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Original version submitted

CRASH Trial Protocol (Corticosteroid randomization after significant head injury)

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The CRASH Trial

A large simple placebo controlled trial, among adults with head injury and impaired consciousness, of the effects of a 48 hour infusion of corticosteroids on death and neurological disability

Worldwide, millions of people are treated each year for severe head injury. A substantial proportion die, and many more are permanently disabled. If short term corticosteroid infusion could be reliably shown to reduce these risks by just a few percent then this might affect the treatment of a few hundred thousand patients a year, protecting thousands from death or long term disability.

When all previous trials of steroids in head injury 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 runs from 6% lower to 2% higher mortality. Thus, the overall result is compatible with there being no benefit, but is also easily compatible with a benefit of a few percent. The CRASH trial will determine reliably the effects on death and on disability of a short term corticosteroid infusion following significant head injury.

To detect or refute improvements of only a few percent in outcome, many thousands of acute head injury patients must be randomised between control and steroid infusions. Such large numbers will be possible only if hundreds of doctors and nurses can collaborate in the participating emergency

departments. 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. Patients participating in this trial are not precluded from enrolment in other trials. The trial design is summarised on the back cover.

CRASH will determine reliably the effects of corticosteroids on death and on disability following significant head injury

PROTOCOL

February 2001

1. Background

Corticosteroids in head injury

Worldwide, 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,¹ often with profound effects on the subsequent quality of life of the affected individuals and their carers.² 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% (e.g. 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 2,000 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 2,000 patients (Figure 1).³ 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 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% confidence interval 0.74 to 1.12; the corresponding odds ratio for death or disability in those trials is 0.90, with 95% confidence interval 0.72 to 1.11.) Hence, the overall result from the previous trials is compatible with there being no real benefit, but it is also easily compatible with a benefit of a few percent. However, the existing trials are too small to demonstrate or to refute either possibility.

Figure 1. Aggregate mortality results from 13 randomised trials of steroids in head injury published before 1997

	Steroid	Control
No. of patients	1,061	1,087
No. who died	396 (37%)	422 (39%)

Absolute benefit of steroids 2%, indicating 1 death prevented for every 50 patients treated: but these previous trial results are also statistically compatible with there being no real benefit at all (or even a small hazard).

Corticosteroids in spinal injury

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 (MP) vs placebo in 333 patients with acute spinal cord injury.⁴ 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.⁵ Recent trials of MP in acute spinal cord injury have indicated slightly more neurological recovery with 48 than with 24 hours of treatment.⁶

Dose selection

Post-traumatic neuronal degeneration can involve lipid peroxidation,⁷ and in cats^{8,9} and mice¹⁰ this can be inhibited by methylprednisolone,¹¹ with 30 mg/kg needed for maximal effect. The dose of steroid used in previous head injury trials was, however, much lower than this,³ and so a trial of the early administration of methylprednisolone in doses that are high enough to inhibit lipid peroxidation may produce slightly greater treatment effects than those in Figure 1. The CRASH trial has therefore been designed to determine reliably:

- the effects of high dose corticosteroid infusion on death and on disability following significant head injury, and
- the effects of such infusion on the risk of infection and of gastro-intestinal bleeding in this setting.

2. Study design

Summary

CRASH is a large simple, placebo-controlled trial of the effects of a 48-hour infusion of corticosteroids on death and on neurological disability, among adults with head injury and some impairment of consciousness. The procedures are described in Figure 2, and on the back page of the protocol. Head injured patients with impaired consciousness who are judged to be 16 years or older are eligible if the responsible doctor is, for any reason, substantially uncertain whether or not to use corticosteroids. 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 a minute or two, and at the end of it the service will specify to the caller which numbered treatment pack to use. The drug or placebo in the pack is made up in saline and, following a one-hour loading dose, is infused over 48 hours (or as close to 48 hours as possible). No extra tests are required, but a short form must be completed 2 weeks later (or after prior death or discharge).

Number of patients needed

Two main factors determine the number of patients needed in a trial. These are the estimated event rate, and the size of the treatment effect.

Estimated event rate: In a recent multi-centre randomised trial in head injury using inclusion criteria similar to those in the CRASH trial, the overall risk of death among controls was 15%, with the risk of unfavourable outcome (dead, unfit for work or needing rehabilitation) being 43%.¹² This trial is one of the most recent randomised trials of corticosteroids in head injury and it would be reasonable to expect a similar risk of unfavourable outcome in the CRASH trial.

Size of treatment effect that should be detectable: Because even a 2% survival advantage for an intervention as simple and widely practicable as corticosteroids would represent a worthwhile benefit, the current trial has been planned to be able to detect a benefit of this size.

