Systemic metabolic effects of combined insulin-like growth factor–I and growth hormone therapy in patients who have sustained acute traumatic brain injury

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Object. Hypermetabolism, hypercatabolism, refractory nitrogen wasting, hyperglycemia, and immunosuppression accompany traumatic brain injury (TBI). Pituitary dysfunction occurs, affecting growth hormone (GH) and plasma insulin-like growth factor–I (IGF-I) concentrations. The authors evaluated whether combination IGF-I/GH therapy improved metabolic and nutritional parameters after moderate to severe TBI.

Methods. The authors conducted a prospective, randomized, double-blind study comparing combination IGF-I/GH therapy and a placebo treatment. Ninety-seven patients with TBI were enrolled in the study within 72 hours of injury and were assigned to receive either combination IGF-I/GH therapy or placebo. All patients received concomitant nutritional support. Insulin-like growth factor–I was administered by continuous intravenous infusion (0.01 mg/kg/hr), and GH (0.05 mg/kg/day) was administered subcutaneously. Placebo control group patients received normal saline solution in place of both agents. Nutritional and metabolic monitoring continued throughout the 14-day treatment period.

The two groups did not differ in energy expenditure, nutrient intake, or use of insulin treatment. The mean daily serum glucose concentration was higher in the treatment group (123 ± 24 mg/dl) than in the control group (104 ± 11 mg/dl) (p < 0.03). A positive nitrogen balance was achieved within the first 24 hours in the treatment group and remained positive in that group throughout the treatment period (p < 0.05). This pattern was not observed in the control group. Plasma IGF-I concentrations were above 350 ng/ml in the treatment group throughout the study period. Overall, the mean plasma IGF-I concentrations were 1003 ± 480.6 ng/ml in the treatment group and 192 ± 46.2 ng/ml in the control group (p < 0.01).

Conclusions. The combination of IGF-I and GH produced sustained improvement in metabolic and nutritional endpoints after moderate to severe acute TBI.

KEY WORDS • insulin-like growth factor • growth hormone • nutrition • traumatic brain injury

EARLY nutritional intervention after acute TBI has been found to improve mortality rates but has failed to achieve a balance in the metabolic and catabolic demands associated with the injury. Primary injury to the brain results in the release of inflammatory mediators and altered cellular signals within the central and peripheral compartments, affecting metabolic response. The acute phase response after TBI has been well characterized and includes hypermetabolism, hypercatabolism, hypoalbuminemia, refractory nitrogen wasting, and immunosuppression. Increased levels of catecholamines, increased cytokine concentrations, and depressed concentrations of IGF-I occur in severe stress conditions, including acute TBI. Growth hormone is another contributor to the metabolic changes observed in the acute phase response.

In noninjured humans, IGF-I is produced systemically and centrally in response to GH and nutritional status. The physiological actions of IGF-I include stimulation of glucose uptake, glycogen synthesis, amino acid transport, mitogenesis, and cellular differentiation in target tissues. Endogenous binding proteins for IGF-I participate in delivery of this hormone to target tissues. The principal binding protein for systemic IGF-I is IGFBP-3. This protein is only one of the IGF binding proteins produced by the liver, but it is structurally distinguished by the presence of an acid-labile subunit. Nutritional intervention and disease states affect IGF-I and IGFBP-3 concentrations, as well as the acid-labile sub-

Abbreviations used in this paper: ARDS = adult respiratory distress syndrome; GCS = Glasgow Coma Scale; GH = growth hormone; GOS = Glasgow Outcome Scale; IGF-I = insulin-like growth factor–I; IGFBP-3 = IGF–binding protein 3; IL = interleukin; TBI = traumatic brain injury.
Although IGF-I mediates GH anabolic actions, disease and nutritional conditions disrupt this relationship and lead to inconsistent benefits when GH has been used alone. Administration of recombinant IGF-I transiently improves nitrogen retention and lowers glucose concentrations in a dose-dependent manner, but concentrations of GH and IGFBP-3 decline. Findings from animal models of injury in which improved metabolic profiles with concomitant GH and IGF-I therapy were shown have led to clinical Phase I studies in humans. In healthy human volunteers, plasma concentrations of IGF-I have been improved and maintained when IGF-I was administered in combination with GH. Nitrogen balance has also been improved with combination treatment, compared to treatment with IGF-I alone. This combination has been evaluated in only a small number of patient populations.

