Methylprednisolone was associated with an increase in death after head injury


Q In patients with head injury, is early administration of methylprednisolone better than placebo for reducing death?

**METHODS**

- **Design:** randomised placebo controlled trial (Corticosteroid Randomisation After Significant Head Injury [CRASH]).
- **Allocation:** concealed.
- **Blinding:** blinded (clinicians and patients).
- **Follow up period:** 2 weeks.
- **Setting:** 239 hospitals in 49 countries.
- **Patients:** 10 008 patients who were ≥16 years of age (mean age 37 y, 81% men) and had sustained a head injury within 8 hours, had a Glasgow Coma Score (GCS) <14, and whose treating physician was uncertain whether to treat with corticosteroids.
- **Intervention:** a loading dose of methylprednisolone, 2 g over 1 hour in a 100 ml infusion, followed up by a maintenance infusion of 0.4 g over 48 hours in a 20 ml/h infusion (n = 5007) or placebo (n = 5001).
- **Outcomes:** all cause mortality. Recruitment was planned for 20 000 patients to give >90% power to show a 2% absolute mortality difference between groups.
- **Patient follow up:** 99.6% (intention to treat analysis). The independent data monitoring and ethics committee reviewed data in article.

**MAIN RESULTS**

The first patient was enrolled in April 1999. Recruitment was stopped in May 2004. At 2 weeks, all cause mortality was greater in patients who received methylprednisolone than in those who received placebo (table). Preplanned subgroup analysis based on time from injury to randomisation (<1 h, >1 to <3 h, or >3 to <8 h) and severity of injury (GCS mild [13 to 14], moderate [9 to 12], or severe [3 to 8]) showed that groups did not differ for mortality according to time since injury (p = 0.05) or injury severity (p = 0.22).

**CONCLUSION**

In patients with head injury, administration of 48 hours of methylprednisolone was associated with an increase in all cause mortality at 2 weeks.

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**Commentary**

Surprised by the 1997 Cochrane review,1 weak supporting evidence, and continued clinical use, the CRASH trial evaluated the effects of high dose corticosteroids on mortality after traumatic brain injury (TBI). Strengths of the study include enrolment of >10 000 patients from 49 countries, concealed allocation, and intention to treat analysis. A minor weakness of the study is that cause of death was not adjudicated. In individual cases, death could be due to causes not attributable to corticosteroid use. However, randomisation in a trial of this size would account for any random variation between groups, and thus the increase in mortality is attributable to the only systematic difference between the 2 groups—the use of corticosteroids. Inclusion of additional baseline information, such as blood alcohol concentration or glycaemic control, would have been useful to further demonstrate balance between groups, but systematic variation influencing the outcome is unlikely. One of the reasons cited for the failure of most clinical trials in TBI from the bench to the bedside is that they are not structured for level of injury.2 One of the reasons cited for the failure of most clinical trials in TBI from the bench to the bedside is that they are not structured for level of injury.2 In a trial of this size, inclusion of the spectrum of TBI patients could be criticised, but the distribution of severity was balanced, and increased mortality was not associated with the range of severity, especially in moderate and severe TBI. Patients receiving corticosteroids were also more likely to die across the range of clinical signs seen in TBI.

The surprising result of the CRASH trial shows yet again that strong evidence is a categorical imperative in health care and should reinforce that “flying blind” when caring for patients is quite unsafe. The lack of a plausible biological explanation for the difference in mortality rates is attributable to the only systematic difference between the 2 groups—the use of corticosteroids. Inclusion of additional baseline information, such as blood alcohol concentration or glycaemic control, would have been useful to further demonstrate balance between groups, but systematic variation influencing the outcome is unlikely. One of the reasons cited for the failure of most clinical trials in TBI from the bench to the bedside is that they are not structured for level of injury.2

Hilaire J Thompson, RN, CNRN, PhD

School of Nursing, University of Washington

Seattle, Washington, USA

Asha Bakshi, MD

Department of Neurosurgery, University of Pennsylvania

Philadelphia, Pennsylvania, USA