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Recombinant Human Growth Hormone Accelerates Wound Healing in Children with Large Cutaneous Burns

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Objective

Two forms of recombinant growth hormone that accelerate the healing of skin graft donor sites in severely burned children were evaluated.

Summary Background Data

Growth hormone has been shown to reduce wound healing times in burned pediatric patients. Through genetic engineering, several different forms have been synthesized; however, not all are marketed currently. Two forms of growth hormone were used in these studies, Protropin (Genentech, Inc., San Francisco, CA), a commercially available product that possesses a N-terminal methionine residue not found in the second form Nutropin (Genentech, Inc., San Francisco, CA), which, as yet, is not commercially available. Through the use of recombinant human growth hormone, rapid wound healing may reduce the hypermetabolic period, the risk of infection, and accelerate the healing of donor sites used for grafting onto burned areas. The two structurally different forms of growth hormone were tested for their efficacy in healing donor sites in severely burned children.

Methods

Forty-six children, with a >40% total body surface area and >20% total body surface area full-thickness burn were entered in a double-blind, randomized study to receive rhGH within 8 days of injury. Twenty received (0.2 mg/kg/day) Nutropin or placebo by subcutaneous or intramuscular injection beginning on the morning of the initial excision. Eighteen patients who failed the entry criteria for receiving Nutropin received Protropin therapeutically (0.2 mg/kg/day). Donor sites were harvested at 0.006 to 0.010 inches in depth and dressed with Scarlet Red impregnated fine mesh gauze (Sherwood Medical, St. Louis, MO). The initial donor site healing time, in days, was reached when the gauze could be removed without any trauma to the healed site.

Results

Donor sites in patients receiving Nutropin ($n = 20$) or Protropin ($n = 18$) healed at 6.8 ± 1.5 and 6.0 ± 1.5 (mean $\pm$ SD) days, respectively, whereas those receiving placebo ($n = 26$) had a first donor site healing time of 8.5 ± 2.3 days. Both groups receiving rhGH showed a significant reduction in donor site healing time compared with placebo at $p < 0.01$. When subgroups were compared, no difference in healing times could be shown with regards to age or time of admission after injury.

Conclusion

Our results indicate that both forms of rhGH are effective in reducing donor site healing time compared with placebo and suggest that accelerating wound healing is of clinical benefit because the patients' own skin becomes rapidly available for harvest and autografting. With this increase in the rate of wound healing, the total length of hospital stay can be reduced by more than 25%.

Thermal injury is particularly severe form of trauma that disfigures the anatomy and disrupts hormonal balance and metabolism. In large thermal injuries, skin loss presents unique problems for the surgeon attempting wound closure. Open wounds promote a hypermetabolic state and provide a port of entry for systemic and wound pathogens.[1,2] In a previous study, administration of recombinant human growth hormone (rhGH) significantly reduced donor site healing times in burned pediatric patients.[3] Human growth hormone is produced by the pituitary gland and its anabolic effects in trauma patients have been studied extensively.[4–6] Initially, growth hormone was obtained post-mortem from human pituitary tissue; however, this has been replaced by genetically engineered recombinant human growth hormone (rhGH).[4–8] Through the use of rhGH, rapid wound healing may reduce the hypermetabolic period, the risk of infection, and accelerate the healing of donor sites used for grafting onto burned areas. We present the results of a prospective, double-blind study to compare a new nonmarketed form of recombinant growth hormone Nutropin (Genentech, Inc., San Francisco, CA), with a placebo, on initial donor site healing time. An additional control group, composed of those patients not eligible for the Nutropin study, received the commercially available form of recombinant growth hormone, Protropin (Genentech, Inc., San Francisco, CA). This then allowed comparison of the Nutropin group with the placebo group, and also allowed comparison with the Protropin-treated patients in this and a prior study from the same institution on donor site healing.

MATERIALS AND METHODS

Forty-six children admitted to the Shriners Burns Institute in Galveston, Texas were entered in a double-blind, randomized study to test the efficacy of Nutropin or placebo on donor site healing. Patients between 2 and 18 years of age, with a >40% total body surface area (TBSA) flame or scald and >20% TBSA full-thickness burn (3rd degree) were given rhGH within 8 days of injury. Those who fulfilled the entry criteria received 0.2 mg/kg/day Nutropin (n = 20) or placebo (n = 26) by subcutaneous or intramuscular injection, beginning on the morning of the initial excision. Subsequent doses were given daily at approximately the same time until the burn wound was 95% closed or the initial donor site was healed. Patients in the study received injections from specific vials provided by the manufacturer. Patients, physicians, and nursing staff members were blinded to the contents of these vials. This study was conducted under the guidelines of the Institutional Review Board of the University of Texas Medical Branch (OSP 91-236 and OSP 93-240).

