Should we treat concussion pharmacologically?

P McCrory

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Research realpolitik

P McCrory

Having recently returned from a series of meetings around the world I am amazed at the extreme variability in clinical sports medicine and research that exists in different countries. I am struck by many similar complaints by geographically disparate clinicians. They are all either “too busy” to write something for the journal or else “just about” to write. It seems that this author’s pre-launch phase is a phenomenon not limited to sports medicine however the need in this discipline is urgent.

This is also something that is seen first hand in the journal. Manuscript submissions from Britain are declining while those from Australia, Europe, and Asia are increasing. This is particularly noticeable in clinical papers. While it may be easy to blame a new editor for this revolution, closer inspection shows that this change has been happening inexorably over a number of years. The journal hasn’t changed, the world has!

There are also a number of big picture issues that deserve discussion. Our specialty suffers from a number of credibility issues that are critical. As various sports medicine colleges and organisations worldwide gather impetus to achieve full specialist recognition, we are all too often regarded by our collegiate peers as being part of a Cinderella specialty. Certainly we lack the historical roots that many Colleges take for granted yet we offer something that is new, important, and distinctly different.

To survive the blowtorch to our collective bellies, we desperately need an evidence base upon which we can develop our guidelines and management pathways. Without this we are lost. Remember the old adage that the plural of anecdotes is not data. How can we develop this evidence base without the involvement of our clinical brethren? It seems our sports science colleagues take much of this for granted. Largely academically based, they have long had the “publish or perish” imperative. In many countries, the sports science leads they way. If only the clinicians would follow.

What then are the barriers for clinicians to publish? I suspect is cultural or political in the broadest sense of those words. Research groups around the world that foster a philosophy of publishing quality research continue to build respect and influence at an international level. This is somewhat limited by the “critical mass” phenomenon. It takes time to build up to a level that sustains itself but when that happens the growth tends to be exponential. The rate-limiting step seems to be leadership. The right person can inspire others to great deeds whereas the wrong person generates mediocrity. The selection of leaders for such groups should be based more on academic merit and/or personal ability than on any “old boy” network.

For solo or small groups where critical mass is difficult or nigh on impossible to achieve, life is tough. Thrown back on limited resources one’s goals have to start small. Having said this, it is a salutary exercise to read the recent obituary of Dr Will Pickles published in the Journal of the Royal Society of Medicine (2001;94:536–40). As a busy country GP this man single handedly discovered or characterised many common illnesses simply by good documentation and an inquiring mind. Yet when I hear clinicians’ talk of needing “protected research time” from their employers to be able to write whatever magnum opus is within them I shudder. Time is not the answer for an excess of academic inertia.

Other new developments may also influence this culture. The privatisation of sports medicine clinics may seem an interesting step but if it comes at the price of stifling research and reducing publication output, is it worth it? This development could be a potential boon to researchers with computerised databases of diagnoses allowing large scale or even multicentre studies to occur. It needs leadership in order to convince health bureaucrats and bean counters that research will actually improve quality and may have the positive spin off of good publicity. Heaven knows some of these health bodies could do with good news from time to time!

What about trainees? Clearly to foster a culture of research and publication amongst registrars is important. These are the people who hopefully will continue these habits long into their careers. In Australia, it is a requirement of the College training programme that all registrars must have at least one paper published in a peer reviewed journal prior to being admitted to Fellowship. Simple but effective. To do this on a wider scale requires some academic mentoring and access to research infrastructure, which is largely the province of academia rather than privatised or corporatised medicine. Still with an administrative body behind the initiative it can easily be achieved. That body may be a medical one or a sports medicine umbrella organisation. The issue is the culture not the name. Unfortunately when the focus is on the development of splinter groups not the broader picture, research gets lost in the mix.

In part, some of the difficulty may relate to the need to demystify the publication process be it the writing, submission, or publication of a journal article. Reading the various journals could be a starting point for some clinicians. There is no point having “a dozen cases ready to write up” if nothing happens. Although most people think of publishing a paper as stroking their ego, the process can be a learning one for the author involved. If someone reads it and gets the message or changes their management appropriately then that is a bonus.

