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Severe Cranioencephalic Trauma: Prehospital Care, Surgical Management and Multimodal Monitoring

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ABSTRACT

Traumatic brain injury is a leading cause of death in developed countries. It is estimated that only in the United States about 100,000 people die annually in parallel among the survivors there is a significant number of people with disabilities with significant costs for the health system. It has been determined that after moderate and severe traumatic injury, brain parenchyma is affected by more than 55% of cases. Head trauma management is critical is the emergency services worldwide. We present a review of the literature regarding the prehospital care, surgical management and intensive care monitoring of the patients with severe cranioecephalic trauma.

Keywords: Neurotrauma; Traumatic brain injury; Emergency; Trauma; Management.

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Introduction

Encephalic traumatic injury is a serious problem around the globe [1-4]. It represents at least half of deaths related to trauma and impacts health care services with high expenses for the health care system, for support and treatment of patients [5-7]. In The United States of America, health expenses are estimated as high as billions of dollars per year, whether directly or indirectly, because of labor productivity loss [7]. Modern trauma response equipment, new diagnostic tools, neurologic surgery centers and intensive care treatment have contributed to decrease mortality rates of patients with brain traumatic injury, where available series in literature report mortality of 35%-42%, especially in those individuals between 15 and 25 years [3,6,8]. Despite these efficacious advantages, there are many aspects

that should be upgraded about the brain traumatic injury management.

The purpose of this article is to give the reader basic elements about brain traumatic injury, starting with the initial evaluation in the emergency room or reanimation areas, until intracranial pressure multimodal monitoring, including strategies for the control of intracranial hypertension in intensive care units. Thus, initial evaluation; neurologic exam and management strategies that will be presented should become key tools for treatment of patients with severe neurologic trauma.

Evaluation

Initial Clinical Evaluation

Many of the achievements related to prognosis of patient with severe brain traumatic injury have stemmed from optimization of prehospital care and better quality attention in the emergency room and during resuscitation, as well as rapid imaging evaluation and identification of potential surgical injuries. All this efforts must be accompanied by multidisciplinary management and organization of emergency response teams, trauma room and support teams (radiology, respiratory therapy, blood bank, clinical laboratory, among others).

The main objective of prehospital care is to remove the traumatized patient from the environment or danger zones and move them to areas where appropriate therapy may be started. Thus, to avoid increase of injury or worsening of initial conditions, these efforts must be accomplished in logic and controlled way. The patient must be evaluated rapidly, immobilized with a cervical neck brace and spinal board to be forwarded to a definitive trauma center. Two clinical variables, hypoxia and hypotension have shown correlation with poor prognosis of these patients. Emergency response personnel should at least be able to identify patients who need respiratory support and to intubate those patients in the field where the traumatic event took place. Generally traumatized patients, with a score lower than 9 in Glasgow Coma Scale (GSC) should be intubated. Intravenous access should be set and circulatory support with resuscitation fluids is mandatory.

Once the patient has arrived to the hospital, the emergency room or resuscitation team will take over. Organized and flow transference care should be promoted to continue with the basic principles of integral attention pointing out secondary injury evasion. A standard emergency room or resuscitation area should have the basic equipment, including access to blood, laboratory service, ventilators and radiology.

Primary Survey

The initial evaluation is called "primary survey". During primary approach, airway, ventilation, circulation, disability and exposure are evaluated (ABCDE). Airway assessment consists in determining the ability of the patient to control their ventilation and respiration. Certain circumstances may block the airway, including an altered consciousness, obstruction by foreign body, fractures or facial edema. Maintaining a permeable airway is a need and orotracheal intubation is the preferred route when needed.

Respiration is next on the list, it is often assessed with the thorax patient, verifying if there is appropriate and symmetric expansion, also it is important an optimal pulmonary auscultation, as well as determining appropriate ventilation with pulse oximetry and carbon dioxide monitoring. Injuries such as pneumothorax and tracheal injury should be assessed in that moment.

Circulation assessment is performed prioritizing blood arterial pressure. In the presence of evidence of blood loss immediate treatment should be started. At least two large peripheral lines should be obtained, at the same time as blood tests (complete blood count, coagulation test). It is not yet defined to use whether crystalloid or colloid fluids for initial fluid resuscitation, however they may be used indistinctly as long as used properly. The following step is disability assessment, it usually consist of a short neurologic assessment using the Glasgow Coma Scale (GCS). The primary medical team may contribute promptly with valuable information for the neurosurgeon when this scale is used. Any altered mental status in a patient without hypotension or hypoxia is suggestive of a brain traumatic injury until proven otherwise, and CT scan is the election image study to confirm this injury.

Secondary Approach

Shortly, the secondary survey starts when primary survey has been completed and the patient has been stabilized. This secondary survey usually consists of a complete reevaluation of the patient and performance of additional tests as indicated by the condition. Detailed clinical history and physical examination, ECG, pregnancy tests, and additional radiologic studies are components of this phase. The moment the neurosurgeon is consulted to assess a traumatized patient; a detailed directed neurologic exam is needed.

Details about initial injury such as time and mechanism, information provided by witnesses and taking some aspects of the initial neurologic exam would be appropriate for the diagnosis and management. Data about the initial decrease of consciousness, convulsive crisis before or after the event, seatbelt use, high or low speed impact or initial motor movements may guide to a rapid decision of management that will be applied to the hospitalized scenario. The neurosurgeon will have to be aware of the development of ABCDE making the respective evaluation. The traumatized patients will be sedated with the goal of protecting airway or facilitating

the appropriate care during initial reanimation efforts. This aspect should be accounted for by the neurosurgeon, as a basic aspect for posterior neurologic assessments. Any intubated patient in whom a brain traumatic injury is suspected should be kept with normocapnia, usually in a normal-low range (pCO_2 30-35 mmHg) to avoid hypercapnia, vascular dilation and progression of cerebral edema. Hypotonic fluids should never be used in a patient with brain and scalp injury to identify any rapid blood loss due to lacerations, and compression and wound closure will be indicated. The combination of hypotension and bradycardia should make us think about neurogenic shock and in that case vasopressor drugs should be used to maintain appropriate arterial tension levels. Any abnormality in coagulation parameters should be corrected aggressively.

