Clinical neuroprotection and secondary neuronal injury mechanisms

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Abstract
Anaesthetists and intensive care physicians commonly encounter cerebral injury in their clinical practice. Insults may arise from cardiac arrest and traumatic brain injury, can follow cardiothoracic, vascular or major orthopaedic surgery, and are also seen in medical conditions including subarachnoid haemorrhage, central nervous system infection, epilepsy and stroke. In all cases, neuronal injury may lead to severe disability or death; however, aggressive early treatment may result in improvements to patient morbidity and mortality. Neuroprotection involves an intervention, initiated before the onset of ischaemia that can modify the cascade of events which lead to permanent cell damage when left unchecked. Neuroresuscitation refers to treatment aimed at restoring blood flow and oxygenation to cells that have already become exposed to an ischaemic insult.

Keywords cerebral protection; secondary brain injury; stroke; subarachnoid haemorrhage; traumatic brain injury

Mechanisms of secondary brain injury
The cascade of events that ultimately results in cerebral cell death begins at the instant of primary brain injury. Following this event, there are many local and systemic insults that may conspire to cause secondary brain injury (Box 1); the most common factors leading to secondary brain injury are hypoxia and hypoperfusion, which result in cellular ischaemia, oedema formation, brain swelling and disruption of the blood–brain barrier (BBB). These in turn increase intracranial pressure (ICP) which further decreases cerebral perfusion.

At a cellular level, ischaemia leads to the conversion from aerobic to anaerobic metabolism with a subsequent increase in lactate production; under these conditions, adenosine triphosphate stores are soon depleted and cell membrane integrity becomes compromised. Ischaemia also results in glutamate and N-methyl-D-aspartate (NMDA) receptor activation and intracellular influx of sodium and calcium ions; this, in turn, increases activation of intracellular proteases and lipases and the release of free radicals and free fatty acids. The ensuing intracellular acidosis, destruction of cell membrane and increase in gene expression for apoptosis causes cellular death.

The treatment goal after cerebral injury, both during the acute resuscitation phase and later in the intensive care unit, is to prevent and treat cerebral ischaemia in order to minimize the degree of secondary cerebral damage and maximize the potential for neurological recovery. Interventions to achieve this goal may be divided into physiological, pharmacological and surgical treatments (Box 2).

Physiological cerebral resuscitation
Both hypotension and hypoxaemia are independently associated with poor outcome after traumatic brain injury (TBI) and other forms of cerebral insult. Early targeted treatment of these variables in the pre-hospital setting and the emergency department often requires little specialist knowledge, drugs or equipment and provides an excellent platform for further management in a general or neurocritical intensive care unit.

Control of blood pressure
Moderate hypotension (systolic blood pressure <90 mmHg) should be avoided if possible as following TBI it is associated with a twofold increase in mortality. Hypotension causes a global reduction in cerebral blood flow (CBF) and hence cerebral perfusion pressure (CPP); this reduction of CPP is further exacerbated by raised ICP. The aim during the initial resuscitation is therefore to elevate mean arterial pressure (MAP) to 80 mmHg or above to preserve CPP at a level of approximately 70 mmHg. This is achieved by appropriate volume resuscitation and, if required,

Learning objectives
After reading this article, you should be able to:
- outline the mechanisms of secondary brain injury
- list physiological methods of cerebral resuscitation
- list some pharmacological and surgical methods of neuroprotection

Mechanisms of secondary brain injury
Local
- Cerebral oedema
- Epileptic seizures
- Expanding haematoma

Systemic
- Hypoxia
- Hypotension
- Hypercarbia
- Hypocarbia
- Metabolic disturbances
- Infection

Box 1

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vasopressor support, which should be titrated using invasive blood pressure monitoring.

**Hypoxaemia**

Hypoxaemia (PaO$_2$ < 8 kPa) is associated with a significant increase in mortality in patients with severe TBI (those with a Glasgow Coma Score <8) and low local brain tissue oxygen tension often indicates ongoing cerebral ischaemia. Aggressive correction of hypoxaemia is therefore mandatory and requires early tracheal intubation and mechanical ventilation. Current guidelines suggest PaO$_2$ levels greater than 13 kPa should be targeted.

**Hypercarbia**

Although reduction in arterial carbon dioxide tension (PaCO$_2$) has long been a tool in cerebral resuscitation, there is little evidence that it improves outcome following TBI. It has been used extensively to cause cerebral vasoconstriction which, by decreasing cerebral blood volume, results in a decrease in ICP. This was assumed to be beneficial; however, there is increasing evidence that excessive hyperventilation may worsen perfusion to ischaemic areas following TBI. Current guidelines suggest PaCO$_2$ is maintained at 4.5–5 kPa.

