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ORIGINAL ARTICLE

Rivaroxaban in cervical and "cervico-cerebral" artery dissections: a new therapeutic option?

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Abstract
Antiplatelet agents and vitamin K antagonists (VKA) are usually used in the treatment of cervical (carotid or vertebral) artery dissections (CADs); however, data about the use of direct oral anticoagulants (DOACs) in these conditions are very limited. DOACs have proven to be effective in stroke reduction in non-valvular atrial fibrillation and, when possible, they are preferred to warfarin because of their better safety profile. We describe four cases of CADs and, firstly in literature, cervico-cerebral (CCADs) in young patients (average age of 42 years) treated with rivaroxaban 20 mg daily. Three of these four dissections had affected the vertebral artery (condition with an unfavorable prognosis and more often complicated by subarachnoid hemorrhages), and the other one was a carotid dissection at the extra-intracranial passage. All patients were followed clinically and with serial neurosonological examinations at 1, 3, and 6 months and with magnetic resonance angiography (MRA) at 6 months. All patients presented a good outcome with vascular recanalization without stroke recurrence or bleedings, even in patients with intracranial vertebral artery involvement. DOACs could be an alternative in young patients with CADs and their use could be considered in intracranial artery dissections too.

Keywords Cervical and cervico-cerebral artery dissections · Stroke · Transcranial color Doppler · Neurosonology · DOACs · Rivaroxaban

Introduction

Cervical and cervico-cerebral carotid and vertebral artery dissections (CADs and CCADs) represent an uncommon cause of cerebrovascular events accounting for 1–2% of all strokes but up to 25% of strokes in patients under 45 years of age [1–4]. The carotid district is most frequently affected, but vertebral arteries are involved in one-third of cases. The term "dissection" implies a tear in the wall of a major artery leading to the development of an intramural hematoma. It can cause stenosis of the lumen, in particular if hematoma is between the intima and media layers, or pseudo-aneurismal dilatation, especially when it collects between the media and adventitia layers. Ischemic stroke can result from artery-to-artery embolism or, less frequently, from a local arterial branch compression, in situ thrombotic occlusion, or hemodynamic impairment [5]. Besides, subarachnoid hemorrhage (SAH) can develop as a consequence of the intradural rupture of an arterial dissecting aneurysm. SAH is less common than ischemic stroke and occurs more frequently in vertebral dissections, especially if intracranial (V4) tract or extra-intracranial (V3–V4) passage is involved [4–6].

Early treatment is very important in preventing cerebrovascular events and minimizing neurologic sequels. American and European Guidelines support both antiplatelet and anticoagulant agents for CAD treatment without evidence of superiority of the one on the other treatment

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in appropriate clinical trials [7, 8]. The therapeutic choice in the case of CAD/CCAD can be related to the features of the dissection and, in general, of the patient [9–11]: anticoagulants in the case of free-floating thrombus, local compression syndrome without stroke, severe stenosis/pseudo-occlusion, multiple embolic lesions, or microembolic high-intensity transient signals (HITS) in transcranial color Doppler examination; instead antiplatelets for large infarct with associated mass effect, hemorrhagic transformation of the infarcted area, high risk of bleeding for the patient, intracranial aneurysm, and intracranial extension of the dissection (especially if the vertebral artery is involved) [5, 11–13]. Direct oral anticoagulants (DOACs) have proven to be effective in stroke reduction in nonvalvular atrial fibrillation and, when possible, they are preferred to warfarin for their safety profile [14–16]. Their safety and potential effectiveness in CADs/CCADs have not been to date investigated.

We present our initial experience with the use of rivaroxaban in four patients with CAD or CCAD.

Methods

Between February 2015 and October 2017, we collected data from four patients with spontaneous CAD or CCAD; their previous modified Rankin Scale (mRS) score was 0 (Table 1). Three patients had vertebral artery dissection and one had right internal carotid artery dissection. DOACs, and specifically rivaroxaban 20 mg daily, were given to our patients in an off-label use, with informed consent.

The choice of direct anticoagulants was mainly motivated, in the absence of absolute contraindications to this treatment, by the patients' refusal to take warfarin, especially for work reasons, and by pathological characteristics of the cases: multiple embolic ischemic lesions in patient 1, severe arterial stenosis in patients 2 and 3, local compression syndrome (Horner) without stroke in patient 4.

All patients were followed clinically and with serial neurosonological exams, specifically echo color Doppler of the supra-aortic vessels (TSA) and transcranial color Doppler (TCCD) exam, respectively, 1, 3, and 6 months after the onset and with magnetic resonance angiography (MRA) at 6 months.

