

## REVIEWS

## Corticosteroids in head injury—the CRASH trial

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The CRASH trial (Corticosteroid Randomisation After Significant Head injury) is a large simple placebo controlled trial, among adults with head injury and impaired consciousness, of the effects of a short term infusion of corticosteroids on death and on neurological disability. The trial has been funded by the Medical Research Council and has Multicentre Research Ethics Committee approval for the UK. The trial is due to start recruiting patients in the spring of 1999.

World wide, some millions of people are treated each year for serious head injury, of whom close to a million die, and a similar number are disabled,<sup>1</sup> often with profound effects on the subsequent quality of life of the affected individuals and their carers.<sup>2</sup> If a treatment as simple as short term corticosteroids produces just a moderate benefit, this could be worthwhile. For example, if corticosteroids reduced the risk of death by just 2% (for example from 15% to 13%), and reduced the risk of permanent disability by a similar amount, then treatment of 500 000 patients would avoid 10 000 deaths and prevent 10 000 permanent disabilities. But, such a benefit would be impossible to demonstrate reliably without large scale randomised evidence. If, for example, 10 000 patients were randomly allocated to receive a corticosteroid infusion and 10 000 a placebo infusion, then a reduction from 15% to 13% dead should be detectable—and a reduction from 15% to 12% would certainly be detectable. By contrast, a trial involving only 2000 patients would probably miss such differences.

So far, all of the randomised trials of corticosteroids in head injury have been small: the largest included only a few hundred patients, and even in aggregate they have involved only about 2000 patients.<sup>3</sup> When all previous trials are combined, the risk of death in the corticosteroid treated group appears to be about 2% lower than in the control group, but the 95% confidence interval (CI) runs from 6% lower to 2% higher mortality. (This overall reduction from 39% dead to 37% dead corresponds to an “odds ratio” of 0.91, with 95% CI 0.74 to 1.12; the corresponding odds ratio for either death or disability in those trials is 0.90, with 95% CI 0.72 to 1.11.) Hence, the overall result from the previous trials is compatible with there being no real benefit, but it is easily compatible with a benefit of a few per cent. However, the existing

trials are too small to demonstrate or to refute either possibility.

Recent evidence of benefit from corticosteroids in acute spinal cord injury has renewed interest in their possible role in brain injury. The Second US National Acute Spinal Cord Injury Study (NASCIS 2) compared 24 hours of methylprednisolone with placebo in 333 patients with acute spinal cord injury.<sup>4</sup> At six months, patients who had received steroids rather than placebo appeared to have greater improvement in motor function, and in sensation to pinprick and touch. Similar results were reported in a Japanese trial of the same regimen.<sup>5</sup>

The CRASH trial has therefore been designed to determine reliably: the effects of high dose corticosteroid (methylprednisolone) infusion on death and on disability after significant head injury, and the effects of such infusion on the risk of infection and of gastrointestinal bleeding.

Accurate diagnosis of a traumatic brain injury is often not possible in the critical stages of assessment and management. Indeed the treatment provided by an emergency physician is based on the assumption of a “worst case scenario” while trying to identify the nature of the underlying pathological changes. Paradoxically, early treatment is likely to be most effective. The CRASH trial has been designed, therefore, as an early intervention when it is possible that the doctor will have a broad working diagnosis but may not have determined the final diagnosis. It follows that the range of clinical scenarios to be included in the trial should be wide and that their exact description does not need to be known to the investigators. While this apparent lack of rigour in such an important clinical trial may appear counterintuitive, the logic of this approach does stand up to scientific scrutiny. This is, of course, good news for emergency physicians and nurses. Since they are busy, and working in emergency situations, the trial involves them in almost no extra work; no special investigations or changes to usual management are required, and data collection is absolutely minimal.

Head injured adults with impaired consciousness are eligible for inclusion in the trial if the responsible doctor is for any reason substantially uncertain whether or not to use corticosteroids. Patients with head injury and impaired consciousness will be unable to give properly informed consent, and in this emer-

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gency situation it may not be medically appropriate to delay the start of treatment until proxy consent can be obtained. Hence, the doctor in charge should take responsibility for entering such patients, just as they would take responsibility for choosing other treatments. Of course, the requirements of the relevant ethics committee should be adhered to at all times.

Numbered drug or placebo packs will be available in each participating emergency department. Randomisation involves giving brief details to a 24 hour free phone service. The call should last only a minute or two, and at the end of it the service will specify to the caller which numbered treatment pack to use. The primary outcome measures are: death from any cause within two weeks of injury and death or dependence at six months. In-hospital deaths, complications, and short term recovery are to be recorded on a single sided outcome form which can be completed entirely from the hospital notes—no extra tests are needed. Long term recovery will be assessed at six months either by a simple postal questionnaire, sent directly to each trial participant from the

CRASH Co-ordinating Centre, or by telephone interview and will not involve any additional work for collaborating hospitals.

The CRASH trial aims to be the largest randomised controlled trial in head injury that has ever been conducted. This will only be possible if doctors and nurses world wide can work together to make it a success. Further information about the trial including details about taking part can be obtained from the CRASH Co-ordinating Centre, Institute of Child Health, 30 Guilford Street, London WC1N 1EH (crash@ich.ucl.ac.uk) or by visiting the CRASH web site <http://www.crash.ucl.ac.uk>.

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## Gastric decontamination—a view for the millennium

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### Abstract

**The management of acute poisoning remains an important part of accident and emergency (A&E) care. Three gastric decontamination procedures have been widely used: gastric lavage, ipecac, and activated charcoal. Their role has recently been reviewed and position statements developed by working groups of the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists. These have important implications for A&E, as they indicate that activated charcoal is now the agent of choice for most poisons, but that in most situations it is probably only effective if given within an hour of overdose. Ipecac is effectively obsolete and gastric lavage has a narrow range of indications, principally for potentially serious amounts of agents not adsorbed by charcoal. Protocols for care of overdose patients should be modified accordingly.**

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The practice of medicine changes for a variety of reasons. New treatments are developed and their effect is measured against those of older, established regimens. The buzz words of the

1990s have been "evidence based medicine" and medical practice in many areas is being reassessed in line with this approach. In the management of drug overdoses traditional teaching 20 years ago was that decontamination of the stomach was an important part of management. The approaches used were gastric lavage and syrup of ipecac. At the time of their introduction these treatments were not subjected to formal clinical trial but anecdotal evidence of tablet recovery convinced clinicians that they were doing good. The development of the orally administered binding agent, activated charcoal, lead to the reconsideration of the optimal way of handling drug overdoses. In addition formal clinical studies began to be applied to this area of medical management as clinicians reassessed the evidence for the treatments they had been using.

The theory behind gastric decontamination seems simple. Toxins in the stomach are very poorly absorbed but once they enter the small bowel the large surface area facilitates passive diffusion and absorption is often rapid, particularly for lipid soluble compounds such as drugs. Therefore removal of a toxin from the stomach might decrease the total amount absorbed and hence reduce toxicity.

Gastric lavage involves administering fluid into the stomach via a wide bore tube. This process is not without hazard. It is associated with transient hypoxia in patients who are

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