Evoked Potentials and the Prognosis of Comatose Patients Receiving Intensive Care

Whilst death is relatively easily identified, its prediction on an individual patient basis during the course of critical illness is more complex. In a hospital setting, anticipating death allows the carers to advise the patient and their loved ones of the prognosis, to withdraw futile, burdensome treatment and to implement end of life care pathways. In comatose patients clinical observation forms the basis of prognostic predictions but is prone to error; for example the widely used Glasgow Coma Scale (GCS), really a clinical measure of consciousness, can be unduly pessimistic.[1] A systematic review of 1,914 comatose survivors of cardiac arrest found five clinical signs which strongly predict death or poor neurological outcome: absent corneal reflexes, absent pupillary response, absent withdrawal response to pain, no motor response at 24 hours, and no motor response at 72 hours, but none which strongly predicted a good neurological outcome.[2] The prediction of good outcomes is perhaps equally important, particularly in identifying those survivors of coma who will require intensive neurorehabilitation. Over the last 25 years there have been many attempts to improve prognostication by adding electrophysiological and biochemical measures of functional integrity and neuronal damage, respectively. Is it time then to introduce such measures into routine clinical practice?

Electrophysiological assessment of the central nervous system initially concentrated on the electroencephalogram and short latency evoked responses, in particular the somatosensory evoked potential (SSEP), whilst latterly investigators have evaluated long latency event related potentials (ERPs), such as the P300 and mismatch negativity (MMN).[3] The assumption is that their detection reflects functional integrity of cerebral neuronal pathways, which are not accessible to the brainstem-focussed clinical examination, and may therefore provide early indications of the potential for neurological recovery and cognition (see reference 4 for a review). In contrast to the GCS, they are not measures of consciousness per se and it is important to emphasise that they provide complementary information to clinical observations. It has recently been elegantly demonstrated by imaging studies, in this and other journals, that there are 'islands' of preserved cerebral function in patients who are unresponsive.[5] Electrophysiological probing of these islands may indicate higher levels of information processing which underpin awareness and responsiveness if not consciousness itself, although of course information processing alone is not consciousness as such. What then is the evidence for the clinical application of evoked and event-related potentials?

We have the benefit of a number of systematic reviews of the significance of bilateral absence of SSEPs in both traumatic and non-traumatic coma 24 hours after onset.[6,7,8] It appears that the bilateral absence of short latency cortical potentials is very nearly 100% specific for prediction of a poor outcome (defined as death or persistent vegetative state)[6] after hypoxic ischaemic and intracranial haemorrhagic insults, but is slightly less predictive after traumatic brain injury (TBI), particularly in children.[7] Indeed after TBI as many as 12 patients out of 777 had favourable outcomes (good or moderate disability) despite bilaterally absent SSEPs.[8] This observation has been detailed in a number of case reports of patients making good recovery after both anoxia and TBI, where barbiturate coma or raised intracranial pressure may have contributed to the loss of cortical responses.[9,10] Clearly this gives cause for concern, especially when poor prognoses tend to become self fulfilling, and demonstrates a need for the judicious use and timing of evoked potential recordings. However, this is true for clinical observations alone and it seems that the predictive value of SSEPs is superior to clinical tests,[11] and can be predictive of a poor outcome even when brainstem function is preserved after anoxia.[12] Indeed the American Academy of Neurology has endorsed the use of SSEPs (with a level B rating) in a decision algorithm for prognostication of comatose survivors after successful cardiopulmonary resuscitation.[13] Perhaps of greater consequence than medication effects, which can potentially be reversed, is that a multicentre trial revealed that there was only moderate interobserver agreement on the interpretation of evoked potentials.[14] Furthermore, although the absence of short latency responses is a poor prognostic feature, their presence does not guarantee the return of consciousness or survival, and we must look to other electrophysiological probes.[15]

Long latency event related potentials (ERPs) have been the subject of several reviews,[16,17] and the findings of one meta-analysis are now known.[18] This analysis pooled data from 10 studies of patients in coma and other low responsive states (GCS <12) of various aetiologies in order to estimate the predictive power (odds ratio, OR, and its confidence limits, CI) of several ERPs measures (see Table).[18] Since the greater the value of the OR (or more precisely the lower limit of its CI) indicates that presence of the ERP component is a significant predictor of awakening, the P300 would seem to be the test of choice. Indeed P300 was the original ERP component reported in four patients who recovered from traumatic coma,[19] which was subsequently confirmed in a large cohort.[20] However, MMN is an automatic process in both sleep and wakefulness whilst P300, in the awake state at least, is modulated by arousal and attention, which clearly can be neither controlled nor assessed in an unresponsive patient. It was largely this potential confounding factor that encouraged investigators to assess the automatic preattentive MMN auditory novelty detection mechanism, and which may account for its apparent greater specificity (91% versus 77% for P300).[18] The presence of MMN has been shown to be predictive of awakening from both acute traumatic and non traumatic coma,[3,21,22] and the vegetative state.[23] Unfortunately its presence has also been seen to falsely predict a favourable outcome (in 16 out of 460 patients).[18] As with short latency responses we are uncertain of the interaction of MMN with sedating agents, and indeed it has been shown to be attenuated by deep sedation with propofol.[24] Its absence is uninformative of prognosis.

In conclusion, there is evidence that both evoked and event related potentials could help refine clinical predictions of outcome from coma. It is fair to say that evoked potential recordings are reliable predictors of poor outcome and are inexpensive, non-invasive tests that can be safely recorded at the patient's bedside. The neurophysiologist

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Table of Odds Ratio with Confidence Intervals (CI) for prediction of survival by various Event Related Potential (ERP) components from pooled data.

ERP component	Odds Ratio (OR)	95% CI	Patient Number
N100	2.85	1.91-4.27	548
MMN	6.53	3.55-12.01	470
P300	8.79	4.88-15.83	313

needs experience to be aware of certain caveats in their clinical application, and in spite of being widely available throughout the UK are probably under-utilised. My own telephone survey of 20 Clinical Neurophysiology departments across England and Wales revealed that all bar one regularly record EEGs in Intensive Care Units, but only five ever record evoked potentials, with just two recording them on a fairly frequent basis. Although in their infancy event-related potentials have shown some promise in heralding awakening and favourable neurological prognoses, and can therefore complement evoked potentials. ERPs are more complex in both their recording technique and interpretation, and will require further evaluation before clinical utility can be achieved. The inherent false positive rates may of course limit the use of electrophysiological predictors of outcome in coma, which is generally a self-limiting condition.

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