NIH Stroke Scale (NIHSS) and mRS were used in clinical evaluation.

Results

We describe the case of four patients treated with rivaroxaban after CAD or CCAD (2 males and 2 females). Their average age was 42. All patients presented with spontaneous dissections diagnosed by ultrasonography and MRA (Fig. 1a–d). In two patients (1 and 3), an intracranial tract of vertebral artery was involved, respectively, in V3–V4 passage and in V4 tract. In this last case, MRI showed multiple ischemic lesions. Patient 2 had a dissection of right extracranial (V2–V3 tract) vertebral artery with consequent cerebellar ischemia. Finally, right internal carotid artery, in both extra and intracranial segment, was involved in patient 4.

All patients were treated with rivaroxaban 20 mg od after a short phase of low molecular weight heparin (15 days in patient 1 and 2–3 days in other patients) and they underwent seriate neurosonological examinations. In three of them, we observed arterial patency after a month. Only patient 1 had an unmodified ultrasonographical exam after a month; however, 3 months after the onset, he also presented arterial recanalization, with ultrasonographic "pearl and string sign."

Sixth months after the beginning of therapy with rivaroxaban, cerebral MRI and MRA were performed in all patients showing a complete arterial recanalization and the absence of new ischemic lesions, even in patient 1 that had presented the most severe clinical and neuroradiological findings at the onset (Table 1).

Treatment compliance was optimal and no patients presented major bleeding, including SAH. We observed only two minor hemorrhagic events (hemorrhoidal bleeding and slight metrorrhagia, respectively, in patients 1 and 3) not requiring anticoagulant discontinuation.

Clinically, NIHSS improved and mRS score at 3 months was 2 in patient 1 and 0 in all other patients.

After 6 months of therapy, all patients stopped rivaroxaban and started antiplatelet treatment.

Discussion

There is little experience in the use of DOACs in CAD/CCAD.

Caprio et al. [17] compared the efficacy and safety of DOACs (apixaban, dabigatran, and rivaroxaban) with traditional anticoagulant (warfarin and low molecular weight heparin) and antiplatelet agents. They included 149 patients: 39, 70 and 40 were treated with DOACs, traditional anticoagulants (AC: Warfarin or treatment dose low-molecular weight heparin) and antiplatelets respectively. The DOAC group had similar rates of stroke recurrence and lower rates of major hemorrhagic complications but worse rates of stenosis compared with other groups.

Mustanoja et al. [18] included 68 patients with CAD; six patients were treated with DOACs (three with dabigatran and three with rivaroxaban) and 62 with warfarin. After 6 months of treatment, rates of arterial recanalization and general outcome were similar between the two groups of patients. Besides, there were neither deaths nor intracerebral

Table 1 Baseline characteristics, imaging findings, and outcome of patients

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Female	Female	Male
Age	41 years	36 years	49 years	43 years
Symptoms at onset	Occipital headache, nausea and vomiting, postural instability, ataxia, dysphagia, dysarthria, and decreased consciousness	Occipital headache, rotatory nystagmus, ataxia, and vertigo	Right cervical pain, paresthesia, and vertigo	Headache and dysesthesia on the left side of face and Horner syndrome
NIHSS at onset	NIHSS 6	NIHSS 2	NIHSS 2	NIHSS 3
Pre-stroke mRS	mRS 0	mRS 0	mRS 0	mRS 0
Dissection features (MRA)	Spontaneous right vertebral dissection in distal extracranial and intracranial segments (intramural hematoma in V3–V4 with involvement of postero-inferior cerebellar artery)	Spontaneous dissection of right extracranial vertebral artery (severe stenosis at V2–V3 passage with filiform flow)	Spontaneous dissection of right intracranial vertebral artery (severe stenosis in V4 tract) in multivessel dysplasia	Spontaneous dissection of left internal carotid artery at the extra-intracranial passage (intramural hematoma in the post-bulbar tract and pseudo-aneurismatic ectasia in the intrapetrous tract)
Brain lesion at onset (MRI)	Yes: right cerebellar and postero-lateral bulbar ischemia	Yes: right cerebellar ischemia	No	No
Neurosonological exam (echo color Doppler of the supra-aortic trunks/TCCD) at onset	Holosystolic spectrum in the right extracranial vertebral artery (V2 tract); its intracranial tract appears badly detectable and presents very low velocities	Intimal flap and stump flow in V2 tract of the right vertebral artery	High-resistance flow in V2 tract of the right vertebral artery; low velocities in its distal intracranial tract	Focal wall ectasia, hypoechoic material surrounding the residue vessel (intramural hematoma), high-resistance flow in post-bulbar tract of left carotid artery. Detection of HITs during transcranial echo color Doppler monitoring of left middle cerebral artery
Neurosonological exam (echo color Doppler of the supra-aortic trunks/TCCD) after 1 month	Unmodified	Reappearance of the flow in V2 and V3 segments and improvement of Doppler signal in V4	Reappearance of the diastolic flow in the right vertebral artery	Recanalization of left internal carotid artery
Neurosonological exam (echo color Doppler of the supra-aortic trunks/TCCD) after 3 months	Reappearance of the flow in right vertebral artery with "pearl and string sign"	Complete recanalization	Complete recanalization	Complete recanalization
MRA after 6 mounths	Complete recanalization	Complete recanalization	Complete recanalization	Complete recanalization
NIHSS and mRS after 6 months	NIHSS 1 mRS 2	NIHSS 0 mRS 0	NIHSS 0 mRS 0	NIHSS 0 mRS 0
Bleeding complication	Hemorrhoidal bleeding	None	Slight metrorrhagia	None

