INTRODUCTION

Traumatic brain injury (TBI) is a serious neuro-disorder commonly caused by road traffic accidents (RTAs), sports related events or violence. [1] It is one of the leading causes of disability and death of young adults in industrialized countries presents a major worldwide social, economic, and health problem. [2] It is the number one cause of coma and is the leading cause of brain damage in children and young adults. It also plays a significant role in half of trauma death. [3]

Epidemiology

Each year, an estimated 1.7 million people in the United States sustain a TBI annually of them 52,000 die, and 275,000 are hospitalized, and 1.365 million, nearly 80%, are treated and released from an emergency department. [4]

In Egypt, RTA is the leading cause of TBI. RTAs are due to ignorance, carelessness, mechanical problems and poor road conditions. These include insufficient pedestrian crossing facilities and deficient traffic signs at intersections. The situation in Egypt is somewhat serious and getting worse year by year, especially exacerbated by the progressing density of traffic. [5]

The risk of experiencing TBI is not equally divided among all age groups. Adolescents, young adults and persons older than 70 years have the highest risk of TBI. Incidence curves show that TBI occurs primarily in people 15-24 years of age followed by another peak in persons more than 75 years old. [6] Because TBI is more common in young people, its costs to society are high due to the loss of the productive years due to death and disability. [6]

Regardless of age, TBI rates are higher in males. Men suffer twice as many TBI as women do and have fourfold risk of fatal head injury, [7] Socioeconomic status also appears to affect TBI rates; people with lower levels of education and employment are at great risk.[8]

Causes of TBI

RTAs are the leading cause of TBI in the United States. RTAs account for approximately 50% of all TBIs in the United Kingdom. [9]

Falls are the second leading cause of TBI. Falls account for 20-30% of all TBI. In individuals aged 75 years or older, falls are the most common cause of TBI. Very young persons also commonly sustain TBI due to falls. [9]

Firearms are the third leading cause of TBI (12% of all TBIs) and are a leading cause of TBI among individuals 25-34 years. Gunshot-related fatal TBIs are higher among men than among women and are more prevalent among African Americans than they are among whites. [9]

Work related TBIs constitute a major cause also of TBI cases all over the world. Incidence varies between 37 cases per 100,000 people for civilians (50% are because of

falls). [9] Alcohol is a major factor in many TBIs and often is associated with the leading cause of TBI (RTAs). Sport related injuries are also important cause of TBI. [9]

Classification of TBI

Head injuries most often have been classified according to:

(A) Severity.

(B) Pathoanatomic type.

(C) Physical mechanism.

(D) Pathophysiology.

(E) CT findings.

(A) Classification by Injury Severity

The 15-point Glasgow Coma Scale (GCS) is the most commonly used neurologic injury severity scale for adults, because of its reliability and generally good prognostic capabilities. [10] (Table 1).

Table (1): Glasgow Coma Scale (GCS) [10]

Glasgow Coma Scale		**Score**
Motor response	None	1
	Extension to pain	2
	Flexion to pain	3
	Withdraws from pain	4
	Localizes to pain	5
	Obeys commands	6
Verbal response	None	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Confused	4
	Orientated	5
Eye opening	None	1
	To pain	2
	To speech	3
	Spontaneously	4
Maximum score	15	

Brain injuries can be classified into mild, moderate, and severe categories according to GCS.[11] GCS score grades a person's level of consciousness on a scale of 3–15 based on verbal, motor, and eye-opening reactions to stimuli. It is generally agreed that a TBI with a GCS of 13 or above is mild, 9–12 is moderate, and 8 or below is severe. Patients with severe TBI have the highest mortality and morbidity. [12]

(B) Pathoanatomic Classification

A pathoanatomic classification describes the location or anatomical features of the abnormality to be targeted by a treatment, and generally falls into the scheme of "where and what" terminology damage from TBI, it could be focal: confined to specific areas or diffuse: distributed in a more general manner. It is common for both types of injury to exist in a given case. [13]

1- Skull fractures

Skull fractures may be seen in the cranial vault or skull base. They may be linear or stellate, open or closed, depressed or non-depressed, simple or compound. [13]

2. Intracranial lesions

Several types of intracranial hemorrhages can occur, including the following: [9]

a. Extradural hematoma.
b. Subdural hematoma.
c. Intracerebral hemorrhage.
d. Intraventricular hemorrhage.
e. Subarachnoid hemorrhage.
f. Hemorrhagic contusions.
g. Brain oedema.
h. Combined hemorrhage.

3. Concussions

Concussion is a transient loss of consciousness followed by immediate and complete recovery which is accompanied by a period of retrograde and post-traumatic (anterograde) amnesia without morphological changes visible through examination or light microscopy.[14] Concussion is caused by deformity of the deep structures of the brain, leading to widespread neurologic dysfunction that can result in impaired consciousness or coma. Concussion is considered a mild form of diffuse axonal injury. [15]

4. Diffuse axonal injury

Diffuse axonal injury (DAI) is characterized by extensive, generalized damage to the white matter of the brain, primarily in regions such as the corpus callosum, basal ganglia, and periventricular white matter. [16] Neuropathologic findings in patients with diffuse axonal injury were graded by Gennarelli and colleagues, as follows: [16]

Grade 1: Axonal injury mainly in parasagittal white matter of the cerebral hemispheres.

Grade 2: As in Grade 1, plus lesions in the corpus callosum.

Grade 3: As in Grade 2, plus a focal lesion in the cerebral peduncle. [16]

Pathology and histology of DAI:

- Diffuse degeneration of white matter.
- 1st 6 hour: axonal enfolding.
- 12 – 24 hour: axonal swelling.
- Later: clusters of microglia, gliosis.
- Years later: wallerian degeneration. [16]

(C) Classification by Physical Mechanism

Etiological classification of head injuries by physical mechanism of injury has certain advantages in understanding how specific forces at specific magnitudes result in predictable patterns of injury. Thus, injuries can be classified according to whether the head is struck or strikes an object (contact or "impact" loading) and/or the brain moves within the skull (noncontact or "inertial" loading). The magnitude and direction of each type or combination of loading forces may predict type and severity of injury. There is considerable, but not perfect, correlation between physical mechanism of injury and pathoanatomic injury type. For instance, most focal injuries, such as skull fracture, brain contusion, and epidural hematoma, result from impact loading, whereas inertial loading generally causes more diffuse injuries such as concussion, subdural hematoma and DAI.[17]

