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The Final Thesis

Ischemic Stroke Reperfusion Therapy Window

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1. SUMMARY

Acute ischemic stroke is a potential life-threatening condition, with an increasing risk in older patients. Presently, two evidence-based treatment methods are predominantly used: systemic thrombolysis with alteplase and mechanical thrombectomy. Intraarterial thrombolysis has been almost entirely replaced by mechanical thrombectomy. For both stroke therapy strategies, strict time windows are recommended. However, a lot of patients present beyond that limit or with unknown time of onset and therefore are not eligible to receive thrombolysis or endovascular therapy. Different studies hypothesized ways on how to prolong the time window. Therefore, brain imaging techniques such as computed tomography or magnetic resonance imaging are needed to show a mismatch between the ischemic core and the penumbra. This is crucial to select patients eligible for treatment in an extended time window. Prolongation of the time window, especially in case of treatment with systemic thrombolysis, might have additional side effects. These can be addressed via adjunctive therapy methods, among other things. Possible methods are presented and could be used as neuroprotective factors or to reduce hemorrhagic transformation due to thrombolysis. Evidence suggests that there are predictive factors for a good functional outcome in stroke patients, such as cerebral collateral blood flow and younger age. Nevertheless, pregnant women or children might also be affected by ischemic stroke. Special patient groups are excluded in a lot of studies, but still need attention so that there are sufficient guidelines on how to treat them. Lastly, a rather new target for therapy is described, which is the usage of HDAC2 inhibitors. This novel strategy might be of great importance in preventing secondary functional loss.

2. KEY WORDS

Stroke; wake-up stroke; unwitnessed onset; mismatch; brain imaging; stroke treatment methods; ischemic reperfusion therapy; extended time window; thrombolysis; thrombectomy; HDAC2

3. INTRODUCTION

‘Time is brain’ is a quote everyone working in a medical field knows. As soon as a stroke is suspected, the clock starts ticking. The vulnerable brain tissue needs to be saved as quickly as possible. With each minute, where a large vessel occlusion ischemic stroke is left untreated, roughly 2 million neurons are dying. (1) Currently, there are strict rules and recommendations for ischemic stroke reperfusion therapy. The risk to experience a stroke increases with age. As people tend to get older, the prevalence of ischemic stroke increases, even though efforts are

being made to decrease modifiable risk factors. People who are experiencing strokes with unknown onset are likely not to receive systemic thrombolysis because of the time which has passed since the patient was last seen without symptoms. In the United States not even 10% of patients experiencing strokes are treated with systemic thrombolysis because of the time-based model of treatment regulations. (2)

The objective of this narrative review is to analyze and report different strategies on how to treat ischemic strokes in different time windows, what adjunctive therapy methods are available and how to proceed in special patient groups. With this knowledge and latest therapy methods, selected patients can be treated up to 24 hours or even longer after they were last seen without symptoms. The possibility of delayed reperfusion is a huge step in neurology.

4. LITERATURE SEARCH STRATEGY

An electronic search for articles of English literature databases such as PubMed, Google Scholar, Cochrane Library, and Neurology Journals was performed. Articles were included if they were published in the last 10 years (from 2012 to 2022). Case reports, reviews, clinical trials, meta-analysis, and guidelines are included. Articles were limited to the English language. Literature related to stroke and stroke therapy were reviewed. Searched terms include acute ischemic stroke, stroke therapy, stroke reperfusion, reperfusion window, imaging modalities, penumbra, thrombolysis, thrombectomy, wake-up stroke, and extended time window.

5. BACKGROUND INFORMATION FOR ACUTE ISCHEMIC STROKE

The term acute ischemic stroke describes an occlusion of a cerebral or neck artery which leads to a decreased blood flow to the region supplied by the occluded vessel. There are three main possible causes for brain infarction: there might be a local occlusion due to cerebral atherosclerosis, an embolization because of the rupture of arterial plaque in the internal carotid artery, or as a secondary cause from an embolization of a blood clot coming from the heart to an intracranial vessel. (3)

Histopathologically, there are 3 distinctive stages following ischemic stroke. Stage I describes non-lethal ischemia with decreased cerebral blood flow, but without neural and vascular cell death. Stage II is lethal ischemia, including neural cell death, but without vascular cell death, and logically, stage III describes lethal ischemia with both neural and vascular cell death. (4)

Common risk factors for ischemic strokes include modifiable and non-modifiable factors. Age is one of the major non-modifiable risk factors. Low birth weight seems to be associated with

a higher risk of stroke in later life. Ethnicity plays a role as well, as Blacks and Hispanics tend to have a higher incidence of stroke. A study showed that their risk for atherosclerosis is higher than that of Whites. A positive family history increases the risk by around 30%. Modifiable risk factors include, among others, physical inactivity, high total cholesterol, hypertension, obesity, diabetes mellitus, smoking, and atrial fibrillation. (5)

Residual cerebral blood flow and collaterals are responsible for a region of potentially salvageable tissue called penumbra. The reduction of cerebral blood flow levels between around 10 mL/100g/min and 25mL/100g/min can identify the penumbra. Levels below this margin show the irreversible damaged brain tissue and are defined as ischemic core. The aim of acute ischemic stroke diagnostics is to identify both regions, especially the penumbra, as saving this region is the basis of treatment. (6,7) These regions can be seen on computer tomography (CT) and magnetic resonance imaging (MRI). (7)

6. BRAIN IMAGING MODALITIES

To begin with, neuroimaging is needed for the diagnosis of stroke. It helps to identify the cause of stroke, plan the treatment, and predict possible outcomes. Moreover, an imaging technique that is fast, safe, and accessible at all times is essential. Consequently, CT is the main modality used nowadays. (8,9)

Non-contrast head CT (NCCT) is an easily accessible and fast way to differentiate between hemorrhagic and ischemic stroke. It is therefore used as a rapid assessment method. Early ischemic changes like cortical swelling or brain edema are visible with this modality. (3,8)

