Evidence-Based Emergency Medicine:

CORTICOSTEROIDS FOR ACUTE TRAUMATIC BRAIN INJURY

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Abstract:

This is a systematic review abstract, which will be a regular feature of the Israeli Journal of Emergency Medicine) 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.

Systemic Review Source:

The source for this systematic review abstract is: Alderson, P. and Roberts, I. Corticosteroids for acute traumatic brain injury. (Cochrane Review). In: *The Cochrane Library,* Volume 2, 2005.

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Objective:

To quantify the effect of corticosteroids on mortality and morbidity in patients with acute traumatic brain injury (TBI), while examining the incidence of adverse side effects or complications and economic effects.

Data Source:

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and specialized database searches. Researchers conducting trials within this field were also

contacted. The last search was conducted in October 2004.

Study Selection:
All randomized controlled trials which utilized corticosteroids versus any control in the setting of acute TBI were included. Patients of all ages with clinically diagnosed TBI of all severities who were treated with corticosteroids (glucocorticoids utilized most often- prednisolone, betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone and triamcinolone). within 7 days of injury were considered eligible. Any trials utilizing corticosteroids within 7 days irrespective of the route or duration were included, regardless of any other treatment interventions. The primary outcomes that were examined were all cause case fatality, any valid measurement of neurological functioning, quality of life and economic impact. The primary adverse side effects examined were numbers of infections and significant gastrointestinal bleeds.

Data Extraction:

Two reviewers initially did the first review, with an updated search in October 2004. The data extracted from each trial included: strategy for allocation concealment, number of randomized patients, length of follow-up and number lost to follow-up. The reviewers believed that allocation concealment was integral to the quality of information, so the Schulz scale was used to assign quality- A being best, C being poorest.(1) If the method for allocation concealment was not well stated, the reviewers contacted the researchers personally to clarify. Scores were then compared and differences resolved by discussion. A fixed effects model was used to calculate dichotomous variables that were reported as relative risks and 95% Confidence Intervals used in studies determined not to have statistically significant heterogeneity.

In the update in 2004, the staff included the results of the CRASH trial that were then available. Other than the data from the CRASH trial, no other trials were found or included. The CRASH trial addition introduced significant heterogeneity when using the fixed-effect risks ratio model to look at pooled data. Subsequently, the results of all of the trials were not pooled.

Main Results:

20 trials were identified with 12303 randomized patients. 17 trials included risk of death using corticosteroid in TBI patients. The largest trial was the CRASH trial (which had approximately 80% of the total number of patients). The relative risk of death was 1.18 (95% CI 1.09-1.27) in the CRASH study, which showed a statistically significant increase in mortality with steroids.

The pooled relative risk was 1.01 (CI 0.91-1.11) for the 9 trials that reported death or severe disability. The CRASH trial was not included as these results were not published at the time of this review. Infection rates which were included in 5 trials had a relative risk of 1.03 (CI 0.99-1.07). This showed no major change in risk of infection. The 10 trials which examined gastrointestinal bleed did not show a significant effect of corticosteroids on the number of GI bleeds with a relative risk of 1.23 (CI 0.91-1.67).

The CRASH study has been the major study looked at by the reviewers. They acknowledge that more information will be extracted, once the data is fully completed and available. Given the fact that the CRASH study was terminated early secondary to the negative impact of corticosteroids on survival, the results of included here have been duly noted. The reviewers believe that the large number of participants, and the quality of the CRASH trial have guided the conclusions in this review.

Although the investigators wanted to look at economic impact of corticosteroids, there was no data gathered in any of the trials.

Conclusion:

Given the extent of data in the CRASH trial, corticosteroids appear to increase mortality in the setting of acute TBI. There is no significant effect on infections or gastrointestinal bleeds in these same patients. As such, patients should not be given steroids in the setting of isolated acute traumatic brain injury.

