

EBEM Commentator

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Corticosteroids for Traumatic Brain Injury

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford, United Kingdom: Update Software; 2002.

The *Annals'* EBEM editors prepared the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To determine the safety and effectiveness of corticosteroids given acutely to patients sustaining blunt traumatic brain injury (TBI).

DATA SOURCES

Trials were identified by means of electronic searches of MEDLINE, EMBASE, and the Cochrane Library. Reviewers also performed a manual search of the reference list of review articles and personally contacted trialists.

STUDY SELECTION

Trials were included if they randomly assigned patients clinically diagnosed with TBI to receive either corticosteroids (in any dose, by any route) or control within 7 days of injury. Trials were excluded if the method of allocation concealment was believed to be inadequate. Patients of all ages and with all TBI severities (mild, moderate, severe) were included.

DATA EXTRACTION

Two independent reviewers assessed trial quality and extracted data. Trial quality was based on the method of allocation concealment. Data extracted included number of patients dead or severely disabled (defined as the Glasgow Outcome Scale categories "persistent vegetative state" or "moderate disability") at the end of the study period. For each trial, relative risks (RR) and 95% confidence intervals (CIs) for the outcome were calculated on an intention-to-treat

basis. For each outcome, trials were grouped if there was no significant heterogeneity among them (χ^2 test, $P > .05$). Pooled RRs were calculated using a fixed-effect model, which assigns weights to each study on the basis of size.

MAIN RESULTS

Nineteen trials with 2,295 patients were identified. Seventeen of these trials limited enrollment to patients with moderate or severe TBI; 2 studies included those with mild TBI. In the 16 trials reporting "death" as an outcome, the mortality was 34.3% (410/1,194) in the corticosteroid group and 32.5% (301/925) in the control group. After assigning weights to each trial, the pooled RR was found to be 0.96 (95% CI 0.85 to 1.08), and the pooled risk difference was a 1.3% reduction. In the 9 trials that included "severe disability" as an outcome, the incidence of death or severe disability was 54.5% (505/927) in the corticosteroid group and 48.5% (340/701) in the control group. The pooled RR was 1.01 (95% CI 0.91 to 1.11).

In the 9 trials reporting the effects of corticosteroids on gastrointestinal bleeding, the rate of major or significant gastrointestinal bleeding (not defined) was 2.2% (18/837) in the corticosteroid group and 1.6% (11/703) in the control group. The pooled RR was 1.11 (95% CI 0.54 to 2.26). In the 4 trials reporting on infections of any type, the infection rate was 28.2% (126/447) in the corticosteroid group and 28.5% (131/460) in the control group. The pooled RR was 0.94 (95% CI 0.76 to 1.16).

CONCLUSIONS

Corticosteroids given acutely to TBI patients resulted in a small but statistically insignificant reduction in mortality. There was no significant differ-

ence between corticosteroid and control groups in the rate of the combined end point of mortality and severe disability, nor in the rates of gastrointestinal bleeding or infection. Because of the relatively small number of patients pooled for this systematic review, small reductions in mortality or severe neurologic disability associated with corticosteroid administration cannot be excluded.

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COMMENTARY: CLINICAL IMPLICATION

There are approximately 170,000 new cases of moderate-severe TBI per year in the United States alone,¹ and many of these cases present initially to emergency departments for care. Despite advances in early detection and surgical management, there has been little improvement in the mortality or resulting disability associated with moderate-severe TBI. The observation that there is a time interval between injury and irreversible brain swelling and brain death gave hope that therapies could prevent or limit brain edema and, thus, positively affect outcome. The results of this systematic review revealed, however, that there was no statistically significant reduction in mortality or severe disability associated with corticosteroid administration in patients with TBI.

Although corticosteroids may, in fact, have no effect on outcome, there are 2 other important possibilities to consider. First, corticosteroids may

improve outcome, but this improvement is masked by biases in the studies or the review. One potential source of bias in this study is unequal distribution of patients with mild, moderate, and severe TBI among corticosteroid and control groups. It is well known that mortality varies as a function of TBI severity; 30% among severe (Glasgow Coma Scale [GCS] score 3 to 8), 7% among moderate (GCS score 9 to 12), and less than 1% among mild (GCS score 13 to 15) TBI.^{2,3} This Cochrane review included trials enrolling patients with TBIs of all severities, but the distribution of the 3 TBI severity groups among corticosteroid and control groups is not revealed. If a disproportionate number of patients with mild-moderate TBI were allocated to the corticosteroid group, a bias toward no effect would result. The bias would be in the opposite direction if more patients with mild-moderate TBI were allocated to the control group. In addition, it seems counterintuitive to include patients with mild TBI in trials where the measured outcome is death or severe neurologic disability, as this group rarely experiences these outcomes. That is not to say that corticosteroids may not affect the neurologic outcome of patients with mild TBI, but that post-mild TBI outcome is more subtle and treatment effects are unlikely to be detected by changes in mortality or Glasgow Outcome Scale (but might be detected by changes in neurobehavioral test scores, for example).

A second possible explanation for the lack of statistical difference between corticosteroid and control groups is that the difference was too small to have been detected by the number of patients in this review. Given the 2,119 patients (approximately 1,000 per group) available from the 16 trials reporting the pri-

mary outcome (mortality), this study has 65% power to detect a 1% difference in mortality between corticosteroid and control groups with a 2-sided α of .05. To increase the power to a more acceptable 90% would have required 3,800 patients (1,900 per group). This is currently planned in the Corticosteroid Administration After Significant Head Injury (CRASH) study, which began in 1999 and has enrolled 3,000 patients to date.⁴

Central to this discussion is the question of what constitutes a “clinically significant” difference in mortality and whether this is the appropriate outcome for TBI. A 1% reduction in mortality seems quite small and translates into a number needed to treat (NNT) of 100. Because the costs and complications associated with the use of corticosteroids are low, a relatively high NNT of 100 may be acceptable to clinicians. If the CRASH investigators do indeed find a 1% to 2% reduction in mortality with corticosteroids, routine administration of corticosteroids to all patients with moderate-severe TBI could potentially prevent more than 1,700 TBI-related deaths per year in the United States alone.¹ Until such time, this review concludes there is no support for its use currently.

TAKE HOME MESSAGE

TBI is an important cause of preventable death and neurologic disability worldwide. Treatments that improve outcome, even improvements that are relatively small, could have tremendous impact. Corticosteroids agents do not appear to reduce the incidence of death or severe neurologic disability after TBI, although the power of this systematic review to detect a small effect was low. Similarly, although corticosteroids do not appear to

increase the risk of gastrointestinal bleeding or infection, small increases in risk may not have been found because of the relatively small numbers of patients studied to date.

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EVIDENCE - BASED MEDICINE TEACHING POINTS

Study power and sample size. The power of a study is its ability to detect a specific difference in outcome between 2 groups. Power is related to Type II error (β), which is the probability of finding no difference between groups when a difference exists. The relationship between them is $\text{Power} = 1 - \beta$; thus the higher the power, the lower the β . The lowest acceptable power is generally felt to be 80% to 90%. The power of a study is calculated from the number of patients (sample size or “n”) in each group and the size of the difference in outcome the investigators are trying to detect. In general, the larger the n, the higher the power. Detecting smaller outcome differences requires higher power and thus larger n. When designing a study, investigators calculate the number of patients needed to detect a “clinically significant” difference in outcome so that the power is at least 80%. When evaluating a negative study that is already published, readers can calculate the power of the study by using the difference in outcome observed and the number of patients in each group. These relationships can be calcu-

lated using standardized tables⁵ or software programs.⁶

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