

Does myoclonus following a cardiac arrest indicate a poor prognosis?

Myoclonus is characterised by sudden, brief and involuntary muscle contractions that may involve a part or all of the body. It can occur in response to sensory stimuli, voluntary movements or spontaneously at rest. It is a symptom that occurs in a variety of metabolic disorders (e.g. chronic renal failure, hepatic failure, respiratory failure or electrolyte imbalance), central nervous system disorders (e.g. lipid storage disease, encephalitis, Creutzfeldt-Jakob disease, ischaemic and anoxic brain injury) and in certain types of epilepsy. In the critically ill patient, apart from isolated myoclonic jerks and muscle contractions associated with focal or generalised seizures, myoclonic jerks are most often seen following cardiopulmonary resuscitation.

Myoclonic status is a well recognised consequence of brain ischaemia secondary to cardiac arrest. The patients are deeply unconscious and the myoclonic jerks usually begin within 12 hr of the cardiopulmonary arrest and last for up to 48 hr. They involve the adductors of the thighs, flexors of the arms, and facial muscles (with intermittent grimacing and eye opening with an upward gaze) and are characteristically resistant to therapy. The patients have burst suppression EEGs and CT scans that may demonstrate cerebral oedema (e.g. loss of gray matter-white matter differentiation) with or without infarction (classically of the watershed areas). The disorder is a particularly poor prognostic sign^{1,4} as it predicts a permanent vegetative state or death in more than 90% of survivors of cardiopulmonary resuscitation.^{5,6} Accordingly, its presence in post cardiac arrest patients who remain comatose often influences the decision to withdraw life support.¹

However, myoclonic status must be distinguished from post-hypoxic intention (or action) myoclonus which, particularly with sedation, may appear as myoclonus status with persistent coma.⁷ This syndrome is highlighted in the three cases that are described in this issue of the journal.⁸

Post-hypoxic intention myoclonus is a disorder that occurs predominantly as a sequel to cerebral anoxia (e.g. during an hypoxic cardiorespiratory arrest secondary to asthma, anaesthetic accidents, airway obstruction or airway abnormalities).⁹ While it has features that may indicate early myoclonic status,^{10,11} it

usually presents after the patient regains consciousness as an intention myoclonus (i.e. a series of irregular myoclonic jerks that are elicited when a limb is moved voluntarily). It only involves the limb that is moved and is often associated with cerebellar dysfunction involving the extremities, facial muscles and even the voice. The myoclonus is usually self-limiting, although prolonged episodes may require treatment with valproic acid.¹² While it can occur following a cardiorespiratory arrest,^{13,14} it is believed that the cerebral lesion is reversible and caused largely by metabolic changes initiated by hypoxia (before the cardiac arrest) which limit brain damage and favor recovery.¹⁵ The disorder is known as Lance-Adams syndrome.¹⁶

Experimentally, unlike an ischaemic insult, near-lethal hypoxia does not cause brain damage,^{17,18} with the pathophysiology of hypoxic brain injury being distinct from that of ischaemic brain injury.¹⁹ The reasons probably relate to hypoxia-induced alterations at the neurochemical and synaptic levels (with selective GABAergic deficiency),^{20,21} without irreversible selective or generalised neuronal infarction. The mechanism of the cerebral protective effect during hypoxia is unknown although in the absence of cardiac arrest, hypoxia is associated with an increase in cerebral blood flow thereby maintaining oxygen delivery and in addition may remove waste products that cause cerebral damage (e.g. lactic acid). Clinically, this is often confirmed with well documented cases existing of complete neurological recovery following up to 2 weeks of coma in patients who suffered extreme hypoxia.^{22,23} Nevertheless, hypoxia will exacerbate ischaemic necrosis,¹⁸ and in patients who have severe hypotension or a cardiac arrest following an hypoxic episode, cerebral infarction does occur.

Clinical examination within the first few days following a cardiac arrest can be difficult as the patient may have been heavily sedated or paralysed. Prognostically, somatosensory evoked potentials (SSEP) performed within 24 hr after cardiac resuscitation have been used to predict a persistent vegetative state.^{24,25} In one study of 66 patients who were successfully resuscitated from a cardiac arrest, cortical evoked potentials from 4 - 48 hr after the cardiac arrest identified a successful outcome in 100% of patients.²⁶ However, as absent scalp potentials are uncommon, some believe that SSEP may not be consistently useful.²⁷

While a CT is often performed, visual assessment of loss of gray matter-white matter differentiation (GWMD) is not reliable as a predictor of poor outcome or death after cardiac arrest.²⁸ Nevertheless, one study found that the Hounsfield unit density of GWMD at the basal ganglial level (i.e. Hounsfield unit ratio of caudate gray matter to posterior limb of the internal capsule

white matter of < 1.18 at the basal ganglial level) was 100% predictive of death in patients who remained comatose following a cardiac arrest.²⁹ In another study of patients who remained comatose after cardiac arrest, with intact brain stem reflexes and without myoclonic status, magnetic resonance imaging using fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted (DW) imaging, detected diffuse and extensive abnormalities of the basal ganglia, cerebellum and cortex in patients who remained in a coma, whereas those who awakened had normal or only localised findings. In this study, none of the patients who underwent electrophysiological tests showed abnormal median SSEP.²⁷

Where does this leave the clinician who has resuscitated a patient from a cardiac arrest and who 12 hours later shows signs suggestive of myoclonic status? It would appear that prognostication is still not easily achieved in less than 72 hours.^{30,31} Thereafter, in the absence of muscle relaxants and sedative agents (the effects of which may be assessed using a peripheral nerve stimulator and minimised using neostigmine, naloxone or flumazenil), if the patient is comatose with no response to pain and CT (or MR) scans reveal cerebral oedema with or without infarction, the prognosis is poor and withdrawal of therapy should be considered. However, if the patient demonstrates an appropriate motor response to pain (e.g. Glasgow coma scale, motor 4 or greater) and CT or MR imaging reveal no generalised cerebral damage, treatment should be continued.

