Guidelines for acute ischemic stroke treatment – Part II: Stroke treatment

Diretrizes para o tratamento do acidente vascular cerebral isquêmico – Parte II: tratamento do acidente vascular

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ABSTRACT

The second part of these Guidelines covers the topics of antiplatelet, anticoagulant, and statin therapy in acute ischemic stroke, reperfusion therapy, and classification of Stroke Centers. Information on the classes and levels of evidence used in this guideline is provided in Part I. A translated version of the Guidelines is available from the Brazilian Stroke Society website (www.sbdcv.com.br).

Key words: stroke, thrombolysis, stroke centers.

RESUMO

A segunda parte das Diretrizes aborda os tópicos de antiagregantes plaquetários, anticoagulantes e terapia de reperfusão para acidente vascular cerebral (AVC) isquêmico. Os critérios para nível de evidência e graus de recomendação estão contidos na primeira parte do documento. Uma versão traduzida destas Diretrizes encontra-se publicada no portal da Sociedade Brasileira de Doenças Cerebrovasculares (www.sbdcv.org.br).

Palavras-Chave: acidente vascular cerebral, trombólise, centros de AVC.

ANTICOAGULANTS, ANTIPLATELET AGENTS, AND STATINS IN ACUTE ISCHEMIC STROKE

Anticoagulation in acute ischemic stroke

In 2004, the Cochrane Collaboration published a systematic review of 22 trials involving 23,547 patients[1,2] who were started on standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, or thrombin inhibitors 2 weeks after the occurrence of a stroke. Although anticoagulant therapy was associated with approximately 9 fewer recurrent ischemic strokes per 1000 patients treated (OR=0.76; 95%CI 0.65–0.88), this benefit was nullified by the occurrence of approximately 9 more symptomatic intracranial hemorrhages per 1000 patients treated (OR=2.52; 95%CI 1.92–3.30).

Early administration (within 48 hours of symptom onset) of heparin in patients with cardioembolic stroke was

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evaluated in a recent meta-analysis[3] which failed to show any significant reduction in recurrence of ischemic stroke or any change in mortality and disability rates. A study of heparin administration in the hyperacute phase (within 3 hours of symptom onset) of acute nonlacunar hemispheric infarction showed that more patients on anticoagulation therapy reached the endpoint of functional independence (38.9 *versus* 28.6%; p=0.025), but had a higher rate of symptomatic cerebral hemorrhage (6.2 *versus* 1.4%; p=0.008), with no increase in mortality[4]. Early discontinuation of the RAPID (Rapid Anticoagulation Prevents Ischemic Damage) trial, after the enrollment of only 67 patients, precluded comparison of unfractionated heparin *versus* aspirin in the prevention of early recurrence[5]. A comparative analysis of the efficacy of low-molecular-weight heparin *versus* aspirin, conducted with Asian patients with intracranial stenosis and acute stroke, did not find heparin to be superior[6].

Recommendations

1) Routine anticoagulation with unfractionated or low-molecular-weight heparin is not recommended in acute ischemic stroke (Level of Evidence 1, Class A Recommendation).
2) Particularly, anticoagulation in the acute phase of ischemic stroke is not recommended for patients with moderate to extensive cerebral infarction due to increased risk of severe intracranial hemorrhagic complications (Level of Evidence 1, Class A Recommendation).

Antiplatelet agents in acute ischemic stroke

Two clinical trials showed a significant benefit of aspirin as to the reduction of morbidity and mortality rates when initiated within 48 hours of symptom onset at daily doses of 160 mg and 300 mg respectively. The primary effect of aspirin appears to be prevention of early stroke recurrence[7,8]. Definitive long-term antithrombotic treatment should be initiated 2 weeks after the episode of stroke[9].

Use of ticlopidine, clopidogrel, dipyridamole, or other antiplatelet agents during ischemic stroke, whether alone or in combination, has yet to be assessed properly[10,11]. The FASTER study evaluated administration of clopidogrel and aspirin to patients with transient ischemic attack or minor stroke within 24 hours of symptom onset as one arm of a factorial design. However, as this trial was interrupted early due to failure to recruit patients at the prespecified minimum enrolment rate, no conclusions could be drawn as to the potential benefit of this combination[12]. In patients who were allergic, non-responsive, or intolerant to aspirin, other antiplatelet agents may be therapeutic alternatives.

Although phase II studies suggest an adequate safety profile, a phase III trial of platelet glycoprotein IIb/IIIa inhibitor (abciximab) in acute stroke was halted due to high rates of bleeding[13].