(D) Classification by Pathopysiology

Alternatively, pathophysiologic mechanisms may form the basis of an etiologic classification and/or characterization of targets for treatment. In head injury, these can include processes which are set in motion by the injury event and take time to evolve, as well as events which compound or complicate the brain injury such as systemic insults. One widely used scheme in head injury related to pathophysiologic processes is that which differentiates "primary" versus "secondary" damage. While authors vary in exactly how these terms are used, in general, primary injury refers to the unavoidable, immediate parenchymal damage occurring at the time of injury, while secondary injury refers to potentially avoidable damage that occurs at variable times after injury. The importance of secondary insults, such as hypoxia, hypertension, hypercarbia, hyponatremia, and seizures, has gained widespread recognition. However, pathophysiologic classification schemes have not been commonly used in treatment trials. Limited availability and usage of sophisticated monitoring techniques needed for measurement of physiologic parameters, and difficulties in distinguishing inevitable but progressive cell damage from potentially reversible injury cascades. [18-22]

Primary injury:

Traumatic brain injury is triggered by an external mechanical force that usually causes skull fracture and abruptly disrupts the brain parenchyma with shearing and tearing of blood vessels and brain tissue. [18-20] This triggers a cascade of events characterized by activation of molecular and cellular responses that lead to secondary delayed injury. [21]

The processes that lead to tissue damage following traumatic brain injury include hematoma formation, vasogenic and cytotoxic edema, and ischemia. Vasogenic edema depends on osmotic and hydrodynamic factors. Cytotoxic edema results from disturbance in energy dependent cellular osmoregulations, so areas surrounding the region of direct trauma suffer from reduced blood flow due to hemorrhage, vasoconstriction and disturbance of venous drainage mimicking ischemic penumbra. [22]

Early ischemic episodes are reported to occur after traumatic brain injury adding a component of ischemia to the primary mechanical damage. Neurons of brain areas perfused at rate less than 12 ml/100g/min are destined to die and represent the ischemic core. Low cerebral blood flow (CBF) or altered neurochemical and electrophysiological cell properties characterize the ischemic penumbra which represents a rim of viable tissue perfused at a suboptimal rate (15-18 ml/100 g/min) around the ischemic core. [23-26] Cells at the center of the ischemic core die within minutes of ischemic onset while the zone that immediately surround the primary penumbral zone is less likely to die as its perfusion is somewhat better but still below the minimal normal rate(55ml/100 g/min). [27, 28]

Secondary injury:

Various pathophysiological mechanisms underlying secondary injury have been hypothesized and are the basis of different proposed therapeutic interventions to prevent serious late sequelae of traumatic brain injury. The processes can be developed in a period of hours or days after the initial primary injury to the head. The breakdown of membrane phosholipids and reduced acetylcholine synthesis and release has been attributed at crucial point in the onset of secondary brain injury. [29-31]

Predisposing factors to secondary brain injuries

- **Hypoperfusion and hyperperfusion**

Both hypoperfusion and hyperperfusion can occur in head trauma patients and both are detrimental as regards outcome, the normal amount of CBF equals to 750ml/min this is 50-54ml blood/100gm of brain tissue per minute. Critical levels of hypoperfusion were identified as 20ml/100gram of brain tissue/min with failure of electrical activity occurring at 15 -20ml/100g/min, and failure of energy metabolism at 10ml/100g/min. CBF should be interpreted in light of cerebral metabolic rate of oxygen consumption (CMRO2). [32,33]

- **Hypoxia and anemia**

TBI is characterized by imbalance between cerebral O_2 delivery and cerebral O_2 consumption. Although this mismatch is induced by several vascular and hemodynamic mechanisms, the final end point is brain tissue hypoxia. Measurements of brain tissue oxygen pressure (Pto_2) has identified the critical threshold for Pto_2 as 10-15mm Hg, below

which infarction of neuronal tissues occur. This is more specific than jugular venous saturation (SJO_2) as it represents focal areas of ischemia rather than a global average. Normally the brain compensates for hypoxia by cerebral vasodilatation on the account of increasing cerebral blood volume (CBV) and intracrainial pressure (ICP) and when the compensatory mechanisms are fully mobilized; further decrease in oxygen supply will result in hypoxia of the brain tissue. [33, 34]

- **Hypocapnia and hypercapnia**

Hypercapnia has long been known to increase CBV and flow, which may lead to increase ICP due to reduced intracranial compliance, while hypocapnia may reduce CBF and CBV, worsening the ischemic damage and shifting O_2 dissociation curve to the left making O_2 release to the tissues more difficult. Patients with head trauma and increased ICP should have a unique ventilator strategy. [35]

- **Hyperthermia and hypothermia**

After TBI, fever frequently develops secondary to infection, thrombophlebitis, drug reaction or defect in central thermoregulatory system. [36] Moreover, some studies found that brain temperature exceeds systemic temperature in head injured patients. [36] Severe hypothermia >32 C° should be avoided in patients with TBI as it may be associated with ventricular fibrillation (VF), cardiac asystole, respoiratory failure, coagulopathy, and ileus. [37]

- **Hyperglycemia and hypoglycemia**

Hyperglycemia has been associated with exacerbation of brain damage with both head trauma and ischemia. In patients with TBI, approximately 50 % of patients present with blood glucose > 200 mg/dl. Peak levels greater than this are associated with a significantly worse outcome up to 1 year post-injury. Hypoglycemia should be carefully watched in TBI patients as it was found to decrease seizure threshold and worsen neurological damage. [38]

- **Acid base and electrolytes disturbances**

Acidosis may increase CBF and ICP in turn while **alkalosis** may decrease CBF and worsen the ischemic damage. Patient should be kept with normal PH unless hyperventilation is to be done for refractory increased ICP. [32]

Hyponatremia after TBI (due to cerebral salt wasting (CSW), syndrome of inappropriate anti-diuretic hormone secretion (SIADH), or hypopituitarism or hypovolemia) may decrease seizure threshold and exacerbate brain edema. [39]

Patients with severe traumatic brain injury (TBI) have a high risk of developing **hypernatremia** over the course of their ICU stay, due to the coexistence of predisposing conditions such as impaired sensorium, altered thirst, central diabetes insipidus (CDI) with polyuria, and increased insensible losses. Unless properly corrected it may worsen the outcome as it was shown that people with TBI that developed hypernatremia has a higher mortality than those who did not. [40]

(E) Classification by Computed Tomography (CT) findings:

Marshall classification: [41]

It utilizes the status of the mesencephalic cisterns, the degree of midline shift in millimeters, and the presence or absence of one or more surgical masses to grade CT findings into four subgroups, defined as follows

Grade 1: Normal CT scan (9.5 % mortality).

