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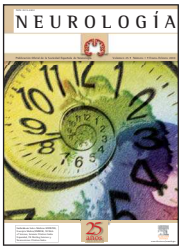

EDITORIAL

Endovascular treatment for acute stroke: an open field to begin

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Abstract
Introduction: The evidence that recanalization and reperfusion of the distal vascular bed in appropriately selected patients is crucial to achieve good functional outcome has triggered interest and research into endovascular treatment of acute ischemic stroke.
Development: Intravenous (iv) thrombolytic therapy is the treatment of choice in patients with acute ischemic stroke; however, it has certain limitations. Endovascular treatment is a promising alternative with theoretical advantages over IV therapy, such as an increased frequency of recanalization and longer therapeutic windows. Endovascular reperfusion strategies include intra-arterial fibrinolysis with drugs, or endovascular mechanical devices for thrombectomy or thrombus disruption, thromboaspiration, or thrombus entrapment in the vessel wall. The ideal of comprehensive treatment of acute stroke would provide specificity to treat an individual patient: with specific arterial occlusion and collaterals and a determined physiology of acute cerebral ischemia. With all this information, we would decide the best therapeutic strategy for the patient, and move from just a time-based approach to include a pathophysiology approach as well, and thus different patients could have different therapeutic windows. The endovascular treatment situation in Spain is heterogeneous and requires human and material resources to enable it to be implemented throughout the country.
Conclusions: Endovascular treatment of stroke is a new therapeutic tool for achieving reperfusion safely in patients ineligible for Alteplase or who have failed reperfusion with an IV fibrinolytic.

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PALABRAS CLAVE
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Tratamiento endovascular del ictus agudo: un campo muy abierto que está por iniciar

Resumen
Introducción: La evidencia de que la recanalización y la reperfusión del lecho vascular distal de pacientes adecuadamente seleccionados son fundamentales para lograr un buen pronóstico funcional ha disparado el interés y la investigación sobre el tratamiento endovascular del ictus isquémico agudo.
Desarrollo: La fibrinólisis intravenosa (i.v.) es el tratamiento de elección en pacientes con ictus isquémico agudo, aunque presenta ciertas limitaciones. El tratamiento endovascular supone una alternativa prometedora con ventajas teóricas sobre el tratamiento i.v., como una mayor frecuencia de recanalización y mayor ventana terapéutica. Las estrategias de reperfusión endovascular incluyen fibrinólisis intraarterial con fármacos o tratamiento mecánico con dispositivos que permiten extracción, aspiración, disrupción o atrapamiento del trombo en la pared. El ideal del tratamiento integral del ictus agudo sería aportar especificidad al paciente individual: tratar una oclusión arterial con unas colaterales y con una fisiología de la isquemia cerebral aguda determinadas. Con todos estos datos, ante cualquier paciente podremos decidir la mejor estrategia terapéutica y pasar de un enfoque del paciente basado únicamente en el tiempo a un enfoque basado también en la fisiopatología; por lo tanto, distintos pacientes tendrían diferentes ventanas terapéuticas. La situación del tratamiento endovascular en España es heterogénea y precisa de recursos materiales y humanos para conseguir su implantación en todo el territorio.
Conclusiones: El tratamiento endovascular del ictus supone una nueva herramienta terapéutica para lograr la reperfusión de una forma segura en los pacientes no candidatos a alteplasa o que no han conseguido reperfundir con el fibrinolítico i.v.

Introduction

Stroke is the leading cause of death for women, the second for men and the leading cause of adult disability and dependency. After a period of nihilism in acute stroke management, intravenous (IV) fibrinolysis with alteplase (recombinant tissue plasminogen activator, rtPA) represented a big change in the therapeutic approach to these patients. Endovascular treatment of stroke is a promising alternative for patients who are not candidates for rtPA or who have not improved with IV fibrinolysis. Evidence that recanalization of appropriately selected patients is crucial for good functional outcome has triggered interest and research in this new endovascular therapy.

Intravenous fibrinolysis: "time is brain"