Acute TBI alters pituitary function and release of GH. In patients with acute, moderate to severe nonpenetrating TBI who received continuous intravenous infusion of IGF-I, nitrogen retention has been improved when plasma concentrations exceeded 350 ng/ml. Sustained pharmacological concentrations have not been observed despite continuous infusion. Both GH and IGFBP-3 concentrations have been lower in TBI patients treated with IGF-I, compared to placebo, suggesting induction of the endogenous feedback system similar to that observed in healthy volunteers. The purpose of this study was to determine if pharmacological concentrations of IGF-I can be achieved and sustained when the combination of IGF-I and GH is administered to patients with acute TBI. The study hypothesis was that combined administration of IGF-I and GH improves nutritional and metabolic parameters after acute, moderate to severe nonpenetrating TBI.

Clinical Material and Methods

Study Design

This study was a prospective, randomized, double-blind, placebo-controlled clinical trial of patients admitted with the diagnosis of acute, moderate to severe nonpenetrating TBI. All patients were treated using standard treatment guidelines for TBI. Intravenous catheters were routinely placed when the admission GCS score was less than 8. Patients aged 18 to 59 years were randomly assigned within 72 hours of injury to receive either IGF-I/GH or placebo. To be included, patients were required to have a GCS score of 4 to 10 after resuscitation and stabilization and within 6 hours of admission. Study groups were stratified by using randomization tables to maintain balance between age (< 35 years, ≥ 35 years), gender (male, female), and qualifying GCS score (one of three scores). Patients were excluded if the injury was considered nonsurvivable (as suggested by a GCS score of 3 and presence of fixed nonreactive pupils), if evidence of other major trauma to vital organs or the spinal cord was present, if a history of chronic disease was present, or if consent was not obtained. All study medications were provided by Genentech, Inc. (San Francisco, CA). The study was approved by the University of Kentucky Institutional Review Board.

Study Protocol

After informed consent was received from the patient’s next-of-kin or representative, patients were randomly assigned to either the active study arm (IGF-I/GH) or the placebo (control) arm (normal saline solution). Patients assigned to the active treatment arm received IGF-I 0.01 mg/kg/hr intravenously by continuous infusion for up to 14 days along with GH 0.05 mg/kg/day injected subcutaneously. The drug solutions were clear and protected from light by aluminum foil. The final infusion volume was 250 ml. Normal saline solution was administered in place of both agents to patients in the placebo arm. Insulin was permitted to keep glucose concentrations below 200 mg/dl, and study medications were stopped if the patient’s glucose concentration fell below 45 mg/dl.

Patients were required to receive enteral or parenteral nutritional support within 72 hours of injury, and at least 14 hours of nutritional support was required prior to study drug administration. Nutritional support continued throughout the 14-day study period or until discharge, whichever occurred earlier. The route of nutrient administration was not dictated by the protocol. The regimen was fixed at 2.0 g/kg/day of protein and 1.25 times the measured energy expenditure for the patient.

Sample Collections and Analysis

Serial collection of blood to analyze IGF-I concentrations and renal and liver function was performed at baseline and over the study period. Consecutive 24-hour urine collections for nitrogen balance were conducted for the first 3 days and repeated during the first and second weeks of the study protocol. To obtain preliminary evidence of potential benefit on systemic inflammatory and immune responses, serial blood collections were performed for systemic cytokines analysis by enzyme-linked immunosorbent assay. In 20 patients, immune response was assessed. Baseline whole blood samples were obtained in those patients and compared to samples obtained in 20 healthy volunteers matched to the patients by age, gender, and race. Quantitative and functional studies were conducted. Functional studies required the separation of peripheral blood lymphocytes by layering onto gradients (Histopaque; Sigma-Aldrich Corp., St. Louis, MO) and centrifugation. Purified T cells were obtained by resetting with sheep red blood cells, which were lyzed and washed for plating in triplicate. Staphylococcus aureus Cowan strain protein A was used to stimulate B cells, and T cells were stimulated using phytohemagglutinin. Samples were analyzed by using flow cytometry.

Data Analysis

A study design of 75 patients per group would provide 80% power to detect a 20% decline in mortality rate if the IGF-I/GH combination had a significant effect on the rate of mortality, evaluated at 6-month intervals up to 2 years. A comparison of GOS scores between groups was done at Day 15. The proportion of patients in each of the five GOS outcome categories was compared between groups by using the Fisher exact test for a 5 × 2 contingency.
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Table. For short-term nutrition-related effects, this study had 80% power to detect a difference in means at least as large as 0.58 of a standard deviation.

