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Mild Hypothermia as Treatment in Cerebral Ischaemic Insult

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Historical Perspective of Hypothermia

The use of hypothermia in the clinical setting has its roots with the ancient Egyptians, Greeks and Romans. Hippocrates packed wounded soldiers in snow to reduce haemorrhage. In the early nineteenth century, Napoleon's surgeon Baron Larrey noticed that wounded soldiers who were near a fire died quicker than those who remained hypothermic. Clinical interest in protective hypothermia began in the 1930s and 1940s, with observations and case reports describing successful resuscitation in patients after plunging in cold water. During this period, Fay first reported positive results from cooling severe brain-injured patients (Tempel Fay, 1943). Other small clinical trials were carried out in the 1960s. Despite occasionally encouraging results in patients, moderate hypothermia (28°–32°C) was abandoned because of uncertain benefits and management problems. Nevertheless, 'hypothermia' as 'step H' was inserted into cardiopulmonary resuscitation (CPR) sequences in 1961. It was then believed that hypothermia must be moderate (less than 32°C) in order to be beneficial.

Experimental research into early moderate hypothermia after cardiac arrest (CA) was revived in the 1990s, when it was found to produce a significant benefit in reproducible outcome models in dogs. More important was the discovery of the potentially beneficial effects of protective/preservative mild cerebral hypothermia (32°–34°C), which is clinically safe, in contrast to moderate hypothermia (28°–32°C), which can cause arrhythmia, re-arrest, infection and clotting problems. In 1987, Hossmann reported that in cats with global brain ischaemia there was a correlation between mild (unintentional) pre-cooling and enhanced electroencephalogram recovery. Safar demonstrated a correlation between good cerebral outcome and mild (unintentional) hypothermia at the onset of ventricular fibrillation (VF) in dog models (Safar et al. 1990). Such studies in dogs confirmed the beneficial effect of resuscitative mild hypothermia on the brain after cerebral insult. However, the translation of data obtained from animal models to humans seemed difficult.

Brain damage related to ischaemia is not only an instantaneous event, but also a process of delayed neuronal death. Diminished cerebral blood flow initiates a series of events called neurotoxic cascades. Observations in animal models of global ischaemia have demonstrated that some hippocampal neurons deprived of oxygen do not die instantly. This delayed cell death has been also confirmed in humans. Although the mechanisms of hypothermia are not entirely understood, it seems that lowering the body temperature protects tissues deprived of oxygen.

Clinical Applications:

Cardiopulmonary Resuscitation

In 2002, two prospective randomised trials compared mild hypothermia with normothermia in comatose survivors out-of-hospital CA (Bernard et al. 2002; *N.Engl.J.Med.*, 2002, Feb. 21). In patients who were successfully resuscitated after cardiac arrest due to VF, mild hypothermia reduced mortality rates and increased favourable outcomes. Based on these studies, in 2003 the International Liaison Committee on Resuscitation recommended that all unconscious adults with spontaneous circulation after out-of-hospital CA should be cooled to 32°–34°C for 12–24 hours when the initial rhythm is VF. Thus, resuscitative mild hypothermia should be used (Level of evidence: Class I) in a selected category of patients resuscitated from CA of cardiac origin, displaying a VF rhythm and with no refractory shock or persistent hypoxemia.

Traumatic Brain Injury (TBI)

In Traumatic Brain Injury (TBI) patients, the neurological damage occurring at the impact site is probably irreversible, however the subsequent brain damage secondary to cerebral oedema occurs hours or even days later. Cerebral blood flow (CBF) reduction secondary to cerebral oedema and increased intracranial pressure (ICP) further enhance the extent of brain damage. Another confounding problem is the presence of

local hyperthermia areas in the brain, as brain temperature is up to 2°C higher than body temperature. In 2001, Clifton et al. conducted a multicentric study including 392 patients from 11 US centres. Despite 48 hours of hypothermia, survival rates and neurological outcomes of patients were unchanged.

Hypothermia was able to reduce ICP, but increased complications. The only group that seemed to benefit from hypothermia were those who were hypothermic at admission. In studies led by Polderman and Zhi, therapeutic mild hypothermia was effective in increasing the survival rate and reducing neurological disability. In both studies, hypothermia was maintained for a longer periods (115.2 h and 62.4 h respectively). In a meta-analysis, McIntyre et al. concluded that hypothermia could be effective in reducing mortality and improving neurological outcomes.

It seems however, that while hypothermia is effective in reducing ICP (Level of evidence: Class I), reducing ICP does not necessarily improve survival rates or neurological outcomes. There is overwhelming evidence that the cooling period should be longer than in CA studies followed by a slow rewarming period. Routine use of hypothermia in TBI is not recommended (Level of evidence: Class III) however controlling fever seems mandatory (Level of evidence: Class IIa).

Stroke

In animal models, hypothermia has been used to protect the brain against focal ischaemia and human studies have yielded promising results so far. In all studies, the number of patients was small and the risk of complication was high, namely pneumonia. Animal studies and preliminary clinical studies have shown that hypothermia may be helpful to reduce infarct size and to improve neurological outcome, however the implementation of hypothermia as treatment for stroke still holds a Class III Level of evidence.

Subarachnoid Haemorrhage (SAH)

No major studies have been conducted concerning the use of hypothermia in Subarachnoid Haemorrhage (SAH). It seems that hypothermia reduces vasospasm, often complicating SAH. Initial results appear promising, but preliminary and inconclusive, therefore the Level of evidence is IV.

Neonatal Hypoxia–Ischaemia

The induction of hypothermia in infants and neonates is easier than the induction of hypothermia in adults, because infants and neonates have a larger surface relative to their body weight, and their thermoregulation is still underdeveloped. Feasibility studies conducted in neonates have shown that induced hypothermia was feasible and did not increase hypothermia-related complications, but the number of the patients was small and an improvement in the neurological outcome was still lacking. Larger randomised studies are needed to corroborate the use of induced hypothermia to prevent the ischaemic brain damage related to hypoxic–ischaemic insult (Level of evidence: Class III).

Paediatric Cardiac Arrest

Few paediatric cardiac arrest outcome studies include large number of patients; most evidence studies are retrospective and overall report low survival and poor neurological outcome of survivors. The Level of evidence is class III.

Other Potential Indications of Hypothermia

Based on the beneficial effects of hypothermia on ICP, resuscitative mild hypothermia is used to prevent ICP increases during hepatic encephalopathy. Other studies have suggested a beneficial effect of resuscitative mild hypothermia on status epilepticus and in acute disseminated encephalopathy. Some caution in the interpretation of these results and their implementation in general clinical use is warranted. Therefore, there is an urgent need for larger, controlled and randomised studies, but in the meantime the Level of evidence in the abovementioned indications rates as class III.

Conclusion

It is clear that the use of resuscitative mild hypothermia as a neuroprotective tool will become more frequent, but physicians need to differentiate when such treatment is already proven and when it still a matter of debate or yet to be investigated. There is increasing evidence that resuscitative mild hypothermia will have some beneficial effect in mitigating brain damage after focal ischaemia such as stroke, TBI and SAH. However, several specific issues need to be resolved such as the peak window of time between the insult and the induction of hypothermia, optimal speed of induction, cooling duration and re-warming phase.

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