Neuro-Update: Stroke

European Neurology

Eur Neurol 2015;73:98–105
DOI: 10.1159/000365210

Received: September 17, 2013
Accepted: June 10, 2014
Published online: November 18, 2014

Stroke Unit Management and Revascularisation in Acute Ischemic Stroke

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Key Words

Bridging · Intra-arterial thrombolysis · Intravenous thrombolysis · Acute stroke treatment

Abstract

Background: Stroke affects one in six people throughout their lifetimes and is the most frequent cause of disability in adults. Several recanalization therapies have emerged and the management of patients in stroke units has improved over the last decades. ***Summary:*** This article examines the current treatment options for stroke patients, summarizing the key clinical evidence, as well as listing the complications and practical issues related to each of these main treatment options. ***Key Messages:*** Recent advances in the treatment of acute stroke include developments in intravenous thrombolysis (IVT), intra-arterial treatment and bridging therapies. ***Clinical Implications:*** Treatment within a stroke unit reduces mortality and disability regardless of age, sex and stroke severity. IVT is widely available and reduces disability when initiated within 4.5 h after the onset of symptoms. The major limitations of IVT are the low recanalization rates and the narrow time frame. Intra-arterial treatment, especially when using newly developed stent-retrievers, achieves very high recanalization rates. It is restricted by its limited availability and by the longer time span required to initiate therapy. Bridging both therapies is a promising approach that combines the advantages of both therapies, but the superiority of this approach remains to be proven. Future strategies to reduce the burden of acute stroke in Europe should focus on immediate access to acute stroke care and dedicated stroke units for all patients.

Introduction

Stroke will affect one in six people during their lifetimes [1] and is the most frequent cause of disability in adults. For the treatment of ischemic stroke, several recanalization therapies have emerged during the last decades: intravenous thrombolysis (IVT), intra-arterial treatment (IAT) comprising local thrombolysis and mechanical procedures, bridging of IVT and IAT, and ultrasound-enhanced thrombolysis. Up to now, only IVT with recombinant tissue plasminogen activator (rtPA), stroke unit management, early aspirin therapy and decompressive craniotomy have demonstrated their efficacy in an evidence-based manner. Despite the clear positive evidence, however, only about 3% of European stroke patients received IVT in 2005 [2]. Insufficient public awareness of stroke symptoms, delayed diagnosis, and the absence of stroke networks or treatment availability are probably the major reasons for the low application of IVT for acute stroke patients.

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0014–3022/14/0732–0098$39.50/0

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This article will review the current treatment options for acute ischemic stroke with special emphasis on patient selection and treatment strategy.

Stroke Unit Management

Stroke unit care of thrombolyzed patients and conservatively treated patients has been investigated in several trials, which have showed that it reduces both stroke-related complications and mortality (OR 0.86, 95% CI: 0.76–0.98, p = 0.02), shortens the hospitalization time and improves outcomes (OR 0.82, 95% CI: 0.73–0.92, p = 0.001 for death or dependency) [3, 4].

Blood Pressure Control
Approximately 60–80% of stroke patients present with arterial hypertension >140/90 mm Hg upon admission. Several potential underlying mechanisms have been implicated, such as elevated intracranial pressure, decreased parasympathetic activity, stress, compensatory mechanisms, or injury to autonomic control systems in the brain stem. Nevertheless, a recent study suggests that the elevation of blood pressure in the acute phase compared to the premorbid condition is lower than expected (an increase of 10.6 mm Hg against the 10-year mean premorbid level) [5]. Hypertension during IVT is associated with a higher risk for symptomatic intracerebral hemorrhage (sICH) [6–8]. Systolic blood pressure above 185 mm Hg or diastolic pressure above 105 mm Hg should be carefully lowered (e.g., with the use of nicardipine or labetalol) before initiating IVT, and then monitored every 15 min during IVT, every 30 min for 6 h post-IVT, and then hourly until 24 h after rtPA treatment.

