Neurología. 2010;**25(5)**:279-286

NEUROLOGÍA

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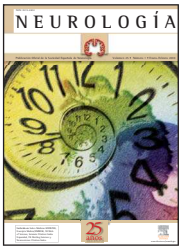

ORIGINAL ARTICLE

Neurovascular intervention in the acute phase of cerebral infarction

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Received on 5th December 2009; accepted on 20th January 2010

KEYWORDS
Ischaemic stroke;
Thrombolysis;
Endovascular procedures;
Cerebral infarction;
Intra-arterial thrombolysis;
Tissue plasminogen activator

Abstract
Background and purpose: Endovascular therapies in acute ischaemic stroke may offer benefits to patients that are not eligible for standard use of intravenous tissue activator plasminogen (iv t-PA) or when this is not effective. Our aim is to present the initial experience in with endovascular techniques in the Community of Madrid.
Methods: We present data from our registry of acute ischaemic strokes treated with endovascular re-perfusion therapies in five University Hospitals in Madrid (Spain) during the period 2005-2009. We recorded demographic data, vascular risk factors, risk severity with the NIHSS (National Institute of Health Stroke Scale), endovascular techniques, complications and mortality rates. Functional outcome and neurological disability at 90 days was defined by the modified Rankin scale (mRs).
Results: A total of 41 patients were treated with endovascular therapies. Mean age was 58.6±19.9, and 56.1%were males. Of those 22 patients had an anterior circulation stroke and 19 had a posterior circulation stroke. Baseline NIHSS score was: median, 17 [range, 2-34]; 7 patients had previously received IV t-PA. The following endovascular techniques were performed: mechanical disruption (26 patients), intra-arterial infusion of t-PA

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(26 patients), angioplasty and stenting (5 patients), mechanical use of MERCI device (3 patients). Partial or total re-canalization was achieved in 32 patients (78%). Only one patient had a symptomatic cerebral haemorrhage. Three months after stroke, 53.6% of the patients were independent (mRs=2) and overall mortality rate was 19.5%.
Conclusions: Acute ischaemic stroke is a potentially treatable medical emergency within the first hours after the onset of symptoms. Stroke endovascular procedures constitute an alternative for patients with IV t-PA exclusion criteria or when this is not effective.

PALABRAS CLAVE
Ictus isquémico;
Trombólisis;
Intervencionismo neurovascular;
Infarto cerebral;
Trombólisis intraarterial;
Activador del plasminógeno tisular

Intervencionismo neurovascular en la fase aguda del infarto cerebral

Resumen
Introducción y objetivos: El intervencionismo neurovascular (INV) en la fase aguda del ictus isquémico es una alternativa válida en los casos en que la trombólisis intravenosa está contraindicada o cuando no ha sido efectiva. Nuestro objetivo es presentar la experiencia inicial del INV en la Comunidad de Madrid.
Métodos: Registro prospectivo de ictus isquémicos tratados con INV en la Comunidad de Madrid (2005-2009). Se recogen variables epidemiológicas, factores de riesgo y gravedad del ictus mediante la NIHSS (National Institute of Health Stroke Scale). Registramos el tipo de técnica, la situación funcional a los 3 meses, mediante la escala de Rankin modificada (eRm), complicaciones hemorrágicas y mortalidad.
Resultados: Se incluyó a 41 pacientes. La media±desviación estándar de edad fue 58,6±19,9 años; el 56,1% varones. Hubo 22 pacientes con ictus de circulación anterior y 19, de circulación posterior. La mediana de la puntuación NIHSS basal fue 17 [intervalo, 2-34]; 7 pacientes recibieron trombólisis intravenosa previa. Las técnicas utilizadas fueron: interrupción mecánica (26 pacientes), trombólisis intraarterial (26 pacientes), angioplastia/*stent* (5 pacientes), extracción mecánica mediante dispositivo MERCI (Mechanical Embolus Removal in Cerebral Ischemia) (3 pacientes). Se consiguió una recanalización parcial o total en 32 pacientes (78%). Un paciente presentó una transformación hemorrágica sintomática (2,4%). Al cabo de 3 meses el 53,6% de los pacientes eran independientes (eRm=2) y la mortalidad general fue del 19,5%.
Conclusiones: El ictus isquémico es una emergencia médica tratable en las primeras horas. El INV es una alternativa terapéutica factible y útil en los casos de contraindicación o ineficacia de la trombólisis intravenosa.

