Multimodal neurological monitoring in neurotrauma. Theoretical considerations for a practical approach

Randy Reina-Rivero, M.M. Rodriguez-Gutierrez, Michael Gregorio Ortega-Sierra, Diego Fernando Jamioy-Cabrera, Juan Felipe Villegas-Lora, D.M. Caycedo-Montiel, Juan David Balanta-Perea, Richard Adrian Vergara-Trujillo, Fernando Bellera, Yelson Alejandro Picón-Jaimes

DOI: 10.33962/roneuro-2021-091
Multimodal neurological monitoring in neurotrauma. Theoretical considerations for a practical approach

Randy Reina-Rivero¹, Maria Manuela Rodriguez-Gutierrez², Michael Gregorio Ortega-Sierra³, Diego Fernando Jamioy-Cabrera⁴, Juan Felipe Villegas-Lora⁵, Daniela Margoth Caycedo-Montiel⁶, Juan David Balanta-Perea⁷, Richard Adrian Vergara-Trujillo⁷, Fernando Bellera⁸, Yelson Alejandro Picón-Jaimes⁹

¹ School of Medicine, Universidad de Cartagena, Cartagena, COLOMBIA
² Future Surgeons Chapter, Colombian Surgery Association, Bogotá, COLOMBIA
³ School of Medicine, Corporación Universitaria Rafael Nuñez, Cartagena, COLOMBIA
⁴ School of Medicine, Universidad Surcolombiana, Neiva, COLOMBIA
⁵ School of Medicine, Universidad del Norte, Barranquilla, COLOMBIA
⁶ School of Medicine, Universidad Libre, Barranquilla, COLOMBIA
⁷ School of Medicine, Universidad San Martín, Cali, COLOMBIA
⁸ Department of Neurosurgery, Centro Policlinico Valencia, La Viña, VENEZUELA
⁹ Valencian International University, Santiago de Chile, Chile, COLOMBIA

ABSTRACT

Multimodal neuromonitoring is used as an adjunct to clinical neurological examination, imaging and other diagnostic studies to obtain the most detailed information about the physiology of the brain. Neuromonitoring has been a standard of care for patients presenting with traumatic brain injury in most critical care centres for the past several years. Neuromonitoring is composed of multiple variables, which not only provides a better dynamic of the pathophysiology of the compromised brain but also how it might respond to the corresponding management procedures. Although the clinical neurological examination is the standard for monitoring the neurocritical patient, the results obtained in the latter may be insufficient or inconclusive to detect or prevent secondary brain injury. Therefore, multiple neuromonitoring tools have been developed to measure different physiological variables that can contribute to a better follow-up of patients with traumatic brain injury. These variables include cerebral blood flow, cerebral electrical activity, cerebral...
metabolism, cerebral oxygenation and cerebral pressure. Thanks to monitoring as an adjuvant in critical care, it has been possible to avoid, identify and manage secondary brain injuries that commonly aggravate patients. This review aims to illustrate the main advantages and most recent recommendations regarding neuromonitoring based on the most current evidence.

INTRODUCTION
The objective of patient management is the identification, prevention and treatment of secondary brain injuries that may aggravate the patient's outcome. Understanding the mechanisms of brain injury and its pathophysiology are necessary for an adequate and patient-oriented treatment. As the primary damage, which represents direct mechanical damage, cannot be influenced therapeutically, the goal of treatment is the limitation of secondary damage (delayed non-mechanical damage). It is influenced by changes in cerebral blood flow (hypo- and hyperperfusion), impaired cerebrovascular autoregulation, cerebral metabolic dysfunction and inadequate cerebral oxygenation. At this case, the neuromonitoring multimodal is useful to observe the alterations [1]. In this manuscript we describe the different tools used for multimodal neuromonitoring in traumatic brain injuries patients such as clinical examination, intracranial pressure, autoregulatory reserve, cerebral oxygenation, cerebral blood flow, cerebral microdialysis and electroencephalogram. ICP measurement, clinical neurological examination along with computed tomography have been the main methods for monitoring TBI patients [2]. Clinical examination is a key point of multimodal neuromonitoring; but despite its accuracy it can often be confounded by intravenous sedation or concomitant metabolic disturbances in the patient. In isolation, the clinical examination may be non-specific and deterioration occurs because of late manifestations of secondary brain injury that could have been avoided with a more complete management of the patient through all the tools that neuromonitoring provides [3]. This review aims to illustrate the main advantages and most recent recommendations regarding neuromonitoring based on the most current evidence.