Physical exam should be performed step by step, usually from head to toe. The scalp examination, head, face, eyes, and ears should alert the neurosurgeon about the possible presence of bone fractures, open wounds, otorrhea, pupil dilation, cerebrospinal fluid fistula or ecchymosis may contribute to the diagnosis. Classically, otorrhea, rhinorrhea, retroauricular ecchymosis, or preorbital ecchymosis may be associated with fracture of cranium base. The neurosurgeon should never use another's physician evaluation; motor, verbal and ocular evaluation should be repeated. In the situation where the patient doesn't respond to stimuli, a firm compression over the sternum or supraorbital region may facilitate the examination. Some warnings: if the patient is intubated the visual and motor scores should be followed with a "T", for example, a patient who does not open the eyes [1] and shows decerebration posture [2] and is intubated, gets "3T". However, the best score will always be used. A patient that localizes in one side [5] but flexes in the other [3], gets a motor score of "5". The possibility of pharmacologic and sedation paralysis should be considered since this drugs modify the Glasgow Coma Scale and lead to erroneous evaluations. Traditionally a score of 14-15 is defined as mild cranioencephalic trauma, scores of 9-13 as moderate and scores below 8 as severe.

A complete and detailed neurologic evaluation is beyond this chapter but an approach to cranial nerves, sensitive exam must be performed. There are few classic pupillary findings and herniation syndromes; at least those will be described. Unilateral pupillary dilation with a background of brain traumatic injury is strongly suggestive of an expansive injury or uncus herniation, especially when associated with hemiparesis. A non-reactive unilateral pupil may be the result of orbit's trauma or optical nerve injury. Bilateral fixed and dilated pupil may suggest global hypoxia and brain death, and fixed myotic pupils suggest thalamic and brain stem hemorrhage.

Initial Radiographic Assessment

Head radiography, cerebral arteriography and ventriculography were the principal diagnostic tool used for trauma by surgeons and neurosurgeons to assess patients with head trauma. Integration of CT in the 70's has revolutionized early evaluation, diagnosis and treatment of patients with trauma. Early visualization of head and its contents is now the standard of care in most of the circumstances when there's a suspected head injury. CT allows quick and appropriate identification of head bones, cerebral parenchyma, intra or extra-axial bleeding, air, foreign body and cerebrospinal fluid. Once primary survey is completed and the patient is clinically stable, a head CT must be performed.

After performing the head CT, evaluation by a neurosurgeon is essential. The primary findings that must be ruled out are fractures of head bones (lineal or comminuted, depressed or non-depressed, open or closed, basilar skull fractures, sinuses or orbital fractures); hematic collections (epidural hematoma, subdural hematoma, intracerebral, intraventricular or subarachnoid hemorrhage); cerebral edema; hydrocephalus; ischemia/anoxia, pneumocephalus; midline deviation.

Acute bleeding seems relatively hyperdense when compared with cerebral parenchyma in a non-contrast-enhanced head CT. Extracranial collections are generally considered surgical if they are larger than 1 cm, surgical management will be detailed further in this chapter. Epidural hematoma is seen as a hyperdense mass, biconvex and adjacent to the cranium. These generally don't extend beyond the suture lines and may be the result of arterial injury, classically medial meningeal artery. Subdural hematomas are usually half-moon shaped; they can extend beyond the suture lines and typically are the result of venous bleeding. Their appearance will depend on the chronicity of the bleeding; acute bleeding is hyperdense, subacute bleeding is isodense and chronic bleeding is hypodense. Traumatic subarachnoid hemorrhage is the most common type of hemorrhage, the bleeding looks hyperdense and it is often localized over the convexity, basal cisterns and major sulci. Intracerebral hemorrhage and contusion present with several bleeding quantity of high density inside the cerebral parenchyma and intraventricular bleeding presents as high signal inside the ventricular system.

Skull fractures are better assessed with bone window. The presence of skull fractures are associated with intracranial bleeding probability, the assessment must include carefully inspection of orbital bones, frontal bone, sphenoid, maxillary bone, etmoidal sinus and temporal bone. Sometimes, finding air or fluid may be the only clue to discover a skull fracture.Air is typically seen black on a standard CT, it may be present in soft tissues, sinuses, intracranial spaces. Ischemia or infarction may not appear early on CT but lost of cortical-subcortical differentiation or discrete edema may lead to the primary diagnosis. Cerebral edema manifests as grooves compression,

ventricle effacement and basal cistern obliteration. Any midline deviation must be objective.

In those cases with skull penetrating injuries or when a possible vascular injury is suspected, a cerebral angiography is the Gold Standard diagnostic test. Other modalities, such as angio-CT and angio-MRI are growing in popularity, due to the availability, familiarity and velocity. These are useful tools and sensibility is close to the one of conventional cerebral angiography. MRI imaging allows better soft tissue evaluation, hematic collections and edema, but the use of it in the acute scenario is limited, mainly because of time limitation. MRI is better designed for evaluation of the late phase. Diffuse axonal injury, ischemic injuries and long term prognosis are some of the potential applications for MRI. Spectroscopy by MRI, magnetoencephalography and tractography will show in the future the possible applications in the area.

Cellular Physiopathology and Clinic of Traumatic Cerebral Injury

Complex cellular pathways and mechanisms implicated on cerebral traumatic injury are extended. The biochemistry and detailed feedback along with the molecular occurrences are reviewed by many authors and are beyond the chapter's objective.We provide a description of clinical and cellular basic physiopathology with the objective of breaking down the most relevant topics. Cellular events, including events related with calcium, mitochondrial alterations, apoptotic mechanisms, genetic alterations and inflammatory mediators are discussed initially.

Cellular Physiopathology of Cerebral Traumatic Injury [4,9-19]

The cellular processes, which involve neuronal injury after a cerebral traumatic injury, are traditionally classified as secondary cerebral injury, unlike the primary or spontaneous injury from the direct trauma itself. Secondary cellular events are believed to happen within hours or days after the initial trauma and may continue for weeks. This is, the secondary mechanism, in which physicians may potentially intervene and it's strongly related to the patient's prognosis.

