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A review on emergency stroke therapy with particular emphasis on thrombolysis, endovascular stroke management and organization of acute stroke care

Introduction

The US Food and Drug Administration's 1996 approval of intravenous tissue plasminogen activator (tPA) as the first approved drug therapy for acute ischemic stroke was a landmark event, changing the way strokes are treated in the US and throughout the world (1). The 2 NINDS tPA trials, initially planned as independent phase II studies, but reported together, demonstrated a benefit for patients treated within the first 3 hours after stroke onset. The efficacy of thrombolytic therapy in acute ischemic stroke is based on restoration of blood flow. Several investigations suggest that only about 30% of cerebrovascular occlusions, varying on the location, respond to intravenous tPA (2). The unexpected low rate of recanalization may be explained by clot composition, re-occlusion caused by excessive thrombin-related platelet activation, or atherothrombotic interactions in cases of local atherosclerotic plaque rupture. The clinical response rate is even lower, only 10-15% of patients entirely remit their presenting deficits. It is therefore assumed that many patients experience the advantage of reperfusion too late in their individual time courses of tissue demise. As a result of these assumptions direct endovascular approaches, novel thrombolytic agents and platelet inhibitors, as well as adjunct procedures are being put to test.

It is generally believed that when a cerebral artery occludes, a core zone supplied by the blocked artery undergoes profound ischemia and rapidly progresses to irreversible infarction. In contrast, a surrounding region, known as the ischemic penumbra, experiences more moderate ischemia and remains potentially salvageable for several hours. The penumbral zone consists of stunned but still viable neurons, the survival of which critically depends on the degree and duration of the ischemia and individual resilience among cell populations (3). Although, the individual time window remains unknown, from clinical experience the time is up for many patients within 3 hours but some patients for reasons that remain unknown improve after reperfusion as late as 8-9 hours after stroke onset (4).

Stroke physicians also recognize the potential hazards of thrombolytic therapy in acute ischemic stroke, in particular hemorrhagic complications. In addition, patients presenting with acute ischemic stroke symptoms often have contraindications to thrombolytic agents. As a result of this, various alternative approaches to restoring blood flow to the ischemic territory are being devised. This review was written to provide the stroke community with an understanding of current stroke interventions, recent promising developments in the field of mechanical device therapies for acute ischemic stroke as well as a systematic review of supportive measures. It furthermore outlines how acute stroke care needs to be organized in order to benefit the patients.

Supportive therapy

Because the therapeutic window for treating acute stroke is so narrow, currently 3 hours for intravenous (1) and up to 8 hours for endovascular approaches (5), prompt evaluation and sound supportive measures are critical components of success. Analogous to strategies targeted towards acute treatment of heart attacks, pathways for rapid evaluation of potential stroke patients are recommended for hospitals and emergency response systems (6). The initial patient contact should determine the time of onset, assess the clinical deficit by using the NIHSS stroke scale and perform a basic physical and laboratory evaluation. Expedited brain imaging with CT or MR is another critical element in the work-up. The time from door to brain imaging, the time sensitive phase prior to treatment in the hospital should not exceed 30 minutes. The choice

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of imaging depends on availability and may vary from plain CT to most sophisticated MR-diffusion/perfusion and magnetic resonance angiography-imaging mainly geared to rule out conditions that may contraindicate thrombolytic therapy. Attempts to stratify patients according to tissue viability and possible recovery prior to treatment initiation by MR technology, although sound in theory, have been all but disappointing in clinical practice to date.

Preservation and recovery, the cornerstone concepts of the emergency treatment of the cerebral ischemia commences with the initial contact with the patient. From this point of view, the currently available methods to achieve this goal include 1.) blood-flow augmentation to the brain, 2.) sufficient oxygenation, 3.) maintaining normothermia and euglycemia, and 4.) flow-restoration. Methods to introduce neuronal protection during the vulnerable phase of ischemia have so far been unsatisfactory and will not further discussed in this review.