CT angiography (CTA) is a fast method to determine large vessel occlusions and to evaluate collateral blood flow. (3) Vessel malformations, thrombi within the arteries, or aneurysms may be detected as well. For this modality, intravenous contrast material is needed. (8,9) This leads to a slight increase in the risk of contrast-induced nephropathy, but the benefits normally outweigh the minimal risk. Therefore, most hospitals perform the CTA without waiting for serum creatinine levels of the patient. (8,10) Nevertheless, if the patient is taking metformin, the drug should be suspended for at least 48 hours after administering contrast material. (8,11) With the help of CTA, one can differentiate if the thrombi either got to the intracranial artery as an embolus or if it has formed in situ. A freshly formed thrombus is more permeable to thrombolytics. Moreover, residual flow on CTA is used to predict the permeability of thrombolytics. Thrombi with a higher grade of residual flow are more prone to thrombolysis. (8,12)

CT perfusion (CTP) is performed via injecting contrast material in the vein and repeating the cerebral CT to observe the enhancement of the brain parenchyma which is proportional to the blood perfusion. With this, the ischemic core can be determined. (9) It involves acquiring multiple scans and by using formulas it generates "estimates of cerebral blood flow, blood volume, and transit time within brain tissue" (8). Currently, CTP anticipates the likelihood of brain tissue to be ischemic by evaluating those three parameters, as well as others such as time-to-peak. It can also predict which regions have an increased risk for hemorrhage after thrombolysis. (8)

MRI is usually not used as a first-line choice for imaging, as it is more time consuming and has relatively more contraindications than CT. Nevertheless, diffusion-weighted image (DWI) is a sensitive and specific way to detect changes earlier than CT. (3,9) DWI is able to identify the ischemic core, whereas perfusion-weighted imaging (PWI) identifies the region adjacent to it. Consequently, PWI/DWI mismatch could identify the penumbra and is often used for that purpose. (13)

Positron Emission Tomography (PET) studies allow the recognition of three distinct regions: core ischemia, penumbra and the area which is not damaged by decreased blood flow. Nevertheless, PET scans are not used in clinical practice because of the radioactivity, limited access and the invasiveness. (13)

7. EVALUATION OF SEVERITY OF STROKE: DIFFERENT SCORES

The National Institute of Health Stroke Scale (NIHSS) is a neurological examination scale consisting of 11 points. It is used to estimate the severity of stroke, predict the outcome and mortality. The score ranges from 0 to 42, with a higher score standing for a more severe stroke. (14) It assesses consciousness, gaze, visual fields, facial movements, motor function of arms and legs, limb ataxia, sensory loss, language, articulation and extinction or inattention. (15)

The modified Rankin Scale (mRS) is a standard outcome measurement in stroke patients. It is especially usable 90 days after stroke, to evaluate improvements. (16) It covers the outcomes from no symptoms (0 points) up to death (6 points). (17)

The Alberta Stroke Program Early CT Score (ASPECTS) is designed to analyze the extent of ischemic changes. It uses 10 points on a CT scan, to evaluate early ischemic changes in patients with occlusion of the middle cerebral artery (MCA). However, adaptations have been made for posterior circulation ischemia as well. The region supplied by the MCA is categorized into 10 segments, each segment standing for one point, which is subtracted if that segment is involved. Consequently, a score of 0 points describes diffuse involvement throughout the whole MCA

territory. The score was initially designed to predict the outcome for systemic thrombolysis. If the final score is 7 or less, a worse outcome is anticipated. (18,19)

FAST (Face Arm Speech Test) is a quick an easy evaluation method to assess whether a patient is likely to experience a stroke or not. It consists of facial weakness, arm weakness, and speech disturbances. The modification of FAST is called BEFAST and additionally includes balance and eyes (diplopia). When any of these items are positive, the test is considered positive. However, these items focus more on anterior circulation occlusions. A trial showed that the test fails to diagnose nearly 40% of posterior circulation strokes, in contrast to only 10% of anterior circulation strokes. Thus, more features need to be addressed, such as vertigo, visual disturbances, and ataxia. (20,21)

8. EVIDENCE-BASED TREATMENT METHODS

The main principle of acute ischemic stroke therapy is to reopen the occluded vessel so that the penumbra is saved. The goal is to reperfuse ischemic brain tissue as soon as possible, to enhance collateral blood flow, and to prevent secondary brain injury. There are two main evidence-based methods to achieve these goals. Either intravenous thrombolysis with alteplase or endovascular treatment are the available options. A combination of both is possible as well. (22)

8.1. Thrombolysis

Recombinant tissue plasminogen activator (tPA) is the only drug which is approved by the U.S. Food and Drug Administration (FDA) to treat ischemic stroke. Alteplase is the drug which is used nowadays. (23) In Europe it is licensed for up to 4.5 hours after the onset of symptoms, whereas in the USA it is only allowed to be used for up to 3 hours. Some countries have a limit of 80 years of age. (22,24) Prior to applying thrombolysis, it is necessary to gather information of the patient, including when the symptoms started, recent surgeries, comorbidities, a neurological examination to evaluate the NIHSS score, test the blood glucose levels, measure blood pressure and perform brain imaging studies. (22)

The standard dosage which is used for alteplase is 0.9mg/kg bodyweight, of which 10% is administered as a bolus and the rest in an infusion over one hour. In total, the dosage should not exceed 90mg. (22)

As intravenous thrombolysis increases the risk of hemorrhage after the treatment, it was studied if only 0.6mg/kg bodyweight of alteplase are sufficient within a time window of 4.5 hours. The results showed that a lower dose of intravenous thrombolysis is inferior in terms of death and

disability after 90 days, even though the risk of intracranial hemorrhage is slightly reduced. Consequently, the optimal dose remains 0.9mg/kg bodyweight. (25)

Even though alteplase is the only approved thrombolytic agent for stroke therapy, there is evidence that tenecteplase is at least as good as alteplase in terms of functional clinical outcome and the occurrence of adverse effects like cerebral hemorrhage. In contrast to alteplase, tenecteplase can be administered as a bolus, as it has a longer half-life. Thus, the administration time is shorter. (26,27) The newest ischemic stroke treatment guidelines even suggest considering tenecteplase as an off-label treatment method in selected patients. However, it is not yet approved by the FDA for stroke therapy, and should presently only be used in case of myocardial infarction thrombolysis. In contrast to that, the European Stroke Organization (ESO) recommends the usage of tenecteplase in special circumstances, for instance in large vessel occlusion with prior mechanical thrombectomy. (15,28,29)