Dr. L. I. G. Worthley
Department of Critical Care Medicine
Flinders Medical Centre
SOUTH AUSTRALIA 5042

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Dangerous manoeuvres?

The recommended treatment for termination of a regular narrow complex tachycardia in a haemodynamically stable patient is the application of a vagotonic manoeuvre, such as Valsalva, followed by intravenous adenosine if the tachycardia persists.¹⁻³ Vagal manoeuvres prolong atrioventricular (AV) nodal conduction time and shorten the atrial refractory period, as does adenosine.⁴ It is the latter action which is thought to be responsible for precipitating atrial fibrillation (AF) on occasions.⁵

Atrial fibrillation can result in severe haemodynamic compromise in patients with an anterogradely conducting accessory pathway such as Wolff-Parkinson-White (WPW) syndrome, by inducing a very rapid ventricular response, over 300 beats/minute on occasions. Adenosine administered to such patients may further enhance conduction through the bypass tract,⁶ which may cause haemodynamic collapse or ventricular fibrillation.

In this issue of *Critical Care and Resuscitation*, Nagappan *et al.*,⁷ report a serious pro-arrhythmic complication in a young female presenting with a regular narrow complex tachycardia. A Valsalva manoeuvre may have precipitated AF with ventricular pre-excitation. This is a rare complication and spontaneous transformation from AV re-entry tachycardia (AVRT) to AF is also well described. The patient's clinical condition deteriorated after the administration of adenosine. Serial ECGs demonstrate AF with increasing pre-excitation and increasingly rapid ventricular rates. Presumably adenosine blocked anterograde AV conduction, while at the same time enhancing conduction

through the accessory pathway. Shortly after adenosine was administered, the patient became haemodynamically unstable and developed ventricular fibrillation requiring multiple DC shocks for restoration of sinus rhythm. A subsequent ECG demonstrates classical features of WPW with a right posteroseptal accessory pathway. Interestingly, all ECG traces while the patient was in AF were consistent with a right posterior septal accessory pathway. A similar clinical situation has been reported previously by Exner *et al.*⁸ They described a patient with an irregular wide complex tachycardia, not recognised as AF with accessory pathway conduction, who developed ventricular fibrillation immediately after 12 mg of adenosine. Administration of intravenous procainamide or ibutilide (i.e. drugs that prolong refractoriness in the accessory pathway and revert atrial fibrillation) is the treatment of choice.⁹

There are several important lessons to be learned from this case report:

- a) Always review previous ECGs if available (this was not possible for Nagappan's patient).
- b) All patients given intravenous adenosine should be in a facility capable of providing advanced life support including electrical cardioversion and defibrillation. If patients are known to have WPW, then adenosine can still be given for a regular narrow complex tachycardia but most importantly, if AF is induced, further adenosine is absolutely contraindicated as are calcium channel blockers such as verapamil.¹⁰ Should AF cause haemodynamic compromise, then electrical reversion should be undertaken immediately, otherwise, intravenous procainamide or ibutilide (currently not available in Australia) should be administered to slow the ventricular rate and possibly pharmacologically cardiovert the AF.⁹
- c) What about vagal manoeuvres, such as Valsalva? Should we avoid these in all patients with a regular narrow complex tachycardia unless a previous electrophysiological study excludes an anterogradely conducting accessory pathway? Clearly, the answer is no. A reasonable course of action is to treat these patients in a facility capable of dealing with malignant arrhythmias (i.e. emergency department, intensive care, coronary care, etc.). If AF is precipitated and the patient is stable then adenosine and/or calcium channel blockers should be avoided and either procainamide or ibutilide given. If one is concerned that procainamide may precipitate hypotension then intravenous amiodarone is a reasonable alternative. Here we are considering the management of a regular narrow complex tachycardia in the hospital setting, but what should patients be told regarding vagal manoeuvres out of hospital? Many patients will already have discovered a vagotonic

manoeuvre for reverting their arrhythmia. A cautionary note would be appropriate if vagal manoeuvres have not been used before. It may be prudent to warn any patient with WPW and episodes of AV re-entry tachycardia, of the remote possibility of faster arrhythmias being provoked if vagotonic manoeuvres are used. Such a patient could be advised to present to hospital, so that vagotonic manoeuvres being used for the first time are performed in a safe environment.