Numbers needed: If the real mortality difference is 15% vs 13% then there is about a 65% chance that a trial involving 10,000 patients will achieve $2P < 0.01$, and a 95% chance that a trial involving 20,000 patients will do so. These calculations assess how well the trial is protected against an unfavourable play of chance. If however, as might well be the case, the actual results are not much distorted by the play of chance and involve 15% vs 13% mortality then a trial of 10,000 would yield $2P = 0.004$, and a trial of 20,000 would yield $2P = 0.00004$ (which is extreme enough to allow some exploratory sub-analyses of which types of patient seem most likely to benefit).

Eligibility

- *Head injured patients (judged to be 16 years or older) within 8 hours of injury who are not fully conscious (any abnormality on the Glasgow Coma Scale), except those for whom corticosteroids are thought to be clearly indicated or contra-indicated.*

All head injured patients who — in the absence of sedation — are observed whilst in hospital to have GCS of 14 or less, and are within 8 hours of the injury, are eligible for trial entry if they appear to be at least 16 years old. Although entry is allowed up to 8 hours from injury, the earlier that patients can be treated the better.

There are no other pre-specified exclusion criteria, as the fundamental eligibility criterion is the responsible doctor's "uncertainty" whether or not to use corticosteroids in a particular adult with

head injury.¹³ Patients for whom there is considered by the responsible doctor to be a clear indication for corticosteroids (such as, perhaps, those who also have an acute spinal cord injury) should **not** be randomised. Likewise, any for whom there is considered to be a clear contraindication to corticosteroids should **not** be randomised. But, all those for whom the responsible doctor is substantially uncertain as to whether or not to give corticosteroids are eligible for randomisation, and as many such patients as possible should be considered for the trial.

Heterogeneity of the types of patients entering such a trial is a scientific strength, not a weakness. If a wide range of patients are randomised then it may be possible for a really big trial such as this one to help determine which (if any) particular types of patient are most likely to benefit from treatment. *Special eligibility considerations:* None. Routine exclusion of patients with gastrointestinal complaints or pregnancy is unnecessary, unless the responsible doctor considers these to be a definite contraindication.

Notes:—

- (1) This short term corticosteroid regimen should not cause serious gastrointestinal bleeding, nor should it cause a large increase in infection.
- (2) Although prolonged use of corticosteroids in pregnancy may affect fetal adrenocortical development, this short term treatment should not do so.

Consent

Patients with head injury and impaired consciousness may be unable to give properly informed consent, and in this emergency 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. However, the requirements of the relevant ethics committee should be adhered to at all times. An information leaflet on the study for patients and their friends and relatives will be available in all drug packs (Appendix 1).

Randomisation

Patients eligible for inclusion should be randomised, and the study treatment started, as soon as possible. Randomisation is done by telephoning a 24-hour toll-free service and takes only about two minutes. The patient entry form (Appendix 2) shows the questions that will be asked by the telephone operator prior to allocation of the treatment packs. The study computer will then randomly assign a treatment pack number that will identify one of the CRASH treatment packs stored in the emergency department. Once a patient has been randomised, we will definitely wish to learn the outcome in hospital, even if the trial treatment gets interrupted or is not actually given.

Study treatment

Each CRASH treatment pack contains:

- 11 × 2g vials of methylprednisolone (MP) or placebo
- 1 × 20mL sterile water for injection (for use with the loading dose)
- 1 × 100mL bag of 0.9% NaCl (for use with the loading dose)
- CRASH stickers (for attaching to infusion bags and patient notes)
- Patient information leaflet and early outcome forms

Treatment	Vials	Dose (MP or placebo)
Loading	1	2g over 1 hour
Day 1	5	0.4 g/hour for ~24 hours
Day 2	5	0.4 g/hour for ~24 hours

Loading

2g MP (or matching placebo) over 1 hour in 100 mL infusion:

1. Add 20 mL water for injection to *one* 2g vial and mix well
2. Add contents of vial to the 100mL bag of 0.9% NaCl provided
3. Infuse over one hour

Daily Maintenance

0.4g/hour for about 24 hours in 20 mL/hour infusion (MP or matching placebo):

1. Remove 100mL from a 500 mL bag of 0.9% NaCl (to make room for the steroid)
2. Add 20 mL water for injection to each of *five* 2g vials and mix well
3. Add all five (about 100mL) to the 500 mL bag of 0.9% NaCl
4. Infuse at 20 mL/hour for about 24 hours
5. Repeat for maintenance day 2

N.B. As children under 16 are excluded, a simple fixed-dose treatment can be used. The dosing regimen is that used in the NASCIS-2 and NASCIS-3 trials of MP in acute spinal cord injury.