Blood-flow augmentation to the brain and blood pressure

Traditional thinking suggests that brain perfusion depends on systemic blood pressure. Although, measures associated with rising systemic blood pressure usually also increase cardiac output and intravascular volume, it is the systemic blood pressure that is considered the principle and only link between the cardiovascular system and brain perfusion by most experts. Several recent investigations have revealed that bloodflow can be re-directed without changes in systemic blood pressure, for instance athletes can divert blood into their muscles during peak exercise without blood pressure changes (7). It has also become evident that blood can be directed away from the brain, for instance an intra-aortic balloon pump supports the heart by diverting blood away from the brain into the coronaries (8). Another maneuver is retrograde transvenous perfusion, a technique used for brain protection during cardiothoracic surgery in circulatory arrest. This method was also devised for ischemic stroke in the 1990s. Arterial blood from the femoral artery is continuously circulated into the intracranial sinuses via balloon-tipped catheters by an external pumping system in an experimental model of cerebral ischemia. Although, the method appeared safe it was ruled too challenging in a small clinical trial involving human patients (9). Another approach that is currently tested in a phase II clinical trial involves an aortic obstruction device positioned into the abdominal aorta increasing vascular resistance with subsequent increase in brain perfusion. Although, no clinical data have yet become available, the method is less challenging and appears to safely increase brain perfusion without increasing the systemic blood pressure. We are currently investigating the relationship between fluid status, cardiac output and cerebral blood flow by comparing non-invasive cardiac output parameters with continuous transcranial Doppler monitoring and assess the impact of volume challenges as opposed to blood pressure changes on brain perfusion in stroke patients.

Sufficient oxygenation to the brain

Maintaining adequate tissue oxygenation is important in the setting of acute cerebral ischemia. The goals are to prevent hypoxia and potential worsening of the brain injury. The most common causes of hypoxia are partial airway obstruction, hypoventilation, aspiration pneumonia, and atelectasis. Patients with decreased consciousness or signs of brain stem dysfunction have the greatest risk of airway compromise because of impaired oropharyngeal mobility and loss of protective reflexes (10). The prognosis of patients who require endotracheal intubation generally is poor; ~50% of these patients are dead within 30 days after stroke (11). Pneumonia is among the leading complications of stroke and is an important cause of death. It is most likely to develop among patients who are seriously ill, and prevention of early aspiration and protection of the airway may be a way to ameliorate this complication. Elective intubation should be considered in the management of patients with acute basilar occlusions as well as those patients with large hemispheric infarcts at risk to develop malignant brain edema after stroke. The elective intubation for patients with acute ischemic stroke undergoing endovascular procedures is discussed controversely. No clinical trial has yet tested the utility of endotracheal intubation in the management of critically ill patients with stroke, and I anticipate that none will be done. It is generally agreed upon that an endotracheal tube should be placed if the airway is threatened (12).

The routine use of oxygen supplementation is also discussed controversially. A small pilot study found that high-flow oxygen may be associated with a transient improvement in neurological impairments (13). The results of a controlled study do not support the use of supplemental oxygen at 3 L/min for most patients with acute ischemic stroke (14). Nevertheless, patients with acute stroke should be monitored with pulse oximetry with a target oxygen saturation level >92%.

Hyperbaric oxygen is used to treat patients with ischemic neurological symptoms secondary to air embolism such as in diving accidents. Studies that have looked into the general use of hyperbaric oxygen as a neuroprotectant in stroke patients have been inconclusive, negative, or suggested even harmful effects. A systematic review confirms the lack of evidence that hyperbaric oxygen improved outcomes after stroke or brain injury (15) At present, data do not support the use of hyperbaric oxygen in the treatment of patients with acute ischemic stroke symptoms (16). Whether there is a role of hyperbaric oxygen to prevent late effects of chronic ischemia, such as vascular dementia, is possible but presently unknown.