8.2. Mechanical Thrombectomy

Mechanical thrombectomy is performed in patients who suffer from an occlusion of the first or second segment (M1/M2) of the middle cerebral artery (MCA), or an occlusion of the intracranial carotid artery. Effects are especially beneficial when it is performed within 6 hours of symptom onset. (22) It can either be used as a primary intervention or secondary to thrombolysis. Techniques include retraction, aspiration, and stenting. (30)

8.2.1. Mechanical Thrombectomy in the Extended Time Window

A multinational, cohort, retrospective study investigated whether patient selection by NCCT has similar clinical and safety outcomes compared to selection by CTP or MRI in the extended time window. Included patients were suffering from a proximal anterior circulation large vessel stroke, presenting within 6 to 24 hours after the onset of symptoms. The results showed that the risk for intracranial hemorrhage or death did not differ between the imaging modalities. Besides, the door-to-puncture time was shorter in NCCT selected patients. Contrast material load, costs, radiation exposure, and resource use are lower in NCCT. Nevertheless, patients included in the study had an ASPECTS of 7 or more, which is recommend considering when choosing patients via NCCT for mechanical thrombectomy. The study findings showed that specific patients could be chosen for thrombectomy by NCCT, which is less costly, simpler, and an alternative to CTP or MRI. (31)

The DEFUSE 3 trial was a multicenter, randomized, open-label trial which showed that it is more beneficial to have thrombectomy as a combination therapy together with thrombolysis

compared to medical therapy alone in patients with onset of symptoms 6 to 16 hours before. Patients included in the study either had a proximal MCA or internal carotid artery occlusion on MRA or CTA. The ischemic core volume had to be less than 70mL, and penumbra volume of at least 15mL. The ratio of ischemic tissue volume to initial infarct volume was 1.8 or more. Patients were assigned to either the endovascular-therapy group, which included thrombectomy plus medical therapy, or the medical-treatment-only group. The combination therapy showed a better functional outcome on the mRS after 90 days. The incidence of symptomatic cerebral hemorrhage was slightly higher, but this was not statistically significant. The overall mortality rate was lower in the endovascular-therapy group. Moreover, the reperfusion rates and vessel recanalization rates were higher in the endovascular-therapy group, leading to the anticipation that a combination therapy is beneficial in selected patient groups. (32)

The DAWN trial was a multicenter, prospective, randomized, open-label trial which included patients with the onset of symptoms 6 to 24 hours earlier. Suitable patients either received thrombectomy plus medical therapy or medical care only. The results were similar to the DEFUSE 3 trial, showing that the outcomes were better in the combination therapy group. (33)

9. PATIENT SELECTION FOR EXTENDED TIME WINDOW THROMBOLYSIS THERAPY

Mainly patients who present within 4.5 hours of onset of symptoms are qualified for intravenous thrombolysis according to current European guidelines, and only in special situations the use of thrombolysis is allowed up to 9 hours. If they present later than this time window, they are only eligible for mechanical thrombectomy. In fact, this is only the case if the occlusion is inside one of the large vessels. Major exclusion criterion for thrombolysis is the time window. But, with diffusion-perfusion mismatch studies, the penumbra can be estimated and patients who are qualified to receive systemic thrombolysis in the extended time window could be identified. Therefore, multimodal imaging techniques are necessary. With this imaging of the penumbra, brain tissue can be defined which is eligible to treatment even outside the standard time window. Treatment decisions should be made on an individual basis and not only depend on the hours passed since the patient was last seen without symptoms. (34)

10. THROMBOLYSIS UP TO 9 HOURS AFTER ONSET OF STROKE

Recently, it has been shown that there might be a functional improvement after the current treatment time window. Patients are currently selected according to time rather than according to possibly salvageable brain tissue. Clinical research recently indicated that patients selected

by imaging evidence for thrombectomy could have a better functional outcome even if thrombectomy is performed up to 24 hours after the onset of symptoms. This led to a large discrepancy between the time windows for thrombectomy and thrombolysis. (32,33,35)

The Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial is a multicenter, randomized, placebo-controlled study, focusing on patients waking up with stroke symptoms and patients with symptoms going on from 4.5 to 9 hours. Patients were selected by automated perfusion imaging. They were involved if hypoperfused regions with salvageable regions were detected. For wake-up strokes, the time of onset was estimated to be in the middle of sleep. Patients were included if the estimated time of onset was below 9 hours, the age had to be above 18 years, NIHSS score between 4 and 26, and premorbid mRS score of 0 or 1. The primary outcome was a mRS of 0 or 1. Secondary outcomes were defined as mRS score at 90 days, reperfusion percentage of more than 50% and more than 90% at 24 hours. Tertiary outcome was a major neurological improvement, which was assessed by the NIHSS after 24 hours, 72 hours, and 90 days after intervention. The results stated that recanalization and neurologic improvement 24 hours after symptom onset was much higher in the alteplase group compared to the placebo group. The ratio of death did not differ significantly in both groups. Symptomatic intracranial hemorrhage was slightly higher in the alteplase group than in the placebo group (roughly 6% compared to 1%). Besides the positive results, it has to be kept in mind that the EXTEND trial had to be terminated early, due to positive results of the WAKE-UP trial described below. (35–37)

The European Cooperative Acute Stroke Study IV (ECASS-IV) was another multicenter, randomized, double-blind, placebo-controlled trial, which included patients according to the same clinical criteria as the EXTEND trial. But in this study, the imaging method was MRI (PWI and DWI sequences) and the perfusion lesion had to be 20mL or more, with a mismatch ratio of 1.2 or more. The trial had to be stopped early because of a decreasing recruitment of patients due to the positive results of other trials. Consequently, the endpoints were not met and thus there was no statistically significant benefit in the alteplase group over the placebo group. (36–38)

11. THROMBOLYSIS IN STROKES WITH UNWITNESSED ONSET AND WAKE-UP STROKES

Wake-up strokes describe a form of ischemic stroke in which patients are going to sleep without any symptoms, while waking up with neurologic deficits. Consequently, the prognosis is

relatively poor, as the time of onset is unknown. (39) Around one quarter of all strokes occur as wake-up strokes. Luckily, newest ESO guidelines nowadays allow the use of thrombolysis under special circumstances in these patients. (29)

Several risk factors are known for wake-up strokes, which may not differ much from the ones of acute stroke. Obstructive sleep apnea, plasma lipid levels, sedentary lifestyle, diabetes, race (especially African Americans), age and gender are known risks. (39)