Plasma concentrations of IGF-I were compared between groups. Nutritional endpoints included calorie and nitrogen balance. Safety endpoints included infection rate, rate of clinically significant fluid retention (refractory intracranial hypertension, ARDS), and incidence of adverse events. The diagnosis of ARDS required a PaO₂ to FiO₂ ratio below 200 for 3 or more days independent of positive end expiratory pressure and radiographic evidence of bilateral infiltration. The highest measured intracranial pressure and baseline intracranial pressure were compared within and between the groups for the first 3 days of treatment. Infections were defined by positive culture results, radiographic evidence, and associated clinical symptoms. Bacteremia, which was not considered an infection, was recorded in the event of positive blood culture results in the absence of other symptoms. Infection was recorded if blood culture results were positive and the criteria for sepsis were met. Instances of multiorgan failure were also recorded. The analysis of the infection rate data emphasized the occurrence of a particular infection, for example, sepsis, within the first 28 days of the study. For this endpoint, three outcomes were possible: at least one episode of infection, or death before the 28th day either with or without infection. Baseline immune parameters were compared between patients with TBI and healthy controls. A univariate comparison between groups was based on the Fisher exact test for a 2 × 2 contingency table.

Tests for serum glucose concentration and nitrogen balance were considered measures of short-term recovery. Each short-term test was measured at several points in time, and repeated-measures analysis of variance was used to compare mean improvement scores between groups. When data were missing due to death of a patient or lack of compliance with data collection, the repeated-measures analysis was based on an estimated generalized least squares procedure.

Results

Patient Population

Between 1995 and 1997, 259 patients were screened for eligibility. Exclusion criteria were imminent death in 14 patients, age in 46, disease in 19, penetrating injury in 8, GCS score in 57, lack of consent in 11, and nondefined reasons in 28 patients. Individual patients could be excluded for more than one reason. Ninety-eight patients were enrolled in this investigation (Table 1). For 97 patients were eligible for analysis; one patient was withdrawn from the study because they entered into litigation requiring premature unblinding of the patient’s treatment assignment. Forty-nine patients were assigned to the active treatment arm, and 48 to the placebo arm. All patients were enrolled and received investigational therapy within the first 72 hours after injury. The study groups did not differ in time to study enrollment and dose initiation. Demographic parameters were not different between the groups, and young male patients constituted the majority of the study participants. All patients were younger than 50 years of age. Duration of study treatment, number of intensive care days, number of hospital days, and rate of completion of both acute and chronic study periods were not different between the groups. External ventricular devices were routinely placed for patients with an admission GCS score less than 8 and were required for 34 patients in the treatment group and 36 patients in the placebo group. Mean peak intracranial pressures were 23.5 ± 1.5 mm Hg in the treatment group and 22.8 ± 1.7 mm Hg in the control group. Pentobarbital was used in 15 treated patients and 13 patients in the placebo group during the 1st study week. No differences in GOS scores were observed at the end of the dosing period. The mortality rate was similar in the two groups, with 10 deaths occurring in the treated group and 11 deaths in the placebo group. Eight deaths occurred in each group within the first 15 days after injury.

