UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
DOCTORAL SCHOOL

MAGNETIC RESONANCE IMAGING CRITERIA FOR THROMBOLYSIS IN HYPERACUTE CEREBRAL INFARCTION IN KOSOVA

PhD THESIS

ABSTRACT

PhD SUPERVISOR,
PROFESSOR ANDREI BONDARI

PhD STUDENT,
ILIR AHMETGJEKAJ

CRAIOVA
2014

TABLE OF CONTENTS

KEY-WORDS: diffusion, perfusion, cerebral infarctions, MRI, thrombolysis.

INTRODUCTION

Stroke is the third leading cause of death in the world, being a pathology with very important social and economic implications.

The extension of ischemic area is related to the caliber of the occluded artery and to intracranial anastomoses.

The pathogenic classification of cerebral ischemic stroke is very important for the therapeutic strategies and is based on modern imagistic methods, such as computed tomography (CT), magnetic resonance imaging (MRI), Doppler ultrasonography, angiography. These methods allow the visualization of ischemic area and of cervical and cerebral arteries [1].

Computed tomography and magnetic resonance imaging are the most important ones.

Actual treatment strategies in ischemic stroke can be regarded as attempts to salvage the ischemic tissue that has potential for complete functional and morphological recovery. Intravenous thrombolysis is the most promising method, but it must be applied after a very accurate selection of the potential patients, including by imagistic criteria.

Before intravenous thrombolysis imaging must answer to some questions. The first of them is there is ischemia or hemorrhage. It is very important to establish that fact because the treatment of the ischemic stroke may lead to death if it is a hemorrhage. The second step consists of establishing of the cerebral tissue with irreversible ischemic changes and of the areas with potential for complete recovery. The next step is represented by the evaluation of the presence of an artery occlusion which can be successfully solved by intravenous thrombolysis [1, 2].

Computed tomography allows only the distinction between ischemia and hemorrhage. The early ischemic signs visible on non-contrast computed tomography are present after 6 hours, too late for thrombolysis. Computed tomographic perfusion imaging and angiography may delineate the hypoperfused area, but it is not able to distinguish between the nucleus of the infarct and the ischemic penumbra, essentials for thrombolytic therapy [1].

The use of MRI in selection of patients with hyper acute cerebral infarction that are suitable for intravenous or arterial application of thrombolysis is an emerging technique. Until a few years ago the selection of patients for thrombolytic therapy with acute stroke was based on CT imaging [3, 4].

Magnetic resonance imaging and magnetic resonance angiography (MRA), especially DWI and PWI functional methods can answer at all three major questions before thrombolysis [1].

Only data from NINDS has demonstrated efficiency of administration of intravenous recombinant tissue plasminogen activator (tPA) within first 3 hours with variable primary outcome, while a current survey suggests that benefits of tPA administration can be extended up to 4.5 hours [5].

BACKGROUND OF THE STUDY

The brain is supplied by a dense network of blood vessels originating in internal carotid arteries and vertebro-basilar arteries.

Stroke represents a neurological deficit of vascular origin. It consists of a parenchymal injury, transient or permanent and a vascular lesion.

The ischemic stroke is characterized by a reversible suffer of cerebral parenchyma in transient ischemic attack or a permanent one, when the blood flow decrease under 10-25ml/100g of tissue/min, secondary to an arterial or venous occlusion [2, 6].

Stroke is a major social and economic problem. Each year about 6 million people all over the world are affected by this malady. A percent of 35 of them die in the first 30 days, and about 50% in the first year. The patients that survive are in 80% of cases invalids. The most common type is ischemic stroke, accounting for 70-85% of cases. Parenchymal hemorrhages represent 20-25% and subarachnoidian hemorrhages of non traumatic causes 5%.

In Kosova stroke is the third cause of death, after cardiac diseases and cancer. Despite that, the most numerous cerebral attacks, especially minors are not leading to death but represents causes of invalidity.

