Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials

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Abstract

Objective: To quantify the effectiveness and safety of corticosteroids in the treatment of acute traumatic brain injury.

Design: Systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury. Summary odds ratios were estimated as an inverse variance weighted average of the odds ratios for each study.

Setting: Randomised trials available by March 1996.

Subjects: The included trials with outcome data comprised 2073 randomised participants.

Results: The effect of corticosteroids on the risk of death was reported in 13 included trials. The pooled odds ratio for the 13 trials was 0.91 (95% confidence interval 0.74 to 1.12). Pooled absolute risk reduction was 1.8% (-2.5% to 5.7%). For the 10 trials that reported death or disability the pooled odds ratio was 0.90 (0.72 to 1.11). For infections of any type the pooled odds ratio was 0.92 (0.69 to 1.23) and for the seven trials reporting gastrointestinal bleeding it was 1.05 (0.44 to 2.52). With only those trials with the best quality of concealment of allocation, the pooled odds ratio estimates for death and death or disability became closer to unity.

Conclusions: This systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury shows that there remains considerable uncertainty over their effects. Neither moderate benefits nor moderate harmful effects can be excluded. The widely practicable nature of the drugs and the importance of the health problem suggest that large simple trials are feasible and worth while to establish whether there are any benefits from use of corticosteroids in this setting.

Key messages

- Traumatic brain injury is an important global cause of death and disability
- Corticosteroids are a widely practicable intervention
- This systematic review shows continued uncertainty over the effects of steroids
- The estimate of absolute risk reduction for death is 1.8% (95% confidence interval -2.5 to 5.7)
- Further large scale randomised controlled trials are needed

Introduction

Traumatic brain injury is a leading cause of premature death and disability. Motor vehicle accidents account for most fatal head injuries. Although road death rates are falling in most industrialised countries, in the rapidly motorising Asian countries they are rising and will almost certainly continue to do so. Road death rates per head in China are already similar to those in the United States, even though there are only five vehicles per 1000 population in China compared with 770 vehicles per 1000 population in the United States. Overall, about 75% of the estimated 850 000 deaths due to road accidents each year occur in the developing world.

In the United States the incidence of disability related to brain injury is estimated to be 33 new cases per 100 000 people per year. As this occurs in young people and is long term, disability related to traumatic brain injury is a major cause of ill health worldwide. In 1961 Galicich and French reported rapid and significant improvement in response to corticosteroids in 28 of 34 people with cerebral oedema either due to brain tumours or postoperatively. This led to their use in other intracranial problems characterised by raised intracranial pressure and in severe head injury. Eighty per cent of patients with fatal head injuries show evidence of increased intracranial pressure at necropsy.

For a problem as common as brain injury, even a moderate reduction in mortality or disability from an intervention as widely practicable as corticosteroids would be important. There have been several randomised controlled trials of corticosteroids in head injury with apparently conflicting findings. Continuing uncertainty about the effects of corticosteroids for this indication is reflected in substantial variation in their use. A recent study in the United Kingdom found that corticosteroids were used in just under half of the intensive care units surveyed. We reviewed the randomised trials that have examined the effects of corticosteroids in acute traumatic brain injury on subsequent death and disability.

Methods

Inclusion criteria

We included studies in the review if they met the following criteria. Firstly, study participants had to have a clinically diagnosed acute traumatic brain injury of any severity. Secondly, the experimental intervention was corticosteroids (those steroids with predominantly glucocorticoid effects–namely, prednisolone, betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and triamcinolone) administered in any dose by any route for any duration started within seven days of the injury. Thirdly, study participants were randomly assigned to treatment or control groups. Studies that used quasi-random methods of allocation, such as alternation, were excluded.

Identification of relevant trials

We searched Medline for 1966 to December 1995 using a combination of the March 1996 update of the optimally sensitive search strategy for trials.
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from the Cochrane Collaboration (earlier version published as referenced) with the MeSH headings "head injuries," "intracranial pressure," "brain edema," and "brain-concussion" including all subheadings. The resulting citations were examined on screen to identify possibly relevant trials and those thus identified were retrieved in full and compared with the inclusion criteria. A search of Embase, years 1974-1996 (performed in March 1996) was done by using a similar approach to that for Medline.

We searched the Cochrane Library in August 1996 using each of the text terms "head," "brain," "dexamet.*," and "steroids."10 We asked the Ottawa Stroke Trials Registry and the United Kingdom based Intensive Care National Audit and Research Centre to search their databases, which contain the results of hand searching many neurological, neurosurgical, intensive care, and emergency medicine journals. Several other journals were also hand searched for this review. All the journals from these sources are listed in an appendix, which is available on the internet at www.bmj.com.

The reference lists of all trials found were searched for additional trials. We attempted to contact all the trialists identified, asking them to identify any further published or unpublished trials. No language restrictions were used.

