MONITORING THE PLAQUETARY RESPONSE TO THE USE OF P2Y12 RECEPTOR ANTAGONISTS USING THE PLATELET REACTIVITY TEST VERIFYNOW™ IN PATIENTS WHO UNDERWENT NEUROINTERVENCIONISM PROCEDURES

Valoración de la respuesta plaquetaria al uso de antagonistas del receptor P2Y12 utilizando el test de reactividad plaquetaria VerifyNow®, en pacientes sometidos a Neurointervencionismo

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Key words (MeSH)
Radiology, interventional
Stents
Platelet aggregation inhibitors

Palabras clave (DeCS)
Radiología intervencional
Implante endoluminal
Inhibidores de agregación plaquetaria

Summary

Objective: To assess the platelet response to the use of P2Y12 receptor antagonists using the platelet reactivity test VerifyNow™ in patients undergoing to neurointerventionism. Methodology: Retrospective cross-sectional descriptive study including 89 patients operated between 2014 and 2017, of which 78 met the inclusion criteria. All patients received dual anti-aggregation protocol. The result to be evaluated with the platelet reactivity test VerifyNow™ corresponds to the response of the patients to the use of P2Y12 receptor antagonists. The test reported measurements on Reaction Units P2Y12 (PRU). Individuals with a PRU value over 240 were considered hypo-responsive to P2Y12 inhibitors while those with PRU values below 60 were considered hyper-responsive. Results: Most of the patients who underwent surgery (69.2%) responded normally. Complications in the study population were 9.1%, including 2 deaths, one of which was from a hypo-responsive patient. Conclusions: The individual platelet response of the population studied to the use of Clopidogrel using the VerifyNow® test was variable and heterogeneous. The study showed that 14.3% of patients with complications had PRU outside the target range and of the total number of patients with values within the target range, only 2% had minor complications.

Resumen

Objetivo: Valorar la respuesta plaquetaria al uso de los antagonistas del receptor P2Y12 mediante el test VerifyNow® en pacientes sometidos a neurointervencionismo. Metodología: Estudio descriptivo transversal retrospectivo, con 89 pacientes intervenidos entre 2014 y 2017, de los cuales, 78 cumplieron los criterios de inclusión. Todos los casos recibieron protocolo de antiagregación dual. El resultado por evaluar con el test corresponde a la respuesta de los pacientes al uso de antagonistas del receptor P2Y12. La respuesta baja a los inhibidores de P2Y12

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se manifestó en aquellos con un valor de PRU > de 240; la respuesta alta se les atribuyó a aquellos con valores de PRU < 60. Resultados: La mayor parte de los intervenidos (69,2 %) respondieron normalmente. Las complicaciones de la población en estudio fueron del 9,1 %, incluidos 2 fallecimientos, de los cuales, uno fue de un paciente de baja respuesta. Conclusiones: La respuesta plaquetaria individual de la población estudiada frente al uso de clopidogrel mediante el test VerifyNow® fue variable y heterogénea. Se evidenció en el estudio que el 14,3 % de los pacientes que tuvieron complicaciones tenían el PRU fuera del rango objetivo y del total de pacientes que presentaron valores dentro del rango objetivo solo el 2 % presentaron complicaciones menores.

Introduction

For about a decade now, antiplatelet drugs have become one of the fundamental pillars of the pre- and post-operative management of neurointerventionist procedures, due to the notable increase in the use of the of endovascular devices deployed in arterial light. As a consequence of the configuration of this type of devices (endoprosthesis or flow shunt devices), double antiaggregation therapy is used, usually in the forms of aspirin and clopidogrel (1). This dual therapy is implemented for two reasons: Aspirin monotherapy turned out to be insufficient in multiple studies (2,3) and platelet inhibition proved to be a requirement for the prevention of acute or subacute thrombosis in surgical procedures such as stent placement in atherosclerotic lesions or in assisted aneurysm treatment with endoprosthesis (4,5). However, patients may occasionally experience stent thrombosis or a thromboembolic phenomenon despite receiving dual therapy plus systemic intraoperative heparinization (6), as a consequence of the response variability to antiaggregation treatment (7,8).

It is known that about 40 % of the patients in management with clopidogrel in the proper dosage and frequency may not have the expected platelet inhibitory effect (9). Consequently, these patients have a significantly increased risk of thrombosis of stenting, bleeding and death (10,11). As a result of the growing evidence of the relationship between the poor or excessive response to the dual therapy and the emergence of unwanted clinical events, emerged the need for individual monitoring of the response to the antiplatelet agents (12,13). Another important factor is related to the cost of drugs, as the value of the of clopidogrel is eight times less than that of prasugrel, three times less than that of ticagrelor, and is included in the Mandatory Health Plan (POS in Spanish).

