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REVIEW

Time window and "tissue window": two approaches to assist decision-making in strokes

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Abstract
Intravenous alteplase given in an appropriate time window has been recommended in guidelines and effects are on the decline over time. In general, the clinical decision is primarily based on whether ischemic stroke patients are sent to hospitals within the time window. However, some patients sent to the hospital over time limitations are eligible to receive intervention for recanalization due to good collateral circulation. In this dilemma, "tissue window" can be more reliable, which means using the penumbra as a major criterion for patient recruitment. Hence, we herein aim to address how could "tissue window" be a complementary approach when it does not conform to the time window's indication and affirming value of the later one. Some efforts obeying the time window are discussed first. In the later sections, we give the details of the definition of "tissue window", and then compare various neuroimaging techniques to determine the penumbra and summarize favorable patterns. Finally, we will focus on how the "tissue window" extends the therapeutic time window under specific circumstances.

Keywords Brain ischemic · Thrombolytic therapy · Neuroimaging · Diffusion magnetic resonance imaging · Penumbra

Introduction

In many western countries, stroke is a major cause of death, followed by coronary heart disease and cancer; stroke is also an important reason of disability [1]. With the burden of stroke gradually increased, the situation is more severe in China nowadays. To save the reversible ischemic brain tissue as much as possible, it is necessary to find appropriate approaches to assist decision-making. The time window mainly focuses on the ischmia time from the onset of initial to recanalization, as early recanalization means preventing infarct area from expanding. However, classical thrombolytics, such as intravenous alteplase, have side effects (e.g., hemorrhagic transformation); therefore, this paper introduces some efforts that reduce the time from onset to reperfusion that could replace intravenous alteplase when it plays a minor role.

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It is not hard to conclude that though some patients are not sent to the hospital during the time window, part of them with sufficient blood supply, may be possible to save. Hence, "tissue window" can be a more transparent and reliable proof, since we could read the degree of ischemia in neuroimaging. The concept of "tissue window", first named by Professor Werner Hacke, was described as penumbra or mismatch [2] when screening patients on the basis of a large area of salvageable cerebral tissue. Little attention has been paid to "tissue window" and this paper makes efforts to present various neuroimaging techniques and favorable patterns. We aim to point out how the "tissue window" works even out of time limitation. Correct clinical decisions and early recanalization are important for good prognosis. We believe that further studies about this will make great sense.

Time window

Time window of intravenous thrombolytics therapy

Intravenous alteplase occupies the preferred position when patients are admitted to hospital early after symptom onset so that alteplase could be given within 4.5 h [3]. Treatment beyond time windows produces no net effects, since the

risks of symptomatic intracranial hemorrhage and death exceed the benefits [4], and, in addition, as the time lapses, the ischemic tissue may have evolved into infarction locus. Furthermore, evidence represented that effects of alteplase were relatively different beyond 3 h, but within 4.5 h of symptom onset, the benefits weaken measurably [5]. We need to note that alteplase also should be avoided to prevent complications in some situations; the most severe complication is hemorrhagic tendency; even with low doses [6], there might be a percentage of symptom intracranial hemorrhage. Alteplase is not normally given to elders who are older than 80 years despite its benefit [7], since they would have a higher risk of hemorrhage. Side effects are one site. The other is that the therapeutic effect does not always work on patients with acute stroke that results from large vessel occlusion [8]; it was concluded that relative resistance to intravenous alteplase may partly account for it. However, proximal artery occlusions (i.e., middle cerebral artery and internal carotid artery) take up the third of acute ischemic stroke [9]. Some efforts have been made to explore other thrombolytics that have pharmacological advantages in treatment, such as tenecteplase [10], which is being compared with alteplase in several randomized trials, although it seems to have increased resistance towards plasminogen activator inhibitor-1 [11]. The primary outcomes indicated that tenecteplase was not superior to alteplase either in efficacy or safety profile. The results differed on the rates of symptom intracranial hemorrhage; some trials reported higher [12], while others had lower rates [13], although these trials used tenecteplase with the same dosages. Higher fibrin specificity could be used to explain higher frequency, and some trials enrolled patients with mild stroke contributed to almost the same outcomes as with alteplase. Factors mentioned above indeed have impact on the stage of "the only evidenced and approved" treatment strategy [14], which means it is necessary to find out alternative therapies and more reliable approaches for enrollment.