Introduction

Currently, ischemic stroke is considered a time-dependent medical emergency, like acute coronary syndrome or multiple trauma. This is due to therapeutic advances that have completely changed its approach, in that previous nihilistic attitudes have been abandoned. Stroke units have shown, with the highest level of evidence, improvement in morbidity and mortality with favourable cost-effectiveness and the capacity to reduce complications and dependency in patients with acute cerebrovascular disease.[1-3] The treatment of ischemic stroke by intravenous thrombolysis with tissue plasminogen activator (t-PA) in the first 3 hours from the onset of symptoms has been proven safe and effective in routine clinical practice in Spain and Europe, as long as it is employed by previously trained teams and following a strict protocol.[4,5] Recently, intravenous t-PA has proven its efficacy and safety when administered between 3 and 4.5 hours after the onset of symptoms.[6] However, unlike stroke units whose actions benefit virtually all types of strokes, only a minority of ischemic strokes benefit from intravenous thrombolysis (5-15%).[1] This is due to the narrow therapeutic window of 4.5 h and to the multiple exclusion criteria for thrombolysis. We know that its benefit is significantly lower when the occlusion occurs in a large-calibre artery, such as the internal carotid artery (ICA), the origin of the middle cerebral artery (MCA) or the basilar artery (BA) trunk.[7]

These have been some of the reasons why endovascular treatment of the acute phase of ischemic stroke is becoming increasingly important as an adjunct to intravenous thrombolysis in cases where it is contraindicated or has been ineffective. The PROACT II study demonstrated the efficacy of intra-arterial thrombolytic therapy with