In conservatively treated patients, blood pressure is recommended to be carefully lowered when systolic pressure is above 220 mm Hg or diastolic pressure above 110 mm Hg, although lowering the blood pressure was not associated with better outcomes according to a Cochrane Review or the more recently published SCAST or CATIS trials [9–11]. There seems to be a U-shaped association between BD and mortality in the periprocedural period: an increase in mortality of 3.8 or 17.9% was found for every 10 mm Hg change above or below 150 mm Hg [12].

Glucose Control
Elevated glucose levels are associated with poorer outcomes during the acute phase [13, 14], but a meta-analysis did not identify a clear benefit of strict glycemic control at 90 days (a benefit was only seen at 30 days), but found a 14% risk of hypoglycemia in patients with strict glycemic control [15]. Nevertheless, it is recommended to avoid glucose levels >11 mmol/l [16].

Temperature Control
Elevated temperatures should be lowered if above 37.5°C [16].

Mobilization
There is an ongoing debate about the best time point to initiate mobilization: early (within 24 h after hospitalization) or delayed mobilization. Two recent randomized controlled trials revealed contrary results, one favoring early mobilization and one delayed mobilization [17, 18]. A Cochrane review concluded that the data are insufficient to support early or delayed mobilization [19].

Antiplatelet Therapy
Aspirin has been the established standard treatment for acute ischemic stroke since two independent trials showed improved outcomes of at least 1 of 1,000 stroke patients [20, 21].

Dual antiplatelet therapy appears to reduce the risk of recurrent stroke over monotherapy, but the increased bleeding risk outweighs the beneficial effects when administered over a longer time period [22, 23]. However, there is growing evidence that the benefits outweigh the risk of bleeding if dual antiplatelet therapy is given over a limited timeframe. A recent Chinese study found that the use of aspirin plus clopidogrel to be superior to a small (75 mg) dose of aspirin alone in the prevention of early stroke recurrence after transient ischemic attack (TIA) and minor ischemic stroke when given over a timeframe of three months [24]. In symptomatic intracranial stenosis, dual antiplatelet therapy was more effective at reducing microembolic signals than aspirin alone, and dual antiplatelet therapy over a limited period of 3 months proved to be superior to stenting with Wingspan stent [25, 26].

Intravenous Thrombolysis

Intravenous thrombolysis with rtPA applied within 3 h of stroke onset proved to be an effective treatment for acute ischemic stroke in the NINDS and ECASS II trials [27, 28]. The ECASS III trial then extended the indication to 4.5 h post-stroke for patients younger than 80 years, with National Institutes of Health Stroke Scale (NIHSS) scores below 25 and without diabetes mellitus or previous stroke [29].

Besides recanalization, the elapsed time to treatment turned out to be one of the most important predictors of outcome in several trials. This is reflected in the ratio of the number of patients that need to be treated in order to prevent one patient from death or disability, that rises from 3 when therapy is initiated within 1.5 h after stroke onset, to 7 when therapy is initiated between 1.5 and 3 h after stroke onset, up to 14 when initiated between 3 and 4.5 h after stroke onset.

Complications

Most instances of sICH occur within 24–36 h after treatment, with a frequency of 7% (95% CI: 5.2–8.7%) in large trials [30]. Older patients, patients with high baseline NIHSS scores, those with arterial hypertension, diabetes mellitus, hyperglycemia, atrial fibrillation, and signs of early infarct demarcation on CT or MRI are at a higher risk for sICH [31, 32].

Treating Patients with Stroke Mimics

It is unavoidable that a few patients with stroke mimic conditions (such as epileptic seizures or metabolic disease) receive IVT before the correct diagnosis can be established. Fortunately, the use of IVT in patients with stroke mimics is rarely associated with complications: a recent multicenter cohort study found a 1% sICH rate after IVT in patients with conditions that mimic stroke [33].

Restrictions

The major restrictions of IVT are the short treatment window and relatively low recanalization rates in patients with proximal vessel occlusions [34, 35], high NIHSS score [36] and thrombus lengths of more than 8 mm [37].

