Pharmacological prophylaxis for preventing thromboembolic disease in patients with cerebrovascular disease

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Introduction: *Cerebrovascular disease is a group of alterations attributed to acute and focal lesions in the central nervous system, mostly secondary to atherosclerosis.* ***Development:*** *In the prevention of cerebrovascular disease, there are two major pharmacological groups, antithrombotic and antiplatelet drugs, which impact quality of life of these patients, thus improving their prognosis.* ***Conclusions:*** *Cerebrovascular disease shares risk factors for thromboembolic disease, so starting prophylaxis is recommended.*

Key words: *Stroke; atherosclerosis, thromboembolic disease; prevention; embolism*

INTRODUCTION

Cerebrovascular disease (CVD) is defined as a group of neurologic disturbances attributed to an acute/focalized lesion of the central nervous system with a vascular origin (1). CVD is the second cause of death around the world, after acute myocardial infarction, according to the WHO. In Colombia, people loses an average of 5 to 9 years of healthy life, because of CVD. It is considered a Public Health problem (2). Atherosclerosis and further atherothrombosis is the main cause of death around the world (3), as it leads to acute myocardial infarction, peripheral arterial disease and Ischemic CVD (4). CVD may

The authors declare that they have no conflicts of interest with respect to this article.
Accepted: 2021/03/06
Received: 2020/06/05

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be hemorrhagic and ischemic. The ischemic variant is etiologically categorized in various ways; however, TOAST classification, has become more relevant all over the world due to its simple use. This identifies potential etiologic factors, such as: atherosclerosis (great vessels), lacunar (small vessels), cardioembolic, other determined causes and cryptogenic factors (5). Atherosclerosis is a chronic pathological condition, defined as the narrowing of a greater artery, caused by an atheromatous plaque which may end up eroding or tearing and it may become complicated as a type thrombosis leading to an ischemic event (4). Additionally, a peripheral arterial disease, regarding the plates found in lower limbs. (6–8). This is the most frequent cause of ischemic CVD (4,6); therefore, its prevention is a key aspect in early management of this disease (4,9).

ATHEROTHROMBOSIS

Atherothrombosis is defined as a thrombotic event, caused by rupture of an atherosclerotic lesion (3,10). Occlusive thrombosis leads to acute myocardial infarction or to cerebral ischemic event (3)

Physiopathology

Atherosclerosis is characterized by endothelial dysfunction and chronic inflammation. Atherogenesis process consists of lipoproteins infiltration, whose oxidation will be a chemotactic factor of monocytes. When endothelium is infiltrated these turn into macrophages and internalize these previously oxidized lipoproteins, thus resulting in foam cell, which will keep oxidizing these lipid metabolites for generating a vicious circle leading to major chronic inflammation and endothelial dysfunction (3).

In these atherosclerotic lesions, (collagen activated) platelets interaction plus the tissue factor are capable to produce a procoagulant condition (3,6,10). Platelets and fibrin are progression factors for atherosclerotic plates. ADP, Von Willebrand factor and collagen exposed by the endothelial lesion are agonists of platelet receptors αIIbβ3. When activated, these produce a massive calcium movement from the intracellular (stored) and the extracellular compartments. Among various processes, oxidation of arachidonic acid, by means of cyclooxygenase II activation, leading to tromboxane A2 synthesis, which finally boosts activation of platelet aggregation (11). So far we have discussed about primary hemostasis. Secondary hemostasis starts when the platelet is activated, on its membrane it projects the platelet factor 3, which promotes fibrin formation, Additionally, in this membrane there are lípidos ligandos from various coagulation factors. At hemostasis starting phase, coagulation factors such as VII and Xa are the protagonists: the latter forms a complex with Va in order to produce a slight quantity of thrombin. Later, the latter substance boosts platelets activation by means of the PAR receptor (amplification stage) and activation is spread (spread stage) to a significant number of platelets, in order to form a clot (12).

PHARMACOLOGICAL PREVENTION

For CVD prevention non-pharmacological measures must be taken into account, such as active exercise and a healthy/balanced diet. When this therapy fails pharmacological measures are used to prevent this disease. There are two main groups considered in this scenario. The etiologic factor determines what type of antithrombotic drug must be used. Antiplatelet drugs are mainly used for prevention before atherosclerosis concomitance, which may cause an ischemic stroke, and anticoagulants for cardiopathies emboliogenas (12).

