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Review

Intensive Care Treatment in Traumatic Brain Injury

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Abstract

Head injury remains a serious public problem, especially in the young population. The understanding of the mechanism of secondary injury and the development of appropriate monitoring and critical care treatment strategies reduced the mortality of head injury. The pathophysiology, monitoring and treatment principles of head injury are summarised in this article.

Key Words: Head injury, intracranial pressure, secondary injury

The epidemiology of head trauma

Head trauma is the disruption of brain functions due to an impact to the head, penetrating injury or a concussion. It is the primary cause of trauma mortality. Head trauma is most frequently seen in the young ones and people >75 years. It is more common among males than females. In our country, the most common causes of head injury are reported to be traffic accidents and falls (1).

The physiopathology of head trauma

Primary and secondary brain injury

Primary injury occurs at the moment of trauma; however, secondary injury occurs gradually as a result of some factors such as hypoxia, hypercapnia, hypotension, increased intracranial pressure and hyperglycaemia after primary injury (Table 1). Treatment of head trauma aims to prevent secondary brain injury, which will decrease morbidity and mortality to a great extent.

Primary injury can be focal or diffuse. Contusion, laceration and intracranial haemorrhage are examples of focal brain injury. On the other hand, diffuse axonal damage and cerebral oedema are types of diffuse brain injury (2).

The first stage of head trauma is characterised by tissue damage caused directly by trauma and damage in cerebral blood flow and brain metabolism. During this period, accumulation of lactic acid due to anaerobic glycolysis, increased membrane permeability and oedema appear. When anaerobic glycolysis cannot provide adequate energy and depletes the existing ATP stores, ATP-dependent ion pumps are damaged. In the second stage of this pathophysiological cascade, terminal membrane activation occurs with an excessive release of excitatory neurotransmitters such as glutamate and aspartate, N-methyl-D aspartate, voltage-dependent sodium and activation of calcium channels. The continuous influx of sodium and calcium into the cell leads to intracellular processes that cause the death of cells. Intracellular calcium activates lipid peroxidases, proteases and phospholipases increases the intracellular concentrations of free fatty acids and free radicals. Moreover, activation of substances such as translocases and endonucleases leads to necrosis or apoptosis by damaging cell membrane and DNA.

Specific pathophysiology of head trauma

Cerebral blood flow

Hypoperfusion and hyperperfusion

Under normal conditions, 50 mL of blood flow per 100 g brain tissue occurs per minute. However, with head trauma, autoregulation of cerebral blood flow deteriorates and cerebral ischemia can develop in association with inadequate blood flow

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Table 1. Causes of secondary injury

Systemic	Intracranial
Hypoxia	Increased intracranial pressure
Hypotension	Hematoma
Anaemia	Convulsion
Hypo/hypercarbia	Infection
Fever	Vasospasm
Hypo/hyperglycaemia	
Hyponatremia	

at the level of 50 mL kg^{-1} dk^{-1} because of increased cerebral oxygen consumption (3). Therefore, while establishing the diagnosis of hypoperfusion or hyperperfusion, it is important to evaluate cerebral oxygen consumption with cerebral blood flow. Cerebral ischemia is a frequent complication after head trauma, and it is encountered in 90% of dead patients (4).

Cerebrovascular autoregulation and CO_2 reactivity

Cerebrovascular autoregulation and CO_2 reactivity are important mechanisms that provide cerebral blood flow. After head traumas, autoregulation of cerebral blood flow is impaired entirely or partially (5, 6). This impairment can occur just after trauma or develop over time, and it can be transient or persistent regardless of the severity of trauma.

Although CO_2 reactivity is impaired in the early stages after trauma in patients with severe brain injury, it is intact in many other patients and facilitates the treatment of intracranial pressure (7).

Vasospasm

Cerebral vasospasm that develops in more than one-third of patients after head trauma is an important factor indicating patient outcome (8). It occurs between the 2nd and 15th day after trauma, and hypoperfusion is observed in 50% of patients developing vasospasm. Vasospasm appears as a result of chronic depolarization of vascular smooth muscle cells.

