Editorial
Do corticosteroids play a role in the management of traumatic brain injury?

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Abstract
Neuroprotective strategies for the medical management of traumatic brain injury (TBI) have been elusive. While laboratory studies provide a conceptual framework for the potential efficacy of corticosteroids in this context, clinical trials testing this hypothesis have yielded no convincing evidence of clinical benefit. Here, we review the five key randomized control trials (RCTs) that have examined this issue. Based on the proposed primary endpoints of these RCTs, the five RCTs consistently showed that corticosteroids do not confer significant benefit in the TBI population.

Key Words: Outcomes, randomized controlled trials, steroids, TBI, traumatic brain injury

BACKGROUND

Traumatic brain injury (TBI) is a leading cause of death and disability, particularly in young adults.1,7,8 It is defined as permanent or temporary impairment of neurologic function secondary to physical insult from an external mechanical force.9 Neurologic injury from TBI is largely attributed to the deleterious effects of the direct mechanical impact as well as secondary cerebral swelling and edema that occur subsequent to this impact. In severe TBIs, the secondary cerebral swelling and edema increase intracranial pressure,10 which in turn, compromises cerebral perfusion, contributing to a feed-forward cycle of ischemic injuries. The control of intracranial pressure in this setting is paramount in the management of TBI. It is in this context that corticosteroids have been used to treat TBI for the past four decades.11

It is well-known that the vasogenic edema and swelling secondary to cerebral neoplasms can be reduced by treatment with corticosteroids.10 Many studies have been carried out to test whether such effects can be duplicated in the TBI patient population. While many randomized control trials (RCTs) have been carried out to test the potential efficacy of corticosteroid in the setting of TBI, most studies were exploratory in nature, with a limited sample size. Of the published RCTs on the matter, only five studies had sample sizes involving >100 patients. We reviewed these five RCTs in this article. Overall, these studies provided no compelling evidence that corticosteroid use in the setting of TBI yielded significant clinical benefit.

RANDOMIZED CONTROL TRIALS

Braakman et al. conducted a single-centered, blinded, randomized controlled trial randomizing 161 patients
with severe TBI to placebo (n = 80) versus a single bolus of 100 mg dexamethasone (n = 81) followed by a taper regimen (100 mg per day between days 1 and 4, 16 mg per day between days 5 and 7, and a taper of 12 mg, 8 mg, and 4 mg for days 8, 9, and 10, respectively). The study included patients who (1) showed lack of eye-opening and verbal response to painful stimuli, (2) did not follow commands, and (3) presented within 6 hours of the TBI. Patients who lacked brainstem reflexes, showed no motor response, or with comorbidities that would contraindicate steroid use (e.g. diabetes mellitus or peptic ulcer disease) were excluded. The description of the inclusion and criteria places the patient population at a Glasgow coma scale (GCS) of <8. Primary endpoints were functional outcome and mortality outcomes at 1 and 6 months. Data from all enrolled patients were available at 6 months. There were no significant differences in the primary endpoints at either time point. Approximately 15% of the patients in both the arms showed neurologic recovery to baseline function at 6 months, whereas 50% of the patient cohort died during this period. The authors noted an increased incidence of severe pulmonary infections in the corticosteroid-treated group relative to the placebo group, although this difference did not reach statistical significance (P = 0.07).

Grumme et al. carried out a multicenter, blinded study randomizing 396 patients with severe TBI (GCS < 8) who were admitted within 4 hours of injury to placebo (n = 187) and the corticosteroid, triamcinolone (n = 209; 200 mg intravenous given on presentation, 40 mg per day for 4 days, then 20 mg per day for the last 4 days). The primary endpoints of this study were Glasgow outcome scale scores (GOS) at the time of discharge and GOS at the 1 year follow-up. The mortality of the steroid-treated group was lower (16%) than the placebo group (21.5%). However, this difference did not reach statistical significance. A total of 375 patients were followed for 1 year; at follow up, the steroid group again had a lesser proportion of observed deaths (21.2% vs. 25.0% of patients treated with placebo), though this difference was not statistically significant. Post-hoc analysis of the data found that TBI patients with a GCS < 8 and with focal traumatic lesion (contusions) who received triamcinolone showed improved neurologic recovery relative to placebo-treated patients (34.8% versus 21.3%, P < 0.05). In this subset analysis, mortality was also lower in the triamcinolone-treated patients relative to the placebo-treated patients (19.6% versus 38.3%, P < 0.05). Demographics and injury severity of the two groups of patients in this post-hoc comparison was not provided. As such, any potential benefit is difficult to interpret.