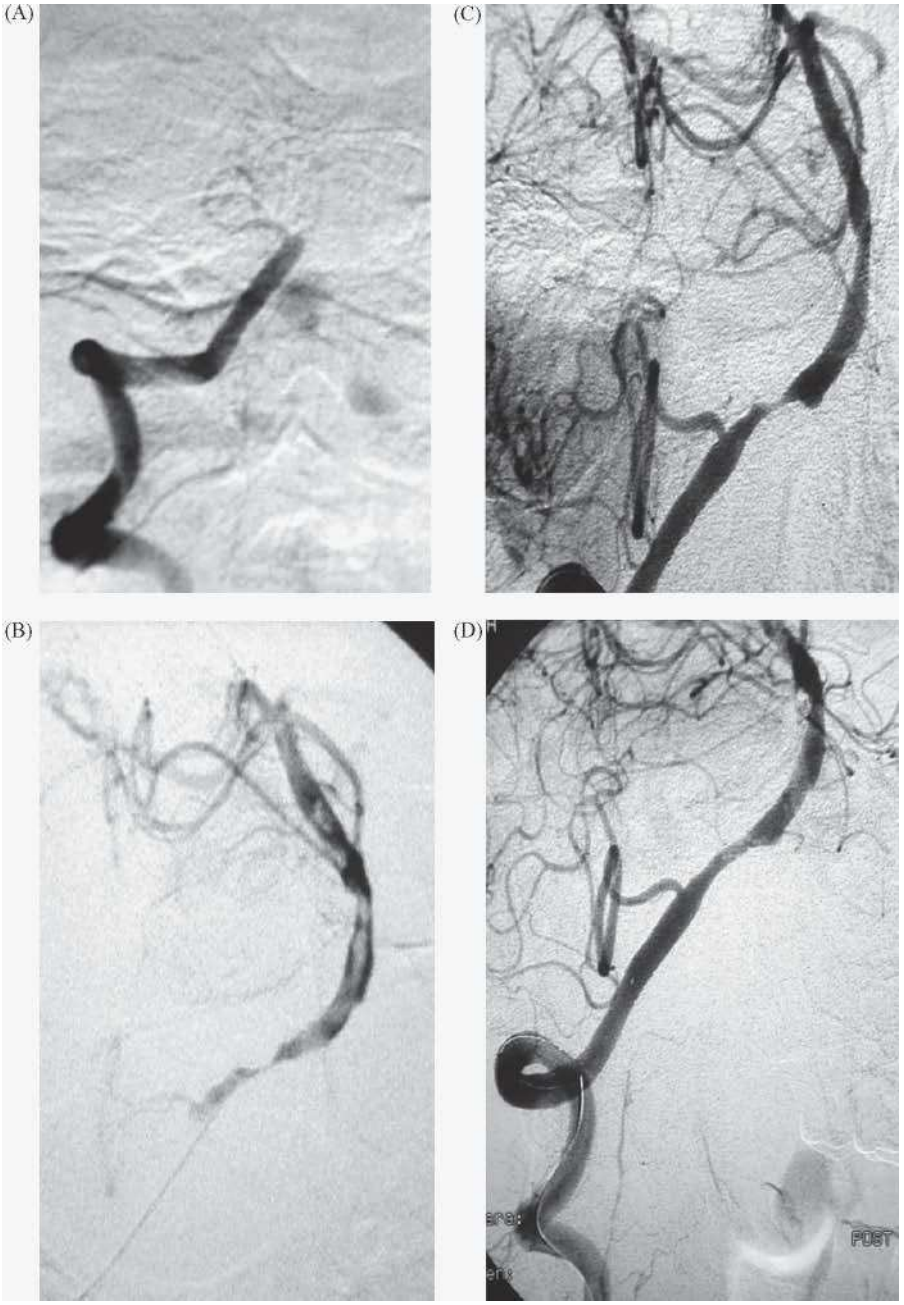

Figure 1 A: Selective digital arteriography of the right vertebral artery (VA) showing complete basilar artery (BA) occlusion in its proximal segment. B: after mechanical thrombus disruption with a microcatheter and local administration of t-PA (5 mg), partial recanalization was achieved in the BA; multiple filling defects are observed, consistent with thrombi. C: complete recanalization is achieved after the administration of a further 5 mg of t-PA; a critical stenosis can be observed in the vertebrobasilar junction. D: final image after angioplasty and intracranial stent placement which shows residual stenosis.

prourokinase in MCA occlusion in a therapeutic window of 6 hours, and obtained an absolute benefit of 15%.[8] Neurovascular intervention (NVI) (fig. 1) has shown its efficacy and safety in large series of patients. In some studies, it even obtained higher rates of arterial recanalization than intravenous treatment.[9] Such intervention includes techniques such as intra-arterial thrombolysis, angioplasty with stenting and mechanical disruption and extraction of the clot.[8,10-12] There is also the possibility of applying it sequentially after intravenous thrombolysis in cases where it has not been effective.[13]

Intravenous thrombolytic therapy is currently a standard practice in Spanish stroke units.[4,14] However, this is not the case with endovascular treatment. These programs require greater organisational and technical complexity and there are very few centres that can offer it. It is necessary to have a multidisciplinary team formed by neurointervention professionals with experience in therapeutic endovascular

techniques and neurologists with experience in cerebrovascular disease. Our goal is to present the initial experience of NVI in the acute phase of ischemic stroke in the Community of Madrid.