Unexpected adverse events

Anaphylactic reactions to intravenous corticosteroids are extremely rare, but should be treated in whatever way the responsible doctor prefers (one possibility being intra-muscular adrenaline 0.5mg, i.e. 0.5 mL of 1 in 1,000 (1mg/mL) solution).¹⁴ It would be expected that 24 hour anaesthetic cover would be available in all hospitals participating in CRASH. If a serious and unexpected adverse drug reaction occurs and is suspected to be related to the study medicine, this should be logged by calling the 24 hour randomisation service, who will inform the CRASH co-ordinating centre in London.

In general, gastro-intestinal bleeds and infections do not need to be reported in this way because some increase in their incidence might be expected with steroids. Likewise, the various medical events that are to be expected in head injured patients do not need to be reported by telephone. All such events are, however, routinely monitored among all patients on the outcome form.

'Unblinding' the allocated treatment in an emergency

In general there should be no need to unblind the allocated treatment. If some contra-indication to corticosteroids develops after randomisation (e.g. severe gastro-intestinal bleeding), the trial treatment should simply be stopped. Unblinding was never found to be necessary in the NASCIS trial of MP in spinal cord injury,⁴ and should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received corticosteroid or placebo (e.g. suspected anaphylaxis). In those few cases when urgent unblinding is considered necessary, the randomisation service should be telephoned, giving the name of the doctor authorising unblinding and the CRASH treatment pack number (if available), and the caller will then be told whether the patient received corticosteroid or placebo.

Measures of outcome

The primary outcome measures are:

- Death from any cause within two weeks of injury
- Death or dependence at six months

In-hospital deaths, complications and short-term recovery are to be recorded on the early 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. This does not involve any additional work for collaborating hospitals.

Analysis

Comparisons will be made of the primary outcome measures, comparing all those allocated methylprednisolone versus all those allocated placebo, on an 'intention to treat' basis. Analyses will be stratified on time from injury to the initiation of treatment, and on severity of head injury as assessed by the Glasgow Coma Scale. Comparisons will also be made of the risks of infection and gastrointestinal bleeding.

3. Organisation

Steering Committee

Dr Colin Baigent	Professor John Pickard
Professor David Chadwick (Chair)	Dr Ian Roberts (co-ordinator)
Mr Kevin Curley	Professor David Yates
Dr Lelia Duley	Mr Jonathan Wasserberg
Professor Marcel Haegi	

Data Monitoring Committee

Professor Rory Collins	Professor Stephen MacMahon (Chair)
Professor Stephen Haines	

The independent Data Monitoring Committee will conduct interim analyses of mortality and morbidity among all trial participants. It will advise the Steering Group if the randomised comparisons in the trial provide both (i) proof beyond reasonable doubt of a difference in outcome between the study and control groups, and (ii) evidence that would be expected to alter substantially the choice of treatment for patients whose doctors are, in the light of the evidence from other randomised trials, substantially uncertain whether to give corticosteroids to patients with head injury.¹⁵

Collaborators' responsibilities

Co-ordination within each participating hospital will be through a local collaborator who will:

- Discuss the trial with medical, neurosurgical and nursing staff who see trauma patients and ensure that they remain aware of the trial and its procedures (there are wall charts, pocket summaries and a set of slides to assist with this)
- Ensure that adults with acute head injuries are considered promptly for the trial
- Ensure that the single sided early outcome forms are completed

Co-ordinating Centre responsibilities

- Provide study materials and a 24 hour randomisation (and unblinding) service
- Give collaborators regular information about the progress of the study
- Help ensure complete data collection at discharge and at 6 months
- Respond to any questions (e.g. from collaborators) about the trial

Publication

The success of CRASH will be entirely dependent upon the collaboration of nurses and doctors in the participating hospitals. Hence, the chief credit for the study will be assigned to them in the main publications, and the collaborators from each participating centre will be named personally in the main report.

Indemnity


The CRASH trial is sponsored by the Medical Research Council (MRC) and not the manufacturers of methylprednisolone. The MRC fully accepts responsibility attached to its sponsorship of the trial, and as such, would give sympathetic consideration to claims for any non-negligent harm suffered by anyone as a result of participating in this trial.

Financial support

Medical Research Council funding covers meetings and central organisational costs only. Pharmacia & Upjohn are donating drug and placebo, but the design, management and finance of the study are entirely independent of them. Methylprednisolone is not a new product. Really large trials of such drugs, involving many hospitals, are important for future patients but are practicable only if those collaborating in them do so without payment (except for recompense of any minor local costs that may arise).