ANTIPLATELET

Acetylsalicylic acid

Acetylsalicylic acid was the first antiplatelet agent used in CVD secondary prevention, and is still widely recognized, although its use is controversial for primary prevention (9,13,14). It is a non-selective irreversible inhibitor of cyclooxygenase which blocks tromboxane A2 production from arachidonic acid in platelets, and in this way it inhibits its aggregation. Additionally it blocks prostaglandin synthesis to the endothelium, thus causing vasodilatation, subsistence of the renal function and reduction of platelet aggregation (4,15). A large-scale study reported that Aspirin significantly reduces cerebrovascular events in patients who are under a

determined term therapy (29 months) (16). Additionally, discontinuation of the treatment has been reported to increase appearance of cardiovascular events (13). Another study compared Aspirin effectiveness at different dose. Low dosage therapy was reported to be as effective as higher dose therapy, which had a higher incidence of adverse events (17,18). Aspirin has not proved differences regarding sex in patients. Acetylsalicylic acid has a Class I Recommendation regarding secondary prevention of atherothrombotic disease and thrombolic events in different scenarios of cardiovascular diseases (13). On the other hand, a high dose of Aspirin has also been associated with gastrointestinal effects. That is why a low dose of Aspirin is a much more advisable choice than much higher doses of Aspirin used for long-term secondary routine prevention.(17)

Clopidogrel

Clopidogrel is a derivative from the Thienopyridine chemical family. It requires hepatic biotransformation into active metabolites, which are believed to act through irreversible modification of the adenosine diphosphate (ADP) P2Y12 receptor, avoiding binding and its activation by ADP. ADP activation of the P2Y12 receptor linked to G-protein is a significant secretion booster of platelets granules, procoagulant and aggregation activity (14). A study reported that among all patients with cerebrovascular conditions, a statistically significant benefit was proved for Clopidogrel against Aspirin. Clopidogrel was generally well tolerated, with a secondary effects profile similar to that of Aspirin(14). Treatment with 75-162 mg of acetylsalicylic acid and 75 mg of Clopidogrel -per day- may be reasonable for high risk selected patients who suffer stable ischemic cardiopathy (Class IIb, level of evidence) (13). 1.3% of major hemorrhage risk increase was correlated with Clopidogrel plus Aspirin. (18)

Dipyridamole

Dipyridamole mainly inhibits phosphodiesterase enzyme in platelets, and further increases intraplatelets levels of cAMP and cGMP, thus inhibiting platelet aggregation and boosting inhibitory actions of platelets of the prostacyclin (PGI2). It additionally inhibits cellular collection and adenosine metabolism, which also plays a role in platelet aggregation inhibition (19). Niu et al., performed a meta-analysis in 2016. They found that using a combined therapy with Aspirin and Dipyridamole was more favorable than using Thienopyridines or Aspirin in monotherapy for secondary prevention of severe vascular events, after TIA or cerebrovascular ischemic accident (17).

Cilostazol

Cilostazol protecting effect may be attributed not only to its antiplatelet effect, but also to effects on other factors associated with the formation of the thrombus (15). Cilostazol may increase production of nitric oxide in the human vascular endothelial cells, thus causing vasodilatation. It additionally, inhibits spread of smooth muscle cells; it reduces concentration of intracellular calcium ions; it increases cholesterol levels of high density lipoprotein in plasma (HDL); it reduces triglyceride plasma level; it boosts angiogenesis and reduces inflammation. All these properties could potentially contribute to secondary prevention of severe vascular events. The main reported adverse effects, apart from hemorrhage, headache, palpitations, dizziness and tachycardia(13). These adverse events may be correlated with relaxation of the vascular smooth muscle (4,13). On the other hand, Cilostazol was significantly associated with a lower recurrence incidence of cerebrovascular events (4).

ANTICOAGULANTS

Warfarin

Warfarin is still the most prescribed oral anticoagulant in most cerebrovascular processes (20). It is characterized by hepatic inhibition of vitamin K and inhibition of coagulation factors dependent on vitamin K (II, VII, IX and X). Use of Warfarin requires periodic control of prothrombin time (PT) and International Normalized Ratio (INR). Usually, PT has been the most frequently used tests for monitoring Warfarin treatment, but thromboplastins used during PT Test tend to vary in their response to Warfarin and may lead to resulting inconsistencies (20, 21).

