New and novel treatments for TBI

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Traumatic brain injury (TBI) is the leading cause of death in the young adult and leads to severe disability, with a substantial burden of physical, psychiatric, emotional, and cognitive disabilities, which disrupt the lives of the patients and their families. The incidence of mild traumatic brain injury (TBI) is higher in New Zealand compared to European countries or the United States. Furthermore, children and young adults (< 35 years) suffer more often from TBI. To change this the New Zealand Accident Compensation Corporation (ACC) has launched the Traumatic Brain Injury Strategy and Action Plan (2017-2021) which has the aim to reduce the incidence, severity and impact of TBI. Severe TBI is mainly caused by road traffic accidents, assaults, falls, and domestic abuse.

Pathophysiology

The extent of the primary injury cannot be influenced by therapy and, therefore, prevention e.g. by helmets or airbags is the only way to avoid the damage. The primary brain damage triggers a cascade of pathophysiologic changes, which then lead to the secondary brain damage. During the first post-traumatic days the aim of the treatment is to minimize the expansion of the secondary damage in order to rescue the potentially salvageable intact brain tissue. Pathologic processes as elevated ICP (due to edema, hemorrhage, obstruction of cerebrospinal fluid flow), diminution of arterial inflow, and consequent reduction in CPP with resulting tissue hypoxia, and loss of cerebrovascular autoregulation increases secondary brain damage. Additionally, inflammation, massive release of excitatory neurotransmitters, apoptotic cell death, high lactic acid concentrations due to anaerobic glycolysis, depleted ATP-stores, increased intracellular Ca^{2+} concentrations, inflammation, generation of free radicals and proteolysis are only some of the identified parameters contributing to secondary brain damage.

Unfortunately, despite intense research and characterization of all these contributing mechanisms, no drug has been identified which can improve outcome after TBI in randomized, prospective clinical trials. This is most likely related to the complex pathophysiology of brain damage, the heterogeneous patterns of damage, and various preexisting diseases of the patients. TBI also influences systemic parameters like interferences of the autonomic nervous system (sympathetic discharge), inflammatory responses, endocrine dysfunctions, electrolyte imbalance, cardiovascular and respiratory disturbances, and impairment of the coagulation cascade. These systemic effects have to be monitored and immediately treated as they also contribute to a deterioration of secondary brain damage.

Novel neuroprotective drugs

Despite decades of experimental and clinical studies and a thorough characterisation of the mechanisms that extend the secondary brain injury no neuroprotective “magic bullet” has been identified. There exist many promising new therapeutic approaches including stem cell therapy, nanoparticles, and investigations on mitochondrial dysfunction, microglial activation, cerebral microcirculation impairment, and the effect of gut dysbiosis following TBI. Digital analysis of large datasets (big data analyses) including genomics, blood biomarkers, advanced MRI combined with clinical data of e.g. physiological variables, frailty, and preexisting diseases might have the power to improve clinical decision making and outcome of TBI patients. Another approach is the combination and individualization of multiple potentially neuroprotective drugs with a special focus on the adequate timing of administration according to the pathophysiology.

Neuroprotective interventions

As the brain has no tolerance for hypoxia, TBI patients demand an immediate and knowledgeable treatment according to the current guidelines. In lack of a neuroprotective drug all therapeutic strategies focus on optimization of the delivery of oxygen and glucose to the brain cells. This includes maintaining adequate CPP, controlling ICP, and optimizing oxygenation. Therefore, in the critical care setting the management of TBI patients should follow established protocols with a close monitoring of parameters including CPP, ICP, and oxygenation status. Clinical standard assessments like continuous measurement of arterial blood pressure, heart rate, and pulse oximetry in combination with monitoring of skin turgor, mucous membrane hydration status, urine output, and GCS have to be performed.

Cerebral perfusion pressure
CPP results from the difference of mean arterial pressure (MAP) minus ICP and should be kept between 60-70 mmHg. Aggressive attempts to maintain CPP above 70 mmHg with fluids and vasopressors should be avoided as this treatment increases the risk of adult respiratory failure. Arterial hypotension with a systolic blood pressure below 90 mmHg is strongly related to poor outcome and has to be avoided in the preclinical and clinical management of TBI patients. There exists a smooth U-shaped relationship between systolic or mean arterial blood pressure and outcome, without any evidence of an abrupt threshold effect. Therefore, the recommendation in the guidelines to maintain systolic blood pressure above 100 mmHg for patients 50 to 69 years old or ≥ 110 mmHg for patients 15 to 49 or > 70 years old, possibly need to be specified for an optimal systolic blood pressure of 135 mmHg. To calculate the CCP the pressure transducer for MAP must be zeroed at the level of the midbrain.

Intracranial pressure
Elevate ICP above 22 mmHg is associated with increased mortality and should be treated. When ICP is elevated the following measures should be performed: optimisation of positioning, osmotherapy, deep sedation with barbiturates or propofol, and ventricular drains. Hyperventilation reduces cerebral blood volume (CBV) and ICP due to its vasoconstrictive effect, but at the same time hyperventilation leads to a mismatch between oxygen delivery and oxygen consumption. Therefore, hyperventilation is only a temporizing measure until other ICP-lowering measures are available. Decompressive craniectomy has been a strategy to lower ICP, but unfortunately, this intervention increases the number of patients surviving in vegetative state or with a severe brain damage but not of those with good outcome.

Oxygenation and ventilation
Patients with GCS ≤8 should be intubated and ventilated. An adequate oxygenation (PaO_2 > 80 mmHg) should be achieved, if necessary by using a positive end-expiratory pressure (PEEP) up to 15 mbar or kinetic therapy (prone position).

Sedation
For sedation of a TBI patient drugs with a short context-sensitive half-life like propofol should be used to facilitate the daily control of consciousness of the patient. Care should be taken to screen patients for the so-called propofol infusion syndrome which can occur when high-dose propofol is used over several days. Most of the barbiturates and benzodiazepines have a longer half-life and are, therefore, less suitable. Low-dose inhalational anesthetic can also be used, while in higher concentrations volatile anesthetics possess a direct vasodilatory effect, which increases CBV and, thereby, ICP. Ketamine was suggested to be contraindicated in TBI patients due to perceived risks of intracranial hypertension, but in intubated and ventilated patients ketamine has no adverse effect on ICP. At the same time Ketamine has several favorable effects like reduced need of supplementary vasopressors and narcotics, activation of bowel movement, and bronchodilatation. Narcotics, like sufentanil, fentanyl, and remifentanil have no negative effects on ICP as long as MAP is maintained. Muscle relaxants can be used in TBI patients, with a potential exception of succinylcholine, which possibly increases ICP. Nitrous oxide and etomidate should not be used in patients after severe TBI.

Additional interventions
Feeding of the TBI patients to attain basal caloric replacement between the fifth and the seventh day after trauma is recommended. Enteral feeding using a transgastric jejunal tube should be started as soon as possible. Early dilatatory tracheotomy facilitates the weaning of the patients and reduces mechanical ventilation days.
Up to 25% of patients with isolated TBI develop deep vein thrombosis (DVT) with the risk of pulmonary embolism. Low molecular weight heparin or low-dose unfractioned heparin should be used in combination with mechanical prophylaxis, despite the increased risk of expansion of intracranial hemorrhage.
The incidence of early posttraumatic seizures (during first week after TBI) can be reduced by phenytoin. As these early posttraumatic seizures do not influence outcome, this prevention is not obligatory. Late posttraumatic seizures are not susceptible to prophylactic interventions.