Dr. K. D. Donovan
Intensive Care Unit
Royal Perth Hospital
WESTERN AUSTRALIA 6000

Assoc. Professor B. E. F. Hockings
University of Western Australia
Sir Charles Gairdner Hospital
WESTERN AUSTRALIA 6009

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Management of brown snake envenoming

Snakebite is not a rare event in Australia, with around 1,000 to 1,500 cases per year, of which 100 - 250 receive antivenom. However, spread across many hundreds of hospitals, few doctors can expect to see more than 2 - 3 cases each year. For some snakes, notably brown snakes of the genus *Pseudonaja*, the rate of significant bites is low, around 20% of cases. It is therefore difficult to conduct trials of treatment for snakebite in Australia and also for one to develop and maintain clinical skills in toxinology. Yet despite these impediments, severe snakebites do occur and require early competent management to optimise outcomes. A solution is a system of experts on call, through the Poisons Information Centres, on the national number, 13 11 26. This, combined with clinical toxinology training courses held in Adelaide, is used to provide a growing cadre of "experts" in diagnosis and treatment of envenoming.

The cases reported by Dr. Simes¹ in this issue of the *Journal* illustrate several issues in the understanding of snakebite. Both cases were categorised as brown snake bites on the basis of venom detection. The clinical pattern would support this diagnosis. Diagnostic algorithms have been developed for Australia, based on the observed characteristics for bites by major snakes. These algorithms are widely available and appear in the new edition of the CSL antivenom handbook.

Brown snakes, now considered the leading cause of snakebites and snakebite deaths in Australia, typically cause minimal to mild local effects and rapidly develop defibrination coagulopathy with some cases also developing renal failure. Myolysis never occurs and paralysis is very rare and seen only in cases where there has been a long delay before receiving antivenom therapy. The coagulopathy is caused by potent venom procoagulants. Outside the protective environment of a platelet plug, prothrombin is converted to thrombin, and fibrinogen is converted to fibrin, which starts to cross-link. There is a brief period at the outset, perhaps lasting only a minute or so, where thrombi can form and cause temporary occlusion of vessels. It is thought that this may explain the rapid onset of cardiac collapse in fatal cases of brown snake bite. Thrombolysis is also quickly activated, so that any thrombi are rapidly destroyed. Thereafter, as fast as fibrinogen is converted to fibrin, it is destroyed, resulting in complete defibrination. This whole process can develop and mature in 10 - 15 minutes from the time venom reaches the circulation. Once totally defibrinated, the patient is at risk of catastrophic bleeding. The absence of haemorrhagins in

the venom reduces the likelihood of such bleeds, but intracranial bleeding is a common cause of Australian snakebite fatalities.

The early and effective management of defibrination after snakebite is clearly crucial in ensuring an optimum outcome for the patient. This is especially true for brown snake bites where defibrination is the principal effect. Only antivenom can neutralise the defibrinating process by removing active procoagulant venom toxins. For any brown snake bite patient with a coagulopathy, the starting dose of antivenom is at least 4 - 5 vials intravenously, with an expectation that another 4 - 6 vials may be needed. For brown snakes likely to inject larger quantities of venom, such as dugites and gwardars in south west Western Australia, a more substantial initial dose may be justified; some local experts have suggested as much as 10 vials for the initial dose.

The accepted management for snakebite coagulopathy is to give an appropriate initial dose of antivenom only, wait at least 3 hours, then re-test plasma coagulation parameters to determine if there has been a response. The response looked for is a rise in the fibrinogen level, not a return to normal values, as the latter will take many hours. If the fibrinogen has increased from essentially zero to detectable levels, then the venom-induced coagulopathy process has been switched off and no further antivenom is required. Further coagulation testing should be repeated after another 2 hours, to confirm the rise in fibrinogen, as it is possible for more venom to enter the circulation late. If the fibrinogen has fallen again, more antivenom is needed. If the fibrinogen has remained static, but still low, it may indicate either a very low level of venom reaching the circulation, or a failure of fibrinogen production. The safest course in this setting is to give further antivenom. If, after several hours, it is clear that fibrinogen has risen but is still at low levels, suggesting that all venom has been neutralised but that fibrinogen production is too slow, then it is reasonable to consider replacement therapy with cryoprecipitate, fibrinogen concentrate or fresh frozen plasma. If any of these products are used while venom procoagulant is still circulating, then they merely become fuel for the defibrination fire, exacerbating the hyperfibrinolysis that occurs and may actually make the coagulopathy worse. The kidneys are involved in clearing the breakdown products of defibrination; therefore the higher load imposed by injudicious use of replacement therapy may exacerbate renal injury. Indeed, the only situation where replacement therapy would be justified before full neutralisation of all venom has been achieved, is in a patient with severe or catastrophic bleeding. Even here, it is doubtful if such treatment would be successful.

In some patients with defibrination coagulopathy, the initial dose of antivenom will prove insufficient, such that the coagulation tests taken 3 hours after the anti-venom infusion has finished will show no significant change in fibrinogen level. In this situation, the correct treatment is to give further antivenom and not replacement therapy with cryoprecipitate or similar. Again, after this dose of antivenom, which in most cases will be similar to the initial dose (i.e. 3 - 5 vials), repeat the coagulation tests after 3 hours to determine if the fibrinogen level has risen. If it has, repeat tests after another 2 hours to check that the level has continued to rise. Only rarely will it be necessary to keep repeating this process through many cycles, thus total antivenom doses should rarely, if ever, reach the figure of 25 vials that were used by Dr. Simes, in his first case.

