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Ischaemic stroke: acute management, intensive care, and future perspectives

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Recently, a number of developments in the acute management of stroke have necessitated active involvement of neurocritical care. This review focuses on the immediate care, including intensive care, that may make a difference to the patient outcome. Recent research, that highlights the importance of acute management of stroke in terms of thrombolysis, thrombolytic agents, decompressive surgery, and hypothermia, has been reviewed.

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Ischaemic stroke is an acute heterogeneous syndrome caused by several major and some uncommon disorders leading to an occlusion of blood vessels supplying brain tissue. After deprivation of oxygen, some neurones die within minutes and irreversible brain injury occurs immediately, erasing its function probably forever. Around the area of necrosis is an area in which the blood supply is marginally sufficient to keep these cells alive. This is called the ischaemic penumbra. If no reperfusion occurs or additional injury is added, a time-related death occurs.[32] Therefore, 'time is brain' summarizes the fact that brain is lost, if time to treatment is delayed. Therapeutic nihilism and insufficient treatment opportunities lead to the fact that stroke is the third most common cause of death and the major cause of disability in industrial countries. Ongoing research has revealed at least essential parts of the pathophysiological cascade after ischaemic stroke led to new established therapies. Experimental approaches will hopefully find their way to the patient.

Acute management

Acute focal neurological signs, such as limb weakness, aphasia, and sudden or fluctuating unconsciousness, guide the differential diagnosis of ischaemic stroke. If stroke is suspected, the patient must be transported without delay to an acute hospital with a computed tomography (CT) scanner, as intracerebral haemorrhage or other causes of acute focal neurological signs cannot be ruled out without imaging. Certainly, the differentiation of various causes of focal neurological signs is essential for appropriate treatment. In principle, the acute management of stroke requires accurate neurological examination, general care management, imaging techniques, treatment, and placement in special neurological units.

Thrombolysis

Resolving the occluding clot of a cerebral artery represents the causal therapeutic approach for the treatment of ischaemic stroke and is preferably done by thrombolytics. So far, thrombolysis by i.v. recombinant tissue-plasminogen activator (rt-PA) is the only therapy approved for acute ischaemic stroke. Its use is essentially limited by the short time-to-treatment window of 3 h after stroke onset, although new magnetic resonance imaging (MRI) techniques can identify patients who might benefit from treatment beyond 3 h. Beside the i.v. administration of rt-PA, intra-arterial injections ultrasound-assisted thrombolysis represent new therapeutic approaches which are discussed later.

Systemic, i.v. thrombolysis in CT-based studies

In 1996, rt-PA was approved for the treatment of acute ischaemic stroke within a time period of 3 h after symptom onset based on large multicentre stroke studies including National Institute of Neurological Disorders and Stroke (NINDS), European Cooperative Acute Stroke Study (ECASS) I and II, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischaemic Stroke (ATLANTIS).[19 42 43 47] Patients were excluded from studies based on the evidence of intracerebral or subarachnoidal haemorrhage by a CT of the brain; 2657 patients (1316 placebo *vs* 1341 rt-PA) with symptom onset up to 6 h before treatment were included. The beneficial effect of rt-PA was proven by the positive effects in the NINDS study. Conditional approval for treatment within the 3 h window was given in Europe based on this experience.

Different meta- and *post hoc* analyses have investigated the effectiveness of thrombolysis, so far. Hacke and colleagues[17] published a meta-analysis of 2044 patients from

NINDS and ECASS I/II. rt-PA not only increased the rate of early haemorrhage, but also reduced worse clinical outcome. The advantage for rt-PA *vs* placebo corresponded to a 'number needed to treat' of 11 within a treatment window of up to 6 h and of 7 within 3 h. The mortality compared with placebo showed no significant difference.

Wardlaw and colleagues[47] analysed data of 5216 patients independently of the time window for treatment, thrombolytic agent, and mode of thrombolysis (intra-arterially or i.v.). The outcome was significantly altered by thrombolysis, although thrombolysis caused increased rates of intracerebral haemorrhage. rt-PA showed the best risk–benefit ratio when thrombolytic agents were compared within the study. Early thrombolysis within 3 h was superior to later treatment.