METHODS
A bibliographic search was carried out in the databases PubMed and Science Direct and in the Google Scholar search engine using the following terms: Intracranial pressure; Critical care, cranioencephalic trauma, multimodal monitoring, articles in English language were included, emphasizing the benefits obtained by performing neuromonitoring by means of the most determinant neurological variables that allow an adequate and complete analysis of brain functionality. The date of publication was not taken into account. A total of 245 articles were identified, including original articles, subject reviews, systematic reviews, letters to the editor, case reports and case series. 42 articles were selected that matched the goal of the article.

RESULTS
Neurological assessment
Of all the modalities of neuromonitoring, the clinical examination of an awake and cooperative patient offers the most comprehensive assessment of the central nervous system (CNS) function. Despite the advances in neuroimaging and other diagnostic tools, the clinical examination performed by a trained staff is still the "Gold Standard" for the assessment of patients with TBI. This evaluation should include the examination of CNS structures at risk in a given patient and a general description such as the documentation of the level of consciousness, for example, through the Glasgow coma scale, motor responses to verbal stimuli and / or painful and the evaluation of brain stem reflexes [2].

Despite being a fundamental component in neuromonitoring, the neurological examination has limitations that may diminish its effectiveness: 1) Patients in the ICU frequently present with an altered state or with diseases that substantially limit the information obtained clinically [2]; 2) Neurological evaluations are often done at different times by different examiners resulting in different findings and relevant changes can go unnoticed; 3) the findings of the neurological examination are influenced by therapeutic interventions frequently done in the ICU such as endotracheal intubation, use of hypnotics / sedatives, analgesics or neuromuscular blockers, among others [3]; Therefore, clinical examination is insufficient to fully evaluate TBI patients and additional test is needed [4].

Multimodal monitoring
Multimodal neuromonitoring (MNM) is used as a
Multimodal neurological monitoring in neurotrauma complements clinical neurological evaluation, diagnostic imaging, among other diagnostic methods, to obtain the most complete documentation of the brain physiological, particularly of changes [5]. MNM integrates several variables, not only providing a better overview of the physiopathology of the injured brain but also how it responds to interventions. Due to the vulnerability of neurocritical patients to suffer silent cerebral infarctions, MNM may timely diagnose deterioration and guide the clinician to intervene before irreversible injuries take place. This is done by direct tissue monitoring, inserting probes into the cerebral parenchymal tissue through a trephine orifice and fixed by a cranial pin system. Although the ideal location of the probe is not available, it is considered essential for the interpretation of the data and it is suggested to monitor brain tissue with a higher risk of secondary injury [3,6].

The MNM integrates many devices such as intracranial pressure (ICP), cerebral oxygenation, cerebral blood flow, autoregulatory reserve, brain electrophysiology, cerebral oxygenation, cerebral microdialysis and electroencephalogram, and will be detailed below (Table 1).

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcranial Doppler</td>
<td>Non-invasive real time with good temporal resolution.</td>
<td>Measures relative rather than absolute cerebral blood flow (FSC). Operator dependent. Failure rate of 5 to 10% (absence of acoustic window).</td>
</tr>
</tbody>
</table>

**Table 1.** Procedures and variables of major importance in the neuromonitoring of patient with acute brain injury [1-7].

**Jugular venous oximetry**
- Evaluates the balance between oxygen supply (blood flow) and demand (metabolism).
- Easy to perform.
- Global and insensitive to regional changes.
- Risk of venous thrombosis, hematoma, carotid puncture.

**PO 2 of brain tissue**
- The bedside gold standard for cerebral oxygenation monitoring.
- Assesses the balance between oxygen supply (FSC) and demand (metabolism).
- Measures regional oxygen tension, so usefulness depends on the location of the probe.

**Near infrared spectroscopy**
- Non-invasive real-time real-time of regional cerebral oxygenation in multiple regions of interest.
- Depends on manufacturer's algorithms.
- Signals affected by extracerebral tissue.

**Microdialysis**
- Measurement of local brain tissue biochemistry.
- Early detection of hypoxic / ischemic injury.
- Uncertain anomaly thresholds.

**Electroencephalography**
- No invasive.
- At real time.
- Correlates with ischemic and metabolic changes.
- Non-convulsive seizure / status epilepticus evaluation.
- Affected by anesthetic/sedative agents.

**Intracranial pressure**
Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) are the most commonly measured physiological brain parameters measured in the neurocritical care unit, and used in many treatment algorithms [7]. There is a large experience with ICP monitoring in TBI patients, aneurysmal subarachnoid hemorrhage, ischemic stroke and intracerebral hemorrhage in neurocritical care [1]. Normal ICP is 7-15mmHg in adults in the supine position, varying according to age, body position and clinical condition [2]. The term "intracranial hypertension" depends on the pathology, but levels above 15mmHg are considered abnormal [7]. An
increase in brain volume activates the regulatory mechanisms, but an alteration of these produces an elevation of the ICP, that is to say an increase of any component of the cranial vault demands a compensatory reduction of another to preserve a normal pressure [8]. The cerebrospinal fluid (CSF) is fundamental for the compensatory space mechanism because it can be distributed to the spinal cord reservoir [9].