The principle issue raised by Dr. Simes in his paper concerns the value of prolonged use of pressure immobilisation first aid. Dr. Simes suggests that keeping this first aid bandage in place for a prolonged period of many hours will have no deleterious effects, because Australian snake venoms do not cause local tissue damage. This is correct for brown snakes, but incorrect for some other species, notably tiger snakes, where prolonged use of first aid has caused local necrosis. There is also no conclusive evidence to support a belief that immobilising snake venom at the bite site inactivates the venom.

It is clear that for each case of snakebite, many factors influence the extent and degree of envenoming. For example, there are variations in venom composition, not just between species of snakes, but within species and even within an individual snake over time. Therefore, the exact nature and degree of envenoming will vary from case to case. It follows that comparisons between cases must be approached with great caution and that Dr. Simes' conclusion, based on 2 cases, that prolonged use of first aid may be beneficial, should be taken as an interesting observation and not a general recommendation. In the report it is unclear if the level of envenoming was similar in each case. As defibrination was the end point for venom-induced coagulopathy and can occur even with small amounts of venom, it may be that case 1 had far more venom injected than in case 2, requiring higher doses of antivenom. It might also be that the snake in case 1 had procoagulants in the venom which were less well recognised by the antivenom than for case 2, thus necessitating higher doses of antivenom. In case 2, the first aid was applied promptly, but envenoming developed anyway. It is quite possible that the first aid in this case was ineffective, especially since no re-envenoming occurred after its removal and symptoms of envenoming were apparent prior to its initial application

The patient in case 1 was a diabetic; it is uncertain how this may have influenced the severity of envenoming. It is also unclear if the first aid was effective in this case, because there was evidence of envenoming prior to removal. The initial dose of antivenom was low in this patient, which might also have contributed to a more protracted course of therapy.

Concerning the management and diagnosis of Australian snake envenoming: a copy of the CSL antivenom handbook may be obtained from a CSL Ltd representative. In addition to providing clinical information, this book also lists other major references, which in turn lead to the wider toxinology literature. The internet site, www.toxinology.com (scheduled to launch in June 2002) will also provide further information.

Professor J. White
Department of Toxinology
Women's and Children's Hospital
SOUTH AUSTRALIA 5006

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Hypothermia as therapy in cerebral injury

In the last few years a series of randomised controlled trials have reported the use of therapeutic mild hypothermia (33°C to 35°C) in two groups of patients: a) post cardiac arrest,^{1,2} and b) acute traumatic brain injury.³⁻⁷ Therapeutic hypothermia was reported to produce improved outcomes in group a) but not uniformly in group b); or rather the "definitive" large-scale trial, 392 patients,⁴ in group b) was unable to demonstrate benefit. Editorial response to these trials differed from endorsement in the case of post cardiac arrest,⁸ to analysis of potential reasons for lack of response in the case of traumatic injury.⁹ What are the factors responsible for these disparities?

General perspectives

All trialists referred to the multifactorial mechanisms which may have been responsible for the protective effect of hypothermia. The non-effect of hypothermia in traumatic cerebral injury was explained in terms of potential differences in these mechanisms with respect to initiating injury.¹⁰ Outcomes in the trials were reported as deaths or scales of cerebral performance. Only one study¹ made specific reference to difficulties

in such assessments¹¹ and no studies reported inter-rater reliability studies of outcome assessment. Despite these potential problems, for all trials it was possible to classify outcome into "poor" (i.e. severe disability, both awake or unconscious, with institutionalisation or death) and "good" (i.e. normal or moderate disability) categories. Given this, it is noted that the normothermic control patients in both groups a) and b) had almost identical "poor" cerebral outcome percentages, at 67% and 60% respectively, suggesting, at least, common functional outcomes. Across the trials, cerebral outcomes were assessed at different times, from hospital discharge through 12 months post discharge. Evidence from one trial,⁶ where outcomes were reported at 3, 6 and 12 months, suggests that the proportion of "bad" outcomes may not have materially changed over this time ($p=0.09$, Fisher exact test).

Time to treatment

The time to reach the target hypothermia (however defined) has been thought to be a critical therapeutic factor, more so in explaining the lack of efficacy of hypothermia in traumatic cerebral injury.^{9,12,13} Over all the trials considered,¹⁻⁷ this target time varied from 2 to 15 hours (mean, 8.6 hours). Using meta-analytic methods (meta-regression, with a restricted maximum likelihood estimator),¹⁴ no linear relationship was demonstrated between log odds of poor cerebral outcome and time to target hypothermia in the 5 cerebral trauma trials ($p = 0.07$); with the outlier⁵ removed (time to target = 15 hours), $p = 0.4$. Similarly, no effect was demonstrated using individual patient data in the largest trial to date in cerebral trauma.^{4,15}

Centre effect

Heterogeneity between participating centres was suggested as a reason for non-effect of hypothermia in cerebral trauma,¹³ and Clifton *et al*,¹⁵ further reported on "inter-centre variance in treatment effect and outcomes" from the original trial.⁴ Such centre variation was thought to have reduced the "overall sensitivity" of the trial and treatment effect reversal was demonstrated for some centres. A considerable literature has accumulated on these issues,^{16,17} but as pointed out by Senn and Harrell¹⁸ and Peto,^{19,20} such heterogeneity (including effect reversal) is to be expected, purely by chance, and at a certain level, may always be demonstrable if the number of centres is at least 8. From the clinical perspective, heterogeneity with respect to such variables may not be a defect, rather a strength.^{20,21}