Practical Issues

Recommended exclusion criteria for IVT are listed in table 1. For routine treatment, 10% of the standard dosage of 0.9 mg/kg body weight is applied as a bolus, followed by the remaining 90% administered over 60 min. Therapy initiation should not be delayed by waiting for laboratory results [38].

Table 1. Inclusion criteria for intravenous thrombolysis

Absolute
CT or MRI evidence of intracranial hemorrhage
Relative
Gastrointestinal or urinary tract hemorrhage in previous 21 days
Major surgery in previous 14 days
Myocardial infarction in previous 3 months
Head trauma of prior stroke in previous 3 months
Blood pressure persistently elevated >185 mm Hg systolic and >105 mm Hg diastolic
Acute trauma (fracture)
International normalized ratio >1.7
Platelet count ≤100,000/mm^3
Blood glucose ≤50 mg/dl
CT evidence of large infarction (>1/3 of middle cerebral artery territory)
Rapidly resolving or minor and isolated deficits
Severely affected patients

Adapted from [74].

Intra-Arterial Treatment

The PROACT II trial was one of the first intra-arterial thrombolysis (IAT) trials, and showed better outcomes with intra-arterial prourokinase application together with low dose heparin, compared to low-dose heparin alone in patients with middle cerebral artery occlusions treated within 6 h after stroke onset [39]. Since then, several mechanical techniques have been developed for thrombus disruption, stenting, and thrombectomy (see Gralla et al., 2012 for a detailed overview) [40] in large vessel occlusions. Most trials included patients within 8 h of symptom onset. The embolectomy devices that were used in the MERCI and Multi-MERCI trials or the Penumbra pivotal trial resulted in higher recanalization rates compared to local prourokinase application (successful recanalization in 46, 57.3, and 81.6% for each trial, respectively) [41–43].

The latest developments in the field of mechanical thrombectomy are stent retrievers. The SWIFT trial found higher rates of TIMI 2–3 recanalization (89 vs. 67%) and mRS outcomes of 0–2 (58 vs. 33%) with the use of the solitaire device compared to the MERCI retriever (see fig. 1) [44]. The TREVO 2 trial found a Thrombolysis in Cerebral Infarction (TICI) 2–3 recanalization in 92% of the patients with the Trevo retriever [45].

The SYNTHESIS trial compared endovascular treatment with IVT in patients treated within 4.5 h after symptom onset and found no superiority of IAT over IVT with regards to the frequency of excellent outcomes (mRS 0–1) [46]. However, these results may have been biased by a 1 h longer median time from stroke to treatment in the IAT group, the inclusion of patients without vessel occlu-

Fig. 1. Solitaire Stent Retriever Thrombectomy of a right middle cerebral artery occlusion.

sion, and intra-arterial treatment of patients without vessel occlusion. Moreover, stent retrievers were used in a minority of patients.

Complications

sICH is observed in 4.5–10.5% of treated patients [30]. Rarer complications include aneurysm of the femoral artery, distal embolus dislocation, and intracranial artery dissection or rupture.

Restrictions

The major restriction of IAT is the delay in the time to start of treatment, as compared to IVT. Formally, clinical efficacy has been proven only in a single randomized controlled trial including patients with M1 or M2 middle cerebral artery occlusion [39].

Practical Issues

In many stroke centers, IAT is considered in patients with proximal vessel occlusions that can be treated within 8 h of symptom onset. It may also be considered in patients with basilar artery occlusions beyond 8 h of symptom onset [47]. There is an ongoing debate on whether performing IAT under general anesthesia is safe, because three retrospective studies revealed less favorable outcomes for patients undergoing this procedure under general anesthesia [48–50].

Bridging Therapy

Bridging IVT and IAT is theoretically a win–win concept, because those patients who recanalize with IVT benefit from early recanalization and those with persistent vessel occlusion despite IVT benefit from the higher chance for recanalization with IAT.

