Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months

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MRC CRASH is a randomised controlled trial (ISRCTN74459797) of the effect of corticosteroids on death and disability after head injury. We randomly allocated 10 008 adults with head injury and a Glasgow Coma Scale score of 14 or less, within 8 h of injury, to a 48-h infusion of corticosteroid (methylprednisolone) or placebo. Data at 6 months were obtained for 9673 (96·7%) patients. The risk of death was higher in the corticosteroid group than in the placebo group (1248 [25·7%] *vs* 1075 [22·3%] deaths; relative risk 1·15, 95% CI 1·07–1·24; p=0·0001), as was the risk of death or severe disability (1828 [38·1%] *vs* 1728 [36·3%] dead or severely disabled; 1·05, 0·99–1·10; p=0·079). There was no evidence that the effect of corticosteroids differed by injury severity or time since injury. These results lend support to our earlier conclusion that corticosteroids should not be used routinely in the treatment of head injury.

Lancet 2005; 365: 1957–59

Published online May 26, 2005
DOI:10.1016/S0140-6736(05)66552-X

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The MRC CRASH trial (corticosteroid randomisation after significant head injury) is a large international double-blind randomised placebo-controlled trial of the effect of early administration of a 48-h infusion of a corticosteroid (methylprednisolone) on the risk of death and disability after head injury.

The background to the trial, methods, and baseline characteristics of the patients randomised have been previously reported in detail.[1] Briefly, we randomly allocated 10 008 adults with head injury and a Glasgow Coma Scale score of 14 or less, within 8 h of injury, to commence either a 48-h infusion of methylprednisolone or matching placebo. The loading dose was 2 g methylprednisolone (or matching placebo) over 1 h in a 100 mL infusion. The maintenance dose was 0·4 g methylprednisolone (or matching placebo) per h for 48 h in a 20 mL per h infusion. Randomisation was achieved either by use of the central telephone randomisation service provided by the Clinical Trial Service Unit in Oxford, UK, or by using a local pack system. In local pack randomisation, the next consecutively numbered treatment pack was taken from a box of eight packs, with an allocation sequence based on a block size of eight, also generated by the Clinical Trial Service Unit. The joint primary outcome measures were death from all causes within 14 days, and death or disability at 6 months. Data on death within 14 days of injury were obtained from a single-sided early outcome form completed at death, discharge, or 14 days after injury, whichever occurred first. Data on deaths after 14 days and within 6 months were obtained by contact with patients' general practitioners, and by access to death certification records. Before the start of the trial, a simple questionnaire version of the Glasgow Outcome Scale was developed and was shown to provide a reliable and valid assessment of disability.[2] Disability at 6 months was assessed by means of this questionnaire, which was either mailed to patients or their carers, administered by telephone interview, or administered during a home visit or hospital appointment. Treatment allocation remained concealed from patients, carers, and interviewers.

For analysis of outcomes at 6 months, we pre-specified that death, persistent vegetative state, and severe disability on the Glasgow Outcome Scale constituted an unfavourable outcome, whereas moderate disability and good recovery constituted a favourable outcome. We planned to report the effects of treatment overall and also subdivided by two characteristics at baseline: time from injury to randomisation (≤1 h, >1 to ≤3 h, or >3 to ≤8 h) and severity of head injury based on the Glasgow Coma Score at randomisation (severe 3–8, moderate 9–12, mild 13–14). Analyses were done on an intention-to-treat basis. The effect measure used was relative risk with 95% CI for the overall risk and 99% CI for the results of subgroups. Homogeneity in treatment effects within subgroups was assessed with a χ^2 test on two degrees of freedom at a 5% significance level.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN74459797. The protocol for this study was peer-reviewed and accepted by *The Lancet*; a summary of the protocol was published on the journal's website.

Follow-up data at 6 months are now available for 9673 (96·7%) patients (table). Of 4854 patients allocated corticosteroids, 1248 (25·7%) died within 6 months of randomisation compared with 1075 (22·3%) of 4819 patients allocated matching placebo, yielding a relative

	Corticosteroid allocated (n=5007)	Placebo allocated (n=5001)
Number with known vital status	4854 (96·9%)	4819 (96·4%)
Dead*	1248 (25·7%)	1075 (22·3%)
Severe disability*	580 (11·9%)	653 (13·6%)
Moderate disability*	852 (17·6%)	813 (16·9%)
Good recovery*	2120 (43·7%)	2213 (45·9%)
Alive (disability status not known)*	54 (1·1%)	65 (1·3%)

*Percentages show proportion of number with known vital status.

