Current advances in ischemic stroke management

Justyna Żyga[1]

[1]Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego w Lublinie

Corresponding author: Justyna Żyga
email: 1996.zyga@gmail.com
ORCID: 0000-0001-5453-1235

Abstract

Stroke is one of the leading causes of morbidity and mortality worldwide with 24.1 million new stroke cases in 2017 and 700,000 more stroke-related deaths, as compared to 2016. Although some patients recover after a stroke, the significant majority continue to have numerous health problems resulting in substantial decrease of life quality. This article reviews the evaluation and the current advances in the management of acute ischemic stroke, starting in the prehospital setting followed by stroke hospital management.

Conclusions: Appropriate treatment of ischemic stroke is essential in the reduction of mortality and morbidity. Therapeutic methods have greatly expanded beyond the utility of intravenous thrombolysis, with more advanced and complex techniques. Mechanical thrombectomy has revolutionised the management through the clot retrieval techniques improving patient outcomes. Appropriate application of the available treatment methods is crucial to optimising outcomes of patients with stroke, starting from pre-hospital accurate assessment. High-quality care of patients with ischemic stroke requires efficient cooperation of multidisciplinary medical staff.

Keywords: ischemic stroke, mechanical thrombectomy, neurology, cerebral stroke

Introduction

A stroke is defined as an acute neurological disorder of the blood vessels in the brain that occurs when the blood supply to an area of the brain stops and the brain cells are deprived of the necessary oxygen. In the United States, 87% of all strokes are ischemic, while intracranial haemorrhage and subarachnoid haemorrhage represent 10% and 3% of all strokes [1]. The main risk factors for stroke comprise hypertension, hypercholesterolemia, smoking, obesity, diabetes, and cardiac arrhythmia [2]. Both in Europe and the US, stroke has been the leading neurological disease in terms of disability-adjusted life years (DALY) resulting in substantial financial

burden on health services and societies. Although some patients recover after a stroke, the vast majority continue to have problems depending on the severity of the stroke. Those complications include various memory, concentration and attention problems, difficulties with speaking or understanding speech, depression and other emotional problems, loss of the ability to walk, sensation and difficulty with swallowing food [3].

Burden of stroke worldwide

Stroke is one of the leading causes of morbidity and mortality worldwide. The burden is increasing despite incredible progress and advancements in stroke management. The Global Burden of Disease studies have estimated that in 2017 there were 24.1 million new stroke cases, 15.7 million additional DALYs and 700,000 more stroke-related deaths, as compared to the previous year [4]. Both in Europe and the US, stroke has been the leading neurological disease in terms of DALYs, more prevalent in the elderly. The financial burden of stroke on health services and societies in Europe is enormous - it is estimated that informal care amounted to €1.3 billion, the cost for health care was €27 billion, while the cost due to lost productivity was €12 billion in 2017 [5].

Causes of ischemic stroke

As mentioned before, strokes are generally divided into ischemic and hemorrhagic. Further, ischemic stroke can be subdivided based on cause. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) is a classification system developed to categorise causes of acute ischemic stroke in order to guide management decisions: [6]
- Large artery atherosclerosis (embolus of thrombosis)
- Cardioembolic
- Small vessel occlusion (lacune)
- Stroke of other determined cause, or unusual cause
- Stroke of undetermined cause

COVID-19 is a multi-system infection which predominantly affects the respiratory system, but also causes systemic inflammation, endothelialitis and thrombosis. Higher risk of vascular incidents was observed in most severely infected patients and those with pre-existing risk factors - particularly older age and comorbidities. The review of 145 papers show that the pattern of stroke differed from that in a non-COVID-19 stroke population. Most of them were ischemic, and there was an increase in large vessel occlusion and multiple territory infarcts suggesting that increased thrombosis and thromboembolism could be possible causative pathways for the disease [7].

Diagnosis - "Time is brain"

There are several scales used to assist medical staff in identifying patients with large vessel occlusion. Identification is the crucial first step in getting the right patient to the right management pathway more quickly and, as the outcome depends on time to reperfusion, might improve outcomes. The meta-analysis of nineteen scoring systems suggested that the stroke Vision, Aphasia, Neglect assessment (VAN), the National Institute of Health Stroke Scale (NIHSS) and the Los Angeles Motor Scale (LAMS) had the best predictive value [8]. NIHSS is a 42-point systematic assessment tool that should be performed within 10 minutes of the arrival of the patient to the emergency department. It helps in fast quantification of the severity of stroke-related neurological deficits. The NIHSS provides insight into the location, the underlying aetiology (cortical versus lacunar) of the stroke and it objectively assesses the neurological status of the patient after reperfusion therapy [9, 10].