The modern era of revascularization therapy for acute ischemic stroke began in the mid-nineties with a study by the National Institute of Neurological Disorders and Stroke (NINDS),[1] about the first 3 hours after the onset of symptoms. The analysis of pooled clinical trials with IV rtPA confirmed the clinical benefit observed within the first 3 h and pointed to an additional benefit after 3 h in some patients.[2] The possibility of obtaining clinical benefit at 3 months decreased with increasing time from stroke onset to initiation of treatment. The benefit of IV rtPA between 3 and 4.5 h was confirmed in the ECASS III study in a subgroup of patients.[3] Intravenous rtPA fibrinolysis was the first approved treatment for acute stroke that treated the vascular occlusion produced by stroke effectively. The treatment is easy to apply and quick and requires no technical expertise or specialised equipment; it requires only an appropriate clinical assessment of the patient by an expert and a cranial computed tomography (CT) scan to rule out bleeding. You can implement it without objectifying the occlusion of a cerebral artery, as the priority is an approach based on how quickly treatment is initiated. However, IV rtPA fibrinolysis is far from being the perfect treatment for all patients. First, it is not applicable for everyone, both because of its narrow therapeutic window and because of exclusion due to, for example, analytical parameters. Second, recanalization rates with IV rtPA in proximal artery occlusions range from less than 10% for internal carotid artery occlusion to 30% for the proximal middle cerebral artery.[4,5] Third, the clinical benefit obtained in the NINDS study shows an absolute increase of 12% in the number of patients with or without minimal disability between the placebo group and the group treated with rtPA at 3 months. This benefit (although underestimated because patients who improved partially were not included) could still be improved with more effective strategies, given the strong impact of cerebrovascular pathology. It has already been shown that

recanalization carries a better prognosis and lower mortality.[6] For all these reasons, new strategies are sought to achieve more complete reperfusion, resulting in a better long-term functional outcome.

Interventional neurovascular treatment: from "time is brain" to the importance of vessel recanalization and distal reperfusion

There are three types of reperfusion strategies. The best known is the recanalization of an occluded artery or antegrade reperfusion. There are other alternative strategies, such as global reperfusion or increased flow, which aims to increase cerebral blood flow to perfuse the vascular bed distal to the occlusion via the leptomeningeal collaterals and/or the collaterals of the Circle of Willis, such as the NeuroFlo catheter.[7]

Endovascular reperfusion strategies include intra-arterial fibrinolysis with drugs, extraction or mechanical treatment with devices that allow aspiration or disruption of the clot or clot entrapment within the wall (stents). Table 1 shows the main studies.

Intra-arterial fibrinolysis has the advantages of direct access to the occluded vessel, being able to instil the fibrinolytic agent within the clot with a lower dose and achieving a greater recanalization frequency. The randomized studies PROACT II[8] and MELT,[9] together with data from PROACT I, have shown a lower mortality and long-term dependence in patients suffering an occlusion of the middle cerebral artery (MCA) who were treated with intra-arterial fibrinolysis compared with controls (58.5 compared to 69.2%; p=0.03; odds ratio [OR]=0.58; 95% confidence interval [CI], 0.36-0.93).[10] However, the rate of recanalization in these studies confirms that intra-arterial fibrinolytic therapy is not the ultimate solution to the challenge of rapid, complete recanalization of an occluded cerebral artery.

Combination therapy of IV fibrinolysis with rtPA, followed by intra-arterial therapy, has been called combined or transitional (bridging) therapy. The EMS,[11] IMS I[12] and IMS II[13] studies evaluated its effectiveness with lower doses of rtPA. Several published studies also support the safety of intra-arterial treatment following the full dose of IV rtPA,[14-16] and show a higher recanalization rate in the combined therapy group, with no differences in mortality, bleeding and symptomatic brain haemorrhage.

As for mechanical devices, the MERCI[17,18] and Penumbra[19] devices are both indicated for the endovascular stroke treatment There are also many other devices available, such as self-expanding intracranial stents,[20] some of them recoverable, which obtain a high rate of safe, effective recanalization.

There are published case series, but given the lack of controlled data, we tend to compare different studies. However, neither the populations nor the objectives of each study are comparable. The explanation of why there is little clinical benefit despite the high rate of recanalization in studies using mechanical devices could lie in differences in clot location and total clot load, baseline severity and time elapsed since symptom onset.

In general, they are patients with greater stroke severity, treated after a longer time. Although the clinical benefit is moderate, we manage to widen the therapeutic window to up to 8 h, treating the most severe patients with safety and greater recanalization frequency (table 1).

The frequency of recanalization of the occluded vessel varies with the method of treatment used: spontaneous recanalization (21%), IV fibrinolysis (46.2%), intra-arterial fibrinolysis (63.2%), combined IV/intra-arterial treatment (67.5%), mechanical treatment (83.6%).[6] The clinical outcome at 3 months was favourable (mRS $\leq$ 2) in 8% of patients without recanalization, in 33% of reocclusions and in 50% of stable recanalization. Mortality at 3 months was 42, 33 and 8%, respectively.[21] However, the relationship between reperfusion and clinical outcome was not always proportional, since other factors such as intensity and duration of ischemia, stroke severity, collateral circulation, cerebral perfusion pressure, location and volume of the lesion were determinants of prognosis. Reperfusion could therefore be followed by improvement, deterioration or death from cerebral oedema or intracerebral haemorrhage.[22]