**Temperature control**

Hypothermia is often induced following TBI but, as yet, studies have failed to provide evidence that it improves morbidity and mortality. Evidence suggests that in certain scenarios, such as post cardiac arrest, ischaemic injury may be reduced when hypothermia is maintained for more than 48 hours.

**Pharmacological strategies for cerebral resuscitation and protection**

The goal of many pharmacological strategies is to reduce the effect of the ischaemic insult by suppressing neurotransmission (and therefore limiting tissue oxygen requirement) and maintaining cellular energy reserves during the initial period of decreased substrate delivery. In addition, pharmacological maintenance of blood—brain barrier integrity reduction in oedema and pharmacological free radical scavenging also limits cellular destruction (Figure 1).

**Anaesthetic agents**

**Barbiturates:** provide cerebral protection by decreasing neuronal energy requirement and therefore oxygen demand; they also have free radical scavenging properties. However, due to their unfavourable side effect profile, high-dose barbiturate therapy is usually reserved for when all other medical and surgical treatments have failed. There is no evidence to show they improve outcome after TBI.

**Propofol:** it is thought to provide neuroprotection by reducing cerebral metabolism and oxygen consumption, in much the same

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**Cerebral protection strategies**

**Physiological**
- Control of blood pressure
- PaO$_2$ maintenance
- PaCO$_2$ control
- Temperature control

**Pharmacological**
- Barbiturates
- Propofol
- Volatile anaesthetic agents
- Hyperosmolar agents
- Nimodipine
- Magnesium

**Surgical**
- Decompressive craniectomy

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**Mechanisms of ischaemic cell death and sites of action of cerebroprotective agents**

- **Barbiturates**
- **Propofol**
- **Volatile anaesthetic agents**
- **Hyperosmolar agents**
- **Nimodipine**
- **Magnesium**

**ISCHEMIA**

- **Glutamate receptor activation**
- **NMDA receptor activation**
- **Sodium influx**

**ISCHEMIC HYPERTENSION**

- **Calcium influx into cells, intracellular calcium**

**ISCHEMIC INFECTION**

- **Activation of protease, lipase, endonuclease**

**ISCHEMIC INFLAMMATION**

- **Leucocyte activation**
- **Free radical release**
- **Cytokine release**

**ISCHEMIC NITRITION**

- **INOS, inducible nitric oxide synthase; NMDA, N-methyl-D-aspartate; NNOS, neuronal nitric oxide synthase**

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**Box 2**

- Control of blood pressure
- PaO$_2$ maintenance
- PaCO$_2$ control
- Temperature control

**Pharmacological**
- Barbiturates
- Propofol
- Volatile anaesthetic agents
- Hyperosmolar agents
- Nimodipine
- Magnesium

**Surgical**
- Decompressive craniectomy
way as barbiturates. However, if used for more than 48 hours in critical care units and at high doses (5 mg/kg/hour) there is a risk of propofol infusion syndrome.

**Volatile anaesthetic agents:** in common with the intravenous agents, volatile agents may provide a degree of cerebral neuroprotection by suppression of neuronal energy requirements. The noble gases xenon and argon are also under investigation as future neuroprotective agents.

**Other agents**

**Hyperosmolar therapy:** mannitol and hypertonic saline (HTS) are the agents currently used in TBI. It is still not fully understood how mannitol produces its benefits, but studies consistently show it is effective in reducing ICP in patients with intracranial hypertension. Hypertonic saline is thought to exert its effect by drawing water across the intact blood–brain barrier by osmosis, therefore reducing the water content of the brain. There is no evidence one therapy provides a superior long-term outcome to the other.

**Nimodipine:** it is a cerebroselective calcium channel blocker used in the treatment of subarachnoid haemorrhage (SAH). It has been shown to improve outcome, probably due to its action in preventing the vasospasm associated with SAH.

**Corticosteroids:** these drugs are no longer indicated in the treatment of raised ICP as evidence indicates they do not lower ICP or improve outcome following TBI.

**Magnesium:** whilst magnesium may improve outcome following subarachnoid haemorrhage, it may produce the opposite effect following TBI. It is routinely given to hypomagnesemic patients.

**Surgical strategies for cerebral resuscitation and protection**

**Decompressive craniectomy**
Decompressive craniectomy involves removing part of the skull bone and opening dura to reduce ICP thus allowing room into which a swelling brain can expand. Evidence suggests it is associated with a good functional outcome in those patients where ICP has been uncontrollable by other medical therapy.

**REFERENCES**