https://doi.org/10.31925/farmacia.2019.1.4 **REVIEW**

USE OF ANTICOAGULANTS IN CEREBRAL VASCULAR PATHOLOGY

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Abstract

The aetiology of ischemic vascular stroke (IVS) is various, the most common cause being cardioembolic, and anticoagulation treatment plays an essential role in the prevention of cerebral ischemic events. Atrial fibrillation (AF) is the pathological condition requiring long-term anticoagulant therapy for preventive purposes, both primary and secondary. Complications, disabilities and mortality are more common in patients who had an ischemic stroke associated with atrial fibrillation than in those without AF. The indication, type and dose of anticoagulant depend on the stage and size of the ischemic lesion, thromboembolic and haemorrhagic risk and patient compliance. According to the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, among the different types of anticoagulants indicated in the case of AF and IS, it would be preferable to use new anticoagulants. Anticoagulation medication is indicated in the acute stage only in patients with a clear thromboembolic source. Anticoagulant treatment has a well-established role over time as a result of numerous clinical trials, its use having a guide recommendation, but the particularity of each case as well as personal experience strengthens the indication.

Rezumat

Etiologia accidentului vascular cerebral ischemic (IVS) este diferită, cea mai comună cauză fiind cardioembolică, iar tratamentul anticoagulant joacă un rol esențial în prevenirea accidentelor cerebrale ischemice. Fibrilația atrială (AF) este starea patologică care necesită terapie anticoagulantă pe termen lung în scopuri preventive, atât primare, cât și secundare. Complicațiile, dizabilitățile și mortalitatea sunt mai frecvente la pacienții care au avut un accident vascular cerebral ischemic asociat cu fibrilația atrială comparativ cu pacientii fără această patologie. Indicația, tipul și doza de anticoagulant depind de stadiul și mărimea leziunii ischemice, de riscul tromboembolic și hemoragic și de complianța pacientului. În conformitate cu ghidurile în vigoare privind utilizarea anticoagulantelor orale antagoniste non-vitamine K la pacienții cu fibrilație atrială, printre diferitele tipuri de anticoagulante indicate în cazul AF și IS, ar fi preferabil să se utilizeze anticoagulante noi. Medicamentul anticoagulant este indicat în stadiul acut numai la pacienții cu o sursă tromboembolică clară. Tratamentul anticoagulant are un rol bine stabilit de-a lungul timpului ca rezultat al numeroaselor studii clinice, utilizarea acestuia având o recomandare orientativă, dar particularitatea fiecărui caz, precum și experiența personală consolidează indicația.

Keywords: stroke, anticoagulants, haemorrhagic risk

Introduction

Vascular stroke (VS) is an important pathology which generates disability and it is also the second leading cause of worldwide mortality [54]. Six months after VS, 50% of patients have motor deficiency, 35% depression, 30% require movement help, 19% have speaking disorders, 26% remain dependent in daily activities, and many are institutionalized [29]. Studies conducted worldwide for a period of 20 years (1990-2010) showed an increase in the incidence of both VS (37%) and HVS (haemorrhagic vascular stroke, 47%), as well as an increase in the rate of stroke deaths by about 20% [18]. Approximately 600,000 new cases of stroke are recorded annually in Europe [37]. In a EUROSTAT report (2016) there is an 18.7% stroke incidence in Romania (2013), this ranking our country second in Europe, after Bulgaria [34].

Treatment of stroke and recovery of post-VS involve significant costs for the patient, which have a significant impact on the quality of life, as well as on health systems, requiring multiple material, financial and human resources. A cost estimation in 27 EU countries estimates an annual level of 27 billion euros, of which 48.6% for medication, investigation, specialist, nursing, 22.3% for indirect costs, and the remaining of 29.1% representing informal expenses [3].

The role of anticoagulants in vascular pathology

Considering these aspects, of particular importance is the primary prevention of VS, by combating both risk factors as well as the secondary prevention, in cases with already established vascular neurological events. Anticoagulant treatment finds its utility in both forms of prevention, consistent with the aetiology of the stroke, the stage of the disease (acute or chronic), associated pathology and evolution under the initiated treatment.

The therapeutic measures in the case of constituted TIA (Transient Ischemic Accident)/IVS are complex. They aim at the pathophysiology, prevention of complications, recurrences, pursuing a quicker and less disability-related neuro-rehabilitation.