Alterations in calcium homeostasis resulting from cerebral traumatic injury have been related to several cellular eventualities. Intracellular calcium influx may occur because of several mechanisms associated with membrane channels or receptors (including excitatory amino acid receptors), membrane alterations or trauma-induced depolarization, resulting in alterations of Na^{+}-K^{+} exchanging systems. It's been demonstrated on experimental and clinical models of cerebral traumatic injury that there is liberation or increase in concentration of excitatory amino acids, particularly glutamate and aspartate, minutes after the initial injury and during several weeks. These excitatory amino acids may attach to specific receptors in the brain, especially N-methyl-D-aspartate (NMDA) and non-NMDA (AMPA-kainate), that activate divalent cations and monovalent such as sodium and calcium. One inside the cell, calcium has been related to different processes, including phospholipases activation, leading to membrane disruption, free radical production that leads to cellular genetic material injury; down regulation of genes that control survival or apoptosis and mitochondrial disruption, leading to cellular death. Specifically, phospholipase A2 and phospholipase C lead to cellular disruption and free fatty acid generation. These fatty acids attached to intracellular free radicals such as nitric oxide, superoxide anion and hydrogen peroxide, represent reactive oxygen species (ROS) which cause DNA injury and cellular membranes and may disrupt cerebral blood flow, blood-brain barer and produce cerebral edema.

Intact mitochondrial function is to regulate energetic metabolism and contribute to cellular homeostasis. Elevated intracitoplasmatic and intramitochondrial calcium alters oxidative phosphorylation and electron transport chain. Cellular death through oxidative process alterations, mitochondrial edema and Na-K-ATP pump disruption are directly related phenomena. Genetic alterations, including overregulation of early oncogenes C-Fos and C-Jun, alter expression of pro-apoptotic and anti-apoptotic genes, their significance is not yet totally understood. Apoptosis od programed cellular death has relation with genetic regulatory control; balance between anti-apoptotic factors such as Bcl-2 and Bcl-X1 and pro-apoptotic factors such as Bax and Bak determine the cellular destination. These relations incline in favor of apoptosis, cysteine-protease family, and denominatedcaspases is a call to get in action. Caspase 8 and 9, known as caspase initiators influence directly caspase 3, the final executor. Activated caspase 3 points its intracellular targets, including cytoskeleton proteins, nucleic acid repair proteins and DNA-ases.

Numerous cytokines, growth factors and inflammatory mediators have been associated with cerebral traumatic injury. Brain-blood barriers disruption allows neutrophils, macrophages and other inflammatory cells to enter the central nervous system. These cells, attached to several mediators such as IL-1, IL-6, ICAM-1, TNF- α, nervous growth factor, FGF among others, have the capacity to destroy or to repair cells. When the blood-brain barrier is disrupted, cellular adhesion molecules reclute leukocytes, resulting in local liberation of ROS, causing cellular injury and death, as well as liberation of more pro-inflammatory substances and cellular mediators.

Antagonism or disruption of these separated yet interrelated processes has become the target for innovating treatments of cerebral traumatic injury. Calcium antagonist, NMDA receptor blockers,

free radicals sweepers, gene regulators, anti-inflammatory substances, antiapoptotic substances and termic regulation are some examples, and all of them are possible points for therapeutic intervention.

Clinical Physiopathology

5 variables have been found to be related to poor prognosis of patients posterior to a cerebral traumatic injury, these variables are: elevated temperature, hypoxemia, hypotension, reduced cerebral perfusion pressure and increase of intracranial pressure. These clinical alterations are called secondary insults; they will aggravate the primary and secondary injuries and, posteriorly, will lead to ischemia and neuronal death. It's through identification, recognition, prevention and treatment of these secondary injuries and secondary insults that there've been progress on the management of patients with cerebral traumatic injury. Treatment paradigms such as cerebral oxygenation optimization and perfusion, maintained intracranial pressures on the normal limit and medical and aggressive surgical treatment constitute the standard of care until this day.

In order to understand the physiopathology of severe cerebral trauma, a brief cerebral physiology review is necessary. Human brain uses glucose as an exclusive energy source to produce adenosine triphosphate (ATP). The pathway through which glucose is used depends on the availability of oxygen, being the two key processes: oxidative phosphorilation and anaerobic glycolysis. Oxidative phosphorilation is much more efficient, producing a total of 38 ATP molecules per molecule of glucose, contrary to the 2 ATP molecules and 2 lactate molecules in anaerobic glycolisis. Two parameters are used for the assessment of cerebral metabolism, cerebral metabolic consumption rate of oxygen ($CMRO_2$) and cerebral metabolic consumption rate of glucose (CMRG) with normal values of 3.3 mg/100g/min and 5.5 mg/100g/min respectively. Given its small percentage relative to total body weight (3%), the human brain uses an extraordinary 20% from the cardiac output to maintain its high metabolic requirement. Although, neurons constitute around 50% of human brain, they represent 90% of total energy output. On the other hand, glial cells use only a 10%. A huge part of this energy output is used in neuronal communication and synaptic transmission, 25% for biosynthesis and cellular transport and 25% to maintain the membrane's ionic gradient. Since human brain lacks of ability to store glycogen, it depends on a constant blood flow to supply oxygen and glucose to the cells. Maintaining a constant blood flow, under diverse circumstances is known as cerebral self-regulation.

Cerebral Self-Regulation

Cerebral self-regulation is a well-studied phenomenon; there are several described mechanisms, importantly self-regulation pressure and metabolic self-regulation. Self-regulation pressure may de described using the Poiseuille's equation. Changes in perfusion pressure will result in blood flow change; thus, blood vessels will adapt to maintain the flow. This phenomenon is generally seen under normal physiologic conditions through blood pressure ranges 50-150 mmHg but the changes are seen under certain pathologic conditions, such as chronic hypertension, which deviates the curve to the right.

Failure of self-regulation pressure is represented by Fick's equation: $CMRO_2$=CBF x AVO_2D, where metabolic rate, cerebral blood flow (CBF) and arteriovenous oxygen gradient are interrelated, so local cerebral blood flow matches the metabolic requirement. The exact cellular mechanism behind the pressure and metabolic self-regulation are completely understood, but there's evidence that vascular endothelium has an integral paper. Studies have shown that an intact vascular endothelium is essential to maintain cerebrovascular homeostasis. Local metabolites and vasoactive substances such as H^+, CO_2, adenosine, K^+, calcium, nitric oxide, endothelinand thromboxane have been proposed as possible mediators in cerebrovascular reactivity and are thought to be responsible of a complex interconnectivity between several substances.

