Beneficial Effects of Extended Growth Hormone Treatment after Hospital Discharge in Pediatric Burn Patients

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Abstract

Objective—Study the efficacy of growth hormone given to severely burned children from discharge to 12 months after burn and for 12 months after the drug was discontinued.

Summary Background Data—We have previously shown that low-dose recombinant human Growth Hormone (rhGH), given to children after a severe thermal injury successfully improved lean muscle mass, bone mineral content, and growth. The aim of the present study was to investigate long-term functional improvements after treatment.

Methods—Forty-four pediatric patients with over 40% total body surface area burns were studied for 24 months after burn. Patients were randomized to receive either rhGH (0.05 mg/kg body weight) or placebo. Height, weight, body composition, serum hormones, resting energy expenditure, cardiac function, muscle strength, and number of reconstructive procedures performed were measured during rhGH treatment and for 12 months after treatment was discontinued.

Statistical analysis used Tukey's multiple comparison test. Significance was accepted at p<0.05.

Results—Height, weight, lean body mass, bone mineral content, cardiac function, and muscle strength significantly improved during rhGH treatment compared to placebo (p<0.05). This treatment significantly increased GH, IGF-I, IGFBP-3 while cortisol serum concentrations decreased (p<0.05). The number of operative reconstructive procedures was significantly lower with rhGH (p<0.05). Improvements in height, bone mineral content, and IGF-1 concentrations persisted after rhGH treatment (p<0.05). No side effects with rhGH were observed.

Conclusions—Administration of rhGH for one year after burn was safe and improved recovery. These salutary effects continued after rhGH treatment was discontinued.

INTRODUCTION

Recovery from a massive burn is characterized by persisting catabolic and hypermetabolic responses. The clinical response is characterized by an increase in resting energy expenditure,
tachycardia, a negative muscle protein balance, bone wasting, and growth retardation.\textsuperscript{2,3,4} These negative clinical responses result in a significant delay in rehabilitation and re-integration of these children back into society. Anabolic agents, such as recombinant human Growth Hormone (rhGH) have been used successfully to attenuate the hypermetabolic and catabolic response during the acute phase after burn.\textsuperscript{5,6} Growth hormone, given to severely burned children, has been shown to decrease whole body catabolism, increase protein synthesis, accelerate wound healing and reverses growth arrest.\textsuperscript{7,8,9,10,11,12} The side effects of rhGH have been well described in the literature and indicate that it is safe for children.\textsuperscript{13} Based on this background, a study at our institution using rhGH for one year after burn showed beneficial effects on lean mass and bone mineral content, as well as on height, in children with \( \geq 40\% \) TBSA burns.\textsuperscript{14} However, it has been unknown what effect this drug administration would have on function or whether endogenous hormone production would recover after drug cessation. To address these questions we have investigated severely burned children for 24 months after burn, 12 months after discontinuation of rhGH, looking additionally at reconstructive procedures, strength, cardiac function, scarring as well as body composition and endogenous hormone production.

\section*{METHODS}
\subsection*{Subjects}
Fourty-four massively burned children were enrolled between 1999 and 2004 in a double-blinded randomized study to test the efficacy of rhGH administered after hospital discharge to 12 months after burn with the patients studied for an additional 12 months after treatment was stopped. Inclusion criteria were: age \( \leq 19 \) years, TBSA burns of \( \geq 40\% \), and availability for studies at discharge, 6, 12, 18, and 24 months after injury. This study was approved by the Institutional Review Board at the University of Texas Medical Branch. Informed written consent was obtained from each patient's guardian with the assent of the child prior to enrollment.

Patients were randomized to receive 0.05 mg/kg rhGH (Lilly, Indianapolis, IN) or placebo subcutaneously daily from hospital discharge for up to 12 months after burn. The dose of rhGH was based on the previously demonstrated beneficial effects seen in children with Turner's syndrome.\textsuperscript{15} Guardians and patients were instructed and supervised in the proper use of the drug and compliance was checked by questionnaires and by checking serum levels of insulin-like growth factor-I (IGF-I). Patients were studied at discharge (4 to 8 weeks after trauma), and 6, 12, 18, and 24 months after injury (Figure 1). At the time of hospital admission and follow-up, patients were examined by physicians including a pediatric endocrinologist and reviewed by a safety committee to screen for compliance and adverse side effects such as hyperglycemia and glucose intolerance. Pubertal development was assessed using the Tanner score\textsuperscript{16} and hand and knee x-rays were taken of each subject at each follow-up period to evaluate possible premature closure of epiphyseal plates induced by anabolic agents.