A combined analysis of the NINDS-study, ECASS I and II, and ATLANTIS was published in 2004.[18] Various criteria common to all studies were combined and investigated by multivariate analysis to define the influence of treatment delay and incidence of intracerebral haemorrhage. Data of 2775 patients showed that the probability for a good outcome decreased with time to treatment. The chance of a good outcome was increased by 2.8 (CI 1.8–4.5), if treatment was started within the first 90 min after symptom onset compared with placebo. This chance decreases to 1.6 (CI 1.1–1.9) at 91–180 min and to 1.2 (CI 0.9–1.5) at 271–360 min, which was non-significant. Moreover, the mortality rate increased and was slightly elevated for the time period of 271–360 min. Symptomatic intracerebral haemorrhage (sICH) occurred in 5.9% of all rt-PA-treated patients compared with 1.1% for placebo ($P<0.0001$). Age was a major risk factor for haemorrhage, although delayed treatment was not associated with increased bleeding rate. Moreover, the data showed that patients with severe stroke, who are frequently excluded from thrombolytic therapy, also benefited from thrombolysis and should therefore not be excluded from treatment.

After approval for stroke treatment, two major studies observed the clinical use of rt-PA during daily routine. These studies were Canadian Alteplase for Stroke Effectiveness Study (CASES) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).[21] CASES included 1135 patients treated by rt-PA in Canada; 37% of patients treated within 90 min had a favourable outcome (mRS 0–1) on day 90 after stroke onset, with 4.6% developing symptomatic cerebral haemorrhage. These results are of major importance as they confirm the safety and effectiveness of rt-PA in daily routine use outside clinical studies. Also, other smaller studies showed similar effects.[15] The preliminary European approval for the use of rt-PA in 2000 was based on two prerequisites: the ECASS III study will test rt-PA in a treatment window of 4.5 h. In parallel, the safety and effectiveness of rt-PA would need to be addressed in the future. The first results of SITS-MOST presented during the European stroke congress in Brussels in 2006 are similar to CASES. Approximately 5000 patients were included in 265 centres.

Recently, two studies were published investigating the safety and effectiveness of systemic rt-PA in older patients.[36 42] Data from CASES were reviewed and patients with an age $\geq$80 yr (n=270) were compared with those aged <80 yr (n=865).[42] The risk of sICH did not differ between these groups [4.4% (95% CI 2.3–7.6) *vs* 4.6% (95% CI 3.3–6.2)]. Favourable outcome, defined as modified Rankin Score 0–1 at 90 days, was less in older patients (26% *vs* 40% in those <80 yr). Ringleb and colleagues[36] showed similar results in a prospectively collected single centre data. Patients aged >80 yr (n=90) were compared with those <80 yr (n=378) and the overall rate of sICH was 6.9% in octogenarians compared with 5.3% in younger patients (P=0.61). Whereas 9.4% of older patients selected for thrombolysis by CT suffered from sICH, no MRI selected patients did; 20.3% of the older patients selected by CT and 15.4% of patients selected by MRI had a favourable outcome, although age remained an independent risk factor for worse outcome. It can be concluded from these studies that older patients do not have an increased risk of sICH. MRI selection helps to decrease the risk of sICH, but does not influence the overall outcome after 3 months.

Systemic, i.v. thrombolysis in MRI-based studies

New MRI techniques including perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), and T2 imaging help to select patients for thrombolytic therapy. The DWI-lesioned brain region indicates irreversibly injured cerebral tissue and represents the so-called 'ischaemic core', whereas PWI indicates areas that are deprived of cerebral blood flow (CBF). The difference between the brain regions PWI and DWI shown to be altered by results in the so-called 'penumbra' in which the CBF is critically decreased but contains brain tissue that can be saved. This area represents the target for further treatment. Although newer studies indicate that this model is oversimplified, the 'mismatch principle' was helpful in a number of studies for stroke treatment.