Grade 2: Cisterns present, shift < 5mm and or lesion densities present <25ml (13.5 % mortality).

Grade 3: Cisterns compressed /absent, shift 0- 5mm and lesion densities present <25ml (34 % mortality).

Grade 4: - Shift > 5mm and lesion densities present <25ml.

- Any lesion surgically evacuated.

- Lesion densities present > 25ml. (56.2 % mortality).

Clinical picture

Symptoms are dependent on the type of TBI (diffuse or focal) and the part of the brain that is affected. [42]

With mild TBI, the patient may remain conscious or may lose consciousness for a few seconds or minutes. [43] Unconsciousness tends to last longer for people with injuries on the left side of the brain than for those with injuries on the right. [43] Other symptoms of mild TBI include headache, vomiting, nausea, lack of motor coordination, dizziness, difficulty balancing,[44] lightheadedness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue or lethargy, and changes in sleep patterns. [43] Cognitive and emotional symptoms include behavioral or mood changes, confusion, and trouble with memory, concentration, attention, or thinking. [43] Mild TBI symptoms may also be present in moderate and severe injuries. [43]

A person with a moderate or severe TBI may have a headache that does not go away, repeated vomiting or nausea, convulsions, an inability to awaken, dilation of one or both pupils, weakness or numbness in the limbs, loss of coordination, confusion, restlessness, or agitation. [43]

When the pressure within the skull (intracranial pressure) rises too high, it can be deadly. [45] Signs of increased ICP include decreasing level of consciousness, paralysis or weakness on one side of the body, and a blown pupil; one that fails to constrict in response to light or is slow to do so. [45] Cushing's triad, a slow heart rate with high blood pressure and respiratory depression is a classic manifestation of significantly raised ICP. [46]

Abnormal posturing (extensor or no response), dilated fixed pupil on one or both sides, decrease in GCS of more than 2 points from the patients prior best score in patients with in initial GCS ≤8 are all signs of cerebellar herniation. (46)

Investigations

- **Plain Skull Radiography (XR)** can diagnose skull fractures, and occasionally to help localization of intracranial foreign bodies such as missile fragments.(47)

- **Computed Tomography (CT)** remains the initial imaging study of choice for patients with acute head injury. In addition, it is almost uniformly available, is rapid and allows easy monitoring of acutely injured patients. (47) The disadvantage of CT arises from insensitivity to subtle non hemorrhagic parenchymal injury. For example, to make a diagnosis of diffuse axonal injury with CT, the clinical picture of severe global neurological dysfunction must be combined with a CT picture of diffuse edema without any focal lesion or potentially with a less alarming CT picture. (48)

- **Magnetic Resonance Imaging (MRI)** It is more useful than CT for detecting injury characteristics such as diffuse axonal injury. (47) However, MRI is not used in the emergency setting for reasons including its relative inefficacy in detecting bleeds and fractures, its lengthy acquisition of images, the inaccessibility of the patient in the machine, and its incompatibility with metal items used in emergency care. (48)

- **Transcranial Doppler (TCD**) provides a means of measuring relative change in cerebral blood flow (CBF) by observing blood flow velocity (FV) in basal cerebral arteries. This method requires a certain degree of technical experience, but it is noninvasive, relatively inexpensive and provides real-time information with high temporal resolution. (47, 48)

- **Laser Doppler Flowmetry** provides real time measure of relative change in capillary perfusion, which is suitable for assessing the microcirculatory response to therapeutic challenge (e.g. mannitol infusion). (48)

- **Transcranial Near-infrared Spectroscopy** is used to detect accurately the presence of an acute intracranial hematoma in head injured patients. So this procedure may have its greatest use in the hemodynamically unstable multiple trauma patients. (48)

- **Positron Emission Tomography (PET)** many of the research work in brain metabolism has involved the use of PET tracers such as short-lived tracers labeled with carbon-11 or flow studies using oxygen-15 labeled water as a marker. (48)

- **Angiography** may be used to detect blood vessel pathology when risk factors such as penetrating head trauma are involved. (48)

- **Evoked potentials (EPs)** have been demonstrated to be particularly useful in predicting outcome from head injury. The single most useful measure is the somatosensory evoked response, although combinations of EPs (somatosensory, auditory, and visual) yield the highest

prognostic accuracy. Deterioration in serially measured EPs, occurring as a result of secondary injury to the brain, has been shown to correlate with poor patient outcome. In the past, EPs have been used primarily in an intermittent manner for determination of prognosis. With further technologic improvements and increased automation of data collection, these techniques may see more widespread use for continuous monitoring in an ICU setting. [48]

Treatment of severe traumatic brain injury:

It is important to begin emergency treatment within the so called "golden hours " following the injury. The management of the primary insult comprises providing the injured brain the best possible physiological condition that allows the recovery of the sublethally injured neurons. [49]

Whilst the management of the acutely head injured patient depends primarily on the prevention of secondary insults and if these eventually happen, timely diagnosis and management of these secondary insults. Surgically correctable intracranial lesions should be recognized early and treated accordingly. On the other hand, concomitant injuries should be recognized and stabilized. [49]

1- Prehospital care

The widespread knowledge of the American College of Surgeons Advanced Trauma Life Support (ATLS®) Courses improved the initial management of trauma victims. This approach is based on the identification of the sequential variables that could cause the victim's death it includes:

A: airway with cervical spine control.

B: breathing.

C: circulation (maintenance of blood pressure, control of hemorrhage).

D: disability (Glasgow Coma Scale).

E: exposure (examination from head to toe).

