From Thrombolysis, to Thrombectomy in Acute Ischemic Stroke

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Abstract: Until the early 1990s, ischemic stroke (IS) was considered a sinister fatality due to a lack of effective recanalization therapy allowing a prompt reperfusion of the ischemic brain, a key factor in reducing neurological disability. Over the past 30 years, the ischemic penumbra has gradually become the target of new reperfusion strategies to reduce ischemic stroke-related neurological disability. Ischemic stroke therapy has benefited from three major advances that upset its management: (1) The benefit of intravenous thrombolysis by Tissue Plasminogen Activator rt-PA. (2) The success of endovascular treatment for large arteries occlusion. (3) The development of stroke imaging. The "time is brain" aphorism anchored IS in the emergency field, which led to rapid transfers to stroke units. We propose to report the main stages of this therapeutic transformation in this major area of public health. Although access to these transformations remains limited in the world and much remains to be done to improve the IS care system, this area has experienced an unprecedented upheaval in the history of neurology.

1. Introduction

Until the early 1990s, ischemic stroke was marked by fate and a mere object of curiosity for neurologists fond of anatomoclinic confrontations. Despite the advances related to the discovery of the ischemic penumbra concept by Astrup [1], patients languished in emergency departments without brain imaging to differentiate between IS or hemorrhagic stroke. This approach was justified for many doctors by the lack of effective recanalization therapy restoring the brain blood flow. However, during the last 30 years, this pathology would benefit from major therapeutic transformations that upset its management and reduce the burden of IS disability. This upheaval lies in two dates: 1995, with the validation of rtPA in acute ischemic stroke in the United States, and 2015, with the approval of thrombectomy for large artery occlusion [2]. In addition, advances in stroke brain imaging have made it possible to better identify the area at risk of infarction whose salvage is the key to reducing neurological disability. As a result, the "time is brain" aphorism anchored IS in the emergency field and has allowed prompt transfer to stroke units. In fact stroke management became very close to myocardial infarction management as IS care has clearly integrated the validated therapeutics in cardiology developed 20 years earlier.

2. Literature Review

2.1. The Penumbra Concept

The penumbra is an unstable dynamic area that circumscribes the ischemic core [1], and its preservation is essential to limit the extent of ischemic damage and subsequent disability. The ischemic penumbra should be considered as a target for reperfusion and neuroprotective treatments.

2.2. Dicovery of Thrombolytics and First Application

The discovery of thrombolytics dates back to the 1930s [3,4]. Although effective in patients with peripheral arteries, these agents such as streptokinase or urokinase were not intended to treat ischemic stroke clots [5]. In 1958, Sussman and Fitch [6] reported the first use in AIS. Overall, early studies of thrombolytic therapy have been associated with disastrous results in the absence of relevant technical conditions and imaging tools to distinguish between ischemic and hemorrhagic stroke, and even pilot studies using angiography were struck by the same degree of inefficacity. However, computed tomography (CT) was not available at this time; accordingly, the distinction between hemorrhagic and ischemic stroke was not possible. In addition, clinical trials with streptokinase in the 1990s failed [7–9]. Some of these failures might be related to the lack of a real stroke network and poor stroke expertise in several countries and likely to an increased therapeutic time window and a higher risk of molecule-specific bleeding.

2.3. Efficacy of Second Generation Drugs in AIS: Intravenous Tissue Plasminogen Activator (rt-PA)

In 1979, the discovery of tissue-type plasminogen activator (t-PA) by Désiré, Baron Collen. Refs. [10,11] would disrupt the therapeutic field of ischemic stroke.

2.4. rt-PA, the First Experimental Approach in IS

The experimental work of Justin Zivin on a thrombo-embolic stroke model in rabbit showed that r-tPA improved neurological status [12]. Thus, this work paved the way to clinical trials.

2.5. Clinical Trials of rt-PA in IS

Tom Brott, Clarke Haley and David Levy developed the first stroke network [13] dedicated to the treatment of the IS by rt-PA. The positive results of NINDS rt-PA stroke study trial led to the approval of *rt-PA* in the USA within 3 h of onset of symptoms in 1995 [2].

2.6. The Lazarus Effect

The unprecedented clinical recovery following this treatment was compared to the resurrection of Lazarus, the greatest miracle accomplished by Jesus. Despite

this effect of r-tPA in IS and the fact that neurologists may dramatically change the world's approach of IS, the NINDS studies were the matter of severe controversy.

2.7. What Happened in Europe During This Time?

During the same period, there was a duel between supporters of rt-PA led by a hero of German vascular neurology, Professor Werner Hacke, and those of streptokinase led by Professor Hommel. Throughout the studies, the t-PA came out the winner of this confrontation, which lasted at least 7 years. Approval of rt-PA required a set of clinical trials involving varying doses and delivery times [14,15].

The pooled analysis of six randomized trials [16] showed that early administration of t-PA was associated with a better outcome, thus t-PA was definitively approved only in 2003 in Europe. The ECASS3 trial also initiated by Werner Hacke allowed successively lengthening the therapeutic window at 4H30 [17,18]. However, alteplase still remained underused; less than 10% of patients receive this treatment in most countries.