Baseline variables

All trials under consideration reported baseline variables between treatment groups. However, two points need to be made regarding this practice: with

appropriate randomisation, differences are due to chance and randomisation into treatment groups without bias does not necessarily lead to groups having "similar" baseline characteristics.²²⁻²⁴ It may be difficult to demonstrate "no" difference between groups, depending upon the number of covariates recorded and comparisons made and protocols for describing just which covariates to tabulate.²⁵ Moreover, variable tabulations are essentially marginal summaries and do not provide insight into the joint distribution of prognostic factors in treatment groups.²⁶

In the Clifton *et al* trial,¹⁵ specific mention was made of the unbalanced assignment of age groups and patients with spontaneous hypothermia to treatment groups (a previously unknown prognostic factor).²⁷ Bernard *et al*,¹ noted differences in percentage of males and bystander performed cardiopulmonary resuscitation between the two treatment groups. Again, this may have been by chance, or due to the atypical randomisation protocol which prescribed odd/even day allocation; circadian and seasonal variations in acute cardiovascular disease have been noted.^{27,28}

However, the question of balance between treatment groups relates not to the validity but to the efficiency of statistical inference.^{29,30} Thus, concerns expressed that such "unbalance" may have affected trial outcome¹³ are misplaced, to the extent that statistical analysis is not invalidated; rather the ability to derive conclusion from the results is affected.

Treatment effect: conditional versus unconditional estimates

Three studies also reported statistically adjusted treatment effect estimates on the basis of either perceived baseline differences between treatment groups or covariates related to outcome:

- a) On the basis of "slightly less severe" traumatic cerebral injuries in computer tomographic (CT) class (the patients being stratified on allocation to a Glasgow coma score (GCS) of 3 to 4 or 5 to 7), Marion *et al*,⁶ adjusted risk ratios (presumably equated with odds ratios) for treatment effect using initial GCS and CT class only. Over all trial patients, unadjusted and significant risk ratios for beneficial treatment effect at 3, 6 and 12 months post hospital discharge moved towards the null and became non-significant. For patients with a GCS of 5 to 7, adjusted risk ratios at 3 and 6 months (but not at 12 months) maintained statistical significance.
- b) In the Bernard *et al* trial,¹ the unadjusted estimate of "good" outcome, in the odds ratio metric was 2.65 (95% CI: 1.02 - 6.88; $p = 0.046$) and in the risk ratio metric 1.84 (0.97 - 3.49). That this estimate had borderline statistical significance is noted, especially as the study protocol details an unspecified and

apparently unblinded interim analysis at 62 eligible patients. The statistical consequences of such data inspections (especially if the interim treatment difference was examined) are known to inflate the probability of a type I error.^{31,32} That is, for 1 or 2 pre-planned interim data inspections, the nominal significance level required to achieve a "true" level of 0.05 (the type I error rate), are 0.03 and 0.021, respectively.³⁴ These figures refer to normally distributed data. Recent investigations in the sample size re-estimation (SSR) literature suggests that calculations for binary data are comparable.^{35,36} The adjusted (odds ratio) estimate via logistic regression, including only two covariates, age and time from collapse to return of spontaneous circulation, was 5.25 (95% CI: 1.47 - 18.76; $p = 0.011$).

- c) In the Hypothermia after Cardiac Arrest Study Group trial,² baseline differences were thought to be due to "random variation", but the risk ratio of six month "good" cerebral outcome "changed only minimally" with the addition of all recorded baseline covariates (risk ratios 1.40 (95% CI: 1.08 - 1.81) vs 1.47 (1.09 - 1.82) respectively). The unconditional odds ratio for "good" outcome was 1.89 (1.17 - 3.05).

That both the adjusted treatment estimate (odds ratio 5.25, equivalent to 2.4 as risk ratio) and its upper 95% CI (odds ratio 18.76, equivalent to 8.57 as risk ratio) in the Bernard *et al*,¹ trial was substantially greater than that of the numerically larger Hypothermia after Cardiac Arrest Study Group trial,² is cause for some comment. The small size of the trial, with relatively few events, is certainly one explanation, to the extent that treatment effects tend to be inflated in small positive trials.³³ Paucity of data/events may be surmounted by the use of exact inference or appropriate estimators.³⁸ In non-linear regression models with randomised studies, covariate adjustment tends to move the treatment effect estimate away from null and to have a variable, unpredictable effect upon the variance of that estimate, as opposed to the increase in precision seen with linear models.³⁴⁻³⁷ On the other hand, omission of balanced covariates, leads to bias in estimates of effect.^{36,38-40} Both trials,^{1,6} also appear to use post-hoc data-driven adjustments, in that the particular limited set of conditioning covariates selected were not pre-specified in methodology statements, as has been recommended;^{30,41-43} such approaches are also known to overestimate treatment effects.^{44,45} It is also uncertain if model selection was undertaken to derive adjusted estimates, such a strategy being problematic in randomised trials. This is not to suggest that one should necessarily condition on "all" covariates,⁴⁶ rather that covariates specified in the design phase are included in the model.⁵² If covariates are orthogonal to treatment, then standard errors of

treatment effects will be minimised.

