Management of acute cerebral ischaemia

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Summary

Stroke is a major public health issue. Many are treatable in the acute stage, provided patients are admitted soon enough. The overall incidence of stroke in Western countries is approximately 2400 per year per million inhabitants, and 80% are due to cerebral ischaemia. The prevalence is approximately 12,000 per million inhabitants. Stroke is associated with increased long-term mortality, handicap, cognitive and behavioural impairments, recurrence, and an increased risk of other types of vascular events. There is strong evidence that stroke patients should be treated in dedicated stroke units; each time 24 patients are treated in a stroke unit, instead of a conventional ward, one death and one dependence are prevented. This effect does not depend on age, severity, and the stroke subtype. For this reason, stroke unit care is the cornerstone of the treatment of stroke, aiming at the detection and management of life-threatening emergencies, stabilization of most physiological parameters, and prevention of early complications. In cerebral ischaemia, besides this general management, specific therapies include intravenous recombinant tissue plasminogen activator, given as soon as possible and before 4.5 hours, mechanical thrombectomy on top of rt-PA or alone in case of contra-indication to rt-PA, in patients with proximal large-vessel occlusion, aspirin 300 mg, immediately or after 24 hours in case of thrombolysis, and, in a few patients, decompressive surgery.

Introduction

Stroke is a major public health issue, because of high incidence rates, high case fatality rates, risks of residual physical and neuropsychological disability, and direct and indirect costs [1]. Many strokes are preventable, and many are treatable at the acute stage, when the patient is admitted soon after the onset [2]. The term cerebral ischaemia covers a wide range of heterogeneous disorders, depending on the severity of the clinical presentation, from transient deficits to severe cases, and the cause, i.e. atherosclerosis, cardioembolism, small-vessel occlusion, rare vasculo-pathies and undetermined causes.

The management of acute cerebral ischaemia has improved dramatically over the last years with the development of intravenous (iv) thrombolysis and more recently mechanical thrombectomy. Any failure to identify in emergency cerebral ischaemia leads to a loss of chance to survive without handicap.
Our objective was to review how acute cerebral ischaemia should be managed in clinical practice during the first hours.

**Diagnostic work-up**

The main clinical characteristics of a stroke are, a sudden onset of symptoms, within seconds or minutes, and focal symptoms and signs, i.e. a neurological deficit explained by a single lesion of the brain. The severity of the neurological deficit should be assessed by the National Institute of Health (NIH) Stroke Scale [3] which quantifies different categories of neurological impairments, including consciousness. It is widely used in monitoring stroke patients. Although it takes only minutes, it is reliable and reproducible, and can be performed by non-neurologists, some training is still required.

Although some symptoms are more frequent in intracerebral haemorrhage (ICH), e.g. headache, loss of consciousness, seizures, none of them is specific enough in an individual patient. Brain imaging is therefore mandatory to differentiate ischaemic stroke from ICH in all patients. This is a crucial stage of the diagnosis, because patients with ICH will require a different diagnostic work-up, acute treatment, and secondary prevention. MRI imaging is the most appropriate technique. T1 and T2 weighted images, and fluid-attenuated inversion recovery (FLAIR) sequences identify old lesions and lesions of non-vascular origin. Diffusion weighted-imaging (DWI) sequences identify acute ischaemic lesions, with changes appearing before T1, T2 and FLAIR changes. T2 sequences identify haemorrhages. Time-of-flight (TOF) sequences visualize occlusions of the intracranial arteries. Perfusion-weighted images (PWI) are useful to evaluate penumbra in case of discrepancy between a small (or no-) abnormality in DWI and a significant clinical deficit. When MRI is not available in emergency or cannot be performed because of contra-indications, a brain computed tomographic (CT) scan without contrast should be performed without delay. In acute cerebral ischaemia, the scan may be normal, especially in very early stages, but it may show early signs of cerebral ischaemia, even within 3 hours: loss of the limits of the lenticular nucleus, loss of the insular ribbon, loss of distinction between grey and white matter. When the middle cerebral artery is occluded, the CT scan may show it as hyperdense. Intracranial occlusions can be detected with CT-angiography.