4. References

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Information for patients, friends and relatives

Appendix 1.

International study of steroids after
head injury

For further information about the
international study of steroids after head injury, contact:
MRC Trial Coordinating Centre
LSHTM, 49-51 Bedford Square, London WC1B 3DP
Tel: 020 7299 4684

Supported by the
MRC
Medical Research Council

This hospital is taking part in an international study to try to find ways to improve recovery after head injury.

In this hospital, patients with head injury are given the usual emergency treatment for head injury. They are also given, by a drip into the arm, a treatment as part of a study that is trying to find ways to improve recovery after head injury.

The treatment in the drip is saline with either an active steroid (called *methylprednisolone*) or an inactive, dummy medicine included in it. The choice of what to give was made randomly by a computer in Oxford. The doctors looking after you do not know whether you got the active or the inactive medicine. This information is kept on a confidential list at another hospital.

All patients in the study, whether or not they got steroids, get the best care available.

The steroid may help recovery by slightly reducing the brain swelling that can occur after head injury. But steroids may make people slightly more prone to infection. We hope to find that steroids do a little more good than harm, but we don't yet know this. The study is being carried out in hospitals in Britain as well as overseas, and will include many hundreds of patients with head injury.

The study involves no extra tests, but we send brief details about how you have been in hospital to the trial centre in London, and about six months after your injury, we will contact you to ask how you are getting on. This information would be used in strict confidence by the people working on the study and would not be released under any circumstances.

If you have any questions about your care, please ask your doctor.

Thank you.



PATIENT ENTRY

QUESTIONS THAT WILL BE ASKED
WHEN YOU CALL THE RANDOMISATION SERVICE

[1] Country

[2] Name of hospital where
patient entered
or give your hospital code

[3] Name of caller

[4] Patient **sex** Male Female

[5] Do you know patient's **name**? Yes No — if No, go to [8]

[6] Family name: _____ [7] Given name(s): _____

[8] Patient Hospital Identification Number (if name unknown):

[9] Do you know patient's **date of birth**? Yes No — if No, go to [11]

[10] Date of birth: ____ / ____ / ____ — or, if not known: [11] Approximate age: _____

[12] Estimated number of hours since injury:

Current Glasgow Coma Scale: three questions will be asked — one or more replies must indicate an abnormality (if unable to assess, e.g. due to intubation, give most recent GCS)

[13] Eye opening:

Spontaneous 4
To sound 3
To pain 2
None 1

[14] Motor response:

Obeys commands 6
Localising 5
Normal flexion 4
Abnormal flexion 3
Extending 2
None 1

[15] Verbal response:

Orientated 5
Confused speech 4
Words 3
Sounds 2
None 1

[16] This GCS is: 1 Current 2 Most recent

Pupil reactivity

[17] Left 1 Yes 2 No 3 Unable to assess
[18] Right 1 Yes 2 No 3 Unable to assess

**Now call ☎ 0800 585 323 with these answers
and write down the treatment pack no. given at the end of the phone call**

Treatment Pack: **Box:**

Get this pack and follow the instructions on it carefully

- **Lost or damaged treatment pack**

1. ☎0800 585 323
2. Ask for “*Lost or damaged treatment pack*”
3. Give answers to questions 1 - 11 overleaf

- **Reporting adverse events**

1. ☎0800 585 323
2. Ask for “*Adverse events*”
3. Give answers to questions 1 - 11 overleaf
4. Give name of person who has reported the adverse event:

5. Give telephone number of person who has reported the adverse event:

- **Unblinding**

In general there should be no need to unblind the allocated treatment. Unblinding should only be done in those rare cases when management depends importantly upon knowledge of whether the patient received corticosteroid or placebo.

1. ☎0800 585 323
2. Ask for “*Unblinding*”
3. Give answers to questions 1 - 11 overleaf



EARLY OUTCOME FORM

Complete at **discharge, death in hospital, or 14 days after injury** whichever occurs first

Attach treatment pack sticker here

1. Hospital name or trial hospital code no. []

2. Patient details or attach a label with these details (for 6-month follow-up)

Family name [] Given name []

Patient identification number (if available) []

Sex M F

Date of Birth [] / [] / [] (day/month/year)

Address []

Postcode [] Tel []

3. Cause of injury Road traffic accident Fall > 2 metres Other []

4. Outcome (tick one box and give date)

Death in hospital Transferred* to other acute care hospital Discharged to rehabilitation centre or nursing home Discharged home Still in this hospital now.

