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Perspective

Hyperacute management of ischemic strokes, a British perspective

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Abstract: Stroke is a common disease that has a high rate of mortality and morbidity. The World Stroke Organization states that there are over 12.2 million strokes a year, with 1 in 4 people over the age of 25 predicted to have a stroke in their lifetime. The British data shows that there are around 150,000 stroke related admissions every year in the UK, with strokes occurring at an increasing earlier age. Strokes are generally classified as ischemic or hemorrhagic, with approximately 83% of all patients presenting with an ischemic stroke. The aim of this article is to provide an overview of the acute management of ischemic stroke in our center—a secondary care specialist hospital in the Northeast of England, with approximately 1000 stroke admissions a year.

Keywords: ischemic stroke; intravenous thrombolysis; endovascular thrombectomy; decompressive hemicraniectomy; atrial fibrillation; venous thromboembolism prophylaxis

1. Introduction

Time is brain [1]. Whilst this is cliché, it does underline the importance of prompt identification and acute treatment of stroke patients. All suspected stroke related admissions in England should have urgent neuroimaging within 1 hour. This helps to identify a hemorrhagic stroke or other obvious pathology e.g., trauma with subdural hemorrhage, or a large space occupying lesion etc., see Figure 1.

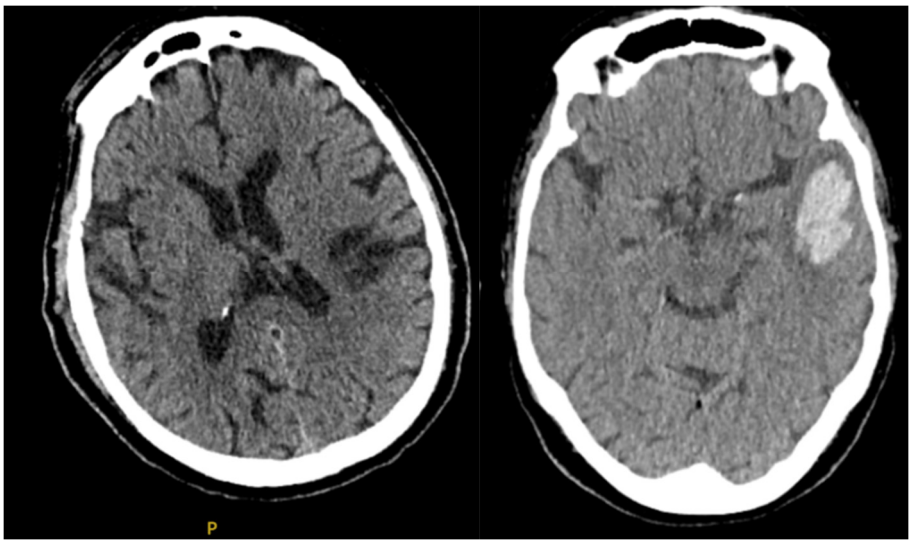

Figure 1. The left image shows a mature ischemic infarct within the left front-parietal area. The picture on the right shows a hemorrhagic bleed within the left temporal lobe.

The UK's Royal College of Physicians recommend that all stroke patients are treated on a dedicated stroke ward with staff familiar with the care of stroke patients [2]. To allow for this, any suspected stroke patient, or admission, should be promptly discussed with the local stroke unit. An acute stroke unit often acts as a direct-admission units, and accepts referrals from General Practitioners, A&E and even straight from the ambulances. Units can get very busy, very quickly, and so such units should have the flexibility to cater for varying levels of admission-pressure. At our unit in Durham, we have 1–2 consultant stroke physicians (attendings) covering morning and afternoons, with a stroke specialist nurse or a specialist doctor (residents or fellows) acting as the first point of contact. In the evenings, the stroke specialist nurse takes direct admissions or referrals with support from the on-call attending stroke physician, either over the phone, via telemedicine, or in-person.

2. Hyperacute care for acute ischemic stroke

2.1. Intravenous thrombolysis

If a patient is referred with new onset neurological symptoms that is consistent with a diagnosis of a stroke, they are immediately admitted to the acute stroke unit. Brain imaging with a CT head scan and a CT angiogram (involving the Carotid/Vertebral vessels and Circle of Willis) gets performed. If there are no features of hemorrhage and depending on eligibility criteria, the patient would be considered for hyperacute treatment. This involves intravenous (IV) thrombolysis (if their NIHSS is ≥ 4) or endovascular mechanical thrombectomy (if their NIHSS is ≥ 6, at a dedicated neuroscience center) [2]. IV thrombolysis and thrombectomy can be done together or as standalone interventions, depending on the patient's eligibility.