Time window of endovascular therapy

The endovascular therapy occupies an important position as complementation of intravenous thrombolytics. Several generations of devices have been produced and different time thresholds have been reported in recent clinical trials. The FDA has admitted the MERCI retriever for cerebrovascular thrombectomy for more than a decade. The efficacy of the third device, the SOLITAIRE stent retriever, was established in a SWIFT trial not only in recanalization but also produced favorable functional outcomes compared with the MERCI retriever [15]. According to a randomized comparison trial, treatment with a TREVO stent retriever has similar advantages over the Merci devices [16]. Obviously, early reperfusion is equally important for patients who are under intra-arterial therapy, but the comforting thing is that when trials enrolled patients 6 h from the onset resulted in improved outcomes [17]. Advanced technology means that the faster process from puncture to thrombus area, reducing the precious time for more ischemic tissue to be rescued; these devices also provide higher rates of recanalized proximal artery occlusions with fewer procedure-related complications (devices fracture, vessel perforation, etc.) [18]. These factors may partly explain the differences in outcomes between trials. Moreover, from the MERCI to SWIFT PRIME [19], these trials enrolled patients with sight discrepancies in median time onset to treatment, which meant a randomized, controlled trial comparing time window was essential for analysis. Nevertheless, more recent attention has focused on how standard intravenous thrombolysis might be complemented by additional or alternative non-pharmacological treatment approaches. A survey that Broderick et al. conducted indicated early thrombectomy compared with alteplase alone improved reperfusion, early neurologic recovery and functional outcome [20].

Novel concepts proposed to reduce time from onset to reperfusion

Along with the new drug discoveries, some concentrations turned to using mobile stroke treatment units, which could provide pre-hospital thrombolysis. A observational registry study found no significant difference between the proportion of patients with a mRS score of 1 or lower with conventional care, but a pre-hospital start of intravenous thrombolysis did [21]. As this was a registry study, these evidences need future large-scale trials to obtain further supporting data. Besides, there are medical and health organizations calling for enhanced community education. If there are friends or relatives who understand and can recognize the common symptoms with stroke patients, those patients might be sent to a hospital sooner for adequate treatment. Another suggestion is establishing a well-trained stroke treatment group in stroke centers; only when the whole group has professional members and advanced technical equipment higher rates of reperfusion could be obtained. If conditions allow, during the transfer to intra-arterial thrombectomy, many stroke centers could begin intravenous alteplase as bridging, making the alteplase given within time window as necessary [22]. Co-administering could be applied for patients who had accepted intravenous thrombolysis but failed then to undergo thrombectomy, which is superior to intervention alone.

"Tissue window"

A central consideration in the development and optimization of novel acute stroke therapies is the concept of the ischemic penumbra, which has a different cerebral blood

supply and metabolism compared with ischemic core; the former suffered less damage, surrounding the ischemic core and has benefits from early reperfusion. Penumbra could be called for "tissue window" [2] as a major criterion for patient recruitment in relative trials. It was used in a DAWN trial [23], described as an area of brain tissue that was poorly perfused but not yet infarcted. In essence, the widely recommended earlier treatment that produced superior outcomes could have a relationship with the ratio of hypoperfused issue and the infarction and the effectiveness changes as the time passes.

Various neuroimaging techniques to define penumbra

We need a superior imaging to determine whether the penumbra is an area at verge of infarction or just hypoperfused [18]. Recent trials about imaging-based selections for reperfusion therapies led to produced mixed results. Demeestere et al. analyzed noncontrast CT (computed tomography) ASPECTS and CT perfusion to determine which one would more accurately and more clearly predict the lesion core of DWI [24]. The results demonstrated that the cutoff CT perfusion core volume and ASPECTS predicted similar outcomes. As for brain perfusion imaging in MRI (Magnetic Resonance Imaging), there were some clinical trials that reported that both of them (using CT or MRI) could reliably distinguish the penumbra from the ischemic core [25]. Diffusion-weighted imaging (DWI) could present irreversible ischemia with a hyperintensity area, while perfusion-weighted imaging (PWI) tended to use a variety of colors to show different extents of hypoperfusion. The most obvious advantage of PWI was that the ischemic penumbra could be identified by abnormal transit time, which could not be determined using DWI.

Favorable patterns of "tissue window" for selection

A problem needing to be solved is the exact definition of favorable patterns for idea clinical response to reperfusion. Table 1 presents data of imaging selection and clinical outcomes in recent trials [24, 26–31]. Some evidence supported a viewpoint that infarction size was the only thing that mattered [32], which reflected the intra-artery treatment benefits. After all, it is easy to guess that even with an obvious penumbra that surrounded a large core could not prevent the damage that had been caused. Findings of the DEFUSE-2 study indicated that target mismatch profile was a promising imaging approach for decision-making for treatment when compared to DWI and PWI [33].This concept was adopted in some trials as a criterion for selecting patients most likely to benefit from intra-artery care. Two studies about imaging-based selection produced different outcomes. In the DEFUSE-2 study [33], researchers defined the favorable pattern as penumbra to infarct core ratios > 1.8; patients after selection reached a higher success rate of reperfusion, while in the MR RESCUE trail, a phase 2b, open-label, randomized clinical trial [34], there was no significant evidence to support imaging. The differences were partly due to the discrepancy of threshold in the selection; the latter defined penumbra to core ratio as greater than 1.2. In addition, the MR RESCUE study included a small part of CT reperfusion as evaluation criteria may account for it, since there were other studies that used MRI perfusion that only acquired positive outcomes.