\subsection*{Body Composition}
Body heights and weights were measured and the percent change calculated for the treatment and placebo group. Total body lean mass (LBM), fat, and bone mineral content (BMC) were measured by dual energy x-ray absorptiometry (Hologic model QDR-4500W, Hologic Inc, Waltham, Mass). To minimize systematic deviations, the Hologic system was calibrated daily against a spinal phantom in the anteroposterior, lateral, and single-beam modes. Individual pixels were calibrated against a tissue bar phantom to determine whether the pixel was reading bone, fat, lean tissue, or air.\textsuperscript{17}
Cardiac Function

Echocardiograms were taken prior to discharge and 12 and 24 months after burn. No test subject presented with or previously suffered other concomitant diseases affecting cardiac function, such as diabetes mellitus, coronary artery disease, long standing hypertension, or hyperthyroidism. Study variables included: resting cardiac output, cardiac index, stroke volume, resting heart rate and left ventricular ejection fraction. Stroke volume and cardiac output were adjusted for body surface area and expressed as indexes. All ultrasound measurements were made with the HP SONOS 100 CF echocardiogram (Hewlett Packard Imaging System, Andover, MA,) with a 3.5 MHz transducer. Recordings were performed with the subjects in a supine position and breathing freely. M-mode tracings were obtained at the level of the tips of the mitral leaflets in the parasternal long axis position and measurements were performed according to the American Society of Echocardiography recommendation. Left ventricular volumes determined at end diastole and end systole were used to calculate EF, SV, CO and CI. Three measurements were performed and averaged for data analysis.

Strength Measurements

Strength testing was conducted on children age $\geq 7$ years using a Biodex System-3 dynamometer (Shirley, NY). The isokinetic test was performed on the dominant leg extensors and tested at an angular velocity of 150°/second. This speed was chosen as it was well tolerated (compared to lower or higher angular speeds) by children of all ages. The patients were seated and their position stabilized with a restraining strap over the mid-thigh, pelvis and trunk in accordance to the Biodex System-3 Operator's Manual. All patients were familiarized with the Biodex test. The administrator of the test demonstrated the procedure, then the test procedure was explained to patients who were allowed to practice the actual movement during three submaximal repetitions without load as a warm-up. More repetitions were not allowed to prevent fatigue. The anatomical axis of the knee joint was aligned with the mechanical axis of the dynamometer before the test. After the three submaximal warm-up repetitions, ten maximal voluntary muscle contractions (full-extension and flexion) were performed. The maximal repetitions were performed consecutively without rest in between. Three minutes of rest were given to minimize the effects of fatigue before the test sequence was repeated. Peak torque was calculated by the Biodex software system. The highest peak torque measurement between the two trials was selected and corrected for gravitational moments of the lower leg and the lever arm.

Reconstructive Procedures

A plastic surgeon, not involved in the study and blinded as to drug use, evaluated the patients of both groups at discharge, 6, 9, 12, 18, and 24 months after burn for the need of reconstructive operations to improve functional outcome. The decision was based on adequacy of the function of eyelids, mouth, neck, and joints.

Scar Assessment

Scars were evaluated clinically by observers blinded to treatment using the Vancouver Scar Scale.

Indirect Calorimetry

Resting energy expenditure (REE) was measured using a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA). Composition of inspired and expired gases were sampled and analyzed at 60-second intervals. Values obtained during a 5-minute steady state were accepted. The average REE was calculated from steady state measurements.
Hormone Panel
Whole blood was withdrawn to determine serum growth hormone (GH), insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), osteocalcin, parathyroid hormone, insulin, cortisol, total thyroxine (total T4), tri-iodothyronine uptake (T3 uptake), and free thyroxine index (FTI). All were measured using enzyme linked immunosorbent assays (ELISA) from Diagnostic Systems Laboratory (Webster, TX). 17

Statistical Analysis
Data are presented as means ± SEM. Statistical analysis used Tukey's multiple comparison test, with significance accepted at p<0.05. Student’s t-test was used for comparing reconstructive procedures with significance accepted at p<0.05. Statistical software (SigmaStat and SigmaPlot, SPSS, Chicago, IL) was used for analyses.

RESULTS
Demographics
Fourty-four patients were studied and randomized to receive rhGH (n=19) or placebo (n=25). The groups did not significantly differ in age, gender, ethnicity, and burn size (Table 1). There was no significant difference between groups for caloric intake, which was measured by a 24 hour dietary recall. Fourteen patients in the treatment group and 18 patients in the placebo group successfully completed the study.