Recommendations

1) Initiation of oral aspirin at a daily dose of 160 to 300 mg within 48 hours after of the occurrence of ischemic stroke is recommended (Level of Evidence 1, Class A Recommendation).
2) To date, there is no evidence to support routine administration of any other antiplatelet agents alone or in combination with other substances (Level of Evidence 2, Class B Recommendation).
3) Administration of platelet glycoprotein IIb/IIIa inhibitors (abciximab) is not recommended in the acute phase of ischemic stroke (Level of Evidence 1, Class A Recommendation).

Statins in acute ischemic stroke

Administration of atorvastatin to acute ischemic stroke patients 1 to 6 months after the event has been shown to reduce recurrence, which suggests that early use of statins reduces vascular risk[14]. Simvastatin was shown to reduce vascular events in patients with history of stroke and to reduce the risk of stroke in patients with other vascular diseases[15]. Withdrawal of statin therapy in the acute phase of stroke may be associated with an increased risk of death or dependency[16].

Recommendations

1) Patients who are already on statins at the time of stroke onset should continue taking them (Level of Evidence 1, Class B Recommendation).
2) Administration of statins after 48 hours of the occurrence of stroke is safe (Level of Evidence 1, Class B Recommendation).

INTRAVENOUS THROMBOLYSIS PROTOCOL

When administered in 4 hours and 30 minutes after the stroke, intravenous recombinant tissue plasminogen activator (rt-PA) has been shown to decrease functional disability as compared to placebo, and has thus become one of the leading specific treatments recommended for acute management of ischemic stroke (Level of Evidence 1A)[17-20]. Diabetic patients with history of prior stroke were excluded from the ECASS III trial, but phase IV studies and meta-analysis suggest benefit in this population as well (Level of Evidence 1B). Streptokinase was assessed in a variety of studies, but its use is no longer recommended due to high rates mortality associated with hemorrhage (Level of Evidence 1A)[21-23].

For greater safety, rt-PA administration should comply with the following criteria[10,11,17,20]:

Inclusion criteria

a) Ischemic stroke in any cerebrovascular territory;

b) Possibility of initiating rt-PA infusion in 4 hours and 30 minutes after symptom onset (which requires precise determination of the symptom onset timing. If symptoms are noted on waking, the last time at which the patient was observed to be normal should be used instead);
c) No evidence on intracranial hemorrhage on head computed tomography (CT) scan or magnetic resonance imaging (MRI);
d) Age >18 years.

Exclusion criteria

a) Use of oral anticoagulants and prothrombin time (PT) >15 s (INR>1.7);
b) Use of heparin in the last 48 hours and prolonged aPTT;
c) History of ischemic stroke or severe head trauma in the last 3 months;
d) History of intracranial hemorrhage or cerebrovascular malformation;
e) Hypodensity of more than one-third of the middle cerebral artery territory on head CT;
f) Systolic blood pressure (SBP) ≥185 mmHg or diastolic blood pressure (DBP) ≥110 mmHg (on 3 separate measurements obtained after with 10 minutes of interval) refractory to antihypertensive agents;
g) Rapid and complete resolution of signs and symptoms before thrombolytic agent administration;
h) Mild neurological deficit (with no significant functional deterioration);
i) History of major surgery or invasive procedure in the last 2 weeks;
j) History of genitourinary or gastrointestinal bleeding in the last 3 weeks, or history of esophageal varices;
k) Arterial puncture at a noncompressible site within the last 7 days;
l) Coagulopathy (prolonged PT [INR >1.7], prolonged aPTT, or platelet count <100,000/mm^3);
m) Blood glucose <50 mg/dL with resolution of symptoms after hypoglycemia was treated;
n) Evidence of endocarditis, septic embolus, or pregnancy;
o) Recent myocardial infarction (occurred in the last 3 months);
p) Clinical suspicion of subarachnoid hemorrhage or acute aortic dissection.

Some centers use multimodal neuroimaging (MRI with diffusion and perfusion imaging or perfusion CT scan) to select candidates for thrombolytic therapy, particularly in patients outside the therapeutic range or when the exact time of symptom onset cannot be determined.

In patients with no recent history of oral anticoagulant or heparin use, rt-PA infusion may be initiated before the results of a coagulation panel are available, but should be discontinued if these results reveal an INR>1.7, a prolonged aPTT as defined by local reference ranges, or a platelet count <100,000/mm^3.

The following factors are not considered absolute exclusion criteria if the treating neurologist is convinced they are unrelated to the patient's acute neurological deficits: blood glucose level >400 mg/dL, epileptic seizure at the onset of neurological deficit, and diagnosis of cerebral aneurysm (Level of Evidence 4C).