The expected higher recanalization rates with bridging therapy compared to IVT alone were indeed demonstrated in the randomized controlled IMS III trial [51] and the RECANALISE study [52]. A recent meta-analysis estimated a pooled recanalization rate of 69.6% (95% CI: 63.9–75%) in 559 patients treated with bridging therapy [53]. Whether or not bridging therapy improves outcomes over IVT alone is less clear. Although the IMS II trial found better outcome scores (measured by the Barthel Index) in patients treated with bridging therapy compared to patients in the NINDS trial, neither the prospective RECANALISE study, nor the IMS III trial showed significant differences in functional outcomes [51, 52]. The IMS III trial only showed a clear trend in favor of bridging therapy compared to IVT alone in patients with NIHSS score >20 ($p = 0.06$). Unfortunately, in the IMS III trial, the new stent retrievers were used in only a very small number of patients and time delays between IVT and IAT were longer than in previous studies [54, 55].

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Table 2. Advantages and disadvantages of the main acute stroke treatment options

	Intravenous therapy	Intra-arterial therapy	Bridging
Time window	4.5 h	8 h, individually >8 h	4.5 h for IVT initiation
Advantages	Widely available Fast initiation Routine therapy High recanalization in distal artery occlusion	High recanalization rates in proximal occlusions Fast recanalization with new thrombectomy devices after beginning of angiography	Fast initiation of intravenous therapy High recanalization rates with IAT also in proximal occlusions
Disadvantages	Low recanalization rates of proximalocclusions, high NIHSS or thrombus lengths above 8 mm Short time window	Usually long time interval to therapy initiation Available only in specialized centers	Not yet evidence based

Nevertheless, the efficacy of bridging therapy with stent retrievers remains to be demonstrated in ongoing trials, such as the SWIFT-PRIME study [56].

Complications

The combined use of IVT and IAT is associated with acceptable rates of sICH, reported as 8.6% (95% CI: 6.8–10.6%) in a recent meta-analysis [53] and 6.2% in the IMS III trial [51].

Restrictions

Compared with IVT, the major restriction is the lack of efficacy demonstrated in randomized controlled trials.

Practical Issues

IVT with rtPA can be performed either with the standard dosage (0.9 mg/kg body weight) or with a reduced 2/3 dosage (0.6 mg/kg body weight). There are no randomized controlled trials that compared the two dosages but a meta-analysis found a similar safety profile alongside better functional outcomes in patients treated with the full dose [57]. The ongoing ENCHANTED trial will address the issue of appropriate rtPA dosing in a prospective randomized study design (NCT01422616).

Table 2 summarizes the advantages and disadvantages of IVT, intra-arterial treatment and bridging therapy.

Ultrasound-Enhanced Thrombolysis

Three different ultrasound-based approaches to improving recanalization success have been tested in randomized controlled trials. In the CLOTBUST trial, use of a 2 MHz transcranial Doppler led to a higher rate of complete recanalization or dramatic clinical recovery within 2 h after administration of rtPA, compared to rtPA alone (49 vs. 30%) with a low rate of complications [58].

A randomized trial with low frequency (300 kHz) higher intensity (700 mW/cm [2]) ultrasound had to be terminated due to increased rates of sICH in patients treated with ultrasound [59]. Three randomized controlled trials tested the addition of microbubbles to ultrasound together with rtPA versus rtPA alone, and found higher recanalization rates in the ultrasound-treated patients [60–62].

A final conclusion regarding the efficacy of ultrasound-enhanced thrombolysis cannot be made based on the available data, and we recommend using this approach only in the setting of clinical trials.