In a non-randomized open-label study of 129 patients, Röther and colleagues[37] investigated the influence of thrombolytic treatment within a 3 h time window on MRI parameters and clinical outcome. Although patients receiving thrombolysis were treated in a rather delayed time window and suffered from worse symptoms than control patients, they achieved a better outcome at 3 months. Another study compared patients who were treated with rt-PA on the basis of MRI within a 6 h time window with the pooled results of the CT-based thrombolysis studies.[44] Thirty-eight per cent of 174 MRI-based thrombolysis patients were treated later than 3 h after symptom onset (3–6 h), but these patients had a significantly better functional outcome compared with the placebo-treated patients and thrombolysis patients of the large CT-based stroke

studies. Moreover, they showed a lower incidence of symptomatic haemorrhage.

Kohrmann and colleagues[25] compared 382 patients treated with rt-PA within and beyond the 3 h window on the basis of CT and MRI findings. Although there was a trend towards better outcome of patients treated on the basis of MRI findings, the rate of cerebral haemorrhage was lower in this group. A multivariate analysis pointed to MRI as an independent predictor for a lower incidence of symptomatic haemorrhage. This study suggests that MRI-based thrombolysis might be safer than CT within a time window over 3 h, and at least as good as CT-based thrombolysis within 3 h.

Intra-arterial thrombolysis

Obviously, local treatment by rt-PA has theoretical advantages compared with systemic administration. Local rt-PA might be more effective and safer, since a higher concentration of rt-PA is reached at the thrombus and only minor systemic side-effects appear. However, intra-arterial thrombolysis (IAT) is still preserved for specialized centres, because the procedure is technically demanding and specialist equipment is required.

So far, IAT studies have included only a few patients and have led to different results in terms of recanalization, safety, and functional outcome. Prolyse in Acute Cerebral Thromboembolism-1 (PROACT) published in 1998 compared intra-arterial pro-urokinase with placebo,[7] and there was no significant difference after 40 patients. After screening of 12 323 patients and angiography in 474 patients, a total of 180 stroke patients were randomized for PROACT II.[11] One hundred and twenty-one were treated by rpro-UK and heparin, and 59 patients were treated with heparin alone. The primary endpoint of clinical outcome at 90 days and the secondary endpoint of recanalization of the occluded vessel were significantly improved by rpro-UK. Mortality was similar between the two groups. There was a high incidence of symptomatic haemorrhage that might be explained by the large strokes included.

Thrombolysis in the vertebrobasilar circulation

Vascular occlusion in the vertebrobasilar circulation often leads to severe neurological deficits that can progress to a 'locked in syndrome' or death. The mortality without intervention is up to 90%.[20]

Data for intervention after vertebrobasilar occlusion are limited to small studies investigating occlusion of the basilar artery using intra-arterial administration of thrombolytics and mechanical recanalization. Lindsberg and colleagues[30] investigated 50 patients with an occlusion of the basilar artery proven by angiography or DSA and recanalization occurred in 52% of 43 patients after systemic administration of rt-PA.

The recent meta-analysis of Lindsberg and Mattle[29] compared i.v. therapy (n=76) with IAT (n=344) and, although IAT resulted in higher recanalization rates [53% (i.v.) *vs* 65%; P=0.05], this was not accompanied by better functional outcome for IAT. The survival rate was 50% for i.v. therapy and 45% for IAT (P=0.82). A good clinical outcome occurred in 22% of patients receiving i.v. therapy and in 24% of those receiving IAT (P=0.48). However, the survival rate without reperfusion was almost zero (2% *vs* 38%).

Another study compared i.v. Abciximab combined with intra-arterial rt-PA, plus possible percutaneous transluminal angioplasty (PTA) and stenting, with a historical control group (intra-arterial rt-PA).[8] The combination therapy was superior in terms of recanalization (45% *vs* 22%), good clinical outcome (34% *vs* 17%), and mortality (38% *vs* 68%; P=0.006).