Cerebral ischemia is caused by a cardiac or arterial embolism in 20% of cases, when the embolus or some other particles forms in a blood vessel distant from the brain, usually in the heart and is carried by the blood stream until it lodges in an artery leading to or in the brain or by degenerative changes in cerebral arteries that lead to thrombus formed and blockaded in an artery carrying blood to a part of the brain. There are also other rare causes, such as vasculitis, arterial spasms, cervical arteries dissection, angio dysplasia, hematological diseases [6].

Major risk factors are represented by age, arterial hypertension, cardiac diseases, especially atrial fibrillation, diabetes mellitus, smoking, etc. [2].

Magnetic resonance imaging, especially DWI and PWI functional methods represents the imaging exploration that can offer all necessary informations for an accurate selection of patients which are suitable for intravenous thrombolysis [1, 7, 8].

Random scientific studies with MRI have suggested that MRI is a more sophisticated method for selection of patients for thrombolysis. Unlike CT, MRI diffusion (DWI) can demonstrate ischemic changes within several minutes after onset. MRI perfusion (PWI) defines areas of hypoperfusion (the tissue at risk) that are potentially recoverable. PWI/DWI mismatch, determines brain tissue with reduced perfusion that extends beyond the margins of diffusive abnormalities acquired on DWI, and these areas are supposed to be in risk of extension of the brain tissue infarction, and could be potentially saved [9, 10].

MRA can be used for imaging of intracranial vessels. In the evaluation of intracranial circulation, if possible, one should obtain a three dimensional acquisition, since this enables the use of thinner voxels. Three dimensional TOF sequences are commonly used for imaging the large intracranial arteries.

MRA appears to provide informations about intracranial arterial occlusion with a high rate of accuracy.

Molecular diffusion is the result of the Brownian random translational motion that involves all molecules. DWI is sensitive to molecular diffusion. It has been widely used in detecting ischemic tissue in very early phase of ischemic stroke. PWI depicts the area that is hypoperfused compared to normal brain.

The concept of the penumbra provides a rational basis for the treatment of ischemia. Treatment strategies in ischemic stroke can be regarded as attempts to salvage the ischemic tissue that still has potential for complete functional and morphological recovery.

The treatment can be generally classified in two different strategies: improvement of blood flow and lowering of the thresholds.

There are multiple therapeutic methods. Intravenous thrombolysis is the most promising method, but it must be applied after a very accurate selection of the potential patients, including by imagistic criteria [11, 12].

Recombinant tissue plasminogen activator administered intravenously during the hyperacute stage has been proved to be effective in hemispheric infarctions [10].

The concept of neuroprotection relies on the principle that the delayed neuronal injury occurs after ischemia.

ORIGINAL CONTRIBUTIONS

CHAPTER 5 – AIM AND WORK HYPOTHESES

The time between first signs of a cerebral stroke and the correct diagnosis is essential. An early accurate diagnosis allows a proper therapy that assures a better recuperation.

The first priority is to determine if it is a stroke, and if the answer is yes if is caused by ischemia or by hemorrhage.

The aim of that prospective study is to establish the optimal protocol of imagistic investigation in order to be capable to diagnose as early as possible a cerebral infarction, in the hyperacute phase, when thrombolytic therapy can be successfully applied.

This study is based on another one, performed by me in Clinic of Neuroradiology at University Clinical Centre Mannheim, Germany, during the three months of continuous professional education, where I have studied for thrombolytic treatment in strokes.

The most important objective is selection of patients with cerebral infarction for MRI that is suitable for thrombolytic therapy as an emerging application.

This prospective work was performed during two years in Prishtina, by evaluating 672 patients in acute phase of a supposed stroke, in the first 24 hours. From them I selected 35 cases potentials for intravenous thrombolisis.

CHAPTER 6 – MATERIALS AND METHODS

The present prospective research was realized between June 2011 and July 2013 in University Clinical Centre from Prishtina, Kosova and in Imagistic Center Prima Prishtina.