11.1. CT and MRI Comparison

A retrospective cohort study compared patients with ischemic strokes in the extended time window (>4.5 hours) or with unknown time of onset, who received intravenous thrombolysis and were selected either by MRI or CT. Primary outcome was the door-to-needle time. Safety outcomes were intracranial hemorrhage and mortality. Efficacy outcomes were the mRS score after 90 days, NIHSS score reduction of at least 8 points or a score of 0 or 1 after 24 hours, and no evidence of stroke on neuroimaging after 24 hours. The findings showed that thrombolysis appeared to be safe in both multimodal CT and MRI imaging. Clinical efficacy outcomes were similar in both arms. The only significant difference was that the door-to-needle time was shorter in CT imaging than MRI. (40)

11.2. CT/CTP-Based Thrombolysis

Non-contrast CT is the preferred routine method to diagnose stroke. Nevertheless, CTP provides more information about the penumbra. A retrospective study analyzed the benefit of using thrombolysis with alteplase in patients selected by CT and CTP. (39,41)

All patients included underwent non-enhanced computed tomography and a part of them CTA and CTP as well. Patients were included if they arrived earlier than 4 hours after awakening with an ASPECT score of more than 6 and/or an ischemic penumbra of more than 50% of ischemic tissue. The included patients were divided into a group which received thrombolytic therapy (rt-PA group) and a group without the therapy (non-rt-PA group). Several parameters were compared between both groups, including the follow up NCCT, mortality rate, NIHSS and mRS at discharge or after 7 days. 75 patients were included in the non-rt-PA group, and 74 patients in the rt-PA group. The neurologic deficit significantly improved in the group treated with rt-PA compared to the non-rt-PA group (in terms of mRS and NIHSS after 7 days). The volume of ischemic lesion was significantly lower on NCCT in patients who received the thrombolysis. The length of the hospital stay was shorter in the rt-PA group and no difference of in-hospital mortality or intracranial hemorrhage was seen. This shows that thrombolysis in

wake-up stroke patients selected with NCCT and/or CTP results in a better functional outcome without increasing negative effects. (41)

11.3. PWI-DWI Mismatch-Based Thrombolysis

The classical model of PWI-DWI mismatch indicates that the "DWI ischemic lesion is located within the PWI hypoperfused brain territory and is also surrounded by ischemic penumbra" (39).

Research showed that it may be safe to use PWI-DWI mismatch to select patients eligible for thrombolysis, which results in better clinical outcome. However, currently there is no unified standard for the parameters involved in the mismatch calculation. Hence, a combined use of PWI-DWI mismatch and DWI-FLAIR mismatch is reported to be used. This has been shown to result in a better outcome. Nevertheless, most studies only take the classical model of PWI-DWI mismatch into account, which is not always the case and leads to an exclusion of posterior circulation strokes. Consequently, further research is needed in this field. (39)

Another retrospective study concluded that patients are presenting about 1.5 hours earlier to the emergency department, when they are having a mismatch. Moreover, the "chance of having a mismatch dropped by 5% for every hour that passed" (34). A relation between the NIHSS score of a patient and the presence of mismatch has been shown. The higher the NIHSS, the higher the chance for having a mismatch. Furthermore, it has been discovered that women were more likely to have a mismatch than men (55% compared to 45% respectively). (34)

11.4. DWI-FLAIR Mismatch-Based Thrombolysis

The WAKE-UP trial is a randomized, double-blind, placebo controlled, multicenter study. It included patients with an unknown time of onset. Patients received either placebo or intravenous alteplase. The imaging method was MRI, where a mismatch between DWI and FLAIR region of ischemia was notable. This suggests that the stroke occurred in the last 4.5 hours. Patients were included if they were between 18 and 80 years of age, NIHSS score 25 or lower and a mRS score of maximum one point. The time since the patients were last seen well had to be 4.5 hours minimum, but no maximum limit was applied. Exclusion criteria were planned thrombectomy, intracranial hemorrhage, NIHSS of more than 25, ischemic regions which were larger than one third of the territory supplied by the middle cerebral artery, and contraindications for alteplase. Primary efficacy endpoint was a favorable clinical outcome, which was measured by different scores including mRS (score of 0 or 1), NIHSS, Glasgow Outcome Scale and Barthel index. The primary safety endpoints were death and a mRS at 90

days of 4 to 6. Secondary safety endpoints were defined as symptomatic intracranial hemorrhage and parenchymal hematoma. The patients either received 0.9mg/kg bodyweight alteplase (10% administered as a bolus and the rest over 60 minutes in an infusion) or placebo. Clinical assessment was performed at 22 to 36 hours after randomization and between 5 and 9 days or at discharge from\ hospital. The latest assessment was after 90 days. Finally, over 5 years a total of 1362 patients were screened, but 859 of them were excluded from the trial. Therefore, the remaining 503 patients were included, and 254 of them received alteplase. The median NIHSS score at baseline examination was 6 (mild) for both groups. The median time between administration of alteplase or placebo was 3.1 hours or 3.2 hours respectively, and the median interval between the time when the patient was last seen without symptoms and the administration of alteplase or placebo was 10.3 hours and 10.4 hours. In the alteplase group, 53.3% of patients had a mRS of 0 or 1 after 90 days, compared with 41.8% in the placebo group. The median score of mRS after 90 days was lower in the alteplase group than in the placebo group and therefore the favorable outcome was achieved more often with alteplase. In the alteplase group, the median infarct volume was lower compared to the placebo group. Safety outcomes occurred in 13.5% in the alteplase group, and 18.3% in the placebo group, death occurred in 4.1% and 1.2%, respectively. Nevertheless, half of the deaths in the alteplase group was not associated with a cerebral cause. The study results showed that the functional outcome in the alteplase group was better compared to the placebo group, even though the risk for intracerebral hemorrhage was slightly higher. (42)