Table: **Outcomes 6 months after injury by treatment allocation**

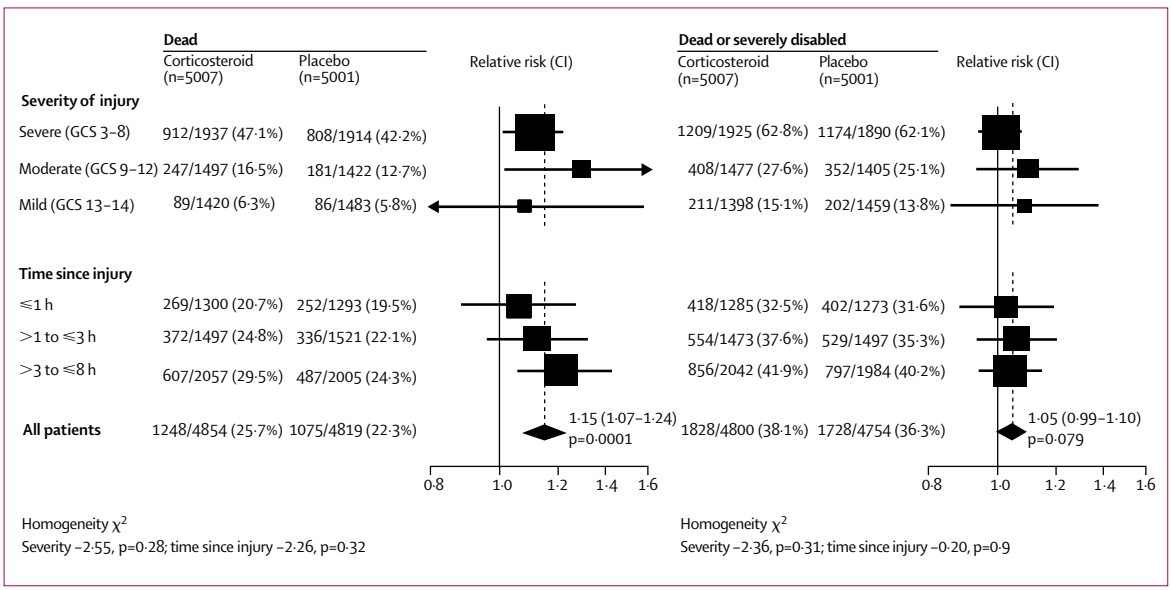

Figure: **Effects of corticosteroid allocation on deaths from all causes and severe disability within 6 months by injury severity and time since injury**
Risk ratios are plotted (black squares with area proportional to the amount of statistical information in each subgroup) comparing outcome in participants allocated corticosteroids to that in those allocated placebo, with 99% CI (horizontal lines ending with an arrow head when the confidence interval extends beyond the scale). Result for all patients and 95% CI is represented by a diamond, with risk ratio and 95% CI stated alongside. Risk ratios greater than unity represent increased mortality or disability with corticosteroid allocation. GCS=Glasgow Coma Score at randomisation.

risk of death within 6 months of 1·15 (95% CI 1·07–1·24; p=0·0001). The risk of death or severe disability at six months was also higher in the group allocated corticosteroids (1828 [38·1%] dead or severely disabled, where disability status was known) than in the placebo group (1728 [36·3%]) with a relative risk of 1·05 (95% CI 0·99–1·10; p=0·079).

There was no clear evidence that the relative risk of death or disability at 6 months differed substantially between groups when stratified by injury severity or time since injury (figure). These results reliably refute any material reduction in mortality or severe disability with corticosteroids in the 6 months after head injury.

The strengths and limitations of the CRASH trial have been discussed in detail elsewhere.[1] In relation to the current analyses, probably the most important methodological issue is the extent of loss to follow-up. This difficulty has been identified as a particular challenge in head injury trials: a systematic review of the methodological quality of head injury trials found that average loss to follow-up was around 20%.[3] However, since the CRASH trial achieved more than 96% follow-up at 6 months, in both treatment groups, the possibility of any material bias is remote. If we assume that the patients lost to follow-up had average prognosis, the risk of death would be estimated as 25·1% with corticosteroids (37·3% risk of death or severe disability) and 21·7% with placebo (35·6% risk of death or severe disability).

These analyses lend support to the conclusion on the basis of the previously reported outcome data at 2 weeks after injury, that corticosteroids should not routinely be used in the treatment of head injury.[1] The apparent hazard may have been inflated by the play of chance and the data-dependent stopping of the trial,[4,5] but these final results still provide clear evidence that treatment with corticosteroids following head injury affords no material benefit. The absence of evidence of any neurological benefit from corticosteroid treatment after head injury might also have implications for the use of corticosteroids in spinal cord injury, which should remain an area for debate.

The ability to predict patient outcome after head injury has an important role in clinical practice and research, and the data collected in the MRC CRASH trial provide an opportunity to examine prognostic factors after head injury. This assessment will, however, be the subject of a separate report.

See Lancet online for webappendix

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See webappendix for the complete list of collaborators.

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Conflict of interest statement

The members of the writing committee declare that we have no conflict of interest.

Acknowledgments

Central randomisation and statistical support was provided by Clinical Trial Service Unit, Oxford, UK. The trial was funded by the UK Medical Research Council. Pharmacia & Upjohn (Pfizer from 2003) provided the Medical Research Council (without charge) the methylprednisolone needed for the trial, a grant-in-aid for preparation of the placebo, and support for collaborators' meetings. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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