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Journal club critique

Corticosteroids increased short and long-term mortality in adults with traumatic head injury

Michael S. Czekajlo[1] and Eric B. Milbrandt[2]

[1] Clinical Fellow, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[2] Assistant Professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

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Expanded Abstract

Citation

Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, Cottingham R, Svoboda P, Brayley N, Mazairac G, Laloe V, Munoz-Sanchez A, Arango M, Hartzenberg B, Khamis H, Yutthakasemsunt S, Komolafe E, Olldashi F, Yadav Y, Murillo-Cabezas F, Shakur H, Edwards P: 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, 364:1321-1328 [1].

Background

Corticosteroids have been used to treat head injuries for more than 30 years. In 1997, findings of a systematic review suggested that these drugs reduce risk of death by 1–2%. The CRASH trial—a multicentre international collaboration—aimed to confirm or refute such an effect by recruiting 20,000 patients. In May 2004, the data monitoring committee disclosed the unmasked results to the steering committee, which stopped recruitment.

Methods

10,008 adults with head injury and a Glasgow coma score (GCS) of 14 or less within 8 hours of injury were randomly allocated 48 hour infusion of corticosteroids (methylprednisolone) or placebo. Primary outcomes were death within 2-weeks of injury and death or disability at 6-months. Prespecified subgroup analyses were based on injury severity (GCS) at randomisation and on time from injury to randomisation. Analysis was by intention to treat. Effects on outcomes within 2 weeks of randomisation were presented in this report.

Findings

Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids (1052 [21.1%] vs. 893 [17.9%] deaths; relative risk 1.18 [95% CI 1.09–1.27]; P=0.0001). The relative increase in deaths due to corticosteroids did not differ by injury severity (p=0.22) or time since injury (p=0.05).

Conclusion

These results show there is no reduction in mortality with methylprednisolone in the 2 weeks after head injury. The cause of the rise in risk of death within 2 weeks is unclear.

Commentary

Head injury is a major cause of morbidity and mortality worldwide. Corticosteroids (steroids) have been used to treat head injury for more than 30 years after early reports of their beneficial effects in patients with cerebral edema due to brain tumors and surgery [2]. By reducing intracranial edema and pressure, it was believed that steroids would improve blood flow, reduce the occurrence of herniation, and, therefore, lead to improved clinical outcomes. Enthusiasm regarding their use in head injury was bolstered, in part, by improvements seen with their use in patients with acute spinal cord injuries [3,4]. Studies examining steroid treatment in acute head injury have provided mixed results, though a recent systematic review suggested a 1-2% lower risk of death for patients treated with corticosteroids [5].

Smashing into this practice is the CRASH (Corticosteroid Randomization After Significant Head injury) trial, a randomized placebo-controlled multicenter trial of early steroids in 10,008 adults with head injury. In this study, head injured subjects with a Glasgow coma scale of 14 or

less received either a loading dose of 2 grams of methylprednisolone followed by a 0.4 gram/hr infusion for 48 hours or matching placebo within 8 hours of injury. Groups were well balanced at baseline with respect to clinically relevant variables. The CRASH investigators initially planned to enroll 20,000 subjects. The trial was stopped early when it was discovered at interim analysis that steroid-treated subjects had significantly higher all-cause 2-week mortality (21.1% vs. 17.9%, p=0.0001). Subsequent follow-up demonstrated that 6-month mortality was also higher in steroid treated subjects (25.7% vs. 22.3%, p=0.0001), with a trend toward increases in the combined endpoint of death or severe disability (38.1% vs. 36.3%, p=0.08) [6]. In neither report did the results differ by injury severity or time since injury.

This well-done study was remarkable for many reasons. The sheer size of this trial is staggering, especially considering the logistics of conducting a blinded, placebo-controlled trial in 239 hospitals across 49 countries. It is also impressive that subjects were enrolled and *randomized* within eight hours of injury. That the investigators achieved 96.7% 6-month follow-up certainly raises the bar for other long-term outcomes studies of critically ill patients.

A few limitations of this study deserve consideration. Few details regarding patient management both before and after randomization were given. No centers from North America were included in this trial. It is difficult to imagine, however, that practice patterns differ sufficiently that the results would have differed were the study conducted in North America. The authors did not report what percentage of subjects had concomitant spinal cord injury, leaving unanswered the question of whether patients with combined head and spinal cord injury should receive steroids.

The key question that remains is *why* corticosteroid-treated subjects fared worse. Complications, such as seizures, gastrointestinal bleeding, and infection, were similar in both groups. The authors note that they remain unsure of the mechanism of increased mortality with steroids. The lack of an identifiable etiology, however, does not diminish the validity or importance of the results.

Recommendation

Based on the results of the CRASH trial, steroids should not be used routinely in the treatment of acute traumatic head injury.

Competing interests

The authors declare that they have no competing interests.

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