Date of death/transfer/discharge [] / [] / []

*If transferred, give name of hospital []

Tick the one box that best describes the patient's head injury-related symptoms now (i.e. at 14 days or prior discharge):—

No symptoms Minor symptoms Some restriction in lifestyle, but independent Dependent, but not requiring constant attention Fully dependent, requiring attention day and night Dead

5. Management and complications

Days in Intensive Care Unit (if not admitted to ICU, write '0' here) []

- Yes/No columns with checkboxes for: Seizure, Haematemesis or melaena requiring transfusion, Wound infection with pus, Pneumonia treated with antibiotics, Other treatment with antibiotics, Neurosurgical operation, Major extracranial injury

6. Head CT scan

Head CT scan done? Yes No —Go to section 7

Date of first head CT scan [] / [] / [] Time: [] (24-hour clock)

- Result of first CT: (tick one or more boxes) Normal scan, Abnormal scan; no evidence of swelling or raised intracranial pressure, Obliteration of the 3rd ventricle or basal cisterns, Subarachnoid bleed, Midline shift >5mm, Non evacuated haematoma, Evacuated haematoma

7. Trial treatment Loading dose: Yes No Hours of maintenance dose: [] hours (1-48)

8. Reliable contact (back-up for 6-month follow-up)

Name [] Address [] Tel []

9. GP


Name [] Address [] Tel []

10. Person completing form (please print):

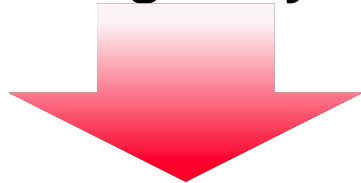
Name [] Position [] Date [] / [] / []

HEAD INJURY

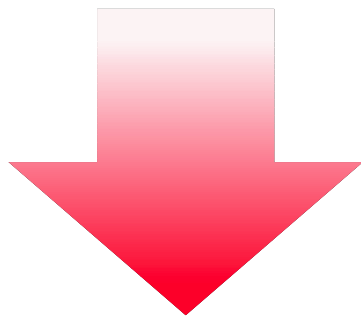
with impaired consciousness?

consider for the **CRASH**  trial of steroids in head injury

Eligibility



Randomisation



48-hour infusion

- ALL adults with head injury in past 8 hours and some Glasgow Coma Scale abnormality
- No clear indication for, or contraindication to steroids, in view of clinician
- *Freephone 0800 585 323* and give:
 - * Patient name and sex
 - * Birth date (if known) or approximate age
 - * Hours since injury
 - * Glasgow Coma Scale: eye opening, motor response, verbal response
 - * Pupil reactivity (Yes/No)
- CRASH pack number will be allocated: get treatment pack and follow instructions on it
- 1-hour loading infusion of 100mL (2g steroid or placebo in saline)
- 48-hour infusion of 20mL/hr: (0.4g/hour steroid or placebo for about 48 hours)

No extra tests: One single-sided outcome form, completed from hospital notes (at discharge, death in hospital, or two weeks from injury, whichever occurs first).

FOR 24-HOUR RANDOMISATION

 **0800 585 323**

Enquiries and study materials:

CRASH Co-ordinating Centre, FREEPOST LON14211, LONDON WC1N 1BR

Tel: +44(0)20 7299 4684

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16 April 2001
Referees' reports

CRASH Trial Protocol (Corticosteroid randomization after significant head injury)

The CRASH Trial management, group, on behalf of the CRASH trial collaborators
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Edward Hall

This manuscript describes the protocol for a multi-center trial of a 48 hour dosing regimen of high dose methylprednisolone sodium succinate (ME) for the treatment of severe traumatic brain injury (TBI). The inspiration for the trial comes from previously published trials showing that similar treatment of spinal cord injured patients with either 24 hr (National Acute Spinal Cord Injury Study II, NASCIS II) or 48 hr (NASCIS III) high doses of MP, if initiated within 8 hrs after injury, is able to significantly improve motor and sensory function over the first year.

While MP is a glucocorticoid steroid that possesses a number of potentially beneficial anti-inflammatory effects, the primary neuroprotective mechanism of action appears to be inhibition of post-traumatic lipid peroxidation. At present, high dose MP treatment of acute spinal cord injury is approved by many countries, and is in widespread use. Dr, Roberts and colleagues reason appropriately that identical dosing ought to be of neuroprotective value in the context of TBI. This is based upon the fact that post-traumatic lipid peroxidation follows a similar time course in SCI and TIBI models. Thus, the inhibition of lipid peroxidation is a rational therapeutic target in both instances. While this reviewer is in full agreement with the rationale for the CRASH trials, there are two important issues that raise significant concern.