**Treatment of acute cerebral ischaemia**

**Stroke unit care**

There is a strong evidence that stroke patients should be treated in dedicated stroke units; each time 24 patients are treated in a stroke unit, instead of a conventional ward, one death and one dependency are prevented [4,5]. This effect does is independent on age, severity, and stroke subtype [4,5]. Therefore, stroke unit care is the basis of stroke management [6,7]. Stroke unit care aim at stabilizing the patient, and preventing complications that may compromise recovery.

Life-threatening emergencies should be detected because of risks of aspiration, status epilepticus, and respiratory failure. Physiological parameters should be stabilised: arterial oxygen saturation (SaO2) (> 93%), glycaemia (< 180 mg), temperature (< 37.5 °C), and hydration. This is necessary during the first few days to prevent a deleterious effect on the penumbra. Adequate blood oxygenation is important to preserve the ischaemic brain tissue, although there is no evidence that O2 to all patients is effective [8].

Atrial fibrillation (AF), heart failure, and myocardial infarction are also frequent [9,10], explaining why continuous cardiac monitoring is necessary for 2-3 days. Many stroke patients are dehydrated, and this is associated with a poor outcome [11]. Although randomised evidence is limited, the delivery of iv fluids (saline 0.9%) is considered as part of the general management of acute stroke, particularly in patients at risk of dehydration due to reduced consciousness or impaired swallowing. Experience in the management of hyperglycaemia supports the avoidance of dextrose in the early post-stroke phase and a strict glycaemic control [12].

As the autoregulation of cerebral blood flow is lost in the penumbra area, any important decrease in blood pressure during the first few hours may be deleterious in the penumbra area. Despite the lack of evidence-based data, high blood pressure should not be treated at the acute stage, unless there is a systolic blood pressure higher than 220 mmHg, an associated life-threatening disorder, such as aortic dissection or severe cardiac failure, or indication for thrombolysis where the systolic blood pressure should always be below 180 mmHg.

Hyperglycaemia occurs in up to 60% of stroke patients without previously diagnosed diabetes mellitus [13,14] and is associated with larger infarct volumes and worse functional outcome [15-17]. The largest randomized trial of blood glucose lowering [12] found no difference in mortality or functional outcomes in patients with mild to moderate blood glucose elevations (median 137 mg/dl). Based on very weak evidence, the European Stroke Organisation (ESO) recommends to reduce blood glucose levels to below 180 mg/dl (10 mmol/L) [6]. It is possible that this target level will be reduced to lower levels in the future, if more evidence is provided, and that a recommendation to prevent large variations in glucose levels is made, as this is the case for intensive care medicine in general.

Hyperthermia is associated with an increased infarct size and a worse outcome [18-21]. A raised body temperature should prompt a search for infection and treatment when appropriate. Stroke unit care aims also at preventing early complications. Specialized detection of swallowing impairment by physicians, nurses, or speech therapists, may lead to a nasogastric tube when necessary. Low molecular weight heparin reduces the risk of deep venous thrombosis and pulmonary embolism but has no
effect on mortality. As it leads to a small, non-significant increase in the risk for cerebral haemorrhagic changes, it should be used only in patients at high risk, i.e. those with leg immobilization, during the first few hours in cerebral infarcts [6], and not before 24 hours in those who receive thrombolytic therapy [22]. The Clots in Legs Or Stockings after Stroke (CLOTS) 3 trial [23] showed that intermittent pneumatic compression reduces the risk of deep venous thrombosis and may improve survival in stroke patients who cannot walk to the toilet with the help of another person. Appropriate caloric intake, early mobilization, and appropriate beds and nursing are recommended to prevent bedsores.

Stoke unit care provides a coordinated multidisciplinary input, with the continuous training of specialized staff members, and reduces mortality and dependency, in part by the prevention of non-specific complications that occur in the first few days [4,5].

Thrombolytic therapy

Iv recombinant Tissue plasminogen activator (tPA) increases the odds of a favourable outcome at 3 months [24,25]. The magnitude of the effect decreases over time. The proportion of excellent outcomes is 8 times higher within 90 min, twice higher within 91-180 min, and 1.4 times higher within 181-270 min [24,25]. Mortality at 3 months is not affected up to 270 min but increases thereafter [24]. Haemorrhagic transformation is associated with increasing age and large infarcts [24]. The dose is 0.9 mg/kg (10% as an iv bolus, 90% as a continuous iv injection over 1 hour). This dose is reduced to 0.6 mg/kg in Japan. Thrombolytic therapy is therefore recommended as soon as possible after stroke onset, with a limit of 4.5 hours and limitations concerning both contra-indications (on-going anti-coagulation, recent major surgery, increased risk of haemorrhage, delay > 4.5 hours, blood pressure >185 mmHg, glucose level > 4 g/l) and strict conditions of use (only after evaluation by a neurologist or a stroke-trained physician, and in a stroke unit) [6].