Decompressive Craniotomy for Malignant Stroke

Anterior Circulation Strokes

Three randomized controlled trials (DECIMAL, DESTINY, HAMLET) examined the effect of early decompressive surgery within 48 h after stroke onset in patients with space-occupying infarction of the middle cerebral artery territory and who were younger than 55 or 60 years [63–66]. Early decompressive craniotomy was associated with reduced mortality and an increased number of patients with favorable outcomes. The DESTINY II study included patients with space-occupying infarcts of the middle cerebral artery territory who were older than 60 years. The study results showed a significant decrease in 1-year mortality (43 vs. 76%), but the majority of survivors (89%) remained severely handicapped [67].

Complications

Infections and bleeding are the most frequent complications. In rare cases with large decompressions, the so-called sinking skin flap syndrome can complicate rehabilitation [68].

Practical Issues

The best time point for performing decompressive surgery in space-occupying infarctions is unknown, but most trial protocols performed craniotomy as early as possible. If it is likely that decompressive surgery is necessary (as for young patients with very large infarctions), it should be performed as early as possible. In patients for whom the situation is less clear, many stroke centers perform surgery in case of clinical deterioration. In the case of threatening malignant infarcts and before surgery, the upper part of the body should be elevated to >30°. Bone reimplantation is usually performed 2–3 months after stroke, but this practice varies between centers.

Posterior Circulation Strokes

In patients with massive cerebellar infarction, close neurological monitoring is mandatory. Despite the lack of controlled trials, decompressive surgery should be considered in patients with complete territorial infarction or infarction of more than 2/3 of the cerebellar hemisphere, beginning hydrocephalus due to herniation, shift of the fourth ventricle, or early clinical signs of brainstem compression.

Recanalization in Patients not Fulfilling the Criteria of the Current Guidelines

Patients with wake-up stroke, beyond 6 h, elderly patients, and patients under oral anticoagulation therapy are usually not considered for recanalization therapies, but they can be considered on an individual basis.

Patients with Wake-Up Stroke and Treatment Beyond 6 h

In wake-up stroke with a last-seen normal time longer than 4.5 h, or in cases of stroke with unclear symptom onset or those beyond 6 h, IAT can be considered in case of large vessel occlusions [69–71]. Whether these patients benefit from therapy is not known. Patients with extensive early signs of infarction on CT or MR imaging should probably not be treated. There are ongoing trials (for wake-up stroke and non-wake-up stroke) that select patients on the basis of MR-based perfusion-diffusion-mismatch finding. At the moment, it is unclear if patient selection upon mismatch improves therapy outcome. Several randomized clinical trials are currently underway to address this issue (AWOKE, NCT01150266; SAIL-ON, NCT01643902; WAKE-UP, NCT01525290; WAKE-UP STROKE, NCT01183533).

Elderly Patients

Most acute stroke treatment trials have excluded patients older than 80 years. Data from non-randomized studies imply that IVT and IAT can be performed safely in the elderly, but outcomes were less favorable when compared to younger patients. Two recent trials found an at least comparable or even better treatment effect of IVT in the elderly compared to younger patients [36, 72]. Therefore, the poorer outcomes in the elderly may be a general reflection of the outcomes in the elderly population as a whole, and as already observed in untreated stroke patients. Nevertheless, elderly patients should be considered for therapy on an individual basis.

Patients Under Oral Anticoagulation

IAT may be considered in patients under oral anticoagulation (INR >1.7) who have large vessel occlusions. One retrospective case series found no increased risk for sICH in 28 patients under anticoagulation therapy who were treated with IAT [73].

Future Perspectives

The main challenges in the field of acute ischemic stroke therapy are to increase the number of patients who can benefit from thrombolysis and the improvement of patient selection for IVT, IAT and bridging therapy. Furthermore, phase II trials indicate that alternative thrombolytic agents, such as Tenecteplase, Desmoteplase, or Reteplase may provide effective treatment alternatives. Ongoing trials will hopefully answer the question on whether hypothermia is as effective in stroke patients as it is in cardiac patients (EuroHYP-1 [NCT01833312], ICTuS2/3 [NCT01123161], ReCCLAIM II [NCT0172 8649]).

Disclosure Statement

The authors declare no conflicts of interest.

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