العلاج الحاد للغاية للسكتة الدماغية الناتجة عن القصور الدموي للمخ

رسالة توطئة للحصول علي درجة الماجستير

في المخ والأعصاب والطب النفسي

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الملخص العربي

تمثل السكتة الدماغية حالياً السبب الرئيسي الثاني المؤدي للوفاة وذلك بعد أمراض القلب و السبب الأول للعجز في المجتمع الغربي.

وتمثل الساعات الأولي عقب حدوث السكتة الدماغية أهمية قصوي للمريض حيث أنها الفترة التي يمكن من خلالها إعطاء مذيباً للجلطة.

وساعد في ذلك التطور الكبير في مجال الأشعة التشخيصية حيث ساهمت الأشعة المقطعية وأشعة الرنين المغناطيسي في فهم باثوفسيولوجيا السكتة الدماغية والتي يمكن الإعتماد عليها لمد الفترة التي يمكن من خلالها إعطاء المذيب.

وبالرغم من أن إعطاء المذيب عن طريق الوريد يمثل طريقة سريعة وبسيطة إلا أنه توجد بعض العيوب مثل ضيق الفترة التي يمكن من خلالها إعطاء المذيب وتحول الجلطة إلي نزيف مما يؤدي إلي الوفاة.

ويمثل إعطاء المذيب عن طريق الشريان حلاً لبعض هذه المشاكل حيث يتم إعطاء المذيب بجرعة أقل وبالتالي تقل نسبة تحول الجلطة إلي نزيف ولهذا يمكن مد الفترة التي يمكن من خلالها إعطاء المذيب.

ومع التطور الكبير في مجال الأشعة التداخلية أصبح الأن يمكن التعامل مع الجلطة ميكانيكياً عندما تكون الجلطة قريبة وكبيرة مع الإستغناء عن المذيب أحياناً مما يؤدي إلي مد الفترة التي يمكن من خلالها التعامل مع الجلطة.

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HYPERACUTE MANAGEMENT OF ISCHEMIC CEREBROVASCULAR STROKE

Essay

Submitted for partial fulfillment of Master Degree

In Neurology & Psychiatry

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بسم الله الرحمن الرحيم

وَمَا تَوْفِيقِي إِلا بِاللَّهِ عَلَيْهِ
تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ

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Contents

LIST OF ABBREVIATION

ADC= Apparent diffusion coefficient

AMPA= Amino-3-hydroxy-5-methyl-4-propionate

APC =Anticoagulant activated protein C

ATLANTIS= The Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke

BA= Basilar artery

BACE= Beta-site APP cleaving enzyme

CBF= Cerebral blood flow

CBV= Cerebral blood volum

CE= Contrast-enhanced

cFN= Cellular fibronectin

COX= Cyclooxygenase

DBP= Diastolic blood pressure

DWI= Diffusion- weighted imaging

ECASS= European Cooperative Acute Stroke Study

EPCR= Endothelial protein C receptor

FDP= Fibrin degradation products

GP= Glycoprotein

HT= Hemorrhagic transformation

IAT= Intra-arterial therapy

ICA= Internal carotid artery

ICAM= Intercellular adhesion molecule

ICH= Intracranial hemorrhage- intracerebral hemorrhage

IL= Interleukins

LBCCA= Ligation of bilateral common carotid artery

LTP= Long-term potentiation of memory

MCAO= Middle cerebral artery occlusion

MMP= Matrix metalloproteinases

MTT= Mean transit time

NIHSS= National Institutes of Health Stroke Scale

NINDS= National Institute of Neurological Disorders and Stroke

NMDA = N-methyl- D –aspartate

NNT= Number needed to treat

NO= Nitric oxide

OGD= Oxygen glucose deprivation

PAR= Protease activated receptor

PROACT= Prolyse in Acute Cerebral Thromboembolism

PWI= Perfusion-weighted imaging

ROS= Reactive oxygen species

RNS = Reactive nitrogen species

RTN = Retrograde transvenous neuroperfusion

SAINT= Stroke-Acute Ischemic NXY Treatment

SBP= Systolic blood pressure

SES= Self-expanding stents

TBI= Traumatic brain injury

TGF= Transforming growth factor

TNF= Tumor necrosis factor

TOAST =Trial of Org 10172 in Acute Stroke Treatment

TOF= Time of flight

TTP= Time-to-peak

VBO= Vertebro-basilar occlusion

VDCC= Voltage-dependent Ca (++) channel

WML= White matter lesions

Pathophysiology Of Stroke

Advances in understanding the pathophysiology and evolution of ischemic brain injury are the obvious rational basis for the development of therapy for acute ischemic stroke ***(Cheng et al.2004).*** The current understanding of pathophysiology has dramatically evolved over the past three decades, from early beginnings in animal studies to the current wealth of information provided by various imaging techniques ***(Saver, 2006).***

Definition And Classification

A stroke is the rapidly developing loss of brain function(s) due to disturbance in the blood supply to the brain. This can be due to ischemia caused by thrombosis or embolism or due to a hemorrhage. As a result, the affected area of the brain is unable to function ***(Donnan et al.,2008)***.