Secondary Injury

Disruption of several already mentioned processes result in cerebral traumatic injury. Focal and global alterations in cerebral metabolism, cerebral blood flow, self-regulation and intracranial pressure contribute to develop secondary injuries. Cerebral metabolic rate in patients with intracranial injuries is typically low, ATP production is low and switch to anaerobic glycolysis is the dominant phenomenon. This results in an increase of lactate concentrations and a non-healthy acidified environment. Disruption in self-regulation, cerebral blood flow and metabolism decoupling, as well as alteration in reactivity to CO2 become other deleterious phenomena around cerebral traumatic injury. These events, coupled with systemic alterations, such as hypoxia and hypotension will result in adverse effects on potentially recoverable neuronal populations. Ischemic cerebral injury is very common after cerebral traumatic injury [4,20]. The brain initially offers a physiologic response decreasing blood flow by extracting important amounts of oxygen from the circulation, but extraction increases to a maximum point and tends to produce blood flow reduction resulting in energetic failure, mitochondrial and cellular disruption. Ultimately, determination of cellular survival versus cellular death will depend on several complex relations between the actual blood flow, the duration and degree of ischemia, specific cellular class, glucose concentration and temperature, among other factors. It's been seen that a relative constant value of blood flow is associated

with recoverable neurons and with irreversible cellular death, with flows of 18 cc/100g/min and 8 cc/100g/min respectively [21-23]. Cerebral perfusion pressure (CPP) and cerebral blood flow are related to intracranial pressure and mean arterial pressure by this equation: CPP=MAP-ICP [24], an increase in intracranial pressure is a common finding in patients with severe traumatic injury and its management is one of the paradigms in the current treatment.

Intracranial Pressure

Monroe-Kelly's hypothesis postulates that the cranium is a rigid structure, a non-expandable box, and mainly three volumes form its content: cerebral parenchyma, cerebrospinal fluid and blood. For blood pressure to be maintained constant, volumes inside cranial vault must be stable. Any additional increase in volume secondary to hyperemia or presence of hematoma will decrease the volume of the other components and will lead to increase of intracranial pressure. Around one third of patients with diffuse cranial injury and half of patients with intracranial tumors will develop increased intracranial pressure [25-27]. Normal intracranial pressure in the adult varies in ranges of 5-15 mmHg and pediatric values in ranges of 0-10 mmHg. Persistent increase of intracranial pressure has been associated with poor prognosis and mortality is directly related to the degree and duration of increased intracranial pressure. When intracranial pressure increases, cerebral perfusion pressure generally decreases; contributing to decrease of cerebral blood flow, ischemia and neuronal death. A great part of clinical targets has been about restricting intracranial pressure increase, maintaining an adequate perfusion pressure and aggressively avoiding ischemic situations closely related to ischemia and hypoxia. Other modalities include intracranial injury assessment and stopping progress of cerebral edema.

Herniation Syndromes

The four, most frequent, herniation syndromes are subfalcine herniation, transtentorial herniation (Uncal), axial (central) and tonsillar herniation. Each of these implies different brain structures and is associated with specific clinical syndromes. Any intracranial expansive mass may result in increase of intracranial pressure and cerebral tissue herniation through dura mater openings and calvarium. Subfalcine or cingulated herniation usually results from a hemispheric expansive mass in anterior and medial fossa with causes the cingulate gyrus to herniate over the falxcerebri. Depending on the degree of herniation, one or both anterior cerebral arteries may be compressed, causing paraparesis. Transtentorial or uncalherniation is typically the result of the presence of an expansive mass in medial or temporal fossa. Here, the uncus herniates over the tentorium cerebelli, resulting in ipsilateral compression of the third cranial nerve and cerebral peduncle, causing classic ipsilateral alteration of the third cranial nerve and contralateral hemiparesis. Uncal herniation may also produce compression of posterior cerebral artery and produce occipital infarction or ischemia.

Central and tonsillarherniation may result from generalized increase of intracranial pressure or supratentorial masses. The first is associated with brainstem displacement towards the foramen magnum resulting in basilar artery decrease and brainstem distortion. This presents with decrease of conscious state, breathing pattern irregularities, hypertension and bradycardia. Tonsillar herniation may also be associated with presence of masses in the posterior fossa, and result in displacement of cerebellar tonsils through foramen magnum compressing the medulla oblongata. Respiratory decompression, apnea and death may be produced.

Although these clinical syndromes are well defined and related to certain pathologies, the brain CT availability is a requirement. Modern tomography allows quick and proper confirmation of suspected pathologies and also clearance of undefined diagnosis.

Intracranial Hypertension: Monitoring Modalities and Treatment Strategies for the Patient with Traumatic Brain Injury

Intracranial Hypertension [28]

Intracranial hypertension is the principal cause of death in patients with traumatic brain injury and contributes to secondary brain injury of it's not managed correctly. As we mentioned previously, the Monroe-Kelly hypothesis proposes that the cranium is rigid and occupied by three volumes: blood, brain and cerebrospinal fluid, at least any additional volume, such as hematomas, cerebral edema, or hydrocephalus will result in increase of intracranial pressure when the compensatory displacements of initial volumes have been exceeded. The capacity to store up to 150 cc of new intracranial volume without any significant increase in intracranial pressure occurs by venous blood displacement to the systemic circulation, outward displacement of cerebrospinal fluid is dependent on time and age. Older patients often present more brain atrophy and this way they distribute a larger amount of volume that expands slowly. Younger patients with acute processes, on the other hand, become symptomatic earlier in the same pathophysiological processes. Space-occupying injuries will be discussed in the next section and it's assumed that these injuries have been surgically drained. Abnormal cerebral self-regulation, blood flow and cerebral edema persist as cause of increase of intracranial pressure.

Clinical trials have shown that patients with traumatic brain injury with ICP greater than 20 mmHg, especially when refractory to treatment, have adverse clinical prognosis and likely to develop cerebral herniation syndromes [29,30]. There's also

recent evidence that cerebral perfusion pressure below 60-70 mmHg is associated with decreased oxygenation of brain's parenchyma, metabolism alteration and prognosis [4]. Neurologic monitoring and treatment's objective is to at least maintain adequate cerebral perfusion, oxygenation and metabolism, also, to limit the progression of increased intracranial pressures, desaturation phenomena and edema, among others.

Monitoring Techniques

Monitoring techniques in patients with traumatic brain injury can be divided into three categories: intracranial pressure monitoring, blood flow monitoring and biochemical substrates monitoring. Selection between the diversity of modalities has become complex. Monitoring capacity of multiple parameters, such as oxygenation and substrate concentration, as well as intracranial pressure are more common each time. As we've previously mentioned, cerebral ischemia, hypoxia and cellular dysfunction are common after a traumatic brain injury, blood flow reduction and substrate supply occur in minutes, highlighting the importance of early reanimation.