Certain factors alter the risk/benefit ratio of thrombolytic therapy, but does not constitute a contraindication to its use[17,24]:

- NIHSS >22
- Age >80 years
- Hyperglycemia

Informed consent form

The risk/benefit ratio of treatment must be discussed with the patient's relatives or legal caregivers, and consent should be reported in writing in the patient record.

Management of arterial hypertension

Use of rt-PA in the treatment of acute ischemic stroke entails a need for strict blood pressure control, as the risk of cerebral hemorrhage correlates with BP levels[24]. Special attention should be given to the risk of iatrogenic hypotension during treatment. In candidates for thrombolytic therapy, adherence to the NINDS rt-PA Stroke Study Group[17,24] is recommended, which accepts the following blood pressure levels in up to 24 hours after the stroke: DBP ≤105 mmHg and SBP ≤180 mmHg (Tables 1 and 2).

Table 1. Management of hypertension prior to rt-PA infusion.

Withhold rt-PA infusion until blood pressure has been controlled
DBP≥110 mmHg or SBP≥185 mmHg:
Metoprolol or Esmolol
Metoprolol: (1 vial=5 mL, 1 mg/mL). IV push: 5 mg every 10 min at a rate of 1 mg/min to a maximum dose of 20 mg.
Esmolol: (1 vial=10 mL, 10 mg/mL). IV push: 500 µg/Kg/min over 1 min. Follow with 50 µg/Kg/min over 4 min. If BP still inadequate: additional 500 µg/Kg/min bolus over 1 min; increase maintenance dose to 100 µg/Kg/min. If BP still inadequate over next 4 min: additional 500 µg/Kg/min bolus over 1 min; increase maintenance dose to 150 µg/Kg/min. If BP still inadequate over next 4 min: additional 500 µg/Kg/min bolus over 1 min; increase maintenance dose to 200 µg/Kg/min (maximum dose). Once desired BP has been achieved, switch to continuous infusion.
Sodium Nitroprusside*
Sodium nitroprusside: (1 vial=50 mg) diluted in 5% dextrose. IV infusion: 0.5–8 µg/Kg/min. Adjust rate every 10 min as necessary.

*To be given in case of asthma, heart failure, severe abnormalities in heart function that would contraindicate administration of beta-blockers, or uncontrolled hypertension.
BD: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 2. Management of hypertension during and after rt-PA infusion.

Monitor blood pressure in the first 24 hours after institution of treatment.
Measure BP every 15 min in 2 hours of infusion Measure BP every 30 min over 6 hours Measure BP every 60 minutes thereafter until hour 24
In patients who require intravenous antihypertensive agents, BP should be measured every 15 min in the first 24 hours.
DBP≥105 mmHg or SBP≥180 mmHg
Metoprolol or Esmolol – see Table 2.
Sodium nitroprusside: (1 vial = 50 mg) diluted in 5% dextrose. IV infusion: 0.5–8 µg/Kg/min. Adjust rate every 10 min as necessary.

*To be given in case of asthma, heart failure, severe abnormalities in heart function that would contraindicate administration of beta-blockers, or uncontrolled hypertension.
BD: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure.

GENERAL CARE

1) Rigorous control is required, with assessment of neurological status every 15 minutes during thrombolytic infusion and every 30 minutes during the first 6 hours after the stroke. In the first 24 hours thereafter, neurological status is recommended to be assessed every hour. Increase in 4 points of more in NIHSS score is related to potential intracranial hemorrhage and an indication for control CT scan. Other signs include severe headache, decreased level of consciousness, a sudden increase in blood pressure, nausea, and vomiting.
2) Blood pressure should be strictly monitored as recommended in Table 2.
3) Antithrombotic agents (antiplatelets, heparin, or oral anticoagulants) should not be administered in the first 24 hours after the administration of a thrombolytic.
4) Central venous catheter placement and arterial puncture should not be performed in the first 24 hours after rt-PA infusion.
5) Urinary catheterization should be performed no sooner than 30 minutes after completion of rt-PA infusion.
6) Nasoenteric tube placement should not be performed within 24 hours of rt-PA infusion.
7) Neuroimaging (cranial CT scan or MRI) is recommended in the first 24 hours of thrombolytic therapy.

Protocol for rt-PA infusion

Two peripheral intravenous catheters should be placed. The rt-PA is to be administered at 0.9 mg/kg to a maximum of 90 mg. Ten percent of the dose should be given as an IV bolus in one minute, and the rest, over the course of 60 minutes by infusion pump. The patient must be monitored for at least 24 hours as to changes in neurologic condition, vital signs, and evidence of bleeding complications[17,24]. Monitoring may be carried out in a special bed for hyperacute stroke management in the Emergency department or, preferably, in a Stroke-specialized Unit. Management should preferably be led by a neurologist with exp erience in the treatment of acute stroke. When a neurologist is not available on site, management may be led by another trained health care provider under the guidance of a neurologist via telemedicine[25].