The first concerns the use of an 8 hr enrollment window. While NASCIS II indeed demonstrated the efficacy of a 24 hr dosing regimen of MP when begun within the first 8 hrs after injury, NASCIS III showed that the efficacy was greater if begun within the first 3 hrs. In view of the fact that post-traumatic lipid peroxidative reactions and their associated pathophysiology have been shown by this reviewer to evolve very rapidly (Smith et al., *S. Neurotrauma* 11:393-404, 1994), I have great concern that the use of an 8 hr instead of 3-4 hr therapeutic window will significantly compromise the efficacy of MP and perhaps lead to an inconclusive trial showing a non-statistically significant trend.

The second misgiving about the CRASH protocol is the planned magnitude of the study (i.e. 20,000 patients). This sample size is based upon the recent meta-analysis by Dr. Roberts and colleagues of 13 randomized steroid TBI trials showing a 2% overall reduction in mortality. However, their meta-analysis gave little or no consideration to the fact that across these 13 trials, the choice of steroid, dosing regimens, treatment window and duration of treatment varied greatly. This reviewer feels strongly that the lumping of various steroids, dosing levels, dosing regimens and treatment initiation times is like comparing apples and oranges. My view would be that the slight overall efficacy is undoubtedly attributable to those few instances where higher steroid doses were given earlier. Similarly, earlier studies of lower doses of MP or other glucocorticoid steroids in human spinal cord injury yielded no evidence of efficacy. It would be highly inappropriate to lump all of those studies together with those of NASCIS II and III which succeeded in demonstrating a significant benefit of high dose MP with sample sizes of less than 200 patients per treatment arm. Thus, based upon the findings of NASCIS II and III, and the demonstration of the benefits of high dose MP in rodent TBI models, it seems likely that it will take nothing like the 20,000 TBI patients to show a clear positive effect, and that the effect size will be much greater than the expected 2%. This is an important consideration since the conduct of a 20,000 patients study will take an inordinately long time to complete, during which the likely benefits of high dose MP will be unavailable to the greater population of severe TBI patients.

Moreover, such a massive clinical trial will assuredly monopolize a large segment of the TBI patient population and compromise the initiation and conduct of trials with other agents.

A third issue concerns the use of a 48 hr dosing regimen. In NASCIS III, this treatment duration was shown to significantly increase the incidence of pneumonias in comparison to patients who received treatment for only 24 hrs. Furthermore, a nearly significant increase in the incidence of severe sepsis was also observed with 48 hrs of dosing vs. only 24 hrs. It is not inconceivable that these immunosuppressive side effects might be more pronounced in comatose TBI patients than in SCI victims.

In summary, while I applaud the efforts of the CRASH Collaborative Group, this reviewer would start the proposed high dose MP treatment within the first 4 post-injury hours and do an initial multi-center trial comparing 48 hrs of placebo vs. MP treatment in a few hundred patients (150 placebo and 150 ME). This would allow a determination of the safety of the 48 hr MP dosing regimen in severe TBI patients while at the same time providing a strong chance of seeing evidence of an improvement in survival.

Competing interests

Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this paper? If so, please specify.

I was employed by Pharmacia & Upjohn, the primary manufacturer and marketer of methylprednisolone sodium succinate, until December 31, 1997. I do not presently hold any stock or other financial interest in that company (now known as Pharmacia Corp.)

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper? If so, please specify.

No

Do you have any other financial competing interests? If so, please specify.

None. I am employed by Pfizer Global Research and Development. While Pfizer presently has a compound in development for traumatic brain injury, its mechanism of action is quite different from the neuroprotective mechanisms associated with methylprednisolone sodium succinate and will if anything be a complementary product.

Are there any non-financial competing interests you would like to declare in relation to this paper? If so, please specify.

No

Open peer review

Submission of this report to BMC is taken as confirmation that you are happy for your signed report to be posted on the BMC website as part of the pre-publication history of this paper.

Agreed

Michael Gaab

The CRASH Trial Protocol describes the "Rationale and Design" of the largest cooperative study in pharmacological head injury treatment ever done; this trial aims to recruit a total of 20.000 patients (!) within five years on an international cooperative basis in order to clarify the effects of the corticosteroid methylprednisolone in high dosage in head trauma.