S: secondary evaluation. [12, 50]

2- In hospital care

1. Trauma system

All regions should have an organized trauma care system Neurosurgeons should have an organized and responsive system of care for patients with neurotrauma. They should initiate neurotrauma care planning, including pre-hospital management and triage, direct trauma center transport, maintain appropriate call schedules, review trauma care records for quality improvement and participate in trauma education programs. [50]

Trauma facilities treating neurotrauma must have a neurosurgery service, an in-house trauma surgeon, a continuously staffed and available operating room, intensive care unit and laboratory. A CT scanner must be immediately available. In rural or weather-bound communities without a neurosurgeon, a surgeon should be trained to perform

accurate neurological assessment, including training to perform life-saving surgical treatment of an extracerebral hematoma in a deteriorating patient. (50)

2. Airway and breathing

Early endotracheal intubation should be performed for patients with a GCS of 8 or less, or are unable to protect their airway. Extreme caution must be exercised when intubating head-injured patients as evidence suggests that the prevalence of cervical spine injury is fourfold to eightfold higher in patients with concomitant head injuries. (51)

Rapid sequence intubation should be performed to all head injured patients especially agitated or combative patients. If possible, a brief neurologic examination should be performed before the patient is given any sedative or neuromuscular blocking agents. Nasotracheal intubation should be avoided because of the risk of direct intracranial injury, especially in patients with basilar skull fractures. (52)

3. Resuscitation of blood pressure and oxygenation

Hypotension (Systolic blood pressure (SBP) < 90 mmHg) or hypoxia (apnea, cyanosis or arterial oxygen saturation (SaO_2) < 90%) must be avoided if possible, or corrected immediately in severe TBI patients if happened. The mean arterial blood pressure (MAP) should be maintained above 90 mmHg through the infusion of fluids throughout the patient's course in attempt to maintain cerebral perfusion pressure (CPP) > 70 mmHg. Patients with GCS ≤ 8 who are unable to maintain their airway or who remain hypoxemic despite supplemental O_2 required that their airway be secured, preferably by endotracheal intubation. (50)

Early post-injury episodes of hypotension or hypoxia greatly increase morbidity and mortality from severe head injury. At present, defining level of hypotension and hypoxia is unclear in these patients. However, ample class II evidence exists regarding hypotension, defined as a single observation of a systolic blood pressure of <90/mm Hg, or hypoxia, defined as apnea/cyanosis in the field or a PaO2 < 60 mm Hg by arterial blood gas analysis, to warrant the formation of guidelines stating that these values must be avoided, if possible, or rapidly corrected in severe head injury patients. A significant proportion of adult and pediatric TBI patients are discovered to be hypoxemic or hypotensive in the pre-hospital setting. Patients with severe head injury that are intubated in the pre-hospital setting appear to have better outcomes. Strong class II evidence suggests that raising the blood pressure in hypotensive, severe head injury patients improves outcome in proportion to the efficacy of the resuscitation. (50)

4. Management of cerebral perfusion pressure (CPP)

Cerebral perfusion pressure (CPP) is the difference between MAP and ICP, so it is a dynamic process depends on balance between MAP and ICP. (53)

Maintenance of a CPP above 70 mm Hg is a therapeutic option that may be associated with a substantial reduction in mortality and improvement in quality of survival and is likely to enhance perfusion to ischemic regions of the brain following severe TBI.

No study has demonstrated that the incidence of intracranial hypertension, morbidity, or mortality is increased by the active maintenance of CPP above 70 mm Hg, even if this means normalizing the intravascular volume or inducing systemic hypertension. [50, 53]

Intracranial pressure

Increased intracranial pressure (ICP)

As the cranial vault is essentially a closed, fixed bony box, its volume is constant. This volume is described by the **Monro-Kellie**[54] , proposed in the early part of the 19th century:

Volume of intracranial (constant) = volume of brain + volume of CSF + volume of blood + volume blood vessels as illustrated in Figure 1 .

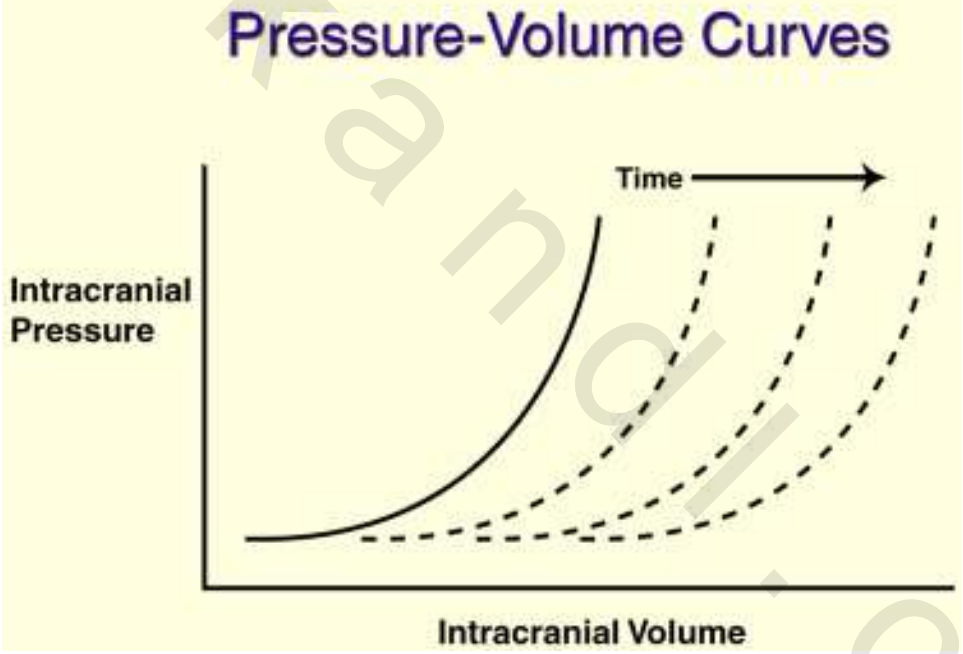

Figure (1): Pressure volume curve.

Mass lesion; as all these components are fluids, and non-compressible, once the cranial vault is filled, it's pressure rises dramatically. This intracranial pressure (ICP) rise can lead to interruption of cerebral blood flow by reducing the cerebral perfusion pressure. As an intracranial mass lesion or oedematous brain expands, some compensation is possible as cerebrospinal fluid (CSF) and blood move into the spinal canal and extra cranial vasculature respectively. Beyond this point, further compensation is impossible and ICP rises dramatically. The normal ICP is 5-10 mmHg. There is no defined set point at which treatment for intracranial hypertension should be initiated, but levels above 20mmHg are usually treated. However it is probably more important to maintain an adequate cerebral perfusion pressure. In a hypotensive patient, even a small increase in ICP

could be harmful. Alternatively, an elevated mean arterial pressure may protect against a raised ICP. ICP monitoring is now a central part of critical care management for the severely brain injured patient. (54)

Intracranial pressure monitoring

The spaces most frequently monitored are the: (54)

1- Intraventricular spaces.
2- Subarachnoid spaces.
3- Subdural space.
4- Epidural space.
5- Intraparenchymal space.