Hemorrhagic complications

The hemorrhagic complications of thrombolysis occur most commonly in 24 hours after starting therapy. Contraindications include deterioration of neurological status, nausea, vomiting, headache, decreased level of consciousness, and abrupt elevation of blood pressure. Should these symptoms arise, the recommended management is as follows:

a. discontinue infusion at the first sign of neurological deterioration or evidence of significant bleeding;
b. ensure that fluid resuscitation is given, with infusion of crystalloid via two peripheral intravenous lines;
c. perform cranial CT scan to confirm bleeding;
d. request the following laboratory tests: hematocrit, prothrombin time, aPTT, platelet count, fibrinogen;
e. give six to eight units of cryoprecipitate if available or two to three units of fresh frozen plasma otherwise. If clinical status continues to deteriorate after four to six hours, give blood products as required according to coagulation panel results. Repeat cryoprecipitate if fibrinogen is low; give fresh plasma if PT or aPTT are abnormal. Infuse six to eight units of platelets if the count is low;
f. give packed red blood cells as required to keep hematocrit within normal range;
g. use fluid resuscitation and/or vasoactive agents to treat hypotension. Avoid hypotonic fluids;
h. in case of bleeding of the central nervous system, consider neurosurgery and hematology consult;
i. consider restarting thrombolytic infusion if CT shows no evidence if intracranial hemorrhage.

Orolingual angioedema

According to the CASES study, this complication may arise in approximately 5% of patients given intravenous thrombolytics (particularly those with insular and frontal cortical infarctions) while on angiotensin-converting enzyme (ACE) inhibitors. The clinical course is usually favorable[26].

Clinicians should be aware of the potential for orolingual angioedema aiming at prompt management, particularly in patients who are prone to this complication (Level of Evidence 4, Class C Recommendation)[26].

Recommendations

1) Intravenous rt-PA therapy is recommended in the forst 4 hours and 30 minutes of after the occurrence of ischemic stroke (Level of Evidence 1, Class A Recommendation).

2) Streptokinase is not recommended for the treatment of stroke (Level of Evidence 1, Class A Recommendation).
3) The inclusion and exclusion criteria for thrombolytic therapy should be followed strictly (Level of Evidence 3, Class C Recommendation).
4) Multimodal neuroimaging may be useful to select candidates for thrombolytic therapy when the exact time of symptom onset cannot be determined or if 4 hours and 30 minutes have passed since the onset of symptoms (Level of Evidence 3, Class C Recommendation).
5) Where no neurologist is available, thrombolytics may be administered under telemedicine guidance (Level of Evidence 3, Class B Recommendation).
6) Thrombolysis should be performed in a monitored bed in the emergency room or, preferably, in a dedicated Stroke Unit (Level of Evidence 4, Class C Recommendation).

PROTOCOL FOR INTRA-ARTERIAL THROMBOLYSIS

The intra-arterial approach to reperfusion therapy in acute stroke is an alternative to intravenous thrombolysis that may provide some advantages, such as increased concentration of the thrombolytic agent at the site of occlusion, a higher recanalization rate, and the potential for use in patients with contraindications to intravenous chemical thrombolysis[27]. On the other hand, clinical benefits may be offset by the greater time required to begin the intra-arterial procedure. Currently, patients selected for intra-arterial therapy are those meeting some exclusion criteria for intravenous thrombolysis. Examples include cases in which 4 hours and 30 minutes and 6 hours have passed since the onset of symptoms, or patients with severe neurologic deficits, recent history of major surgery, or evidence of large extra- or intracranial artery occlusive disease on imaging tests. The CT criteria for exclusion of intravenous thrombolysis and those for exclusion of intra-arterial therapy are identical. However, the amount of data to support the use of intra-arterial therapy in these settings is limited. In the PROACT II phase III trial, patients who received intra-arterial treatment of proximal MCA occlusion with prourokinase 6 hours after symptom onset had a significantly higher recanalization rate and a improved prognosis significantly when compared to controls[28]. In this study, symptomatic bleeding occurred in 10% of treated patients and 2% of controls ($p<0.06$). Prourokinase is not FDA-approved and is not available as reperfusion therapy. Further small randomized clinical trials of prourokinase (PROACT I)[29] and urokinase (MELT)[30] and a meta-analysis of the PROACT I, PROACT II, and MELT trials suggest that intra-arterial thrombolysis can be beneficial in patients with proximal MCA occlusion. Although intra-arterial thrombolysis with rt-PA is not supported by randomized clinical trials, data from observational and nonrandomized comparative studies suggest it can be beneficial[31,32]. A nonrandomized trial compared patients with and without hyperdensity of the MCA territory at baseline CT who were then given intravenous or intra-arterial rt-PA. Intravenous rt-PA therapy was associated with less favorable outcomes in patients with hyperdense MCA sign as compared to patients without it[33]. Although observational studies of urokinase and rt-PA for intra-arterial treatment of basilar artery occlusion have shown encouraging results, there are no randomized clinical trials with adequate statistical power[34-36]. A systematic review found no significant differences between intravenous or intra-arterial thrombolysis for basilar artery occlusion[37].

