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Thrombolytic therapy for acute stroke: the hidden dimension

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There are many dimensions in the struggle to provide better care for patients with ischemic stroke including patient education, logistic organization both before and during hospitalization, economic, and legal issues, as well as the continuing quest for more effective therapies.

For years, the management of acute ischemic stroke, has been a source of frustration and dismay for physicians, families, and even patients alike, as effective treatment to reverse a neurologic deficit was lacking.

Now, despite the availability of thrombolytic therapy that leads to better outcomes, the exasperation continues as the percentage of patients receiving such treatment languishes in the single digits.

Cornerstone to the improvement of stroke therapy is the development of guidelines and education of physicians involved in the treatment of these patients. But education is not enough as some neurologists have chosen not to participate in the care of stroke patients, which makes clear that if neurology wishes to retain acute stroke care as part of their "turf," those willing to care for these patients within the specialty must be knowledgeable about current best treatment and be part of a peer review system to monitor the care delivered.

These steps are important considering that at the base of effective stroke management is its prompt and accurate recognition. But what lead the need of rapid recognition and treatment was the understanding of the pathophysiological phenomenon called ischemic penumbra which provided the medical community with a lucid explanation of acute ischemic stroke and the rationale of the treatment. In addition, it had driven home the message that for many stroke patients salvation of critical brain tissues is possible.

One would imagine that with these fundamentals we are better equipped to tackle the dark cave of acute stroke management. However the situation is more complicated considering that regardless of how accurate or rapid the diagnosis is made, the definite imaging diagnosis of penumbra is still a source of controversy as I will explain. For years and in absence of a better marker for potentially salvageable tissue, Time is brain has been an appropriate mantra for the prompt delivery of stroke care, and the earlier articles and works emphasized its importance. But like the "Carrier pigeon" it has become, in my opinion, a myth that should be replaced by Physiology is brain, as imaging technology can potentially free us from the time constrains by objectively demarcating the penumbra regardless of the time frame and therefore unleashing this hidden dimension that can help expand the benefit of thrombolysis to a wider acute stroke patients population. Considerable efforts have been made to squeeze more of the now ancient concept of Time is brain trying to expand the benefit in favor of stroke patients. In a study by Rudd et al. (2010), they could show from observational data extracted from the National Sentinel Stroke 2008 Audit, that thrombolytic rates are low in the United Kingdom. Fourteen percent of patients were potentially suitable for thrombolysis using the 3-h time window.

The number increased only marginally if the window was extended to include those up to 4.5 h. There is no doubt that the biggest impact on increasing the proportion of patients suitable for thrombolysis would be by increasing the number of patients presenting early and by demonstrating that the treatment is safe and effective in patients over 80 years.

Contemporary effective stroke care is complex, and its optimization requires the cooperation and efforts of many individuals with different training and skills, this must be emphasized as a crucial factor. Efforts paid in this direction should be more encouraged when we speak "time is Brain" language to purify the current guidelines from some beliefs that actually hinder the benefit of thrombolysis from reaching a wide population of patients. On the other hand, the reading coming from similar studies should not hinder the efforts invested in developing technology of imaging the brain physiology; the main core of "Physiology is brain" language.

Imaging holds the key for further development despite some limitations. Perfusion/diffusion mismatch can provide a working estimate of the ischemic penumbra in hyperacute stroke and has been successfully used to triage patients. Physiology is brain can expand the therapeutic window for thrombolytic therapy. When large CT-based clinical trials (The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995; The NINDS and t-PA Stroke Study Group, 1997; Hacke et al., 2004) failed to prove the benefits of intravenous tissue plasminogen activator (tPA) administration in ischemic stroke patients beyond 3 h of the onset, the concept of PWI/DWI mismatch emerged which is the volume difference between a PWI lesion and DWI lesion on MRI scans. It was proposed to facilitate the selection of patients with a salvageable area as PWI/DWI mismatch is considered to represent the tissue that is not irreversibly injured and can respond to early reperfusion therapy. In order to clarify the clinical significance of PWI/DWI mismatch in the selection of candidates for tPA therapy, some multicenter trials were performed. Results of desmoteplase in acute ischemic stroke (DIAS), dose escalation of desmoteplase for acute ischemic stroke (DEDAS), DIAS-2 did not definitely demonstrate the clinical benefits of desmoteplase administration in patients with PWI/DWI mismatch between 3 and 9 h of onset; moreover, DIAS-2 could not prove any effect of the drug. However, many lacuna of the study were revealed that explain these shocking results and were considered enough rationale for the dawning of the DIAS-3 trial. Diffusion and perfusion imaging evaluation for understanding stroke

evolution (DEFUSE), in which tPA was administered to all participants between 3 and 6 h of stroke onset, showed that the occurrence of early reperfusion led to a favorable clinical response in patients with PWI/DWI mismatch. In contrast, early reperfusion was not beneficial in patients without PWI/DWI mismatch. In echoplanar imaging thrombolysis evaluation trial (EPITHET), stroke patients who showed PWI/DWI mismatch between 3 and 6 h of the onset were assigned to receive either alteplase or placebo. Lesion growth was lesser in patients with alteplase than in those who received placebo, although the difference was not statistically significant because of a small number of participants (Heidenreich et al., 2008; Kakuda and Abo, 2008). Although these results supported the importance of the PWI/DWI concept, there still remain some issues to be resolved. Regarding the definition of PWI/ DWI mismatch, a larger mismatch ratio than the one that has been typically used seems to be recommended.

The application of MRI-based decision making strategy for stroke patients may facilitate the assessment and treatment of stroke patients beyond 3 h of stroke onset, and is expected to allow the use of tPA for a substantially greater number of patients. In retrospectively analyzed study, conducted upon 97 patients. In 20 of 97 patients (21%), the diagnosis changed after MRI. In 25 of 97 patients (26%), the presumptive treatment plan was changed after MRI evaluation. Thirteen patients had their treatment changed from thrombolytic to non-thrombolytic therapy. Three patients were changed from non-thrombolytic to intra-arterial (IA) thrombolysis. In one patient, treatment was changed from intravenous (IV) to IA thrombolysis, and in five patients it was changed from IA to IV thrombolysis. In two patients, systemic heparin was added to antiplatelet therapy (Heidenreich et al., 2008; Kakuda and Abo, 2008). So, the utility of MRI, shown here to improve patient stratification into best-treatment options, demonstrates the value of using MRI to optimize care in hyperacute stroke patients.

Yet, no matter what we do, many patients will fail to reach the hospital within the short timeframe currently recommended for administration of IV thrombolytic therapy. This leaves the medical community perplexed to search for the other hidden angle that could complete the picture. Till all hidden dimensions for the picture are discovered the battle will continue without clemency.

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