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Diagnosis, monitoring and prognosis of secondary brain damage in icu patients with traumatic brain injuries

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SPECIAL ARTICLE

DIAGNOSIS, MONOTORING AND PROGNOSIS OF SECONDARY BRAIN DAMAGE IN ICU PATIENTS WITH TRAUMATIC BRAIN INJURIES

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Abstract

Traumatic brain injury (TBI) is the brain injury that occurs whenever a physical force that impacts the head leads to neuropathology. The types of primary TBI are penentrating TBI or non-penetrating TBI and it can lead to intracerebral contusions, hemorrhages or extra-axial hematomas. Patients with TBI can also have skull fractures or concussions. The injury severity can be classified in many ways but the most established and common used is the Glascow Coma Scale (GCS). However, with the GCS, each of the severity criteria has limitations and might mot be an accurate predictor of TBI severity and outcome when used alone. For this reason it is often used in conjunction with other parameters (Abbreviated Injury Scale - AIS).

Secondary Brain Damage is the injury that occurs to the TBI patient not at the time of the accident, but during the following minutes, hours or days. There are many mechanisms that lead to development of cerebral edema, blood-brain barrier disruption, vasospasm, increase in volume of bleeding, contusions and intracranial hypertension. These mechanisms can act either in cellular level or systemic level. The cellular mechanisms that lead to secondary brain damage include necrosis or apoptosis, mitochondrial dysfunction, excitotoxicicty, formation of free radicals, changes in cerebral glucose metabolism and inflammation. The mechanisms at systemic level include hypoxia-cerebral oxygenation, hypo or hypertension, hypo or hyper-capnia, anemia, hyponatremia and hyper or hypoglycemia.

The first tool to diagnose severe TBI and secondary brain injury is neurological assessment. Neuroimaging is one of the most important ways for diagnosis. Computed Tomography (CT scan), Magnetic Resonance Imaging (MRI), cerebral angiography, transcranial Doppler, CT perfusion, Xenon CT, MRI diffusion, MRI perfusion, MRI spectrometry and Positron Emission Tomography (PET) are possible ways of imaging that not only help in the diagnosis but give important information that help in choosing the correct management. Moreover, neuromonitoring, helps in the correct management of the patient.

Key-words: Traumatic brain injury, Glascow Coma Scale, Abbreviated Injury Scale, secondary brain damage.

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INTRODUCTION

Brain injury is called any damage to the brain that can affect a person physically, emotionally or behaviorally. Depending on the cause, brain injuries can be categorized into traumatic or non-traumatic brain injuries. Non-traumatic injuries are those that do not occur as a result of an external force or a trauma. The main cause is usually a stroke, which is the interruption of blood supply to a section of the brain. Depending on the part of the brain affected and the extent of blood shortage, the consequences of a stroke vary widely. A stroke in the left hemisphere may result in a degree of paralysis or loss of feeling on the right side, reduction in the right field of vision, loss of speech and comprehension. A stroke in the right hemisphere may result in a degree of paralysis or loss of feeling on the left side, difficulty in expressing emotions and impulsive actions. Other causing factors are illnesses such as cancer or tumors and infectious diseases such as brain infections or inflammation. In addition, lack of oxygen or toxicity is also factors responsible for non-traumatic injury.[1-6]

Traumatic brain injuries (TBI) occur when physical external forces impact the brain either from a penetrating object, or a bump, blow or jolt to the head. Traumatic brain injuries can vary from mild to severe depending on the type of injury and can be divided into two categories: a) penetrating or open TBI where the skull is pierced by an object such as a knife or a bullet and b) non-penetrating (or blunt TBI or closed head injury) where the injury is caused by an external force which results in the movement of the brain within the skull. Usual causes of non-penetrating TBIs are falls, motor vehicle crashes, sport injuries or being struck by an object.[1-6]

Traumatic brain injury is one of the most common causes of mortality and disability from trauma worldwide, especially in children and young adults, under 45 years old. TBI is found to be more frequent than other common diseases including breast cancer, AIDS, Parkinson's disease and multiple sclerosis. Male people between 14 and 24 years old constitute the most commonly affected group from TBI. Females, children and older people also may be at risk for TBI, though female patients not only sustain TBI less frequently, but when they are affected they seem to have better outcome compared to that of males. Though the great advance in emergency and intensive care medicine has ameliorated the mortality rate related to TBI, still many deaths are attributed to trauma. In addition, people that survive the injury most probably they will suffer from neurological and neuropsychological problems. The most common causes of TBI are falls and occur most frequently to young children and older people. The next two more common causes of TBI are unintentional blunt trauma, followed closely by motor vehicle accidents. Unintentional blunt trauma is an accident that involves being struck by or against an object such as sport-related injuries. Bicycling, football, playground activities, basketball and soccer result in the most TBI related emergency room visits. Finally TBIs can be caused by a blast trauma from roadside bombs and since 2014 has become a common cause of injury.[1-6]