Saul et al. carried out a single-center, blinded study randomizing 100 TBI patients (GCS < 8), admitted within 6 hours of injury to placebo and steroid treatment (methylprednisolone 250 mg bolus, followed by 125 mg every 6 hours for 7–10 days). Patients with other body system injuries were excluded. The primary outcome measurement was GCS improvement at 72-hour post-treatment and GOS at the 6 month follow-up evaluation. There were no significant differences in the primary outcome measurements at either time point. In a post-hoc analysis, the patients were classified as responders or nonresponders based on the rate of neurologic recovery in the first 3 days. In this post-hoc analysis, there was a trend that responders (patients who showed neurologic recovery in the first 72 hours) receiving steroids were more likely to have a favorable recovery (when defined as good recovery/disabled status) versus patients remaining with poor outcome (defined as vegetative status/dead). Seventy-four percent of the patients in the steroid responder group were not vegetative/dead versus 56% in the placebo treated responder group. However, this difference did not reach statistical significance.

The German Ultrahigh Dexamethasone Head Injury Study (GUDHIS) randomized 300 patients with moderate or severe (GCS = 3–12) brain injury to placebo versus steroid treatment (500 mg of dexamethasone within the first 3 hours, followed by 200 mg after 3 hours, and 200 mg every 6 hours for 48 hours). The primary outcomes were GCS improvement on day 5, GOS at 10 months after the injury, and the time elapsed to improve patients to a GCS equal to or greater than 8. Data from approximately 90% of the patients in each arm were available at the 10 month follow-up. No statistical difference was seen between the dexamethasone-treated group and the placebo group in any of the primary endpoints of efficacy and safety. Approximately 15% of the patients in both the arm showed neurologic recovery to baseline function at 10 months whereas 60% of the patients died during this period.

Corticosteroid Randomization After Significant Head Injury (CRASH) was a multicenter, double-blinded, placebo controlled RCT that enrolled and randomized 10008 patients with head injuries and GCS < 14 to either 48 hour infusion of methylprednisolone (2 g for 1 hour followed by 0.4 mg for 48 hours) or placebo. Randomization and initiation of steroid treatment was performed within 8 hours of injury. Exclusion criteria included physician determination of any contraindication for glucocorticoid use. Primary outcome included death within 2 weeks or disability/mortality within 6 months. The study initially planned to enroll 20000 patients, however, the interim analysis after enrolling 10008 patients revealed that the risk of death within 2 weeks from entering the study was higher in the corticosteroid arm (21.1% vs 17.9%, P = 0.0001). Only 44 patients of the entire cohort were lost to follow-up, with 22 patients lost in both the arms. 96.7%
of the enrolled patients were available for the 6-month follow-up. Again, the 6-month mortality was higher in the steroid-treated arm relative to the placebo arm (25.7% vs 22.3%, \( P = 0.0001 \)). The relative increase in death rate was found throughout all subgroups of injury severity and was independent of time to treatment. No significant differences were noted between both the study arms in terms of 6-month disability and steroid-related or TBI-related complications were comparable between the two arms.

**Expert opinions**

“It has not been possible to demonstrate practical benefits of corticosteroids in the TBI population.”