Ischemia is due to interruption of the blood supply, while hemorrhage is due to rupture of a blood vessel or an abnormal vascular structure. 80% of strokes are due to ischemia; the remainder are due to hemorrhage. Some hemorrhages develop inside areas of ischemia ("hemorrhagic transformation"). It is unknown how many hemorrhages actually start off as ischemic stroke ***(Donnan et al.,2008).***

There are various classification systems for acute ischemic stroke. The TOAST classification is based on clinical symptoms as well as results of further investigations; on this basis, a stroke is classified as being due to (1) thrombosis or embolism due to atherosclerosis of a large artery, (2) embolism of cardiac origin, (3) occlusion of a small blood vessel, (4) other determined cause, (5) undetermined cause .***(Donnan et al.,2008)***.

The most common subtypes of ischemic stroke are atherosclerosis (large vessel), cardioembolic, and lacunar (small vessel).The exact percentages of each subtype vary depending on race, ethnicity, age, and sex ***(Baumgartneret al.,2003).***

The atherosclerosis, or large vessel stroke, is defined as a greater than 50% stenosis of the carotid, middle cerebral, anterior cerebral, posterior cerebral, basilar, or vertebral arteries. This subtype carries the greatest chance of causing significant clinical deterioration ***(Albers et al.,2001).***

A cardioembolic stroke is defined as one in which cardiac conditions, such as myocardial infarction within 6 weeks of stroke onset, congestive heart failure, mitral stenosis, artificial heart valve, atrial fibrillation or flutter, or thrombus present in the ventricle, are present contributing to the formation of a clot and potential embolism ***(Schneider et al.,2004).***

Small vessel stroke, or lacunar stroke, is a small ischemic lesion occurring deep in the cortical tissue, with traditional clinical syndromes and no potential large vessel or cardiac causes ***(Baumgartneret al.,2003).***

A more specific definition divides lacunar stroke into 3 conditions. Condition A is a deep infarct of 1.5 cm in diameter and is accompanied by clinical symptoms. Condition B reveals no brain images representing an infarct, yet the patient demonstrates clinical symptoms of a stroke. Condition C occurs when the scan shows a 1.5 cm deep infarct with a clinical syndrome that is not one of the classical syndromes of lacunar stroke ***(Schneider et al.,2004).*** Lacunar strokes carry the best chance for recovery and survival ***(Albers et al.,2001).***

Stroke without an obvious explanation is termed "cryptogenic" (of unknown origin); this constitutes 15-20% of all ischemic strokes ***(Donnan et al.,2008).***

Ischemic Penumbra

The penumbra concept of focal ischemia is of considerable interest for the understanding of stroke pathophysiology because it is the conceptual basis not only for the progressive evolution of ischemic injury, but also for the therapeutic reversal of the acute neurological symptomatology arising from stroke ***(Fisher, 2004).***

The brain's response to acute ischemia is influenced by the severity and duration of the insult. Experimental stroke models suggest that there are different ischemic thresholds for cerebral dysfunction and cell death. Normal cerebral blood flow is approximately 50 to 55 mL/100 g/min. When blood flow drops to about 18 mL/100 g/min, the brain has reached the threshold for synaptic transmission failure. Although these cells are not functioning normally, they do have the potential for recovery. The second level, known as the threshold for membrane pump failure, occurs when blood flow drops to about 8 mL/100 g/min. Cell death can result. The difference between these two blood flow levels (8 to 18 mL/100 g/min) has led to the concept of a perifocal ischemic region, or ischemic penumbra, in which there is loss of the EEG and flat evoked potentials but normal ATP and extracellular concentrations of k+ ***(Metwally,2010).***

Ischemic penumbra is usually peripheral in location, where blood flow is sufficiently reduced to cause hypoxia, severe enough to arrest physiological function, but not so complete as to cause irreversible failure of energy metabolism and cellular necrosis ***(Ginsberg, 2003)***.

Ischemic penumbra is a dynamic process. It exists for a short period of time even in the center of ischemia, where irreversible necrosis propagates to the neighboring tissue over time. it is very short for the core

of ischemia and may extend to several hours in the moderately ischemic surrounding tissue ***(Heiss, 2000).***

To better understand the ischemic penumbra, it is worthwhile to review the pathophysiologic mechanism of ischemic brain damage. Reviewing the "four tissue compartments concept" is a very good strategy for understanding the ischemic process. The compartments can be distinguished by the various physiological imaging modalities during acute ischemic stroke: 1) the unaffected tissue; 2) the mildly hypoperfused tissue, but this is not usually at risk (the oligemic tissue); 3) the tissue at risk (the ischemic penumbra); and 4) the tissue already irreversibly damaged (the ischemic core) ***(Baron, 2001)***.