NIHSS, National Institutes of Health Stroke Scale; *mRS*, modified Rankin Scale; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *TCCD*, transcranial color Doppler exam

hemorrhages in the DOAC group, but a case of death and a case of intracerebral hemorrhage in the warfarin group.

Both reports, as well as another in literature [19], recommended further greater studies in order to compare the safety and efficacy of DOACs with traditional medical therapy (antiplatelets, warfarin, and low molecular weight heparin) in the case of CAD.

So far, there are no studies about the use of DOACs in dissections affecting intracranial artery segments.

In our four patients, rivaroxaban was effective and safe, even in the cases with severe steno-occlusion and/or with involvement of intracranial vertebral artery. After 6 months of treatment with rivaroxaban, we observed arterial recanalization and the absence of new brain ischemic lesions in all patients, without major bleedings (including SAH).

Given probable concomitant antiplatelet effect of rivaroxaban hypothesized in some studies [20] and better safety profile in comparison with warfarin, rivaroxaban could be

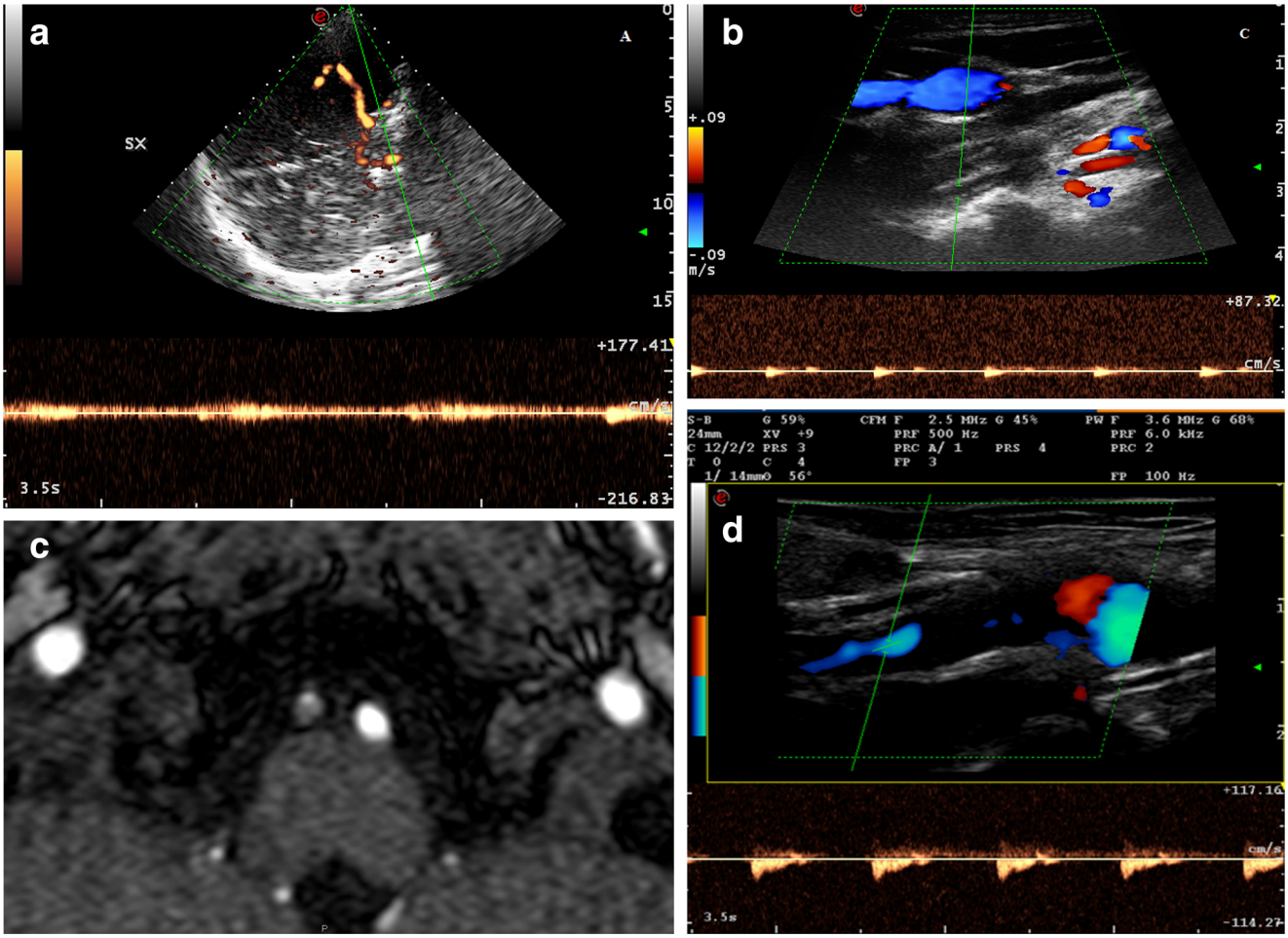

Fig. 1 **a** Transcranial color-coded duplex sonography (TCCD), occipital window: the right vertebral artery in the intracranial tract appears badly detectable except for a colorimetric spot. In its distal tract, it shows a spectrum with very low velocity and high turbulence (patient 1). **b** Echo color Doppler of supra-aortic vessels: an holosystolic with low-velocity spectrum (stump flow) is detectable in V2 tract of the right vertebral artery. In B-mode imaging, intimal flap with partial double lumen is visible (patient 2). **c** magnetic resonance angiography (MRA): right vertebral artery stenosis (patient 3). **d** Echo color Doppler of supra-aortic vessels, longitudinal view of the left carotid artery: hypoechogenic signal (intramural hematoma) around the minimal residue flow and typical stump-flow (patient 4)

an optimal option to prevent neurological sequels in patients with CAD and CCAD.

In a previous study [21], the rate of full recanalization after a vertebral dissection is 45.9% at 3 months, 62.3% at 6 months, and 63.9% at 12 months. In our cases, the rate of full recanalization was 100% at 3 months, probably thanks to the faster achievement of an effective level of anticoagulation with DOACs compared with warfarin.

