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### Management of Acute Stroke: ICU Care and Extending the Time Window for Thrombolysis (K. Wartenberg)

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**Stroke care in the intensive care unit is focussed on stabilisation of vital and metabolic parameters. Timely recanalisation by means of intravenous, intraarterial thrombolysis or mechanical clot disruption remains the most powerful treatment to improve the outcome of stroke victims.**

#### Introduction

Stroke is the third leading cause of death, with a person dying every 3-4 minutes of a stroke. On average, every 40 seconds someone is experiencing a stroke (Rosamond et al. 2008). Approximately 3% of total healthcare expenditure is attributable to cerebral ischaemia with cerebrovascular diseases costing European Union healthcare systems 21 billion euros in 2003. The costs to the wider economy including informal care and lost productivity amount to 34 billion euros (Flynn et al. 2008).

Evidence is accumulating that patients treated in stroke centres with designated stroke and intensive care units focussed on detailed and expedited stroke care have better functional outcomes and that patient care is more cost effective (Roquer et al. 2008; Saka et al. 2008). With the development of complex acute stroke treatment targeting early reperfusion with intravenous and/or intraarterial thrombolysis, sonothrombolysis, mechanical clot disruption, and application of neuroprotective strategies, these units specialised in stroke patient care will become even more important.

About 5-20% of all ischaemic strokes develop into space-occupying, life-threatening strokes associated with a mortality rate up to 80%. These encompass internal carotid (ICA) or middle cerebral artery (MCA) infarctions covering about 50% of MCA territory, brain stem and cerebellar infarctions. Clinical deterioration can be expected from day 1 through 7 in approximately 50% of the patients (Aiyagari and Diringer 2002).

Acute stroke patient care begins in the field with recognition of the symptoms and getting the patient to emergency department (ED) as soon as possible. There has been an attempt to centralise care in designated and certified stroke centres with the capacity for rapid stroke evaluation and treatment (Dion 2004; Douglas et al. 2005). In the ED, a computed tomography scan (CT) or magnetic resonance imaging (MRI) of the brain including a arteriogram and a perfusion sequence should be obtained along with blood work, electrocardiogram, chest radiograph, and a decision about the best strategy of thrombolysis or mechanical recanalisation should be made (Adams et al. 2007, 2008). The patients undergoing thrombolysis, at risk for neurological deterioration or development of massive space-occupying infarction should be monitored in an intermediate care stroke or an intensive care unit.

#### Early Reperfusion Strategies

Time is brain, i.e. the more time that passes between the beginning of stroke symptoms and a plan to recanalise the affected blood vessel, the more brain cells are going to die.

Currently, the administration of intravenous (IV) recombinant tissue plasminogen activator (rtPA) 0.9 mg/kg, given within 3 hours of symptom onset is the only approved acute stroke therapy based on the NINDS trial (Table 1) (1995b, Adams et al. 2007). At first, 10% of the total dose is given as an IV bolus, followed by infusion of the remainder over 1 hour. The earlier this therapy gets applied, the better the outcome (good outcome= modified Rankin Scale 0-1 at 90 days, Odds Ratio (OR) 2.8 for treatment from 0-90 min, OR 1.6 within 90-180 min, OR 1.4 within 180-270 min) (Hacke et al. 2004). A variety of randomised trials investigating the effect of IV rtPA, IV urokinase, or IV streptokinase applied within different time windows up to 6 hours did not demonstrate any improvement of outcome (Table 1). Attempts to improve safety and efficacy as well as to extend the time window lead to two recent trials, DEDAS and DIAS, which tested IV desmoteplase, a thrombolytic agent derived from bat saliva with higher fibrin specificity and reduced likelihood for neuronal damage in ischaemic brain. MRI diffusion/perfusion mismatch was applied

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to determine the existence of an ischaemic core (already infarcted tissue) and a penumbra (potentially salvageable tissue) within a 9-hour time window. In these two phase II trials, the outcomes of the desmoteplase-treated patients were significantly better (Table 1) (Furlan et al. 2006; Hacke et al. 2005). However, the DIAS II trial that randomised 193 patients to placebo, IV desmoteplase 90 mcg/kg or 125 mcg/kg, did not demonstrate any difference in neurological outcomes and an increased mortality rate in the group with the higher dose of IV desmoteplase (Hacke W et al. presented at ESC 2007). Another study that investigated the treatment effect of IV rtPA versus placebo 3-6 hours after stroke onset also evaluated MRI diffusion and perfusion mismatch criteria. Between the treatment and placebo groups among all patients and in the patient group with a diffusion and perfusion mismatch, there was no difference in neurological outcome and mortality (Davis et al. 2008). The DIAS III and IV trial is about to start. The aim is to compare the neurological outcome at 90 days of patients randomised to IV desmoteplase 90 mcg/kg or placebo 3 to 9 hours after symptom onset based on CT or MRI criteria including demonstration of arterial narrowing or occlusion on CT or MR Angiogram.

