ANNALS OF SURGERY
Vol. 229, No. 2, 298–302

Perioperative Growth Hormone Treatment and Functional Outcome After Major Abdominal Surgery

A Randomized, Double-Blind, Controlled Study

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Objective
To evaluate short- and long-term effects of perioperative human growth hormone (hGH) treatment on physical performance and fatigue in younger patients undergoing a major abdominal operation in a normal postoperative regimen with oral nutrition.

Summary Background Data
Muscle wasting and functional impairment follow major abdominal surgery.

Methods
Twenty-four patients with ulcerative colitis undergoing ileoanal J-pouch surgery were randomized to hGH (12 IU/day) or placebo treatment from 2 days before to 7 days after surgery. Measurements were performed 2 days before and 10, 30, and 90 days after surgery.

Results
The total muscle strength of four limb muscle groups was reduced by 7.6% in the hGH group and by 17.1% in the placebo group at postoperative day 10 compared with baseline values. There was also a significant difference between treatment groups in total muscle strength at day 30, and at the 90-day follow-up total muscle strength was equal to baseline values in the hGH group, but still significantly 5.9% below in the placebo group. The work capacity decreased by approximately 20% at day 10 after surgery, with no significant difference between treatment groups. Both groups were equally fatigued at day 10 after surgery, but at day 30 and 90 the hGH patients were less fatigued than the placebo patients. During the treatment period, patients receiving hGH had reduced loss of limb lean tissue mass, and 3 months after surgery the hGH patients had regained more lean tissue mass than placebo patients.

Conclusions
Perioperative hGH treatment of younger patients undergoing major abdominal surgery preserved limb lean tissue mass, increased postoperative muscular strength, and reduced long-term postoperative fatigue.

Loss of nitrogen is part of the metabolic reaction to major surgical trauma,[1] resulting in an obligatory loss of protein and muscle wasting.[2] It is a concern to surgeons because the catabolic response is correlated with the overall surgical morbidity rate, causing prolonged convalescence[3] and muscle weakness.[4] Human growth hormone (hGH) is a potent anabolic agent with profound effects on protein, carbohydrate, and lipid metabolism. After trauma, hGH stimulates the use of fat as an energy substrate and conserves protein.[5] Accordingly, hGH treatment has been proposed as a possible strategy to counteract muscle protein loss in surgical stress.

In several clinical studies, the administration of hGH has improved nitrogen balance in catabolic patients and after surgery.[6–10] It has been suggested that adequate nutrition is essential during hGH treatment to attenuate nitrogen wasting.[11] Accordingly, hGH treatment has been combined with parenteral nutrition in a majority of studies[10,12–14] because

Supported by Novo Nordisk A/S in the form of drugs and equipment.
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Accepted for publication June 5, 1998.

sufficient nutritional intake is a well-known difficulty in the early days after major abdominal surgery. However, postoperative total parenteral nutrition is not recommended for routine clinical use, and there are profound metabolic differences between enteral and parenteral nutrition.

To have a clinical impact in relation to surgery, hGH treatment must improve the actual clinical outcome (in terms of the effects on nitrogen balance). A previous study reported that hGH-treated patients maintained lean body mass and hand-grip force throughout the postoperative period after major abdominal surgery, whereas significant reductions were found among placebo-treated controls.[7] However, strength measurements were performed in only four controls and five hGH-treated patients, and the patients received parenteral nutrition. Recent studies on patients undergoing cholecystectomy (moderate surgical trauma) demonstrated reductions in infection rate, duration of hospital stay, and postoperative fatigue in the hGH-treated group.[15,16]

The aim of the present study was to evaluate short- and long-term effects of perioperative hGH treatment on physical performance and fatigue in younger patients undergoing a major abdominal operation in a normal postoperative regimen with oral nutrition.

PATIENTS AND METHODS

Trial Population

Patients aged 18 to 50 with ulcerative colitis admitted to the Department of Surgery L, University Hospital of Aarhus, to undergo elective ileal anal reservoir (J-pouch) surgery were evaluated for inclusion in the study. Patients with diabetes, a history of cancer, or obesity, those receiving systemic steroid treatment at the time of surgery, or those receiving medical treatment for liver, heart, or kidney diseases were excluded before randomization. After randomization, patients were excluded in case of reoperation and according to trial medication precautions. The study was performed in accordance with the Helsinki Declaration II, and informed consent was obtained. The study was approved by the local ethical committee.