Effect measures

Measures of effect were considered by the Hypothermia after Cardiac Arrest Study Group trial.² In particular, risk ratio estimates were derived from odds ratio using a transformation after Zhang *et al.*⁴⁷ That odds ratios do not approximate risk ratios, except with rare outcomes, and are often misinterpreted as risk ratios, needs to be reiterated,^{48,49} the latter are in fact available “directly” from multivariable regression estimators.^{50,51} The advantages of the various metrics (or scales) of treatment effect have been extensively discussed.⁵² The odds ratio has superior statistical properties and is the key parameter in the linear logistic model. The log odds scale is unbounded in both directions, but is numerically greater than the risk ratio when underlying event rates are frequent. Risk ratio is sensitive to small counts and is bounded above in a manner dependent on the control group risk. Although more intuitive as a measure than odds ratio, it has the peculiarity that the relative risk of dying is unrelated to that of surviving.⁵³ Risk difference is immediately intuitive and expresses the consequences of no therapy (unlike both odds and risk ratios), but is constrained from -1 to 1 and suffers from potential bias with varying time to follow-up which may also impact on the derivation of number needed to treat (NNT).⁵⁴ The Hypothermia after Cardiac Arrest Study Group provided estimates of NNT to prevent one unfavourable neurological outcome (NNT = 6; 95% CI 4 - 25), although the NNT has not been without its critics.⁵⁵

Specific focus, traumatic brain injury

As revealed by the title of the editorial accompanying the Clifton *et al* paper, “a good idea proved ineffective”,⁹ the efficacy of hypothermia in traumatic brain injury is not established. The total number of patients enrolled into the 5 trials was 673 and the primary cerebral outcome, as good versus poor, was only available at differing times post hospital discharge: 3 months (2 trials), 6 months (2 trials) and 12 months (1 trial). If we assume that these outcomes do not significantly change from 3 through 12 months (see above), then the pooled risk ratio (random effects estimator) for poor outcome was 0.88 (95% CI: 0.71 - 1.09; $p = 0.23$). Cumulative estimates,⁵⁶ are seen in Figure 1 in the log odds metric. Further, large positive outcome trials would appear to be necessary to establish significant efficacy.

Specific focus, post-cardiac arrest

The two trials in post cardiac arrest patients, yielded apparent positive treatment effects. Primary cerebral

outcome was not assessed beyond hospital discharge for the Bernard *et al* trial,¹ but there was no difference in the cerebral performance status in the subset of patients actually discharged alive (good versus poor outcome: 21/0 in the hypothermia group and 9/2 in the normothermia group; $p = 0.11$, Fisher exact). In the Hypothermia after Cardiac Arrest Study Group trial,² a similar result is obtained for patients discharge out of hospital and assessed at 6 months (good versus poor outcome: 64/20 in the hypothermia group and 42/24 in the normothermia group; $p = 0.11$, Fisher exact). The same results are obtained if we discount for deaths occurring after discharge (6 and 7 respectively; $p = 0.22$). Hospital deaths were characterised only in the Bernard *et al* trial,¹ and equal numbers of patients died in the two treatment groups (5 in the hypothermia and 4 in the normothermia group). No evidence was adduced that hypothermia was cardioprotective, in fact the tendency to hyperglycaemia in the hypothermia group of Bernard *et al*,¹ may be inimical.⁶³ In the Hypothermia after Cardiac Arrest Study Group trial,² the hospital death rate was improved with hypothermia ($p = 0.03$, Fisher exact), but we are given no information as to the causes of death.

The protective effect then is apparently manifesting itself by preventing “early” catastrophic non-cardiac (presumably cerebral) deaths, but with no impact upon the less severe forms of cerebral injury. Such would appear to be counter-intuitive, although there may be a confounding effect of small numbers and insensitivity of cerebral performance scales alluded to above. The impact of non-blinding of the studies exaggerating treatment effects, a point raised by the Hypothermia after Cardiac Arrest Study Group,² must also be considered. Furthermore, it is also apparent that in this trial up to 25% of recorded temperatures in the normothermic group were $\geq 38^{\circ}\text{C}$ for a number of hours. In the absence protocol statements as to what constituted “normothermia”, this may have been a source of bias in terms of eventual cerebral outcomes.

The question of what constituted appropriate effect size also needs clarification. Both trials reported preliminary studies where outcome rates were initially investigated; such studies are unfortunately known to have wide confidence intervals for control rates and may be unrepresentative:

- a) Bernard *et al*, in a pilot trial over the years 1993 to 1996, reported in 1997 a “good” outcome with therapeutic hypothermia in 50% (11 of 22) of patients compared with “poor” outcome in 14% (3 of 22) of historical controls (1991 - 1993) treated with standard measures. On the basis of this study, the initial sample size was set for a treatment effect

