Chapter 14. Corticosteroids

I. RECOMMENDATIONS

Strength of the Recommendation: Weak.
Quality of the Evidence: Low, from two reports of one small, moderate-quality class II study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

The use of corticosteroids is not recommended to improve outcome or reduce intracranial pressure (ICP) for children with severe traumatic brain injury (TBI).

C. Level III

There are insufficient data to support a level III recommendation for this topic.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Corticosteroids are widely used in treatment of a variety of pediatric illnesses, including neurologic conditions such as brain tumors and meningitis. Steroids are thought to restore altered vascular permeability (1), inhibit tumor induced angiogenesis (2), and decrease edema and cerebrospinal fluid production (3, 4) as well as diminish free radical production (3). These mechanisms of action provide a rationale for potential benefit in neurologic diseases. Administration of steroids to patients with symptomatic brain tumors is standard care and preoperative administration is beneficial for patients undergoing resection. However, the efficacy of steroids to attenuate morbidity among pediatric patients with acute bacterial meningitis remains controversial (5). A number of corticosteroids are available; however, only dexamethasone has been reported in studies of pediatric TBI. This chapter addresses the use of corticosteroids as a neuroprotective agent to treat cerebral edema and improve Glasgow Outcome Scale in pediatric TBI. The question of the use of corticosteroids in the treatment of refractory hypotension was not addressed by the studies. Finally, the role of steroid therapy, both efficacy and toxicity, remains less well known in children compared with adults.

IV. PROCESS

For this update, MEDLINE was searched 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 20 potentially relevant studies, none were added as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two reports of one moderate-quality class II trial met the inclusion criteria for this topic and provide evidence to support the recommendation (6, 7).

A study by Fanconi et al (6) was a randomized, prospective, placebo-controlled clinical trial on 25 pediatric patients with severe TBI using dexamethasone at 1 mg/kg/day for 3 days (n = 13) vs. placebo (n = 12). Baseline characteristics did not differ between groups. Dexamethasone treatment did not influence ICP (mean of 14 mm Hg in both groups), cerebral perfusion pressure, number of interventions required, duration of intubation, or 6-month Glasgow Outcome Scale vs. placebo. However, steroid treatment vs. placebo significantly suppressed endogenous-free cortisol levels up to day 6. In addition, steroid treatment resulted in a trend toward increased bacterial pneumonia vs. placebo (seven of 13 vs. two of 12, respectively, p = .097). Although this study appeared to be carefully performed, limitations included use of the Richmond screw to assess ICP, fluid restriction, and the use of hyperventilation to a PaCO2 of 25–30 mm Hg as part of standard care.

The study by Kloti et al (7) reported on 24 of the same 25 patients from the study described previously. Additional outcomes in this report included duration of ICP monitoring; steroid treatment produced no difference between groups. The small sample size for this trial limits the ability to make definitive conclusions regarding neurologic outcomes or complications. However, suppression of cortisol production by steroid treatment was clearly documented.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

The most recent Guidelines for the Management of [Adult] Severe Traumatic Brain Injury (8) summarize studies of corticosteroid administration in adults and found that it did not improve functional outcome or mortality or lower ICP. They provide a strong class I recommendation against administration of steroids to improve outcome or lower ICP and caution that use is associated with increased risk of mortality and thus contraindicated. However, the studies in the adult guidelines do not specifically report on steroids use for pediatric patients after severe TBI.

B. Information Not Included as Evidence

Children with severe TBI have been observed to have higher rates of generalized hyperemia and more diffuse swelling after injury compared with adults, which could, theoretically, serve as a basis for the possible need for different approaches to the management of brain edema (9, 10). One report of steroid therapy in patients with severe TBI indicated better outcomes for children vs. adults (11); however, this difference may be the result of age and cannot be directly attributed to steroid-associated benefit. Several reports included in the 2003 pediatric TBI guidelines were excluded from this document because they failed to meet the more rigorous inclusion criteria. A study by Cooper et al (12) looked at a combined group...
Table 1. Evidence table