Cerebral metabolic dysfunction

Cerebral metabolism reflects cerebral oxygen and glucose consumption. Cerebral energy state indicates phosphocreatine and ATP concentrations; both are frequently reduced after head trauma (9).

Cerebral oxygenation

After head trauma, imbalance occurs between cerebral oxygen delivery and cerebral oxygen consumption and subsequently hypoxia appears in brain tissue. When partial pressure of oxygen decreases below 10-15 mmHg in brain tissue, infarction develops in the brain (10). Brain tissue hypoxia may occur even in the presence of normal intracranial pressure (ICP) and cerebral perfusion pressure (CPP) (11). Therefore, for treatment of head trauma, balance between oxygen delivery and cerebral oxygen consumption should also be taken into consideration in addition to ICP and CPP.

Increased excitatory neurotransmitters and oxidative stress

After head trauma, the concentration of excitatory amino acids, particularly glutamate increases (12). This increased glutamate stimulates receptors in neurons and astrocytes and leads to Ca^{+2}, Na^{+} and K^{+} fluxes (13). This triggers catabolic processes and causes cell injury and breakdown of the blood–brain barrier.

Impaired antioxidant system after head trauma leads to an increase in free oxygen radicals. Thus, it causes peroxidation in cells and veins, protein oxidation, disruption of mitochondrial electron transport and DNA damage (14).

Oedema

After head traumas, vasogenic oedema associated with the breakdown of the blood–brain barrier and cytotoxic oedema associated with intracellular water accumulation can occur. Cytotoxic oedema is more frequent; however, both oedema types can increase intracranial pressure and can lead to secondary injury (15). It is suggested that aquaporins (AQPs), particularly AQP4, play a regulatory role in water transport of the brain.

Inflammation

Head trauma induces a complex immunological and inflammatory tissue response. Released cytokines, prostaglandins and other components activate polymorphonuclear leucocytes. Leucocytes stimulate endothelial adhesion molecules and stimulate secretion of intracellular adhesion molecules (ICAM-1) and vascular adhesion molecules (VCAM-1). This inflammatory response forms scar tissue within days and even months (16).

As a result, head trauma leads to imbalance between cerebral blood flow and metabolism, release of excitatory amino acids, oedema, inflammation and apoptosis due to mechanical stress developing in the brain tissue. Physiopathology of head traumas should be well understood for the proper treatment of this complex process.

Treatment of head trauma

The severity of head injury is classified as mild, moderate and severe in accordance with the Glasgow Coma Scale (GCS) (Table 2, 3).

Airway safety

Head trauma patients whose GCS Scores are below 9 should be intubated for adequate oxygenation and ventilation. Conditions such as most trauma patients having a full stomach, delayed gastric emptying due to the response of stress to trauma, spinal cord injury at cervical level in 10% of head traumas, possible airway trauma, skull base fracture, risk of hypovolemia, hypoxemia and increased intracranial pressure prevents creation of a consensus on the intubation technique. In general, orotracheal intubation is performed using hypnotic and neuromuscular blockers. During laryngoscope,

Table 2. Glasgow coma score
Eye response
1. No eye opening
2. Eye opening in response to pain stimulus
3. Eye opening to speech
4. Eye opening spontaneously
Verbal response
1. No verbal response
2. Incomprehensible sounds
3. Inappropriate words
4. Disoriented
5. Oriented
Motor response
1. No motor response
2. Extensor response to pain (decerebrate)
3. Abnormal flexor response to pain (decorticate)
4. Normal flexor response to pain
5. Localizes to pain
6. Obeys commands

Table 3. Classification of head traumas	
GCS	**Stage**
3-8	Severe head trauma
9-12	Moderate head trauma
13-15	Mild head trauma
GCS: Glasgow coma score	

cricoid compression should be used to decrease the risk for aspiration. Moreover, "in-line" axial stabilization is recommended to reduce the direct enhancing effect of laryngoscope on cervical injury because of possible cervical trauma and atlantoaxial dislocation (17).