In sports medicine, we have a clear choice. Publish or perish. We have reached a level of medical sophistication where to go upward we need to have solid foundations of evidence beneath us. As they say in the Olympics; Citius, Altius, Fortius

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Boxing

Boxing and the brain

P McCrory

Revisiting chronic traumatic encephalopathy

C hronic traumatic brain injury or chronic traumatic encephalopathy (CTE) is considered by some authorities to be the most serious health problem in modern day boxing. The condition is often referred to by a number of names in the medical and non-medical literature including dementia pugilistica and “punch drunk” syndrome.

Whilst there exists great controversy regarding the ethics of boxing, one of the key medical issues is the risk of a boxer developing CTE either during or after his boxing career. Recent evidence suggests that exposure to boxing alone is insufficient to cause this condition.

It is believed that CTE represents the cumulative long term neurological consequences of repetitive concussive and subconcussive blows to the head. CTE is more common in professional rather than amateur boxers, however, CTE has been documented in other sports such as American football, ice hockey, rugby, horse racing, and soccer.

CTE is clinically characterised by a combination of speech and gait disturbance, pyramidal tract dysfunction, memory impairment, extrapyramidal features, behavior or personality changes, and psychiatric disease. It is salient to review the original paper discussing the neuropathology of CTE. Although individual case reports had been published of boxers with chronic dementing illnesses, the seminal paper discussing the association of neuropathological findings in boxers was published by the English pathologist, John Corsellis. He studied the brains of 15 retired boxers and retrospectively studied their fight histories. While a number of characteristic changes were noted in these brains, it is the boxers’ histories that deserve specific note. Of the fighters studied, their exposure to boxing ranged between 300 and 700 bouts in the course of their careers. This was in addition to sparring and other fight training that would have occurred.

The issue then that needs consideration is that in this day and age we would seldom see a fighter with such a record. Even the top professionals report fight careers of 30–50 fights before retirement, an order of magnitude less than that described in Corsellis’ landmark study.

Recent research in boxers has also suggested that CTE in boxers may be associated with a particular genetic predisposition. The apolipoprotein E-ε4 gene (ApoE), a susceptibility gene for late onset familial and sporadic Alzheimer’s disease, may be associated with an increased risk of CTE in boxers.

In a non-boxing population, ApoE polymorphism was significantly associated with death and adverse outcomes following acute traumatic brain injury as seen in a neurological unit. In a recent prospective study, ApoE genotypes were tested for their ability to predict days of unconsciousness and functional outcome after six months. There was a strong association demonstrated between the ApoE allele and poor clinical outcome.

Furthermore, ApoE deficient (knockout) mice have been shown to have memory deficits, neurochemical changes, and diminished recovery from closed head injury when compared to controls. It is suggested that ApoE plays an important role in both neuronal repair and antioxidant activity resulting in ApoE knockout mice exhibiting an impaired ability to recover from closed head injury.

How then does this help the debate on the risks of boxing? Firstly we need to reconsider the original evidence on exposure as a risk factor for CTE. The simplistic assumption based on epidemiological data from previous studies that CTE is a manifestation of the length of a boxer’s career and hence exposure to punches needs to be readdressed.

Similarly the development in understanding of the genetic risk that a boxer may carry developing CTE means that this area may need to be re-examined in light of current day research. This issue also raises a number of ethical issues, if a boxer is found to be homozygous for the ApoE e-4 phenotype should his boxing career be curtailed? At the very least, informed consent, and genetic counseling should be undertaken.

Whilst one may argue the ethics and morality of boxing, it behooves us as scientists and clinicians to at least place the medical arguments regarding risk of injury on a scientific footing.


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Author’s affiliation
P McCrory, Editor

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EDITORIALS

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EDITORIALS

Concussion treatment

Should we treat concussion pharmacologically?
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The need for evidence based pharmacological treatment for the concussed athlete

The medical management of concussion in sport has traditionally involved close observation and “masterly inactivity”. With the use of clinical assessment and neuropsychological testing we have the ability to individualise patient management and determine safe and appropriate return to play strategies. At the present time, the sports physician has no evidence based pharmacological treatment to offer the concussed athlete. The ability to treat concussion with specific drug therapy requires an understanding of the pathophysiological changes that accompany concussive injuries.