Temperature and Glucose

Increased body temperature (fever) in the setting of acute ischemic stroke is associated with poor neurological outcome (increased risk of morbidity and mortality), although the reasons remain unclear. Fever may be secondary to the stroke, its cause, such as infective endocarditis, or may be the result of a complication, such as pneumonia. Because of the negative effects observed with fever, lowering an acutely elevated body temperature might improve the prognosis of patients with stroke (17). Measures include antipyretic medications and cooling devices. Small clinical trials have tested the utility of aspirin, ibuprofen, or acetaminophen in lowering body temperatures and in improving outcomes after stroke. Some studies found that either aspirin or acetaminophen was modestly successful in achieving normothermia but the effects are not likely to have a robust clinical impact (18). Although treating fever after stroke makes intuitive sense, no data demonstrate that the use of medications to lower body temperature among either febrile or afebrile patients improves neurological outcomes after stroke. Seeking and treating the source of fever are reasonable.

Hypoglycemia may produce neurological signs that mimic ischemic stroke and should always been considered in patients presenting with focal neurological deficits. Hypoglycemia may lead to brain injury and should therefore be promptly corrected.

Hyperglycemia is detected on admission laboratory panels in approximately one third of patients with stroke (19) Elevations of blood glucose concentration in non-diabetic patients may simply represent a stress response, however, clinical studies suggest an association with poor outcomes after ischemic stroke. The detrimental effects of hyperglycemia are not clearly understood but may worsen reperfusion injury including hemorrhagic transformation of the infarct (20). Recent clinical and imaging studies have also highlighted the detrimental effects of hyperglycemia in stroke. Baird et al (21) found volume expansion of ischemic stroke on imaging studies and poor neurological outcomes in patients with persistent hyperglycemia (blood glucose level >200 mg/dL) during the first 24 hours after stroke. These reports provide reasonable evidence that persistent elevations of blood glucose levels could be harmful and suggest that correction of hyperglycemia is important in the acute management. However, similar to temperature management, the clinical relevance of maintaining strict euglycemia and the targeted level of blood glucose remain unknown. Several studies have looked into the utility of intensive insulin protocols in managing critically ill patients and demonstrated benefit, such as reduction in death and complications, including infections and renal failure, with aggressive management of hyperglycemia. In contrast, the recent GIST-UK trial, although underpowered due to lack of enrollment, found no relevant clinical benefit of variable-dose insulin versus placebo in patients presenting within 24 hours of stroke onset (22). Thus, currently, a reasonable empiric approach is to correct patients with a blood glucose level exceeding 200 mg/dL (11.1 mmol/l (Red.)).

Flow-restoration.

Intravenous thrombolytic therapy.

Within the "magic" 3 hours.

The concept of thrombolytic therapy is based on the fact that flow restoration requires viable brain tissue to attain a clinical benefit. The time since onset of stroke symptoms is the commanding variable for the medical management of patients with acute cerebral ischemia. It is accepted by most that this time is variable, maybe as long as 12 hours - in some patients - rather than exactly three hours and depends on patient as well as stroke characteristics. Unfortunately, efforts to determine a biological rather than a chronological time window are still in their infancy. Until a biological threshold can be well assessed we adhere to the time-window when stratifying patients to a particular intervention. While with each minute the viability of the brain tissue to be rescued diminishes the odds for reperfusion injury to hemorrhagic conversion likewise increase with time elapsed. The delicate balance of gain and harm explains the initial apprehension of many physicians towards thrombolysis for acute stroke patients. Over the past 12 years, however, most of these initial concerns have disappeared because the benefit far outscores the harm if thrombolysis is conducted mindfully (23).