The MR WITNESS trial is an additional multicenter, prospective study which tested the safety of intravenous thrombolysis in unwitnessed onset strokes. Patients were selected according to a quantitative mismatch of DWI with FLAIR. All patients received neuroimaging consisting of DWI, FLAIR, and gradient echo T2-weighted sequences. The primary outcome was defined as the safety of intravenous alteplase, which describes the risk of symptomatic intracranial hemorrhage. Secondary outcome was the risk of symptomatic brain edema. Functional outcomes were evaluated with mRS after 90 days. Patients were included if they were between 18 and 85 years of age. The onset of stroke symptoms was unwitnessed but had to be within 4.5 and 24 hours since last seen well. The median NIHSS of included patients was 7. The results displayed that the risk of symptomatic intracranial hemorrhage did not increase, as well as symptomatic brain edema risk and mortality ratio. The results were compared with the ones of the ECASS-3 trial. The usage of quantitative mismatch between DWI and FLAIR resulted in a larger group of patients which could be included, compared to qualitative diffusion-FLAIR

mismatch. The low risk of intracranial hemorrhage might be related to the fact that the strokes included were potentially milder. A higher NIHSS score has been shown to be a predictor of worse outcome, as well as current tobacco smoking and pre-stroke disability could possibly lead to a non-favorable outcome. (43)

11.5. Intra-Arterial Therapy in Wake-Up Strokes

A prospective Swiss study compared the safety of intra-arterial therapy in 4 groups: onset of symptoms below 6 hours, onset more than 6 hours without a stated upper limit, unknown time of onset, and wake-up stroke. Patients were classified as unclear-onset stroke if the symptoms started while they were awake, but no time could be recalled. Patients who had a wake-up stroke were included in the <6 hours group, instead of the wake-up stroke group, if they were last seen awake and without neurological symptoms less than 6 hours before treatment. At first, patients underwent a thorough neurological examination, including NIHSS evaluation, blood tests, electrocardiography, and CT and/or MRI. Patients received the intra-arterial therapy if the NIHSS was 4 or higher, there was no hemorrhage visible upon imaging, the area of ischemia matched with the symptoms, the symptoms started less than 24 hours ago, there were no contraindications for thrombolysis, and the patient gave informed consent. Intra-arterial treatment was performed either on a pharmacological basis with urokinase, mechanically, or in a combined pattern. At least 24 hours after the treatment, another neuroimaging was performed, and after 90 days after the mRS was used to evaluate the clinical outcome. The results showed that intra-arterial treatment is safe for selected patients in the described groups. The study selected patients on a case-to-case basis and MRI criteria in the group with symptoms beyond 6 hours and unknown time of onset. As the study was ongoing for 19 years, imaging techniques and inclusion criteria improved enormously during that time. (44)

12. DELAYED REPERFUSION AFTER 24 HOURS

Current evidence suggests that delayed recanalization is still better than no recanalization. A study focusing on 21 patients with basilar artery occlusion concluded that successful endovascular recanalization beyond 48 hours after symptom onset was achieved in 81%. (45)

In internal carotid artery (ICA) occlusions it is suggested that delayed reperfusion either by endovascular therapy or hybrid surgery (for instance endovascular technique in addition to carotid endarterectomy) resulted in up to 95% recanalization rates, depending on the exact type of occlusion. The best results were shown in type A (“a tapered occlusion with supraclinoid

reconstitution of the ICA" (45)) and type B ("an abrupt occlusion with supraclinoid reconstitution" (45)). Mechanical thrombectomy is suggested to be the preferred method compared to intravenous thrombolysis. (45)

Nevertheless, in patients where recanalization cannot be completed promptly, the clinical outcome is dependent on the perfusion of penumbra. Evidence suggests that high arterial blood pressure leads to better functional outcomes as this reduces the infarct volume because penumbral perfusion increases due to collaterals. (45)

13. BRIDGING THERAPY

Intravenous thrombolysis prior to endovascular therapy is called bridging therapy. This might have several positive effects such as faster recanalization, prolonging of the time window for endovascular therapy (due to partial resolution of the thrombus), and peripheral thrombi will dissolute. Nevertheless, tPA takes time, increases the risk of hemorrhagic transformation, is cost intensive and might even delay further treatment. Currently it is recommended not to perform bridging if thrombolysis would delay thrombectomy, but otherwise bridging therapy should be used as standard treatment. (46,47)

14. RISK OF ALTEPLASE IN THE EXTENDED TIME WINDOW

Alteplase is known to increase the risk of intracranial hemorrhage within the first 48 hours after administration. It has been shown that the risk of hemorrhage transformation might increase in the extended time window. Recently, several predictive methods have been studied to evaluate the risk of hemorrhagic transformation after thrombolysis. Several scores are formed including SEDAN, HAT, SITS SICH, and MSS. These scores were rarely used in clinical practice and more commonly used in research. The main factors these scores are focusing on are the blood glucose levels, NIHSS, age, CT findings, and risk factors such as hypertension. Most of them report an increased risk of hemorrhage with higher age and blood glucose. Interestingly, the risk for hemorrhage is higher, the higher the NIHSS, and consequently the more severe the stroke is. (46,48)

Disruption of the blood brain barrier (BBB) is associated with hemorrhagic transformation and parenchymal hematoma. Nevertheless, there is "no clear dependence between the time from symptom onset to imaging and the severity of BBB disruption" (49). In elderly people for example, the BBB permeability is increased in general, which leads to a poorer integrity. Imaging techniques of the BBB are helpful in identifying more patients which could receive

tPA even outside of the time window. Trials ascertained that the BBB disruption is not time dependent and progresses distinctive in each patient. (49)

15. ADJUNCTIVE THERAPY APPROACHES

Several factors have been suggested to be the cause of complications related to systemic thrombolysis. The main mechanisms include “disruption of the blood-brain-barrier (BBB), damage to microvessels, and the toxic and non-thrombolytic actions of tpA” (50). Consequently, adjunctive therapy methods have been studied, which could potentially target these mechanisms. Possible hemorrhagic bleeding, following systemic thrombolysis, should be addressed by adjunctive interventions. The most ideal adjunctive therapy would include decreasing the risk of hemorrhagic bleeding as well as having neuroprotective properties. (50,51)

15.1. Pharmacological Adjuvants

It has been shown in male rats that administering oral vitamin C (ascorbic acid) 5 hours after stroke, reduces the infarct volume and cerebral edema and exerts neuroprotection. However, the influence on hemorrhage transformation is not yet determined. (50)

Atorvastatin was found to have neuroprotective functions in terms of decreasing the embolus’ size and infarct volume, improving neurological functions and microvasculature, without increasing the risk of hemorrhage. Therefore, statins are favorable add-ons to systemic thrombolysis. (50)