The current problems of the evidence available on endovascular revascularization are the lack of randomized studies, small patient samples, absence of adequate controls and lack of a principal criterion for the evaluation of effectiveness. The studies were carried out with different patterns of peri-procedural anticoagulation or different antiplatelet patterns during or after the procedure in the case of stent placements. Definitions should be standardised; an example is that of recanalization with Thrombolysis in Myocardial Infarction (TIMI) scale, which assesses the recanalization of the occluded vessel, but is different from distal bed global reperfusion.[23]

There are studies that limit the endovascular treatment to a single technique: only fibrinolytic or only one endovascular device. The reality of a patient with acute stroke is that it may be necessary to use multiple resources and significant technical skill is required.

The ideal comprehensive treatment for acute stroke would be to provide specificity for each individual patient when treating a specific arterial occlusion, with specific aetiology features (fresh clot, previous atheromatosis, carotid dissection), with specific collaterals, with specific ischemic preconditioning and a specific physiology of acute cerebral ischemia. With all these data, we would be able to select the best therapeutic strategy and move from an approach based on time to an approach based on brain physiology for each patient. Different patients would thus have different therapeutic windows.

The ischemic penumbra is the ischemic brain tissue that is functionally damaged and at risk of stroke, but with the potential to be saved by reperfusion, in conjunction or not with other strategies. If reperfusion does not take place, it is recruited into the infarcted core. Multimodal neuroimaging, multiparameter magnetic resonance imaging (MRI) and perfusion CT can help to select patients by assessing the ischemic penumbra. MRI assesses the mismatch between the infarcted core on diffusion-weighted imaging (DWI) and the hypoperfused region on perfusion-weighted imaging (PWI).[24] The region of ischemic penumbra is

Table 1 Main studies on endovascular treatment of stroke

	Design	Population	TT	Recanalization (TIMI 2-3)	Favourable prognosis at 3 months	SICH	Mortality
NINDS placebo[1]	RCT. Placebo	n=211; NIHSS, 17	118±35.3 min	(?)	mRS 0-1: 21%	1%	24%
NINDS rtPA[1]	RCT. IV rtPA (0,9 mg/kg)	n=182; NIHSS, 14	115±36.7 min	(?)	mRS 0-1: 38%	6.6%	21%
PROACT II[8]	RCT. IA ProUK + IV heparin versus control (IV heparin). MCA occlusions. Disruption with guide was not allowed	n=180 (121 IA); NIHSS, 17	IA: 4.7 h [4-5.3]. C: 5.1 h [4.2-5.5]	IA: 66%; C: 18% TIMI 3: 19% versus C 2%	mRS≤2: IA 40% versus C 25% (p=0.04)	IA: 10%; C: 2%	IA: 25%; C: 27%
MELT[9]	RCT. IA UK versus medical treatment. MCA occlusions. Disruption with guide was allowed. Stopped prematurely	n=114; NIHSS14	199±61 min; 206±54 min	IA: 73.7%; TIMI 3: 5.3%C (?)	mRS=2: IA 49.1% versus C 38.6%; p=0.3; mRS≤1: 41.2%versus 22.8%; p=0.045	IA: 9%; C: 2%	IA: 5.3%; C: 3.5%
IMS I[12]	Prospective. Open. IV rtPA (0.6 mg/kg). If AAO IA rtPA up to 22 mg	n=80; NIHSS, 18	TT IV 136±30.2 min; TT IA 217±46.7 min	56%	mRS=2: 43%	IA: 6.3%	IA: 16%
IMS II[13]	Prospective. Open. IV rtPA (0.6 mg/kg). If AAO IA rtPA up to 22 mg	n=81; NIHSS, 19	IV TT 140±31.3 min	58%	mRS=2: 46%	IA: 9.9%	IA: 16%
MERCI[17]	Prospective. Open. Allowed IA drugs. ICA, 19%; occlusions in T 14%; MCA 57%; AB 9%	n=141; NIHSS, 20	4.3±1.7 h	60.3%(Merci + fibrinolytics) 48%(Merci)	mRS=2: 27.7%	IA: 7.8%	IA: 44%
Multi-MERCI[18]	Prospective. Open. Group 1: IV rtPA < 3 h with AAO + Merci. Group 2: Isolated mechanical thrombectomy with Merci. IV fibrinolytic and IA drugs were allowed	n=164; NIHSS 19	4.3 h [3.2-5.3]	68%(Merci + fibrinolytics); 55%(Merci)	mRS=2: 36%	IA: 9.8%PH-2: 2.4%	IA: 34%
Penumbra[19]	Prospective. Open. Ischemic stroke < 8 h with AAO. Penumbra device, IA fibrinolytic drugs were allowed (n=12). ICA 18%, MCA 70%, vertebrobasilar 9%	n=125; NIHSS 17.6	4.3±1.5 h	81.6%; TIMI 3: 27.2%	mRS=2: 25%	IA: 11.2%PH-2: 1.6%	IA: 32.8%