Nutrition Endpoints

Both groups were hypermetabolic at baseline. Measured energy expenditure was 2271 ± 575.6 kcal/day in the placebo group and 2366 ± 627.8 kcal/day in the treatment group at baseline and remained elevated throughout the study period (Table 2). Neither group reached calorie or protein intake goals, but overall mean calorie and protein intake did not differ between the groups. Mean daily glucose concentrations were higher in the treatment group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Group</th>
<th>IGF-I/IGF–Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>29 ± 8.6</td>
<td>30 ± 10.1</td>
</tr>
<tr>
<td>sex (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>male</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>qualifying GCS score</td>
<td>6.7 ± 1.5</td>
<td>6.4 ± 1.6</td>
</tr>
<tr>
<td>baseline severity of injury</td>
<td>(no. of patients)*</td>
<td></td>
</tr>
<tr>
<td>I</td>
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<td>1</td>
</tr>
<tr>
<td>II</td>
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<td>V</td>
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<td>8</td>
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<tr>
<td>VI</td>
<td>2</td>
<td>3</td>
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<tr>
<td>weight at admission (kg)</td>
<td>76.1 ± 12.9</td>
<td>75.2 ± 12.9</td>
</tr>
<tr>
<td>time b/wn injury &amp; drug dosing (hrs)</td>
<td>52 ± 11.5</td>
<td>54 ± 12.9</td>
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<tr>
<td>no. of days drug administered</td>
<td>11 ± 4.3</td>
<td>11 ± 4.2</td>
</tr>
<tr>
<td>no. of patients finishing 14 days of treatment</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>intensive care unit stay (days)</td>
<td>12 ± 8.9</td>
<td>15 ± 9.4</td>
</tr>
<tr>
<td>hospital stay (days)</td>
<td>17 ± 10.0</td>
<td>22 ± 14.8</td>
</tr>
<tr>
<td>no. of deaths</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>incomplete follow up (no. of patients)</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* Based on an evaluation of computed tomography (CT) scans using the Traumatic Coma Data Bank classification. The CT data presented are prior to the first dose of the study drug. One patient did not have a predose, or baseline, CT scan available.
Baseline serum IL-6 and IL-8 concentrations were elevated: 509 ± 153 pg/ml and 1776 ± 470 pg/ml, respectively. Mean values of IL-6 decreased in both groups over the study period, and endpoint values did not differ greatly between groups (306 ± 140 pg/ml for the placebo group and 258 ± 202 pg/ml for the treatment group, respectively). When compared to baseline, the mean IL-8 value increased in a nonsignificant fashion in the placebo group (2076 ± 516 pg/ml); in the treatment group there was no change when compared to baseline (1612 ± 533 pg/ml). Trends toward increases in the counts of natural killer cells and T-cell subsets (CD8, CD4) receptors were observed in both groups; however, there was no significant difference between groups in these values.

**Plasma IGF-I Concentrations**

Plasma IGF-I concentrations were determined in 30 patients in the placebo group and 32 treated patients. Mean pretreatment baseline IGF-I concentrations were 169 ± 97.7 ng/ml in all patients with TBI, 136 ± 81.0 ng/ml in the placebo group, and 201 ± 113.7 ng/ml in the treatment group (Fig. 1). The difference between groups was not significant. Baseline values were below 150 ng/ml in 10 subjects in the placebo group and 17 treated subjects. The placebo group mean concentration during the first 24 hours was 144.8 ± 84.2 ng/ml, and seventeen patients had values below 150 ng/ml at this point. This pattern continued during the 1st week after TBI, with the overall mean concentration of 177.7 ± 113.5 ng/ml for the 2nd through 7th days in the control group. By the 2nd week, overall concentrations averaged 210 ± 119.5 ng/ml.

<table>
<thead>
<tr>
<th align="left">TABLE 2</th>
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<tbody>
<tr>
<td align="left"><strong>Summary of nutritional parameters during administration of placebo or IGF-I/GH in patients with acute TBI</strong></td>
</tr>
<tr>
<td align="left">Parameter</td>
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<tr>
<td align="left">-----------</td>
</tr>
<tr>
<td align="left">no. of patients</td>
</tr>
<tr>
<td align="left">measured energy expenditure (kcal/day)</td>
</tr>
<tr>
<td align="left">nonprotein calorie intake (kcal/day)</td>
</tr>
<tr>
<td align="left">protein intake (g/day)</td>
</tr>
<tr>
<td align="left">nitrogen balance (g/day) †</td>
</tr>
<tr>
<td align="left">serum glucose concentration (mg/dl)</td>
</tr>
<tr>
<td align="left">min</td>
</tr>
<tr>
<td align="left">max</td>
</tr>
</tbody>
</table>

* Values for nutritional parameters are presented as least squares means ± standard errors of the mean.
† Significant difference (p = 0.0001).
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In contrast, concentrations exceeding the physiological range (>400 ng/ml) were achieved in 31 treated patients during the first 24 hours, with a group average of 422 ± 219.7 ng/ml. Values less than 150 ng/ml were not observed in this group. Plasma IGF-I concentrations reached steady state at approximately 72 hours of drug infusion. The overall mean values in this group were 1255 ± 425.3 ng/ml during the first week and 1433 ± 504.0 ng/ml during the second week, significantly higher than in the control group (p < 0.01). The overall mean concentration of IGF-I during the 14-day treatment period in the treatment group was 1003 ± 480.6 ng/ml, compared to 192 ± 46.2 ng/ml in the placebo group (p < 0.01).