In the United States (USA), the number of deaths from TBI is greater than 50.000 per year and constitutes 33% of all civilian trauma-related deaths. It is estimated that in US every 15 seconds a TBI occurs and as a consequence 1.7 million head

injuries per year are generated. The main causes of TBI are falls, motor vehicle accidents and assaults and the majority of patients are male young adults. As these young people are probable to suffer from trauma-related disability, extended rehabilitation and reintegration is required. It is reported that approximately 80000 are left with permanent disability.

In Europe, according to a systematic review of brain injury epidemiology published in 2006, 150-200 hospital admissions with TBI per 100000 of the population were reported. These patients represent the 0.015 – 0.02% of total population. The age group of 15 – 35 years old is the one of higher risk especially for males, as the ratio of males/females is found to be 2.5:1. The death rate from TBI in Europe is 14 – 30 per 100.000 of the population. Those data are derived from national studies realised in Denmark, Sweden, Finland, Portugal, Germany, and from local studies realised in regions within Norway, Sweden, Italy, Switzerland, Spain, Denmark, Ireland, the U.K. and France.

In Greece the incidence of patients with severe TBI is estimated to 10.000 per year. According to the Hellenic Society of Trauma and Emergency Surgery, more than 50% of patients with TBI were due to traffic accidents and approximately 30% were due to falls. The ratio of male patients/female patients was approximately 2.5:1. Most people with TBI are of age between 15 - 44 years old, though TBIs were found to be more lethal in the age group of 45-64 years old. [5, 7-12]

DIAGNOSIS OF SECONDARY BRAIN DAMAGE

TBI occurs in two phases: primary and secondary TBI. The primary injury, as analyzed in the first part, is the result of the direct physical impact to the brain parenchyma, which leads as a consequence to structural and shearing injury of neurons, injury to vessels and interruption of neurochemical processes. All these, result in hemorrhage, edema and compression of intracranial structures. A cascade of events starts within minutes of the primary injury and these pathophysiologic processes may last from hours to days. The result is further neuronal injury, termed as secondary brain damage. While primary injury cannot be altered after the time of trauma, secondary damage sometimes can be prevented.

The causes of secondary brain damage can be categorized into those that occur on cellular level and those that occur on the systemic or extracerebral level. Factors that contribute to secondary brain damage on systemic level are mainly ischemic in nature and include hypoxia, hypotension, hypercapnia, acidosis and hyperglycemia. The mechanisms of secondary TBI on the cellular level include: necrosis - apoptosis, mitochondrial dysfunction, excitotoxicity, disruption in ATP metabolism, and disruption in calcium homeostasis, increase in inflammatory mediators and cells, free radical formation, DNA damage, brain glucose utilization disruption, microcirculatory dysfunction and microvascular thrombosis. The mechanisms of secondary brain injury will be further analyzed in the next paragraph. All these factors lead to development of cerebral edema, blood-brain barrier disruption, vasospasm, increase in volume of bleeding and contusions, and intracranial hypertension.[17-18, 20-21]