Material and method

This is a prospective registry of cerebral stroke cases treated with NVI in the acute phase at five teaching hospitals in Madrid with stroke units during the period 2005-2009. The indication for treatment was carried out during working hours in every case, but the procedure was extended to call hours in the majority, despite the absence of a NVI shift. This register lists the baseline patient characteristics, vascular risk factors, time from symptom onset at the start of the procedure, aetiology and severity of stroke measured by the National Institutes of Health Stroke Scale (NIHSS).[15] The treatment indication, technique used during the procedure and NIHSS score at 24 h and at 7 days were also collected. The effectiveness of the procedure was assessed at 3 months using the modified Rankin scale (mRS),[16] as was the rate of recanalization achieved. Procedure safety was assessed by mortality at 3 months and the percentage of symptomatic cerebral haemorrhagic transformations, according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria.[5]

Diagnostic and therapeutic protocol

The therapeutic window was 8 h for anterior circulation stroke and 24 h in cases of posterior circulation stroke. The indications and contraindications of the procedure are given in table 1.

On arrival at the emergency service, the patient is evaluated by the neurologist on call through the medical history, examination, neuroimaging tests (computerized tomography [CT] or magnetic resonance), electrocardiogram, x-ray, blood count, comprehensive biochemical analysis and haemostasis. If all criteria for endovascular treatment are met, the patient is moved to the neuroradiology room, where haemodynamic and respiratory constants are monitored. The patient is kept awake or under light sedation for better evaluation during the procedure. If necessary, the patient is sedated and intubated. Diagnostic arteriography is performed by femoral artery catheterisation and selective contrast injection in both carotid and vertebral arteries to verify the location and type of arterial occlusion. Anticoagulation is initiated with 5,000 units of sodium heparin before starting the therapeutic procedure while haemodynamic and neurological monitoring are continued.

In cases where the indication for the procedure was a lack of efficacy of intravenous thrombolysis, the patient had previously received t-PA at doses of 0.9 mg/kg within the first 4.5 hours after symptom onset, as indicated by the standard protocol.[5] After completion of drug infusion, the patient was reassessed and, if there was no neurological improvement, a diagnostic digital arteriogram or CT angiography was performed. If the arterial occlusion persisted, the endovascular procedure was carried out as mentioned above.

The decision on the type of endovascular technique is based on the embolic or thrombotic nature of the occlusion, its location (artery and segment) and the thrombotic load. In each case the procedure is as follows:

- Intra-arterial thrombolysis: t-PA is prepared and 1 mg distal boluses are infused, in the interior and proximal to the thrombus. Angiographic control is performed after each infusion. The procedure is repeated until arterial recanalization is achieved or until a maximum dose of 22 mg is reached. In some cases, abciximab and urokinase are used.
- Mechanical disruption of the thrombus: the occluded artery is catheterised and a microcatheter is passed repeatedly through the thrombus to fragment it.
- Mechanical thrombus removal: the thrombus is removed using the MERCI device (Mechanical Embolus Removal in Cerebral Ischemia).
- Angioplasty and stent placement: in cases with atherothrombotic occlusion and major arterial stenosis, angioplasty is performed with use of balloon and subsequent implantation of stents in the stenotic arterial segment.

The procedure finished once arterial recanalization was achieved or, if this was not possible, when the therapeutic window ended or the maximum dose of t-PA was administered. Other reasons for stopping the procedure were neurological deterioration not clearly associated with the arteriography-observed arterial occlusion, haemodynamic or respiratory complications or the presence of contrast extravasation.

Once the procedure was completed, the patient was moved to the stroke unit or intensive care unit (if ventilation support is required), where he was monitored for 24-48 h. Anticoagulation with intravenous heparin was maintained

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Ischemic stroke patients with a evolution time longer than 4.5 h at the time of neurological assessment
Absolute contraindication for intravenous thrombolysis: anticoagulation with INR >1.7; NIHSS >25 or major surgery in the last 3 months
Basilar artery occlusion
Lack of efficacy of intravenous thrombolysis with t-PA performed within 4.5 hours after symptom onset
Exclusion criteria
Stroke in the previous 3 months
History of central nervous system haemorrhage
Advanced severe or terminal illness or at risk of haemorrhage
Platelet count <100,000/μl
Arterial hypertension >185/110 mmHg at the start of the procedure
Neurovascular intervention team not available