Plasma IGFBP-3 values were evaluated in both groups. The baseline mean concentration was 2.7 ± 0.65 μg/ml, which was within normal limits (1.4–4.3 μg/ml). After 24 hours, the mean value in the placebo group had not changed significantly (2.5 ± 0.92 μg/ml), but the mean value in the treatment group began to increase (3.3 ± 1.39 μg/ml), although the difference was not significant. During the 1st week, overall mean values in the treatment group increased to 5.7 ± 1.66 μg/ml, compared to 3.0 ± 0.90 μg/ml in the placebo group (p < 0.05). During the second week, the overall mean values were 6.6 ± 1.71 μg/ml in the treatment group, compared to 3.7 ± 0.97 μg/ml in the control group (p < 0.05). The control group values were stable from the first week to the second week.

Clinical Parameters and Adverse Events

For the majority of safety endpoints, no significant difference between groups was observed (Table 3). Hypokalemia, hypercalcemia, and bacteremia were more frequently reported in the treatment group. Cerebrospinal fluid cultures positive for bacteria were observed in five patients in each group during the treatment phase of the protocol. There was no evidence of fluid retention differences between the two groups. Adult respiratory distress syndrome developed in five treated and nine placebo patients.

There was no significant difference in infection rate or type during the study protocol. Infection developed in 70% of the control patients and 82% of the treated patients during the study. The most common infection was pneumonia, followed by urinary tract infections. *Staphylococcus, Klebsiella, Enterobacter, and Serratia* species and *Pseudomonas aeruginosa* were the most frequent isolates. Sepsis was recorded for six patients in the placebo group and for five treated patients.

**Discussion**

In this study, the combination of nutritional support and growth factor therapy following acute TBI generated a positive nitrogen balance within the first 24 hours after injury, and this anabolic state was maintained throughout the dosing protocol. With the addition of GH to IGF-I, serum concentrations exceeding the physiological range were achieved without evidence of clinically significant adverse events. Although serum glucose concentrations were higher with the growth factor regimen, they remained significantly below thresholds affecting outcome.\(^{3,11,102–104}\) There was no evidence of increased fluid retention, intracranial pressure, infection risk, or mortality rate with this combination therapy. Cytokines and immune parameters were not significantly affected by this treatment in the population studied. These results confirm earlier observations that refractory nitrogen wasting after acute TBI can be safely modulated by combining nutrition support with growth factor therapy.\(^{41}\) The anabolic conditions observed in this protocol were superior to those reported when either GH or IGF-I were administered as single agents to critically ill patients.

In severe TBI, pituitary dysfunction alters GH secretion, reducing plasma IGF-I concentrations.\(^{3,26,36,53,64}\) Re-
sidual endogenous pituitary responsiveness to GH stimuli has been correlated with survival following severe TBI.16 The physiological effects of GH include stimulation of DNA and RNA synthesis, enhancement of nitrogen and mineral retention, regulation of immune function, and stimulation of lipolysis, protein synthesis, and insulin and IGF-I release, antagonizing insulin’s effects on glucose homeostasis.15,16,111 Upon GH binding, the liver generates an acid-labile subunit and binding protein (IGFBP-3) for transport of IGF-1 to systemic target organs.25 Insulin-like growth factor–I, previously known as somatomedin C, has been recognized as the stimulus for many effects originally attributed to the actions of GH. For example, IGF-I enhances glucose uptake in cells, ameliorates relative insulin resistance, and reduces blood glucose, C-peptide, and insulin levels.31 The actions of IGF-I also include cellular proliferation and differentiation, suppression of protein degradation, and increased amino acid uptake. Altered production of acid-labile subunit or IGFBP-3 significantly affects IGF-I systemic concentrations and could affect cellular delivery. When GH has been given to patients with either severe head or spinal cord injury, IGF-I levels improved, but serum glucose concentrations increased.3 In a catabolic illness, GH administration does not predictably improve IGF-I concentrations and generates significant metabolic complications.

Guidelines for the management of patients with TBI have included the development of optimal nutrition regimens.3 Inadequate nutritional support has been reported to increase morbidity and mortality rates after acute TBI.47 Doses of GH required for nitrogen sparing in catabolic conditions are five to 20 times the replacement dose.89,105 At this dosing range, significant hyperglycemia, fluid retention, and immune modulatory effects have been reported.11,90,101 Moderate to severe TBI has been accompanied by serious infectious complications in 50 to 75% of patients.82–86 Anergic responses to common skin test antigens have occurred in up to 80% of these patients, and mitogen response of peripheral blood mononuclear cells has been depressed.82–87 Patients with TBI are also at risk for pulmonary dysfunction, intracranial hypertension, elevated central nervous system concentrations of lactate, and hyperglycemia.3,39,51,110 The potential for GH to exacerbate these complications is a major factor limiting its utility as a single agent for anabolic therapy following TBI.

