EBEM Commentators
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Corticosteroid Treatment for Acute Ischemic Stroke

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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: Qizilbash N, Lewington SL, Lopez-Arrieta JM. Corticosteroids for acute ischaemic stroke (Cochrane Review). In: *The Cochrane Library.* Issue 3. Oxford, United Kingdom: Update Software; 2002.

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

OBJECTIVE

To determine the effect of systemic corticosteroids in presumed acute ischemic stroke.

DATA SOURCES

The Cochrane Stroke Group Trials Register was searched. The Stroke Group Trials Register is compiled by volunteers who hand search 41 journals and numerous conference proceedings. Because much of stroke research is performed in Europe, the group also has translators that work in 12 languages. Unpublished and ongoing trials are identified through Internet searches of clinical trials and research registers. Drug companies and trialists are also personally contacted. The review was updated in February 2002 from the review published in August 2001. The authors contacted numerous researchers in the field to inquire about ongoing and unpublished trials; none were identified.

STUDY SELECTION

Studies were included if they were randomized controlled trials comparing any form (intravenous, intramuscular, or oral) of corticosteroids to placebo for the treatment of acute presumed ischemic stroke. Furthermore, treatment with corticosteroids or placebo had to have begun within 48 hours of stroke onset, and clinical outcome had to have been assessed. By presumed ischemic stroke, the

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authors meant that the researchers made some sort of effort to exclude hemorrhagic stroke, although only 1 of the 7 trials included actually used computed tomography (CT) to make the distinction.

DATA EXTRACTION

Two authors independently selected trials, extracted data, and assessed the quality of the trials. Odds of death, functional outcome, and adverse effects were assessed with 95% confidence intervals (CIs).

MAIN RESULTS

A total of 22 trials were identified, of which 7 fulfilled the inclusion criteria (n=453 patients) and were included in this updated review. Two of the 7 studies used betamethasone, whereas the remainder used dexamethasone. Corticosteroid treatment was associated with very variable change in odds of death (95% CI 0.68 to 1.72). No meaningful analysis could be derived for functional outcome, because the studies did not use common neurologic impairment scales or common time intervals for assessment, making it impossible to pool data for analysis. Similarly, only 1 of the 7 studies reported adverse effects in a systematic manner, thereby precluding meta-analysis. Overall, adverse effects were infrequent and consisted of gastrointestinal bleeding, infection, and hyperglycemia.

CONCLUSION

On the basis of all trials to date, corticosteroids in the setting of acute ischemic stroke have not shown any beneficial effect on death, neurologic impairment, or functional outcome.

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COMMENTARY: CLINICAL IMPLICATION

Each year, more than 700,000 people in the United States suffer strokes, making it the third leading cause of death and the leading cause of disability.[1] Acute stroke is associated with a high mortality (20% to 50%) and is a leading cause of disability.[1] Given its impact and cost, any therapies that alleviate the burden of stroke suffering are of paramount importance to practitioners. Attitudes toward corticosteroids for the treatment of acute ischemic stroke are divided between those who think that the anti-inflammatory actions of steroids are of some general benefit versus those who think that there is no conclusive evidence to support their use, particularly given their well-known adverse effects. Although it is true that corticosteroids can cause gastrointestinal bleeding, hyperglycemia, and infection, the ability of steroids to decrease vasogenic edema in the ischemic penumbra is potentially of significant benefit.

The authors of this Cochrane review think, however, that there is no such benefit, and go on to conclude that they do not even advocate any further trials. Such a position may be too harsh for a variety of reasons. First, the studies included in this review are very old. Second, patient selection varied; only 1 of 7 studied patients with definite versus presumed ischemic stroke. Third, patients were not risk-stratified on the basis of what is currently known about stroke mortality. Moreover, stroke research has advanced in important ways since the publication of these early trials. Currently, all patients have a brain CT scan to rule out hemorrhagic stroke, often receive a standardized physical examination consisting of at a minimum the National Institutes of Health Stroke Scale,[2] and receive improved and evidence-based stroke care. The introduction of American Heart Association guidelines for acute management of stroke including vital signs and blood sugar management has lead to further standardization of variables.[3] Finally, the studies included did not use common outcome scales or common assessment time points.

Many of the limitations of the included studies could be overcome by a well-designed multicentered trial that enrolls a selected population of stroke patients, with variables such as severity, location, and time of onset of symptoms specified. Improved methodologic quality could result in a more robust trial, which may provide more valid conclusions. The authors comment that it makes sense that corticosteroids would be most useful in patients with larger strokes, because they presumably have the largest amount of vasogenic edema. A trial including only those with moderate-to-severe stroke may still be worthwhile, given these unanswered questions.

For practicing emergency physicians, acute ischemic stroke and any related management issues are of extreme importance. Consequently, until additional evidence is available, emergency physicians should focus

their attention on identifying those stroke patients who qualify for thrombolysis, provide appropriate antiplatelet agents, and ensure supportive evidence-based stroke treatment is provided to all patients under their care.

TAKE HOME MESSAGE

To date, the trials examining systemic corticosteroids in acute ischemic stroke have not demonstrated any important clinical benefit. This conclusion is, however, based on a small number of older studies that have many limitations. Until such time as a large randomized controlled trial is conducted, the use of corticosteroids in the management of acute stroke cannot be supported.

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EVIDENCE-BASED MEDICINE TEACHING POINTS

Equivalence versus difference not detected. The inability to identify the difference between treatments in a systematic review often occurs, and this may be caused by a type II error or true equivalence. This review found no benefit of corticosteroids on reducing death or improving functional outcome in survivors. However, it does concede that "the present review would be compatible with the notion that corticosteroids are beneficial in high risk patients with large infarcts and much vasogenic edema." As in this review, a systematic review that produces a wide CI that includes clinically important differences should alert the reader to be cautious not to conclude the treatments are the same. Conversely, equivalence can only be claimed when the 2 treatments differ by such a small amount that a clinically important benefit has been ruled out. Finally, caution should be exercised when equivalence is being claimed in the face of heterogeneity. In summary, failure to find a difference does not necessarily mean that there is no benefit to a given intervention (ie, equivalence is not proven).

Authorship biases in systematic reviews. It is interesting that an industry scientist is the primary author of this review. Bias is an important issue in systematic reviews, and authors can influence reviews in many important ways. First, systematic reviews require a team approach, and one is always concerned when industry sponsorship and single authorship is identified. Caution is warranted when the authorship of a review is single because there is a strong possibility of bias at the study selection phase. Because the industry employee here is surrounded by other, nonindustry collaborators, selection and data extraction biases are unlikely. Second, industry bias may enter a systematic review when the sponsor's therapies are included in the review. Although the company employing this reviewer does produce corticosteroids (methylprednisolone), it does not appear that this affiliation unduly biased the results of the present review. The conclusion does not appear to favor the drug or the company, because the author concludes there is insufficient evidence to support the use of corticosteroids. Finally, the industry author is an experienced reviewer, having produced other Cochrane reviews, edited a textbook on evidence-based dementia, and worked previously at Oxford University as a clinical lecturer in gerontology.

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