All patients with suspected ischemic stroke must have emergent brain imaging, and in most situations a non-contrast head computed tomography scan is sufficient for initial management. In the majority of cases, the first 24 h are crucial. Computed tomography (CT) must be done before thrombolytic treatment of hyperacute ischemic stroke, but the significance of early ischemic change on CT is unclear. The Alberta Stroke Program Early Computed Tomography

Score (ASPECTS) objectively quantifies, topographically, ischemic changes in the anterior circulation on CT of the head and identifies patients who are unlikely to recover after reperfusion therapy. An ASPECTS of 0 points indicates extensive ischemic changes, while a normal CT image is rated at 10. According to a study evaluating the utility of ASPECTS, its score ≤7 was associated with functional dependence and death at three months, and a predicted functional outcome with a sensitivity of 78% and specificity of 96% [10]. This CT score is simple, reliable and identifies stroke patients unlikely to independently recover despite thrombolytic treatment [11].

The fields of artificial intelligence (AI) and machine learning (ML), now play an important role in the early prediction of various diseases. A systematic review of twenty studies found that some versions of AI have good predictive power to increase accurate stroke diagnosis. Variations of AI, including ML methods of random forest learning and convolutional neural networks were used. Comparison of variable AI programs and human analysis show that algorithms based on machine learning are faster than physicians, with better accuracy and efficacy. AI used to assist in interpretation of traditional stroke imaging outputs may reduce false-negative human errors in image interpretation, increase efficiency of stroke triage, and therefore minimise neuronal death and long-term morbidity and mortality. However, diagnosis of acute stroke by AI has not yet been perfected and errors still exist. The most often reported reasons for failure include radiologic scan abnormalities from concomitant brain injury, inadequate contrast boluses, artefacts resulting from patient motion and tortuous vessels. Authors conclude that AI applied to stroke diagnosis has the potential to improve healthcare. There still remains a lack of randomised controlled trials comparing AI software. Standardised methods for validation and comparison of this class of tools are needed for further studies [12].

Management of acute ischemic stroke
The three main principles of acute stroke care include achieving timely recanalization of the occluded artery with reperfusion of the ischemic tissue, optimising collateral flow and avoiding secondary brain injury. The management of acute ischemic stroke starts with the prompt recognition of the diagnosis in the field. The primary therapeutic goal during acute stroke management is the timely restoration of blood flow to the salvageable ischemic brain tissue at risk for cerebral infarction. Reperfusion strategies are the most effective interventions for acute ischemic stroke. The treatment also includes adequate hemodynamic management, monitoring of ischemic brain edema and early recognition of systemic complications such as infections, cardiac arrhythmias, heart failure or venous thromboembolism [13]. The two evidence-based approaches to reperfusion are chemical thrombolysis with intravenous recombinant tissue plasminogen activator and endovascular thrombectomy with retrievable stent [10].

Recombinant tissue plasminogen activator
The use of recombinant tissue plasminogen activator is subject to strict indications, in which time plays an important role. The initial evaluation of a patient with a possible acute stroke should focus on establishing whether the patient is eligible for reperfusion therapy. Necessary information includes the time the patient was last known to be well, medical conditions or recent surgery that would contraindicate thrombolysis, neurologic examination to calculate the NIHSS score, a capillary glucose level, blood pressure and brain imaging [10, 14]. The United States Food and Drug Administration (FDA) has only approved recombinant tissue plasminogen activator for use within 3 hours of stroke onset, but regulatory agencies in most other countries (including those in the European Union) have approved its administration within 4.5 hours of stroke onset - it is the time when the patient was last seen healthy. The sooner alteplase is administered, the greater chances of recanalization are obtained, therefore fast clinical diagnosis plays a significant role. It should be underlined that stroke incidents in one-third cases occur during sleep. The patient notices symptoms only after waking up and it is usually too late for pharmacological treatment. The use of alteplase at this moment is associated with significant risk of inducing a hemorrhagic stroke due to extent of damage to the brain tissue [13].

Intracranial haemorrhage is the most devastating complication of fibrinolisis associated with increased risk of morbidity and mortality outcomes. The rate of intracranial haemorrhage was reported to range from two to seven percent with most of the events developing within 36 hours after infusion. Detailed diagnostics and strict adherence to the guidelines minimise this percentage [13, 15]. No other thrombolytic agent has been approved for use in ischemic stroke. Similarly the routine use of low-molecular-weight heparins, heparinoids and thrombin inhibitors is not recommended. No evidence shows that anticoagulants reduce the odds of death. Despite possible prevention of recurrent stroke, deep vein thrombosis and pulmonary embolism, the risk of serious haemorrhages increases significantly, thus the potential complications outweigh their benefits [16]. While alteplase is the only licensed thrombolytic FDA agent for ischemic stroke, tenecteplase has potential advantages over the former agent in having greater fibrin sensitivity, a longer half-life and lower costs. In randomised-control trials tenecteplase have been shown to be at least effective as alteplase for neurological improvement [17].