Bryostatin is a protein kinase C modulator. Through several mechanisms, it is considered that bryostatin decreases the damage to tight junction proteins within the BBB. Therefore, as a co-treatment with tPA, it is thought to have a beneficial effect upon hemorrhage caused by thrombolysis, as well as BBB disruption. (50)

The phosphodiesterase enzyme III (PDE-III) inhibitor Cilostazol decreased the infarct volume and hemorrhagic transformation in mice, as well as improving neurological deficits. Brain edema, morbidity and mortality were decreased. (50)

The tetracycline antibiotic minocycline has been shown to inhibit the activity of metalloproteinases (MMP). The treatment with minocycline 4 hours post-stroke, together with tPA at 6 hours post-stroke led to a reduced infarction size, and improved brain hemorrhage at 24 hours after stroke. MMPs are known to play a role in the disruption of the BBB, and plasma levels are lower in patients treated with minocycline. (51)

Fasudil is a Rho kinase inhibitor which was originally developed for the treatment of cerebral vasospasms in subarachnoid hemorrhage patients. In combination with tPA it showed to alleviate hemorrhagic transformation after 18 hours. Moreover, decreased mortality and increased locomotor activity is demonstrated in the combination group. Fasudil decreased the activity of MMP-9 which prevented injury to endothelial cells in both acute and subacute cerebral injury. (51)

Myeloperoxidase (MPO) is an inflammatory enzyme, expressed in inflammatory and other cells such as neutrophils, microglia, monocytes, astrocytes, and neurons. In ischemic stroke patients an increased activity of MPO was shown. Consequently, MPO activation contributes to inflammation, oxidative stress, and brain damage severity. Several traditional herbs are reported to inhibit MPO activity and therefore reduce cerebral ischemia-reperfusion injury. Flavonoids, such as quercetin, reduced the size of the infarcted core and neural damage due to oxidative stress. They have anti-oxidative properties and act in an anti-inflammatory way. Polyphenol has as well anti-oxidative and anti-inflammatory properties and additionally acts as a neuroprotectant by inhibiting MPO activity. Examples for polyphenolic compounds include resveratrol, curcumin, and cannabidiol. Several other compounds are studied until now and showed positive effect by targeting MPO so far, therefore decreasing the infarction size and improving neurological outcomes. Medicinal herbs could bring promising results in targeting MPO activity and reducing reperfusion injuries in the future. (52)

Acidic postconditioning (APC) is a therapy method where the patient inhales 20% CO2 during reperfusion. This is hypothesized to reduce cerebral ischemia. The mechanism is not yet fully understood, but studies showed that acidosis helps to remodel healthy mitochondria on one hand, and on the other hand remove defective ones via the mechanism of mitophagy, which has neuroprotective effects. Mitochondria are considered to be “the principal source of reactive oxygen species upon cerebral ischemia reperfusion” (53). The process of APC-induced mitophagy is thought to be facilitated by PARK2 recruitment to mitochondria. APC treatment extended the reperfusion time window by approximately 2 hours and had neuroprotective effects even after 6 hours. (53)

15.2. Non-Drug Adjuvants

Several studies displayed, that normobaric hyperoxia therapy might protect the blood-brain-barrier against ischemic damage, by inhibiting the production of reactive oxygen species and inhibiting the damage of tight junction proteins. This reduced the hemorrhage transformation of systemic thrombolysis, brain edema, infarction volume and mortality in rats. Neurological

functions have improved after the co-treatment of oxygen and thrombolysis. Besides, it is hypothesized that this form of treatment could increase the therapeutic window of systemic thrombolysis in ischemic stroke patients up to 7 hours or more. (50,54)

Mesenchymal stem cell transplantation is considered to be a method which reduces stroke volume and the risk of hemorrhage, while improving the functional outcome. (50) The transplanted stem cells migrate to the area of cerebral infarction and induce tissue healing. The cells secrete neuroprotective factors which activate angiogenesis and neurogenesis. There is evidence suggesting that the cells could be administered intravascularly as well, which would be an alternative for intracranial transplantation, but further studies are needed in this field. (55)

Thrombolysis in the extended time window leads to reactive hyperemia which results in damage to the neurovascular tissue and is considered a sign of reperfusion injury. This can be suppressed via mild hypothermia. Local brain hypothermia in cerebral ischemia is thought to have neuro- and vasculoprotective effects. Cooling the brain to around 33°C within 10 minutes and keeping it at this level for 30 minutes after tPA, led to reduced side effects caused by tPA treatment after 6.5 hours post-stroke onset. Hypothermia reduced the BBB breakdown, decreased brain edema, reduced the infarction size, enhanced neurological functions, and improved the safety of tPA and endovascular therapy in extended time windows. (56)

16. PREDICTORS OF GOOD OUTCOME

A retrospective clinical Chinese trial investigated which parameters predict good outcomes in stroke patients. The study included 63 patients, with a median age of 64 years. The median NIHSS was 8 (interquartile range 3-13). Patients who were presenting late (>4.5 hours after onset) or waking up with stroke symptoms were included. The used imaging modality was CT. 66.7% of the included patients had a good outcome after 90 days (mRS 0 to 2) and 3 patients died during 90 days of observation. First, this outcome shows that tissue-window is a safe and effective way to suggest patients for thrombolysis outside of the presently accepted time window. The patients' older age was associated with a poorer outcome after 90 days. A possible reason for this might be fewer synapses and reduced volume of cortical gray matter. Not only a higher ASPECT score, but also a higher regional leptomeningeal score on CT were found to correlate with good outcomes. The rates of death as well as symptomatic intracranial hemorrhage were increasing when ASPECTS value decreased. Moreover, good collateral circulation is related to a better outcome. The larger the infarct core, the ischemic penumbra, and the sum of both the worse the prognosis for the patient. However, this does not exclude all

patients with larger perfusion lesions from thrombolysis treatment. The ischemic penumbral size is the most important factor to identify salvageable tissue and patients who are likely to benefit from reperfusion therapy. Despite the larger lesion suggesting a worse outcome, it must be kept in mind that a smaller region in a core functional area such as brain stem, might be even worse than a larger lesion in other areas. Hence, the NIHSS is another important predictor. A lower baseline NIHSS suggests a better functional outcome. (57)