For patients who have undergone acute IVS, the risk of recurrence is estimated at 11.1% *per* year, at 24.4% at 5 years, increasing significantly at 10 years (39.5%) [27, 39]. This data may be larger in reality because not all TIAs or even VSs benefit from diagnosis because many are silent or with non-specific VS symptoms, the patient not presenting himself to the doctor. Thus, anticoagulants, by influencing some factors involved in the coagulation cascade, intervene in lowering the risk of recurrence of vascular embolisms with different localizations, including the cerebral level, being a major pharmacological class in antithrombotic therapy. Furthermore, in the case of installed thrombosis, they reduce the risk of aggravation by acting directly on the thrombus, thus limiting its extension.

Anticoagulants prove their usefulness, along with other specific care measures, in the prevention of thromboembolic phenomena caused by the condition of the neurological patient (prolonged bed immobilization, muscle tone decrease).

Studies have shown an efficacy of anticoagulant therapy in the prevention of symptomatic pulmonary thromboembolism and deep vein thrombosis, but without a significant effect on the mortality rate or degree of disability in patients previously treated for stroke. Also, no statistical differences were found between the types of anticoagulant, but an important element remains the risk/benefit ratio for each. Thus, the anticoagulant choice should take into account the risk of haemorrhage, which can not be definitely established, but can be assessed by bleeding scores and the therapeutic decision is based mainly on clinical the experience [14, 57].

Influence of anticoagulants on the pathophysiological mechanisms of ischemic stroke

The aetiology of ischemic stroke is various. Knowing the pathophysiological mechanisms of cerebral ischemia and coagulation is essential. These are the basis of the therapeutic indication according to the guidelines and justify the emergency measures necessary for the observation of the concept of the therapeutic window. IVS has thrombotic causes (45%), embolic causes (20%), but in a significant percentage of cases the aetiology is unknown (cryptogenic) [28].

Thrombosis is initiated in the vascular wall as a result of endothelial dysfunction, especially due to the presence of many vascular risk factors (AHT – arterial hypertension, endothelial dysfunction, carotid atheromatosis). There are rare situations where radiotherapy or local trauma triggers the thrombogenic process.

Cardiac embolism (auricular intracytopathic thrombosis or left ventricular hypokinesia, atrial fibrillation (AF), *patent foramen ovale*) or arterial (carotid or aortic) atheromatosis is frequently incriminated in IVS occurrence.

Surgical interventions may predispose patients to IVSs by increasing the risk of developing intra or post-procedural emboli (blood, fat or airborne). There are other rare causes, especially in the youngs, but with a major impact on the evolution, prognosis and quality of life of the patient, such as arterial (carotid or vertebral) dissections, clotting disorders [41], infectious or toxic (through drug abuse) [7].

A distinct cerebral vascular pathology is represented by venous sinus thrombosis, the leading cause of cerebral venous infarction, with a clear indication of anticoagulant therapy, initiated from the onset phase. If a thrombophilic or prothrombotic status is associated, chronic anticoagulation is required.

Atrial fibrillation is the pathological condition requiring long-term anticoagulant therapy for preventive purposes, both primary and secondary. The type and dose of anticoagulant is recommended taking into account the associated pathology and the risk of bleeding. Classical anti-vitamin K therapy has its proven beneficial role over time, but with some limitations such as slow-setting effect, narrow therapeutic window, the need for routine monitoring of coagulation, the influence on the therapeutic concentration of certain foods or drugs, frequent dose adjustments, sometimes unpredictable and with bleeding risks. All these limitations sometimes lead to therapeutic inefficiency.

Patients with AF and IVS experience a high rate of complications and recurrences, often with severe disability and a significant mortality.

A 2005 study demonstrated that recurrence of ischemic vascular events after one year and the incidence of death were more common in patients with AF (6.9% *versus* 4.7% respectively 49.5%

versus 27.1%) [9]. Other studies compared the risk of stroke and death in AF patients, whether or not with anti-vitamin K treatment. The results indicated a 64% decrease of stroke risk and 26% decrease of death due to anticoagulant therapy [19, 35].

In 2009, the RE-LY study (The Randomized Evaluation of Long-Term Anticoagulation Therapy) demonstrated the superiority of non-vitamin K antagonist oral anticoagulants (NOAC) treatment (dabigatran) - at high dose (150 mg x 2 *per* day) compared to anti-vitamin K therapy, in terms of reducing the risk of IVS with 35%, mortality with 15%, intra-cerebral haemorrhage with 59%, but with 48% more frequent digestive bleeding. The results were similar for major haemorrhage [12, 13]. Researches on 110 mg once-a-day dosing therapy with dabigatran have showed similar effects in reducing stroke risk, mortality and gastrointestinal haemorrhage, but a risk of 70% intracranial haemorrhage and 20% major haemorrhage. The favourable RE-LY profile was also confirmed by an FDA study (U.S. Food and Drug Administration) conducted in 134,000 real-life patients [23].