2.8. Intravenous Tissue Plasminogen Activator t-PA for Wake Up Stroke

Until 2015, due to the unknown time of symptom onset, patients with wake-up or without witness stroke were not treated by T-PA [19], although wake-up stroke accounted for almost 20% of ischemic stroke [20,21]. A German neurologist, Pr Götz Thomalla from the University Medical Center Hamburg—Eppendorf, suggested that the mismatch between a visible acute ischemic lesion on DWI and the absence of marked parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR) images (DWI–FLAIR mismatch) may likely identify an ischemic stroke that occurred within 4.5 h of stroke onset [22]. As a result, the WAKE-UP trial showed that rT-PA was effective in patients with such imaging patterns [23].

2.9. Intravenous Tissue Plasminogen Activator t-PA Treatment between 4.5 and 9 h after Known Onset with the Use of Advanced Imaging

The introduction of perfusion imaging methods (CT/MRI) allowed patients to be treated in a later time window due to a better analysis of tissue at risk of infarction [24]. In patients who were imaged with CT perfusion or perfusion-diffusion MRI, within 4.5–9 h, a meta-analysis has shown that thrombolysis with rT-PA improves the neurological outcome [25].

3. Mechanical Thrombectomy: A Breakthrough Therapy in IS Treatment. Overview of Thrombectomy Trials

Most people with large artery occlusion fared poorly with *rt-PA*. Although previous trials published in 2013 were associated with negative outcomes, [26–28], further studies documented the benefit of thrombectomys within 6 hours from symptom onset [29–37]. These results were likely related to a better patient selection, shorter door-to-arterial access times and improvement of devices.

3.1. Endovascular Treatment Up to 16 or 24 h

Recently the time window for mechanical thrombectomy was extended up to 16 or 24 h if advanced stroke imaging identify a salvageable penumbra. Therefore, current guidelines recommend thrombectomy in the 6- to 24-hour time window for patients meeting these imaging criteria [38,39].

4. Thrombectomy Some Outstanding Issues

4.1. Thrombectomy in Minor IS

The benefit of thrombectomy in patients presenting with anterior circulation LVO and minor stroke is still debated [40]. However, a substantial proportion of minor strokes are subsequently disabled at 90 days [41,42]. Patients with minor strokes and proximal occlusions may experience clinical deterioration due to collateral failure if not promptly recanalized [43], especially since thrombectomy for minor stroke patient (NIHSS $\leq$ 5) seems effective [44].

4.2. Thrombectomy for Distal Occlusion

The benefit of thrombectomy in patients with distal occlusion is less obvious [45]. However, some observational data have suggested a potential benefit in proximal M2. Accordingly, further research are needed to confirm the benefit of thrombectomy in distal M2 occlusion and even in anterior or posterior cerebral artery occlusion.

4.3. Thrombectomy for Large Core Volume

Large core volume is associated with severe disability [46]. Several randomized controlled trials have recently confirmed the potential benefit of mechanical thrombectomy regardless of the initial core volume.

4.4. Thrombectomy for Basilar Artery Occlusion

Since the masterful description of Kubik and Adams [47] basilar artery occlusion remained a therapeutic challenge. Attempts at intra-arterial thrombolytic treatments gave rise to some hope in the 1990s [48]. More recently, clinical trials demonstrated lower rates of death and an improved modified Rankin scale with thrombectomy as compared to the best medical management [49–51].

4.5. Direct Thrombectomy Versus Standard of Care

The DIRECT-MT study (Direct endovascular thrombectomy with or without Intravenous Alteplase in Acute Stroke) [52] found similar results between direct thrombectomy and combined thrombolysis–thrombectomy arms; however, further studies are needed to validate this approach.

5. Pathway Design for IS Care in the Era of Endovascular Thrombectomy

Although the effectiveness of thrombectomy is clearly validated, the eligibility is still poor. Treatment delivery depends on the existing local network. Currently, there are two models; first, the drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. Subsequently, patients may be transported to the nearest comprehensive stroke center (CSC) to undergo EVT. Secondly, the mothership model, where patients are routed directly to a CSC for IVT administration and, if appropriate, mechanical thrombectomy.

5.1. Prehospital Triage

Several prehospital triage tools have been proposed to distinguish patients with proximal occlusion from distal occlusion. Four prehospital triage tools to detect or predict LVO can be distinguished: prehospital triage scales, telemedicine supported triage, on site computed tomography (CT)-angiography, and some experimental noninvasive tools [53–56]. However, currently they are no prehospital triage scales available with acceptable sensitivity and specificity [57].

The inclusion of CT and CT-angiography in mobile stroke units (MSUs) may establish on site the distinction between LVO and non-LVO . MSUs may shorten the time to treatment both for IVT and EVT, which has been proven [58].

5.2. The Main Limitation for Thrombecctomy is the Low Number of Interventional Neuroradiology Specialists a Call for the Decompartmentalization of Specialties for the Same Purpose: the Prompt Reperfusion of the Ischemic Brain

The main limitation for thrombectomy is the low number of interventional neuroradiology specialists compared to what is observed in cardiology. We need to increase the number of physicians trained for this task, thus increasing the eligibility to thrombectomy. Indeed, we now face an overwhelming shortage of neurointerventionists that may compromise IS treatment. Therefore, other physicians trained in neurointerventional procedures must now fill this gap in AIS, in order to increase patients eligibility for mechanical thrombectomy.

6. Conclusions

This review highlighted the major transformations over the past 30 years in ischemic stroke therapy. The road is still long to increase access to optimpal stroke care, but the tools exist, and our main fault would be not to use them more effectively to reduce the handicap of a condition that we have stored for years in the locker room of fatality.

Conflicts of Interest: The authors declare no conflict of interest.

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