Table 2 Baseline patient characteristics following neurointerventional treatment

	All	Anterior circulation	Posterior circulation	p
Patients	41	22	19	
Age (years)	58.6±19.9	58.3±18.2	59±16	NS
Males	23 (56.1)	13 (59.1)	10 (52.6)	NS
HT	20 (48.7)	10 (45.5)	10 (52.6)	NS
Diabetes	3 (7.31)	3 (13.6)	0	NS
Dyslipidemia	14 (34.1)	8 (36.3)	6 (31.6)	NS
Smoking	9 (21.9)	2 (9.1)	7 (38.8)	NS
Prior stroke or TIA	10 (24.3)	5 (22.7)	5 (26.3)	NS
Auricular fibrillation	11 (26.8)	8 (36.3)	3 (15.8)	NS
Prior antiaggregation	9 (21.9)	4 (18.2)	5 (22.7)	NS
Prior anticoagulation	8 (19.5)	5 (22.7)	3 (15.8)	NS
Prior t-PA	7 (17.1)	3 (13.6)	4 (21.1)	NS
Baseline NIHSS	17 [8-32]	15 [8-27]	19 [2-34]	NS
Baseline systolic pressure (mmHg)	152±31	146±28	154±32	NS
Baseline glycaemia (mg/dl)	133±55	122±59	140±36	NS
Time to procedure (min)	393±345	271±70	452±395	0.001

HT: hypertension; NS: not statistically significant; TIA: transient ischemic attack.
The data express n (%), mean±standard deviation or median [range].

for 4 h. A cranial CT was performed 24 h after the procedure or sooner if there was neurological worsening.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 15.0. For the analysis of quantitative variables, we used the mean and standard deviation; for qualitative variables, we used absolute and relative frequencies.

Results

Baseline characteristics

The study included 41 patients during the study period; 22 patients (53.6%) presented anterior circulation stroke and 19 patients (46.4%), posterior circulation stroke. The baseline patient characteristics are summarised in table 2. The mean±SD age was 58.6±19.9 [range, 29-82] years and 56.1% were male. Most strokes had a degree between moderate and severe (NIHSS, median 17 [range, 2-34]). Cardio-embolic strokes were the most frequent (33%), followed by strokes of unusual aetiology (32%), those of unknown origin (25%) and atherothrombotic strokes (20%). Intravenous t-PA had been given previously to 7 patients (17.1%). In all patients, diagnostic angiography showed arterial occlusion.

Indications for NVI were: absolute contraindication for intravenous thrombolysis in 15 cases (36.6%), therapeutic window over 4.5 h in 13 cases (31.7%), lack of efficacy of intravenous thrombolysis in 7 cases (17.1%) and BA occlusion in 6 cases (14.6%).

The technical procedures used were: mechanical thrombus disruption in 34 patients (82.9%), intra-arterial thrombolysis in 27 (65.8%), angioplasty and stent placement in 8 cases (19.5%) and mechanical thrombus extraction with a MERCI device in 3 cases (7.3%). In 27 patients (65.6%),

Table 3 Independence and mortality at 3 months

	All	Arterial recanalization	No arterial recanalization	p
Patients	41 (100)	32 (78)	9 (22)	
Modified Rankin scale ≤2	22 (53.6)	20 (62.5)	2 (22)	0.03
Mortality	8 (19.5)	4 (12.5)	4 (44.4)	0.03
Anterior territory	22 (100)	17 (77.2)	5 (22.8)	
Modified Rankin scale ≤2	13 (59.1)	12 (70.6)	1 (20)	0.04
Mortality	1 (4.5)	0	1 (20)	NS
Posterior territory	19 (100)	15 (78.9)	4 (21.1)	
Modified Rankin scale ≤2	9 (47.3)	8 (53.4)	1 (25)	NS
Mortality	7 (36.9)	4 (26.6)	3 (75)	NS

The data express n (%).

several procedures were combined. Total or partial recanalization was achieved in 78% of cases (table 3).