NEUROLOGICAL ASSESSMENT

The primary tool for clinically evaluating a patient

with TBI is the neurological examination. Examining the patient with TBI in a detailed way and understanding the extent of neurologic impairment is absolutely necessary. Minimum documented neurological observation should be: GCS scale, pupil size and reactivity, limb movements, respiratory rate, heart rate, blood pressure and temperature. Beside GCS, a new scoring system has been developed in 2005, called the "Full Outline of UnResponsiveness" (FOUR). The FOUR scale is superior to GCS as it provides further information like brainstem reflexes, visual tracking, breathing patterns and respiratory drive. It has also the advantage that critically ill intubated patients can be evaluated, as it does not depend on verbal response. In addition it can differentiate between a locked-in state and a vegetative state, via the addition of testing eye tracking, thus incorporating midbrain and pontine functions. Another advantage of the FOUR scoring is that it gives all components equal weight, while the GCS scale is weighted towards motor responses. There are five scores for each type of response. For eye response the scores are: E4 for eyelids open or opened, tracking or blinking to command, E3 for eyelids open but not tracking, E2 for eyelids closed but open to loud voice, E1 for eyelids open but closed to pain and E0 for eyelids remaining closed with pain. For motor response the scores are: M4 for thumbs up, fist or peace sign, M3 for localizing to pain, M2 for flexion response to pain, M1 for extension response to pain and M0 for no response to pain or generalized myoclonus status. For brainstem reflexes the scores are: B4 for pupil and corneal reflexes present, B3 for one pupil wide fixed, B2 for pupil or corneal reflexes absent, B1 for pupil and corneal reflexes absent and B0 for absent pupil, corneal and cough reflex. For respiration pattern the scores are: R4 when the patient is not intubated, and he is with a regular breathing pattern, R3 when the patient is not intubated but he has a Cheyne-Stokes breathing pattern, R2 when he is not intubated and he has an irregular breathing, R1 when the patient breathes above ventilatory rate and R0 when he breathes at ventilator rate or apnea.[11, 19, 20, 26]

NEUROIMAGING

Neuroimaging provides supportive information and there are many techniques that can be used:

The primary neuroimaging modality used for patients with TBI is **Computed Tomography (CT)**. When performed without the use of contrast it takes only a few minutes to be performed and can provide useful data. The main indications for CT are: GCS score less than 15, loss of consciousness for longer than 5 minutes or antegrade amnesia, clinical evidence of basilar skull fracture, depressed skull fracture on clinical examination, penetrating injury, anisocoria or fixed and dilated pupils, any neurological deficit, known bleeding diathesis and anticoagulant treatment. In addition CT can be performed when there are symptoms for high risk such as focal neurological deficits, penetrating head wound, palpable depressed skull fracture, and impaired mental status that is not caused by drugs or other intoxicants. CT scan images can show fractures, hemorrhages, hematomas, hydrocephalus, contusions and brain tissue swelling. It generally provides sufficient information for appropriate surgical management.

Magnetic Resonance Imaging (MRI) is another imaging modality that can be used in patients with

TBI. MRI can provide greater structural detail than CT, it is a more sensitive test and can show subtle changes in the brain that the CT might have missed. Though MRI does not affect acute clinical care, it is useful for prognostication, particularly as brainstem lesions and diffuse axonal injury that are not easily seen in CT can be easily identified in MRI. MRI is superior to CT when it delineates corpus callosal pathology in white matter diffuse axonal shearing injury. However, MRI has some disadvantages as in penetrating TBI there is a great risk of heat and movement of retained foreign bodies by the MRI's high magnetic field. Also when the patient is clinically unstable MRI cannot be performed because clinical monitoring during the study is difficult. Finally, MRI is quite more expensive and time-consuming in the emergency department setting.

Other imaging modalities include **cerebral digital subtraction angiography (DSA)**, which is recommended when a cerebrovascular injury is suspected and **transcranial Doppler** when vasospasm or other cerebral blood flow issues are of concern. Transcranial Doppler is a bedside non-invasive technique that can provide useful real time physiological data, as it can diagnose vasospasm, which is a secondary injury with high incidence among patients with TBI. The incidence of vasospasm in patients with blast-related penetrating TBI reaches 50%. Thus, it is recommended that patients, especially those with acute penetrating TBI from explosives, should undergo regular Doppler assessment and if moderate or severe vasospasm is found then cerebral angiography can be performed as it might be more invasive but it will offer a definite diagnosis and endovascular intervention. While conventional angiography is the gold-standard technique for these cases, **CT angiography** is widely available in facilities and offers some more advantages. Its sensitivity in diagnosing vascular injury is higher even than that of **MRI angiography**.

The last years, more neuroimaging modalities have been introduced for the diagnosis of brain injury. These include CT perfusion, Xenon CT, MRI diffusion, MRI perfusion, MRI spectrometry, Positron Emission Tomography (PET). CT perfusion is a modified angio-CT and with the use of a non-diffusible tracer, cerebral blood volume and regional cerebral blood flow (CBF) can be measured (quantitative) at high resolution. Xenon CT is another method that helps in measuring quantitatively regional CBF, using Xenon as a contrast diffusible agent. This method has many advantages: it provides reliable results with high spatial accuracy, it allows the combination of regional CBF with CT imaging and it is a technique that can be applied at bedside with the introduction of portable CT scanner. MRI diffusion is a technique that quantifies with a ratio the typology of regional brain edema either this is cytotoxic or vasogenic. With MRI perfusion a non-quantitative mapping of regional perfusion can be produced and allows a description of penumbra, the area in which reduced perfusion is mismatched from the cytotoxic edematous area. MRI spectrometry is a technique that produces semi-quantitative mapping of cerebral metabolites suggesting areas of ischemia and excitotoxicity. Finally, PET is an imaging technique that offers a quantitative measurement of regional cerebral metabolic rate for glucose. When combined with CT, the technique is then called PET-CT and it offers information about the metabolic rate for glucose in combination with traditional CT imaging.[2,11,16-17,26]