Last consideration is about the use of neurosonology in both diagnosis and follow-up of CADs. Ultrasounds are useful in the diagnostic initial phase thanks to their good sensitivity (from 80 to 96% in the internal carotid artery and from 70 to 86% in the vertebral artery) and easy accessibility and they can indicate second-level diagnostic exams (MRA and angio-CT) [22, 23].

Echo color Doppler of the supra-aortic vessels allows the evaluation of direct/specific findings (double lumen, hyperechoic intimal flap, and hypoechoic intramural hematoma) and indirect/non-specific findings (localized increase of arterial diameter, occlusion or stenosis in the absence of plates, upstream high-resistance Doppler signal, and downstream hemodynamic signs) [23]. The transcranial color Doppler exam [24] allows the evaluation of downstream intracranial consequences of the dissection (reduced flows in major intracranial arteries, inversion of the ophthalmic flow) [25, 26] and it can detect HITS. They result from artery-to-artery embolism and represent potential prognostic factors [27].

Furthermore, ultrasonography represents an exceptional tool for serial monitoring of dissection and recanalization rate, thanks to easier availability without the burden of radiations, high costs, and contrast toxicity risk of more invasive techniques [27, 28].

Conclusion

To date, the best treatment of CAD is still on debate, as there is no evidence of superiority of oral anticoagulants over

antiplatelet treatment in randomized trials [10–12]. Besides, there is little experience in the use of DOACs in CADs, in particular in the case of intracranial involvement (CCADs). Considering their pharmacokinetic, pharmacodynamical, and practical profiles (easier to handle and with less interference with foods or medications), the use of DOACs could be an alternative in CADs, even for young people with an active life [17–19]. Our experience has showed good results for rivaroxaban in this setting, even in the case with greater bleeding risk (dissection of intracranial vertebral artery). However, its limitations include retrospective nature and small number of patients; thus, further greater studies are necessary in order to evaluate the safety and efficacy of DOACs in CAD and especially in CCADs.

Compliance with ethical standards

Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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