Eighteen patients who failed the entry criteria for receiving Nutropin, received Protropin therapeutically at 0.2 mg/kg/day. Twelve of these patients received Protropin within 8 days of injury. The remaining 6 patients were admitted later (16–23 days), because of geographical location. Reasons for exclusion from the Nutropin study are presented in Table 1. Length of stay (LOS) was the time period, in days, from admission until the wound was 99% closed.

RESUSCITATION AND NUTRITION

All subjects were resuscitated by a standard formula with intravenous fluids administered to maintain a urinary output of 1.0 to 1.5 mL/kg/hr. Electrolyte supplementation was given to achieve appropriate serum concentrations.[9] Enteral nutritional support was given to meet calorie requirements calculated from age, body surface area, and burn size.[10–12]

SURGERY

One of three surgeons excised and grafted the entire wound, excluding the face and perineum, within 48 hours of admission. Excised areas were covered with 2:1 meshed autograft, 4:1 meshed autograft with 2:1 meshed cadaveric allograft overlay, or 2:1 meshed cadaveric allograft alone if sufficient autograft donor skin was unavailable for complete 4:1 coverage. Donor sites were harvested using an electric dermatome set at 0.006 to 0.010

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Table 1. CHARACTERISTICS AND CRITERIA FOR EXCLUSION FROM THE NUTROPIN STUDY FOR THOSE RECEIVING PROTROPIN WITHIN 8 DAYS OF INJURY

Patients	Age (yrs)	Sex	% TBSA burn	% 3rd burn	Reason for exclusion from Nutropin study
1	7.1	F	27	26	TBSA burn < 40%
2	0.6	M	46	25	Age < 2 yrs
3	1.5	F	55	47	Age < 2 yrs
4	1.3	M	60	60	Age < 2 yrs
5	1.8	M	62	60	Age < 2 yrs
6	1.3	F	46	46	Age < 2 yrs
7	2.0	F	67	67	foreign national*
8	4.5	M	56	40	foreign national*
9	2.0	F	40	35	foreign national*
10	4.2	F	80	80	foreign national*
11	12.0	M	40	40	foreign national*
12	1.2	M	90	90	Age < 2 yrs

* Foreign nationals were excluded from the double-blind Nutropin study when they were not available for follow-up after discharge.

inches and dressed with Scarlet Red (Sherwood Medical, St. Louis, MO) impregnated fine mesh gauze.

On the third postoperative day, the donor site was examined by one of two evaluators. Using sterile technique, each of the four corners of the gauze was gently lifted using forceps and minimal tension to determine the adherence of the dressing to the underlying tissue. Any unattached dressing was trimmed away. This procedure was repeated daily until the Scarlet Red impregnated gauze was no longer adherent to the underlying donor site wound. For the purposes of this study, healing time was defined as the time, in days, for the initial donor site to heal as indicated by atraumatic removal of the Scarlet Red gauze (the first harvest of a designated donor site).

STATISTICAL ANALYSIS

Data presented in tables and text are means ± SD. One-way analysis of variance and the Scheffe Multiple Comparison Test were used where appropriate. Significant differences were accepted at $p < 0.05$. The effect of sex, age, and percent full-thickness burn on healing times were determined by regression analysis.

RESULTS

Twenty-six burned children received placebo and 20 received Nutropin in a randomized, double-blind study. Eighteen children received therapeutic Protropin, 12 within 8 days of injury and 6 between 16 and 23 days after injury. The time of admission had no significant effect on healing times in patients receiving therapeutic Protropin (Table 2). In the 18 patients given Protropin, those 6 months to 2 years of age were compared to those older than 2 years (Table 3). No significant difference for healing times between those aged 6 months to 2 years and those older than 2 years of age could be shown. These comparisons indicate that neither age nor time of admission had any influence on healing times within the Protropin study groups. All patients receiving Protropin were, therefore, combined into a single group of 18 pa-

Table 2. CHARACTERISTICS OF PATIENTS RECEIVING PROTROPIN AND DONOR SITE HEALING TIMES OF LATE ADMISSIONS *VS.* THOSE ADMITTED WITHIN 8 DAYS OF INJURY

Admitted	n	Age (yrs)	Sex % Male	TBSA % Burn	3rd-Degree % Burn	Donor Site Healing Time (days)
>8 days	6	5.2 ± 3.3	50	57 ± 18	55 ± 17	6.0 ± 1.8
<8 days	12	3.3 ± 3.2	50	56 ± 17	51 ± 20	6.0 ± 1.1

Data presented as mean ± SD.

