [2].

Thienopyridines inhibit the ADP-dependent pathway of platelet activation. It is known that ADP plays an important role in both hemostasis and thrombosis. Its transduction within the platelets involves two receptors: P2Y1 and P2Y12. Of these, the second plays a fundamental role in the platelet aggregation process. In particular, it promotes an enhancement of platelet secretion independent of the synthesis of thromboxane A2 (TXA2), causes the stabilization of platelet aggregates induced by thrombin and promotes the regulation of platelet function [3].

Thienopyridines can indirectly or directly inhibit the platelet P2Y12 receptor. For a rapid action we can therefore use the direct inhibitors of the P2Y12 receptor such as ticagrelor and cangrelor.

The International Guidelines recommend the suspension of clopidogrel and ticagrelor 5 days before surgery, while prasugrel must be interrupted 7 days before surgery, in compliance with the elimination kinetics of the mentioned antiplatelet drugs [4].

In the case of thrombotic risk prevailing over hemorrhagic risk, bridge therapy with cangrelor in continuous infusion is recommended, and must be started 2-3 days after discontinuation of clopidogrel and ticagrelor and 3-4 days after discontinuation of prasugrel, according to well-known protocols in literature [5, 6].

In this way, anti-aggregation is activated, with substantial benefits on the patency of previously stented coronaries, avoiding the false safety given by heparin which, being an anticoagulant, facilitates perioperative bleeding without the benefits of anti-aggregation.

But the hope of solving the bleeding / thrombosis problem with generalizable algorithms can produce controversial effects on the surgical population.

The best indication, as can also be seen from the case report by Verzelloni A et al. [7], is to study residual platelet activity with monitoring of platelet function.

Indeed, literature data have reported a large variability in platelet reactivity after discontinuation of thienopyridine therapy, which means that a considerable number of patients are not adequately protected when discontinuing thienopyridine therapy for up to one week. [8].

This is related to the finding in the literature of a lack or reduced activity of antiplatelet agents, despite the correct dose and adherence to therapy.

The mechanism, commonly called resistance to antiplatelet agents, is actually due to the multifactoriality of the atherothrombosis process which involves a reduced bioavailability of the antiplatelet drug, pharmacodynamic alterations, different production sources of TXA2, presence of alternative ways of platelet activation, increased platelet turnover, genetic factors, tachyphylaxis [9].

Specifically, for clopidogrel, extrinsic factors must be considered, such as interaction with other drugs and reduced intestinal absorption, and intrinsic factors, such as platelet P2Y12 receptor polymorphisms and hepatic cytochrome P450 3A4 polymorphisms [8].

We are therefore faced with two situations that may have different but coincident meanings: a low antiplatelet activity, which must be carefully evaluated in order not to run the risk of undertreatment, and a suspension of thienopyridines with unjustifiably prolonged periods, in the hope of seeing a reactivation of the platelet activity.

Only the monitoring of platelet activity enables us to highlight the real activity of the antiplatelet drug, both to improve its action and to monitor the effects of anti-aggregation upon suspension.

While there are various laboratory investigations capable of measuring the individual response to aspirin, such as the direct dosage of TXA2 produced by platelets, or the analysis of platelet function with specific tests, the discourse with thienopyridines is different [10].

Since clopidogrel specifically inhibits one of the two ADP receptors (P2Y12), the measurement of maximum platelet aggregation from ADP by optical aggregometry is the most common laboratory method used to evaluate the response to clopidogrel. The 'point of care' method most recently proposed as an alternative to traditional tests is the VerifyNow P2Y12 Assay [11]. The state of phosphorylation of VASP (vasodilator-stimulated phosphoprotein) represents a specific intracellular marker of the residual activity of the P2Y12 receptor and can be measured with flow cytometry. This technique is probably the most specific indicator of the residual activity of the P2Y12 receptor in patients treated with a P2Y12 inhibitor. The test result is expressed in Aspirin Reaction Unit (ARU) or P2Y12 Reaction Unit (PRU) which express a percentage of inhibition of platelet aggregation associated respectively with treatment with ASA and / or inhibitors of the P2Y12 platelet receptor. However, it is a painstaking method, which requires expert personnel and has a high cost, so it is not suitable for large-scale application [12].

Viscoelastic tests provide a dynamic assessment of coagulation, exploring the time to clot formation and clot strength. Using specific activators or inhibitors, additional factors may ALSO be explored, such as the contribution of fibrinogen to clot strength. Since the early days, various attempts have been made to

measure platelet function with viscoelastic testing. In general, the difference between the maximum clot strength and the contribution of fibrinogen are considered an index of the contribution of platelets. However, this parameter does not clearly separate platelet count from function; furthermore, the large thrombin generation of standard activated viscoelastic assays activates platelets through the activated receptor protease, bypassing the other pathways. For this reason, standard viscoelastic tests cannot be used to assess platelet reactivity under the effects of aspirin or P2Y12 inhibitors. To overcome this limitation, a specific test (platelet thromboelastography mapping) was developed. This test was evaluated against the gold standard of light transmission aggregometry and other point-of-care tests, with conflicting results. In general, the use of viscoelastic tests to evaluate the effects of antiplatelet agents is still limited. On the contrary, the contribution of platelets to the strength of the clot in the context of coagulopathy causes bleeding, which is considered an important parameter for triggering targeted therapies [12].

For clinical use and the promptness of the result, the point of care systems of the TEG-Platelet Mapping (TEG-PM) type are easier, which use a single cartridge capable of carrying out all the analysis.

The TEG-PM analyzer is used to detect platelet function. The analyzer measures the percentage of platelet inhibition activated by adenosine diphosphate (ADP) and arachidonic acid (AA). This parameter is calculated by comparing the maximum amplitude (MA), which represents the viscoelastic force of the thrombus, created through three TEG channels as follows: 1) The MA reflects thrombin-activated platelets (MA Trombin) measured from a citrated blood activated with kaolin / Ca2 + sample; 2) a sample of heparinized blood activated by reptylase and activator F, which represents the contribution of fibrin alone to the strength of the clot (MA Fibrin); and 3) heparinized blood mixed with 2-mM ADP (MA ADP) or 1-mM AA (MA AA) combined with activator F as platelet agonists reflects the platelet response to ADP and AA. The equation 100 - ((MA ADP or MA AA) – MA Fibrin) / (MA Thrombin - MA Fibrin)) × 100 is used to calculate the percentage of platelet inhibition in response to ADP and AA [12, 13].

What can be seen from the case report by Verzelloni et al. [7] has a double value, beyond the case itself.

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Secondly, the use of point of care methodologies for the evaluation of platelet aggregation allows us to evaluate the adequacy of the anti-aggregation, facilitating, where resistance or percentages of anti-aggregation are lower than expected, modification of the therapeutic regimen.

We could therefore speak of TAT, that is “tailored antiplatelet therapy”.

In conclusion, we can finally arrive at a personalized anti-platelet therapy by minimizing side effects or lack of effects.

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