At 3 months, 22 patients (53.6%) were independent (mRS=2), 62.5% when arterial recanalization was achieved compared to 22% when it was not achieved (p=0.03). There were 5 cases (12.2%) of cerebral haemorrhagic transformation but only 1 (2.4%) was symptomatic. Overall mortality was 19.5%, rising to 44.4% in cases without recanalization and compared to 12.5% in recanalized cases (p=0.03).

Anterior circulation strokes

Twenty-two patients were treated within the first 8 hours from symptom onset; 17 patients presented occlusion of the MCA, 4 of the ICA and 1 of the anterior cerebral artery (ACA). The mean±standard deviation of time to the start of the procedure was 271±70 min. The NIHSS score changed from a median of 15 [range, 8-27] at the onset of stroke to 10 [0-27] at 7 days. At 3 months, 13 patients (59.1%) were independent (mRS=2) and 1 patient died (4.5%). The rate of cerebral haemorrhagic transformation was 13.6%, but only 1 case (4.7%) was symptomatic. Arterial recanalization was achieved in 17 cases (77.2%), and was complete in 15 (68.2%). Arterial recanalization was associated with a higher rate of independence at 3 months (70.6 versus 20%; p=0.04).

Posterior circulation strokes

Nineteen patients were treated in the first 24 hours after symptom onset; 16 presented occlusion of the BA, 2 of the posterior cerebral artery (PCA) and one of the vertebral artery (VA). The average time to the start of the procedure was 452±395 min. The median NIHSS score changed from 19 [range, 2-34] at the onset of stroke to 10 [0-32] at 7 days. At 3 months, 9 patients (47.3%) were independent (mRS=2) and 7 patients died (36.9%). The rate of cerebral haemorrhagic transformation was 10.5% and none was symptomatic. Arterial recanalization was achieved in 15 cases (78.9%). Arterial recanalization was associated with a higher rate of independence at 3 months (53.4 versus 25%) and a lower mortality (white blood cell count 26.6% versus 75%), although the differences were not significant.

Discussion

In Spain, intravenous thrombolysis with t-PA is standard practice in stroke units; however, there is little experience with NVI.[17-19] In this article, we present the initial experience in the acute phase of cerebral stroke in the Community of Madrid. The teams involved at the different hospitals, both of neurologists and neuroradiologists, had no previous experience in such procedures. However, they did have extensive experience in the treatment of ischemic stroke, in the case of neurologists, and of endovascular treatments such as embolisation of aneurysms or carotid angioplasties, in the case of neuroradiologists.

The baseline characteristics of patients included in our records have some differences with respect to those patients treated habitually at stroke units. Particularly striking is the lower average age of these patients (59 years), lower prevalence of classical cerebrovascular risk factors such as arterial hypertension and diabetes, and higher rate of BA thrombosis and stroke of unusual cause. We believe that these differences could be explained by a bias in the indication of endovascular treatment that has probably led to the inclusion of more severely ill and younger patients, in whom risk factors are less prevalent.

In 68.3% of cases, NVI was indicated by the inability to administer intravenous t-PA, either for having exceeded the therapeutic window or by exclusion criteria. In 17% of cases, the indication was due to acute BA thrombosis and to lack of efficacy of intravenous thrombolysis in another 17%. This type of indication took place primarily in the last year of the register in light of the published safety and efficacy data.[13]

Neurovascular intervention combines different techniques having endovascular arterial recanalization as their main objective.[17] In our registry, the type and combination of techniques used were tailored to each case on the basis of arteriography findings and evolution of the procedure, to achieve recanalization with the least possible patient risk. In 65.6% of our patients, the combination of at least two of these procedures was required, leading to a very high recanalization rate (85%). The most commonly used thrombolytic agent was t-PA, although we also used urokinase and abciximab. The low rate of mechanical extractions performed was due to the relative novelty of the MERCI device and to the fact that it was not available in all centres.

