

Chapter 16. The use of corticosteroids in the treatment of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

1. *Standards.* There are insufficient data to support a treatment standard for this topic.

2. *Guidelines.* There are insufficient data to support a treatment guideline for this topic. The use of steroids significantly reduces endogenous cortisol production. The use of steroids may have an associated increased risk of complications of infection in children.

C. *Options.* The use of steroids is not recommended for improving outcome or reducing intracranial pressure (ICP) in pediatric patients with severe traumatic brain injury (TBI). Despite two class II studies failing to show efficacy, the small sample sizes preclude support for a treatment guideline for this topic.

D. *Indications from Adult Guidelines.* The majority of available evidence indicates that steroids do not improve outcome or lower ICP in severely head-injured adult patients (1). The routine use of steroids is not recommended for these purposes.

II. OVERVIEW

Corticosteroids have been commonly used in children, for a wide range of neurologic diseases, to reduce edema (due to tumors, infection, inflammation) and to lessen its neurologic effects. The potential of steroid use in adults following TBI was first indicated in literature reporting the benefits of edema reduction and clinical improvement in brain tumor patients. As summarized in the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1), there is evidence that steroids are useful in reducing cerebral edema, attenuating free radical production, and affording other beneficial effects in experimental models of TBI, but clinical evidence did not support its use. In the adult literature reviewed, corticosteroids did not improve functional outcome or prove useful in

reducing ICP in patients with severe TBI. The studies cited in the adult guidelines did not specifically report on the use of corticosteroids in pediatric patients following severe TBI, but there was a suggestion of potential efficacy in younger patients. A specifically pediatric review was necessary to determine whether there is adequate evidence to support recommendations for children.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 45 potentially relevant studies, eight were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

In clinical practice, steroids have been used in an attempt to reduce posttraumatic swelling and improve outcome in both adults and children. The role of steroids remains uncertain in the treatment of TBI, particularly as it relates to the pediatric population.

Cooper et al. (2) performed a prospective, randomized, double-blind clinical trial with adults and children using dexamethasone. There were 76 total patients, ten of whom were ≤ 10 yrs of age, and 32 who were less ≤ 20 yrs of age. Only severely injured patients were included, and each of the patients was randomized to one of three groups—placebo, low-dose steroids, and high-dose steroids. The adults were given standard doses, whereas the children were given weight-related doses. Assignment to the groups was randomized on entry into treatment, but there was no stratification by age. Glasgow Outcome Scale (GOS) was assessed at 6 months. The analysis performed was on the relation of treatment to outcome. The authors reported that in

older patients there was no difference in outcome with the use of steroids. Because of the small number of children included, no conclusions could be drawn regarding steroid use in pediatric TBI.

Fanconi et al. (3) performed a randomized, prospective clinical trial on 25 pediatric patients using dexamethasone at $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ for 3 days ($n = 13$) and 12 controls treated with an alternate standard regimen. Outcome was determined by 6-month GOS and response by endogenous free cortisol levels. In this study, there was no difference in effect on ICP or cerebral perfusion pressure and no difference in 6-month outcome. There was a statistically significant suppression of cortisol levels up to 6 days posttreatment. As well, there was a significantly increased bacterial infection rate in those patients treated with steroids.

Gobiet (4) reported on a case control series of 205 children: 139 who did not receive steroids, and 66 who did. The intervention was high-dose dexamethasone, although no specific dose was reported. The nonsteroid treatment group was a consecutive sample of 139 patients from the years 1972–1974 who were treated with neither ICP monitoring nor aggressive intensive care unit therapy. The later steroid treatment group (recruited 1974–1975) received ICP monitoring, intensive care unit management, and steroid therapy. There was no length of follow-up reported, but the measures of outcome included mortality rate, length of intubation, ICP, seizures, and scholastic performance. The authors reported that there was decreased mortality rate with the use of steroids but no difference with regard to length of intubation, time of unconsciousness, incidence of seizures, or neurologic outcome. A comparison between the groups in this study is compromised because significant differences in timing and approach may confound many subtle variables of treatment. However, given the lack of differ-

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Cooper et al. (2), 1979	Prospective, double-blind study of 76 patients with severe head injury (42 of whom were <20 yrs of age, ten of whom were <10 yrs of age). The patients were stratified for severity and treated with placebo or weight-related doses in the children. Six-month GOS was then determined.	III	No significant difference in 6-month outcome in the older children and adults. Potentially improved outcome in children <10 yrs of age, although numbers were too small to determine true differences.
Fanconi et al. (3), 1988	Prospective, randomized clinical trial of 25 patients treated with placebo or 1 mg·kg ⁻¹ ·day ⁻¹ × 3 days. Endogenous free cortisol and 6-month GOS were determined.	II	Steroid treatment resulted in no difference in ICP, CPP, or outcome. Steroid treatment significantly suppressed endogenous free cortisol and increased infection rate.
Gobiet (4), 1977	Retrospective review of 205 children who received "high-dose" dexamethasone vs. no steroids. The early nontreated group was from 1972 to 1974; the treated group was the later, more aggressively treated population with ICP monitors in treatment of intracranial hypertension.	III	No difference in acute variables or outcome, although there was a suggestion of decreased mortality rate in the treated group.