Brain herniation: The following types of herniation are recognized:

a. Subfalcine herniation: The cingulate gyrus of the frontal lobe is pushed beneath the falx cerebri when an expanding mass lesion causes a medial shift of the ipsilateral hemisphere. This is the most common type of herniation. (55)

b. Central transtentorial herniation: This type of injury is characterized by the displacement of the basal nuclei and cerebral hemispheres downward while the diencephalon and adjacent midbrain are pushed through the tentorial notch. (55)

c. Uncal herniation: This type of injury involves the displacement of the medial edge of the uncus and the hippocampal gyrus medially and over the ipsilateral edge of the tentorium cerebelli foramen, causing compression of the midbrain; the ipsilateral or contralateral third nerve may be stretched or compressed. (55)

d. Transcalvarial herniation: In which the brain squeezes through a fracture or a surgical site in the skull. (55)

e. Downward infratentorial: This injury is marked by an infratentorial herniation in which the tonsil of the cerebellum is pushed through the foramen magnum and compresses the medulla, leading to bradycardia and respiratory arrest. (56)

f. Upward (upward cerebellar or upward transtentorial): Increased pressure in the posterior fossa can cause the cerebellum to move up through the tentorial opening in upward or cerebellar herniation. (57)

Indications for intracranial pressure monitoring

1- Comatose head injury patients (GCS 3-8) with abnormal CT scans should undergo ICP monitoring.
2- Comatose patients with normal CT scans have a much lower incidence of intracranial hypertension unless they have two or more of the following features at admission:
    a. Age over 40.
    b. Unilateral or bilateral motor posturing.
    c. A systolic blood pressure of less than 90 mm Hg. (53)

Intracranial pressure monitoring technology

In patients who require ICP monitoring, a ventricular catheter connected to an external strain gauge transducer or catheter tip pressure transducer device is the most accurate reliable method of monitoring ICP and enables therapeutic CSF drainage. Clinically significant infections or hemorrhage associated with ICP devices causing patient morbidity are rare and should not deter the decision to monitor ICP. Parenchymal catheter tip pressure transducer devices measure ICP similar to ventricular ICP pressure but have the potential for significant measurement differences and drift due to the inability to recalibrate. These devices are advantageous when ventricular ICP is not obtained or if there is obstruction in the fluid couple. Subarachnoid or subdural fluid coupled devices and epidural ICP devices are currently less accurate. (53)

Intracranial pressure treatment threshold

An absolute ICP threshold that is uniformly applicable is unlikely to exist. Current data, however, support 20-25 mm Hg as an upper threshold above which treatment to lower ICP should generally be initiated. (53)

Treatment of increased intracranial pressure (Figure 2,3)

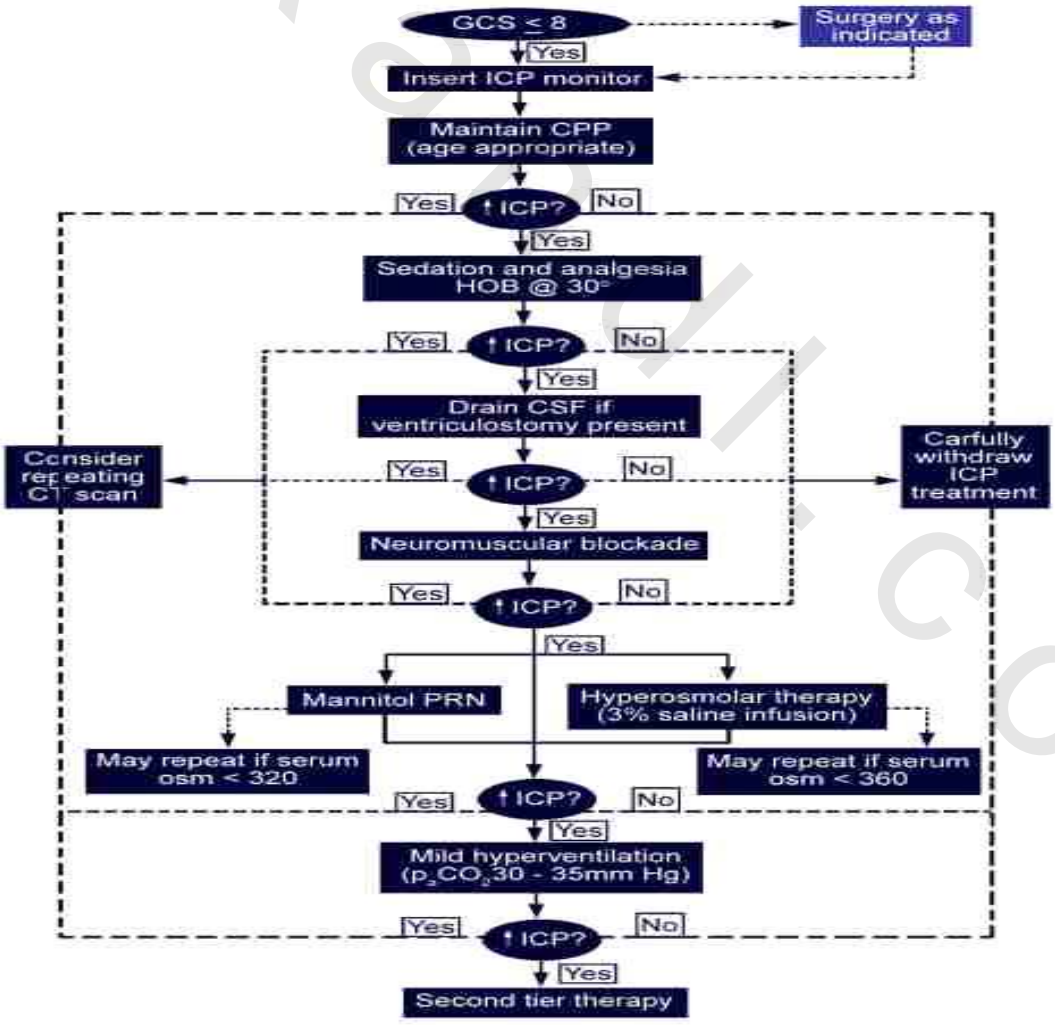

Figure (2): Critical pathway for the treatment of established intracranial hypertension in traumatic brain injury, according to the Society of Critical Care Medicine guidelines. GCS = Glasgow Coma Scale; ICP = Intracranial Pressure; CPP = Cerebral perfusion pressure; HOB = Head of bed; CSF = Cerebrospinal fluid; PRN = As needed. (52)