PATHOPHYSIOLOGY OF SPORT RELATED CONCUSSION

Concussive brain injury has long been thought to evoke immediate and irreversible damage to the brain. While this may be true in moderate to severe traumatic brain injury, the evidence that this occurs in milder injuries such as concussion is not compelling. Recent experimental evidence suggests that the pathogenesis of axonal dysfunction resulting from head trauma is complex.7

In addition, studies of moderate to severe traumatic brain injury have revealed that a cascade of neurochemical, ionic, and metabolic changes occur following experimental brain injury.8 The assumption is that similar changes occur in milder injury although this remains controversial. Most notably, an injury induced ionic flux across the cell membrane due to the release of the excitatory amino acids, has been shown to increase glycolysis that results in a state of metabolic depression due to a decrease in both glucose and oxidative metabolism accompanied by a decrease in cerebral blood flow.9,10 Each element of this cascade has a different time window that may have important implications in treating concussed individuals.

TREATMENT OPTIONS

There are many pharmacological management options that have been proposed for all grades of brain injury. Readers are referred to some of the larger texts and recent reviews on these topics for more complete discussion.11–13 The list below outlines some of the recent developments and areas where treatment may have a role. In many cases, the evidence is based upon studies of severe brain injury and readers need to interpret this in light of the discussion above. These treatments are summarised in table 1.

Corticosteroids

Corticosteroids have been utilised for many years in experimental neurotrauma, initially based upon their ability to stabilise lysosomal membranes and reduce tissue oedema. There are a number of studies that suggest both positive and negative benefits of using corticosteroids in severe brain injury.14 Other steroid compounds, particularly the lazaroids or 21-amino steroids, that inhibit lipid peroxidation also have protective benefit in neurotrauma models. One such compound, tirilazad mesylate has been shown to improve behavioural recovery in mice.9

Free radical scavengers and antioxidants

Treatment with vitamin C or E, if administered pre-injury, has been shown to provide protection in various models of central nervous system (CNS) trauma where free radicals are generated.15–17 Some concern however has been raised by the large epidemiological studies of antioxidant use for cardiovascular disease where antioxidant therapy was associated with an increase in cancer incidence. The mechanism for this is not known.

Drugs inhibiting arachidonic acid metabolism

Toxic breakdown products of arachidonic acid metabolism may exacerbate CNS injury. These include thromboxanes, peptidyl leukotrienes, and free radicals. Studies of cyclo-oxygenase inhibitors (for example, ibuprofen) and mixed cyclo-oxygenase-lipoxygenase inhibitors have shown therapeutic benefit in animal models of spinal cord injury.16 No specific trials of this therapy have been performed with mild traumatic brain injury.

Drugs that modify monoamine function

There is a well documented sympathoadrenal response following traumatic brain injury, however, whether blocking this response has a therapeutic benefit is unknown. It has been known anecdotally since the Second World War, that cholinergic antagonists such as scopolamine can reduce the behavioural deficits following moderate to severe brain injury. A recent randomised trial however was terminated prematurely because of unacceptable psychomimetic side effects suggesting that this agent may not be a practical treatment option.18

Glutamate receptor antagonists

Increased extracellular levels of glutamate and aspartate correlate with brain injury severity in animal models.19 Treatment with NMDA antagonists, AMPA antagonists, and magnesium have suggested a protective benefit in animal and limited human studies.20 These agents may be of increasing importance once safety and other issues are dealt with.