Taking into account the considerations described above, the VerifyNow® test (AccrivaDiagnostics, San Diego, California, USA) was included in our preoperative protocol for all patients who require the use of endovascular devices deployed in the arterial light, with the purpose of making a more objective interpretation of the patient's response to clopidogrel therapy, based on evidence from previous case studies undergoing endovascular intracranial aneurysms treatment (14).

The study has two main objectives: 1. Evaluate the individual plaquetary response to the use of P2Y12 receptor antagonists by means of the VerifyNow® test on patients undergoing neurointervention at the "Neurodinamia" center in Cartagena, Colombia, and share the experience with the scientific community. 2. Associate the values of platelet response units (PRU) with the success of the surgical technique and prediction of thromboembolic or hemorrhagic complications. A secondary objective is to characterize the population studied, in order to enrich our understanding of the local epidemiology

1. Theoretical Framework

For the definition of structured questions, the PICO Strategy (PICoR)was used. The main bibliographic sources used, were: EMBASE, Pub Med, VHL, LILACS and manual search. All articles included were critically read.

2. Methodology

The sample was obtained from the Neurodynamics Center database. All patients who were given the VerifyNow® test prior to neurointervention procedures between March 18, 2014 and November 10, 2017 were reviewed retrospectively. Data from the PRU test recorded in the database were taken. Each case was then classified into subgroups according to these values and associated with the days during which the patient took antiaggregation therapy, statin use, and types of complications. The institutional protocol indicates that all patients receive double platelet antiaggregation seven days before the intervention. Informed consent was obtained for all procedures. The aspirin reaction unit (ARU) test was not performed because the incidence of resistance is < 2 %.

2.1. Patient data

In addition to all the test results, the following patient information was recorded: age, sex, previous use of statins for at least seven days, type of lesion diagnosed, type of device used, and types of complications developed. The sample was 78 patients chosen according to the following inclusion criteria: there was an endovascular procedure (carotid stent placement, brain flow diversion stent placement, use of balloon and coils or brain balloon occlusion test). All cases received an antiaggregation protocol with aspirin (100 mg per day) and clopidogrel (75 mg per day) seven days prior to the procedure. Exclusion criteria include patients with a diagnosis of chronic kidney disease, blood dyscrasias, pregnancy, administration of a fibrinolytic agent, or use of IIb/IIIa receptor antagonist glycoproteins 24 hours prior to the intervention.

2.2. Platelet reactivity test

The level of platelet reactivity was quantified using the VerifyNow® P2Y12 test, which is a turbidimetric optical detection system and was used according to the manufacturer's instructions. This device uses fibrinogen-coated microbeads, an adenosine diphosphate (ADP) agonist of 20 μm and light transmittance. As platelet complexes precipitate, the solution

picks up a change in light transmittance, which is measured to evaluate the level of aggregation (15,16). Recently it has been demonstrated that the measurement of platelet reactivity, particularly by VerifyNow®, can be altered in renal dysfunction. This is secondary to the fact that patients with renal insufficiency have lower hemoglobin levels (17,18). To ensure that the results will not be influenced by this possible bias, patients with renal dysfunction CKD-EPI < 45 mL/min/1.73 m2 were excluded. The test results were reported as follows: P2Y12 'PRU' reaction units (table 1).

Table 1. Test reference values*

Variables	Values
PRU	
Normal response	60-240
High response	< 60
Low response	> 240

*PRU Target Values Thrown by VerifyNow® Test used to assess the platelet response to the use of clopidogrel.

Source: Prabhakaran et al (19); Kayan et al (20).

2.3. Description of the protocol of the P2Y12 receptor antagonist test

- All VerifyNow® test results analyzed in this study were performed prior to the surgical procedure. In the database it became evident that:
- In patients with normal response (PRU between 60 and 240) the intervention was considered without changes in its antiaggregation scheme.
- In patients with low response (PRU > 240) modifying the therapy to 90 mg ticagrelor, oral, every 12 hours was considered.
- In patients with high response (PRU < 60) modifying the clopidogrel therapy (75 mg) every other day or every 72 hours and reassess with a new test after 7 days was considered.

It should be noted that in the institution where the study was conducted, other variables are taken into account, in addition to the results of the antiplatelet aggregation test, in order to make decisions about the intervention, such as the clinic of each case, the type and location of the lesions, the prognosis of each of the pathologies, the patient's age, sex and comorbidities.