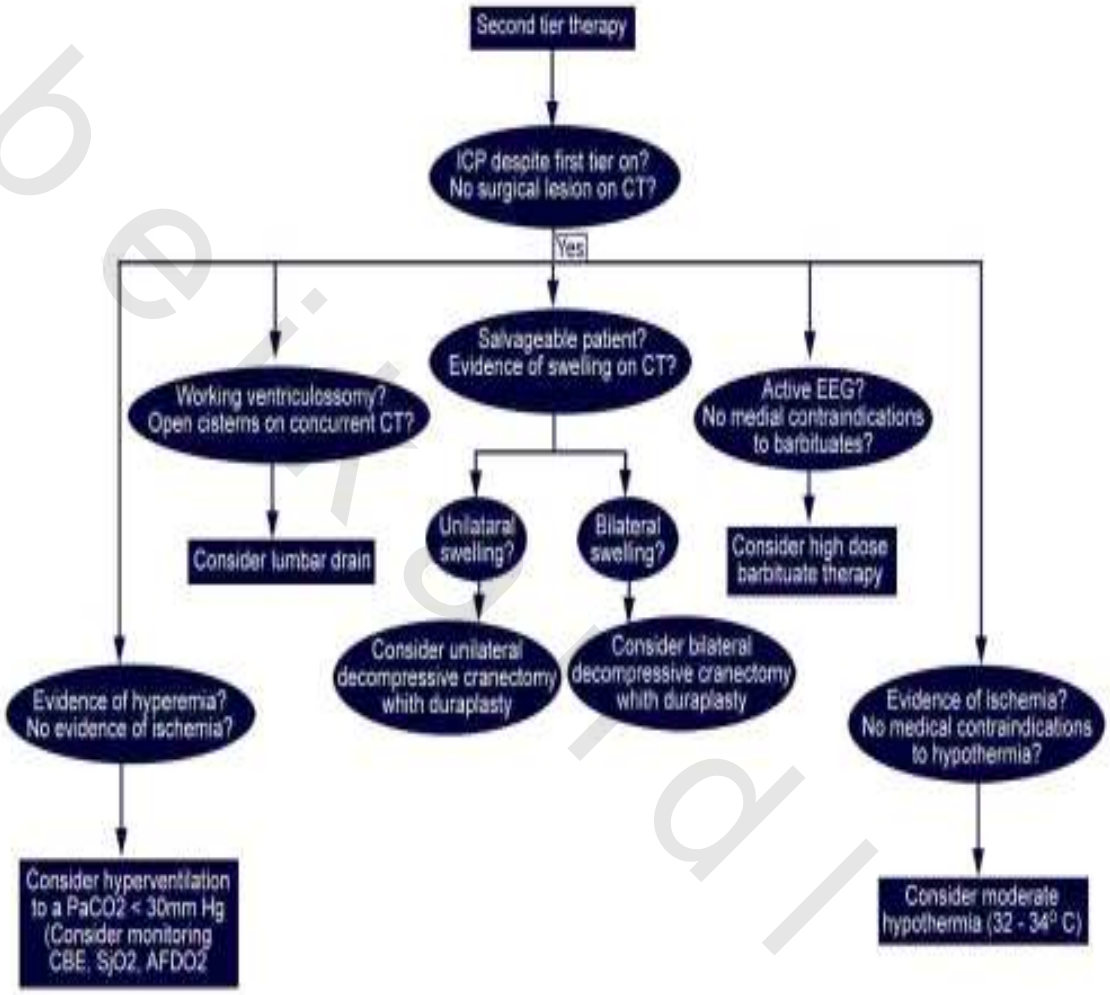

Figure (3): Second tier therapy for the treatment of established intracranial hypertension in traumatic brain injury, according to the Society of Critical Care Medicine guidelines. ICP = Intracranial pressure; CBF = Cerebral blood flow; SjO2 = Jugular venous oxygen saturation; AJDO2 = Arterial-jugular venous difference in oxygen content. (52)

Elevation of the head of the bed

Manipulation of the head of the bed to optimal levels to decrease venous obstruction may help to control ICP. Traditionally, 30º elevations of the head in midline position is thought to be optimal, although this has not been confirmed by pediatric studies. (52)

Sedation and analgesia

Sedation and analgesia are also important adjuncts to minimize increases in ICP. However, sedatives and analgesics must be judiciously chosen to prevent unwanted side effects (eg, hypotension). Short-acting and reversible medications, such as fentanyl, are commonly used. Short-acting benzodiazepines, such as midazolam, are also commonly used and have the added benefit of increasing the seizure threshold. (52)

CSF drainage

Ventricular drains have long been used for the drainage of CSF in patients with hydrocephalus. With the advent of ventricular ICP monitoring, ventricular drainage for patients with increased ICP has also been commonly used. (58)

Hyperosmolar therapy

Mannitol is effective for control of raised ICP at doses of 0.25 g/kg to 1 g/kg body weight. Hypotension (systolic BP≤90 mm Hg) should be avoided. (58) Mannitol has long been successfully used to treat increased ICP, especially following traumatic brain injury in adults. Mannitol is an osmolar agent with rapid onset of action via 2 distinct mechanisms.(52) Initial effects of mannitol result from reduction of blood viscosity and a reflex decrease in vessel diameter to maintain cerebral blood flow through autoregulation. This decrease in vessel diameter contributes to decreasing total cerebral fluid volume and pressure. This mechanism of action is transient (lasting about 75 min) and requires repeated dosing for prolonged effect. Mannitol exhibits its second mechanism of action through osmotic effects. It increases serum osmolality; thus, water is shifted from intracellular compartments to the intravascular space, and cellular edema is decreased. Although slower in onset, this mechanism lasts up to 6 hours in duration. (58)