Thrombolytic therapy with rtPA (0.9 mg/kg body weight, maximum dose 90mg) given within 3 hours after stroke onset, significantly improves outcome in patients with acute ischemic stroke (1): the NNT to achieve a favorable clinical outcome after 3 months is 7. By contrast, the ECASS (European Cooperative Acute Stroke Study) and ECASS II studies did not show statistically significant superiority of rtPA for the primary endpoints when treatment was given within 6 hours (24, 25). Trials with rtPA, involving a total of 2,889 patients, have shown a significant reduction in the number of patients with death or dependency (OR 0.83; 95% CI 0.73-0.94) (26). A pooled analysis of individual data of rtPA trials showed that, even within a 3-hour window, earlier treatment results in a better outcome (0-90 min: OR 2.11; 95% CI 1.33 to 3.55; 90-180 min: OR 1.69; 95% CI 1.09 to 2.62) [386]. This analysis suggested a benefit up to 4.5 hours, currently under investigation in the ECASS III trial. In the NINDS (National Institute of Neurological Disorders and Stroke) Study the presence or extent of early infarct signs had no effect on treatment response within the 3-hour time window (27). Nevertheless, European regulatory agencies do not advocate rtPA treatment in patients with extended early infarct signs on CT-scan, very severe neurological deficits (NIHSSS >25), or age above 80 years.

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise and brain CT is assessed by an experienced physician. Whenever possible, the risks and benefits of rtPA should be discussed with the patient and family before treatment is initiated. Blood pressure must be below 185/110 mmHg before, and for the first 24 hours after thrombolysis.

Sonothrombolysis.
Continuous transcranial ultrasound was associated with an increased rate of early recanalization after rtPA in a small randomized trial (2); this effect was also observed in the CLOTBUST study, in which transcranial Doppler monitoring for 2 hours with tPA therapy tripled the chance of complete and sustained recanalization. This early augmentation of reperfusion resulted in a trend toward favorable clinical recovery and may be further facilitated by the administration of microbubbles (28). However, a randomized clinical trial has recently been terminated for undisclosed reasons.

Beyond 3 hours.
Intravenous rtPA may be of benefit also for acute ischaemic stroke beyond 3 h after onset, but is not recommended in clinical routine. The results of the presently last study attempting to extend the 3 hour time window (ECASS III) was presented at the 6th World Stroke Congress in Vienna, September 24-27th 2008. The use of multimodal imaging criteria may be useful for patient selection, however, new imaging tools have not been able to identify subgroups that benefit from iv-thrombolysis beyond 3 hours of onset in clinical trials.

Although, available data on mismatch and vascular patency, as defined by multimodal MRI or CT, are still too limited to guide patient selection in clinical practice, they may very well facilitate endovascular therapy in those patients ineligible for iv-thrombolysis.

Novel endovascular approaches to reperfuse occluded cerebral arteries and maintain patency

The goal to rapidly and effectively dissolve clots by delivering thrombolytic agents directly into the thrombus was studied by the PROACT study group and although it has not resulted in approval of an intra-arterial thrombolytic it has led to the promotion of endovascular interventions (29). Although, presently, possible clinical benefits associated with more effective clot clearance may be counterbalanced by delays to initiating treatment.

With the evolving concept of interventional management of stroke, several options of multimodal reperfusion therapy are being evaluated. Options include emergency angioplasty and stenting as well as mechanical disruption or extraction of the thrombus. Such mechanical interventions are usually performed in combination with either "bridging" intravenous or intra-arterial thrombolysis. It is now accepted by most interventionalists that procedures need to be tailored to clinical scenarios in an individual patient. Time-window, stroke size and location, as well as severity among other patient characteristics are considered when planning the approach (30).

Besides the challenge to reperfuse the target vessel, sustained arterial patency and forestalling distal embolization are intended. An array of devices has become available in recent years to aid with these tasks. Several clot-retrieving devices to grasp and physically remove clots have become available. Among them, the MERCI clot retriever (Concentric, Mountain View, CA) has become the gold standard since it received labeling to remove clots from intracranial arteries in the USA (5). Another method employs clot aspiration PENUMBRA aspirator system (Penumbra, Alameda, CA) (31). The EKOS catheter (EKOS Corporation, Bothwell, WA) that employs the concept of local sonothrombolysis is currently in clinical stud-

The MERCI clot retriever has become the gold standard since it received labeling to remove clots from intracranial arteries

ies (32). Several other devices, including microsnares and other retrieval devices are used off-label or are under investigation. Furthermore, placement of both balloon-mounted and self-expanding stents is successfully performed in conjunction with thrombolytic therapy or physical clot retrieval (33-35). The rationale for acute stenting is the prevention of vessel reocclusions that occur after reperfusion with other modalities. Recent reports have established stent placement as an independent predictor of recanalization of both intracranial and extracranial acute cerebrovascular occlusions (36). Steady improvements of neurointerventional equipment have produced self-expanding stents for intracranial applications. In comparison to traditional balloon-mounted stents they can be navigated through the cerebral vasculature with more ease deployed much more gentle with sufficient radial force at significantly lower pressures than balloon expandable stents.

