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Review

Reconsidering the role of hypothermia in management of severe traumatic brain injury

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ABSTRACT

Over the past two decades there has been considerable interest in the use of hypothermia in the management of severe traumatic brain injury. However despite promising experimental evidence, results from clinical studies have failed to demonstrate benefit. Indeed recent studies have shown a tendency to worse outcomes in those patients randomised to therapeutic hypothermia. In this narrative review the pathophysiological rationale behind hypothermia and the clinical evidence for efficacy are examined. There would still appear to be a role for hypothermia in the management of intractable intracranial hypertension. However optimising therapeutic time frames and better management of strategies for complications will be required if experimental evidence for neuroprotection is to be translated into clinical benefit.

1. Introduction

The past two decades has seen enormous interest in the use of hypothermia in the context of severe traumatic brain injury (TBI). The rationale is that therapeutic cooling of the brain can prevent or attenuate some of the secondary brain injury due to damaging inflammatory and neuroexcitatory cascades and elevated intracranial pressure (ICP).

Laboratory and animal studies [1–6] have shown promising results however evidence of efficacy in clinical studies has been less forthcoming [7–12]. Indeed, recent trials not only failed to demonstrate benefit but also revealed a tendency towards clinical harm [7,8,11,12]. In view of these results the time may have come to reconsider the role of hypothermia in the management of severe TBI.

The aim of this narrative review is to re-examine the pathophysiological rationale behind hypothermia, assess the clinical evidence for efficacy and consider future directions.

2. The pathophysiology of TBI

In order to appreciate the pathophysiological rationale and possible limitations for hypothermia in the context of neurotrauma there are two concepts that require consideration: firstly, the Monro–Kellie doctrine, and secondly, the concept of neuroprotection.

2.1. The Monro–Kellie doctrine

Despite considerable advances in the management of TBI we are still bound by the Monro–Kellie doctrine, which was first described over 200 years ago. In 1783 Alexander Monro deduced that the cranium was a "rigid box" filled with a "nearly incompressible brain" and that its total volume tends to remain constant [13] (Fig. 1). The doctrine states that any increase in the volume of the cranial contents (the brain, blood or cerebrospinal fluid [CSF]), will elevate ICP. Furthermore, if one of these three elements increases in volume, it must occur at the expense of the volume of the other two elements. In 1824 George Kellie confirmed many of Monro's early observations [14]. When the brain is injured and starts to swell or there is a mass lesion such as an intracerebral haematoma, in order to maintain cerebral perfusion, compensation is made at the expense of a reduction in the volume of blood and CSF. As the brain becomes progressively more swollen or a mass lesion increases in size these compensatory mechanisms become exhausted and for incrementally smaller increases in volume there are progressively greater increases in pressure until tonsillar herniation occurs.

An understanding of this concept is important in order to appreciate how management strategies for patients with severe TBI have evolved over recent years. Throughout the 1980s, patients were routinely hyperventilated [15,16], placed in a barbiturate coma [17,18], or more recently rendered hypothermic because these measures have been shown to consistently reduce ICP. Given the strong association between intracranial hypertension and poor outcome [19,20] the rationale was that by lowering the ICP, cerebral perfusion would be improved and this in turn would prevent

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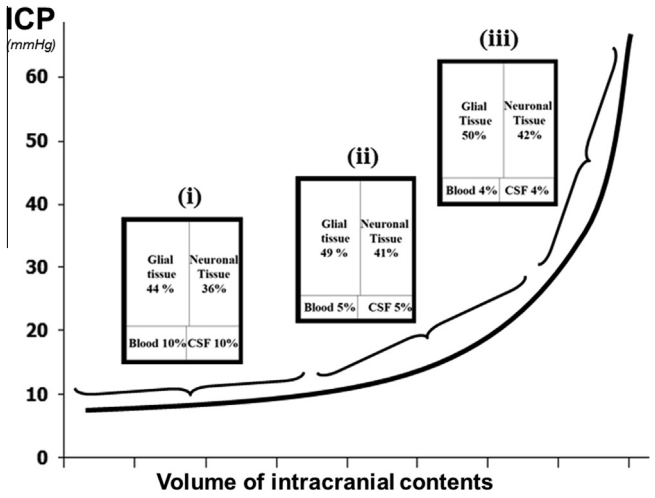

Fig. 1. The Monro–Kellie doctrine. (i) In normal physiological circumstances any increase in volume of the constituent components of the intracranial compartment does not cause a significant increase in ICP because of compensatory decrease in volume of either blood or CSF. (ii) Partially compensated intracranial hypertension. As the brain progressively swells initial compensation is at the expense of blood and CSF. (iii) Decompensated intracranial hypertension. As the cerebral swelling worsens or a mass lesion enlarges there comes a point when the compensatory mechanisms start to fail and for smaller increases in swelling there are incrementally greater increases in ICP. CSF = cerebrospinal fluid, ICP = intracranial pressure.

secondary brain injury and improve clinical outcome. However, several clinical studies failed to show these therapeutic interventions provided benefit and in certain circumstances may have resulted in a worsened outcome [11,15,17].