With advancements in the field of interventional neuroradiology, the focus shifted to recanalisation of larger intracranial arteries and more severe strokes. The results of the PROACT I and II trials investigating the effect of intraarterially applied urokinase were promising, showing significantly better functional outcome and a higher recanalisation rate with the treatment compared to placebo. These hopeful results did not lead to approval of this management approach, though. Most stroke centres have developed protocols that offer intraarterial (IA) treatment with either rtPA, abciximab (Ng et al. 2008), mechanical devices such as the PENUMBRA clot aspiration system and concentric MERCI clot retriever (Bose et al. 2008; Flint et al. 2007; Smith et al. 2008), clot disruption with guidewires and microcatheters, acute balloon dilatation and stent application (Ng et al. 2008). The choice of treatment is based on the individual patient's vasculature. The time windows are usually 6-8 hours from symptom onset for the anterior circulation and 12-24 hours for the posterior circulation. The IMS trial is the only randomised study investigating the effect of bridging of IV and IA thrombolysis. Patients with acute ischaemic stroke receive IV rtPA standard dose or 0.6 mg/kg rtPA followed by IA rtPA, application of the MERCI device, the EKOS small vessel ultrasound infusion system delivering low intensity ultrasound, or a combination of either device with IA rtPA up to 22 mg.

The combination of high frequency ultrasound (2 MHz) delivered by transcranial Doppler sonography (TCD) with IV thrombolysis within 3 hours of symptom onset was found to be even more effective. The CLOTBUST (Combined Lysis of Thrombus in Brain Ischaemia using Ultrasound and Systemic TPA) trial randomised 126 patients with MCA occlusion that received IVrtPA to continuous TCD or placebo monitoring. The patients undergoing TCD monitoring in addition to IV rtPA achieved significantly more complete recanalisation and/or dramatic clinical recovery within 2 hours as well as a trend to improved functional outcomes at 3 months (Table 1) (Alex androv et al. 2004). Ultrasound transducers have been incorporated into catheters for intraarterial delivery of thrombolytic drugs, which generate a 360° circumferential pulse to add to the effect of intraarterial thrombolysis. Ultrasound enhanced thrombolysis can be further amplified by adding gaseous microspheres (micron-sized lipid or albumin shells that expand and give stronger reflected echos when exposed to ultrasound). The combination of IV thrombolysis, 2 MHz continuous ultrasound, and Levovist air microspheres (Bayer Schering AG, Berlin, Germany) in patients with acute MCA occlusion lead to high sustained recanalisation rates (55%) (Molina et al. 2006). While this area is being explored with ongoing phase I and II trials, a large, randomised, placebo-controlled trial, ECASS III, was published recently. The study demonstrated that the time window of IV thrombolysis with rtPA after acute ischaemic stroke can be successfully expanded. Patients were enrolled 3-4.5 hours after symptom onset to receive IV rtPA 0.9 mg/kg or placebo, the treatment group had significantly better functional outcomes at 3 months (Table 1) (Hacke et al. 2008). If the extension of the time window from 3 to 4.5 hours gets approved, this treatment will offer more benefit to patients with acute ischaemic stroke who do not make it to the hospital early.

#### **ICU Care of Stroke Patients**

Intensive care management of the stroke patient begins in the ED. Airway, breathing, and circulation should be assessed and managed. The patients should be intubated if they are unable to protect their airway due to oropharyngeal weakness.

#### **Blood Pressure**

When parts of the brain are ischaemic, then there are areas of disturbed autoregulation with tissue at risk and dependent on systemic blood flow for sufficient perfusion. This especially applies to patients with extra- and intracranial cerebral artery stenosis. Based on this background, several small studies postulated that induced hypertension with IV fluids and vasopressors may be beneficial in acute ischaemic stroke and is not associated with any severe adverse events (Hillis et al. 2003) (Schwarz et al. 2002). The vasopressor of choice is phenylephrine, a pure alpha-1 agonist. In absence of any randomised studies, the guidelines recommend to refrain from any blood pressure (BP) reduction, unless systolic BP exceeds 220 mm Hg and the diastolic BP 120 mm Hg (systolic >180 mm Hg, diastolic >110 mm Hg within 24 hours after thrombolysis) (Adams et al. 2007, 2008; Oliveira-Filho et al. 2003).