Thrombolysis with alteplase is an effective treatment to re-establish circulation following an ischemic stroke. According to the Sentinel Stroke National Audit Program (SSNAP), the UK's stroke registry, approximately 20% or all stroke admissions in the UK are thrombolyzed [3]. Our center's thrombolysis rate is roughly similar.

IV thrombolysis is indicated for patients with a suspected ischemic stroke (with no hemorrhage on brain imaging) with an NIHSS ≥ 4 who present within 4.5 hours of symptom onset, or from when they were last known well [2]. However, with evolving research, we are slowly moving towards an image-based criteria, but this relies on the use of advanced imaging like MRI brain scans or perfusion imaging with CT or MRI. Studies like WAKE-UP [4] and DEFUSE 3 [5] have led us to thinking more about saving the penumbra, which is brain tissue that can be salvaged with thrombolysis or thombectomy [6]. MRI is being increasingly used to identify DWI-FLAIR mismatch [4] to select suitable patients for thrombolysis. CT or MR Perfusion imaging is not well established in the UK, though some centers have started to incorporate this routinely.

Alteplase is the only licensed fibrinolytic drug for the indication of acute ischemic stroke and involves a 10% bolus dose followed by the 90% infusion over one hour. There have been studies recently published on the use of Tenecteplase, a genetically modified variant of alteplase, in hyperacute stroke. Tenecteplase has been used for several years in cardiology. For acute ischemic stroke thrombolysis, it takes less time to prepare and can be administered as a single bolus, without the need for an infusion, unlike alteplase. Several studies in recent years have proved its safety against alteplase. The European Stroke Organization or ESO (as of February 2023) has recommended the use of Tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg for patients with an acute ischemic stroke of <4.5 hrs duration who are eligible for intravenous thrombolysis [7]. At our center, we are working on how this can be incorporated within our standard operating practices, but we have not started using Tenecteplase routinely for acute ischemic strokes.

In patients with acute ischemic stroke of <4.5 hours duration and eligible for IV thrombolysis, who use direct-acting oral anticoagulants (DOACs) within the last 48 hours, there is limited research on the safety of using IV thrombolysis. Some studies and anecdotal evidence exist on IV thrombolysis in those who have measured anti-Xa activity <0.5 U/ml (for factor Xa inhibitors) or thrombin time <60 s (for direct thrombin inhibitors) [8]. Also, there have been arguments on using reversal agents like idarucizumab (for those using dabigatran) or andexanet alfa (for those using apixaban or rivaroxaban) prior to intravenous thrombolysis. Based on the quality of evidence, the European Stroke Organization presently does not recommend IV thrombolysis in those who have taken DOACs within 48 hours, irrespective of anticoagulation activity on blood tests or in combination with reversal agents [8]. The ESO have however given an "expert consensus statement" encouraging its use [8]. Given the necessity to ensure the anti-Xa activity tests are done in a timely manner and the theoretical concerns that idarucizumab may potentiate the prothrombotic activity in the acute phase of ischemic stroke and increase the risk of ischemic events [9], at our center, we have not incorporated this practice into our standard operating procedure, but review decisions on a case-by-case manner. Also, we do not presently plan to use andexanet alfa as a reversal agent for those taking apixaban or rivaroxaban prior to intravenous thrombolysis; this is particularly in view of the limited evidence on its use for this purpose, cost (approximately £ 15000/patient) [10] and the fact that the infusion of andexanet alfa requires two hours, which may have implications for the eligibility of patients to receive alteplase within the approved time window of 4.5 h [8].

3. Endovascular thrombectomy

Over the past decade, there have been several successful trials proving the benefits of endovascular thrombectomy for acute ischemic stroke patients with a large vessel occlusion. A large

vessel occlusion (LVO) is generally described as an occlusion of the distal internal carotid artery, proximal middle cerebral artery, or basilar artery. Thrombectomy is considered routinely in patients with a LVO and NIHSS ≥ 6 who present within 6 hours of symptom onset, from when they were last known well, who have an mRS < 2 [2]. In cases of posterior circulatory ischemic strokes with a vessel occlusion causing disabling neurological deficits, the timeframe may be extended to 24 hours in selected cases [2].