A meta-analysis of four clinical trials (RELY [49], ENGAGE AF-TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48) [22], ROCKET AF[44], ARISTOTLE [24]), which compared the effect of NOACs (dabigatran, edoxaban, rivaroxaban, apixaban) with anti-vitamins K in preventing IVS in patients with AIF, revealed a low risk of recurrence of cerebral ischemia in NOAC treatment. The extension of the RELY study, the RELY-ABLE study (The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients with Atrial Fibrillation), showed the maintenance of the systemic or cerebral embolism prevention effect without increasing the risk of major bleeding or death, irrespective of the cause, for a longer period than 6 years [17]. These side effects of NOAC *versus* anti-vitamin K were also followed in other studies, such as the Danish study of 2016 showing superior safety for dabigatran and apixaban compared to rivaroxaban or anti-vitamin K. With regard to low doses of NOAC, data showed that dabigatran is preferable to apixaban or rivaroxaban, given that, under similar conditions of recurrence and mortality risk, it has caused a significantly lower number of haemorrhages. Apixaban and dabigatran had a significantly lower risk of death or major bleeding accidents compared with wafarin [52]. The existence of idarucizumab, the specific neutralizing agent, increases the safety of dabigatran treatment, which makes it even more recommended for emergency surgery, bleeding, but also for recurrence of IVS with thrombolysis indication.

There have been studies comparing the prophylactic effect of anticoagulants with that of the antiaggregants. In 2012, the AVERROES (Apixaban *Versus* Acetylsalicylic Acid (ASA) study to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) highlighted the importance of anticoagulant treatment in the AIF, demonstrating a superior efficacy to anti-platelet therapy, both in primary and secondary prevention of IVS/TIA, in patients who presented AF [16]. Antiaggregants are used in the presence of AF only in the acute phase of IVS, for a variable period, determined by the IVS aspect and the risk of bleeding. Thus, the 2016 European Society of Cardiology (ESC) Guidelines for the management of atrial fibrillation developed in collaboration with European Association for Cardio-Thoracic Surgery (EACTS) [59] point out that in an acute AF and IVS patients no immediate anticoagulant medication (Class III A) should be administered. In most patients, it is recommended to initiate anticoagulant therapy after 4 - 14 days since the clinical onset, with high results after 90 days of treatment on systemic embolism or haemorrhage [42]. The elevated blood pressure of stroke (assessed by the functional score NIHSS - The National Institutes of Health Stroke Scale score), the high haemorrhage risk (assessed by CHADS-VASC score) and the anticoagulant type are factors that may affect the favourable outcomes of the anticoagulant therapy. Mild or moderate stroke with a NIHSS < 9 has a low risk of haemorrhagic transformation, as demonstrated by a rivaroxaban study in 2016 [21].

Also, in the case of AF patients who receive anticoagulant medication and develop a moderate/severe IVS, it is necessary to discontinue anticoagulation for a period of 3 - 12 days. It will be resumed according to the size/appearance of the acute stroke and the risk of bleeding (class II indication, evidence C) [25].

In the event of a haemorrhagic transformation of IVS, initiation or maintenance of antiaggregant or anticoagulant therapy is dictated by the specificity of each case, taking into account the indications, associated pathology, bleeding risk, stroke severity, with Class II guidance recommendations, B level evidence [32]. The presence of a cerebral haemorrhage in anticoagulated patients with AF requires interruption for 4 - 8 weeks, assessing the risk of bleeding, identifying and combating the factors predisposing to haemorrhage. Combination therapy following stroke or TIA is not recommended for patients associating coronary artery disease and atrial fibrillation because it has not shown a decrease in the risk of new vascular cerebral events (Class III indication, evidence B),

except for coronary stent implant or unstable angina.

Of the different types of anticoagulants indicated in the case of AF and IVS, it would be preferable to use NOACs, both in terms of efficacy, but also of safety and compliance with the treatment.

The therapeutic indication of anticoagulants depending on the stage of stroke

The efficacy of anticoagulants has been clinically proven and sustained over time by numerous multi-centred studies and their results have grounded evidence-based medicine and have received guidance in medical practice. There have been controversies as to when to initiate anticoagulant therapy after an ischemic stroke. Anticoagulant treatment in the acute phase of IVS can be only discussed after a throughout assessment of the risk of bleeding depending on the appearance of the cerebral vessels and the size of the stroke, and of course after exclusion of brain bleeding or other conditions with haemorrhagic risk (AHT, etc.). The magnitude of an infarction can be clinically appreciated by performing the NIHSS score, but imaging is more advantageous, preferably by angioCT (angio computer tomography) - CT scan (ASPECT score - Alberta Stroke Program Early CT Score) because it is possible to identify asymptomatic areas, most often in the association cortex.

