



Editorial

Predicting neurological outcome in post cardiac arrest patients treated with hypothermia

Early prognostication after cardiac arrest is challenging. Accurate prediction of likely outcome is required to avoid withdrawal of treatment in patients who may go on to have a good neurological outcome, or to prevent ongoing futile life support. Therapeutic hypothermia (TH) has been shown to improve neurological outcome in comatose patients after cardiac arrest and its use has been widely adopted in intensive care units.^{1,2}

In 2006, the American Academy of Neurology (AAN) published guidelines on prognostication after cardiac arrest but most of the included studies predate the routine use of TH.³ The guidelines identified three reliable methods for identifying a poor prognosis: clinical examination (3 signs: absent corneal reflexes or absent pupillary reflexes or extensor (M2) or absent motor response (M1)), a raised serum neuron-specific enolase (NSE) ($>33 \text{ mcg l}^{-1}$) and absent N20 on somatosensory evoked potentials (SSEPs).

In this issue Bisschops et al. present their retrospective review of 103 patients treated with TH after cardiac arrest.⁴ The combination of M1 or M2 and absent pupillary responses to light and absent corneal reflexes was invariably associated with an unfavourable outcome but because it occurred in only 14.9% of patients the authors consider it to be of limited value. By day 3, 11.1% of patients with a favourable outcome still had at least one of the above clinical features and on this basis the authors question the reliability of the 2006 AAN prognostic guidelines in patients when treated with TH.

Clinicians need to understand the limitations of the current evidence. The confidence intervals (CI) on a false positive rate (FPR) for a prognostic test are simply a reflection of the sample size. If there are no false positives, the upper limit of the 95% CI can be estimated roughly as $3/n^5$; for example, if there are no false positives among 50 patients the upper limit of 95% CI will be $3/50 = 6\%$.

The AAN guideline for serum markers is based on a single level 1 study of 231 patients with no good outcomes in the 60% of patients with an NSE of greater than 33 mcg l^{-1} , a FPR of 0% CI 0–3%.⁶ More recently, Steffen et al. found that a much higher cut off value of NSE ($>78.9 \text{ mcg l}^{-1}$) was required to give a FPR of 0% in a single study of 97 hypothermia-treated patients.⁷

The AAN guideline for use of SSEPs suggests using the absence of N20 response as a marker of poor prognosis. Based on a meta-analysis of 8 studies they found an FPR of 0.7% (CI 0–3.7%). Since then, the absence of N20 response was reassessed with TH. In one study, SSEP was done during TH with an FPR of 0% (CI 0–8%),⁸ and in another, SSEP was repeated after TH giving an FPR 0% (CI 0–30%).⁹ Of concern, in a recent series of 36 patients with an absent N20 after TH, one patient survived with intact cognitive function.¹⁰

Myoclonic status epilepticus is associated with a poor prognosis (AAN FPR 0% CI 0–8%) and the rare cases with a good outcome may in reality be cases of Lance–Adams syndrome, which is a different clinical entity often caused by a hypoxia-induced cardiac arrest rather than a primary cardiac arrest.^{11,12}

The use of clinical criteria has been investigated more thoroughly. The AAN clinical guidelines are based on three studies (one of which includes a few patients treated with TH) and suggest that any of the three signs above (motor score of M1 or M2, absent pupil responses, absent corneal responses) could be used to identify a poor prognosis. A recent prospective study after TH had strikingly different findings with a FPR of 24% for absent motor response to pain, and an FPR of 4% for incomplete recovery of brainstem reflexes at day 3.¹³

In the study by Bisschops et al., four of the 36 patients with a favourable outcome had at least one of the three clinical signs at day 3.⁴ However, it should be noted that two of those patients were still sedated when they were assessed. The presence of all three signs together at day 3 reliably predicted poor outcome but this occurred infrequently (14.9% of patients) resulting in a low sensitivity. All patients with all three clinical signs at day 3 were considered to have a poor prognosis and treatment was withdrawn which made a poor outcome a self-fulfilling prophecy.

The predictive value of combinations of any two components was not assessed. Bisschops et al.⁴ suggest that clinical examination is of little value in predicting outcome but, despite this, it will identify accurately a proportion of patients with poor outcome. Out of 103 patients studied, 36 had a good outcome. Of the other 67 with a poor outcome, 10 had all three neurological signs (motor score M1 or M2, absent pupil responses, absent corneal responses) and treatment was withdrawn. Of the remaining 57, 55 died in hospital and two ended up in long-term nursing care.

It is not clear whether TH alters the time course of clinical and electrophysiological examination findings. Therapeutic hypothermia may result in depressed neurological function, delayed sedative clearance or improved outcome for a given early clinical pattern. A trial assessing application of the above criteria at days subsequent to day 3 is needed but will be difficult to conduct and result in increased financial cost and emotional burden on families.

A pragmatic approach is therefore needed pending further research. Patients should be assessed once re-warmed and no earlier than day 3 post cardiac arrest. If they have absence of both pupil and corneal reflexes and extensor (M2) or no motor response (M1) then withdrawal should be considered. If true myoclonic status

epilepticus is confirmed then withdrawal should also be considered. The remaining patients are more complex. A proportion will either obviously clinically improve or die despite treatment. In a small proportion of survivors the prognosis will remain unclear and in these patients a decision needs to be made in conjunction with relatives to determine at what point treatment withdrawal should be considered.

Worldwide there are cultural differences that influence the treatment of patients after cardiac arrest. In Japan, treatment withdrawal is less likely to occur^{14,15} and outcomes after cardiac arrest might provide an insight into prognosis in patients in whom treatment is withdrawn in the UK, Europe or the USA. More studies are required to improve outcome prediction in cardiac arrest treated with TH and these trials will be challenging to conduct. A difficult ethical debate is needed to balance the risk of severely disabled survival against the risk of withdrawal of treatment in a potential neurologically intact survivor.

Conflicts of interest statement

None declared.

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20 March 2011