ICP monitoring methods

ICP Monitoring provides information on the state of cerebral self-regulation and is essential for the treatment of severe TBI. ICP may be measured by parenchymal microtransducers or intraventricular catheters, the later considered the "Gold Standard" for ICP monitoring [9,10]. In addition, subarachnoid and epidural devices are also used, but they are less precise [2].

Intraventricular catheters are inserted into the lateral ventricles, and connected by fluid-filled tubing system to a pressure transducer [8,11]. This method allows to measure the global ICP and allows medication administration and therapeutic drainage of CSF. Risks associated with IV catheters are hemorrhages [12] and ventriculitis, often managed by exchanging to catheters impregnated with antibiotic [13]. Monitoring with intraparenchymal microtransducers the same precision as intraventricular catheters, lower infection rates, lower risk of hemorrhage, and can be easily placed providing continuous monitoring of the ICP. However, it is limited by its inability to be recalibrated [9]. Similar to clinical neuro examination, ICP monitization alone is not sufficient to diagnose all relevant physiological brain derangements generated by the brain injury [14].

Other noninvasive ICP monitoring techniques have been proposed as alternatives to direct ICP measurement including transcranial Doppler, EEG, pupillometry and ultrasound measurement of the diameter of the optic nerve sheath (DONS) [15]. DONS is an ophthalmological technique used to measure ICP, because the optic nerve sheath is adjacent to the dura of the brain and contains CSF that communicates with the cerebral subarachnoid components, so it can be useful as a means to detect indirectly the increase in the CIP. The pupilometer measures ICP indirectly by quantitatively evaluating pupillary reflex. There is no evidence that non-invasive measures of the ICP has the same clinical utility as direct invasive monitors [15].

Cerebral perfusion pressure

CPP is a surrogate measurement of cerebral blood flow. CPP is the difference between mean arterial blood pressure and ICP measured by invasive methods [2,16]. When cerebral autoregulation is normal, any increase in CPP causes compensatory vasoconstriction, reducing cerebral blood volume and ICP [1]. However, when autoregulation is lost, elevated CPP (higher than 120mmHg) can cause an increase in brain flow causing cerebral hyperemia, edema and hypertensive encephalopathy [2]. Monitoring both the ICP and CPP is frequently done in patients with TBI, subarachnoid hemorrhage and intracranial hypertension [17].

Vascular self-regulation

Vascular self-regulation is a fundamental brain protective mechanism from variations in cerebral blood flow, CSF and blood pressure after TBI. This is evaluated using the index of reactivity to pressure (PRx) which is the coefficient between the mean arterial pressure (MAP) and the ICP. A negative PRx indicates a preservation of self-regulation. On the other hand, when there is an increase in the volume of the cerebral vascular compartment, the ICP is increased and we are talking about a positive PRx, this indicates a deterioration of the self-regulation [18]. Reactivity to cerebrovascular pressure is defined as the ability of vascular smooth muscle to respond to changes in transmural pressure and is determined by observing the response of ICP to changes in blood pressure [19]. This index allows us to calculate the cerebrovascular reactivity and give value to the cerebral autoregulatory reserves [9,20]. In addition, cerebrovascular reactivity can be evaluated with the oxygen reactivity index which is the mobile correlation between tissue oxygen pressure (PtiO2) and PPC. PRx is considered a global measure of self-regulatory status, while ORx represents regional self-regulation due to the focal nature of PtiO2 [13,20].

Cerebral blood flow

Maintaining adequate cerebral blood flow (CBF) is fundamental therapeutic target and is quantified by neuroimaging modalities including ultrasonography,
Multimodal neurological monitoring in neurotrauma

CT scan, positron emission tomography, and MRI [9]. The advantage of these techniques is their good spatial resolution. Limitation includes the need to transport the critically ill patient to the radiology department and are not continuous, providing information at a single point in time [21]. The ideal neuromonitoring demands continuous measurements that can be done at the bedside [3,11].

Continuous "real-time" CBF monitoring is relatively new in neurocritical care and the technology is still being developed and refined. However, another modality, transcranial Doppler (TCD) has been used to evaluate focal regions of the brain with thermal diffusion flowmetry [9].