Whilst this notion seemed counterintuitive, the negative effects that these interventions have on cerebral blood flow suggest a reason for treatment failure. Notwithstanding the potential neuroprotective effects of barbiturates [21] and hypothermia [4,6,22], the predominant mechanism by which these three therapeutic modalities can rapidly reduce ICP after TBI is cerebral vasoconstriction. Hyperventilation reduces the arterial carbon dioxide which in turn alkalinizes the CSF and induces a reflex vasoconstriction [15]. Barbiturates and hypothermia depress neuronal activity and reduce cerebral metabolism, which leads to a reduction in cerebral blood flow and blood volume due to autoregulatory flow metabolism coupling [23–25]. The subsequent reduction in cerebral blood flow has been clearly shown in several studies [15,23–27]. In view of the well known deleterious effect that ischaemia has on outcome [28] it is perhaps not entirely surprising that, although these measures reduce ICP, they do not necessarily provide long-term clinical benefit [2,7–9,15,29].

2.2. Cerebral neuroprotection

Traditionally primary brain injury has been defined as occurring at the moment of impact and secondary injury follows thereafter and consists of a wide range of molecular and cellular pathophysiological mechanisms. However it is now realised that there is considerable overlap between the two processes and a substantial amount of cell death that occurs many hours later is due to a series of deleterious inflammatory and neurochemical processes that are initiated at the time of injury [30–32]. This concept is well illustrated by the glutamate neuroexcitatory cascade which is one of many such responses initiated at the time of injury and amplified by secondary insults such as hypoxia and hypotension [33] (Fig. 2).

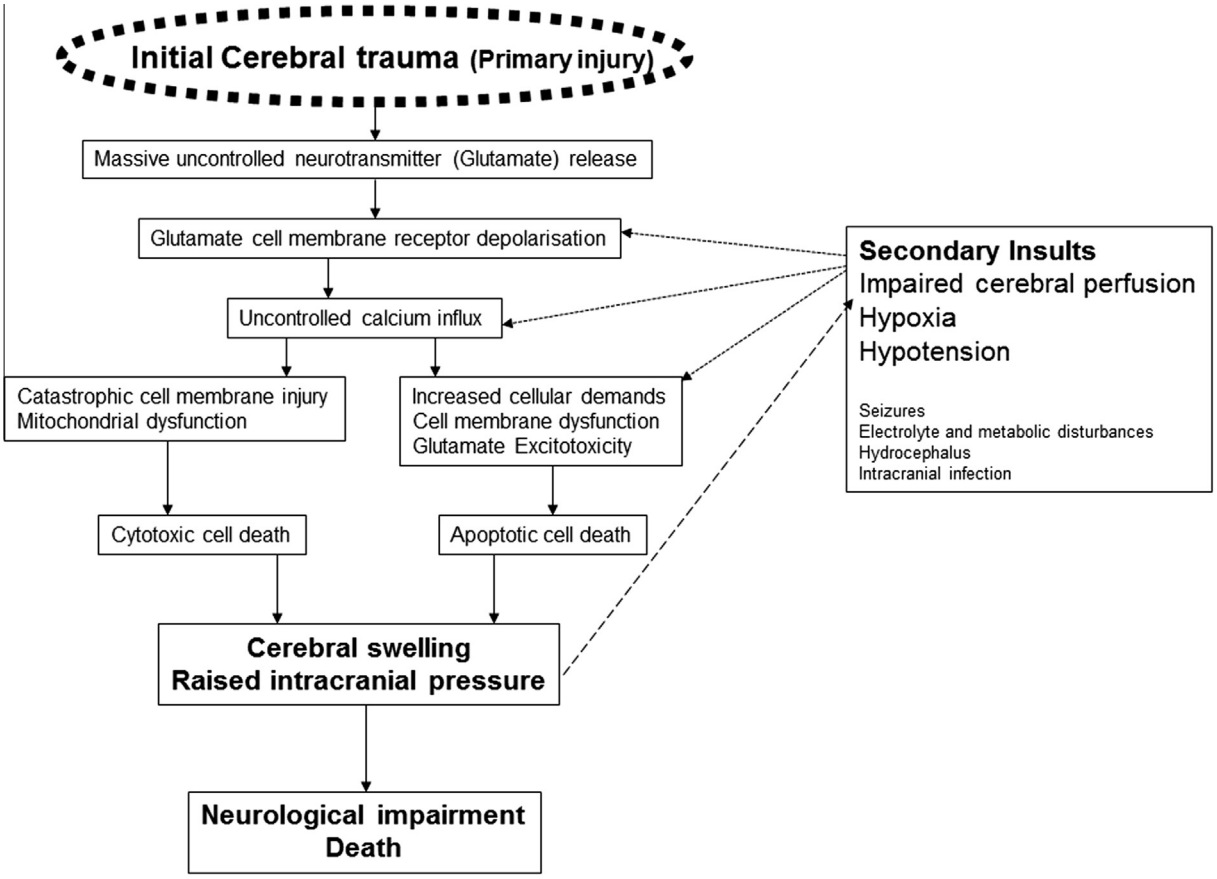

Fig. 2. A simplified schematic representation of the neuroexcitatory cascade. The primary injury triggers a massive uncontrolled release of the neurotransmitter glutamate which triggers the cascade leading to cytotoxic and apoptotic cell death. The cascade is reinforced by secondary insults.