The topics of this study / this protocol is original and of high scientific value: in spite of 25 years of research and discussion, the question of efficacy of high-dose glucocorticoid therapy in severe head injury remains open. Initial euphoric reports on impressive benefits (1, 2) did not fulfill the criteria of prospective randomized trials of class I, even not of class II quality; later double-blind prospective trials without "significant" effects did not allow reliable conclusions due to too small numbers of patients, uneven distribution of prognostic factors etc. (3). In the pathophysiologically more uniform spinal cord injury a significant and quantitative, though limited effect could be demonstrated with methylprednisolone. However, adequately designed studies with the numbers of patients achievable on a nationwide study basis revealed (e.g. 4,5), that in the very variable head injuries with their large range of pathophysiology no evidence will be possible with clinical endpoints like mortality and glasgow outcome scoring; due to high β -error, "ceiling effects" etc., much larger

numbers of patients will be required. Nevertheless, evaluation of morphological brain edema by CT (4) and of clinical scores (5) still support the hypothesis that there might exist at least a subgroup of brain trauma which will benefit from steroids (e.g. with edema formation as main prognostic factor). The insufficient number of patients is also the reason for the apparent failure of other, more recent drug studies in head injury like the HITEAC study with aminosteroid (6) etc.

The convincing concept of the CRASH protocol is initially based on a skillfull metaanalysis of the steroid studies available so far, which was published separately in 1997 (7). In combining 13 randomized studies with a total of 2.000 patients available before the CRASH design in 1997, a decrease in mortality of about 2 % (from 39 to 37 %) appears with a 95 % confidence interval from 6 % lower to 2 % higher mortality (fig. 1). Based on these data, the CRASH protocol is based on the high number of patients needed to achieve a 95 % chance to detect a 2 % survival advantage in a study using (simple) entry criteria with an expected overall risk of death in the placebo branch of 15 %. The statistical basis for the study is carefully evaluated, the dosage of the methylprednisolone treatment is based on the maximal experimental effect on lipid peroxidation as factor for traumatic neurone degeneration (30 mg) and is similar to the later prolonged NASCIS treatment scheme with 48 hours of drug infusion (8). Eligible patients are 16 years or older within 8 hours of injury having a GCS of 14 or less; this simple entry criterium as well as the restriction of outcome data to one sheet of early outcome (at discharge, death in hospital, or 14 days after injury whichever occurs first) and outcome at six months (death or dependence easily evaluated by telephone interview or simple one-sheet postal questionnaire) allows the collection of 20.000 patients with the multi-national cooperation of a great number of centers (now around 70) around the world as the first real large-scale head injury trial in head injury.

An effective, fast randomization is provided by a 24-hour free-toll telephone service, a co-ordinating center provides the study materials, keeps all participants informed and helps in complete data collection; an independent data monitoring committee performs interim analyses. The independence of management and financing of the study by the Medical Research Council (MRC) from the drug manufacturer (Pharmacia & Upjohn) must be considered as an advantage ensuring interest-independent progress and analysis.

The manuscript is well written, as well as the study information material given to the participating centers, patients and their relatives. The English is perfect. So in summary, this study must be considered as a milestone in drug research in head injury; for the first time, the concentration to simple entry criteria and outcome data allows the collection of the high number of patients required to achieve a real "evidence-based" basis for steroid indication in a independently organized world-wide investigation. This will probably not only clarify the real value of corticosteroids in head injury; I consider this study as a new standard in the design of drug studies in the complex matter of clinical head injury.

A publication of the CRASH study protocol is recommended in present form; this is a paper of considerable general medical as well as scientific interest. All competent centers / hospitals treating significant numbers of patients with head injuries are encouraged to contact their National study Co-ordinator or the London Center and to consider participation; as faster the endpoint of 20.000 study patients will be achieved as better will be the statistical quality of the result. The quality of study depends not only on the total number of patients included, it increases also if the endpoint of 20.000 patients included is achieved as fast as possible (reduction in variation). Further informations about the trial including details about taking part can be obtained from the CRASH Co-ordinating centre, FREEPOST LON 14211, LONDON WC1B 3BR, , E-mail CRASH@lshtm.ac.uk, or by visiting the web site at <http://www.lshtm.ac.uk>.

(For publication, five keywords should be included – e.g. "head injury, edema, steroid treatment, methylprednisolone, prognosis").