CEREBROSPINAL FLUID ANALYSIS

Cerebrospinal fluid (CSF) is a dynamic metabolic active substance, which can give valuable information in many occasions such as inflammatory conditions or subarachnoid hemorrhage. As a result it can occasionally be useful in TBI. It is obtained by a procedure called lumbar puncture. As it is in direct contact with the extracellular matrix in the brain, its composition reflects biochemical changes in this organ, therefore its analysis can show alterations that can help in the diagnosis of TBI. There are several biomarkers that can be used in order to indicate BBB integrity, neuroinflammation, as well as axonal, neuronal and astroglial damage. It is important to mention that there are many studies and there is a lot of research in order to find biomarkers that will help in diagnosing secondary brain injury and will help in the patient's prognosis.

The BBB as it has been already mentioned has an important role in maintaining a regulated microenvironment for reliable neuronal signaling. The CSF serum albumin ratio is a common biomarker of BBB function. Albumin is synthesized in the liver and consequently most of albumin in CSF is derived from the blood via passage across the BBB. An increase in this ratio indicates BBB disruption, which is found in patients with severe TBI associated with a neuroinflammatory response.

After severe TBI, there is an acute inflammatory response within the CNS. This response is reflected in the concentration of various CSF components such as inflammatory proteins. Levels of inflammatory proteins such as IL-6, IL-8 and IL-10 are increased in the CSF in cases of severe TBI. The magnitude of the rise correlates with the patient's outcome and in some cases also with the extent of BBB dysfunction, as shown by the CSF: serum albumin ratio.

Acute axonal injury in severe TBI can be identified by a high concentration of tau protein, a protein highly expressed in thin, nonmyelinated axons of cortical interneurons. Total tau protein levels in ventricular CSF correlate with lesion size and clinical outcome in patients with TBI. Also, neurofilament light polypeptide helps in the diagnosis of axonal injury. Neurofilaments are composed of neuron-specific intermediate filaments. Each intermediate filament consists of one light subunit plus either a medium subunit or a heavy subunit arranged head-to-tail. High levels of phosphorylated heavy subunits have been demonstrated in the ventricular CSF of patients with severe TBI.

Finally, γ-Enolase is a glycotic enzyme enriched in neuronal cell bodies. Its level in CSF can identify severe TBI as it strongly correlates with mortality. More specifically its concentration is higher in non-surviving patients than in survivors. Its prognostic value can be combined with other TBI severity scores such as GCS score [31, 32].

NEUROMONITORING IN SECONDARY BRAIN DAMAGE

Patients with severe TBI and secondary brain injury are nursed in ICU and require special attention, care and management. Neuromonitoring refers to the continuous monitoring of the brain function with the use of digital technology. It helps in the recording of many parameters in a constant way; these parameters are brain and body temperature, intra-cranial pressure, blood pressure and oxygenation, pH, brain metabolic and electrophysiological situation, cerebral perfusion and other parameters.

Therefore, essential monitoring includes electrocardiography (ECG), arterial oxygen saturation (SpO2); capnography (end-tidal CO_2, $PetCO_2$), arterial blood pressure (arterial catheter), central venous pressure (CVP), systemic temperature, and urine output, arterial blood gases and serum electrolytes and osmolality. Invasive arterial pressure allows beat-to-beat monitoring of ABP and regular assessment of arterial blood gases and glucose.

The advantage that neuromonitoring offers is that secondary brain injury becomes perceptual in early stages, before the patient deterioration, and therefore there is the opportunity to prevent them with the appropriate treatment either this is surgical or conservative.[28,30,33]

INTRACRANIAL PRESSURE

Intracranial pressure (ICP) is the cerebrospinal fluid pressure. ICP monitoring offers continuous display of ICP, accurate calculation of cerebral perfusion and assessment of intracranial compliance. ICP is measured with the use of a catheter implanted either inside the brain parenchyma or inside the ventricular system. In the case of the intraventricular position the catheter's tip is positioned at the level of Foramen of Monro without loss of fluid from the system. ICP can be recorded at various sites in the cranial vault. For example it can be recorded in the subdural, the subarachnoid or the epidural space, though the recordings of ICP in the subdural and epidural space underestimate true ICP levels.