Data extraction and study appraisal

We each extracted the following information independently from each trial: strategy for concealment of allocation, number of randomised patients, duration of follow up, and number lost to follow up. The major outcome data sought were numbers of deaths and numbers of people disabled at the end of the study period. All but one study (see Faupel et al18) used the Glasgow outcome scale11 to assess neurological outcome; the categories for persistent vegetative state, severe disability, and moderate disability were combined into "disability" for this review. This enabled inclusion of the one trial that did not use the Glasgow outcome scale but used a similar ordinal categorisation of function. Where there was more than one steroid group in a trial (for example, low dose and high dose) those groups were combined. We also extracted data on side effects or complications when they were reported by using the authors' definitions of these.

As there is evidence that the quality of concealment of allocation particularly affects the results of studies, each of us scored this quality on the scale of the Ottawa trialists.12 We tested for heterogeneity using a χ² test. Summary odds ratios were calculated in RevMan 3.0 software13 with the Mantel-Haenszel method. We tested for heterogeneity using a χ² test.

Results

The combined search strategies identified 18 reports of trials that satisfied the inclusion criteria.14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 Two were reports of the same trial28 29: this trial was excluded after contact with the first author showed that concealment of allocation had been inadequate. Contact with one trialist showed that allocation had been concealed by using a third party to prepare and supply the drug and placebo preparations.26 The trial by Hermsniemi and Troupp was published as an abstract by Schulz et al as shown below, assigning 1 to poorest quality and 3 to best quality12: 1=trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth); 2=trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and, 3=trials deemed to have taken adequate measures to conceal allocation (for instance, central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).

When the method used to conceal allocation was not clearly reported the author was contacted, if possible, for clarification. We then compared the scores allocated and resolved differences by discussion.

Statistical methods

Summary odds ratios were calculated in RevMan 3.0 software13 with the Mantel-Haenszel method. We tested for heterogeneity using a χ² test.
Subgroup analysis—For the two main outcomes—death and death or disability—we performed a subgroup analysis by analysing the trials with only the highest quality of concealment of allocation. This was not done for the other two outcomes because of the small numbers of events involved. For death, the summary odds ratio was 1.04 (0.83 to 1.30) and for death and disability 0.97 (0.77 to 1.23).

Discussion

This systematic review summarises the evidence from randomised controlled trials of corticosteroids in acute traumatic brain injury.

Methodological issues

The inclusion of an Embase search identified one study not found on Medline. Contact with trialists enabled us to include data from two large unpublished studies but not from others.

Numbers of events were small for infections and gastrointestinal bleeds, resulting in wide confidence intervals around the estimate of effect.

None of the tests for heterogeneity yielded significant results. When death was the outcome, however, the upper limit of the 95% confidence interval in the trial by Faupel et al did not overlap with the lower limit in the trial by Dearden et al. In Faupel's trial the outcome was assessed "at discharge," yet overall 19% of the participants were classified as "unconscious stabilised." The apparently short follow up period may account for the incongruous result.

Other sources of variation may include severity and pathology of the head injury, variations in corticosteroid regimens (for example, drug, dose, route), and temporal trends in the use of other interventions. The use of corticosteroids in spinal cord injury suggests that the timing of administration is important, so this is another possible source of variation.

When we excluded trials with less than the highest quality of concealment of allocation the differences between experimental and control groups was reduced for both death and death or disability. This is consistent with the evidence that inadequate concealment of allocation results in overestimates of the effect of treatment, but it could also be due to random variation. There were several trials in which the true quality of concealment was not known, which makes interpretation difficult.

Implications

Despite 25 years of randomised controlled trials of the use of corticosteroids in patients with head injury, their effects are still not clear. In this review the risk of death in those given corticosteroids was 1.8% less than in the control groups (95% confidence interval 5.7% less to 2.5% more) when we used the trials' average control death rate of 35.4% as the background rate.

The recent guidelines from the Brain Trauma Foundation on the management of severe head injury include a standard (a recommendation made with a "high degree of clinical certainty") that "the use of glucocorticoids is not recommended." These guidelines reviewed six of the randomised trials used in this systematic review and did not attempt a quantitative overview of them. Even with 14 trials, as in this systematic review, considerable uncertainty remains over the effects of corticosteroids.

Can this uncertainty be resolved? To do so would require large randomised trials. For example, a trial with 90% power to detect a 2.6% reduction in risk of death from 35.4% (the total control mortality in this review) to 32.8% at the 0.01 level of significance would require about 20 000 participants. Such large trials to detect effects of this size can be justified when the health problem is important and the treatment widely practicable. Corticosteroids for acute traumatic head injury meet these criteria. Without such a trial clinicians and patients and their families are being forced to make important decisions on the basis of inadequate evidence.

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