Table 3. PATIENTS AGED < 2 YEARS COMPARED TO THOSE > 2 YEARS OF AGE WHO RECEIVED PROTROPIN

	n	Age (yrs)	Sex % Male	TBSA % Burn	3rd-Degree % Burn	Healing Time (days)
Protropin 0.5 < 2.0 yrs	9	1.4 ± 0.5	56	56 ± 15	52 ± 18	6.0 ± 1.1
Protropin > 2 yrs	9	6.5 ± 2.8*	44	56 ± 17	53 ± 18	6.0 ± 1.4

Data presented as means ± SD.
* Significance declared at $p < 0.05$.

tients for analysis. Burn sizes and patient characteristics for the Nutropin, Protropin, and placebo groups are depicted in Table 4. Age, sex, and burn size were shown to have no significant effect on donor site healing time within each group. The mean age in the Protropin group, however, was significantly less than the placebo group (Table 4). A comparison of healing times for those receiving Nutropin, Protropin, and placebo within 8 days of injury are presented in Figure 1. Patients receiving Nutropin (n = 20) or Protropin (n = 18) had first donor site healing times of 6.8 ± 1.5 and 6.0 ± 1.5 days, respectively, whereas those receiving placebo (n = 26) had a first donor site healing time of 8.5 ± 2.3 days. Both groups receiving rhGH showed a significant reduction in donor site healing time compared to placebo at $p < 0.01$.

Nine patients receiving Nutropin required insulin episodically throughout their hospital stay. No significant difference could be shown in donor site healing times between those receiving Nutropin plus insulin and those receiving Nutropin alone (Table 5). Only one patient receiving Protropin, admitted more than 8 days after injury, required therapeutic insulin. The average length of hospital stay for those receiving Nutropin and Protropin was 40 days, whereas for those receiving placebo, the average length of hospital stay was 55 days.

DISCUSSION

Many investigators have attempted to modulate the hypermetabolic response in burn patients.[4-6,13-16] Over the past 40 years, studies have shown that exogenous human growth hormone may reduce the catabolism of severe trauma by reversing or reducing protein and fat breakdown. Recently, rhGH has been shown to be beneficial by reducing nitrogen loss in stressed patients.[4-6,16] Belcher et al. studied the effect of rhGH on nitrogen balance in burn victims and concluded that rhGH was of no appreciable benefit.[17] It should be pointed out, however, that the dose of rhGH administered was less than that used in this study.

Growth hormone is released from the pituitary gland in response to stress both at night and at various times throughout the day. In patients who are recumbent for most of the time, the precise time of day for optimal administration of exogenous rhGH still has to be determined. We assumed that growth hormone given in conjunction with morning feeding would be most beneficial.

Whether rhGH specifically influences the fibroblast and other wound healing tissues to accelerate repair or whether the reduction in catabolic loss of fat and peripheral muscle increases availability of macromolecules for tissue repair is not known. It is recognized that growth hormone influences glucose metabolism.[18,19] Total parenteral nutrition (TPN), occasionally used in trauma patients, also is a promoter of hyperglycemia. In this study, no patient received TPN. Hyperglycemia often is treated clinically with exogenous insulin, which may, if given in sufficient quantities, have an anabolic influence on protein kinetics. Studies using a hyperinsulinemic eugly-

Table 4. PATIENT CHARACTERISTICS AND BURN SIZE FOR ALL PATIENTS RECEIVING RHGH

	n	Age (yrs)	Sex % Male	TBSA % Burn	3rd-Degree % Burn	Donor Site Healing Time (days)
Placebo	26	8.4 ± 4.8	73	67 ± 15	56 ± 21	8.5 ± 2.3*
Nutropin	20	7.1 ± 4.5	70	63 ± 17	53 ± 20	6.8 ± 1.5
Protropin	18	3.9 ± 3.2*	50	56 ± 17	53 ± 19	6.0 ± 1.5

Data are presented as means ± SD.
* Significant difference at $p < 0.05$.