In the UK, endovascular thrombectomy is often conducted in a tertiary center, by an interventional team. This comprises an interventional neuroradiologist, radiographer, anesthetist, theatre staff and stroke team (who will take over post-procedure care). The procedure involves intra-arterial clot extraction using a stent retriever and/or aspiration techniques. This has been well researched and referenced, one of the most notable papers being the HERMES collaboration publication of 2016, which pooled patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA) done between December, 2010 and December, 2014 [11]. They ascertained that with endovascular thrombectomy, there were significant improvements in functional outcomes at 90 days, with the number to treat for reduced disability of 2.6 [11].

According to the SSNAP annual report in 2021, 2% of all stroke patients underwent thrombectomy [12]. In our region, we use a "drip and ship" model, where a suspected large-vessel-occlusion acute ischemic stroke, presenting within 6 hours, gets transferred to the nearest neuroscience center for endovascular thrombectomy. We attempt to thrombolysis all eligible patients prior to transfer but have sent patients for a primary thrombectomy alone (where thrombolysis isn't done due to contraindications). Once patients have had their procedure done at a tertiary center, they are transferred back for ongoing care at the referring secondary care center.

There is presently no restriction on attempting endovascular thrombectomy in eligible patients who are on DOACs [8].

3.1. Post thrombolysis and thrombectomy care

Intravenous thrombolysis with alteplase helps reduce the risk of disability from an ischemic stroke in approximately 35% of cases, with approximate 6% cases demonstrating hemorrhagic transformation (see Figure 2), 3% being fatal [13]. As such, patients should be followed up closely within the first 24 hours, with an emphasis on blood pressure and neurological examination. Post-thrombolysis brain imaging 24 hours after intravenous thrombolysis should also be performed, usually with a non-contract CT head. If there is evidence of neurological deterioration, the patient should be sent for urgent brain imaging at once. Patient should be treated as per intracranial hemorrhage, which is out of the scope of this article.

Intravenous thrombolysis can be associated with angioedema of the oropharynx, which can cause airway compromise and thus must be recognized and managed promptly with steroids, antihistamines and/or involvement of the intensive care team etc. We have around 1–2 cases per year of angioedema following thrombolysis, so it is fortunately rare.

Mechanical Thrombectomy is associated with a lower risk of intracerebral hemorrhage compared to thrombolysis. The procedure can be complicated by cerebral oedema, vessel re-occlusion and access site complications post thrombectomy, such as groin hematoma, access-site bleeding, pseudoaneurysms, infection etc.

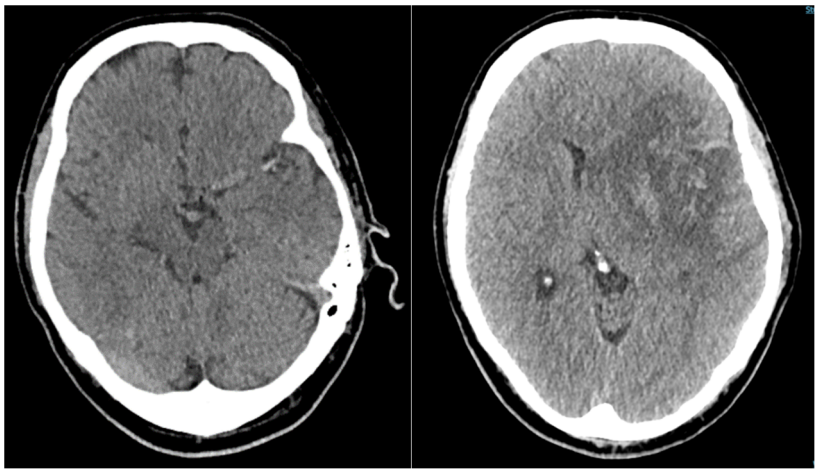

Figure 2. The CT head on the left shows pre thrombolysis CT scan with a hyper-dense left middle cerebral artery sign, and the CT head on the right shows the same patient with a post thrombolysis hemorrhagic transformation.

If a patient received intravenous thrombolysis or mechanical thrombectomy, then we aim to keep the blood pressure controlled to below 180/105 mmHg for 24 hours post thrombolysis [13]. If they haven't received intravenous thrombolysis, RCP guidelines state it is permissible to allow blood pressure to be up to 220/120 mmHg [2], unless there are other medical condition that would benefit from stricter blood pressure control [14]. In patients needing tight blood pressure control, we often use intravenous or transdermal glyceryl trinitrine, or intravenous labetalol but no specific agents have been recommended by the RCP or ESO.