Recommendations

1) Intra-arterial thrombolytic therapy is a valid option to selecting patients with ischemic stroke due to MCA, carotid, or basilar artery occlusion if given in 6 hours after the stroke (Level of Evidence 2, Class B Recommendation) and, by extrapolation of the results of intravenous thrombolysis studies, rt-PA is used as the thrombolytic agent (Level of Evidence 4, Class C Recommendation).
2) Intra-arterial thrombolytic therapy should only be performed in centers staffed by interventional radiologists experienced in cerebrovascular techniques and with rapid access to a catheterization laboratory (Level of Evidence 2, Class C Recommendation).
3) Intra-arterial thrombolytic therapy may be considered for patients with contraindications to intravenous thrombolysis (Level of Evidence 4, Class C Recommendation).
4) In eligible patients, intravenous thrombolysis should not be deferred in favor of intra-arterial therapy (Level of Evidence 3, Class C Recommendation).
5) Intra-arterial thrombolytic therapy is recommended for the treatment of acute basilar artery occlusion in selected patients (Level of Evidence 4, Class C Recommendation).

PROTOCOL FOR COMBINED (INTRAVENOUS AND INTRA-ARTERIAL) THROMBOLYSIS

The best for combined thrombolysis is a synergy between the advantages of each method, combining the ease of administration and speed of intravenous thrombolytic therapy and the higher recanalization rates and potentially superior outcomes of its intra-arterial counterpart[38,39]. The Interventional Management of Stroke Study (IMS) I compared a group of patients who underwent IV thrombolysis with low-dose rt-PA (0.6 mg/Kg) followed by arteriography and IA thrombolysis in case of persistent occlusion[40]. As there was no control group, patients in the experimental group were compared to patients in the NINDS study. Combined thrombolysis was associated with functional outcomes similar to those of IV thrombolysis and superior to those of placebo. The rate of bleeding was similar to that reported in the NINDS study

(6.6%). These results were confirmed by the IMS II trial[41]. More recently, another group of investigators used a protocol consisting of full-dose IV rt-PA plus IA thrombolysis in case of recanalization failure[41]. Transcranial Doppler has been recommended as a search method for patients in this setting[42,43]. The IMS III trial, comparing IV thrombolysis and combined thrombolysis in 3 hours after the occurrence of stroke, is currently underway.

Recommendations

1) There is insufficient high-level evidence to recommend combined thrombolysis as first-line therapy (Level of Evidence 4, Class C Recommendation).
2) Combined thrombolysis should preferably be performed in a controlled clinical trial setting (Level of Evidence 5).
3) Combined thrombolysis may be considered on a named-patient basis, pending informed consent, when there is persistent arterial occlusion and high risk of permanent sequelae (Level of Evidence 4, Class C Recommendation).

PROTOCOL FOR MECHANICAL THROMBOLYSIS

There are countless endovascular interventions under study as potential treatment options for extracranial and intracranial large vessel occlusion[44-48]. These interventions include emergency angioplasty with stent placement, mechanical clot fragmentation, clot removal with up-to-date devices, suction thrombectomy and stent retriever thrombectomy.

Mechanical procedures are sometimes combined with intravenous or intra-arterial thrombolytic therapy.

A meta-analysis comparing the natural evolution of ischemic stroke (no treatment) with different forms of reperfusion therapy showed that recanalization was the most important independent factor for good outcome, with a strong association with functional independence and lower mortality[49].

Angioplasty and stenting

Data on angioplasty and stent placement in the acute phase of ischemic stroke are limited[50-52]. Angioplasty and stenting have been used to treat acute stroke secondary to carotid artery dissection[53]. In a case series, emergency carotid angioplasty with stent implantation in addition to intra-arterial thrombolysis was performed in patients with stroke due to arterial embolism. This study reported favorable outcomes in the endovascular treatment group as compared with controls[54]. Combined angioplasty and thrombolysis, with or without stent placement, has also been used in patients with basilar artery occlusion[55,56].