	Group I No ICP Monitoring or Steroids	Group II ICP Monitoring and Steroids
Number	139	66
Died	58	10
% mortality	41.7%	15.8% (<i>p</i> < .001)

Reference	Description of Study	Data Class	Conclusion
Gobiet (5), 1977	Retrospective review of 100 patients using no steroids, normal dose steroids, and "high-dose" steroids in differing doses. The different treatment regimens were not specifically delineated, nor was the relationship between the use of other therapies. Only acute measures were performed.	III	There was no difference in outcome. Steroids reduced brain edema, but there were no data confirming this.
Hoppe et al. (6), 1981	Case series of 22 patients maximally treated with a conglomeration of regimens.	III	Younger patients had a better outcome.

Age, yrs	GOS 1-3	GOS 4-5	% Good Outcome
<20	3	19	86
≥20	9	14	61
Total	12	33	

Reference	Description of Study	Data Class	Conclusion
James et al. (7), 1979	Case control study of nine patients. Group 1 received no or low-dose steroids, and group 2 received high-dose steroids. Neurologic exam and 6-month GOS were determined.	III	No improved long-term outcome based on GOS due to low numbers, although reported improved GCS, mean ICP and ICP wave fluctuations, acute neurologic exam, and ICU and hospital course in the acute period.

Group	GOS 1-3	GOS 4-5	% Good Outcome
Group 1, no or low-dose steroids (n = 4)	3	1	25
Group 2, high-dose steroids (n = 5)	0	5	100
Total	3	6	

Table 1. Continued

Reference	Description of Study	Data Class	Conclusion		
Kloti et al. (8), 1987	Prospective, randomized clinical trial of 24 patients. Group 1 received dexamethasone (1 mg·kg ⁻¹ ·day ⁻¹), and group 2 received no steroids. Urinary-free cortisol in the acute period and 6-month GOS were used for outcome.	IIA	There was near complete suppression of endogenous cortisol, and no difference in long-term outcome.		
	Group	GOS 1–4	GOS 5	% Good Outcome	
	Group 1, steroids 1 (n = 12)	3	9	75	
	Group 2, no steroids 2 (n = 12)	4	8	67	
	Total	7	17		
Reference	Description of Study	Data Class	Conclusion		
Kretschmer (9), 1983	Retrospective review of 107 patients, 51 of whom received a loading dose of dexamethasone, 20–25 mg, and then received a dosing based on whether body weight was < or >35 kg (not based on a mg/kg schedule), in conjunction with standard therapy. This series included penetrating injuries, mild to moderate head injuries, as well as differences in severity between treated and nontreated groups.	III	There was lowered mortality rate in the steroid group in patients with intracranial hematomas and severe injuries (GCS 5–7), although the small numbers precluded conclusion of efficacy.		
		Intracranial Hematomas	% of Patients	GCS 5–7	% of Patients
	Group 1 (steroids)				
	Favorable	15	88.2	14	63.6
	Unfavorable	2	11.8	8	36.4
	Mortality	2	11.8	3	13.6
	Group 2 (no steroids)				
	Favorable	11	57.8	9	60
	Unfavorable	8	42.1	6	40
	Mortality	7	36.8	5	33

GOS, Glasgow Outcome Scale; ICP, intracranial pressure; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; ICU, intensive care unit.

ence between the groups on other variables measured, one might fairly conclude that the addition of an aggressive treatment protocol with ICP monitoring may reduce mortality rate.

Gobiet et al. (5) reported on the study of 100 patients, including 40 children, but there was no separate report of results in the pediatric group. The authors reviewed their experience with ICP monitoring, hyperosmolar therapy, and treatment with or without high-dose steroids in two consecutive patient groups. The earlier patients in the series (1973–1974) all had ICP monitoring and a “standard” therapeutic regimen. The later patients (1975) received steroids in addition to the previous therapies. No conclusion for the use of dexamethasone in pediatric TBI can be drawn from this study because the data for children are confounded with adult measures.

Hoppe et al. (6) reported a case series of 22 patients <19 yrs of age who received intensive therapy in a multiple-treatment regimen including steroids, barbiturates, and hyperventilation. The steroid treatment was dexamethasone 120 mg, given at admission, 6 and 72 hrs after injury, combined with 4 mg every 6 hrs. They reported outcomes measured by 3- and 6-month GOS. Their only conclusion with regard to children was that younger patients had better outcomes, but the authors did not report a specific relation of outcome to the use of dexamethasone.