Long term, we recommend achieving a systolic blood pressure below 130 mmHg, except for people with severe bilateral carotid artery stenosis, for whom a systolic blood pressure target of 140–150 mmHg is appropriate [13].

3.2. Decompressive hemicraniectomy

In patients who develop a severe ischemic stroke involving the middle cerebral artery, there is a risk of worsening brain damage or death secondary to raised intracranial pressure and brain herniation. Such patients may be considered for an urgent neurosurgical procedure called decompressive hemicraniectomy within the first 48 hours, where a piece of the skull is removed to allow the brain to swell, relieving the raised intracranial pressure. However, it is important to note that decompressive hemicraniectomy is a lifesaving procedure, but it does not have any statistically significant impact on the level of disability sustained by patients [15], so they may have a higher chance of survival, but with the prospect of living with severe disability. The National Institute of Health and Care Excellence (NICE), the UK's health standard's advisory authority, have prepared helpful patient aids (leaflets) which are often used when discussing this procedure with patients or their families [16,17].

3.3. Criteria for decompressive hemicraniectomy [3]

(1) Pre-stroke mRS < 2.

(2) Clinical deficits indicating infarction in the territory of the MCA with a NIHSS of 15 or more, and radiological correlation showing at least 50% of the MCA territory with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cubic centimeters on diffusion-weighted MRI.

(3) Decrease in the level of consciousness to a score of 1 or more on item 1a of the NIHSS.

(4) Treatment to be offered within 48 hours of stroke symptom onset.

(5) Clear explanation to the patient or family that this procedure may save the patient's life, but survival would be met with a high probability of severe disability.

4. Some general considerations post-stroke

All patients, irrespective of whether they are eligible for IV thrombolysis or thrombectomy, should be admitted to a dedicated acute stroke ward where they can be cared for by a multidisciplinary team trained in stroke management, see Figure 3.

Figure 3. MDT Involvement in post stroke care. Reproduced by inspiration from Kurup et al. [18].

Patients with acute stroke are at risk of significant disturbances to physiological homeostasis. Roughly 5% of acute stroke patients develop urinary sepsis and 9% require antibiotics treatment for pneumonia [19]. The 2016 National stroke guidelines advised that patients are to be kept in a stroke ward and for close monitoring of level of consciousness, blood glucose, blood pressure, oxygen

saturation, hydration and nutrition, temperature and cardiac rhythm and rate. Stroke patients are also known to be at greater risk of depression and a mood screen should be done for all stroke patients.

4.1. Antiplatelets in stroke

In our unit, all stroke patients admitted with an acute ischemic stroke are started on aspirin 300 mg daily for 14 days. This can be prescribed as an oral preparation or in the form of a suppository for those who are unable to swallow. Only in patients who receive IV thrombolysis or thrombectomy is this delayed by 24 hours, after a repeat CT head. Generally, we put patients on clopidogrel 75 mg daily from day 15 (or sometimes sooner, depending on medication tolerability and discharge plans).

Following an increase in evidence of the use of dual antiplatelets in stroke, notable aspirin 75 mg with clopidogrel 75 mg [20,21], at our center we often consider their use for 3 weeks after the stroke, followed by clopidogrel 75 mg daily alone lifelong. This is reserved for strokes with an NIHSS of less than 4; essentially minor strokes or those with a small infarct volume. Dual antiplatelets may also be used in situations where a patient suffered a stroke due to a dissection in the carotid or vertebral vessels, or if stenting was done as part of a thrombectomy procedure or post-carotid intervention for severe stenosis [22]. If a patient isn't tolerant of clopidogrel, then NICE and RCP recommends the use of aspirin and dipyridamole in combination as an alternative [2]. In our experience, dipyridamole is often poorly tolerated, and compliance is poor. So aspirin monotherapy can be considered in such cases.

At our center and regionally, prescribing anticoagulation and antiplatelets in combination is not routine practice in post-stroke secondary prevention in those without atrial fibrillation. However, in selected cases this may be considered, e.g., secondary stroke prevention in patients with clinical atherosclerosis [23].

4.2. Anticoagulation in stroke and atrial fibrillation

Patients who present with an ischemic stroke and atrial fibrillation will need to be anticoagulated but there is often a debate on the ideal time (re)start anticoagulation. The benefits of starting anticoagulation early would be to prevent the formation of intramural thrombus, hence lowering the risk of an extension of the stroke or further re-strokes. However, this would also increase the risk of a hemorrhagic transformation. The European Heart Rhythm society advises [24]:

(1) start after 3 days for small, non-disabling infarct or mild stroke.
(2) start after 6 days for moderate stroke.
(3) start after 12 days for large infarcts or severe stroke.