In terms of safety and efficacy, our results are similar to those of other published series.[17,20] The rate of cerebral haemorrhagic transformations was very low, especially the symptomatic (one single case). This once again proves that the introduction of novel therapies in the field of cerebrovascular diseases can be carried out in a safe and effective manner, provided that they are implemented by teams of experts on the disease using strict protocols and with data being collected and evaluated prospectively.[4,21]

Posterior circulation strokes represented 46.4% of the series and, in particular, BA thrombosis accounted for 39%. Strokes in this territory have differential characteristics, such as their high mortality (over 90% in BA thrombosis) and an increased therapeutic window (up to 12 h in case of sudden onset and 24 h in fluctuating or progressive cases, due to greater ischemia tolerance).[22] In cases of BA thrombosis, arterial recanalization with intravenous thrombolysis is difficult, and endovascular treatment can be an option at the start or after failure of intravenous therapy. Our results in this type of stroke were very satisfactory, with 47.3% of patients being independent at 3 months and a mortality of 36.9%.

Arterial recanalization is a prognostic factor for cerebral stroke. The percentage of recanalizations that we obtained by being able to combine several endovascular techniques was high (78%). This associates recanalization with a significant decrease in mortality and dependency at 3 months. Intravenous thrombolysis achieved recanalization in only 30-50% of cases, depending on the nature of the obstruction (embolic or thrombotic) and arterial location.[7]

However, it can be administered a very short time after the patient arrives at the hospital, unlike NVI, which requires a greater organisational structure and a longer time for its initiation. For this reason, patients with an indication of intravenous thrombolysis should be treated with it, and endovascular techniques should be used in cases in which it had not been effective.

The number of patients treated in the register during that period was very low in comparison to the number of cases treated at strokes units[23] and the number of intravenous thrombolysis they perform.[14,21,24] This is due to the previously-mentioned organisational difficulties and the lack of permanent NVI coverage. However, like other studies, our series makes it clear that there is a need to provide effective recanalization alternatives through endovascular procedures for patients in whom systemic thrombolysis cannot be used. It also supports the claim that it is possible to perform these techniques safely, improving patient prognosis, and states the need to implement its launch in suited centres. The Stroke Health Care Plan[25] proposes equity in obtaining emergency specialist care and has demonstrated that applying this in different regions has improved local attention. The implementation of the Stroke Care Plan in the Community of Madrid[26] in January 2009 guaranteed access to a stroke unit for stroke cases with less than 6 hours evolution, with the possibility of benefiting from intravenous thrombolysis. In addition, the plan studied and provided the basis for efficiently organising continued availability of NVI techniques for candidate patients. This study should serve as a support for extending this plan to offer NVI services 24 h a day, 7 days a week for all patients in whom it is indicated.

Cerebral stroke is a medical emergency which is treatable in the early hours. Neurovascular intervention is a feasible and useful therapeutic alternative in strokes in which intravenous thrombolysis is contraindicated or has not been effective.

Financing

This work has not received funding from any private or public entity.

Conflict of interests

The authors declare no conflict of interests.