Mechanical clot fragmentation

In one study, 16 patients with MCA occlusion and 16 with internal carotid artery occlusion were treated with mechanical thrombectomy with or without local administration of a thrombolytic agent[57]. A Swiss study reported higher recanalization rates with mechanical clot fragmentation in patients who had received intra-arterial thrombolytic therapy[58].

Clot removal

Several devices have been used for mechanical removal of clots from occluded arteries[59,60]. In the MERCI study, arterial recanalization was achieved with the use of a device that physically removed the thrombus from the lumen of the occluded vessel[61]. In 48% of patients managed with the device, recanalization was achieved in up to eight hours after symptom onset. No randomized clinical trials with prognostic data are available for any intra-arterial recanalization device. Although the FDA has approved the MERCI device for recanalization of intracranial arteries, its clinical effectiveness has yet to be established. MERCI is not available in Brazil.

Suction thrombectomy

The Penumbra stroke system uses an aspiration device to extract the thrombus in acute ischemic stroke[62]. All prospective (single arm) and retrospective studies reported rates of recanalization of 83 to 100% in patients treated in the first eight hours of symptom onset[48,62]. Intracranial hemorrhage and vessel perforation or dissection occurred in 0 to 5% of patients[48]. Despite high recanalization rates, only 25 to 30% of patients achieved functional independence[62], probably because of late recanalization in many cases.

The FDA has approved the Penumbra system for recanalization of intracranial arteries in the US, as well as the Brazilian National Health Surveillance Agency (Anvisa) in Brazil.

Stent retriever thrombectomy

Stent retrieval devices are a combination of removable cerebral stents and clot retrievers to be used in the first eight hours of symptom onset[62]. Examples include the Solitaire and Trevo devices. In a recent meta-analysis of 30 observational studies[63] with 262 acute stroke patients treated with the Solitaire device, successful recanalization was achieved in 90% of cases (range, 67–100%). The rates of symptomatic hemorrhagic complications and mortality were 7 and 11%, respectively, and functional independence (mRS 0 to 2) was achieved by 47% of patients. The Solitaire device was approved for treatment of stroke in Brazil in 2012.

Recommendations

1) Although the use of the MERCI device is an acceptable intervention for removal of intra-arterial thrombus in patients carefully selected, its effectiveness in improving prognosis after stroke is still uncertain (Level of Evidence 2, Class B Recommendation). Further clinical

trials of this device are required before its role in the emergency management of stroke can be defined.

Other devices available in Brazil could be useful for thrombectomy in an attempt to achieve reperfusion in acute stroke patients with large vessel occlusion admitted to care within 8 hours of symptoms onset, being ineligible for intravenous thrombolysis or in whom endovenous treatment has failed (Level of Evidence 2, Class B Recommendation).

DESIGNATION OF REFERRAL CENTERS FOR DIAGNOSIS AND TREATMENT OF STROKE

In its National Opinion Statement on Stroke[64], the Brazilian Stroke Society proposed a classification of referral centers for the diagnosis and treatment of acute stroke. This classification was updated in 2009 to include centers with telemedicine capabilities and backup hospitals (Table 3).

Table 3. Recommendations for the classification of hospitals by complexity level with respect to resources available for managing stroke patients.

Backup hospitals are those lacking the resources required for thrombolytic therapy. These facilities will serve as a backup for admission for low-complexity stroke patients, patients who are outside the therapeutic range for thrombolysis, with hemorrhagic stroke and favorable prognosis.

Level C hospitals are those with the minimum infrastructure required for thrombolytic therapy, but no 24-hour on-site neurology service. In these hospitals, thrombolysis may be performed by clinicians or emergency physicians under the guidance of a neurologist from a higher-complexity center via telemedicine.

Level B hospitals are those with the minimum infrastructure required for thrombolytic therapy, plus:

- a dedicated, properly trained, neurologist-led Stroke Team;
- written clinical and care protocols;
- neurologist available 24/7 within 30 minutes of admission (on site or on call);
- nursing staff trained in emergency management and care of stroke patients;
- emergency department with continuous cardiovascular and respiratory monitoring equipment;
- Intensive Care Unit;
- laboratory available 24/7;
- emergency CT scan available 24/7;
- neurosurgery team available 24/7 within 2 hours of notification;
- blood bank.

