Commentary

The CRASH trial: the first large-scale, randomised, controlled trial in head injury

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Abstract

The global epidemic of head injuries is just beginning. Many are caused by road traffic crashes. It is estimated that, by 2020, road traffic crashes will have moved from its present position of ninth to third in the world disease burden ranking, as measured in disability adjusted life years. In developing countries, it will have moved to second. The Corticosteroid Randomisation After Significant Head Injury (CRASH) trial is a large-scale, randomised, 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. Following a successful pilot phase, which included over 1000 randomised participants, the main phase of the trial is now underway. Over the next 5 years, the trial aims to recruit a total of 20,000 patients. Such large numbers will only be possible if hundreds of doctors and nurses can collaborate in emergency departments all over the world. The trial is currently recruiting, and new collaborators are welcome to join the trial (see www.crash.lshtm.ac.uk).

Keywords brain injury, emergency medicine, head injury, injury, neurotrauma, trauma

The global epidemic of head injuries is just beginning. At present, over one million people die each year and a similar number are disabled from brain injuries, often with profound effects on the quality of life of the affected individuals and their carers [1].

Road traffic crashes account for most of the deaths, and car use is rapidly increasing in many countries. It is estimated that, by 2020, road traffic crashes will have moved from its present position of ninth to third in the world disease burden ranking, as measured in disability adjusted life years, and will be ranked second in developing countries (Tables 1–3).

The identification of effective treatments for head injury is of global health importance. The CRASH trial is the largest randomised, controlled trial in head injury ever conducted; almost 2000 patients have already been recruited. It will, however, only be possible to reach the recruitment target of 20,000 if doctors and nurses worldwide join the trial and help to make it a success. The protocol of the trial has been

Table 1

World disease burden ranking in 1990

Causes	DALYs (1000s)	% total
Lower respiratory infections	112,898	8.19
Diarrhoeal diseases	99,633	7.22
Perinatal conditions	92,313	6.69
Unipolar major depression	50,810	3.68
Ischaemic heart disease	46,699	3.39
Cerebrovascular disease	38,523	2.79
Tuberculosis	38,426	2.79
Measles	36,520	2.65
Road traffic accidents	34,317	2.49
Congenital abnormalities	32,921	2.39

Road traffic accidents were the ninth largest burden worldwide in 1990 as measured by disability adjusted life years (DALY).

CRASH = Corticosteroid Randomisation After Significant Head Injury.

Table 2

Projected world disease burden ranking in 2020

Causes	DALYs (1000s)	% total
Ischaemic heart disease	82,325	5.93
Unipolar major depression	78,662	5.66
Road traffic accidents	71,240	5.13
Cerebrovascular disease	61,392	4.42
Chronic obstructive pulmonary disease	57,587	4.15
Lower respiratory infections	42,692	3.07
Tuberculosis	42,515	3.06
War	41,315	2.97
Diarrhoeal diseases	37,097	2.67
HIV	36,317	2.61

Road traffic accidents are projected to become the third largest burden worldwide as measured by disability adjusted life years (DALY).

published and is freely accessible online [2,3], and there is also a website with further information and guidance [4].

The CRASH trial is a large-scale, randomised, 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. Following a successful pilot phase that included over 1000 randomised participants, the main phase of the trial is now underway. The trial aims to recruit a total of 20,000 patients over the next 5 years.

Why we need this trial

There are several reasons for conducting the CRASH trial at the present time. First, animal studies have shown that high dose methylprednisolone can reduce post-traumatic neuronal degeneration [5,6]. Second, patients with spinal cord injury who are treated with corticosteroids rather than placebo within 8 hours of injury appear to have greater improvement in motor function, and in sensation to pinprick and touch [7,8]. Third, there are wide variations within and between countries in the use of corticosteroids in head injury [9]. Finally, a meta-analysis of randomised trials of corticosteroids in head injury shows that existing trials are too small to demonstrate or to refute the possibility of a moderate but clinically important benefit [10].

Table 3

Projected developing country disease burden ranking in 2020

Causes	DALYs (1000s)	% total
Unipolar major depression	68,837	5.60
Road traffic accidents	64,388	5.24
Ischaemic heart disease	64,328	5.24
Chronic obstructive pulmonary disease	52,677	4.29
Cerebrovascular disease	51,518	4.19
Tuberculosis	42,364	3.45
Lower respiratory infections	41,107	3.35
War	40,190	3.27
Diarrhoeal diseases	36,960	3.01
HIV	33,962	2.76

Road traffic accidents are projected to become the second largest burden in developing countries as measured by disability adjusted life years (DALY).

Keep it simple, recruit thousands

Head-injured adults with impaired consciousness are eligible for inclusion in the trial if the responsible doctor is, for any reason, uncertain of whether to use corticosteroids. Patients with head injury and impaired consciousness may be unable to give properly informed consent, and in this emergency situation it may not be appropriate to delay the start of treatment until relatives' 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. However, the requirements of the research ethics committee must be adhered to.

Numbered drug or placebo packs will be available in each participating emergency department. Randomisation involves calling a 24-hour free phone service. The call should last only 1 or 2 min, and at the end of it the service will specify which numbered treatment pack to use. If, for any reason, telephone randomisation is not feasible, randomisation can also be carried out by fax.

The outcome measures are death from any cause within 2 weeks of injury, and death or dependence at 6 months. In-hospital deaths, complications, and short-term recovery are recorded on a single-sided outcome form that can be completed entirely from the hospital notes. No extra tests are needed. Long-term recovery is assessed at 6 months, either by a simple postal questionnaire sent directly to each trial participant from the national co-ordinating centre or by telephone interview. It will not involve additional work for collaborating hospitals.

Competing interests

None declared

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Appendix

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