Factor XA Inhibitors

Factor Xa inhibitors are directly bound to the active site of the Factor Xa, thus blocking coagulation factor activity (22). Rivaroxaban is orally administered, and causes a reversible inhibition. It has an estimated average life of 8 to10 hours. Apixaban, in turn, has an average plasmatic life 8 to 15 hours. Betrixaban has an average life of 15 hours. Edoxaban has an average life of 9 to 11 hours. Additionally, one third is renally eliminated. (23)

Rivaroxaban is a substrate for P-glucoprotein; therefore, its administration along with other P-glucoprotein and CYP3A4 inhibitors (for instance, Ketoconazole) results in higher pharmacological concentrations of Rivaroxaban; therefore its use is contraindicated (22).

DISEASES ASSOCIATED WITH CEREBROVASCULAR DISEASE

Cerebrovascular diseases are associated with other disorders with common development of thromboembolic disease. These are risk factors to suffer such disease, and among we may name atherosclerosis, antiphospholipid syndrome, arterial hypertension, and several other types of cancer. (24)

It is well known that the existing correlation among cerebral ischemic events and atherosclerotic emboli. The risk of this occurrence ranges from 15% to 20%, and it is mainly associated to carotid atheromas. (25, 26) Severity of a thromboembolic ischemic event depends on compromised blood irrigation and therefore, from the anatomical area involved. (27) The most frequent consequences are permanent disability, ranging between 15 to 30% (6)

Atherosclerosis is considered as a multifactor disease as well, where apart from defining endothelial, inflammatory processes, of extracellular and procoagulant lipids, we also have genetic factors. (6,28) That is the case of those associated to LDL/HDL cholesterol and triglycerides, associated to single nucleotide polymorphism (SNP) which make genes, such as ABCG5, ABCG8, PCSK9, SORT1; ABO, LDLR, APOE and LPA blood type are involved in the disease pathogeny. (28)

Another significant CVD aspect, caused by atherosclerosis are external factors, taking into account that such factors are found in patients with coronary disease/peripheral vascular disease risks. (6) Therefore, hypertension, dyslipidemia, obesity, diabetes mellitus and smoking habits put together disorders with which cerebral/peripheral thrombolic events are more frequently correlated with, as these cause endothelial damage associated to nitric oxide, reactive species of oxygen and endothelin. (6,7,26) Apart from personal conditions, such as age, sex, race, and genetic predisposition-inheritance (26)

Finally, CVD prognosis will depend on access to health, due to the high costs on attention, treatments and services the patients are exposed to, which may lead -in the long term- to appearance of nervous deficit. (26)

Antiphospholipid syndrome is defined as an autoimmune disease linked to thrombolic events. The most frequent are deep venous thrombosis and pulmonary thrombosis. (29,30) Additionally, the most frequent manifestation of this is ischemic cerebrovascular accident, whose risk has been reported to be six times higher in people having positive antibodies, such as anticardiolipin antibody and antibody against 2-glycoprotein I. (29,30)

CONCLUSION

Cerebrovascular diseases are a condition associated to multiple pathologies linked to hypercoagulability, such as autoimmune diseases, antiphospholipid syndrome, systemic lupus erythematosus, among others, and with damage of the vascular endothelium, such as atherosclerosis and diabetes mellitus. These are a significant risk factor for thromboembolic disease. That is why pharmacological and thromboembolic disorders prevention is recommended.

REFERENCES

1. Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke. 1989 Oct;20(10):1407–31.
2. WHO. WHO | The Atlas of Heart Disease and Stroke. WHO. 2010;
3. Tatsumi K, Mackman N. Tissue Factor and