When GH was combined with IGF-I in an aggressive nutritional support regimen, blood glucose concentrations in treated patients were not significantly different from those patients in the placebo control. After brain injury, catabolic hormones and cytokine levels increase, and nor-epinephrine levels up to seven times higher than that observed in uninjured patients have been reported.21,69,70 This endogenous response results in hyperglycemia, insulin resistance, compromise of the immune system, and persistent loss of protein. Hyperglycemia is a factor in poor outcome following TBI and trauma.72,80,100 Correlations between admission GCS scores, serum glucose concentrations exceeding 200 mg/dl, and poor outcome have been documented following acute TBI.100 Daily glucose concentrations exceeding 170 mg/dl in patients with a GCS score greater than or equal to 8 have also been associated with poor outcome.54 In the patients with TBI in our study, the IGF-I/GH combination did not produce daily glucose concentrations exceeding either threshold affecting outcome. The combination of IGF-I and GH with nutritional support addresses many factors contributing to the persistent catabolic state accompanying moderate to severe brain injury without requiring the high-dose GH regimens associated with metabolic complications.

In a large prospective, randomized clinical trial of critically ill adults, high doses of GH as a single agent increased morbidity and mortality rates, primarily from infectious complications and septic shock.93 The high mortality rate reported in this European GH trial led to a halt of our investigation despite major differences in study design.93 No patient with acute TBI was enrolled into the European trial, and the doses studied were higher than those used in our investigation. The dose of GH in the current clinical trial was only 0.05 mg/kg/day, within an acceptable range reported to improve nitrogen balance and IGF-I concentrations when given alone.92 The maximum glucose concentrations in the treated patients and patients in the placebo group in our study were similar to those observed in the European GH study. Daily mean glucose concentrations in our study were far below those in the European study. A blood glucose concentration goal of 145 mg/dl has been suggested as a target for critically ill adults.59 This parameter was achieved in patients with TBI in our study who received IGF-I/GH in combination with an aggressive nutritional support regimen. Sepsis and infectious morbidity rates were not different in the patients with acute TBI who received GH combined with IGF-I. We also did not observe effects on B cells, T cells, natural killer cells, or cytokines that would suggest a negative effect of this combination on the depressed immunity already observed in this patient population.43,44,58 In our investigation, low doses of both GH and IGF-I, in combination, were successful in producing nitrogen sparing, while avoiding the uncontrolled infections and septic shock observed with higher GH doses in critically ill adults.

The addition of IGF-I to GH and nutritional support addresses many of the known factors contributing to the persistent catabolic state accompanying moderate to severe brain injury.74 Restoring IGF-I concentrations is an important component of improved nutritional response in catabolic conditions, although the optimal concentration and duration of treatment have not been defined. After acute TBI, rapid increases in plasma IGF-I concentrations to more than 350 ng/ml transiently improved nitrogen retention and improved trends in 6-month outcomes.41 When IGF-I has been given as a single agent, the endogenous production of GH decreases and systemic concentrations of IGF-I begin to fall, despite continued infusion of recombinant IGF-I.108 This paradox occurs because of associated decreases in binding proteins for IGF-I that are responsible for maintaining plasma concentrations. To our knowledge, the combination of GH and IGF-I is the only regimen that has successfully overcome this endogenous feedback system and generated sustained anabolic conditions.

Conclusions

This investigation combined three treatment strategies known to independently address some component of the metabolic profile following acute, moderate to severe
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nonpenetrating TBI. Nutritional support alone is not effective in achieving anabolic conditions and utilization of nutrients. Growth hormone alone is not an option in critically ill patients, and IGF-I alone cannot maintain positive metabolic changes throughout the prolonged recovery. By combining these three approaches, extremes in glucose concentration were avoided and fluid requirements did not result in significant retention that affected morbidity or mortality rates. Although cytokines and immune parameters did not differ significantly between the groups, the lack of difference in infection rates is an important finding in light of the concerns with both nutrition support and GH therapy. The combination of GH and IGF-I therapy achieved and sustained IGF-I plasma concentrations above the physiological level in patients with acute, moderate to severe nonpenetrating TBI, and nutritional parameters were improved. For these patients this anabolic cocktail, combining IGF-I and GH, safely and effectively modulated the systemic metabolic response and effectively attenuated refractory nitrogen wasting following acute, moderate to severe nonpenetrating TBI.

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Disclaimer

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References

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