Cerebral collateral circulation is a key factor in predicting the functional outcome of a patient. Main sources for collaterals are anastomoses from the facial, maxillary, and middle meningeal arteries to the ophthalmic artery, as well as dural arteriolar anastomoses from the middle meningeal artery and occipital artery. Primary collaterals describe the collateral blood flow for the circle of Willis, whereas secondary collaterals involve the ophthalmic artery, pial collaterals and anastomoses. The method used to identify collaterals is mainly CTA. Here, the measurement of the collateral blood flow is basically the mismatch between the ischemic core and the penumbra. Obviously, the volume of penumbra tissue is dependent on the number of collaterals, and therefore a poor collateral status is a poor prognostic factor for the functional outcome. Areas that are known to have poor collaterals, for instance the basal ganglia, are likely to be infarcted faster. (58,59)

Cerebral venous supply is less often focused on in terms of diagnostic and prognostic factors. Nevertheless, it is the main reservoir of cerebral blood volume and consists of deep and superficial veins. Recently, the Prognostic Evaluation based on Cortical vein score difference in Stroke (PRECISE) score was developed to assess venous collateral blood flow and see if it is related to perfusion mismatch and the prognosis of stroke. A trial showed that a higher PRECISE score, was related to poor superficial vein filling and unfavorable clinical outcome. (58)

Optimized cardiac output might increase the arterial blood pressure slightly, and consequently there is a better collateral blood flow to the penumbra. This reduces the final infarct volume and leads to better functional outcomes. This is why blood pressure should not be reduced too much or too fast in ischemic stroke patients. (45,60)

Several drugs are thought to improve the collateral blood flow such as nitric oxide, albumin, or tumor necrosis factor-α inhibitors. Chronic use of statins is related to a greater collateral score. Inhaled nitric oxide might increase the penumbral blood flow and reduce the infarct volume. Several genetic studies are analyzing what factors are enhancing collaterogenesis. Some of them could bring promising results in the future, as the collateral blood flow definitely protects the brain in acute ischemic stroke and is an important factor to address in stroke therapy. (58,59)

17. THROMBOLYSIS IN SPECIAL PATIENT GROUPS

17.1. Pregnancy

Pregnancy is a risk factor for acute ischemic strokes. The incidence of stroke during pregnancy and postpartum period is 30:100,000. (61)

Major reasons for not administering thrombolysis in pregnancy are the risk of maternal or fetal bleeding complications, which could even result in fetal loss. Preeclampsia or other forms of hypertension during pregnancy increase the risk for stroke even more, in addition to the fact that these women are likely to experience more complications and poorer outcomes. However, recent study data anticipated that pregnant and postpartum women have a similar outcome when receiving reperfusion therapy, compared to non-pregnant women. Nevertheless, fewer women were treated with thrombolysis as monotherapy, mainly due to pregnancy itself or recent surgery. (62)

An interesting case review describes the use of alteplase in a 28-weeks-pregnant, 35-year-old woman in an extended time window. She had an initial NIHSS of 4. An MRI including MR angio- and venography was performed and an occlusion of the distal M2 branch of the right middle cerebral artery was found. Due to the location, mechanical thrombectomy could not be performed. The imaging showed only hypoperfusion, but no infarction was yet visible, even though the time passed since last seen normal was already more than 4.5 hours. Thus, systemic thrombolysis with 0.9mg/kg bodyweight (10% as a bolus, the remainder over 60 minutes) was performed 8.5 hours after the onset of symptoms. The patient noted resolution of the symptoms and complete recanalization was visible during MRA after 24 hours. She took low-dose aspirin and enoxaparin until 24 hours before her elective induction. The child was born healthy with an uncomplicated vaginal delivery. This case impressively describes the possibility of successful treatment without adverse effects in pregnant women in an extended time window. (61)

17.2. Childhood

Ischemic stroke rarely affects children or neonates. The estimated incidence is around 1.6/100,000 children/year. Newborn children have the highest incidence with 1:4000 live births. Currently, pediatric guidelines are only based upon limited evidence. (63,64) Mainly all information about the usage of tPA in children comes from case reports, small case series or

hospital databases. The usage of thrombolytic agents could be considered in patients below the age of 18 years. Up to 2% of children with acute ischemic stroke are reported to have been treated with tPA in the United States. The risk of symptomatic intracranial hemorrhage is the main concern when administering tPA. However, the risk is thought to be lower, in younger patient groups. (65)

Children often present differently with acute ischemic stroke compared to adults. They might even present with non-specific symptoms such as cardiorespiratory symptoms in neonates. Possible clinical presentations are shown in Table 2. Due to the difference in presentation, the median time for diagnosis is significantly longer when compared to the adult patient group. (66)

Table 1. Possible clinical AIS presentation.

Perinatal AIS	**Childhood AIS**	**Stroke-Like Symptoms**
Seizures	Hemiparesis	Migraine
Cardiorespiratory symptoms	Facial unilateral weakness	Headache
Altered consciousness	Speech disorder	Confusion
Failure to thrive	Vision abnormalities	Syncope
Feeding intolerance	Altered Consciousness	Nausea and Vomiting
		Seizure with Todd paresis
		Bell palsy
		Altered consciousness

Modified from Klučka et al., Pediatric Patient with Ischemic Stroke: Initial Approach and Early Management. (66)

In neonates it is currently recommended to treat with supportive care. The usage of aspirin, low-molecular-weight-heparin or unfractionated heparin is rarely indicated, as it increases the risk of recurrent strokes. The usage of thrombolytics and mechanical thrombectomy is uncommon in newborns because of limited evidence for their use. (64)

In childhood, tPA or endovascular therapy are still discussed controversially. The TIPS trial showed that due to differences in childhood plasminogen levels, children might need higher

dosage of tPA compared to adults. Nevertheless, the current recommendations suggest the adult dose of 0.9mg/kg bodyweight, in a time window of up to 4.5 hours. (64,65)

Endovascular thrombectomy might outclass systemic thrombolysis, as the time window is longer for the intervention. Yet, there are special considerations such as smaller arteries, limitations for radiological contrast material due to the child's weight, or radiation exposure in young ages. In fact, studies have shown that children may have a good functional outcome, without any neurological deficits, even without treatment in one-third to one-half of cases. Consequently, the risks of treatment might counterbalance the benefits, especially in a child with a low pediatric NIHSS score. (64)