Pitfalls of mannitol include its potential to accumulate in regions of cerebral vascular interruption and cause a reverse osmotic shift, therefore increasing brain edema and increasing ICP; this risk is reported with continuous infusions. For this reason, intermittent mannitol boluses are recommended. Also, mannitol has been linked to acute tubular necrosis and renal failure at serum osmolality levels greater than 320 mOsm/L. (59)

More recently, hypertonic saline has been shown to be an effective therapy for intracranial hypertension following pediatric TBI. Hypertonic saline, typically 3% saline, has an osmolar mechanism of action similar to that of mannitol, without the diuretic effects.(60) Added theoretical benefits of hypertonic saline include improved vasoregulation, cardiac output, immune modulation, and plasma volume expansion. (60) Patients using hypertonic saline have tolerated serum osmolalities of as much as 360 mOsm/L. However, in the author's institution, reversible renal insufficiency has been noted with the use of hypertonic saline when serum osmolality approached 320 mOsm/L, thus, caution should be used. (60)

Risks of hypertonic saline administration include rebound intracranial hypertension after withdrawal of therapy, central pontine myelinolysis with rapidly increasing serum sodium levels, subarachnoid hemorrhage due to rapid shrinkage of the cerebrum and tearing of bridging veins, and renal failure. (60)

Hyperventilation

Although ventilation at the lower end of eucapnia may be beneficial in decreasing ICP, hyperventilation has the potential to reduce ICP via reflex vasoconstriction in the presence of hypocapnia. The vasoconstriction leads to decreased cerebral blood flow, decreased overall cerebral fluid volume, and, therefore, decreased ICP.[52] In cases of refractory intracranial hypertension, mild hyperventilation (PaCO2 of 30-35 mm Hg) may be beneficial in decreasing ICP. [58]

Excessive hypocapnia may lead to ischemia secondary to insufficient cerebral blood flow. Ensuing respiratory alkalosis also shifts the hemoglobin-oxygenation dissociation curve to the left, making release of oxygen to tissues more difficult. [52] Although aggressive hyperventilation (PaCO2 <30 mm Hg) may be necessary in emergency situations such as impending herniation in a patient with Cushing's triad (hypertension, bradycardia, and irregular respirations), it is not commonly used as a prolonged therapy for the reduction of ICP due to its association with worse long term neurologic outcomes. [52]

Barbiturates

High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Heamodynamic stability is essential before and during barbiturate therapy. [58] The use of high-dose barbiturate therapy, such as pentobarbital, has been successful in the management of increased ICP. This class of medication suppresses cerebral metabolism, thus decreasing oxygen demand. Barbiturates also have the added benefit of neuroprotection through mechanisms such as inhibition of free radical lipid peroxidation and neuronal membrane disruption. It should be noted that barbiturate therapy in the patient with TBI requires continuous EEG monitoring. With EEG monitoring, barbiturate infusion may be titrated to achieve burst suppression.[52]

Despite the potential benefits of barbiturates, their adverse effects on the cardiovascular system limit their use to refractory intracranial hypertension. Barbiturates may cause both myocardial depression and hypotension that requires fluid resuscitation and inotropic support, ability to perform neurological examination is also lost when barbiturates are used to control ICP. Additionally, barbiturate therapy may result in immune suppression, leading to sepsis and ileus with subsequent feeding intolerance. [52]

Hypothermia

Hyperthermia has long been correlated with poor outcome in patients with traumatic brain injury, and control of fever is an important initial intervention to limit secondary brain injury. More recently, induced moderate hypothermia (32-34°C, 89.6-93.2°F) has emerged as a potentially useful strategy. A recent phase II clinical trial demonstrated that 48 hours of moderate hypothermia initiated within 6-24 hours of acute traumatic brain injury reduces ICP and was "safe," although a higher incidence of arrhythmias (reversed with fluid administration or rewarming) and rebound ICP elevation after rewarming were reported. Until further clinical studies are performed, moderate hypothermia is reserved for patients with persistent intracranial hypertension refractory to other medical interventions. Problems associated with hypothermia include increased bleeding risk, arrhythmias, and increased susceptibility to infection and sepsis. [52]

Decompressive craniectomy

When medical therapies for treatment of intracranial hypertension remain refractory, decompressive craniectomy is a surgical option. Patients typically undergo this procedure within the first 48 hours of initial injury. (61)

5. Antiseizure prophylaxis

Anticonvulsants are indicated to decrease the incidence of early post-traumatic seizures (within 7 days of injury). (52)

Prophylactic use of phenytoin or valproate is not recommended for preventing late post-traumatic seizures. (52)

6. DVT prophylaxis

Graduated compression stockings or intermittent pneumatic compression (IPC) stockings are recommended, unless lower extremity injuries prevent their use, use should be continued until patients are ambulatory. (52)

7. Nutrition

Replace 140% of resting metabolism expenditure in nonparalyzed patients and 100% in paralyzed patients using enteral or parenteral formulas containing at least 15% of calories as protein by day 7 after injury. The preferable option is use of jejunal feeding by gastrojejunostomy due to ease of use and avoidance of gastric intolerance.

Data show that starved head-injured patients lose sufficient nitrogen to reduce weight by 15% per week. Class II data show that 100-140% replacement of resting metabolism expenditure with 15-20% nitrogen calories reduces nitrogen loss. Data in non-head injured patients show that a 30% weight loss increased mortality rate. Class I data suggests that non-feeding of head-injured patients by the first week increases mortality rate. The data strongly support feeding at least by the end of the first week. It has not been established that any method of feeding is better than another or that early feeding prior to 7 days improves outcome. Based on the level of nitrogen wasting documented in head-injured patients and the nitrogen sparing effect of feeding, it is a guideline that full nutritional replacement be instituted by day 7. (50)

The use of steroids is not recommended for improving outcome or reducing ICP in patients with TBI. (52)

Prognosis:

The outcome after TBI is strongly correlated with age, initial GCS, pupil reactivity and size, ICP, surgical intracranial lesions (extent of midline shift), and secondary brain injury. (62)

The Glasgow Outcome Scale (GOS) Table (2)

The Glasgow Outcome Scale (GOS) is the most widely used outcome measure after traumatic brain injury, it allows the overall social outcome of most patients to be assessed reliably on the basis of a structured interview which concentrates on social and personal functioning, without the need for detailed neurological and psychological evaluation.(63)

