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Induced Hypothermia and Fever Control in Neurological Injury: Cost-effectiveness Issues

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In recent years, the issue of temperature management in critically ill patients, in particular those with neurological injuries, has gained increasing attention from the critical care community. An increasing body of evidence has shown that the development of fever in patients with various types of neurological injury is associated with an increased risk of adverse outcome. This has been shown most clearly in patients with ischaemic stroke, where the absolute risk of adverse outcome (death or permanent neurological impairment) increases by 2.2% for every degree of temperature increase. A similar increase in risk has been reported for post-cardiac arrest patients.

A link between fever and adverse outcome has also been reported in patients with other types of brain injury, such as traumatic brain injury, subarachnoid haemorrhage, and post-ischaemic injury following cardiac arrest. The fact that these associations persist after multivariate analysis suggests that the relationship is causal, i.e. that fever generates additional brain injury. This view is reinforced by observations from various animal experiments, which have shown that the extent of experimentally induced neurological injuries increases significantly if the animal is externally warmed. The risk conferred by fever appears to be independent of its cause; infectious fever, "central" (neurological) fever, and fever occurring during reperfusion injury are all linked to increased neurological injury.

Mild Hypothermia Benefits Certain Patients

If hyperthermia is harmful to the injured brain, it seems reasonable to assume that perhaps hypothermia could be protective. Indeed, it is becoming increasingly clear that induction of mild hypothermia (lowering of body temperature to between 32°C and 34°C) in the hours following injury can be neuroprotective, particularly in patients with post-anoxic injury. Hypothermia can be applied in numerous clinical situations; it has been used to decrease intracranial pressure (ICP) in patients with traumatic brain injury or ischaemic stroke, to mitigate myocardial injury following myocardial infarction, to reduce the inflammatory response in ARDS, and in numerous other situations.

However, positive effects of hypothermia have been most convincingly demonstrated in patients with global post-ischaemic brain injury. Two multicentred RCT's have shown improved outcomes associated with cooling in newborn babies with post-anoxic injury due to perinatal asphyxia; two RCTs have shown benefits in adult patients who remained comatose after a witnessed cardiac arrest, who had an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT). Regarding the latter category, the European Resuscitation Council (ERC) has recently incorporated the use of induced hypothermia in selected patients following cardiac arrest into the ERC guidelines for resuscitation.

Growing Potential Indication for Induced Hypothermia

In the United States around 400,000 patients per year have a cardiac arrest. The number in Europe is similar. Between 20% and 38% of these patients have VF or VT as the first recorded rhythm. With appropriate emergency care around 70% of these patients can reach the hospital alive. Thus the group of patients with a potential indication for induced hypothermia is fairly large, particularly if all cardiac arrest patients admitted to the ICU were to be treated with induced hypothermia, as is the current policy in most units already using hypothermia as a medical treatment. Calculations regarding the number needed to treat (NNT) to achieve one additional patient with favourable neurologic outcome have put this number at six. This figure is likely to be conservative, since in the above-mentioned studies the time intervals until initiation of cooling and achievement of target temperature were relatively long (eight hours in the largest adult study, six hours in the neonatal studies). The effects of hypothermia are likely to be greater if treatment is started earlier and cooling rates are faster.

Cost-Effectiveness of Induced Hypothermia

Using the NNT of six as a basis for calculations, hypothermia treatment appears to be highly cost-effective in most settings. The prices of the

currently available cooling devices range from €10.000 to €48.000, roughly comparable to the price of a mechanical ventilator. The efficacy of the different cooling devices varies considerably; efficacy can be judged based on:

- Speed of cooling;
- ability to maintain target temperature within a narrow range;
- ability to achieve slow and controlled re-warming; and
- absence or low frequency of side effects.

Furthermore, most cooling devices use disposable materials such as surface cooling pads or intravascular catheters to cool patients while one device uses partly re-usable cooling pads. The prices for these disposable materials range from €90 to €800 per patient.

Increased Workload Impacts Cost-effectiveness

The cost-effectiveness of cooling devices should not be judged solely on the basis of their purchase price and the price of the disposables. The associated workload of the medical and nursing staff is of equal and perhaps even greater importance. The amount and type of workload required for effective use of the cooling devices that are commercially available varies considerably. Which device is most appropriate and cost-effective, depends strongly on the specific setting.

In this regard, there will be considerable differences between low-volume and high-volume ICUs. High-volume units may simply be large hospitals with a large number of ICU beds, and/or units that treat many patients with hypothermia, perhaps for different indications. Units that use cooling devices for indications other than cardiac arrest, to treat patients with traumatic brain injury or to control fever in patients with neurological injuries, will usually need more than one cooling device, as these patients usually require treatments of longer duration.

Conclusion

Naturally, the costs per patient will vary considerably, and will be determined by the factors listed above. For high-volume units a relatively expensive device, with cheaper disposables, may be the best choice, whereas a low-volume unit may opt for a cheaper device with more expensive disposables. Depending on the volume of patients, the costs per patient may vary from €1000 per patient in a very low-volume setting to less than €200 per patient in high-volume units. With an NNT of six for one additional patient with favourable outcome, without an increase in the length of stay, it becomes clear that hypothermia is indeed one of the most cost-effective treatments currently available in intensive care.

Even when using the price at the top end of the range above to calculate the overall costs, this would require an investment of €6000 to save one patient; the price per quality-adjusted life-year would still be less than €900. This compares highly favourably with many routine interventions in the critical care setting. As the actual price per patient will be significantly lower in most settings, cooling devices are undoubtedly a worthwhile investment.

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