Intracranial Pressure Monitoring [31-37]

Intracranial pressure can't be trusted when it's based on estimations from the clinical exam or radiologic criteria alone. In patients whom intracranial hypertension is suspected, intracranial monitoring is the current gold standard for its assessment. In traumatic brain injury, some of the indications for monitoring are: EG lower than 9, with abnormal brain CT and, patients with a score lower than 9 with a normal brain CT but older than 40-years-old with hypotension or abnormal motor postures.

Intraventricular catheters coupled with traditional fluids are the standard method and have low cost, but may experience alterations or malfunctioning. Optic fiber (Integral Neuroscience-Plainsboro, NJ) and devices with transducer tip (Codman-Rayham, MA) may be placed inside the ventricle or brain parenchyma and may be appropriate to measure for several days, but they are usually expensive and they can't be recalibrated after they've been placed. There are also monitoring systems that can monitor compartments separately allowing measurement of ICP and cerebrospinal fluid drainage, of this type the Speilgelberg (Hamburg, Germany) transducer is known.

Intracranial Flow Monitoring

- Transcranial Doppler [38-42]

Transcranial Doppler is a cheap and non-invasive technique that provides data about cerebral hemodynamics, and may alert the treating physician about possible adverse events. Transcranial Doppler works with an ultrasonic pulse signal that is transmitted through a thin area of the cranium. The blood flow speed is determined and the flow volume may be estimated multiplying the speed by the transverse area of the vessel. Since the amount of collateral flow and actual vessel diameter are not known, transcranial Doppler can't provide quantitative data about regional tissue perfusion. Changes in flow speed can at least provide relative data considering changes in volume flow. Typically, flow speed greater than 200 cm/sec indicates severe vasospasm, vessel narrowing and imminent infarction. Hyperemia, a common phenomenon posterior to a traumatic brain injury, may lead to increased flow speeds. Commonly known Lindegaard index or hemispheric index (MCA/ACI extracranial) may help us to differentiate both situations, with normal values lower than 2 and critical values greater than 3.

- Xenon-enhanced Computed Tomography

Tomography with xenon is probably the most adequate non-invasive method to determine the regional and global cerebral blood flow. Xenon is a radio-dense, inert, and quickly diffusing substance that allows us to make precise quantitative measures that are needed to determine the blood flow. To perform a xenon-enhanced CT, a brain CT is performed and then seriated tomographies while inhaling xenon to 28-33% are performed, posteriorly, through complex mathematic molding, quantitative values are produced based on the Fick principle which postulates that the uptake or release of any substance from an organ is the product of the arteriovenous difference of that substance multiplied by the blood flow of that organ (consumption or production=A-V difference. Q).

As other techniques, xenon-enhanced CT is not exempt of errors, so, in order to obtain reliable results the patients must have an optimal cardiovascular condition. There are two invasive methods currently available to assess local blood flow and correlate closely to xenon-enhanced CT; thermic diffusion method and laser-Doppler method. Both methods require open craniectomy for their placement, due to their limited applications; also these methods can only measure small focal areas of brain tissue, than may not be representative of the global blood flow status.

- Infrared spectroscopy [43-47]

This technique implies transmission of light from an emitting-light source to a sensor, and it has been developed to monitor cerebral oxygenation, blood flow and blood volume in adults and children. Infrared spectroscopy has some technical aspects that require improvement, for example, light transmission works adequately in neonates because of their cranium and semitransparent scalp, adult monitoring can be difficult because of the increase of density of brain tissue. Using this technique in reflectance mode may help to overcome this problem. This way the transmitter and receiver are separated by specific distances over the scalp with premises that a fixed, emitted and light-reflected quantity of

light maintains an elliptical pathway whose deepness is proportional to the distance of separation between transmitter and receiver.

The cerebral oxymeter (SomaneticsInc, Troy MI, Invos Cerebral Oxymeter) is a device used to estimate oxygen saturation on the brain. A couple optical transceivers are placed in the scalp and light signal attenuation of two wave longitudes is used to estimate regional oxygen saturation. Although these measurements can help us identify critical clinical parameters and help the treatment, infrared spectroscopy is not a standard or sufficient technique. These values have to be applied to the context of other measurements to support of sush measures, instead of indicating the medical actions to be followed.

Substrate Monitoring

- Jugular venous-oxygen saturation ($JVSO_2$) [48-51]

As the cerebral flow decreases, oxygen extraction is increased to compensate, but initially the metabolic cerebral rate doesn't change. Decreases in blood flow exceed the compensatory mechanisms and the supply is incapable to maintain the requirements, metabolic rate decreases and the anaerobic metabolism starts to act. Monitoring of $JVSO_2$ initially started on 1930 as a promising method to detect changes in global brain oxygenation after trauma, but posteriorly, it has shown to be more difficult that thought initially. $JVSO_2$ in normal subjects is typically above 60%. Decrease to ranges of 50% or less is associated with altered cerebral metabolism, and values lower than 20% are associated with non-reversible ischemic injury and worse prognosis.

- Oxygen pressure (PO_2) [49, 52-56]

A more direct approach to measure global or focal cerebral alterations consist in the collection of intraparenchymal sensors with the system Licox® (GMS-Integra-Kiel-Mielkendorf, Germany). Licox® sensors are smaller and can be inserted easily, with a sampling area of 14 mm approximately that has shown to be adequate. Also, it provides the ability to measure local temperature fluctuations, since it has been shown that the temperature of system is different from the central temperature. Diffusion of oxygen in the blood to the extracellular space provides the substrate for the measurement and Licox® system integrates all the oxygen arterial and venous tensions in the area. Normal brain oxygen concentration varies between 20-40 mmHg. Values lower than 10-15 mmHg should be considered a sign of tissue hypoxia and values lower than 5-10 mmHg are indicative of imminent infarction.