Table (2): The Glasgow Outcome Score (GOS)

Item	Score
Death	1
Persistent vegetative state (Patient exhibits no obvious cortical function)	2
Severe disability (Conscious but disabled)	3
Moderate disability (Disabled but independent)	4
Good Recovery	5

Resistin

In the last two decades, the diagnostic instruments for the prediction of severity or the potential outcome of head injuries have hardly changed. The application of biomarkers could lead to the expeditious diagnosis in the case of sedated, unconscious, or polytraumatized patients even before the application of neuroimaging techniques. [64]

Resistin belongs to a novel family of cysteine-rich proteins called resistin-like molecule or found in inflammatory zones proteins. It is also known as adipose tissue-specific secretory factor (ADSF). [65]

In humans, resistin is expressed primarily in inflammatory cells, especially macrophages. [66]In primates, pigs, and dogs, resistin is secreted by immune and epithelial cells, while, in rodents, it is secreted by adipose tissue. [67]

Discovery

Resistin was discovered in 2001 by the group of Dr Mitchell A. Lazar from the University of Pennsylvania School of Medicine. [68] It was called "resistin" because of the observed insulin resistance in mice injected with resistin. [69] Resistin was found to be produced and released from adipose tissue to serve endocrine functions likely involved in insulin resistance. [70] This idea primarily stems from studies demonstrating that serum resistin levels increase with obesity in several model systems (humans, rats, and mice). [69] Since these observations, further research has linked resistin to other physiological systems such as inflammation and energy homeostasis. [71, 72]

Resistin is a cytokine whose physiologic role has been the subject of much controversy regarding its involvement with obesity and type II diabetes mellitus (T2DM).[67] Furthermore, resistin has been shown to be involved in inflammatory processes. Some proinflammatory agents, such as tumor necrosis factor-α, interleukin-6 and lipopolysaccharide, can regulate resistin gene expression. Recent studies have shown the regulation of proinflammatory cytokine expression by resistin. [73]

Structure

Resistin is cysteine-rich proteins, The length of the resistin pre-peptide in human is 108 amino acid residues and in the mouse and rat it is 114 aa; the molecular weight is ~12.5 kDa. [74]

Role of resistin in inflammation

Inflammation is the first innate immune response to infection or irritation resulting from leukocyte (neutrophils, mast cells, etc.) accumulation and their secretion of inflammatory, biogenic chemicals such as histamine, prostaglandin, and pro-inflammatory cytokines. [75] As cited, it has recently been found that resistin also participates in the inflammatory response. [76]

In further support of its inflammatory profile, resistin has been shown to increase transcriptional events, leading to an increased expression of several pro-inflammatory cytokines including (but not limited to) interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α). It has also been demonstrated that resistin upregulates intercellular adhesion molecule-1 (ICAM1) vascular cell-adhesion molecule-1 (VCAM1), all of which are occupied in chemotactic pathways involved in leukocyte recruitment to sites of infection. [77] Resistin itself can be upregulated by interleukins and also by microbial antigens such as lipopolysaccharide, which are recognized by leukocytes. [78] Taken together, because resistin is reputed to contribute to insulin resistance, results such as those mentioned suggest that resistin may be a link in the well-known association between inflammation and insulin resistance. [79]

In accordance, it is expected that, if resistin does indeed serve as a link between obesity and T2DM while at the same time contributing to the inflammatory response, then we should also observe proportional increases in chronic inflammation in association with obesity and insulin resistance. In fact, recent data have shown that this possibility is indeed the case by demonstrating positive correlations between obesity, insulin resistance, and chronic inflammation, which is believed to be directed in part by resistin signaling. [80] This idea has recently been challenged by a study showing that increased levels of resistin in people with chronic kidney disease are associated with declined renal function and inflammation, but not with insulin resistance. [81] Notwithstanding, regarding resistin and the inflammatory response, we can conclude that resistin does indeed bear features of a pro-inflammatory cytokine, and could act as a key node in inflammatory diseases with or without associated insulin resistance. [80]

Role of resistin in obesity and insulin resistance

Much of what is hypothesized about a resistin role in energy metabolism and T2DM can be derived from studies showing strong correlations between resistin and obesity. The underlying belief among those in support of this theory is that serum resistin levels will increase with increased adiposity. [82, 83] Conversely, serum resistin levels have been found to decline with decreased adiposity following medical treatment. [84] Specifically, central obesity (waistline adipose tissue) seems to be the foremost region of adipose tissue contributing to rising levels of serum resistin. [70] This fact takes on significant implications

considering the well understood link between central obesity and insulin resistance; marked peculiarities of T2DM.[85]

Although it seems that resistin levels increase with obesity, can we conclude then that such serum resistin increases are accountable for the insulin resistance that appears to be associated with increased adiposity? Many researchers in their respective studies have shown that this is indeed the case by finding positive correlations between resistin levels and insulin resistance. [86, 87] This discovery is further authenticated by studies that confirm a direct correlation between resistin levels and subjects with T2DM. [88] Provided that resistin is at least in part due to the insulin resistance coupled to T2DM, fabricating drugs that specifically target cascades leading to decreased serum resistin in T2DM subjects will deliver immense therapeutic benefits. [89]

Resistin has been shown to cause "high levels of 'bad' cholesterol (low-density lipoprotein or LDL), increasing the risk of heart disease. resistin increases the production of LDL in human liver cells and also degrades LDL receptors in the liver. As a result, the liver is less able to clear 'bad' cholesterol from the body. Resistin accelerates the accumulation of LDL in arteries, increasing the risk of heart disease. resistin adversely impacts the effects of statins, the main cholesterol-reducing drug used in the treatment and prevention of cardiovascular disease. [86]

Role of resistin in traumatic brain injury

It is evidenced that resistin could be produced by the brain and pituitary gland. [90] Furthermore, resistin mRNA was increased in the cortex of hypoxic, ischemic and traumatic animal brain. [91] In the patients with ischemic stroke, high plasma resistin level has been associated with higher mortality and disability. [92] Recently, it was reported that high levels of resistin are present in the peripheral blood of patients with intracerebral hemorrhage are associated with poor functional outcome. [93] These findings suggest that resistin could contribute to the prognosis of patients with brain injury. [94]