Calcium channel antagonists

It has been proposed that the entry of calcium through voltage-dependent channels may contribute to secondary brain injury. Despite the intuitive logic of

Table 1 Summary of treatment options

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<th>Treatments that are possibly effective</th>
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Abbreviations: CNS, central nervous system; TRH, thyrotrophin releasing hormone
treatment with calcium channel antagonists, a number of randomised trials of various agents have failed to demonstrate protective benefit. Recently a novel calcium channel agent, S-empamil, has been shown to be beneficial in experimental injury.16

Opiate receptor antagonists
Endogenous opioids contribute to secondary damage following CNS trauma. Studies have suggested that the kappa opioid receptor or its isoforms may be significant in the modification of these injuries. Reanalysis of data from randomised trials of spinal cord injury have suggested a benefit from naloxone although the dose studied may have been too high.17 18

TRH and TRH analogues
Thyrotrophin releasing hormone (TRH) was originally identified in the treatment of acute spinal cord injury because of its ability to antagonise many of the actions of endogenous opioids. This agent may also have effects on platelet function, leukotriene activation, and excitatory amino acid release. Protective effects in CNS injury are dose-related and are found even when treatment is delayed up to 24 hours.20 21

Neurotrophic factors
The ability of injured neurons in the adult brain to recover from injury depends on the expression of growth related genes and the responsiveness to survival and growth signals in the environment.

Nerve growth factor: The neuroprotective efficacy of intracerebral nerve growth factor infusion has been demonstrated during the acute phase of experimental head injury. This beneficial effect of nerve growth factor may be related to its ability to attenuate traumatically induced apoptotic cell death.22

Insulin-like growth factor-1: Intravenous insulin-like growth factor-1 has been evaluated for the treatment of moderate to severe head injury in a phase II safety and efficacy trial.23 Bcl-2: This proto-oncogene has actions similar to those of brain-derived neurotrophic factor in promoting the regeneration of severed CNS axons in the mammalian CNS.24 The mode of this action is likely via extracellular signalling pathways that are involved in both neuronal survival and axon elongation.

Hypothermia
Significant morbidity and mortality of patients with traumatic brain injury is associated with post-traumatic inflammatory complications. Hypothermia has been suggested as a treatment to lessen these inflammatory reactions. Hypothermia, applied immediately after severe traumatic brain injury, reduces the post traumatic increase in interleukin-1 beta mediated nerve growth factor production.25 Thus, hypothermia, while reducing the inflammatory response, may also hinder the brain’s intrinsic repair mechanism. In phase 1 and phase 2 trials, short (<48 hours) periods of moderate (32–33°C) hypothermia are well tolerated and provide limited evidence of a beneficial effect on the outcome following moderate to severe traumatic brain injury. Phase 3 randomised controlled trials are currently underway.26

Hyperbaric oxygen therapy
The delivery of high concentrations of oxygen under pressure has been proposed as a means of enhancing cerebral oxygenation and hence injury recovery post-injury. Possible mechanisms of action include cerebral vasoconstriction, improvement in glucose metabolism and reduction of cerebral oedema. Hyperbaric oxygen may also have a potentially harmful effect on the injured brain by supplying oxygen for free radical reactions that result in iron-catalysed lipid peroxidation. In severe brain injuries, randomised trials have demonstrated an improved mortality rate with hyperbaric therapy however there was no improvement in functional outcome at 12 months.27

OTHER TREATMENT STRATEGIES
There are a number of other agents that have been utilised either in small clinical trials, experimental studies or reported anecdotally to be of benefit. Agents such as anion transport inhibitors28 and cytokines29 have been proposed as well as combination therapy directed at a number of elements of the injury cascade.20 Even nutritional supplements, such as creatine, have been proposed to be of benefit in severe traumatic brain injury.30 Further randomised controlled trials are necessary with all these agents prior to consideration or their recommendation for widespread clinical use.

CONCLUSION
In summary, at the present time the clinician has no evidence based pharmacological treatment to offer the concussed athlete. Although as physicians we often feel the need to treat “something” rather than sit idly by and observe the clinical state, it is critical that we bear in mind the Hippocratic aphorism “Primum non nocere”. And to paraphrase Hippocrates further: Life is short, the art is long, opportunity fleeting, experience deceiving, and judgment difficult. Thus medicine was almost three millennia ago and remains true today.


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Author’s affiliation
P McCrory, Centre for Sports Medicine Research & Education and Brain Research Institute, University of Melbourne, Melbourne, Australia 3004

Correspondence to: Dr P McCrory, PO Box 93, Shoreham, Vic 3916, Australia; pmcmcrory@compuserve.com

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