Cerebral perfusion pressure

After airway safety is reached, haemodynamic resuscitation should be provided. With impaired autoregulation in head traumas, cerebral blood flow (CBF) completely becomes dependent on the mean artery pressure (MAP). Adequate cerebral perfusion due to increased intracranial pressure can be obtained with high level of MAP.

In the studies conducted aiming at transcranial doppler and jugular bulb oxygen saturation in Edinburgh University, cerebral perfusion pressure is recommended to be 70 mmHg (CPP=MAP–ICP) (11, 18).

According to another approach, the Lund concept, it is aimed to reduce cerebral oedema by increasing plasma colloid oncotic pressure through albumin therapy, to decrease cerebral blood volume by using selective cerebral vasoconstrictors such as dihydroergotamine, to maintain CPP at the level of 50–55 mmHg through metoprolol and clonidine therapy and to provide negative fluid balance (19). With this approach, hyperaemia can be prevented, which may result from high level of MAP. However, poor results due to negative fluid balance have led to the change of the Lund concept, and it has been recommended to maintain CPP at the level of 60–70 mmHg with normovolemia.

On the other hand, it is suggested to maintain the level of CPP at 50-70 mmHg in the guideline of severe head trauma (20).

Norepinephrine can be used in addition to the appropriate fluid treatment to regulate blood pressure. In our clinical practice, we aim to keep CPP at the level of 70 mmHg during the first 48-71 h in severe head traumas. However, higher levels can cause cerebral oedema and acute respiratory distress syndrome (ARDS) (21).

Ventilation

Volume-controlled ventilation is suggested for intubated patients because regulation of $PaCO_2$ value is necessary. All patients should be ventilated at normal levels, and the value of $PaCO_2$ should be maintained at the level of 38–42 mmHg. In patients whose ICP cannot be reduced below 20 mmHg despite drainage of adequate cerebrospinal fluid (CSF) from ventricular catheter, administration of mannitol or hypertonic saline and sedation. ICP can be decreased by creating vasoconstriction in brain veins through mild and short-term hyperventilation.

In head trauma cases, hypoxia and hypotension are the two factors that mostly lead to secondary injury. When oxygen partial pressure decreases below 60 mmHg, CBF and ICP therefore increases. The value of PaO_2 recommended for avoiding hypoxemia and providing maintenance is approximately 100 mmHg. The most important negative effect of positive pressure ventilation on cerebral oedema while providing adequate oxygenation is increased central venous pressure and impaired cerebral venous drainage. In patients with severe head trauma, application of positive end-expiratory pressure (PEEP) above 10 cmH_2O will result in increased ICP.

Monitoring intracranial pressure

ICP should be measured in severe trauma patients whose GCS is below 9 and/or who have CT findings, including intracranial hematoma, contussion and oedema and it should be below 20 mmHg. It is known that mortality and morbidity rates increase when ICP is above this level (22).

Although many methods are available for the measurement of intracranial pressure, prominent approaches for this measurement are catheter and intraparenchymal microtransducer systems (23). Because the measurement of ICP with subarachnoid and epidural catheters has low validity, they are used less frequently (23). The gold standard method for ICP measurement is performed with a catheter localised in the lateral ventricle through a small "burr hole" from the right fron-