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Glucocorticoids (mortality)

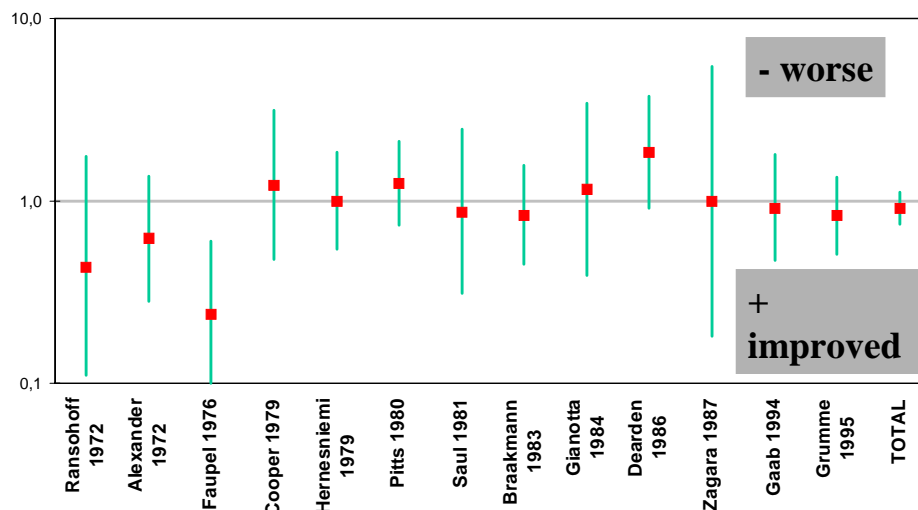


Fig. 1: Mortality of head injury with steroid treatment – analysis of 13 studies
 Published until 1997. Mod. acc. to Alderson & Roberts 1997

4 June 2001

Response to referees' comments

CRASH Trial Protocol (Corticosteroid randomization after significant head injury)

The CRASH Trial management, group, on behalf of the CRASH trial collaborators
[crash@lshtm.ac.uk]

The reviewer is "in full agreement with the rationale for the CRASH trial" but raises four concerns.

1. The reviewer feels that the 8 hour enrolment window is too long and would prefer instead a 3-4 hour window

We appreciate that results from animal studies suggest that early administration of corticosteroids is important for maximal effect and that the time from injury to treatment is also believed to be important in acute spinal cord injury.¹ However, while the effect of corticosteroids may be greatest with early administration, the treatment effect is unlikely to be an all-or-nothing phenomenon and the effect of later treatment, although it may turn out to be smaller, may still be worthwhile.² In the CRASH trial entry is allowed up to 8 hours from injury although it is emphasised that earlier that patients can be treated the better. In a large trial like CRASH, it should be possible to examine the overall effectiveness of corticosteroids and which (if any) particular types of patient are most likely to benefit from treatment.

2. The reviewer believes that the benefit from corticosteroids in head injury is likely to be greater than 2%, in which case "it will take nothing like 20,000 patients to show a clear positive effect."

We can reassure the reviewer that if, as he anticipates, there is clear evidence of benefit from corticosteroids before 20,000 patients have been enrolled, the independent data monitoring committee will inform the trial Steering Committee that this is the case. As described in the protocol, the independent Data Monitoring Committee will conduct regular interim analyses of mortality and morbidity among all trial participants. It will advise the Steering Committee if the randomised comparisons in the trial provide both (i.) proof beyond reasonable doubt of a difference in outcome between the study and control groups, and (ii) evidence that would be expected to alter substantially the choice of treatment for patients whose doctors are, in the light of the evidence from other randomised trials, substantially uncertain whether to give corticosteroids to patients with head injury.

3. The reviewer is concerned that the CRASH trial will monopolise a large segment of the brain injury population and thus compromise trials of other agents.

The CRASH trial is an international multi-centre randomised controlled trial. World-wide about 5.5 million people sustain intra-cranial injury each year and over the 4 year period of the CRASH trial some 22 million people will have sustained an intra-cranial injury.

3. Recruitment for the CRASH trial would therefore involve only 0.1% of all patients with head injuries. Furthermore, as stated in the protocol, patients participating in this trial are not precluded from enrolment in other trials. For these reasons, we believe that the concern that the CRASH trial will compromise the conduct of trials of other agents is unjustified.

4. The reviewer is concerned about possible side effects with a 48 as opposed to a 24-hour dosing regimen.

The safety of trial participants is an issue of utmost importance to the CRASH trial management group as it is to all trial collaborators. A 48-hour methylprednisolone (MP) infusion is being used in the CRASH trial because among patients with spinal cord injury who began treatment more than 3 hours after injury, those treated for 48 hours recovered more motor function than those treated for 24 hours.⁴ There was no difference in mortality between the groups treated with 24-hour and 48-hour infusions.⁴ We would also point out that the Data Monitoring and Ethics Committee will conduct regular interim analyses of mortality and morbidity among all trial participants and, as per the terms of reference in the protocol, will advise the Steering Committee if there is cause for concern.

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