Mechanical thrombectomy

Mechanical thrombectomy seemed to be a promising technique as a complement of iv thrombolysis in patients with proximal occlusions, when the disappointing results of the first randomised trials were published in 2013 [26-28]. However, these trials suffered many methodological limitations, such as small sample size, lack of standard treatment in patients randomised to no intervention, excessive delay between decision and treatment. Five new trials published in 2015, without these limitations, and use of new generation of devices, provided a clear evidence that endovascular therapy on top of standard care (including iv thrombolysis when appropriate) significantly improve outcomes in patients with acute cerebral ischemia due to proximal large-artery occlusion in the anterior circulation [29-33]. A meta-analysis of these 8 trials [34], including 2413 patients showed that patients with large-vessel occlusion, anterior circulation strokes, and who received the best medical therapy (including rt-PA when appropriate) who were randomised in the interventional arm, were more likely to be independent after 3 months (odds ratio for modified Rankin scale score 0 to 2: 1.73; 95% confidence interval 1.18-2.53). The number needed to treat to have 1 patient independent more was 9.3. The rate of haemorrhagic transformations and the mortality rate were not significantly modified. The subanalysis of the 5 last trials, with more appropriate protocols, increases the magnitude of the effect with a number needed to treat of 5. These trials also showed that the onset-to-treatment time is strongly associated with outcomes. In patients under oral anticoagulant, mechanical thrombectomy is the only strategy of recanalisation that can be proposed in patients have a large-artery occlusion.

Antithrombotic therapies

Aspirin 300 mg at the acute stage, then 50–160 mg daily, prevents nine dependencies or deaths per 1000 patients treated. Because of the large number of patients who can receive aspirin, this small individual effect provides a reasonable effect in terms of public health. Aspirin should not be started until 24 hours after any thrombolysis. Recently, the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial [35] showed that Asian patients who received within 24 hours a loading dose of clopidogrel, on top of aspirin, for a minor ischaemic stroke or a TIA, followed by 75 mg clopidogrel and 75 mg aspirin for 90 days, had a better outcome without an increased risk of bleeding. This result needs to be confirmed in a European population. Unfractionated heparin or low molecular weight heparin do not provide any overall benefit, because the decreased early ischaemic recurrences are counterbalanced by haemorrhagic transformations. There is no reason to recommend heparin routinely during the acute stage of ischaemic stroke, even in patients with AF.

Decompressive surgery

Decompressive surgery (hemicraniectomy) reduces mortality and disability in patients who have a recent large infarct in the middle cerebral artery territory. To be effective, surgery should be performed before the occurrence of malignant infarct. The best selection criterion is the volume of abnormality on DWI performed within the first 24 hours, a volume of 145 cm³ being a good predictor for further malignant infarcts. Therefore, good candidates for surgery are those patients with severe ischaemic strokes below 60 years of age, who have > 145 cm³ of diffusion abnormality on MRI [6,36]. The effect of hemicraniectomy is important, the number of patients needed to be treated to prevent one death being 2. The Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY II) showed a benefit in patients aged 61 years or older, but less important than in younger patients [37].
Conclusion and perspectives

Cerebral ischaemia is an emergency, and the delay is absolutely crucial to have a better efficacy of treatments and less safety issues. Stroke unit case is the cornerstone of the management, and iv thrombolysis alone or in combination with mechanical thrombectomy are the most effective treatment to prevent death or dependency. Patients at risk of malignant infarct should be identified early, to be selected for decompressive surgery. Aspirin reduces the risk of early recurrences, but should not be given in the first 24 hours after thrombolysis. Future improvements may come from neuroprotective measures, especially hyperthermia, new thrombolytic agents with a higher selectivity for the thrombus, and pre-hospital management of stroke in equipped ambulances [38]. These ambulances may allow pre-hospital thrombolysis and selection of patients eligible for mechanical thrombectomy needing direct admission in appropriate centres.

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References