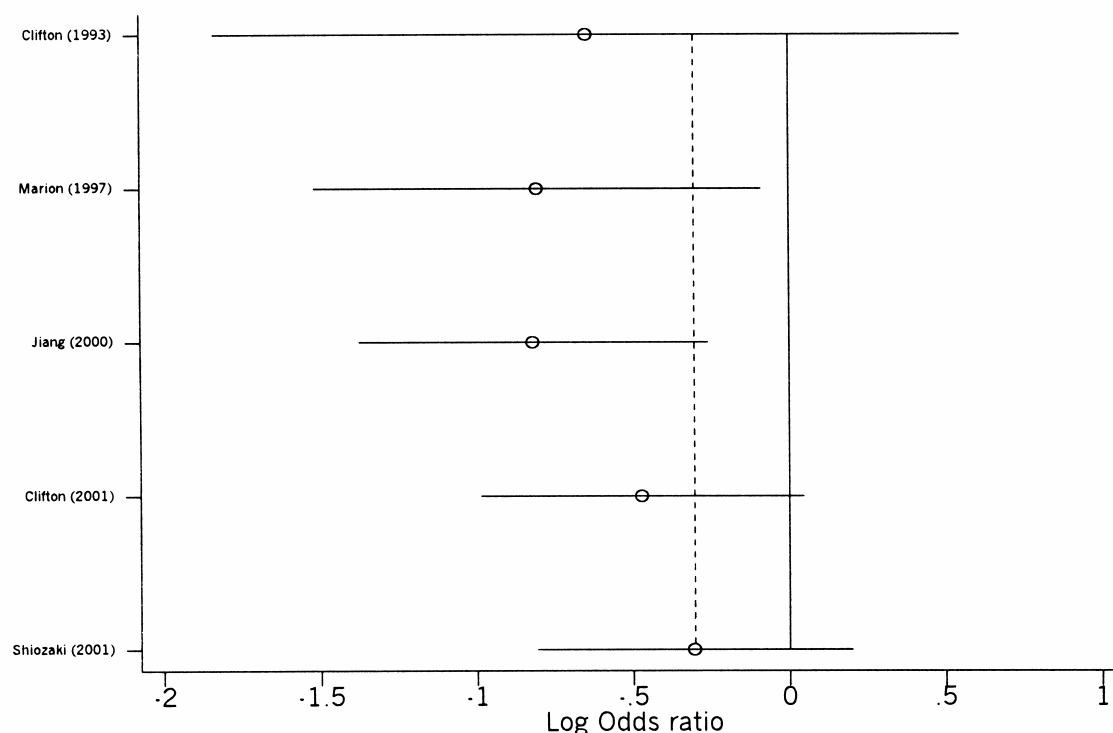


Figure 1. Cumulative meta-analytic estimate of therapeutic hypothermia on “poor” outcome in cerebral trauma. Vertical axis = trials in year order. Horizontal axis = treatment effect, log odds ratio. Solid vertical line = null effect (+ log odds ratio, “poor” outcome; - log odds ratio, “good” outcome), dashed vertical line = point estimate of final treatment effect. Horizontal lines = 95% CI of cumulative treatment effect for trials. Circles = point estimates of cumulative treatment effect.

of 36% at a power of 0.8; 31 patients in each group. This would appear to be a substantive treatment effect, given the known problems of estimating such rates using non-concurrent controls. The change over time in control rates may also be problematic and was evident in the prospective study, where the rate of good outcome in the normothermic group had almost doubled to 26.5%. To prevent underestimation of the sample size based upon an unrepresentative estimate of control rates (see above), Gould has recommended using the 75th percentile of the confidence distribution of the (population) variance. In this case, the 95% CI of the assumed underlying control rate (14%) is 3% to 35% and the 75th percentile would correspond to a control rate of 24%, much closer to the observed trial control rate of 26.5%. Under this scenario, the sample size to achieve a treatment group “good” outcome rate of 50% (corresponding to a treatment effect now of 24%) would increase to 61 in each group.

Evidence from four recent “positive” trials of therapy in the critically ill, suggests a treatment difference of 3.4% to 16% (average 8.7%), albeit for mortality. In the Bernard *et al* trial, the risk difference was 22.4% (95% CI: 13.2% to 43.4%) and the observed post-hoc power for the trial was

42%. However, such calculations are known to be methodologically flawed; what can be estimated is the precision of the (observed) difference for any given power and “clinically important difference”, after Goodman and Berlin. For a total sample size of 62, power of 0.8 and treatment effect of 36%, the predicted precision is $\pm 25\%$ and for a hypothesised 0% difference between treatments, the observed treatment effect in the trial (22.4%) is not excluded; that is, it is within the $\pm 25\%$ precision bounds. This uncertainty of effect is consistent with the p value of 0.06 for primary outcome by the Fisher exact test which is recommended in the current context of randomisation inference. On the basis of these analyses, plus the effect of the unspecified interim analysis (see above), the status of the “observed” treatment effect is questioned.

- b) The initial pilot study the Hypothermia after Cardiac Arrest Study group reported a good outcome at six months review with hypothermia in 52% (14 of 27) of patients versus 26% in unspecified historical controls. On this basis the trialists planned to enrol a total of 500 patients. In the prospective trial methodology statements, no sample or effect size was provided and enrolment was stopped at a total of 275 patients for ad-hoc reasons (lack of funding). The control rate for “good” outcome was also noted