Ekkehard Kasper, Beth Israel Deaconess Medical Center, Boston

Various experimental models have confirmed the surprisingly beneficial impact of high-dose steroid application in reducing metabolic damages caused by e.g. lipid peroxidation, thus yielding improved physiological tissue recovery and function. This remains an encouraging fact that has its roots in sound laboratory studies. However, despite various attempts to replicate such observations in the clinical realm, it has not been possible to demonstrate comparable practical benefits of corticosteroids in the TBI population. Of the five pertinent RCTs, only post-hoc analysis by Grumme et al.\(^{[5]}\) and Saul et al.\(^{[11]}\) suggested benefit. In contrast, the largest RCT to date (CRASH) could not corroborate a clinical benefit for steroid use in such a setting, however, instead reported increased early mortality rates. The discrepancy between laboratory experiments and clinical outcome brings up a number of questions: (A) Are we selecting the right patients for our TBI RCTs? (B) Do we have the right drugs or right drug doses? and (C) Are we measuring the right endpoints? Only by scrutinizing these key issues will we be able to determine whether corticosteroid improve outcomes in TBI patients.

“If the TBI patients that I treated are reflective of the general TBI population, I do not believe any RCT will be sufficiently powered or funded to test the efficacy of corticosteroid in the TBI setting.” Lawrence Marshall, University of California, San Diego.

The introduction of corticosteroids into neurosurgical practice by Dr. Donlin Long in the 1970s had a profound impact. Initial studies of corticosteroid in severe TBI suggest improved survival, although at the cost of increased vegetative and profoundly injured patient population. The survival benefit was not subsequently confirmed in multiple RCTs. Despite these results, corticosteroids are still favored by many neurological surgeons and critical care physicians. The rise and fall of glucocorticoid use in TBI mirrors numerous novel therapies where hope triumphs over fact. That said, in my care of TBI patients, I have witnessed two patients with an intracranial pressure (ICP) monitor in place. Both patients had reproducible reductions in ICP in response to corticosteroid administration. However, these two patients are unique among the thousands of other TBI patients that I had cared for in my career. If the TBI patients that I treated are reflective of the general TBI population, I do not believe any RCT will be sufficiently powered or funded to test the efficacy of corticosteroid in the TBI setting.

**EDITORIAL COMMENTS**

There is perhaps no drug more used and misused in neurosurgery than corticosteroids. Most severe injuries treated by neurosurgeons are accompanied by subsequent inflammation which is thought to further compromise neurologic function. Proponents of corticosteroid therapy point to their potent and well-established anti-inflammatory effects as avenues to mitigate the physiologic consequences of these injuries. It is fair to say that most practicing neurosurgeons have, at one time or another, witnessed remarkable clinical response to high dose corticosteroid treatment in trauma patients. It is also a fact that such response is not a routine phenomenon.

As mechanisms of corticosteroid function became better elucidated, we now understand that its role in neurosurgery is most efficacious against inflammation related to vasogenic edema but not cytotoxic edema. The efficacy of corticosteroids against tumor-related vasogenic edema is undisputed. We routinely observe brain tumor patients with deficit attributable to vasogenic edema to improve after corticosteroid administration. These observations contrasts those in the TBI or traumatic spinal cord injury patients, where cytotoxic edema predominates.

It remains unclear whether the pathophysiologic processes in a subset of TBI patients involve vasogenic edema. In TBIs where vasogenic edema predominates, patients may benefit from corticosteroid treatment. As such, diagnostic modalities (e.g. advanced physiologic imaging, serum biomarkers, etc.) are needed to make such determinations. Given the current level of evidence and the available diagnostic tools, we do not believe that corticosteroids should be administered routinely in TBI patients. To the extent that RCTs are expensive and consuming of clinical resources, clinical investigators have an ethical responsibility to triage hypothesis and test only therapeutic agents/strategies that are most likely to benefit TBI patients. Given this need for triage and with the available RCT data, we do not believe that further testing of corticosteroid without an understanding of the pathophysiologic processes (e.g., vasogenic versus cytotoxic edema) underlying the various forms of TBI is warranted. RCT resources and efforts should be directed toward more promising therapeutic agents or strategies.
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