- Microdialysis [57-60]

After a traumatic brain injury, the cerebral microenvironment changes rapidly. Liberation of excitatory amino acids, calcium influx, failure of membrane pumps, and accumulation of lactate are only a few alterations that underlay neurological-traumatic pathology. Some of these changes have been reported with the use ofmicrodialysis in humans. It's been reported correlation between adverse clinical effects (increased intracranial pressure, hypotension and hypoxia) and increases of dialyzed concentrations (lactate, potassium, excitatory amino acids) or decrease (glucose) after a traumatic brain injury. Cerebral microdialysis consists in a sensor (0.62 Dia) that is placed in the cerebral parenchyma; it was used initially on 1980 by Mayerson *et al*. in models of Parkinson disease [61,62]. Cerebral microdialysis has been combined with other modern techniques of brain monitoring such as ICP and PO2 sensors. The sensor is perfused slowly with a sterile extracellular fluid allowing the sampling and identification of diverse molecules such as glucose, lactate, potassium, pyruvate, nitric oxide and glutamate. Microdialysis is not a perfect tool. One of the aspects that must be considered is that measures correspond to relative concentrations of extracellular molecules, not to actual concentrations, causing problems when we try to compare data between different equipment and centers. Another disadvantage is that it has a poor temporary resolution.

Treatment Strategies

As we mentioned earlier, the objective of monitoring is to maintain adequate cerebral perfusion, oxygenation and metabolism, while we limit elevations of intracranial pressure, saturation and edema, among others. Specific values that may be useful as a guide include the maintenance of a CPP between 60-70 mmHg, ICP below 20 mmHg, JVSO2 above 50 mmHg and local tissue oxygenation above 15-20 mmHg. Traditionally, the treatment of increased intracranial pressure starts with less morbid measures. Headboard elevation maintaining a normotensive, euthermic and normocapnic patient are routine measures, as well as prevention of hypoxia, mild sedation and analgesia should be the initial steps for patients with brain trauma. Those are the first line known strategies; progression to other is related to elevation of intracranial pressure and should never be used as prophylaxis.

Cerebrospinal Fluid Drainage [28,63,64]

A fundamental strategy for the management of increased intracranial pressure is the cerebrospinal fluid drainage. Drainage of small quantities of cerebrospinal fluid is an effective strategy. Additionally a theoretical advantage implies the removal of neurotoxic compound from the cerebrospinal fluid such as glutamate, aspartate and calcium. Elimination and removal of these substances from cerebrospinal fluid, which are known to be present after a traumatic brain injury, represent undisputed theoretical advantages.

Sedation and Muscle Relaxation [57-69]

The next step is constituted by sedation and

neuromuscular relaxation. Agitation, anxiety, abnormal movements and resistance to mechanical ventilation can contribute to elevation of intracranial pressure. Sedatives such as midazolam or lorazepam; opioids such as morphine or fentanyl; neuromuscular-blocking agents such as vecuronium or rocuronium and propofol are used frequently. Routinely use of neuromuscular paralysis has been associated with pulmonary complications and extended stay.

Osmotic Diuretics [70-73]

Mannitol is, in the actuality, the osmotic diuretic of election and it's given in bolus at doses of 0.25-1 g/kg. This substance has the capacity to decrease intracranial pressure 15 minutes after the administration and the effect persists for 3-4 hours. There is controversy about the route of administration; some support the application of intermittent bolus while others support the continuous application. No matter the route, there is sufficient evidence of the therapeutic effects of mannitol, including blood flow improvement and oxygen supply to the brain. Also, there's evidence about the use of loop diuretics, like furosemide and parallel use to the mannitol to reduce more aggressively ICP [74]. Superior effects of mannitol are better when osmolarity is between 300-320 mOsm. However, some aouthors suggest the use of saline hypertonic solution, but there's no evidence this is superior to mannitol.

Hyperventilation [75-82]

Lundburg was the first to introduce hyperventilation as a treatment method for elevated ICP in the 50's [83], he specifically demonstrated decrease of it in patients with brain tumors and traumatic brain injury when arterial PCO2 decreases below 40-25 mmHg. Posterior trials showed that hyperventilation leads to cerebral vasoconstriction, cerebral blood flow decrease and ICP reduction. Also, it has been demonstrated that in the peripheral zone of contusion there is low blood flow. Routinary hyperventilation (arterial PCO2 20-25 mmHg) has been related to adverse prognosis [84,85], because of this it is recommended to maintain a PCO_2 around 35 mmHg. Aggressive hyperventilation should only be used in severe circumstances and for short periods of time.

Decompressive Craniectomy

Although the surgical indications will be mentioned posteriorly, decompressive craniectomy for treatment of refractory intracranial hypertension will be discussed shortly. Procedures of surgical decompression are a controversial subject, but there's some evidence that the use may reduce mortality rates. For example, Gower and coworkers reported reduction of mortality of 80–40% in patients who underwent subtemporal decompression, in the context of refractory intracranial hypertension [86]. Guidelines of management for surgical treatment of traumatic brain injury by Bullok and coworkers [87-90] recommend the following:

- Decompressive craniectomy including subtemporal decompression, temporal lobectomy, and hemispheric decompressive craniectomy are options of management for patients with intracranial hypertension and diffuse parenchymal injury with clinical and image evidence of imminent cerebral herniation.

Barbiturate-Induced Coma

The use of barbiturates is in the first line of treatment for patients with refractory intracranial hypertension. This can act as free racial cleanser, decreasing the cerebral metabolic rate, producing cerebral vasoconstriction in non-injured areas to supply blood to affected areas, maintaining calcium homeostasis and lysosome stabilization. Routinary use of barbiturates in non-selected patients has not proved to reduce mortality or morbidity after a brain traumatic injury [91,92]. Eisenberg and coworkers [93], in a randomized multicenter trial showed that there's the double opportunity to control IPC in patients with intracranial hypertension when barbiturates were used. Barbiturates may produce severe hypotension; the neurologic exam can't be performed when these drugs are used. The patients with cardiovascular instability are not good candidates to use this measure. Pentobarbital is the most frequently used and catheter monitoring with Swan-Ganz catheter is required. We can use barbiturate-induced coma when other measures haven't been useful to manage intracranial hypertension.

Hypothermia

This measure has been studied and used for decades, in the last years resurgence has appeared and several researches have been made [94-97]. Moderate therapeutic hypothermia (32-35 ˚C) has shown to reduce intracranial pressure but has no relation with mortality reduction after a traumatic brain injury. Hypothermia reduces the cerebral blood flow, the metabolism and inflammation. We recommend the use of moderate hypothermia for 49-72 hours in severe traumatic brain injuries, establishing as soon as possible after the trauma.