Transcranial Doppler measures non-invasively the speed of blood flow by emitting and receiving high frequency energy in the form of waves. The change in frequency reflects the speed and direction of cerebral circulation [22]. It can be done at bedside but is limited for being operator dependent [9].

Fluxometry by thermal diffusion allows the measurement, through a catheter inserted in the white matter, of the local cerebral blood flow. The catheter consists of 2 thermistors. One measures brain temperature and the other rises slightly at a temperature higher than the first [3,18]. The energy required to maintain the temperature difference between the two thermistors is proportional to the conductive properties of heat of the white matter [23], which remain constant as long as the catheter is correctly positioned and does not move, and the convective cooling of the cerebral blood flow, which is reported in conventional units of ml/100 g/min [3].

Cerebral microdialysis: metabolic monitoring in real time

The cerebral microdialysis is a technique that consists of extracting and quantifying the substances of the cerebral interstitial space. It is a laboratory tool introduced in the 90s and its clinical use approved in Europe in 1995 and in the United States in 2002 [3]. The physiological premise to obtain tissue metabolites lies in the assumption that it is essential to know when the transition from an aerobic to an anaerobic metabolism occurs which results in an energy failure [24].

In practice, microdialysis focuses on markers of cerebral energy metabolism (glucose, lactate and pyruvate), neurotransmitters (glutamate) and cell damage markers (glycerol). Measurements of glucose, pyruvate and lactate provide information on the relative contributions of aerobic and anaerobic metabolism to bioenergetics [25]. As for glycerol, it is a lipid component of neurons and its elevation is commonly associated with death / irreversible cellular ischemia. The increase in glutamate concentrations has been associated with hypoxia, ischemia and reduced brain tissue oxygenation (PbtO2) or CPP [1,26].

Electroencephalography

Several studies have shown that seizures are relatively common in patients with severe TBI., and are frequently non-convulsive, which may go unrecognized. Prophylactic anti-seizure medication is indicated to all patients with severe TBI [27].

Seizure identification after TBI has important implications for the management and prognosis of the patient [11]. The electroencephalogram has long been used to study electrical activity of the brain and diagnose seizures [16].

Continuous electroencephalography (cEEG) is instrumental in diagnosing seizures [28]. Late detection and treatment result in a significant decrease in the efficacy of anticonvulsant drugs. Unrecognized seizures, particularly if prolonged (status epilepticus), may raise intracranial pressure, metabolic demand, excitotoxicity and worsen primary brain injury [29]. There are limitations for the use of cEEG in the ICU. These include: 1) The availability of trained personnel to place the electrodes, 2) artifacts, and 3) The lack of trained professionals able to interpret the EEG in a timely manner. Additionally, there is an inherent degree of variability between the different interpretations [30]. The invasive cEEG is also available to identify crises that are not visible using scalp electrodes. The use of this modality can provide greater sensitivity to detect crises and improve the signal-to-noise ratio when compared to surface electrical activity [31].

Measuring cerebral oxygenation

Oxygenation is vital to cellular homeostasis and neuronal integrity, and can be used as a marker for tissues at risk of secondary injury. Brain tissue oxygen (PbtO2) and jugular venous oxygen saturation (SjvO2) allow continuous real-time evaluation of cerebral oxygenation [32].
PbtO2 provides information on 2 contexts: 1) it can evaluate oxygenation when there are normal values of PPC, and 2) it can diagnose cerebral hypoxia secondary to low perfusion when the PPC is within normal limits.

The jugular venous oxygen saturation provides information on global cerebral oxygen. The catheter is placed in the dominant internal jugular vein and advanced to the upper part of the jugular bulb [33,34]. Normal values range between 55 and 75%. Lower values indicate increased oxygen extraction and risk of ischemia. The compensatory mechanisms for poor oxygen supply or an increase in demand is increased oxygen extraction [31]. In decompensated states, ischemia may occur while high SjvO2 indicates hyperemia, decreased metabolic demand or even cell death [3,35]. It is necessary to carry out a greater number of prospective multicenter studies, especially in low- and middle-income countries where there are not enough specialized centers and high-quality mass training in neurological and neurosurgical monitoring, in order to improve the management of patients with neurotrauma and reduce the burden of neurological diseases [36-40]. In the same way, involve students and residents from early stages of their process, so that they are related to this type of recent techniques [41,42].

Conclusions
MNM integrates different equipments and measures that allow real-time monitoring of brain and identification of pathophysiological changes that occur after TBI. MNM allows early detection and compression of physiological changes caused by the injury, which will facilitate the determination of proper management of the neurocritical patient.

References
22. Calviello LA, Zeiler FA, Donnelly J, Uryga A, de Riva N,