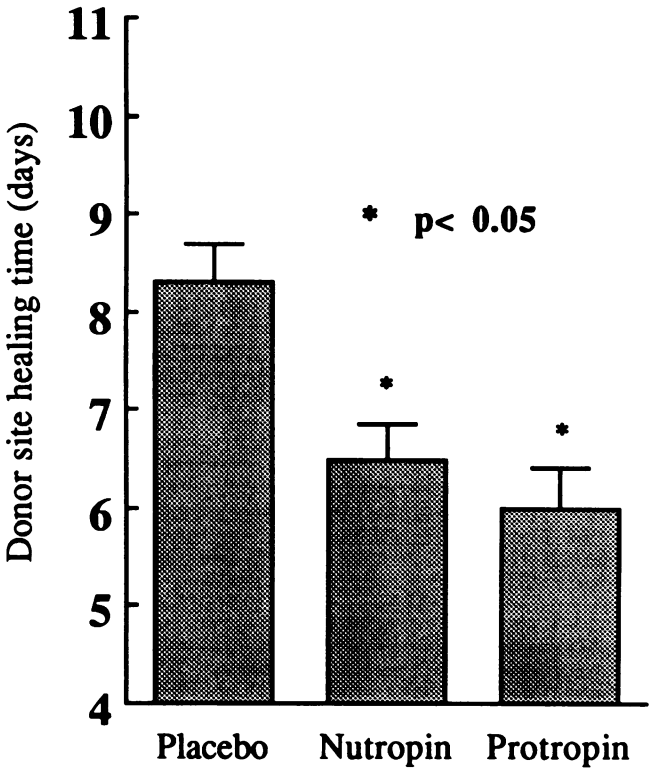

Figure 1. Histogram showing healing times (days) of the initial donor sites for each study group receiving either placebo (normal saline, n = 26), Nutropin (n = 20, 0.2 mg/kg/day) or Protropin (n = 18, 0.2 mg/kg/day daily). Both forms of rhGH show a significant reduction in average healing times compared to placebo. Data presented as mean ± SEM. *Significant difference compared to placebo at $p < 0.01$.

cemic clamp have shown an increased rate of protein synthesis, thus, theoretically increasing the availability of protein for wound repair.[16] Previous studies from this institution suggest that the combination of rhGH and insulin does not improve protein kinetics when compared with rhGH alone;[16] however, others have found that in stressed patients, rhGH and insulin combine to improve protein kinetics.[20] Nine children in the Nutropin study who received exogenous insulin (range 6–151 units/day) were compared to 11 who required no insulin. Data indicate that there was no significant difference in initial donor site healing times. In addition, these results confirm the findings of an earlier report from this institution on the effect of Nutropin alone,[3] compared to placebo, on initial (first) donor site healing time (placebo: 9.1 ± 0.4 days, n = 17, compared with 8.5 ± 2.3 days, n = 26, and Nutropin: 7.4 ± 0.6 days, n = 8, compared with 6.4 ± 1.2 days, n = 11). The reduction in the initial donor site healing time in this study for both the placebo and Nutropin groups is a reflection of the larger numbers in each group.

In children receiving Protropin, nine patients were 6 months to 2 years old, and nine were older than 2 years. When these subgroups were compared, there was no difference in healing times, suggesting that Protropin is effective in children of all ages. Of those receiving Protropin, 6 children were given their rhGH 8 or more days after injury[16–23] and 12 received Protropin less than 8 days after injury. No significant difference in healing time could be shown between these groups, suggesting that delayed admission did not influence healing times.

The dose of rhGH used in this study was based on a previous investigation in which a plasma disappearance curve was constructed after administration of 0.1 mg/kg/day or 0.2 mg/kg/day.[3] This, in addition to other clinical information, indicated that 0.2 mg/kg/day would produce an effective response in donor site healing.

Our results indicate that both forms of rhGH are effective in reducing donor site healing time compared with placebo and suggest that accelerating wound healing is of clinical benefit because the patients' own skin becomes rapidly available for harvest and autografting. Further, by reducing donor site healing times, the length of hospital stay in children receiving a cutaneous full-thickness burn can be reduced by more than 25%. This study confirms the previous one in that both donor site wound healing time and hospital stay were reduced by recombinant human growth hormone.

Table 5. PATIENTS RECEIVING NUTROPIN PLUS INSULIN COMPARED TO THOSE RECEIVING NUTROPIN ALONE

	n	Age (yrs)	Sex % Males	TBSA % Burn	3rd-Degree % Burn	Healing Time (days)
Nutropin	11	5.4 ± 4.0	73	58 ± 14	49 ± 16	6.4 ± 1.2
Nutropin + insulin	9	9.2 ± 4.7	67	68 ± 19	58 ± 24	7.1 ± 2.5

Data presented as means ± SD.

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