Design

The study was double-blind, randomized, and placebo-controlled. Patients received 12 IU/day biosynthetic hGH (Norditropin, Novo Nordisk A/S, Gentofte, Denmark) or placebo from 2 days before surgery to 7 days after. Twice daily, hGH or placebo was injected subcutaneously on the thigh using an injection pen (Nordiject 24, Novo Nordisk A/S). Randomization was stratified for type of operation (proctectomy or proctocolectomy), and each stratum was block-randomized. The average operating time was 3 to 4 hours, and patients received a normal postoperative regimen, including a nasogastric tube in the early postoperative days and early mobilization. As main outcome parameters, we studied muscular strength, work capacity, fatigue, and lean tissue mass of the limbs. We also evaluated the changes in nutritional intake, nitrogen balance, lean body mass, fluid distribution, and metabolism; these data will be published separately.

Total Muscular Strength

The maximal isometric strengths of four muscle groups were measured on the side of the dominant hand using a strain-gauge mounted on a dynamometer chair (Metitur, Jyväskylä, Finland).[17] With the arm flexed 90°, hand grip strength, pinching (fingers 1 and 2 fully extended) strength, and arm flexion (in semiprone position) strength were measured. Knee extension strength was assessed with the ankle fastened to a strain gauge and the knee flexed 60°. The maximal strength of three efforts was used, and total muscular strength (TMS) was the sum of all four muscle groups.

Limb Lean Tissue Mass

The regional changes in lean tissue mass (LTM) of arms and legs were measured using dual energy x-ray absorptiometry (Hologic QDR-2000, Waltham, MA). These scans were performed on postoperative day 7; the remaining tests were done on day 10.

Work Capacity

Work capacity was measured on an Ergometer 900 (Ergoline, Bitz, Germany), which auscultates pulse and blood pressure every minute. The initial work load of 25 W was increased by 25 W every 3 minutes until discontinuation. The changes in work capacity were estimated as change in pulse at a workload of 1.5 W per kilogram body weight.

Fatigue

Subjective fatigue from 1 (fit) to 10 (fatigued) was scored by the patients using the Kehlet ordinal fatigue scale.[18] No analgesics were used before any of the muscle strength, work capacity, or fatigue tests.

Statistical Analysis

Data from patients receiving at least one dose of medicine were analyzed on intent-to-treat basis and were double-keyed into a locked database. The main data analysis was done at the Department of Biostatistics, University of Aarhus using SAS 6.11 (SAS Institute Inc., Cary, NC). Data were log transformed when appropriate. Student's t test or the unpaired t test was used for comparison. $P < 0.05$ was significant.

Table 1. CLINICAL DATA

	hGH	Placebo
Men/women	5/7	5/7
Proctectomy/proctocolectomy	11/1	10/2
Age (years)	31 (8.2)	35 (8.8)
Height (m)	1.73 (0.05)	1.73 (0.08)
Weight (kg)	71.4 (12.8)	72.8 (14.7)

Mean values ± SD

RESULTS

Subjects

Of 24 included patients, 22 received full treatment and 19 completed the full study. There was one dropout in each treatment group, and three patients were withdrawn (one due to unknown pregnancy detected at surgery; one patient in each group had ileus and underwent reoperation). Baseline values for participants are shown in Table 1. There was no significant difference in energy or protein intake between treatment groups during the intervention period or before the follow-up examinations.

Total Muscular Strength

There were significant reductions in mean TMS in both treatment groups (hGH, $p = 0.01$; placebo $p < 0.01$) on postoperative day 10 compared with baseline values. However, the 17.1% reduction found in the placebo-treated patients was significantly greater than the 7.6% reduction in the hGH-treated patients ($p = 0.02$) (Fig. 1). Thereafter, TMS increased in both groups, but at day 30 it was still significantly below baseline (by 13.1%) in the placebo-treated group ($p < 0.01$), compared with only 4.1% in the hGH group ($p = 0.05$). The 9% difference was significant ($p = 0.03$). At postoperative day 90, TMS was equal to baseline values in the hGH group but was still 5.9% below baseline in the placebo group ($p = 0.03$). The difference between the two treatment groups did not reach significance ($p = 0.07$).