Under normal conditions cardiac and respiratory pulse are superimposed on the baseline level of ICP, resulting in a characteristic waveform. It is important to mention that ICP values are dependent on the intrathoracic pressure, which influences venous outflow from the intracranial space. In cases where ICP increases, there are obvious certain pathological waveforms on the ICP record: there are termed as Lundberg A (plateau waves, ICP>50 mmHg), B (pressure pulses, ICP > 20 mmHg to 50 mmHg) and C waves (figure), defined by their peak pressures and duration. Not rarely, though there are changes in ICP, that cannot be easily classified as one of these patterns.

Generally, it is suggested that all patients with severe TBI (GCS<9) and an abnormal CT scan, should be followed with ICP monitoring. ICP monitoring is also recommended in patients with severe TBI and a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing or systolic blood pressure < 90mm Hg. The reason is that these patients are of similar risk for an increase in ICP with those with an abnormal CT scan. However, it is not considered necessary in patients who are considered to be unsalvageable or in older patients and in general patients that are not expected to develop intracranial hypertension. Usually each center has developed its own protocol according to which it is decided whether the patient will be ICP monitored. Exclusion criteria often include patients with bilateral unreactive midriasis, with untreatable lesions or extracranial lesions difficult to manage, patients with high GCS motor score (≥5) or patients of advanced age. Patients with a potentially evolving lesion or a diffuse lesion at risk of high ICP should be ICP monitored even if they have a less severe initial neurological score.

There is more than one method that ICP can be measured and each method measures in different

anatomical sites. The most common anatomical sites are the epidural and intraventricular spaces and the parenchyma. The methods include fluid-coupled systems with an external transducer and fibre optic and piezo-resistive systems. The **ventricular method** is a reliable method with low cost. It is most accurate, its recalibration is possible and it gives the opportunity to withdraw CSF in order to lower ICP. The fact that it allows fluid release in order to treat ICP elevation is really important and this is the reason that it constitutes the most preferred method. Its greater disadvantage is that there is a high risk of infection and hemorrhage. The **parenchymal method** is also reliable and it has the advantage of simple catheter insertion. In this method recalibration is not possible and there is also a small risk of hemorrhage. In addition it is an expensive method. The **epidural method** is simple with low infection rate, though it is expensive and there is the risk of artifacts. Its recalibration is not always possible. In general, the preferred site for ICP monitoring device is the right frontal lobe, which the non-dominant hemisphere and eloquent brain tissue can be minimized. However, this may or may not be the tissue involved in the head injury, and interpretation of pressure readings may be difficult if the monitor is sited in the middle of an expanding contusion. There are suggestions that the combination of ICP and MABP is more important than ICP alone. Thus Cerebral Perfusion Pressure (CPP) may be a more appropriate measure and target than ICP, where CPP is defined as the difference between mean arterial pressure and mean ICP [CPP= MABP-ICP]. The normal value of ICP is 15mmHg. Though conventionally the threshold of ICP value for treatment is 20 mmHg, it is recommended that after a few days the threshold be elevated to 25mm Hg. The threshold for CPP treatment is not stable but depends on the type of CT, the age and previous arterial hypertension. For example older patients might need a CPP within 70-90mm Hg, while children and young adult patients should have a CPP target not below 50mm Hg.

Intracranial hypertension leads to a reduced cerebral perfusion and as a consequence to cerebral ischemia. The primary goal of an adequate CPP is to maintain CBF and tissue oxygenation. ICP can be controlled by a variety of methods such as hyperventilation, hyperosmolar therapy, hypothermia, the use of barbiturates and finally with neurosurgical interventions.[17,20,30,34-37]

Hyperventilation: A reduction in Pa_{CO2} causes cerebral vasoconstriction, leading to a reduction cerebral blood volume (CBV) and ICP. However, hyperventilation has been shown to exacerbate cerebral hypoperfusion and may result in ischemia. Moderate hyperventilation to a Pa_{CO2} value of 4 – 4.5kPa is reserved for those with intractable intracranial hypertension and should be guided by monitoring such as jugular venous oxygen saturation to ensure adequate cerebral oxygenation.