2.4. Procedure data

The following data corresponding to the procedure were taken into account: date of completion and assistive devices used (brain flow diverting stent graft, carotid stent). In addition, the occurrence of any type of associated complication within the first 30 days following the procedure was evaluated by medical history.

2.5 Statistical analysis

Electronic data processing was performed using EPI INFO version 7.2.0.1 for calculations of descriptive measures, central trend and association strength analysis. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1 Patients and devices

The characterization of the studied population can be seen in table 2. Initially, 89 patients undergoing surgery were included, 78 of whom met the established criteria. One of the patients was counted twice because double antiplatelet therapy was initiated on two separate occasions for two different procedures. At that time, there were only 77 different individuals. The median age was 64 years (interquartile range 53-71), the age interval in which the greatest number of interventions was performed was between 61 and 80 years (53.8% of cases), followed by 41 to 60 years (32.1%). 69.2% of the population was female. The two types of lesions intervened were cerebral aneurysms (71.8% of cases) and carotid stenosis (28.2%). The most commonly used type of endovascular device was the flow redirection device (Figure 1).

Table 2. Characterization of the population studied*

Variables	*n*	%
Average age (RIC)	64 (53-71)	
1-20	1	1,3
21-40	8	10,4
41-60	25	32,1
61-80	42	53,8
> 80	1	1,3
Sex		
Female	54	69,2
Male	24	30,8
Type of Injury		
Cerebral aneurysm	56	71,8
Carotid stenosis	22	28,2
Use of statins	11	14,1
Antiaggregants scheme ≥ 7 days	58	74,4

*Distribution of patients by age range, sex, type of injury, use of statins, and days of antiaggregation that were tested VerifyNow®.

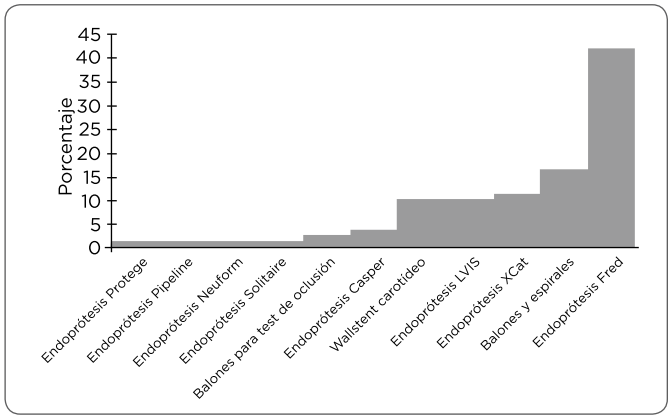

Figura 1. Tipos de dispositivos endovasculares utilizados*
*Distribución de pacientes según el tipo de dispositivo utilizado para el manejo de las lesiones, en la muestra sometida a la prueba VerifyNow®.

3.2 VerifyNow® Test Results

Of the total number of patients, 74.4% received clopidogrel therapy for a time greater than or equal to 7 days prior to the procedure, no higher initial dose or load was administered in any of the cases. Overall, PRU values ranged from 4 to 313, with an average of 134.96 +/- 76.28. 69.2% of the cases had normal response, followed by 19.2%, corresponding to patients with high response, the remaining 11.6% were those with low response (table 3).

3.3 PRU values according to antiaggregation time

The 78 cases included were divided into two large groups according to the duration of antiplatelet therapy: those who received antiaggregation for a period of time equal to or greater than 7 days (74.4% of the population), for whom the mean PRU was 127 ± 72, and those who received therapy for a period of time less than 7 days, for whom the mean of these variables was 158 ± 83 and 35.3 ± 8.9%. It is noteworthy that in the group of patients who received therapy for less than 7 days, the PRU was higher, which showed less antiplatelet response (Table 3).

Table 3. Behavior of the patients according to the values thrown by the test*

Variables	Total	< 7 days *n* = 20	≥ 7 days *n* = 58	days *p*
PRU	134 ± 76,3	158 ± 83	127 ±72	0,11712
Normal response	54 (69,2)	13 (65,0)	41 (70,7)	0,93798
High response	15 (19,2)	4 (20,0)	11 (19,0)	0,99998
Low response	9 (11,5)	3 (15,0)	6 (10.3)	0,99998

*Patient behavior according to PRU values and days of clopidogrel therapy, obtained from the VerifyNow® test sample.