Work Capacity

Baseline heart rates (at a workload of 1.5 W per kilogram body weight) were 146 in the two treatment groups. As expected, the mean heart rate increased after surgery and then dropped again during the follow-up (see Fig. 1). Compared with baseline, the heart rate at day 10 increased by 16% in the hGH group and by 23% in the placebo group; this difference between groups did not reach statistical significance. At day 30, mean heart rate in both treatment groups was close to baseline levels, and at day 90 there was a relative decrease of 4% and 3% in the hGH and placebo groups, respectively.

Postoperative Fatigue

The median fatigue scores are shown in Figure 1. Preoperative fatigue scores were similar in the two groups and increased to the same high level on postoperative day 10. At postoperative day 30 and 90, however, the hGH-treated patients were less fatigued than placebo patients, and at day 90 the hGH patients scored slightly better than before surgery. The difference between the groups did not reach statistical significance at day 30 ($p = 0.06$) but was highly significant at day 90 ($p = 0.008$).

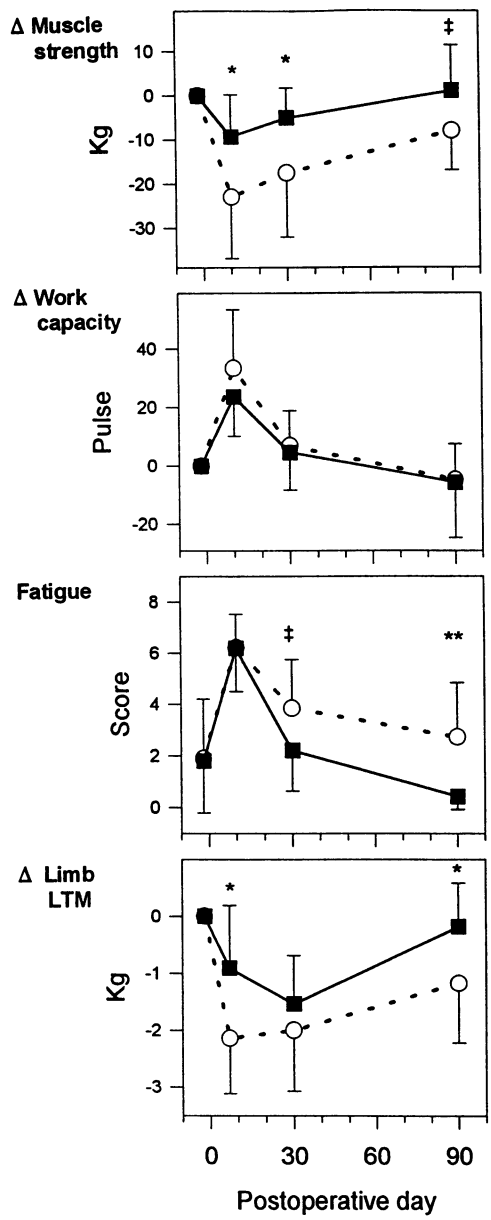

Figure 1. Postoperative changes in muscle strength, work capacity, fatigue, and limb lean tissue mass of hGH-treated (■) and placebo-treated (○) patients (mean ± SD). ‡ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, hGH *vs.* placebo.

Limb Lean Tissue Mass

The changes in limb LTM are shown in Figure 1. On postoperative day 7, the limb LTM was reduced by 4.4% in the hGH-treated group ($p = 0.02$) and by 9.9% in the placebo group ($p < 0.01$). This difference between groups was statistically significant ($p = 0.01$). At day 30, the limb LTM had declined in both groups without significant difference. At day 90, limb LTM was reduced by 5.4% ($p = 0.06$) in placebo-treated patients, whereas limb LTM equalled the baseline value in the hGH group. At this point, the difference in change between the two groups was significant ($p = 0.03$).