Hyperosmolar therapy: This type of therapy is really useful in patients with an acute increase in ICP. The most commonly used agent in this therapy is mannitol, given in intermittent boluses rather than continuous infusions as this way it seems to be more effective. However, special attention needs to be taken in order to prevent serum osmolarity increasing as this might lead to neurological complications, renal complications and other complications including hypotension, intravascular volume depletion, hyperkalemia and rebound

intracranial hypertension. Lately, the use of hypertonic saline is increasing as it has fewer side-effects and may control ICP refractory to mannitol.

Hypothermia: Moderate hypothermia effectively reduces ICP and is often included in management algorithms. However, studies have failed to prove an association with consistent and statistically significant reduction in mortality.

Barbiratures: Barbiturates has proved to lower ICP but there is little evidence that they improve the patient's outcome. As they are associated with significant cardiovascular instability they are reserved only for refractory intracranial hypertension. Dosage is titrated to produce burst suppression with electroencephalography (EEG).

Neurosurgical interventions: The main effective intervention is drainage of CBF via an external ventricular drain. More specifically, this method can be applied when the "ventricular" method of measuring ICP has been used. When intracranial hypertension cannot be cured with medical therapy then a **decompressive craniectomy** is a useful method. In this procedure a section of skull vault is removed, allowing the brain to expand and the ICP to decrease. However, there is little consensus on its use, and studies have shown that the outcome for these patients is worse than those who are treated with medical therapy. For this reason, decompressive craniectomy is currently reserved for when other methods of ICP control have failed.[30]

ELECTROPHYSIOLOGICAL MONITORING

In patients with severe TBI it is important to comprehensively monitor cerebral metabolic and functional endpoints in order to allow the physician to determine the physiological, functional and metabolic status of the brain and to choose the correct targeted therapy for each patient. Electroencephalogram (EEG) is a useful tool in clinical neuromonitoring of severe TBI. It can monitor the depth of coma, detect non-convulsive seizures or seizures activity in pharmacologically paralyzed patients and it can diagnose brain death. It can also detect non-convulsive status epilepticus, motor evoked potentials (MEP), somatosensensory evoked potentials (SSEP) and brainstem auditory evoked response (BAER). There are suggestions for a continuous EEG in patients with TBI in order to diagnose post-traumatic seizures. Usually, patients with severe brain injury have 24-hour EEG monitoring, while MEP, SSEP, and BAER may be evaluated at regular intervals. Sensory-evoked potentials can yield data on current brain function in very severe TBI patients. However, their use is very limited in the initial management of TBI.[28,34]

JUGULAR VENOUS SATURATION MONITORING

Jugular saturation monitoring (SjO_2) is a newer method adjunct to ICP that allows the clinician to monitor cerebral oxygen extraction for any given CPP and it can demonstrate cerebral hypoxia. Up to now, continuous SJO_2 monitoring is not necessary, as it has not been shown to be of benefit. However, episodic SJO_2 monitoring can sometimes detect episodes of cerebral ischemia and increased oxygen extraction allowing this way the optimization of hyperventilation in the treatment of intracranial hypertension. In addition, a decline of SJO_2 can be a sign of a very critical CPP and low levels of SJO_2 can also be associated with critical levels of anemia. SJO_2 is not frequently used as it is considered to be a more confirmative monitoring than an informative

one. Also, SJO_2 after the early few days reflects more the decline of cerebral metabolic rate for oxygen ($CMRO_2$) than the appropriateness of CBF. Values of SJO_2 that are stable high indicate post-traumatic $CMRO_2$ depression or the result of therapies that induce a decline of neuronal activities such as deep sedation, hypothermia or the use of barbiturates. Another similar well-documented technique is brain tissue oxygen monitoring ($PbrO_2$ or $PtiO_2$), which is more frequently used since the late 1990's. The probe is a fine parenchymal device into a selected area of the brain parenchymal and connected to a digital monitor.[17]

BRAIN TISSUE OXYGEN LEVELS – THERMAL DIFFUSION REGIONAL CEREBRAL BLOOD FLOW

Both, brain tissue oxygen levels ($PtiO_2$) and thermal diffusion cerebral blood flow (TD-rCBF) measurements constitute an alternative to SJO_2. Though these monitoring devices are extremely focal, when placed in apparently normal brain they are sensitive to the same variables that affect SJO_2, which is a recognized global monitoring modality. The main advantage of TD-rCBF over $PtiO_2$ is that it is not affected by multiple factors, while $PtiO_2$ is a proxy of rCBF, arterial oxygenation, and regional cerebral metabolic rate for oxygen ($rCMRO_2$). Though the regionality of these methods is a great limitation, it is also the main reason that they can be placed in perilesional edematous regions, as there they can easily document the way that the penumbra is sensitive to changes of physiological variables. Unfortunately, in clinical practice the placing of the sensor in the edematous area has success only in 50% of patients.[20]