Ultrasound-enhanced thrombolysis

Ultrasound influences connections within the fibrin network of a thrombus and leads to small microstreams of plasma through the thrombus.[1 35] Owing to this effect there is improved effectiveness of rt-PA and ultrasound is suggested to improve and increase the speed of reperfusion after thromboembolic ischaemic stroke. Alexandrov and colleagues[1] showed in 126 patients (all treated by rt-PA, 63 of whom received additional ultrasound) that ultrasound improved the rate of early recanalization or dramatic clinical improvement (42% *vs* 30%; P=0.03). There was no significant difference in the outcome at 3 months, probably due to the small patient numbers. Another study was terminated early because of the increased rate of haemorrhage most probably due to the high-energy, low-frequency ultrasound.[5]

The suggested beneficial effects of ultrasound might be improved further by the so-called 'microbubbles'. Small gas or air-filled microspheres, which are normally used as contrast agent during ultrasound examination, might enhance the intravessel effectiveness of ultrasound. A pilot study in 111 patients showed enhanced recanalization with a combination of microbubbles and ultrasound compared with ultrasound/rt-PA and rt-PA alone.[35] Phase II studies are currently underway.

New thrombolytic agents

The 'Desmoteplase In Acute Stroke' (DIAS) study recruited stroke patients within a time window of 3–9 h after symptom onset and randomized them to either placebo or treatment by the new thrombolytic agent desmoteplase.[16] Patients were treated by different doses of desmoteplase on the basis of an MRI mismatch. Whereas the first part of the study used a non-weight-adapted dosage, the second part utilized a lower weight-adapted dosage (62.5 $\mu g\,kg^{-1}$, 90 $\mu g\,kg^{-1}$, and 125 $\mu g\,kg^{-1}$ body weight). Desmoteplase in a dose of 125 $\mu g\,kg^{-1}$ led to a higher reperfusion rate, which correlated with a significantly better clinical outcome. The incidence of symptomatic haemorrhage was small (2.2%). The companion study in the US named Dose Escalation of Desmoteplase for Acute Ischaemic Stroke (DEDAS) showed similar results.[12] Currently, DIAS-2 is

proceeding. Whereas DIAS 1 and DEDAS used only MRI for inclusion criteria, DIAS-2 uses MRI for some patients and modern CT techniques including CT, CT-angiography, and perfusion CT for others. The preliminary results are expected in the near future.

Intensive care

Decompressive surgery

Acute ischaemic stroke is followed by swelling of the infarcted brain area. Depending on the size and location of the infarct, complications can occur due to increased intracranial pressure (ICP) and consequent herniation or compression of the brain stem. These might lead to additional injury of vital brain tissue and cause death.

Decompressive surgery for supertentorial infarcts

Large supratentorial infarcts and large infarcts in the cerebellum can lead to this dangerous scenario. Decompressive surgery represents a treatment opportunity and has been studied mainly in large infarcts in the area supplied by the middle cerebral artery (MCA). The clinical scenario of the so-called 'malignant infarct' is characterized by a severe neurological deficit, including hemiplegia, head- and gaze deviation, and progressive deterioration in consciousness. Unilateral pupil dilation and increase of ICP follows within 2 to 5 days after stroke onset and is accompanied by ICP >30 mm Hg. Previous studies showed a mortality rate of up to 80% in these patients. Decompressive surgery produces space for the swollen brain by removal of a large part of bone, reducing the risk of compression of the surrounding brain tissue and of herniation. Moreover, CBF is improved in the surrounding brain area.