3.4 Use of statins

Of the total population studied, 14.1% used statins for more than 7 days prior to the intervention, for whom the mean PRU was 157.2 ± 67.1.

3.5 3.5. Thromboembolic and haemorrhagic complications

Complications that arose in the first 30 days after surgery were included in the database and classified into two large groups: major and minor. Among the major complications were two cases of stent thrombosis and death, with an average PRU value within the target range, because patients could not continue with double antiaggregation in post-surgery due to inconvenience with medication acquisition. In the minor complications there were two cases of gastrointestinal tract haemorrhage due to overantiaggregation and two cases of myointimal hyperplasia. In 91% of the cases there were no complications (Table 4).

Table 4. Values given by the test according to complications*

Complications	PRU 60-240	PRU > 240	PRU < 60	PRU p value
Minors				
Myointimal hyperplasia				0,0459
Case 1	X			
Case 2			X	
Digestive tract hemorrhage				0,5313
Case 1	X			
Case 2	X			
Olders				
Death				0,1748
Case 1	X			
Case 2		X		
Cerebral infarction	X			

*PRU values in each of the complications evidenced 30 days after the intervention in individuals submitted to the VerifyNow® test.

4. Discussion

Currently, in Colombia there is not enough local evidence to show accurately the behavior of P2Y12 inhibitors in patients requiring neurointervention. However, international evidence shows an association between platelet resistance and thromboembolic complications around coronary and carotid stent placement (19,21). On the other hand, low and high response to clopidogrel has been associated with embolic and hemorrhagic complications, respectively (3,22,23). A recent randomized trial showed that modification of the antiplatelet scheme for patients with high platelet reactivity reduced the rate of thromboembolic events in endovascular device placement in unbroken aneurysms from 11.1% to 1.6%, without increasing the risk of bleeding (24). In the experience of the center, in 71% of the cases that presented complications, PRU was evidenced outside the objective ranges, which is compatible with what was found in the literature. The results obtained make it possible to elucidate a possible relationship between low response according to PRU values and the appearance of myointimal hyperplasia.

On the other hand, the results agree with what has already been exposed in the literature regarding the high and dynamic variability of the response of antiplatelet therapy with clopidogrel (14), observed in the great variation of PRU values (from 4 to 313). In addition, there were cases of patients with PRU values outside the target range, despite having received clopidogrel therapy for more than 7 days, and cases of adequate responses to the drug in patients who took it for less than 7 days.

Another point to highlight is what has been reported in the literature regarding the interference of statins in clopidogrel metabolism (25). It was found that the majority of patients who stated their consumption manifested an inadequate mean PRU. Additionally, a thromboembolic complication and a hemorrhagic complication, respectively, were evidenced for this same group. However, it cannot be stated that there is a causal relationship between statin consumption and possible alterations in clopidogrel metabolism in the population studied.

With respect to haemorrhages of the digestive tract, it should be taken into account that there are other factors, such as a history of acid peptic disease, variables related to gastrointestinal complications or any other medication, which could be related to its appearance (26).

Multiple criteria were taken into account before making the decision to reschedule the surgical procedure, in addition to the modification of the therapy received, so most patients with a PRU outside the target range were intervened. However, since there was a complication rate of less than 10% of the total number of patients, there is no doubt that new studies including other factors, such as clinical evolution of each case, type and location of lesions, prognosis of each of the pathologies, age, sex and comorbidities, should be carried out before reprogramming is defined. The PRU cut-off point was assigned based on the studies performed on the date of the procedures (19,26), while the current literature suggests lower cut-off points (PRU < 180) (27,28).

Limitations of greatest relevance to this study include those inherent in that it was performed retrospectively, in a single center and the size of the patient sample.

5. Conclusions

Individual platelet response to clopidogrel use was variable and heterogeneous. It was evidenced that in 50% of the patients who had complications, the PRU measured in the test was outside the target range and of the total number of patients with values within the target range of PRU only 2% had minor complications. When clopidogrel was administered together with aspirin for more than 7 days, the best PRU values were obtained. It is not possible to establish a causal relationship between the appearance of complications and test values, probably due to the statistical limitations previously mentioned, which makes it necessary to carry out cohort studies with a greater number of patients. Clopidogrel continues to be the drug of choice for double antiaggregation, due to costs, accessibility of the drug by health companies and its tolerance. Platelet antiaggregation tests are a very useful tool in the programming of patients undergoing endovascular techniques with intracerebral or carotid stent placement, given that they provide security when choosing medication and evaluate the inherent response of the patient.

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Received for assessment: July 16, 2018
Accepted for publication: November 20, 2018