The major concern during the initial hemodynamic evaluation of the acute ischemic patient is the viability of the penumbra zone. The degree of perfusion abnormality and the duration of the ischemia should be considered when predicting the fate of the total lesion. However, in clinical settings, predicting the viability of the penumbra zone is a complex task. Warach proposed "The 4-factor model" for this purpose .The model consisted of a time factor, a hemodynamic factor, a tissue factor and an intervention factor. There is no absolute viability threshold that is independent of time, and there is no absolute time window for the tissue viability ***(Warach, 2001).***

Studies of brain injury have shown that focal cerebral ischaemia initiates a series of pathological events, where cells in the penumbra are subjected to various pathological processes leading to their own and their neighbours' death. The molecular consequences of brain ischaemia include temporal changes in cell signalling, signal transduction, metabolism, and gene regulation /expression ***(Slevin et al., 2005).***

Molecular Mechanisms of Injury Progression

In the border zone of permanent focal ischemia or in the central part transient vascular occlusion, cellular disturbances may evolve that cannot be explained by a lasting impairment of blood flow or energy metabolism. These disturbances are referred to as molecular injury. The molecular injury cascades are interconnected in complex ways, which makes it difficult to predict their relative pathogenic importance in different ischemia models. In particular, molecular injury induced by transient focal ischemia is not equivalent to the alterations that occur in the penumbra of permanent ischemia. The relative contribution of the following injury mechanisms differ therefore in different types of ischemia ***(Nicotera, 2003).***

Mechanisms of ischemic injury include edema, microvascular thrombosis, programmed cell death, and infarction with cell necrosis. Inflammatory mediators contribute to edema and microvascular thrombosis. Edema, if severe or extensive, can increase intracranial pressure. Many factors may contribute to necrotic cell death; they include loss of ATP stores, loss of ionic homeostasis, lipid peroxidative damage to cell membranes by free radicals, excitatory neurotoxins, and intracellular acidosis due to accumulation of lactate ***(Metwally,2010).***

Ischemic Cascade

The ischemic cascade induced by focal brain ischemia is complex and many additional components were discovered only recently ***(Chong et al., 2005).***

If the flow is not reestablished in the blocked vessel, a series of destructive mechanisms or ischemic cascade occurs , leading to the cell death in the area of blood flow disruption. Ion channel disruption also

occurs with an increase in calcium influx into the cell. Excitatory amino acids, glutamate and aspartate, are released. As these destructive agents act in the ischemic neuronal bed of cells, there is production of arachidonic acid, oxygen free radicals, nitric oxide, and eicosanoids. The end result is cerebral edema, cell damage, and neuronal cell death ***(Lindsbert, 2004).***

Excitotoxicity

Glutamate mediates excitotoxic synaptic transmission via activation of N-methyl- D -aspartate (NMDA), Amino-3-hydroxy-5-methyl-4-propionate (AMPA) or kainate receptors. When glutamate is released from presynaptic terminals, it allows Na + and Ca 2+ influx that depolarizes the membrane. While this is vital for neuronal plasticity, additional activation of receptors results in neuronal death. Glutamate is released in an uncontrolled manner in ischaemic areas. The glutamate-calcium cascade induces a necrotic lesion and Ca 2+ -mediated excitotoxicity plays an important role in brain infarction ***(Mitsios et al.,2006)***

NMDA receptors are highly permeable to Ca 2+ , Na + , K + and H + cations. Their activation is a primary cause of neuronal death after ischaemia that is accompanied by temporary elevation of extracellular glutamate. Ca 2+ influx mediates NMDA neurotoxicity while Na + influx contributes to swelling of neuronal cell bodies. Normally the free Ca 2+ concentration in the cytoplasm is approximately 1/10,000 of its extracellular concentration. The export of Ca 2+ from neurons into the extracellular environment occurs via processes that are linked to energy utilization. Energy failure in the brain during hypoxia results in a passive efflux of K + from cells, enhancing Ca 2+ entry and release into neurons. The unregulated rise in intracellular cytoplasmic Ca 2+ links glutamate

excitotoxicity to biochemical processes resulting in further injury, i.e. oxidative stress ***(Mitsios et al.,2006)***

Oxidative stress

Plenty of reactive oxygen species are generated during an acute ischemic stroke and there is considerable evidence that oxidative stress is an important mediator of tissue injury in acute ischemic stroke. After ischemic brain injury, the production of reactive oxygen species (ROS) may increase leading to tissue damage via several different cellular molecular pathways. Radicals can cause damage to cardinal cellular components such as lipids, proteins, and nucleic acids leading to subsequent cell death by modes of necrosis or apoptosis. The damage can become more widespread due to weakened cellular antioxidant defense systems. Moreover, acute brain injury increases the levels of excitotoxic amino acids which also produce ROS, thereby promoting parenchymatous destruction. ***(Valko et al.,2007)***.

The increase in oxygen free radicals triggers the expression of a number of pro-inflammatory genes by inducing the synthesis of transcription factors, hypoxia inducible factor 1, interferon regulator factor 1 and STAT3. As a result, cytokines are upregulated in the cerebral tissue and consequently, the expression of adhesion molecules on the endothelial cell surface is induced, including intercellular adhesion molecule 1 (ICAM-1), P-selectin and E-selectin which mediate adhesion of leukocytes to endothelia in the periphery of the infarct ***(Yilmaz and Granger, 2008).***

Inflammation

Brain infarcts evoke a strong inflammatory response which is thought to contribute to the progression of ischemic brain injury Both focal and