AAO: angiographic arterial occlusion; C: control; IA: intra-arterial; ICA: internal carotid artery; IV: intravenous; MCA: middle cerebral artery; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PH-2: parenchymal haematoma type 2-type haemorrhagic transformation; ProUK: prourokinase; RCT: randomized clinical trial; rtPA: recombinant tissue plasminogen activator; SICH: symptomatic intracerebral haemorrhage; TIMI: Thrombolysis In Myocardial Infarction; TT: time to treatment; UK: urokinase.

maintained by each patient's collaterals. However, there is some controversy, as the DWI may contain areas of penumbra and the PWI may overestimate the penumbra. The DWI/PWI mismatch is a widely used and widely available strategy, with the potential to act as a guide in selecting patients who are candidates for revascularization treatment with an extended therapeutic window. Other methods of estimating the penumbra are the clinical-DWI mismatch or MR angio-MRI-DWI.[25] Perfusion CT has proven to be an alternative to multimodal MRI for patient selection in thrombolytic therapy. There are currently randomized controlled studies underway with patient selection using multimodal neuroimaging, such as MR Rescue (MR Imaging and Recanalization of Stroke Clots Using Embolectomy) or DAWN (DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention), with some very interesting preliminary results.[26]

Current situation of neurointervention in Spain

In the article published in this edition of *Neurologia*, Cruz Culebras et al[27] present preliminary data from the endovascular treatment of stroke in the Region of Madrid. Some very interesting results are presented: in 41 patients with a median NIHSS of 17, a total or partial recanalization was obtained in 78% of cases, with 2.4% of symptomatic hemorrhagic transformation, an overall mortality of 19.5% (higher in those without recanalization) and clinical benefit (modified Rankin Scale, mRS $\leq$ 2) in 53.6% It was a heterogeneous patient group and the endovascular procedure protocol was not standardised among different hospitals. There was also no consensus regarding patient selection with multiparameter imaging. Nevertheless, this is a very interesting start that should make us professionals reflect on the real possibility of applying endovascular treatment to patients with ischemic stroke and large-vessel occlusion in a safe, effective manner.

It presented 41 patients over a period of four years, so it could be said that this type of endovascular treatment was not performed routinely in this Region. There is a plan for endovascular treatment of stroke in progress, but at the moment only one hospital in Madrid has a neurointervention doctor on call. The current situation in Spain concerning the introduction of endovascular treatment of stroke has not been resolved; although some regions have started it, there are still large differences between them. In some hospitals, treatment is part of daily clinical practice, but the reality is that in most of them it is carried out in isolated cases, without an established protocol, at the expense of personal effort and legal risk for the professionals involved. While endovascular treatment of stroke is part of the daily routine treatment of these patients in the rest of Europe and the United States, in Spain we still have some way to go.

In Spain, there are still some geographical areas in which stroke patients are not evaluated by a neurologist on call, they cannot be admitted to a stroke unit and they do not receive IV treatment with rtPA or they receive it later because neurologists on call are only localised. It is common for multiparameter imaging not to be available 24 hours a day to assist in selecting patients. There are not enough professionals trained in neurointervention to perform procedures, or in those places where they are available, a medical on-call schedule has not been established. To improve the situation, the Health Care for Stroke Plan and the National Stroke Strategy have laid the groundwork for this situation to be changed in the short term. It will be essential to provide the necessary human and material resources as well as collaboration between different specialists for this situation to work in reality and thus be able to benefit our stroke patients and contribute to scientific evidence.

Conclusions

In light of the current evidence, we can say that recanalization and reperfusion in a patient with acute ischemic stroke and large-vessel occlusion lead to a better prognosis and lower mortality. Current imaging techniques make it possible to single out the occluded vessel quickly and reliably. At times, the aetiology, collaterals and even the pathophysiology of cerebral ischemia in that particular patient can also be identified. Alteplase treatment should be started without delay, provided it is indicated, and we cannot ignore the rest of the information provided by imaging techniques. Endovascular treatment of stroke represents a new tool for achieving safe reperfusion in patients who are not candidates for alteplase or who have failed to be reperfused with it. However, much remains to be done, and randomized controlled clinical trials are needed to establish further evidence substantiating the benefit of endovascular treatment of acute ischemic stroke.

Conflict of interests

The authors declare no conflict of interests.

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