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What is new in the management of the acute ischaemic stroke?

Co nowego w leczeniu ostrego udaru niedokrwiennego mózgu?

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Abstract

Stroke is a major challenge for medicine in the 21st century. Despite modern diagnostics and even revolutionary methods of treatment, stroke is still the main cause of permanent disability and the second cause of death worldwide. Recent clinical trials have led to a breakthrough in the treatment of stroke. On their basis, many scientific societies updated the guidelines for the management of stroke. We present the most important changes in prehospital care, emergency evaluation, in-hospital non-specific treatment and specific treatment with intravenous thrombolysis and endovascular therapies. The paper is based on the recent recommendations of American Heart Association/American Stroke Association; Canadian Stroke Consortium and the Canadian Association of Emergency Physicians; European Stroke Organisation and Polish Neurological Society. Problems related to the pre- and in-hospital management of patients with acute ischaemic stroke, with a particular emphasis on the dilemma on whether to bypass a primary stroke centre to transport the patient to a comprehensive stroke centre offering endovascular thrombectomy, and the problem of reducing door-to-needle time for intravenous thrombolysis are discussed. The recommendations for the treatment of arterial hypertension and hyperglycaemia in acute ischaemic stroke and the problem of extended time window for intravenous thrombolysis and endovascular thrombectomy are also discussed.

Keywords: ischaemic stroke, acute phase, most important changes in the guidelines

Streszczenie

Udar mózgu jest poważnym wyzwaniem dla medycyny w XXI wieku. Pomimo nowoczesnej diagnostyki i rewolucyjnych metod leczenia nadal stanowi główną przyczynę trwałej niepełnosprawności i drugą przyczynę śmierci na świecie. Wyniki badań klinicznych z ostatnich lat doprowadziły do przełomu w leczeniu udaru mózgu. Na ich podstawie wiele towarzystw naukowych zaktualizowało wytyczne dotyczące postępowania w udarze. W pracy przedstawiono najważniejsze zmiany w wytycznych związane z opieką przedszpitalną, oceną stanu chorego w ostrym stanie, postępowaniem wewnątrzszpitalnym, leczeniem nieswoistym i swoistym za pomocą dożylnej trombolizy i terapii wewnątrznaczyniowych. Jako podstawa naukowa wykorzystane zostały najnowsze zalecenia towarzystw: American Heart Association/American Stroke Association, Canadian Stroke Consortium i Canadian Association of Emergency Physicians, European Stroke Organisation oraz Polskiego Towarzystwa Neurologicznego. Omówiono problemy związane z postępowaniem przed- i wewnątrzszpitalnym u pacjentów z ostrym udarem niedokrwiennym, w szczególności związane z dylematem, czy należy omijać podstawowy oddział udarowy w celu przetransportowania pacjenta do centrum kompleksowego leczenia udaru, oferującego trombektomię wewnątrznaczyniową, oraz kwestię skrócenia czasu od drzwi do igły u chorych poddawanych dożylnej trombolizie. Przedstawiono również zalecenia dotyczące leczenia nadciśnienia tętniczego i hiperglikemii w ostrej fazie udaru oraz wydłużenia okna czasowego dla dożylnej trombolizy i trombektomii wewnątrznaczyniowej.

Słowa kluczowe: udar mózgu niedokrwienny, ostra faza, najważniejsze zmiany w wytycznych

INTRODUCTION

Stroke is a major challenge for medicine in the 21st century. Despite modern diagnostics and even revolutionary methods of treatment, stroke is still the main cause of permanent disability and the second cause of death worldwide (GBD 2013 Mortality and Causes of Death Collaborators, 2015; Mozaffarian et al., 2015). Recent clinical trials have led to a breakthrough in the treatment of stroke. On their basis, many scientific societies updated the guidelines for the management of stroke (Ahmed et al., 2017; Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018; Fiehler et al., 2016; Kobayashi et al., 2018; Powers et al., 2018). The changes concerned mainly prehospital care, emergency evaluation, non-specific treatment and specific treatment with intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). The key change in the guidelines is that selected patients may receive EVT up to 24 hours after stroke.
We present the most important changes introduced in the latest recommendations of American Heart Association/American Stroke Association, Canadian Stroke Consortium and the Canadian Association of Emergency Physicians and European Stroke Organisation for patients with acute ischaemic stroke (AIS).