MICRODIALYSIS

Cerebral microdialysis is a recently developed invasive laboratory device, bedside monitor to analyze brain tissue biochemistry. It is a technically feasible method that helps in monitoring biochemical disturbances in the brain. Usually, a catheter is inserted in "susceptible" brain tissue to measure biochemical changes in the area of brain most vulnerable to secondary insults. A second catheter is placed in apparently normal tissue for comparison. Different assays are available to measure dialysate concentrations including glucose, lactate, pyruvate, glycerol, and glutamate. Although it cannot measure the rate of molecular production or consumption, it gives the opportunity of detecting at the bedside conditions of metabolic crisis with lactate production in excess of pyruvate, abnormal cell firing and cytotoxic damage associated with glutamate elevation, and excessive consumption or defect in the metabolism of glucose. Cerebral hypoxia or ischemia has found to result in a significant increase in the lactate : pyruvate ratio (LPR). The threshold for LPR > 20-25 is considered a threshold for cerebral ischemia is considered 20-25 and is associated with poor outcome in TBI. Although, microdialysis is a well-established tool that provides additional assistance in the management of patients with severe TBI, its use is very limited.[17,28]

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial Doppler (TCD) is a non-invasive method used to measure CBF velocity and estimate autoregulation. Its use is continuously increasing in the neuromonitoring of TBI. It can diagnose complications such as vasospasm, critical elevations of ICP and decreases in CPP, carotid dissection, and

cerebral circulatory arrest (brain death). It is important that it can predict post-traumatic vasospasm before its clinical manifestation. TCD is suggested a non-invasive alternative technique for assessment ICP and CPP. It has a high overall sensitivity for confirming brain death (75-88%) and a high overall specificity (98%). However, it has the disadvantage that it is operator dependent and relatively unstable and for this reason though it is an established monitoring modality in neurocritical care, it is routinely applied only in a few centers.[17,28]

NEAR INFRARED SPECTROSCOPY

Near infrared spectroscopy is a monitor of cerebral oxygenation and CBV. It has the advantage that it is a continuous, direct and a non-invasive tool. In cerebral tissue, there are two main light–absorbing compounds, called chromophores, hemoglobin (Hb) and cytochrome oxidase. This method is based on the fact that these chromophores have differential absorption properties in the NIR range. More specifically at 760 nm, Hb occurs primarily in the deoxygenated state (deoxyHb), whereas at 850 nm, it occurs in the oxygenated state (oxyHb). Hence, by monitoring the difference in absorbency between these two wavelengths, the degree of tissue deoxygenation can be evaluated. Compared to SjO_2, NIRS is a less accurate method in determining cerebral oxygenation. Although, NIRS is an evolving technology and a potential as a clinical tool for bedside cerebral oxygenation and CBF measurements, its use in neurocritical care remains very limited due to limited availability and high cost of these devices.[4,28]

BRAIN TEMPERATURE

In literature, it is observed that after head injury, the brain temperature compared with body temperature is up to 3^0C higher. Elevated temperature is a common secondary systemic insult to the injured brain and it is a prognostic factor of the patient outcome. There are invasive, as well as non-invasive, continuous cerebral temperature monitoring devices for measuring the brain temperature. However, brain temperature monitoring is not widely used during neurocritical care of patients with severe TBI due to limited availability and high cost of these devices.[4,28]

CONTINOUS EVOKED POTENTIAL MONITORING

Another promising monitoring modality is continuous evoked potential monitoring, which has the unique ability to detect any reduction in neuronal activity in association with declines in CPP. Though new equipment allows it application at the bedside, it has the major disadvantage of forcing wave morphology into analyzable data. Current most studies analyze rather the relationship with outcome than describing patterns guiding therapy and management.[17]