In our unit, we adopt these guidelines roughly, but often perform brain imaging with a CT head or MRI brain prior to starting anticoagulation.

4.3. Cholesterol management

Unless contraindicated, high intensity statin therapy, like atorvastatin 40–80 mg daily, should be initiated in all ischemic stroke patients [22]. At our center, we aim to reduce non-HDL cholesterol by more than 40% of baseline by 3 months. If this reduction is not achieved by then, we enquire about medication compliance, lifestyle changes, and increasing the dose if appropriate. We may consider the

addition of Ezetimibe 10 mg OD in addition to statin therapy, especially in those who have familial hypercholesterolemia [22].

4.4. Venous thromboembolism prophylaxis

After the CLOTS3 trial which showed the effectiveness of intermittent pneumatic compression (IPC) in preventing DVTs, NICE guidelines now recommend the use of IPCs for the VTE prophylaxis within 3 days of acute stroke for people who are immobile [25,26]. It is to be used for 30 days or until the patient is independently mobile/ discharged, whichever comes first.

Due to the difficulty in ensuring correct and consistent application, in our unit we have adopted a pragmatic approach with early chemoprophylaxis, using prophylactic low molecular weight heparin in ischemic stroke patients. We start chemoprophylaxis between day 3–7, depending on infarct size, patient's neurological state and blood pressure parameters [27]. This is not too dissimilar to the European Stroke Organizations stance [8].

4.5. Swallowing

Patients should have their swallowing screened, using a validated screening tool, by a trained healthcare professional within four hours of arrival at hospital and before being given any oral food, fluid, or medication [19]. Until a safe swallowing method is established, patients with dysphagia after acute stroke should be kept nil-by-mouth and clinically assisted nutrition and hydration should be commenced. Often this is with intravenous or subcutaneous fluids. A nasogastric tube feeding plan should be considered within 24 hours [19].

4.6. Glycemia control

Patients with acute stroke should be treated for hyperglycemia, to maintain a blood glucose concentration between 5 and 15 mmol/L with close monitoring to avoid hypoglycemia [24].

4.6.1. Driving advice

As per the UK's Driver and Vehicle Licensing Agency or DVLA, the government organization responsible for maintaining a database of drivers and vehicles in Great Britain, any patient diagnosed with a stroke must not drive a car or motorbike (personal license) for a month after their diagnosis. If they have ongoing neurological problems after the first month, then they need to continue to stop driving and inform the DVLA who then assesses their suitability to return to driving. Drivers of buses, coaches/lorries or commercial licenses usually have stricter rules, often involving an immediate notification to the DVLA and possible suspension of driving for a year [28].

5. Conclusions

Stroke is a disease that causes great mortality and morbidity to its sufferers. As such, it is important that each hospital has a robust and effective method to manage patients who are suspected of having a stroke and that physicians are familiar with the acute management of stroke. This would

reduce the time spent on processes and allows more patient to present on time for thrombolysis and thrombectomy, reducing the disability suffered by the stroke patients. This article aims to discuss some of the evolving advanced decisions in hyperacute treatment, but by no means covers the full breath of expanding research and treatment offered to stroke patients.

6. Key points

(1) The acute management of a stroke is best handled in a stroke unit, where staff are familiar with the management of stroke. This can help ensure that there are systems in place for necessary investigations, or referral to neurosurgery to take place, in a prompt manner.

(2) Thrombolysis with intravenous alteplase 0.9 mg/kg is indicated in suitable patient who presents within 4.5 hours of symptoms onset (or last known to be well) and an NIHSS $\geq$ 4. With advanced imaging like MRI and CT or MR perfusion scans, this time restriction may be extended.

(3) Mechanical thrombectomy is indicated in patients with a large vessel occlusion who presents within 6 hours of symptoms onset (or last known to be well) and an NIHSS $\geq$ 6. As with point 2, with advanced imaging, this time restriction may be extended.

(4) Treatment with intravenous tenecteplase at 0.25 mg/kg is now being recommended by ESO in those who would otherwise be eligible for intravenous alteplase.

(5) There is ongoing evolving evidence on the safety and use of intravenous alteplase in those eligible acute ischemic stroke patients presenting within 4.5 hours who have taken DOACs within 48 hours, but this is being reviewed.

Conflict of interest

All authors declare no conflict of interest regarding the publication of this paper.

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