Endovascular treatment - mechanical thrombectomy
Mechanical thrombectomy procedure provides an access through blood vessels to the clot for its fragmentation and extraction, resulting in restoration of circulation in the affected area. Thrombectomy is reserved for patients who can still be treated before the onset of necrosis - also in case of contraindications for thrombolytic treatment. The treatment window usually covers the first 6 hours for strokes of the anterior circulation area, while for the posterior area it is 8-12 hours [14]. Two clinical trials disrupted the time window concept in acute ischemic stroke, showing excellent clinical outcomes in patients treated up to 24 hours from symptom onset [18, 19].
Mechanical thrombectomy is of benefit to most patients with acute ischemic stroke caused by occlusion of the proximal anterior circulation. In five randomised-control trials, a total of 1287 patients with acute ischemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 hours of symptom onset or standard care, with a primary outcome of reduced disability on the modified Rankin Scale at 90 days. All of these trials favour thrombectomy for patients with acute ischemic stroke with large vessel occlusion, which can significantly improve patients' 90-day outcomes compared with standard care [20]. Despite promising outcomes, there are numerous and strict indications and contraindications for thrombectomy that should be taken into account before intervention [21].
The long-term outcomes of acute large vessel occlusion in anterior circulation treated by endovascular treatment was assessed in the 5-year observational study of patients who received thrombectomy in 28 comprehensive stroke centres in China. At 5 years, out of 657 patients, 190 of them (28.9%) had an excellent outcome, 261 patients (39.7%) had a favourable functional outcome, 317 patients (48.2%) died and 129 (28.2%) had stroke recurrence. Multivariate analyses identified that younger age, lower modified Rankin Scale score at 90 days and absence of stroke recurrence were significantly associated with favourable outcome at 5 years. Those results indicated that the beneficial effect of endovascular treatment in patients with acute large vessel occlusion can be sustained for at least 5 years. Authors conclude that reducing the risk of stroke recurrence by anticoagulation for atrial fibrillation may be a crucial strategy to improve long-term outcome [22].

Sphenopalatine ganglion stimulation
Many patients with acute ischemic stroke are not eligible for thrombolysis or mechanical reperfusion therapies due to contraindications, inaccessible vascular occlusions, late presentation, or large infarct core. Sphenopalatine ganglion (SPG) sends parasympathetic innervations to the anterior cerebral circulation. The benefit of SPG stimulation in acute ischemic stroke is likely conferred not only by potent collateral augmentation, but also blood-barrier stabilisation, direct neuroprotection, and neuroplasticity enhancement with reduction of infarct size. It offers an alternative, potentially more widely deliverable, therapy.

A review of 26 pre-clinical and clinical studies found that sphenopalatine ganglion stimulation is safe with very minimal reports of treatment-associated adverse events. It can be indicated for patients with acute ischemic stroke who are ineligible for thrombolytic therapy. An increase in cervico-cranial blood flow and improvement in hand motor function has been found. The results indicate that SPG stimulation can be deployed in a simple and practical manner in the clinical setting, moreover it can augment and improve the applicability of mechanical thrombectomy and fibrinolysis. Further studies clarifying the relative contribution of these mechanisms and the stimulation protocols that maximise each may help optimise SPG stimulation as a therapy for acute ischemic stroke [23].

Macrophage inhibitory factor

The mechanism of the macrophage migration inhibitory factor (MIF) is about exerting a neuroprotective effect by inducing brain-derived neurotrophic factor (BDNF) expression and reducing apoptosis. Kim et al. investigated whether the MIF promotes neurological recovery in an in vivo mouse model of ischemic stroke. Mice models of middle cerebral artery occlusion received the MIF via the intracerebroventricular route. Administration of MIF was associated with significantly reduced total infarct volume. Expression levels of BDNF and MAP2 tended to be higher in contrast to the control group. The MIF exerts a neuroprotective effect in an in vivo ischemic stroke model. The MIF facilitates neurological recovery and protects brain tissue from ischemic injury, indicating a possibility of future novel therapeutic agents for stroke patients [24]. Another study performed on 40 rat models was aimed to investigate the effects of early treadmill exercise on recovery from ischemic stroke and to determine whether these effects are associated with the expression levels of MIF and BDNF in the ischemic area. The results demonstrated that early exercise (initiated 48 hours after the middle cerebral artery occlusion) could improve motor and neuronal recovery after ischemic stroke [25].

Summary

Appropriate treatment of ischemic stroke is essential in the reduction of mortality and morbidity. Management of stroke involves a multidisciplinary approach that starts and extends beyond hospital admission. Therapeutic methods have greatly expanded beyond the utility of intravenous thrombolysis, with more advanced and complex techniques. Initiation of the use of mechanical thrombectomy has revolutionised stroke management through the clot retrieval techniques improving patient outcomes. Appropriate application of the available methods is crucial to optimising outcomes of patients with stroke, starting from pre-hospital accurate assessment. As time plays the most important role, further studies are needed in developing effective assessment of patients for rapid clinical decisions and management with proper treatment methods.

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