BIOCHEMICAL MARKERS

A variety of serum biochemical markers for brain dysfunction have been investigated and used, although interest in some of these such as CK-BB and LDH 1 has been short lived. On the other hand there are many promising results from clinical studies in particular as far as the **GFAP**, the **MBP** and the **S-100B protein** concern. It is obvious that the literature regarding the S-100B protein is quite more extensive. On the other hand minimal literature is available for FABP, tau proteins, Hsp70s, RANTES,

and other serum inflammatory factors and their role as serum markers of brain damage. The assessment of the primary brain injury and the detection of ongoing secondary brain damage during intensive care period seem to be the most promising clinical applications. However, further clinical and experimental studies have to be performed in order to identify new more reliable serum brain biochemical markers, clarify their precise release mechanisms from damaged cells (glial cells or neurons) through the brain blood barrier and validate their clinical utility.[43, 44, 45]

A prominent role in prevention and prognosis of secondary brain damages is played by the scientifically as well as highly trained nursing stuff of the emergency department and intensive care unit. Their main purpose is the systematic monitoring and accurate recording of all the parameters that will determine the path of the condition of the patient. In the event of variation of the above mentioned parameters, the nursing stuff, have to inform the physician and then follow each protocol applicable to the respective cases.

PROGNOSTIC FACTORS FOR PATIENTS WITH SECONDARY BRAIN DAMAGE

The outcome of patients with severe head injury can be defined crudely in terms of death and survival. Late studies have shown that the mortality rate in severe head injury (GCS<9) has decreased from 50% to approximately 30-40%. However, the quality of survival is a most important issue. For this reason, the **Glasgow Outcome Scale** is a scale that has been invented in order to describe the overall social capability or dependence of the individual. It constitutes of five main categories:

1. Death.
2. Vegetative state (absence of awareness).
3. Severely disable (conscious but disabled and dependent).
4. Moderately disabled (disabled but independent).
5. Good recovery (resumption of normal life).

Categories 3-5 can be subdivided into further degrees of disability.

The Glasgow Outcome Scale is a practical scale to assess disability, which can be applied with consistency by a wide range of clinicians. Used in conjunction with the Glasgow Coma Scale, the Glasgow Outcome Scale forms the basis for the comparison and cost-benefit analysis of different regiments of treatment.

Though the evidence base for the treatment of patients with secondary brain damage is extremely limited, there are some documented factors that influence the outcome and therefore they are considered prognostic factors. The main factors are the nature and the extent of intracranial and extracranial damage, the depth and the duration of post-traumatic coma, the patient's age, the genes, the general medical health and previous state of function, the quality of available clinical care and the access to rehabilitation centers.

Social-environmental factors, as socioeconomic status, social support, caregiver and family functioning also can influence outcomes after TBI. Access to rehabilitation services can be negatively impacted by a lack of specialty providers, particularly in rural areas, as well as a lack of financial resources available to a person with TBI. The availability and level of insurance coverage are especially important.

Early imaging reduces time to detection of life-threatening complications and is also associated

with better outcomes. Also, advances in understanding the pathophysiology, monitoring, and imaging of brain injury have allowed the development of evidence-based intensive care management strategies and there is good evidence that this improves outcome. In addition it is documented that early nutritional support is associated with better outcomes. In patients with severe TBI, adequate nutrition that is started early after injury is associated with enhanced immunity, decreased infectious morbidity, shortened length of hospitalization, improved neurological recovery and reduced mortality.

In literature only a few predictive models for patient outcomes after severe TBI have been proposed. A relatively simple prognostic model using 7 predictive baseline characteristics including age, motor score, pupillary reactivity, hypoxia, hypotension, computed tomography classification, and traumatic subarachnoid hemorrhage has been reported to accurately predict 6-month outcome in patients with severe or moderate TBI. A predictive model based on age, absence of light reflex, presence of extensive subarachnoid hemorrhage, ICP, and midline shift was shown to have high predictive value and to be useful for decision making, review of treatment, and family counseling in case of TBI.[7, 17, 20, 27, 30, 35-36, 38-41]

CONCLUSIONS

Traumatic Brain Injury is a serious public health problem all over the world. Each year, traumatic brain injuries contribute to a substantial number of deaths and cases of permanent disability. Most probably patients with severe TBI will have secondary brain damage and will need to be nursed in the ICU. Diagnosis needs to be realized early in order to prevent every possible complication and deterioration of the patient's status and to offer the appropriate management. Management of TBI in intensive care is very difficult and it is becoming more difficult when the complications and organ dysfunctions are added. There are many factors that influence the patient's outcome and many of these are related to the management in the ICU. Therefore when special protocols for the patient treatment are followed in conjunction with the proper support therapy and close management, the mortality and morbidity of TBI patients can be decreased and patients can be offered an ameliorated quality of life after the injury.

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