PREHOSPITAL CARE

Emergency medical services (EMS), neurological experts and local, regional, and state agencies should cooperate to create triage protocols to facilitate rapid identification and assessment of patients with suspected stroke. It is recommended that all EMS technicians and paramedics are familiar with a simple prehospital stroke scale to identify potential stroke patients (Kobayashi et al., 2018).
In ischaemic stroke care, fast reperfusion is essential for disability free survival. The time between the onset of symptoms and the start of infusion of recombinant tissue plasminogen activator (rt-PA) (onset to needle time, ONT) is the single most important modifiable risk factor for stroke prognosis (Swartz et al., 2014). IVT with the administration of alteplase (rt-PA) is still the gold standard for the treatment of AIS (Ahmed et al., 2017; Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018; Fiehler et al., 2016; Kobayashi et al., 2018; Powers et al., 2018). Randomised controlled trials (RCTs) have consistently shown that EVT with stent retrievers with and without additional administration of IVT is superior to IVT alone in anterior circulation stroke patients with large artery occlusion, but there is insufficient evidence to recommend a prehospital stroke scale to predict large artery occlusion (LAO). Prehospital scales are inadequate to exclude LAO with certainty and many triage positive patients may not have LAO (Goyal et al., 2016). There is still insufficient evidence for the routine use of mobile emergency stroke units (Kobayashi et al., 2018).

A dilemma on whether to bypass a primary stroke centre (PSC) to transport the patient to a comprehensive stroke centre (CSC) offering EVT remains a major problem. PSCs with no access to computed tomography (CT) angiography (CTA) should have pre-planned arrangements for rapid transfer of selected patients. They should offer intravenous alteplase as appropriate and then rapidly transfer the patient to a CSC for more advanced imaging and EVT. The recommendations of the expert groups say that further research is needed before a definitive recommendation on whether bypassing thrombolysis centres in favour of EVT (mothership) outweighs the transport to the nearest thrombolysis centre for alteplase followed by transfer for EVT (drip-and-ship) can be made (Ahmed et al., 2017).

IN-HOSPITAL MANAGEMENT

The new guidelines recommend the establishment of a door-to-needle (DTN) time goal of ≤60 minutes in ≥50% of AIS patients treated with intravenous (IV) alteplase. A further decrease in DNT (45 minutes or lower) is postulated (Błażejewska-Hyżorek et al., 2019; Powers et al., 2018). In Canada, a target DNT of less than 60 min in 90% of treated patients, and a median DNT of 30 minutes are recommended (Boulanger et al., 2018). Hospitals should establish systems to allow for brain imaging within 20 minutes of arrival to the emergency department in ≥50% of patients for whom IV alteplase and/or thrombectomy may be indicated. Data from the American register of Paul Coverdell National Acute Stroke Program conducted under the auspices of American Stroke Association/American Heart Association, which collected data of approximately 500,000 patients, showed that the percentage of patients treated with DNT ≤45 minutes increased from 10.7 to 40.5 in the United States between 2008 and 2017 (Tong et al., 2018). An example of a perfectly functioning system of management in patients with acute phase of stroke is the Helsinki model, in which alteplase is administered in the CT laboratory (Meretoja et al., 2012, 2013).

NEURORADIOLOGICAL ASSESSMENT

The new recommendations define minimum criteria for neuroimaging. At a minimum, CT scanners should be available on a 24/7 basis to image patients with non-contrast CT and CT angiography. The availability of CT perfusion and/or magnetic resonance imaging (MRI) may also assist in patient selection for AIS beyond 6 hours from onset. Diagnostic radiologists/neuroradiologists with sufficient training and experience in the interpretation of these imaging studies shall be available on a 24/7 basis (Boulanger et al., 2018; Powers et al., 2018). A non-contrast CT scan or MRI should be used as first line initially to identify the presence and type of

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stroke – ischaemic or haemorrhagic. Although magnetic resonance diffusion (MRI-DWI) is more sensitive than CT in the detection of acute cerebral ischaemia, CT is more frequently used in clinical practice due to the lower cost of testing and better accessibility to acute service (Brazzelli et al., 2009; Chalela et al., 2007; Hwang et al., 2012; Wardlaw et al., 2014).

All patients with suspected AIS who arrive within 4.5 hours and are potentially eligible for IVT should undergo immediate brain imaging with non-contrast CT without delay to determine eligibility for thrombolysis. All patients with suspected AIS who arrive within 6 hours and are potentially eligible for EVT should undergo immediate brain imaging non-contrast CT and CTA without delay, from arch-to-vertex, including the extra- and intracranial circulation, to identify large vessel occlusions eligible for EVT. A validated triage tool, such as ASPECTS, should be used to rapidly identify patients who may be eligible for EVT treatment (Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018; Powers et al., 2018).