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Data Class, Quality, and Reasons</th>
<th>Results and Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design: randomized prospective, placebo controlled trial</td>
<td>Class II</td>
<td>Steroid treatment resulted in no differences vs. placebo in ICP, cerebral perfusion pressure, and 6-month Glasgow Outcome Scale, duration of ICP monitoring, or duration of intubation. Steroid treatment vs. placebo significantly suppressed endogenous free cortisol levels from day 1 to day 6. Steroid treatment resulted in a trend toward increased bacterial pneumonia (7 of 13 vs. 2 of 12 vs. placebo, respectively, ( p = .097 )).</td>
</tr>
<tr>
<td>N = 25; 13 steroid, 12 placebo (Fanconi)</td>
<td>Moderate quality: randomization and allocation concealment methods not described; unclear if outcome assessors were blinded</td>
<td></td>
</tr>
<tr>
<td>N = 24; 12/12 (Kloti)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: range 1.4–15.8 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score: ≤7</td>
<td></td>
<td></td>
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<tr>
<td>Protocol: dexamethasone at 1 mg/kg/day vs. placebo</td>
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<td></td>
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<tr>
<td>Outcome: 6-month Glasgow Outcome Scale, ICP, duration of ICP monitoring, duration of intubation, cerebral perfusion pressure, free cortisol levels, and complications</td>
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</tbody>
</table>

ICP, intracranial pressure.

of children and adults with severe and moderate TBI. Only ten patients were ≤10 yrs of age. In this subgroup, two of four (50%) in the placebo group compared with five of six (83%) in a combined low- and high-dose steroid group had a good outcome, which did not reach statistical significance. A study by Gobiet et al. (13) compared two cohorts, one from 1972–1974 without steroid treatment and a second from 1975–1976 with steroid treatment, and suggested a reduction in mortality. However, important differences between groups in ICP monitoring and intensive care unit care were also described, making it impossible to determine the effect of steroids on outcome. A study by James et al. (14) reported a case series of nine children with severe TBI and compared two doses of dexamethasone (1 mg/kg or 0.25 mg/kg) vs. no steroid in groups with sample sizes of only two in some groups, limiting any ability to assess for a treatment effect. A study by Kretschmer (15) reported a case series of 107 children in 1983 with TBI. Fifty-six received steroids and 51 received dexamethasone in addition to standard therapy. Reasons for exclusion of this study were the inclusion of 29 cases of penetrating injury, selection bias—24 of 29 cases of penetrating injury were in the no steroid group, and inclusion of patients with mild or moderate TBI. Overall mortality did not differ with treatment (24% vs. 23%). The authors reported a trend toward reduced mortality with steroid use in the subgroup of children with intracranial hematoma: from 36.8% to 11.8% in the placebo vs. steroid groups, respectively. Although no significant beneficial effect of steroids was reported, the exclusion violations in the overall study, small sample size, and major limitations in the study design preclude the ability to make meaningful conclusions with regard to corticosteroid therapy in pediatric TBI.

VII. SUMMARY

The recommendation regarding steroid administration to treat severe TBI in pediatrics is based on two reports of one class II trial, which indicates that steroid treatment is not associated with improved functional outcome, decreased mortality, or reduced ICP. Significant suppression of endogenous cortisol levels was documented with dexamethasone treatment and trends toward increased incidence of pneumonia were observed. Given the lack of evidence for benefit in children and the potential for harm from infectious complications and known suppression of the pituitary adrenal axis, the routine use of steroids to treat children with severe TBI to lower ICP or improve functional outcomes or mortality is not recommended.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Further studies are needed to determine risk factors for pituitary dysfunction and appropriate screening in the acute and chronic phases after severe TBI in children because alterations in the endogenous steroid response could have important implications on management, complications, and outcome (16).
- Future research should consider testing the efficacy of the use of corticosteroids for treatment of severe TBI in pediatric patients as distinct from adults. However, if a corticosteroid trial is considered, preliminary data are needed for careful assessment of potential toxicities, including infectious complications, hyperglycemia, and detrimental effects on nutritional status.

REFERENCES


11. Hoppe E, Christensen L, Christensen KN: The clinical outcome of patients with severe head injuries, treated with highdose dexamethasone, hyperventilation and barbiturates. *Neurochirurgia (Stuttg)* 1981; 24:17–20