Body Composition
Percent change in height increased with rhGH compared to placebo for up to 24 months after burn, p<0.05 (Figure 2). Bone mineral content was improved during rhGH treatment and continued to improve for 24 months after burn compared to placebo, p<0.05 (Figure 3). Percent changes in LBM and weight were higher at 12 months after burn in the rhGH group compared to placebo, p<0.05 (Figure 4).

Cardiac Function
Children treated with rhGH showed an improvement in left ventricular function during the treatment period with an increase of 12±24% (SD) in the ejection fraction compared to1±20% for placebo, p<0.05. Other cardiac measures were not significantly changed with rhGH treatment.

Strength Measurements
Strength measures significantly improved with rhGH at 12 months after burn compared to those receiving placebo (Figure 5). There was no significant effect on leg strength once the drug was discontinued.

Reconstructive Procedures
The number of reconstructive procedures from hospital discharge to the end of the study period was significantly lower in the group receiving rhGH compared to placebo (Table 1).

Scar Assessment
The scar evaluation did not reveal any significant differences between groups.
Indirect Calorimetry

There was no significant difference between rhGH and placebo in the percent of predicted REE, with the decrease in predicted REE similar over time in each group.

Hormone Panel

Recombinant human growth hormone administration increased serum GH, IGF-1, IGFBP-3 and decreased cortisol concentrations when compared to placebo, p<0.05 (Figures 6, 7, 8, 9). Effects on IGF-1 and cortisol serum levels persisted for one year after rhGH was discontinued, p<0.05. Osteocalcin was elevated 18 months after burn in the rhGH group compared to placebo, p<0.05. Insulin, parathyroid hormone, total thyroxine (total T4), tri-iodothyronine uptake (T3 uptake), and free thyroxine index (FTI) were not significantly different between groups.

Side Effects

No adverse side effects such as hyperglycemia, changes in the predicted Tanner scores or premature closure of growth plates were observed during the study period.

DISCUSSION

Fluid resuscitation, early burn wound excision and closure, early enteral nutrition, as well as infection control have significantly improved survival of severely burned children. With these successful developments, burn care has focused on rehabilitation. Previous studies indicate, that the hypermetabolic and catabolic response after a massive burn persist for at least one year following wound closure. A net loss in lean body mass for up to 9 months after trauma has been demonstrated. Recombinant human growth hormone has been shown to improve the catabolic response during the acute phase after burn in both, children and adults. The effects of rhGH administration given from hospital discharge to 12 months after burn have been previously studied at this institution, with height, weight, bone mineral content, and lean body mass significantly improved when compared to placebo. In that study rhGH was given to pediatric burn patients for a period of 8 to 11 months, but, there were concerns regarding a rebound phenomena from possible suppression of endogenous growth hormone production once rhGH was discontinued. It was also unclear, whether benefits would continue after drug cessation, or whether there would be functional benefits from treatment.

Our current study showed a significant increase in height and bone mineral content during the treatment period which continued to improve in the year after rhGH was discontinued. A possible rebound phenomenon regarding effects on body composition after treatment was discontinued was not observed for any of the analyzed variables.

Functional improvements with rhGH treatment have not been previously described. We report the effects of rhGH on body function for up to two years after burn. Based on our previous studies, we chose muscle strength, reflected as peak torque, as a relevant measurement as it requires a combination of several complex body systems, including muscles, nerves, and overall cognitive function. We observed that the increase in lean body mass was concomitant with a significant improvement in muscle strength during the first year of the study period in children treated with rhGH when compared to placebo. We also analyzed left ventricular function by echocardiography which had improved significantly after one year of rhGH administration. In addition to improved function, the number of reconstructive procedures performed by a blinded and independent plastic surgeon whose indication for surgery followed an algorithm for functional improvement was reduced over 50% in patients treated with rhGH compared to placebo in the first 2 years after injury. A previous study investigating the effects of long-term treatment with rhGH did not show any adverse effect of rhGH on scar maturation.
or immunohistochemical characteristics in severely burned children when compared to placebo. We might speculate that the improvements seen with rhGH in body function have lead to a higher daily activity level, thus preventing scar contractures during the critical first 12 months of scar maturation leading to reduced requirements for reconstructive procedures for functional needs.