NON-SPECIFIC TREATMENT

Blood pressure control

The recommendations for the treatment of hypertension in the acute phase of ischaemic stroke were maintained. Both, high and low blood pressure (BP) in the acute phase is associated with stroke recurrence, death and poor functional outcome (Leonardi-Bee et al., 2002). The results of large clinical trials published in recent years did not show the benefits of lowering arterial pressure in AIS (ENOS Trial Investigators, 2015; He et al., 2014; Sandset et al., 2011). BP lowering is not recommended in patients with AIS who do not receive recanalisation therapy, unless patients present with very high BP (>220/120 mm Hg).

Data from the SITS register have point to associations between high systolic BP, both at baseline and after treatment, and symptomatic intracerebral haemorrhage (sICH) (Ahmed et al., 2009).

Current guidelines recommend the use of BP in patients treated with IVT thresholds from the clinical trials. It is suggested to maintain BP ≤185/110 mm Hg before treatment, and ≤180/105 mm Hg for the first 24 hours after treatment (Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018; Powers et al., 2018).

In patients treated with endovascular recanalisation, maintaining BP pre-, intra- and postprocedural BP ≤185/110 mm Hg is recommended (Boulanger et al., 2018; Powers et al., 2018). Currently, we have only reports from several observational studies and from the MR CLEAN trial. High intraprocedural BP, increases in BP after thrombectomy and large drops in BP are associated with poor long-term functional outcome (Boulouis et al., 2017; Goyal et al., 2018b; Schonenberger et al., 2018).

Glucose control

The presence of hyperglycaemia during the first 24 hours from stroke onset is independently associated with less favourable neurological outcomes and increased mortality risk for patients with AIS or ICH. Hyperglycaemia is an independent predictor for sICH and unfavourable clinical outcomes in patients with AIS treated with IVT, and is independently associated with adverse outcomes in patients with LAO treated with EVT (Goyal et al., 2018a; Lin et al., 2018).

A Cochrane meta-analysis of RCTs using insulin infusion to control hyperglycaemia in acute stroke highlights the lack of any clinical efficacy with an additionally increased risk for hypoglycaemic episodes (Bellolio et al., 2014). However, the American Heart Association/American Stroke Association guidelines suggest that hyperglycaemia in acute stroke patients may be treated as in any other hospitalised patients with a therapeutic target of 140–180 mg/dL using intravenous insulin therapy. Current international guidelines do not provide separate recommendations for hyperglycaemic patients receiving EVT.

All guidelines recommend that hypoglycaemia should be corrected immediately (Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018; Powers et al., 2018).

SPECIFIC TREATMENT

Extended time window for IVT

The results from the Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial demonstrated that selected patients with mild-to-moderate ischaemic strokes and an unknown time of symptom onset, treated with alteplase, may also benefit from treatment. Patients in this trial were selected on the basis of a pattern of diffusion-weighted imaging–fluid-attenuated inversion recovery (DWI-FLAIR) mismatch and the limited size of the diffusion focus (≤1/3 of the medial cerebral artery area, ≤1/2 the area of the anterior cerebral artery and ≤1/2 of the posterior cerebral artery area) (Thomalla et al., 2018). Therefore, IVT is recommended for patients with an unknown onset time presenting of a DWI-FLAIR-mismatch on acute MRI and meeting other criteria from the DOWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial (Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018).

Endovascular thrombectomy

Enlarged time window for EVT

EVT has been proven to be effective in LAO in the anterior cerebral circulation within the first 6 hours

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of stroke onset (Goyal et al., 2016). However, two prospective trials showed its high efficacy up to 24 hours after suspected symptom onset with careful patient selection (Albers et al., 2018; Nogueira et al., 2018).

The DAWN trial investigated the safety and efficacy of EVT performed 6–24 hours after the onset of ischaemic stroke, including wakeup strokes, and the mismatch was defined according to the clinical deficit, age and infarct volume. Infarct volume was assessed with the use of diffusion-weighted MRI or perfusion CT and was measured with the use of automated software (Albers et al., 2018). In DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke), the patients, last known to be well between 6 and 16 hours, were included using automated software to detect the initial infarct volume, with AIS and internal carotid artery (ICA) or M1 segment of the middle cerebral artery occlusion and a target mismatch on multimodal CT or MRI (Nogueira et al., 2018). Therefore, perfusion/core imaging is required in the 6–24 hours window, with a clinical and imaging profile similar to patients included in DAWN/DEFUSE (Błażejewska-Hyżorek et al., 2019; Boulanger et al., 2018; Powers et al., 2018).

Excellent results of WAKE-UP, DOWN and DEFUSE 3 trials have given a chance to treat patients previously out of reach for reperfusion therapy and have opened a new chapter in the treatment of AIS.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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