In 2005, a self-expanding reconstrainable nitinol stent system for intracranial use has been introduced (ENTERPRISE, Cordis Neurovascular, Miami, FL) (34). The particular advantages of this system are rapid access to the intracranial target vessel by delivery through a standard microcatheter and the possibility of recapturing and redeploying the stent after partial initial deployment. The system acts as a temporary endovascular bypass through the clot while aiding in its resolution at the same time. The concept of using a reconstrainable self-expanding stent as a temporary device in the setting of acute stroke is novel and may prevent some of the feared stent-related complications, such as stent stenosis/thrombosis, subarachnoidal or parenchymal hemorrhages and avoid prolonged multiple antiplatelet agent therapy. For the moment, the usefulness of mechanical endovascular procedures other than the MERCI device for treating intracranial artery occlusions has not been established to date.

Organization of acute stroke care

Great strides have been made in particular in Scandinavian countries by means of organizing stroke care within hospitals. Guidelines are followed by standardized protocols and attention is drawn to early systematic rehabilitation in “stroke-units”, which have been adapted throughout the world (37). Numerous studies have shown and continue to show the robust effects on survival and functional outcomes of stroke patients are attained by the organization of stroke care. Although, the reasons are not fully understood, much of the benefit relates to fewer complications observed in these patients. Reduction of thrombembolic and infectious impediments along with early systematic rehabilitation efforts have greatly impacted the in-hospital death rate, length of stay and discharge disposition of stroke patients. Challenges for the future remain the organization of acute stroke care to enhance reperfusion while protecting viable brain tissue and ameliorating reperfusion injury (6). A major obstacle is and will always be the recognition of stroke symptoms by patients and bystanders. The patients, often elderly, unsupervised, either too incapacitated by the symptoms or unable to realize the seriousness of the situation often do not call attention to their medical emergency thus missing out on the opportunities of acute stroke management. Another issue, the prompt recognition of stroke symptoms by paramedics and emergency personal has much improved since attention and coverage of modern stroke therapies by the mass media. Delivery and receiving of acute stroke patients has yet to be enhanced and standardized in most communities. The precedence that should be followed in developing an acute stroke response system is the out-of-hospital and hospital management of cardiac emergencies. Cardiac emergencies are effectively screened and triaged by emergency personal for possible interventions. Pre-specified protocols, such as those dealing with myocardial infarction, identify clinical scenarios suitable for intravenous thrombolysis versus percutaneous cardiac interventions and deliver patients to the appropriate institution for rapid management, curtailing the time interval from onset to treatment (38-42). The fundamental difference between emergency management of myocardial infarction and stroke presently is the necessity of hospital brain imaging before initiating thrombolytic therapy in patients with stroke. Nevertheless, the design of an effective stroke response model should integrate triaging to different institutions with supportive in-the-field measures. Currently, emergency responses provided to patients with suspected cardiac arrest might best exemplify the ideal stroke response system. When a cardiac arrest is called in first responding paramedics provide ACLS and may be joined by a physician if necessary. Successful resuscitated patients that regain consciousness are transported to the next available facility for further cardiac care those who remain unconscious are transported to a dedicated institution providing comprehensive care, including adjunctive therapeutic cooling (43-45). In the same manner, patients with acute stroke have to be triaged in the field and delivered to a hospital for a primary response, i.e. intravenous thrombolysis if they meet prespecified criteria or to a comprehensive center to receive care at the highest level, including endovascular procedures and critical care if necessary.

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