#### **Glucose**

Up to 60% of the patients have increased plasma glucose levels within the first 2 hours after stroke, about half of those have no history of diabetes mellitus. There is an association between hyperglycaemia and larger infarct volumes, increased mortality and poorer long term functional outcome after stroke as well as higher intracerebral haemorrhage rates. It is unclear whether hyperglycaemia is a marker of the severity of injury as stress response or a true cause of additional cerebral injury (Williams et al. 2002; Bruno et al. 2004; Capes et al. 2001; Baird et al. 2003; Gray et al. 2004).

The UK Glucose Insulin Stroke Trial (GIST-UK) randomised patients 933 patients within 24 hours of acute stroke to continuous glucosepotassium- insulin (goal: 4-7 mmol/L) or saline infusions for 24 hours. The trial was stopped prematurely due to slow enrolment and failed to demonstrate a difference in mortality and functional outcome at 90 days, but mean systolic blood pressure was significantly lower in the treatment group (Gray et al. 2007). As the benefit of maintaining euglycaemia has been substantiated in certain medical and surgical ICU patient populations (Van den Berghe et al. 2006), there is hope that other studies will show an advantage in functional outcome for patients kept normoglycemic in the future. In the meantime, severe hypoglycaemia <2.8 mmol/L should be treated with dextrose or 10-20% glucose infusions,

serum glucose levels > 10 mmol/L should be lowered with insulin infusions according to the guidelines (Adams et al. 2007, 2008).

### **Fever**

Increased body temperature after ischaemic stroke and neurological injury is significantly associated with higher mortality, worse functional outcome, and increased ICU and hospital length of stay (Greer et al. 2008). Fever should lead to a search of an infection focus, but routine use of antibiotics without a source of infection is not recommended (Adams et al. 2007, 2008). Several feasibility trials demonstrated that reduction of hyperthermia by means of pharmacological measures (paracetamol, nonsteroidal anti-inflammatory drugs), surface and intravascular cooling devices is safe. Shivering and rebound cerebral oedema remain of concern. Neurological performance tends to be improved at normal temperatures (Mayer et al. 2004), but so far it remains to be shown that maintenance of strict normothermia improves outcome after stroke.

### **Cerebral Oedema and Intracranial Pressure**

Patients that experience neurological deterioration after a massive stroke should receive treatment for brain swelling and high intracranial pressure (ICP). For patients with large ICA or MCA infarctions less than 60 years old, hemicraniectomy will improve mortality and neurological outcome if performed within 48 hours of symptom onset (NNT 2) (Vahedi et al. 2007). Osmotherapy with IV mannitol or IV hypertonic saline given as bolus or continuous infusion and hypothermia (33-35°C) are treatment options for patients developing cerebral oedema who are not suitable for a hemicraniectomy. Monitoring of ICP in these patients may be misleading as development of midline shift to the other hemisphere and subsequent herniation may proceed while the ICP is normal.

Cerebellar infarction can cause secondary neurological deterioration due to additional brain stem ischaemia or development of cerebellar hemispheric swelling with hydrocephalus and compression of the brain stem. Delayed deterioration may be rapid, therefore the decision to intervene should be made early in the course. There are no randomised, controlled trials to evaluate timing or method of intervention. Small trials suggested a staged approach based on the appearance of the fourth ventricle:

1. Normal size and no neurological deterioration if observation
2. Normal size and neurological deterioration of the patient if external ventricular drain (EVD) if hydrocephalus, suboccipital decompression if no hydrocephalus
3. Compression, but no effacement of the fourth ventricle and no neurological deterioration (alert, awake) if observation, suboccipital decompression and/or EVD at the time of neurological deterioration
4. Compression and effacement of the fourth ventricle if immediate suboccipital decompression and EVD (Kirolos et al. 2001).

Another study suggested placing an EVD for management of obstructive hydrocephalus after cerebellar stroke and proceeding with suboccipital craniotomy if there is no clinical improvement (Jensen and St Louis 2005). However, there is usually brain stem compression at various degrees mandating suboccipital decompression early when neurological deterioration occurs.

### **Conclusion**

The management concepts of acute ischaemic stroke in the ICU and the options for early reperfusion in a timely fashion are evolving. The current focus of ICU management includes neuromonitoring, adequate perfusion (BP), normoglycemia, normothermia, and early recognition of neurological deterioration with initiation of the appropriate surgical or medical treatment of brain swelling. The recent investigations in the field of early reperfusion involve expansion of the time window for IV thrombolysis, safer thrombolytics, and combination of IV, IA thrombolysis and different ultrasound techniques.

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