Level A hospitals are those capable of providing comprehensive care to acute stroke patients. A Level A hospital has all the resources of a Level B facility plus:

- Stroke Unit, including physically delimited facilities;
- multidisciplinary team qualified for care and management of high-complexity stroke patients;
- diffusion and perfusion magnetic resonance imaging;
- transcranial Doppler;
- transesophageal echocardiography;
- magnetic resonance angiography or CT angiography;
- diagnostic catheterization with digital angiography capabilities;
- interventional neuroradiology service available 24/7;
- possibility of early rehabilitation services for stroke patients, including integration with rehabilitation hospitals and secondary hospitals by means of a referral and counter-referral system;
- 24/7 telemedicine support from other hospitals in the network.

References

1. Gubitz G, Sandercock P, Counsell C. Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev 2004CD000024.
2. Sandercock P, Counsell C, Kamal AK. Anticoagulants for acute ischemic stroke. Stroke 2009;40:483-484.
3. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. Stroke 2007;38:423-430.
4. Camerlingo M, Salvi P, Belloni G, Gamba T, Cesana BM, Mamoli A. Intravenous heparin started within the first 3 hours after onset of symptoms as a treatment for acute nonlacunar hemispheric cerebral infarctions. Stroke 2005;36:2415-2420.
5. Chamorro A, Busse O, Obach V, et al. The rapid anticoagulation prevents ischemic damage study in acute stroke--final results from the writing committee. Cerebrovasc Dis 2005;19:402-404.
6. Wong KS, Chen C, Ng PW, et al. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. Lancet Neurol 2007;6:407-413.
7. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349:1641-1649.
8. The International Stroke Trial (IST): a randomised trial of aspirin,

subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349:1569-1581.

9. National Collaborating Centre for Chronic Conditions. Stroke: National clinical guideline for diagnosis and initial management of acute stroke and transient ischemic attack (TIA). London: Royal College of Physicians 2008.
10. Adams Jr. HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38:1655-1711.
11. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507.
12. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol 2007;6:961-969.
13. Adams Jr. HP, Effron MB, Torner J, et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke 2008;39:87-99.
14. Amarenco P, Bogousslavsky J, Callahan A, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-559.
15. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
16. Blanco M, Nombela F, Castellanos M, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology 2007;69:904-910.
17. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
18. Wahlgren N, Ahmed N, Davalos A, 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;369:275-282.
19. The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-774.
20. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.
21. Donnan GA, Davis SM, Chambers B, et al. Streptokinase for acute ischemic stroke with relationship to time of administration: Australian Streptokinase (ASK) Trial Study Group. JAMA 1996;276:961-966.
22. Multicenter Acute Stroke Trial - Europe Study Group (MAST-E). Thrombolytic therapy with Streptokinase in acute ischemic stroke. N Engl J Med 1996;335:145-150.
23. Multicenter Acute Stroke - Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin and combination of both in treatment of acute ischemic stroke. Lancet 1995;346:1509-1514.
24. Hacke W, Kaste M, Olsen TS. Acute treatment of ischemic stroke. Cerebrovasc Dis 2000;(Suppl):S22-S33.
25. Meyer BC, Raman R, Hemmen T, et al. Efficacy of site-independent telemedicine in the STRokE DOC trial: a randomised, blinded, prospective study. Lancet Neurol 2008;7:787–795.
26. Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology 2003;60:1525-1527.
27. Qureshi AI. Endovascular treatment of cerebrovascular diseases and intracranial neoplasms. Lancet 2004;363:804-813.
28. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial. JAMA 1999;282:2003-2011.
29. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: A Phase II Randomized Trial of Recombinant Pro-Urokinase by Direct Arterial Delivery in Acute Middle Cerebral Artery Stroke. Stroke 1998;29: 4 - 11.
30. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. Stroke 2007;38:2633-2639.
31. Mattle HP, Arnold M, Georgiadis D, et al. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. Stroke 2008;39:379-383.
32. Nedeltchev K, Fischer U, Arnold M, et al. Long-term effect of intra-arterial thrombolysis in stroke. Stroke 2006;37:3002-3007.
33. Agarwal P, Kumar S, Hariharan S, et al. Hyperdense middle cerebral artery sign: can it be used to select intra-arterial versus intravenous thrombolysis in acute ischemic stroke? Cerebrovasc Dis 2004;17:182-190.
34. Macleod MR, Davis SM, Mitchell PJ, et al. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. Cerebrovasc Dis 2005;20:12-17.
35. Brandt T, von Kummer R, Muller-Kuppers M, Hacke W. Thrombolytic therapy of acute basilar artery occlusion. Variables affecting recanalization and outcome. Stroke 1996;27:875-881.
36. Hacke W, Zeumer H, Ferbert A, Bruckmann H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. Stroke 1988;19:1216-1222.
37. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 2006;37:922-928.
38. Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial rt-PA versus intra-arterial therapy of acute ischemic stroke: emergency management of stroke (EMS) Bridging trial. Stroke 1999;30:2598-2605.
39. Ernst R, Pancioli A, Tomsick T, et al. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. Stroke 2000;31:2552-2557.
40. The IMS Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the intervencional management of stroke study. Stroke 2004;35:904-912.
41. IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. Stroke 2007;38:2127-2135.
42. Ribo M, Molina CA, Rovira A, et al. Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial Doppler/MRI selection protocol. Stroke 2005;36: 602-606.
43. Tsivgoulis G, Sharma VK, Lao AY, Malkoff MD, Alexandrov AV. Validation of transcranial Doppler with computed tomography angiography in acute cerebral ischemia. Stroke 2007;38:1245-1249.
44. Harrigan MR, Guterman LR. Endovascular treatment of acute stroke. Neurosurg Clin N Am 2005;16:433-444.
45. Molina CA, Saver JL. Extending reperfusion therapy for acute ischemic stroke: emerging pharmacological, mechanical, and imaging strategies. Stroke 2005;36:2311-2320.
46. Nesbit GM, Luh G, Tien R, Barnwell SL. New and future endovascular treatment strategies for acute ischemic stroke. J Vasc Interv Radiol 2004;15:S103-110.
47. Leary MC, Saver JL, Gobin YP, et al. Beyond tissue plasminogen activator: mechanical intervention in acute stroke. Ann Emerg Med 2003;41:838-846.