James et al. (7) reported a retrospective case series of nine pediatric patients with severe TBI. Group 1 received no or low-dose steroids (dexamethasone = 0.25 mg·kg⁻¹·day⁻¹), and group 2 received high-dose steroids (1 mg/kg every 6 hrs for two doses and then 1 mg·kg⁻¹·day⁻¹).

The children otherwise received standard treatment for severe TBI. Outcome was determined by their course and length of stay in the intensive care unit and in the hospital and 6-month GOS. The authors concluded that steroids improved Glasgow Coma Scale (GCS) and neurologic exam by 7-days postinjury, shortened intensive care unit and hospital stay, and decreased mean ICP and ICP wave fluctuations. There was no increase in gastrointestinal hemorrhage or in pulmonary infection. There was no significant difference in GOS outcome at 6 months, although group 2 tended to have better outcomes.

Kloti et al. (8) performed a prospective, randomized clinical trial in 24 severely head-injured children. Group 1 received steroids at 1 mg·kg⁻¹·day⁻¹, and group 2 received no steroids. The children were otherwise treated with stan-

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standard therapy. In this study, outcome measures included urinary-free cortisol to assess cortisol excretion as well as functional outcome using the 6-month GOS. There was no difference between the two groups with regard to mean ICP stay, duration of intubation, or 6-month GOS. In group 1, there was complete endogenous cortisol suppression. In group 2 patients, free cortisol was increased 20-fold from normal basal conditions, reaching maximum levels at 1–3 days after injury. In addition, 50% of patients in group 1 developed pneumonia compared with only 15% in group 2.

Kretschmer (9) reported a retrospective review of 107 head-injured pediatric patients with a pathologic finding on computed tomography scan, 51 of whom received steroids. Dexamethasone was given as a bolus (20–25 mg) and then as an infusion based on body weight (above or below 35 kg). The patients otherwise received standard treatment for severe TBI. The two groups differed significantly: a) the study included 29 patients with penetrating injuries, 24 of whom were in the no-steroid group; b) for contusive injury, 29 of 42 patients were treated with steroids; c) mild to moderate head injuries (GCS 8–15) were included but not equally distributed in assignment, resulting in different average severity in the treated and nontreated groups (mean GCS of 7.4 vs. 9, respectively). Outcome was measured by the GOS, but length of follow up was not

reported. Although the overall mortality rate between groups did not differ (24% vs. 23%, treated vs. untreated, respectively), the authors concluded that steroid treatment reduced mortality rate in patients with intracranial hematomas (36.8% vs. 11.8%) and in those with initial GCS 5–7 (33% vs. 14%). Dexamethasone, however, was not useful in the most severely injured patients (GCS 3–4), the mild and moderately injured, or those with penetrating injuries. Because the groups were not evenly balanced on mechanism of injury or severity, conclusions on the efficacy of using steroids in pediatric TBI cannot be drawn from this study.

V. SUMMARY

The majority of available evidence indicates that steroids did not improve functional outcome in pediatric patients with severe TBI. A few studies reported beneficial effect on outcome, but they all had design problems, so recommendations for steroid use cannot follow from their results. In addition, there were as many studies that were inconclusive or lacking any evidence of efficacy. A few studies did not show evidence of complications from steroid use, but two others reported significantly increased rates of infection (bacterial infections and pneumonia) and suppression of endogenous cortisol, which further lessens any enthusiasm for the use of this treatment. With the lack of sufficient evidence for beneficial effect and the potential for increased complications and suppression of adrenal production of cortisol, the routine use of steroids is not recommended for children following severe TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Efficacy

Despite the lack of sufficient clinical evidence of efficacy, there may be subgroups of children with severe TBI who might benefit from the use of high-dose steroids in treatment. Examples of candidate conditions are certain types of pathology (like diffuse swelling or intracranial hematomas), different levels of severity (moderately severely injured, GCS 5–7), and age at injury (school-age children). Further experimental and clinical

studies that use high-dose steroids with stratification of these variables among the comparison groups will be necessary before recommendations for treatment can be made.

Complications

Future trials also will need to address the issue of complications, specifically infection and gastrointestinal hemorrhage, and whether preventive interventions (e.g., antibiotics and/or H₂ blockers) are effective in reducing or eliminating occurrences.

Endogenous Cortisol

There is evidence that endogenous cortisol production is suppressed with the administration of corticosteroids following severe TBI. The significance of the suppression of endogenous cortisol production and its effect on clinical course and outcome, as well as the effect of an increased catabolic response, needs to be answered.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 16. Steroids

1. exp craniocerebral trauma/
2. head injur\$.tw.
3. brain injur\$.tw.
4. 1 or 2 or 3
5. exp steroids/ or "steroids".mp.
6. glucocorticoids, synthetic/ or "synthetic glucocorticoids".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)