Surgical Indications

The most important surgical complication of traumatic brain injury is the development of cerebral hematoma; this is present in 45% of severe traumatic injuries and in 15% of moderate injuries, producing approximately 100 thousand surgical patients a year. Quick drainage of an intracranial hematoma can be one of the most rewarded and effective surgical treatments, but despite the quick diagnosis and drainage, high mortality and morbidity persists in certain conditions such as acute subdural hematoma. There're generally five situations in which treatment for traumatic brain injury is indicated: epidural hematoma, subdural hematoma, intraparenchymal

hematoma, cranial fractures and sustained elevated intracranial pressure. Penetrating injuries will not be discussed and the indications for management of elevated ICP have already been discussed. In 2006, Bullock and coworkers [87-90] published the guidelines for surgical management of traumatic brain injury; shortly we'll discuss the surgical indications for each one of the mentioned entities. The details of the surgical techniques scape the objective of this text, normal blood parameters, blood availability and cardiovascular stability are prerequisites for surgical management.

Epidural Hematoma [98-100]

Reported incidence of epidural hematoma caries from 2-4% of patients with cranial injury and up to 9% of patients with Glasgow score below 9. The peak incidence of epidural hematoma is between 20-30 years, being infrequent in alders and neonates. Traffic accidents, falls and violence are the cause of more than 90% of epidural hematomas, classically the epidural hematoma results from injury of medial meningeal artery. Venous and sinuses bleeding may also be the cause. Epidural hematoma may occur in the temporal or parietal-temporal region. Mortality for epidural hematoma ranges in 10% and factors such as age, Glasgow coma scale, pupils, associated intracranial injuries; intracranial pressure disruptions and the period of time between the neurologic deterioration and the drainage have shown relation with the prognosis. Through a careful analysis of the available literature, Bullock and coworkers' management guidelines [87-90] recommend the following:

1. Surgical drainage of any epidural hematoma with volume greater than 30 cc.
2. Patients with an epidural hematoma with a volume lower than 30 cc, can be considered as non-surgical if they present any of the following criteria:
   a. Width minor than 15 mm.
   b. Midline deviation minor than 5 mm.
   c. Glasgow coma scale score greater than 8 and without focal neurological deficit.

All trauma patients are initially followed conservatively and CT will be performed in the 4-6 initial hours. The presence of focal neurological deficit, deterioration in the neurologic exam, or increase of hematoma's volume should be surgery indication. Epidural hematomas have been associated to rapid neurologic deterioration.

Acute Subdural Hematoma [101-103]

Acute subdural hematoma is a common intracranial injury that presents in patients with cranial trauma. This injury is defined as the injury that occurs within the first day's posterior to the injury. The chronic subdural hematoma has a different incidence, presentation, and management strategy. The reported incidence of chronic subdural hematoma when associated with mild, moderate and severe cranial trauma is around 11% [20]. Frequently there're associated injuries to acute subdural hematomas and in 30-40% they present alone. Cranial fractures, subarachnoid hemorrhage, intracerebral hematomas and contusions are found associated injuries. Other injuries may also be found like thoracic, abdominal and extremity trauma.

In general, the mortality rate of acute subdural hematoma is greater than in patients with epidural hematoma, 60-90%. Factors like age, GCS, pupils, associated intracranial injuries, intracranial pressure and the period of time between the neurological deterioration and drainage have been reported in the literature as important prognostic factors. Through a detailed review of the literature in relation to these hematomas the guidelines of Bullock and coworkers [87-90] recommend:

1. Surgical drainage of all acute subdural hematomas with diameter greater than 10 mm or midline deviation greater than 5 mm taking in count the GCS.
2. All patients with an acute subdural hematoma and GCS score below 9 should undergo monitoring of intracranial pressure.
3. Patients with GCS score below 9, with acute subdural hematoma whose diameter is minor than 10mm and midline deviation is minor han 5 mm can be considered for non-surgical treatment since they will have the ICP monitored and they should maintained without pupil alterations and ICP below 20 mmHg, drainage is recommended when GCS score decreases more than 2 points in the time period between the injury and hospital admission, or if the patient presents pupil asymmetry or ICP exceeds 20 mmHg.

Intraparenchymal Injuries

Traumatic intraparenchymal injuries are a diverse group of focal injuries that consist of intracerebral hematomas and contusions, is also includes non-focal injuries such as hemispheric edema and diffuse injuries. Intraparenchymal injuries may have a frontal, temporal, parietal, occipital or combined localization, it presents in 15 – 35 % of patients with traumatic brain injuries. Guidelines for surgical management of traumatic brain injury by Bullock and coworkers [87-90] recommend:

1. Patients with intraparenchymal injuries and signs of progressive neurological deterioration related to the injury, untreatable intracranial hypertension or signs of mass effect in brain CT should be managed surgically.
2. Patients with GCS score from 6 to 8 with frontal and temporal contusions greater than 20 cc of volume or midline deviation of more than 5 mm or cistern compression evidenced in brain CT and patients with injuries greater than 500 cc should be managed surgically.
3. Patients with intraparenchymal injuries that do not show evidence of neurological deterioration,

who present controlled ICP and without significant mass effect on CT may be managed with neurologic monitoring, serial imaging and conservatively.

4. Decompressive procedures, including subtemporal decompression, temporal lobectomy and hemispheric decompressive craniectomy are treatment options for patients with refractory intracranial hypertension and diffuse parenchymal injuries with imminent clinical and radiographic evidence of cerebral herniation.

Cranial Fractures

The strategies of management for cranium fractures are directed to decrease the risk of infection, to treat bone deformity, to decrease the risk of epilepsy and to decrease neurological deficit when present. The presences of cranial fractures are related to the presence of other intracranial injuries. Depressed and open fractures are the type of fractures that require most of the cases, surgical management. On the other hand linear closed fractures may have conservative management, depressed fracture represent the 6% of cranial injuries and infection rates, neurologic morbidity, mortality and late epilepsy may occur in the 10%, 11%, 15% and 15% respectively.

After a careful review of the literature, the guidelines for management by Bullock and coworkers [87-90] recommend:

1. Surgical elevations and debridation of open and depressed fractures of greater than the cranium thickness of greater than 1 cm or evidence of dural disruptions, associated with hematomas, sinus compromise, injury contamination, infection, or major cosmetic deformity.

2. Patients with open fractures may be treated non-surgically and some of the criteria previously mentioned are found.

3. Simple depressed or lineal fractures may be managed conservatively.

The time for surgical correction and debridation is important; they should be performed within the 24-27 hours after the incident. Antibiotics are recommended for the treatment of all open cranial fractures [104,105].