Some important issues in craniectomy are unresolved. These include the timing of surgery, age of the patients, and overall effectiveness. All studies show only preliminary trends because of the small number of patients and inconsistent study design. In a study of 32 patients, our group demonstrated that early decompression within the first 24 h after symptom onset was superior to delayed treatment if the patient had already herniated.[39] Although the mortality was reduced to 20% compared with a historical control group, functional outcome, assessed using the Barthel index, was superior, with an index of 80. None of the surviving patients showed a poor outcome with complete dependency. A major determinant for the effectiveness on ICP is the size of the removed bone flap and a bone flap diameter of at least 12 cm^2 is recommended.[45] Two studies show that younger patients, with an age below 50 yr, benefit from such surgery whereas older patients do not.[22 28] An intact family background was an independent predictor for a positive outcome. So far, there is uncertainty whether patients with an infarct in the dominant hemisphere should be treated at all but, surprisingly, these patients developed a good to moderate speech comprehension and a lower rate for depressive mood.[46]

Unfortunately, no study has yet included a control group and comparison of mortality rates is difficult because of the use of historical controls from 7 to 8 yr ago. There have been improvements in general ICU practice during this period that might in itself have improved survival in the absence of decompressive surgery. Meanwhile five randomized trials have been designed to investigate the efficacy of decompressive surgery: The Hemicraniecomy And Durotomy Upon Deterioration From Infarction Related Swelling Trial (HeADDFIRST) randomized 26 patients between 2000 and 2003. The final results, however, have not yet been published.[9 10] Between 2001 and 2004, four other studies were initiated: one in the Philippines called Hemicraniectomy For Malignant Middle Cerebral Artery Infarcts (HeMMI) and three European trials called Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) in The Netherlands, Decompressive Craniectomy In Malignant middle cerebral artery infarcts (DECIMAL) in France, and Decompressive Surgery for the Treatment of malignant Infarction of the middle cerebral artery (DESTINY) in Germany.[30] The concern of many clinicians is not about survival, but rather about clinical outcome and the quality of life of survivors. Thus, the primary endpoint in DESTINY is not mortality, but functional outcome at 6 months, since a reduction in mortality might be outweighed by a major disability in survivors facing a life of dependency, pain, and hopelessness.

Decompressive surgery in cerebellar infarction

Patients suffering from cerebellar infarct may require decompressive surgery if a mass effect develops. This might be due to the infarct size, type of underlying vascular lesion, haemorrhagic transformation, and inadequate collateral blood flow. Patients with a lesion of two-thirds or more of the posterior cerebellar artery territory are considered to be at risk for subsequent deterioration. Causes include mass effect in the posterior fossa compressing the brainstem and occlusive hydrocephalus. The German–Austrian Cerebellar infarction Study observed the clinical course and neuroradiological features of 84 patients with massive cerebellar infarction.[23]

not every therapeutic decision can be studied in a randomized manner. As the level of consciousness is the most powerful predictor for outcome, patients with large cerebellar infarction should be observed on a stroke or intensive care unit.

Therapeutic hypothermia

Induced therapeutic hypothermia represents one of the most effective neuroprotective methods in animal studies of focal cerebral ischemia.[4] Lessons from these experiments show that the neuroprotective effectiveness depends on many issues. Hypothermia is more effective if it is induced as early as possible, although delayed hypothermia may still offer some neuroprotection, if the duration of cooling is increased.[4] Even experimentally, some features are not clear including ventilation strategy, timing and rate of rewarming, optimal depth of hypothermia, and associated electrolyte and fluid management. Experimentally, hypothermia seems to be safe when combined with rt-PA.[26] It is important to notice how many pathophysiological pathways are influenced by hypothermia in contrast to most pharmacological agents that interfere with only a few of them. To mention some, hypothermia reduces the energy and oxygen demand of brain tissue, inflammatory reaction, apoptotic process, oxygen free radicals, and neurotoxic glutamate, and stabilizes the blood–brain barrier.[4] Although studies of patients in cardiac arrest proved the neuroprotective effects of the method for the first time,[3 33] stroke studies are more disappointing. Reasons for this include the heterogeneity of the study designs, and hypothermic treatment in the late neuroprotective time window or beyond.[13 14] Hypothermia was tested in patients with large ischaemic stroke and was induced several hours up to days after stroke onset.[38] Hypothermia was safe and feasible. Schwab and colleagues[39] showed that hypothermia was effective in controlling ICP due to the mass effect of large ischaemic territories. Moreover, hypothermia reduced the mortality after large ischaemic stroke in the territory of the MCA from 80% in a historical control group down to 44%.[40] The major risk for these patients was rebound intracranial hypertension in the rewarming period. Controlled and slow rewarming by $0.1^{\circ}C\,h^{-1}$ steps was superior to fast, uncontrolled rewarming.[41] Regarding neuroprotective effects, three major studies must be mentioned. Kammersgaard and colleagues[24] showed that modest hypothermia of 35.5°C was possible in awake stroke patients and that this target temperature could be reached within a mean time of 3 h and maintained for 6 h. There were small patient numbers in this study and significant effects on the outcome could not be expected. COOLAID (Cooling for Acute Ischaemic Brain Damage) I and II investigated combination therapy of moderate hypothermia and thrombolysis by rt-PA (27). Whereas COOLAID I confirmed only the safety and feasibility of the procedure itself,[27] COOLAID II pointed to possible effectiveness based on MRI examination.[6] MRI showed a non-significant decrease of infarct growth but, again, the small number of patients precluded statistically significant results. In conclusion, at the present time, hypothermia cannot be recommended for stroke treatment.