References

1. Masjuan J. Unidades de Ictus: el mejor tratamiento para los pacientes con ictus. Neurología. 2009;24:285-7.
2. Fuentes B, Díez-Tejedor E. Stroke Units. Many questions, some answers. Int J Stroke. 2009;4:28-37.
3. Fuentes B, Díez-Tejedor E. Unidades de Ictus: una necesidad asistencial coste-efectiva. Neurología. 2007;22:456-66.
4. Rodríguez-Yáñez M, Álvarez-Sabín J, Díez-Tejedor E, Castillo J, por el Comité SITS-MOST España. Tratamiento trombolítico en el ictus isquémico agudo en España: experiencia del registro SITS (Safe Implementation of Thrombolysis in Stroke). Neurología. 2009;24:288-91.
5. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke WH, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275-82.
6. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-29.
7. Saqqur M, Uchino K, Demchuk AM, Molina C, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007;38:948-54.
8. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. JAMA. 1999;282:2003-11.
9. Lisboa RC, Jovanovic BD, Alberts MJ. Analysis of the safety and efficacy of intra-arterial thrombolytic therapy in ischemic stroke. Stroke. 2002;33:2866-71.
10. Stead LG, Gilmore RM, Bellolio F, Rabinstein A, Decker WW. Percutaneous Clot removal devices in acute ischemic stroke. A systematic review and meta-analysis. Arch Neurol. 2008;65:1024-30.
11. Gobin YP, Starkman S, Duckwiler GR, Grobelny T, Kidwell CS, Jahan R, et-al. MERCI 1. A phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke. 2004;35: 2848-54.
12. Nakano S, Iseda T, Yoneyama T, Kawano H, Wakisaka S. Direct percutaneous transluminal angioplasty for acute middle cerebral artery trunk occlusion. An alternative option to intra-arterial thrombolysis. Stroke. 2002;33:2872-6.
13. The IMS Study investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke study. Stroke. 2004;35:904-12.
14. Zarza B, Alonso de Leciñana M, García-Barragán N, López-Sendón J, Cruz-Culebras A, Masjuan J. Influencia de la curva de aprendizaje y del código ictus extrahospitalario en el tratamiento trombolítico del ictus agudo. Neurología. 2008;23:349-55.
15. Lyden P, Brott T, Tilley B, Welch KMA, Mascha EJ, Levine S, et al. Improved reliability of the NIH stroke scale using video training. Stroke. 1994;25:2220-6.
16. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke. 1988;19:1497-500.
17. Martínez Fernández E, González-García A, Gil-Peralta A, González-Marcos JR, Mayo A. Resultados del intervencionismo en el ictus agudo. Neurología. 2008;23:21-8.
18. Méndez JC, Masjuan J, García N, Leciñana M. Successful intra-arterial thrombolysis for acute ischemic stroke in the immediate postpartum period: case report. Cardiovasc Intervent Radiol. 2008;31:193-5.
19. Ribo M, Molina CA, Álvarez B, Rubiera M, Álvarez-Sabin J, Matas M. Intra-arterial administration of microbubbles and continuous 2-MHz ultrasound insonation to enhance intra-arterial thrombolysis. J Neuroimaging. 2010;20:224-7.
20. Mandava P, Kent TA. Intra-arterial therapies for acute ischemic stroke. Neurology. 2007;68:2132-9.
21. Masjuan J, Alonso de Leciñana M, García-Barragán N, Zarza B, Díaz-Sánchez M, Martínez-Castrillo JC, et al. Tratamiento trombolítico del ictus isquémico agudo en un centro sin experiencia previa. Desarrollo de la organización interna y primeros resultados. Rev Clin Esp. 2006;206:485-90.
22. Davis SM, Donnan GA. Basilar artery thrombosis: Recanalization is the key. Stroke. 2006;37:2440.

23. Fuentes B, Díez-Tejedor E, Ortega-Casarrubios MA, Martínez P, Lara M, Frank A. Consistency of the benefits of stroke units over years of operation: an 8-year effectiveness analysis. Cerebrovasc Dis. 2006;21:173-9.
24. Simal P, García A, Masjuan J, Alonso de Leciñana M, Fuentes B, Díaz F, et al. Trombólisis en Madrid: ¿cada vez más y mejor? Análisis de series temporales durante 4 años. Neurología. 2009;24:804-7.
25. Álvarez-Sabín J, Alonso de Leciñana M, Gállego J, Gil-Peralta A, Casado I, Castillo J, et al. Plan de atención sanitaria al ictus. Neurología. 2006;21:717-26.
26. Grupo de trabajo Asociación Madrileña de Neurología y Servicio Madrileño de Salud. Atención a los pacientes con ictus en la Comunidad de Madrid. Consejería de Sanidad; 2009. Available at: http://www.madrid.org/cs/Satellite?c=CM_Publicaciones_FA&cid=1142553237007&idConsejeria=1109266187266&idListConsj=1109265444710&language=es&pagename=ComunidadMadrid%2FEstructura&pid=1109265444699&sm=1109265844004.