Commentary:

Traumatic brain injury (TBI) is a major public health problem, accounting for one-third of all traumatic deaths. A study completed by the

Centers for Disease Control (CDC) in 2001 estimates that 1.4 million people sustain a TBI in the United States each year. Of these, 50,000 will die of their injuries, while another 90,000 will survive with permanent disabilities (2). A hospital in northern Israel reported a similar annual incidence of 25 TBI's per 100,000 (3). The direct medical cost associated with TBI in the United States has been estimated at $4 billion dollars (4).

In both the United States and Israel, falls were the most common cause of TBI, followed closely by motor vehicle collisions (2,4). Motor vehicle collisions were the leading cause of TBI-related deaths in the United States for decades, but improvements in vehicle safety have reduced mortality rates 42% from 1979 to 1992. In 1990, firearms surpassed motor vehicles as the leading cause of TBI-associated deaths (5). However, in the rapidly motorizing Asian countries the rates of vehicle associated deaths is steadily increasing (6).

Despite the massive clinical and economic impact of TBI, few proven beneficial treatments exist. In recent years, a number of promising therapies based on positive preclinical data have fizzled in clinical trials. Glutamate antagonists (Selfotel, Cerestat, D-CPP-ene), free radical scavengers (PEG-Orgatine), and IGF-1 with growth hormone all failed to show statistically significant improvement in clinical trials. Trials of physiological manipulation such as hyperventilation, hypothermia, and maximizing cerebral blood flow also failed to improve outcome (7).

Corticosteroids have been used to treat brain edema due to tumors or surgery since a 1961 study by Galicich and French. Since that time, the use of corticosteroids had been expanded to any cause of brain edema and/or increased intracranial pressure, including TBI. The effect of even a modest benefit in morbidity or mortality, given the incidence of TBI and the paucity of proven interventions, would be substantial. A number of studies on the effect of corticosteroids in TBI have been published, with conflicting results.

In the previous review by the same author published in the Cochrane 2002 the relative risk of death using corticosteroids with approximately 2000 patients in 16 trials was 0.96 (CI of 0.85 to 1.08). A 15 % chance that corticosteroids would improve survival but an 8% chance it would increase death. This prompted a much larger study (CRASH) with Dr Roberts participating as one of the Primary Investigators.

This updated review summarizes the role of corticosteroids in TBI. The review includes 20 randomized controlled trials for a total of 12,303 subjects. Seventeen trials reported the effect of corticosteroids on mortality. The results ranged wildly, with relative risks from 0.42 to 3.00. There was significant heterogeneity that could not be explained with a sensitive analysis that removed trials based on adequate allocation concealment and therefore the results were not pooled. It is unfortunate, that the authors did not expand their sensitive analysis using a widely accepted quality tool such as the Jadad criteria. (8) Of the 17 trails, only two demonstrated statistical significance. The Faupel study (1976), which compared low dose and high dose dexamethasone to placebo in 95 patients, came out in favor of corticosteroids (RR 0.42; 95% CI 0.24 to 0.71) and the treatment of 4 patients would translate into one saved life (NNT 4) . However, the larger and more methodologically sound CRASH trial (2004) reported a significant *increase* in mortality (RR 1.18; 95% CI 1.09 to 1.27) with the number needed to harm of 31. The CRASH trial compared 48 hours of high dose methylprednisolone (given within 8 hours) to placebo in adults 16 and over with a GCS of 14 or less. The trial enrolled 9964 patients before being terminated early due to the negative effect of steroids on TBI. Pooled data revealed no impact of corticosteroids on the combined outcome of death or severe disability (RR 1.01; 95% CI 0.91 to 1.11). Also, pooled data on significant adverse events showed no statistical difference in GI bleeding or infection (RR 1.23 and 1.03; 95% CI 0.91 to 1.67 and 0.99 to 1.07, respectively).

In summary, the data currently available do not demonstrate a beneficial effect of corticosteroids on traumatic brain injury. In fact, the largest and most sound trial to date indicated an *increase* in mortality. The Brain Trauma Foundation's evidence-based *Guidelines for the Management of Severe Traumatic Brain Injury* states: "The use of steroids is not recommended for improving outcome or reducing intracranial

pressure (ICP) in patients with severe head injury" (9).

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