I have examined 672 patients in the first 24 hours after beginning of a supposed stroke. They all undergo brain MRI evaluation for stroke. From them I have selected those that were referred to me in the first 6 hours and than I have selected 35 patients suitable for thrombolysis.

A MRI 1.5T Siemens Symphony and a General Electric Signa of 1,5 T were used for brain scan with appropriate head coil. I applied standard sequences and the protocol for hyperacute ischemia, consisting of a T2 FSE or TSE sequence, MRA, DWI and PWI. Intravenous bolus of Magnevist 0,15 ml/kgcorp was administrated for PWI.

I have studied in the beginning the distribution by age, sex and the presence of risk factors, such as arterial hypertension, cardiac diseases, especially atrial fibrillation, diabetes mellitus, smoking, personal history of another stroke.

In the second step I analyzed IRM features on all sequences.

For functional sequences and for hemo sequence the results were positive or negative the analysis being qualitative.

I analyzed than the presence of obstruction on 3D TOF images and, in positive cases I classified them after their location.

Post processing images in order to establish the mismatch that represents the criteria for indicating thrombolysis was performed with RAPID system.

CHAPTER 7 – RESULTS

There is no predominance of masculine or feminine sex. 346 cases of all 672 patients were males and 326 females.

Of all patients, 36 presented positive mismatch and 35 were potentials for intravenous thrombolysis. 18 of them were males and 17 females. One female pacient was not potential for thrombolysis because she presented dezoxyhemoglobin signal.

The distribution after age was:

- 20-29 years – 1 patient
- 30-39 years – 2 patients
- 40-49 years – 9 patients
- 50-59 years –12 patients
- 60-69 years – 8 patients
- 70-80 years –4 patients

The others was examined between 6 and 24 hours after beginning and did not have positive mismatch, or if they have mismatch the thrombolytic therapy was no longer suitable for them because of the delay.

A great number of patients were diagnosed with hemorrhagic infarct, aneurisms, arteriovenous malformations or expansive intracranial processes.

Depending on the arterial territory I find the predominance of middle cerebral artery and a rare implication of the anterior cerebral artery, both in the initial lot and in the 35 patients selected as potentials for thrombolysis.

CHAPTER 8 – DISCUSSIONS

The 35 patients selected as potentials for application of intravenous thrombolysis represent 5,21% from all patients (n=672), in concordance with literature.

The presence of a mismatch DWI/PWI offers data about the territories that can be repermeabilized after thrombolysis [13]. They depend on the interval of time between the moment of beginning of the symptoms and the IRM examination [14].

In my study the majority of patients were investigated between 6 and 24 hours, which mean that they were not potentials for thrombolytic therapy.

DWI allows the visualization of the ischemic tissue in the first minutes after installation, this tissue being in hypersignal and the normal tissue in hyposygnal. On ADC (Appearant Diffusion Coefficient) images the ischemic tissue is in hyposignal. In our cases the imagistic aspects were consistent with those described in the literature [15].

False positive results consisting in DWI hyperintensity may be caused by artifacts determined by bones and pneumatic cavities from the skull base, as it ios revealed in our study, concordant with other studies [16].

Of all 36 patients in which I performed MRI in the first six hours and with positive mismatch only in one case (2,78%) I found hemosiderine deposits, while other studies [17] find them in 12,2% of cases.

CONCLUSIONS

In hyperacute cerebral ischemia I found the predominance of the middle cerebral artery implication.

The patients with microinfarctions are not suitable for intravenous thrombolysis because there is no penumbra or it is very small.

The terminal branches of posterior cerebral arteries presents positive mismatch, so in this location the cases are potential for thrombolytic therapy, but the central branches are not suitable.

The affectation of anterior cerebral artery is rare, both in all patients and in the lot of 35 selected patients.

Internal carotid artery territory of thrombosis is very large, including middle cerebral artery anterior cerebral artery, in young patients because of edema and mass effect. In some of these cases I found positive mismatch, but the penumbra was very small.