The serum hormone panel provides indications as how the effects of rhGH might be mediated. One proposed mechanism of action of rhGH is through stimulation of hepatic production of IGF-1 and its binding protein IGFBP-3. This is supported by our results in which serum growth hormone, IGF-1, and IGFBP-3 were significantly elevated compared to placebo. After discontinuing treatment 12 months after burn, serum concentrations of growth hormone and IGFBP-3 were no longer significantly different compared to placebo. Interestingly, IGF-1 was still significantly elevated at 18 months after burn, at a time when rhGH had been discontinued for 6 months. Elevated levels of IGF-1 may reflect an additional production induced by the increased LBM in those children who received rhGH. The compliance of patients receiving rhGH injections at home has been correlated to IGF-1 serum levels. Besides the elevation of endogenous anabolic hormones, rhGH significantly reduced serum cortisol concentrations which is a known mediator of catabolic reactions. This decrease in cortisol was observed during rhGH treatment as well as in the following year after the drug was discontinued. The significant increase of osteocalcin, a marker for bone turnover, at 18 months after burn in those receiving rhGH may be associated with the increase in height and BMC in the second year of the study relative to placebo. The nutritional intake was not different between groups, thus we attribute these findings to the effect of rhGH. Adverse side effects associated with anabolic therapy such as glucose intolerance, precocious sexual development, or early epiphysial closure were not noted at follow-up visits.

The high cost for approximately 10 months of rhGH treatment has been of some concern. With the number of reconstructive operations required during the first 2 years after discharge reduced by 50%, the cost of rhGH is offset by reduced surgical expenses. For example, 10 months of drug treatment for the average patient in this study (7 years old, 34.5 kg body weight) receiving 0.05 mg/kg/day rhGH would cost approximately $18,000. Surgical expenses for each operative intervention including the day of hospital stay would be approximately $8,000. The average patient in the placebo group required a total of 4 operations, resulting in $32,000 in expenses, whereas the average patient in the rhGH group required only 1.8 operations, resulting in $14,400 plus $18,000 for rhGH, thus resulting in total expenses of $32,400 or nearly the same cost as those receiving placebo. The reduced time in pain and recovery is considered well worth any small additional cost.

In summary, severely burned children who received rhGH after hospital discharge showed improved body composition and function as well as hormone metabolism requiring fewer reconstructive procedures when compared to placebo. We conclude, that rhGH given subcutaneously at a daily dose of 0.05 mg/kg body weight after hospital discharge is safe for severely burned children and successfully attenuates burn induced catabolism and improves body function.

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References


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Study Design

Inclusion criteria: TBSA > 40 %, Age ≤ 19 years

- **RhGH** 0.05 mg/kg subcutaneously
- **Placebo** injection subcutaneously

**Or**

- **No treatment**

**time after burn**

- Injury
- Discharge
- 6 months
- 9 months
- 12 months
- 18 months
- 24 months

- Dexa
- Serum
- Echo
- Physical X-rays
- Dexa
- Serum
- Echo
- Physical X-rays
- Dexa
- Serum
- Echo
- Physical X-rays
- Dexa
- Serum
- Echo
- Physical X-rays

*Figure 1.*
Study protocol for Body composition including Dexa, height and weight, serum (hormone analysis) and clinical assessment (CA) measures. Clinical assessments include physical examinations and screening for adverse side effects which are evaluated by a committee of five clinical experts including a pediatric endocrinologist to decide whether the treatment should be discontinued.
Figure 2.
Percent change in height from baseline (dc) to two years after injury. Values are means ± SEM.
* Significant difference between rhGH and placebo, p<0.05.
Figure 3.
Percent change in bone mineral content (BMC) from discharge to 24 months after burn. Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.
Figure 4.
Percent change in lean body mass (LBM) when measured by Dual Energy X-ray analysis. Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.
**Figure 5.**
Percent change in muscle strength (Nm/kg BW). Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.
Figure 6.
Serum concentrations of human growth hormone with time after burn. Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.
Figure 7.
Effects of rhGH on Insulin-like growth factor-1 with time. Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.
Figure 8.
Effects of rhGH on Insulin-like growth factor binding-protein-3 with time. Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.
Figure 9.
Serum concentrations of cortisol with time after burn. Values are means ± SEM. * Significant difference between rhGH and placebo, p<0.05.

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Table 1
Patient demographics and reconstructive procedures.

<table>
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<tr>
<th></th>
<th>Growth Hormone</th>
<th>Placebo</th>
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<tr>
<td>Patients enrolled</td>
<td>19</td>
<td>25</td>
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<tr>
<td>Male/Female ratio</td>
<td>13/6</td>
<td>17/8</td>
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<tr>
<td>Age (years)</td>
<td>7 ± 5</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>TBSA (%)</td>
<td>59 ± 15</td>
<td>60 ± 18</td>
</tr>
<tr>
<td>Third-degree burn (%)</td>
<td>48 ± 25</td>
<td>47 ± 27</td>
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<tr>
<td>Reconstructive Procedures</td>
<td>1.8 ± 1.3</td>
<td>4.1 ± 2.5</td>
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Significant difference in reconstructive surgical procedures between rhGH (0.05 mg/kg body weight) and Placebo group (p<0.05).