Atherothrombosis. J Atheroscler Thromb. 2015;22(6):543–9.
4. Capodanno D, Alberts M, Angiolillo DJ. Antithrombotic therapy for secondary prevention of atherothrombotic events in cerebrovascular disease. Nat Rev Cardiol. 2016 Oct;13(10):609–22.
5. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35–41.
6. Alexandrov A V, Alagona P. Stroke and atherothrombosis: An Update on the Role of Antiplatelet Therapy. Int J Stroke. 2008;3(3):175–81.
7. Thiruvoipati T, Kielhorn CE, Armstrong EJ, Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes : Epidemiology , mechanisms , and outcomes. 2015;6(7):961–9.
8. Conway AE, Reddick WE, Li Y, Yuan Y, Glass JO, Justin N, et al. NIH Public Access. 2015;56(5):405–12.
9. Ntalas I V., Milionis HJ, Kei AA, Kalantzi KI, Goudevenos JA. Antiplatelet Treatment in the Secondary Prevention of Coronary and Cerebrovascular Disease. Angiology. 2014 Jul;65(6):473–90.
10. Olie RH, van der Meijden PEJ, Ten Cate H. The coagulation system in atherothrombosis: Implications for new therapeutic strategies. Res Pract Thromb Haemost. 2018 Apr;2(2):188–98.
11. Ruggeri ZM. Platelets in atherothrombosis. Nat Med. 2002 Nov;8(11):1227–34.
12. Iván Flores-Rivera O, Karina Ramírez-Morales D, Martín Meza-Márquez J, Arturo Nava-López J. Revista Mexicana de Anestesiología Fisiología de la coagulation. Vol. 37. 2014.
13. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol. 2018;15(8):480–96.
14. Jamieson DG, Parekh A, Ezekowitz MD. Review of Antiplatelet Therapy in Secondary Prevention of Cerebrovascular Events: A Need for Direct Comparisons Between Antiplatelet Agents. J Cardiovasc Pharmacol Ther. 2005 Jul;10(3):153–61.
15. Cleland JGF. Is Aspirin useful in primary prevention? Eur Heart J. 2013 Nov;34(44):3412–8.
16. Toyoda K. Pharmacotherapy for the Secondary Prevention of Stroke. Drugs. 2009;69(6):633–47.
17. Niu P-P, Guo Z-N, Jin H, Xing Y-Q, Yang Y. Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: an updated network meta-analysis. BMJ Open. 2016 Mar;6(3):e009013.
18. Fintel DJ. Antiplatelet Therapy in Cerebrovascular Disease: Implications of MATCH and CHARISMA Results for Cardiologists. Clin Cardiol. 2007;30(12):604–14.
19. Balakumar P, Nyo YH, Renushia R, Raaginey D, Oh AN, Varatharajan R, et al. Classical and pleiotropic actions of dipyridamole: Not enough light to illuminate the dark tunnel? Pharmacol Res. 2014 Sep;87:144–50.
20. Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. J Thromb Thrombolysis. 2017 Apr;43(3):365–79.
21. Norwood DA, Parke CK, Rappa LR. A Comprehensive Review of Potential Warfarin-Fruit Interactions. J Pharm Pract. 2015 Dec;28(6):561–71.
22. Jalota A, Scarabelli TM, Saravolatz L, Bakhsh MU, Agrawal P, Jalota R, et al. Novel Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation. Cardiovasc Drugs Ther. 2014 Jun;28(3):247–62.
23. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. Cochrane Database Syst Rev. 2015 Jun;
24. Ganau M, Prisco L, Cebula H, Todeschi J, Abid H, Ligarotti G, et al. Risk of Deep vein thrombosis in neurosurgery: State of the art on prophylaxis protocols and best clinical practices. J Clin Neurosci. 2017;45(2017):60–6.
25. Amlie-lefond C. Childhood stroke : the devil is in the details Hypertension : the

most important preventable risk factor for cerebrovascular disease. Lancet Neurol. 2018;10(7):606–7.
26. Castillo J, Luna A, Ugarriza I, Zarranz JJ. 16 - Enfermedades vasculares cerebrales. Sixth Edition. Neurología. Elsevier Espa8#241;a, S.L.U.; 2018. 301-357 p.
27. The M. Vascular disease and infarcts. 2018;
28. Montagnana M, Danese E, Lippi G. Genetic risk factors of atherothrombosis. 2014;124(9).
29. Miesbach W, Gilzinger A, Gökpinar B, Claus D, Scharrer I. Prevalence of antiphospholipid antibodies in patients with neurological symptoms. Clin Neurol Neurosurg. 2006;108(2):135–42.
30. Pahor A. Immunobiology Antiphospholipid antibodies and atherosclerosis : Insights from Rheumatoid arthritis – A five-year follow-up study ˇ ziˇ. 2018;216(2011):1331–7.

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