Intensive Care Management

Patients with traumatic brain injury can usually be taken to intensive care unit. Principles of general management include control of temperature, arterial pressure, sedation, ventilation and nutrition, among others.

Fever [106-108]

Fever is defined as a body temperature above 38º C; it's associated with cerebral vasodilation, ICP increase and increase of cerebral metabolic rate. Post-injury hyperpyrexia has been strongly associated with worsening of clinical prognosis in several experimental trials. Elevated temperature must be managed aggressively with antipyretics, cooling devices and infectious causes should be identified and treated. As we mentioned earlier, moderate hypothermia may have some neurologic-protective effect.

Arterial Pressure

The management of arterial pressure in the traumatic brain injury results from the adequate balance between the appropriate control of cerebral perfusion pressure and avoiding vascular congestion, progression of cerebral edema and elevation of intracranial pressure. Hypotension is a finding in the affected population by traumatic brain injury; systolic pressure below 90 mmHg is associated with worse prognosis [109,110]. Mean arterial pressure should be maintained within 90-100 mmHg. The initial treatment will consist in colloid, crystalloid and blood infusion. An arterial line must be set, central venous catheter and in some cases a Swan-Ganz catheter may be necessary. Systolic pressure elevations above 160 mmHg may be deleterious and must receive adequate therapy. The use of beta-blockers and alpha-adrenergic antagonists are preferred over vasodilators like hydralazine and nicardipine.

Sedation and Analgesia [111-113]

The use of sedation will allow a better management of intracranial pressure, ventilatory support and arterial pressures control, hypotensive drugs with long medium life or those that affect and increase cerebral metabolic requirements should be avoided, the commonly used drugs are lorazepam, morphine, fentanyl, proprofol and dexmetomedine.

Mechanical Ventilation

It's recommended that all the patients with severe traumatic brain injury are intubated and supported with mechanical ventilation. Those patients with no control of the airway, those with bronchoaspiration, hypoxia and hypercapnia will have a worse prognosis. It's crucial to maintain an oxygen pressure above 60 mmHg and saturation levels above 90% [113]. Routine sampling of arterial gases, along with ventilation data and thorax radiographies will help the optimal management. Mechanical ventilation will help us manage CO2 concentrations, a fundamental parameter in ICP manipulation. The application of early tracheostomy is basic for those patients that will depend on a ventilator, will present risk of developing pneumonia and will stay in the intensive care unit for a longer period of time.

Nutrition [114-117]

Nutritional support should start as soon as possible; it must achieve total replacement of all nutrients within the first week. Optimal support is crucial for the recovery of this kind of nutrients, where we'll have a quicker cicatrization, neuronal recovery and

immune system reinforcement. Normally, the caloric energetic output in traumatic brain injury is 150% in relation to the normal caloric energetic output, based on weight, age and height. Energetic output at rest may be calculated with the Harris-Benedict equation. If the patient is under barbiturate-induced coma or under neuromuscular paralysis the caloric energetic output will be 100-120% from normal. Normal values of caloric energetic output are 1500-2000 kcal/day, and in a patient with severe trauma the goal is to supply 3000-4000 kcal/day. Enteral intake is the preferred route, but we can use parenteral nutrition when necessary. In those patients with prolonged stays we must consider percutaneous gastrostomy, being this technique a secure and effective technique for drug administration.

Antithrombotic Prophylaxis [20,118]

Deep venous thrombosis prophylaxis is required but it can complicate in the context of an intracerebral hemorrhage. Venous thromboembolism is a well-known complication in patients with trauma; it's been reported in more than 60% of patients when prophylaxis is not used. Risk factors for this complication: spinal cord injury, cranial trauma, pelvic fracture, long bone fracture and age. Several trials have shown than using intermittent-compression devices and low dose of heparin may reduce the incidence of deep venous thrombosis and pulmonary embolism. In this institution, compression devices are used in all patients. Those patients with non-complicated post-operatory period receive low doses of heparin since the first day after the surgery. There's no available evidence for patients with intracranial hemorrhage and the use of anticoagulation, we mention in this text that some patients won't need anticoagulant measures until day 4 or 5 after the trauma or after surgery.

Glycaemia Management

Briefly, we'll mentioned that hyperglycemia [119-122] and hypoglycemia [123] have been associated with adverse prognosis in patients with traumatic brain injury, meticulous control of glucose levels is fundamental for the general care in the intensive care unit.

Sodium Control [124-127]

Low sodium levels may present because of two mechanisms: one of them is the syndrome of inappropriate antidiuretic hormone secretion (SIADHS) and cerebral salt-wasting syndrome. Both processed imply decreased serum sodium and high urinary sodium concentration. The management for SIADHS implies fluid restriction until 500-100 cc/day. Demeclociline is inhibitor of ADH in the renal collector tubule and may be considered as an alternative management [128]. Severe or symptomatic hyponatremia requires rapid correction using saline hypertonic solution carefully, considering at all times osmotic demyelination. On the other hand, the management of cerebral salt-wasting syndrome implies replacement of fluids with normal saline solution.

Epileptic Crisis

Presentation of epileptic crisis in patients with neurologic trauma, when not controlled, leads to an increase of the cerebral metabolic rate, cerebral hypoxia and ischemia, and secondary cerebral injury. Posttraumatic may present, increasing cerebral injury. It's been estimated in 15% of patients. The prophylactic use of anticonvulsants has shown to reduce the incidence of early posttraumatic epilepsy (those that present within the first week), but in late posttraumatic epilepsy this data has not been confirmed [129,130]. Routine use of anticonvulsants is recommended in patients with traumatic brain injury during the first week and if there's no evidence of crisis, we may suspend the medication. Coma-induced patients or those in the intensive care unit, usually receive anticonvulsants for a prolonged period of time, especially those with intraparenchhymal injuries that compromise the temporal lobe, or those with history of epilepsy. Classically phenytoin is started in the shock room and it's continued in the intensive care unit.

Gastric Prophylaxis

Stress-induced gastric ulcers are frequents in all trauma patients. Incidence is very high in patients with severe cerebral trauma, sepsis, coagulopathy and hypotension. The proposed mechanism is overproduction of gastrin and hydrochloric acid. Prophylactic administration of H_2-blockers, proton pump inhibitors and gastric protectors is recommended to reduce the incidence of these ulcers.

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