Future perspectives

Stroke treatment is currently limited more or less to thrombolysis as the only approved procedure. However, there are many potential therapeutic options for stroke patients with effectiveness yet to be proven. Imaging techniques such as MRI and CT, perfusion-CT, and CT-angiography have to be tested against each other in further stroke trials to obtain the maximal information for identifying treatable stroke patients. New thrombolytics such as desmoteplase are in the pipeline, but results have to be validated in phase III studies. Probably, ultrasound-enhanced thrombolysis will shorten the time to reperfusion and perhaps microbubbles can be 'loaded' with neuroprotective agents. Ongoing or recently completed studies such as DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middel Cerebral Artery) are desperately needed to prove or refute the effectiveness of decompression after large cerebral infarcts on functional outcome. Indications for surgical decompression have to be identified, for example, age limit or whether patients with infarcts of the dominant hemisphere also benefit.

More and more clinical studies address the importance of hyperglycaemia and insulin resistance as a factor severely affecting critically ill patients.[48 49] Interventional studies suggest that tight glucose control can improve outcome in critically ill surgical patients and also in medical ICU-patients in terms of morbidity. It is intriguing to suggest similar beneficial effects also in neurointensive care. Only a subgroup of patients with neuro ICU-disease has been studied in these two large trials. Intensive insulin therapy prevented secondary injury in the peripheral and central nervous system, by reduced incidence of critical illness polyneuropathy and ventilator dependency, and by lowering ICP and producing improved long-term rehabilitation of ICU patients. However, these data remain inconclusive and larger randomized trials are required to address these issues.

In the opinion of the authors, hypothermia remains a hot neuroprotective option because it has been successful after cardiac arrest, and it has multiple neuroprotective features. However, many factors will determine whether its success after cardiac arrest can be transferred to stroke patients. The most important question is whether it can be delivered to a majority of stroke patients effectively. So far, most studies conclude that moderate hypothermia of 33°C is only feasible in sedated and artificially ventilated patients and treatment on stroke units has hitherto been excluded. Moreover, mild deficits will not be treated by a method that depends on mechanical ventilation for its

success. Another factor that needs resolving is how fast a sufficient degree of hypothermia can and should be reached. From all the different methods, the safest and most feasible must be identified for stroke treatment. This might also include preclinical cooling.

At least experimentally, neurotrophic factors such as erythropoietin and granulocyte colony-stimulating factor (G-CSF) are extremely interesting substances as they influence many different pathways of the pathophysiological cascade after stroke.[2] They reduce apoptosis, glutamate release, and inflammation, and probably increase neuroregeneration. In contrast to other substances tested in stroke patients, they have been used for decades in patients for other indications. Currently, phase II and III studies are underway.[31]

Perhaps, future stroke therapy will consist of all, or a combination, of these procedures distilled into a 'therapeutic cocktail'.

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