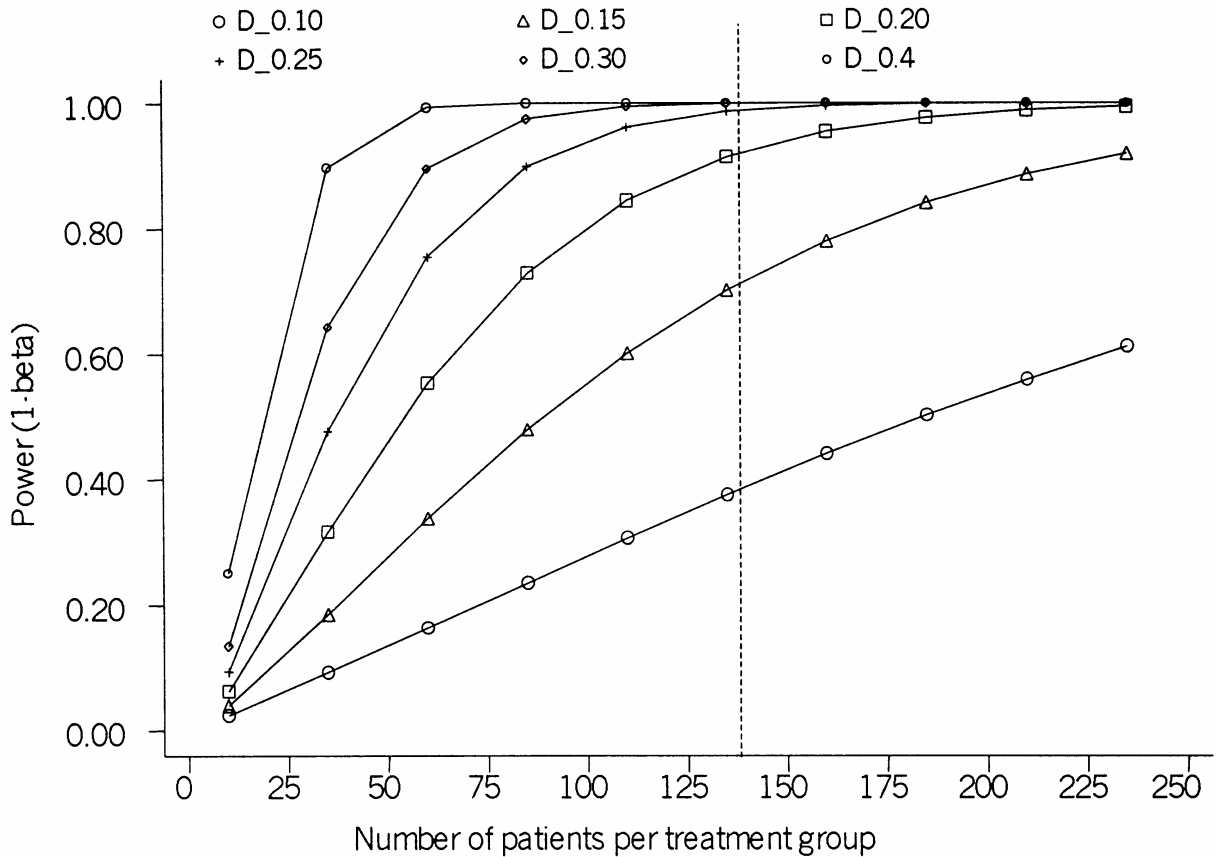


Figure 1. Cumulative meta-analytic estimate of therapeutic hypothermia on “poor” outcome in cerebral trauma. Vertical axis = trials in year order. Horizontal axis = treatment effect, log odds ratio. Solid vertical line = null effect (+ log odds ratio, “poor” outcome; - log odds ratio, “good” outcome), dashed vertical line = point estimate of final treatment effect. Horizontal lines = 95% CI of cumulative treatment effect for trials. Circles = point estimates of cumulative treatment effect.

to have “improved” to 39%. No indication of interim analyses was given, perhaps unusual in multicentre trial planning to enrol 500 patients and using innovative therapy. It is useful to look at power curves for the estimated effect size(s) implied by a total sample size of 500. This is seen in Figure 2, where power is plotted against sample size (per group) by differences between the two groups of 0.1, 0.15, 0.2, 0.25, 0.3 and 0.4, with one group fixed at a base proportion of 0.26, the historical control rate for “good” outcome. For a total trial size of 450 patients, 80% power is established for an effect size of approximately 12-13%. For the prospective trial, with total patient number of 275, power was 0.8 for a reduced effect size of 17-18% (again, we use this latter estimate for pedagogical reasons only).

Thus some caution is needed in understanding what effect size would be appropriate for the hypothermic intervention after cardiac arrest and the performance of both trials in respect of this.

Overview

That clinical trials such as reviewed are very difficult to perform is attested to by the long recruitment times and patient exclusions. All trials recorded a low and acceptable incidence of side effects of therapy. No rationale has been provided for prolonged hypothermia,⁵ and no compelling evidence exists for pre-hospital hypothermia. With respect to therapeutic hypothermia in cerebral trauma, at this juncture no advantage is demonstrable. In the case of post cardiac arrest, a treatment effect was claimed in both trials, but the methodological concerns raised above would counsel caution towards these claims and not mandate hypothermia as a current standard of care. Future studies should report separate analyses for both deaths and scaled cerebral outcomes; the latter should be analysed as ordinal data.

Dr J. L. Moran
 Dr. S. L. Peake
 Intensive Care Unit
 Queen Elizabeth Hospital
 SOUTH AUSTRALIA 5011

Associate Professor P. Solomon
 University of Adelaide
 Adelaide
 SOUTH AUSTRALIA 5000

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