An interesting case report is presenting a 9-year-old boy, with a suggested M1 segment occlusion of the middle cerebral artery, diagnosed by MRI. The boy was last seen normal 7 hours before that. He was thought to be a good candidate for mechanical thrombectomy, as he presented with a small core infarction and large penumbra. The recanalization was achieved within 1.5 hours of completion of the MRI, which made a total time of 8.5 hours after the onset of symptoms. Upon discharge the child had a pediatric NIHSS score of 1 and a mRS of 1. This leads to the assumption that children might benefit from endovascular therapy in an extended time window. (63)

17.3. Posterior Circulation Stroke

Posterior circulation stroke (PCS) is an infarction within the territories of the vertebral, cerebellar, posterior cerebral, and basilar artery. These vessels supply the medulla oblongata, pons, cerebellum, mesencephalon, thalamus, and regions of the temporal and occipital lobe. A lot of collaterals are present in the posterior circulation, and symptoms vary widely. Common symptoms include dizziness, unilateral limb weakness, dysarthria, gait ataxia, headache, nausea and/or vomiting, and nystagmus. This variety of symptoms is one reason for a potentially late diagnosis of PCS. (67)

NCCT is less sensitive to detect PCS (sensitivity 41.8%) compared to anterior circulation stroke (ACS). DWI is the main imaging modality used nowadays to identify PCS. Yet, it must be kept in mind that these types of strokes have a 5 times greater chance to be DWI-negative up to 72 hours after symptom onset. FLAIR has a low sensitivity and specificity which makes it harder to rely on DWI-FLAIR mismatch imaging. In the extended time window, it is recommended to use MRI PWI-DWI mismatch if available. To predict the clinical outcome, it is suggested to use the ASPECTS score applied to the posterior circulation (pc-ASPECTS) upon pre-intervention DWI. (68)

Most of the available data about the efficacy and safety of tPA in the extended time window comes from trials focusing on anterior circulation strokes. A retrospective cohort study compared the usage of tPA in an unknown or extended time window in patients having a PCS to an ACS. The results showed a trend for slightly lower incidence for hemorrhagic transformation in PCS patients compared to ACS patients following thrombolysis. There were no statistical differences in early neurologic improvement, mortality rates or functional outcomes between both groups. These results describe that intravenous thrombolysis has similar outcomes in PCS patients compared to ACS patients and can be used in special patient groups even outside the normal time window. (69)

18. HDAC2 AS A NEW TARGET

Histone deacetlyases (HDACs) are a family of enzymes which change histones by removing acetylgroups from the acetylated amino acid lysine. Consequently, they regulate the transcription of genetic information and the epigenetic repression. HDACs are further classified into 4 major classes (I-IV). Class II HDACs have two subclasses (IIa and IIb). Two isoforms of IIa HDACs (4 and 5) are commonly expressed in the brain and seem to play a role in the regulation of neurodegeneration. They are predominantly expressed in the cytoplasm. (70)

Class I HDACs on the other hand are restricted to the nucleus where they control the transcription. They include HDAC1, HDAC2 and HDAC3. Animal studies showed that HDAC2 in the peri-infarct cortex may be a key mediator for functional loss poststroke. The upregulation of HDAC2 after stroke has been shown to be caused by the production of free radicals and inflammatory factors due to tissue ischemia. It has been shown that inhibiting class I HDACs 5-7 days after stroke promotes functional recovery by improving survival and easing neuroinflammation. Moreover, inhibition of HDAC2 leads to a reduced release of gamma aminobutyric acid (GABA). GABA interacts with free radicals and therefore leads to neuroinflammation. Targeting HDAC2 consequently prevents secondary functional loss and opens a new time window in stroke treatment. (71)

19. CONCLUSION

Considering all types of ischemic stroke, only around 10% receive intravenous thrombolysis in most stroke centers. (72) Minimizing the time from the onset of symptoms until the start of the treatment is essential. Nevertheless, there are patients who are presenting late or are suffering

from wake-up stroke. Those patients should be evaluated thoroughly to maximize the treatment efficacy.

This review highlights in a narrative fashion different imaging modalities and treatment strategies for various time windows and special patient groups. There is no one best imaging modality, as all of them have their advantages and disadvantages. Further studies are needed to identify which imaging technique works out best for which patient.

Several trials are listed which hypothesize that the usage of thrombolysis and endovascular treatment leads to favorable outcomes in the extended time window. Major limitations of studies like ECASS 4 and EXTEND are that patients are included as wake-up strokes which were likely not to be in the extended time window. This might be a reason why the hemorrhage risk was relatively low. Another hypothesis is that a favorable penumbral pattern decreased the risk of hemorrhage formation. Studies support this, by showing favorable outcomes in patients with enhanced collateral blood flow leading to better penumbral perfusion. Consequently, calculating penumbral tissue improves safety in the extended time window stroke therapy. (73)

Further investigation is needed to identify special occlusion types and specific patient groups who would benefit from delayed reperfusion after more than 24 hours. The DAWN and DEFUSE trials suggest using endovascular therapy up to 24 hours and newest evidence even suggests the re-evaluation of intervention beyond that time window. Further research is needed to evaluate the effectiveness after 24 hours. (45)

Posterior circulation stroke patients are likely to be recognized late. FAST and NIHSS do not include main symptoms from posterior circulation stroke like gait ataxia or visual field disturbances which might lead to the late recognition. (67) Adaptations like the BEFAST scale now additionally include coordination (Balance) and diplopia (Eyes). This is an improvement to the standard FAST scale. (21)

Recently, adjunctive therapy methods showed promising results. Further investigations could improve stroke outcomes in various time windows, but explicitly in delayed reperfusion. Increasing the collateral blood flow and preventing blood-brain-barrier disruption seem to be important targets. (50) Therapy methods targeting secondary functional loss are not always the earlier the better, as there is a period most critical for secondary neuron loss. Treatment with trichostatin A (HDAC inhibitor) for example was found to be ineffective in early stages after stroke. Nevertheless, early physical therapy is needed in addition to these kinds of treatment. Targeting HDAC2 in post-stroke phase brings hope for stroke surviving patients. (71)

To conclude, carefully selected patients are likely to benefit from reperfusion methods in the extended time window. Patients should be selected upon a case-to-case basis and with the help of best possible imaging modalities for each specific case, rather than relying solely upon the time passed since last seen without symptoms. Further investigations are needed to update treatment guidelines and prolong the time window. It is mandatory to elaborate guidelines which are rather focusing upon the individual patient than the strict time window.

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