DISCUSSION

The present study differs significantly from previous studies on hGH effects in relation to major surgical stress by the homogeneity of patients and the use of a standard postoperative regimen, including oral nutrition. Further, we focused on the effects of perioperative hGH treatment on physical performance and fatigue. Treatment was confined to a 10-day perioperative interval. Nevertheless, hGH treatment had a positive effect on TMS, fatigue, and limb LTM 3 months after the treatment period when compared with placebo. The hGH-treated patients experienced only half the decline in muscular strength that was seen in the placebo-treated group.

A postoperative deterioration of skeletal muscle strength after abdominal surgery was clearly seen in the present study. The reduction was most significant 10 days after surgery, but TMS values remained below baseline until day 90 in the placebo group. Based on its positive effects on protein metabolism, hGH has been suggested as a way to improve muscle function after surgery,[19] but so far this hypothesis has been addressed in only a limited number of studies. Jiang et al[7] reported that hand grip force was preserved throughout the postoperative period after major abdominal surgery in five patients receiving hGH, compared with a 10% reduction in four placebo-treated patients. These data were supported by the present study, where the muscle test involved several muscle groups in both upper and lower extremities. In addition, the follow-up evaluation of muscle function disclosed a positive impact of perioperative hGH treatment that lasted ≥90 days after the surgical procedure.

The long-term effects of hGH intervention on muscle strength are presumably related to a reduction in postoperative skeletal muscle wasting. Although we tried to improve the anabolic effect of hGH treatment by initiating injections 2 days before surgery, the patients in both treatment groups were in negative nitrogen balance until postoperative day 8 to 9. However, there was a significant attenuation of the nitrogen loss in the hGH-treated group during the first 3 to 4 days after surgery (data not shown). Our data show a significant preservation of limb LTM in the hGH-treated patients at both 7 and 90 days after surgery; this supports reports of hGH's effects on skeletal muscle metabolism during catabolism.[20] When interpreting the present data, however, it must be noted that body water is included in the LTM measurements. Because hGH replacement significantly increases total body water during treatment, at least part of the difference in limb LTM measured at day 7 must be due to edema in hGH-treated patients.

In patients who underwent a moderate surgical trauma (cholecystectomy), hGH treatment was previously shown to reduce fatigue at day 5 after surgery compared with placebo[16]; however, at day 30 this effect was no longer significant. This was probably the result of the shorter fatigue period after cholecystectomy. In the present study we attempted to evaluate the effect of hGH on fatigue after major surgery, and the impact of the J-pouch procedure was demonstrated by a high median fatigue score of 6.2 at postoperative day 10. On postoperative days 30 and 90, the hGH-treated patients were less fatigued than their placebo-treated controls, and these data imply that hGH works by shortening the fatigue period rather than diminishing its magnitude. This positive and long-term effect of hGH treatment on fatigue might be related to the improved preservation of muscular strength in the hGH-treated patients.

Major surgery is known to reduce postoperative work capacity by 5% to 10%.[18,21] This was confirmed in the present study: the mean heart rate increased by 19% on postoperative day 10 compared with baseline. The significant reduction in work capacity is probably related to the young age of our patients, who have daily activity levels higher than those of elderly persons. Work capacity is usually restored to preoperative levels within weeks after surgery, which might explain why the long-term improvements in muscle strength and fatigue among hGH-treated patients were not followed by reductions in pulse rates during work. There is evidence that hGH has favorable cardiovascular effects. Replacement therapy in GH-deficient patients increased cardiac output[22] as well as physical performance,[23] and in patients with chronic congestive heart failure hGH treatment acutely improved cardiac output.[24] This indicates a possible inotropic effect of hGH not caused by myocardial growth that could be beneficial to the reduced postoperative physical performance. The present data showed a 7% difference in work capacity at postoperative day 10 in favor of hGH-treated patients. The variability in postoperative work capacity was larger than expected, and although the difference between treatment groups was not statistically significant, these results are encouraging with respect to further studies on larger patient groups.

The present study has shown that perioperative hGH intervention, combined with a normal postoperative regimen after major surgery, induced a long-term improvement in muscle mass, muscle strength, and fatigue in younger patients. Because postoperative fatigue and long-term impairment of physical capacity emerge in a significant number of surgical patients, the present findings indicate that

short-term hGH treatment could play a role in relation to major surgical trauma. The prolonged convalescence among older patients should be considered in future studies in an attempt to identify surgical patients who might profit from this therapy.

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