

Methylprednisolone caused an increase in death after head injury

Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. 2004;364:1321-8.

QUESTION

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

METHODS

Design: Randomized 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 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 at 2 weeks. 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 interim analyses at least annually and determined whether to reveal unmasked results to the steering committee.

MAIN RESULTS

The first patient was enrolled in April 1999. In May 2004, recruitment was stopped. 2-week 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 randomization (≤ 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 severity of injury ($P = 0.22$).

CONCLUSION

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

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*See Glossary.

Methylprednisolone vs placebo for head injury at 2 weeks†

Outcome	Methylprednisolone	Placebo	RRI (95% CI)	NNH (CI)
All-cause mortality	21%	18%	18% (8.6 to 27)	32 (22 to 63)

†Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

Corticosteroids are used for patients with traumatic head injury to a variable degree worldwide. A meta-analysis of 13 randomized trials in adults with this condition suggested benefit but did not exclude harm (pooled common odds ratio 0.91, 95% CI 0.74 to 1.12) (1, 2). The international CRASH trial was designed to resolve this issue by randomizing 20 000 patients to corticosteroids or placebo to detect a mortality reduction from about 35% to 33% with 90% power. The 2 primary outcomes were all-cause mortality at 2 weeks and death or disability at 6 months. Surprisingly, the trial stopped early after accrual of 10 008 patients because of a statistically significant 20% relative risk increase in 2-week mortality. Fast-track publication of these results necessitated deferral of 6-month data. The harmful effect of corticosteroids seems to be independent of injury severity, time since injury, and computed tomography diagnosis.

Although the mechanisms mediating increased mortality are unclear, these results are likely to be valid. Trial methods were outstanding,

including concealed random allocation, blinding of patients and clinicians, intention-to-treat analysis, and 99% follow-up. CRASH is the largest randomized trial in emergency medicine, the protocol for which was formally registered and previously published to enhance transparent reporting. These results should prompt discontinuation of corticosteroids in treatment of head injury. They should also prompt larger and more rigorous studies to reevaluate the safety of corticosteroids in spinal cord injury.

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References

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