A notable trait of "tissue window": allows a wider time threshold for therapy

"Tissue window" also provides a prolonged time window for endovascular therapy in patients that are slowly deteriorating. This application possibility was further verified by a

Table 1 Imaging selection and clinical outcomes in recent trials

Study	Core	Penumbra to core ratio	Clinical outcomes
EXTEND-IA [26]	Perfusion infarct < 70 ml	Ratio > 1.2	mRS 0–2.71 vs. 40%; $P = 0.01$
SWIFT PRIME [27]	Perfusion infarct < 50 ml	Ratio > 1.8	90 days mRS 0–2.60 vs. 35%
MR RESCUE [28]	Predicted core < 90 ml	Ratio > 1.4	90 days mRS mean score, 3.9 versus 3.4; $P = 0.23$
Bivard, 2014 [29]	Ischemic core < 70 ml	Ratio > 1.8	90 days mRS 0–2, 13.8, $P < 0.001$
Lansberg, 2017 [30]	Ischemic core < 70 ml	Ratio > 1.8	OR = 6.6(95% CI 2.1–20.9)[a]
DEFUSE 2 [31]	Ischemic core < 70 ml	Ratio ≥ 1.8	OR = 5.2(95% CI 1.4–19)[a]
Demeestere, 2017 [24]	CT Perfusion core ≥ 50 ml[b]	Not required	AUC 0.79 [95% CI 0.67–0.90]
Demeestere, 2017 [24]	DWI lesion ≥ 70 ml[b]	Not required	AUC 0.95 [95% CI 0.90–1.00]

OR odd ratio, *CI* confidence interval; *mRS* modified ranking scale, *AUC* area under the receiver operating characteristic curve

[a]Means increased odds of favorable clinical response

[b]Means imaging approaches predicted poor clinical outcomes

study using CT perfusion for selection of patients for endovascular therapy [26]. Not only did it assist decision-making for stroke thrombolysis, but also made the time window to remain open [35]; that meant that for patients with target mismatch, it was quite possible to receive good prognosis after reperfusion, even after being admitted to the hospital over the limit of 6 h, some of them still waiting for approval to receive intervention. In this sense, time limitation of endovascular was no longer 6 h for qualifying patients. This could be seen in the DAWN trial [23], which included patients with occlusion of a large cerebral vessel and who arrived at the hospital between 6 and 24 h after the onset of stroke. It was halted on the basis of results of a prespecified interim analysis. Evidences of perfusion CT/MRI-based selection with tenecteplase for thrombolysis also supported the extended time windows of 24 h [36]. Contrary to these positive outcomes, a randomized trial of intravenous thrombolysis that required evidence of penumbra imaging did not produce the expected results [28], probably because they selected patients using relatively loose criteria and small penumbra. However, the efficacy does not mean generally extending the therapeutic time window as practicable. It seems that only the proportion of patients with occlusion of large vessels and who have a small infarction and a large penumbra acquired priority outcomes even in late times [23].

Non-traditional modes of "tissue window"

Despite pH-weighted magnetic resonance imaging being used infrequently now, in a proof of principle clinical study, various degrees of intracellular acidosis represented varying degrees of brain damage. The findings supported the need for further investigation of pH-weighted imaging [37]. The ability of the MRI has been limited to detecting pathophysiological processes; however, according to PET studies [38], PET was not only accorded with the requirements for detecting and quantifying metabolic processes, but also imaging at the neurovascular interface contributed to the understanding of cerebrovascular diseases.

Discussion

Intravenous rtPA remains the standard of care for patients with acute ischemic stroke who presents within 4.5 h from onset of symptoms. Endovascular therapy has a moderately wider time window. Compared to time window, penumbra profiles are visualized under imaging devices; once it exceeds the time limit, it may be the only objective one to assist decision-making for treatment.

Comprehensively, we try a retrospective application of time window and to focus on other novel techniques or concepts applied for early reperfusion for obeying the time window. What is equally important is the superiority of the "tissue window". It allowed endovascular therapy 6–16 h from onset after perfusion imaging for patient selection in the DEFUSE-3 trial [39]; assessing the salvageable area based on data analysis would be more precise. Several lines of evidence suggested that neuroimaging was fast becoming a potential approach to predicting infarct volume [40]. Considering the cost of advanced techniques, the "tissue window" could be much more widely available only when economic considerations allow, while the time window would still play an important role for a long time.

There exist disputes about the most favorable patterns for good clinical outcomes when comparing various randomized trials; penumbra to core ratios of > 1.8 were approved by most studies. Besides, we still have a way to go to evaluate the perfusion map; a notable example is that although a severe reduction of perfusion in the occluded artery, if recananlized early enough, it might not grow into infarcts [41]. We cannot forget that imaging is only the substitution of immediate brain metabolism.

Various modes of efforts to hasten reperfusion therapy should be made to attain wider applications for time window. Recent trials explored other aspects about penumbral salvage (e.g., if the growth rate of early imaging evidence was relevant to clinical outcome. [42]) giving us more details for future applications. Taken together, both approaches require investigative progress to increase the number of stroke patients receiving accurate therapy in the near future.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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