The utility of anticoagulants in the acute stage has been demonstrated in the case of TIA in patients with evident thromboembolic source, such as AF, auricular thrombosis, thrombophilic status, otherwise not being superior to anti-aggregation therapy. There are divided opinions about the type of anticoagulant, the dose, the mode of administration and duration of treatment [1].

Unfractionated heparin and low molecular weight heparins (LMWHs) were evaluated for their role in acute IVS in terms of preventing progress, reducing disability and preventing recurrences, but the results of the studies did not clear these issues. Thus, in a Norwegian study, patients with embolic stroke treated in emergency with dalteparin had an 8% rate of early recurrence (the first 7 days) [6], while another study revealed a risk of early recurrent embolism of 12% [10, 11] in the same type of stroke without anticoagulant treatment.

The effect of unfractionated heparin was evaluated as compared to the saline solution administered intravenously within the first 3 hours since the onset and continued for 5 days [31] in the case of superfluous IVS. The monocentric study was conducted on 418 patients with non-lacunar hemispheric strokes (with cardioembolic, atherothrombotic or unknown/ undetermined), and observed that the favourable outcome after 90 days was in favour of the heparin-treated group (38.9% *vs*. 28, 6%, p = 0.025), with a higher risk of intramuscular or extracranial haemorrhage, but without a higher incidence of mortality. Other inconclusive results were the consequence of not taking into account the aetiology of stroke when heparin was administered immediatetly [15].

Following numerous clinical trials, the new Stroke Management Guide (2018) does not recommend emergency anticoagulation therapy with the goal of immediate prevention of recurrence or improvement of clinical outcome or general outcomes [57, 60]. Regarding the utility of NOACs or factor Xa inhibitors in acute thrombotic IVS, a well-established indication [4] has not been demonstrated [4], and there is insufficient data to do so (Class II recommendation, B level evidence).

The ARTSS study (Argatroban with Recombinant Plasminogen Activator for Acute Stroke) in 2012 demonstrated the efficacy of the association between the tissue plasminogen activator and argatroban in partial or complete thrombosis patients proven by transcranial Doppler and did not show an increased risk of bleeding in the case of association compared to mono-therapy [5].

TOAST study (The Trial of Org 10172 in Acute Stroke Treatment) with danaparoid administered in the first 7 days since the onset [51] *versus* placebo, revealed a better evolution under anticoagulation for patients with severe or occlusive atherosclerosis (68% *versus* 55% with placebo), but did not notice a significant difference compared to placebo in terms of overall outcomes at 3 months (75% *versus* 74%). The Doppler exam has the role in identifying patients who may be recommended for this treatment.

In the case of IVS due to large vessel occlusion, the comparative evolution of nadroparin anticoagulant treatment (0.4 mL x 2 *per* day subcutaneously) *vs*. anti-aggregation (aspirin 160 mg/day) initiated in the first 48 hours for 10 days, in the FISS study, did not reveal statistically significant differences after 6 months (73% *versus* 69%) [58]. In this regard, the Guidelines for Early Management of Patients with Acute Ischemic Stroke mention that urgent or short-term anticoagulation in the case of symptomatic stenosis of the internal carotid artery or non-occlusive extracranial thrombosis is not sustained, intravenous heparin having the same utility as well as LMWHs, with class II indication, B level evidence [40,55]. To reduce the risk of recurrence or other cardiovascular events in the case of non-cardioembolic stroke, the platelet antiaggregant has Class I indication and its substitution with warfarin is not beneficial (Class III recommendation).

In case of arterial dissection (vertebral or carotid in extracranial segment), both anti-aggregation and anticoagulant treatment can be administered between

3 and 6 months (class II recommendation, B evidence), without statistically significant differences after 3 months regarding the risk of major bleeding and mortality, regardless the cause of ischemic stroke or dissection side [8,33]. Anticoagulation treatment is taken into account in the presence of coagulation disorders in patients with ischemic stroke (Class II indication, B level).

Conclusions

Anticoagulants are an elective medication in the primary and secondary prevention of ischemic stroke by cardioembolic mechanism. The type and dose of anticoagulant are dictated by the characteristics of each case. The timing of initiation of the anticoagulant is established in most patients with IVS and AF according to the 2016 ESC Guidelines for the management of atrial fibrillation (developed in collaboration with EACTS). Anticoagulant treatment has its well-established role over time as a result of numerous clinical trials, its use having a guide recommendation, but the specificity of each case, as well as personal experience strengthens the indication.

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