Figure 1. Intraventricular catheter system

tal region. It provides information about the whole intracranial pressure. The advantages of intraventricular catheters (IVC) are to allow periodical calibration, CSF drainage for treatment when the level of ICP increases and medications such as antibiotics to be given intraventricularly. Their disadvantages include difficulty in placement in patients with increased ICP because it is an invasive method and the risk for hematoma, seizure and infection that may reach the rate of 10%. Infection risk increases particularly 4 days after placement. This risk can be reduced with catheters covered with antibiotics. Moreover, to decrease this risk, the necessity of catheters should be re-evaluated every day and they should be changed if it is used for more than 4 days. If growth is not observed in CSF samples and no clinical and laboratory findings of infection are available, catheters can remain for more time. In patients whose intracranial pressure is not increased and who are medically stable, catheters should be removed if daily amount of drainage is a little. However, in cases without findings of blood and infection, catheters requiring intense drainage (>200 mL per day) can be recommended to be changed with closed system (ventriculoperitoneal shunt). In cases in which more CSF drainage is performed for treatment, increased production of CSF also increases the need for shunt. Therefore, the most appropriate methods for increased ICP can be preferred following the acute period (CPP >65 mmHg). Another technical point that must be considered is that pressurized irrigation fluid is not used for catheter-dependent pressure transducer system. As is known, in transducer systems including pressurized fluid, hourly fluid is administered for pathway clarity (3-5 mL h^{-1}). However, administering fluid into the head will increase both infection risk and ICP. CSF can be taken from intraventricular catheters; however, it is not appropriate to administer fluid into the head for any reason (such as removing the blockage) (Figure 1) (23).

Microtransducer-tipped ICP monitoring systems can be placed into the brain parenchyma or subdural space after the bone window or craniotomy. It is stated that this technique provides information consistent with intraventricular catheters. Its advantages include low level of complications and infection risk. On the other hand, its disadvantage includes initialization failure over time, unable to be calibrated after placement and depicting only regional measurement values. Fiber optic or pneumatic technologies are used for this method.

Other techniques used for brain monitoring in head trauma cases

Transcranial doppler is a non-invasive technique that can measure systolic flow velocity of the middle cerebral artery. The results of this method seem consistent with direct measurement methods such as xenon and A-V oxygen content trends. Normal systolic velocity is <120 cm sn^{-1}. By repeating these measurements at different PCO_2 levels, the response of CBF to CO_2 can be determined. Slow diastolic flow is indicative of intracranial hypertension and impaired effective cerebral perfusion. In addition, diastolic wave analysis can be an early or late sign of increased ICP. Pulsatility index value (systolic velocity-diastolic velocity/systolic velocity) above 1.6 is a signal for poor prognosis.

Cerebral blood flow autoregulation can be evaluated either by pressure reaction index (PRx), which is a sum of arterial pressure and spontaneous slow waves on the ICP trace, or by jugular venous bulb saturation (SjO_2), or brain tissue oxygen tension ($pBrO_2$ 4.5-6.7 kPa normal) or noninvasively by near infrared spectroscopy.

Cerebral autoregulation can be measured with PRx, which is obtained through accumulated spontaneous slow waves in ICP and arterial blood pressure.

Biochemistry of the brain can be identified with the cerebral microdialysis method. Glucose, lactate, pyruvate, glycerol and glutamate can be measured and normal values have been defined. In cases of cerebral hypoxia/ischemia, the ratio of lactate-pyruvate increases.

Fluid therapy

Most of the head injury cases are hypovolemic because of trauma. While treating hypovolemia, a strategy that will not lead to cerebral oedema should be determined. The most important point is the composition of the fluid rather than its volume. Hypo-osmolar fluids that will cause a decrease in serum osmolarity should be avoided. In presence of severe fluid loss, cristalloids and colloids should be used together and normovolemia should be achieved.

It should be kept in mind that thromboplastin released from brain cells in severe head injuries can lead to consumption coagulopathy (24).

Steps of treatment in severe head injuries

1. In severe head injuries, if ICP is above 20 mmHg despite CSF drainage from intraventricular catheter, mannitol or hypertonic saline therapy should be administered. Rec-

Table 4. Treatment steps of head injuries
GCS <9, ICP monitoring, CPP=70 mmHg
ICP >20 mmHg
CSF drainage
ICP >20 mmHg
ICP >20 mmHg, Mannitol & Hypertonic saline
ICP >20 mmHg
Sedation, Mild hyperventilation ($PaCO_2$ 30-35 mmHg)
ICP >20 mmHg
Decompressive craniotomy, Barbiturate-induced coma, Hypothermia

GCS: Glasgow Coma score; CPP: cerebral perfusion pressure; ICP: intracranial pressure; CSF: cerebrospinal fluid

ommended dose of mannitol is 0.25-1 g kg^{-1} (25). When mannitol cannot provide adequate effect, the use of hypertonic saline is suggested (26).