48. Baker WL, Colby JA, Tongbram V, et al. Neurothrombectomy devices for the treatment of acute ischemic stroke: state of the evidence. Ann Intern Med 2011;154:243-252.

49. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;38:967-973.

50. Hayashi K, Kitagawa N, Takahata H, et al. Endovascular treatment for cervical carotid artery stenosis presenting with progressing stroke: three case reports. Surg Neurol 2002;58:148-154.

51. Du Mesnil De Rochemont R, Sitzer M, Neumann-Haefelin T, Harmjanz A, Berkefeld J. Endovascular recanalization of acute atherothrombotic carotid artery occlusion holds up progressive stroke. Neuroradiology 2004;46:583-586.

52. Gupta R, Schumacher HC, Mangla S, et al. Urgent endovascular revascularization for symptomatic intracranial atherosclerotic stenosis. Neurology 2003;61:1729-1735.

53. Cohen JE, Leker RR, Gotkine M, Gomori M, Ben-Hur T. Emergent stenting to treat patients with carotid artery dissection: clinically and radiologically directed therapeutic decision making. Stroke 2003;34:e254-257.

54. Nedeltchev K, Brekenfeld C, Remonda L, et al. Internal carotid artery stent implantation in 25 patients with acute stroke: preliminary results. Radiology 2005;237:1029-1037.

55. Kirton A, Wong JH, Mah J, et al. Successful endovascular therapy for acute basilar thrombosis in an adolescent. Pediatrics 2003;112:248-251.

56. Lin DD, Gailloud P, Beauchamp NJ, Aldrich EM, Wityk RJ, Murphy KJ. Combined stent placement and thrombolysis in acute vertebrobasilar ischemic stroke. AJNR Am J Neuroradiol 2003;24:1827-1833.

57. Noser EA, Shaltoni HM, Hall CE, et al. Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? Stroke 2005;36:292-296.

58. Berlis A, Lutsep H, Barnwell S, et al. Mechanical thrombolysis in acute ischemic stroke with endovascular photoacoustic recanalization. Stroke 2004;35:1112-1116.

59. Yu W, Binder D, Foster-Barber A, Malek R, Smith WS, Higashida RT. Endovascular embolectomy of acute basilar artery occlusion. Neurology 2003;61:1421-1423.

60. Schumacher HC, Meyers PM, Yavagal DR, et al. Endovascular mechanical thrombectomy of an occluded superior division branch of the left MCA for acute cardioembolic stroke. Cardiovasc Intervent Radiol 2003;26:305-308.

61. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke 2005;36:1432-1438.

62. Meyers PM, Schumacher HC, Connolly ES, Jr., Heyer EJ, Gray WA, Higashida RT. Current status of endovascular stroke treatment. Circulation 2011;123:2591-2601.

63. Koh JS, Lee SJ, Ryu CW, Kim HS. Safety and efficacy of mechanical thrombectomy with solitaire stent retrieval for acute ischemic stroke: a systematic review. Neurointervention 2012;7:1-9.

64. Raffin CN, Fernandes JG, Evaristo EF, et al. [Clinical and interventional revascularization in the acute ischemic stroke: national opinion]. Arq Neuropsiquiatr 2006;64:342-348.