The predominance of the patients that are potentials for intravenous thrombolysis with ages between 50 and 59 years, followed by those with ages of 40-49 years represents a strong argument for the standardization of this modern therapy. These patients are social actives.

The imagists are prepared to perform an appropriate selection of cases with hyperacute cerebral ischemia that can be treated with recombinant tissue plasminogen activator administered intravenously.

If in all 672 patients analysed could be performed magnetic resonance in the first 3-6 hours, the number of potential cases could be greater. It is very important to have a good collaboration with other specialists, to increase the educational level of the people, in order to be able to offer a chance for recovery in a shorter time, with lower costs of these patients.

Kosova is a country in development and the application of this modern and demonstrated efficient therapeutic method in hyperacute ischemic stroke is not started yet. Some steps was made and I hope that this study provide pertinent arguments to support an accurate imagistic selection of potential patients for intravenous thrombolysis.

SELECTIVE BIBLIOGRAPHY

1. Sunshine JL. CT, MR Imaging, and MR Angiography in the Evaluation of Patients with Acute Stroke. *J Vasc Interv Radiol* 2004 15: S47-S55.
2. Opriş Ligia. Imagistica cerebrală prin rezonanţă magnetică. Ed. SOLNESS, Timişoara,2004: 11-30, 55-73, 229-242.
3. Chelsea S. Kidwell at al.: Magnetic Resonance Imaging Detection of Microbleeds Before Thrombolysis, Stroke.2002; 33: 95-98 doi: 10.1161/hs0102.101792.
4. Nighoghossian N, Hermier M, Adeleine P, Blanc-Lasserre K, Derex L, Honnorat J, Philippeau F, Dugor JF, Froment JC, Trouillas P. Old microbleeds are a potential risk factor for cerebral bleeding after ischemic stroke: a gradient-echo T2*-weighted brain MRI study. Stroke. 2002;33: 735–742.
5. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, AlbersG, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators.
6. Smith WS. Pathophysiology of Focal Cerebral Ischemia: a Therapeutic Perspective. J Vasc Interv Radiol 2004 15: S3-S12.
7. Mulkern V. Robert. Fast Imaging Principles. Cap. 6 în Atlas W. Scott. Magnetic Resonance Imaging of the Brain and Spine. Volume 1. LIPPINCOTT WILLIAMS @ WILKINS, 2002: 127-196.
8. Basser J. Peter. Diffusion and Diffusion Tensor MRI Imaging. Cap. 7 în Atlas W. Scott. Magnetic Resonance Imaging of the Brain and Spine. Volume 1. LIPPINCOTT WILLIAMS @ WILKINS, 2002: 197-214.
9. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques.
10. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–1587.
11. Connors JJ. Pharmacologic Agents in Stroke Prevention, Acute Stroke Therapy, and Interventional Procedures. J Vasc Interv Radiol 2004 15: S87-S101.
12. Higashida RT and Dion J. Interventional Treatment and Management of Ischemic Stroke. J Vasc Interv Radiol 2004 15: S1.
13. Warach S. ReoPro Retavase Reperfusion of Stroke Safety Study— Imaging Evaluation (ROSIE). Presented at the 29th International Stroke Conference. San Diego, California; February 5–7, 2004. (Abstract)
14. Baird AE, Warach S. Magnetic resonance imaging of acute stroke. J Cereb Blood Flow Metab. 1998;18:583–609
15. Latchaw RE. Cerebral Perfusion Imaging in Acute Stroke. J Vasc Interv Radiol 2004 15: S29-S46.
16. Singh V. Critical Care Assessment and Management of Acute Ischemic Stroke. J Vasc Interv Radiol 2004 15: S21-S27.

17. Jansen O, Schellinger P, Fiebach J, Hacke W, Sartor K. Early recanalisation in acute ischaemic stroke saves tissue at risk defined by MRI. Lancet. 1999; 353: 2036–2037.