2. If ICP is above 20 mmHg despite osmotic diuretic therapy, short-term hyperventilation is recommended with sedation and $PaCO_2$ at the level of 30–35 mmHg. Lower values can lead to cerebral ischemia. Hyperventilation longer than 6 h is ineffective because the effect of decreased $PaCO_2$ on brain pH is compensated in this period.

3. Despite all, if ICP is over 20 mmHg, decompressive craniotomy, high-dose barbiturate-induced coma and hypothermia can be applied as the last step.

4. Decompressive craniotomy is recently used very often in cases with head trauma. During this surgical procedure, certain amount of bone is removed and a dura is opened. The dura can be left open or duraplasty can be performed. Primary decompressive surgery is performed in patients for whom it is anticipated that ICP control will be provided with difficulty because of CT findings of patients or the brain being very rigid during operation. On the other hand, secondary decompressive craniotomy is performed in patients whose ICP cannot be reduced in spite of the most appropriate medical therapy (27).

5. Barbiturate-induced coma: In patients whose ICP is high despite any medical and surgical treatment, high-dose phenobarbital therapy can be administered.

6. Hypothermia: The effects of hypothermia on survival have been investigated in cases with head injury. Hypothermia can induce coagulation disorders and increase the risk for bleeding, and rewarming process can lead to an increase in ICP. At present, there are no sufficient data showing that hypothermia therapy is beneficial for the cases with head trauma (Table 4) (28).

Antiepileptic drugs such as phenytoin, carbamazepine and phenobarbital can be used to prevent early seizures. In the treatment of head trauma, steroids are not used.

Treatment of fever and hyperglycaemia

It has been reported that fever negatively affects survival after brain damage because it increases the need for O_2. Therefore, regardless of an underlying reason, normothermia should be provided in case of cerebral oedema. The agent recommended to protect against increased body temperature is paracetamol (325-650 mg every 4-6 h). Some positive effects of surface cooling techniques have also been reported.

In patients with ischemic stroke, subarachnoid haemorrhage and head injury, a relationship has been revealed between hyperglycaemia and poor prognosis. Hyperglycaemia deteriorates brain damage and cerebral oedema. It has been reported that adequate glycaemic control has significantly increased survival rate in patients hospitalized in the general intensive care units (20% of them with head trauma and undergone craniotomy). The point to be considered here is to avoid hypoglycaemia and to regulate blood glucose in a wider interval (between 80 and 180 mg dL^{-1}) rather than to control at a rigid limits.

Nutrition supplementation

Patients with head trauma should begin to be fed as soon as possible after providing haemodynamic stability (within 72 h at the latest) and if possible, enteral feeding should be used. In addition, required calorie level should be reached in a week at the latest. Osmotic contents of formula foods should be given attention because they can increase hypo-osmolar state and cerebral oedema.

Aquaporins

It has been suggested that AQP4 inhibition can be a new approach in the therapy of cerebral oedema. Pharmacological modulation of AQP4 looks promising. However, this therapy performed in a laboratory environment has not been able to be transferred to the clinic yet. AQP-targeted treatment by using agonists and antagonists in the brain seems appropriate at present. Carbonic anhydrase inhibitors, quaternary ammonium compounds and mercury sulfhydryl compounds inhibit lithium, silver and gold activate AQPs; however, these are in vivo toxic agents.

Conclusion

The main principle in the treatment of head trauma cases is to decrease ICP and to ensure cerebral perfusion pressure to be at the adequate level. Medical and surgical techniques are used together for this treatment. It has been revealed that the treatment of head trauma patients in trauma centres offering rapid surgical intervention, computed tomography and measurement of intracranial pressure reduces the rate of mortality (29).

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