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RAPID COMMUNICATION

Short-term application of low-dose growth hormone in surgical patients: Effects on nitrogen balance and blood glucose

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Abstract

AIM: To investigate the effectiveness and safety of recombinant human growth hormone (rhGH) in postoperative patients.

METHODS: A total of 48 consecutive patients undergoing abdominal operations were randomized to receive either subcutaneous rhGH (0.15 IU/kg) or placebo (menstruum) injections daily for 7 d after surgery. The two groups had similar nutritional intake. Blood samples for serum fibronectin, albumin, prealbumin, transferrin and the total lymphocyte count, as well as glucose levels were collected to study the rhGH effect. Basal laboratory evaluation, and nutritional status were estimated on d 1 before as baseline and d 3 and 10 after operation using standard laboratory techniques. Nitrogen balance was measured from d 3 to 9 after operation.

RESULTS: The cumulative nitrogen balance was significantly improved in rhGH group compared with the placebo group (11.37 ± 16.82 *vs* -9.11 ± 17.52, $P = 0.0003$). Serum fibronectin was also significantly higher in the rhGH group than in the placebo group (104.77 ± 19.94 *vs* 93.03 ± 16.03, $P < 0.05$), whereas changes in serum albumin, prealbumin, transferrin and total lymphocyte counts were not statistically significant. Mean blood glucose levels were significantly higher in the rhGH group from d 3 to 6 after operation.

CONCLUSION: If blood glucose can be controlled, low-dose growth hormone together with hypocaloric nutrition is effective on improving positive nitrogen balance and protein conservation and safe is in postoperative patients.

Key words: Growth hormone; Nutritional support; Abdominal surgery; Hyperglycemia; Nitrogen balance

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INTRODUCTION

Patients undergoing abdominal surgery often suffer severe trauma or infections associated with the catabolic responses[1], which cannot be prevented with conventional parenteral or enteral nutritional formulas[2,3]. Administration of recombinant human growth hormone (rhGH) has been shown to significantly maintain the nitrogen balance in surgery patients receiving either parenteral or enteral nutrition[4-7]. However, it is still uncertain whether short-term treatment with low-dose rhGH is effective as well and whether its effect on blood glucose will lead to more severe outcomes. Furthermore, there is a lack of well-controlled prospective clinical studies investigating the clinical value of serum proteins as nutritional assessment indexes in GH-treated patients. The objective of the present study was to evaluate the relative nitrogen and protein conservation effects associated with administration of rhGH together with hypocaloric nutritional support after elective abdominal surgery. In addition, we measured the changes in blood glucose levels, the effects of hyperglycemia caused by rhGH administration on postoperative convalescence and other adverse events during GH treatment period.

MATERIALS AND METHODS

Patients

The study was conducted in accordance with the guidelines for Good Clinical Practice and the provisions of the Declaration of Helsinki in 1995 as revised in Edinburgh 2000, and approved by the Ethical Review Committee of West China Hospital. Only those who consented to participate after explanation of the objectives and the protocol were included in the study. Signed, informed consent was obtained from all patients and their close relatives.

Forty-eight adult patients were enrolled in the study, and all met the following criteria: undergoing an elective

abdominal operation; aged 18-75 years; willing and able to comprehend the protocol and give written informed consent. Exclusion criteria were as follows: severe bacterial infection, liver and renal dysfunction, previous or current treatment with corticosteroids, diabetic mellitus or fasting glucose levels greater than or equal to 7.0 mmol/L, metabolic diseases, gestation, severe malnutrition (serum albumin < 21 g/L), tumor recrudescence or metastasis.

Study design

The study was a randomized**,** prospective, double-blind, placebo-controlled clinical trial. Eligible patients were arranged randomly as follows: rhGH or placebo group with each group including 24 patients. The randomization codes were prepared with the random number table according to the design of a computer. Patients, surgeons and nursing staff members remained blind to the allocation status of the study drugs throughout the experimentation.

After the operation, all patients received continuous combined intravenous or/and enteral nutrition. The daily total caloric requirement was 20 kcal/kg and total nitrogen requirement was 140 mg of nitrogen/kg. Parenteral nutrition (PN) solution was prepared aseptically using commercially available products, including vitamins, trace elements and electrolytes (Addamel, Vitalipid, Soluvit and Glycophos; Fresenius Kabi Deutschiand GmbH, Bad Homberg, Germany). Amino acid injections were provided as Novamin 8.5% and 11.4% (Fresenius Kabi Deutschiand GmbH). Energy calories were provided with glucose and fat emulsion injections (glucose 50% and Lipovenos® MCT 20%; Fresenius Kabi Deutschiand GmbH). All the nutrients were given in an all-in-one bag. Enteral nutrition (EN) emulsion (Fresubin®, Fresenius Kabi Deutschiand GmbH) was provided orally or *via* a nasogastric tube with a continuous perfusion pump.

Postoperatively, patients received general intravenous infusions with only glucose on d 1; PN provided only half of total caloric and nitrogen requirement on d 2 and all of total requirement on d 3; on d 4, PN provided 2/3 of total requirement and EN provided another 1/3; on d 5, PN provided 1/3 of total requirement and EN provided 2/3; only EN emulsion was given from d 6 to 9.

From d 3 to 10 post operation, patients were randomly assigned to receive identical-looking treatments consisting of either rhGH (JINTROPIN®, 0.15 IU/kg) or menstruum injections (1 mL, consisting of glycin, mannitol, lactose and sodium bicarbonate) subcutaneously once daily. rhGH and placebo were provided by GeneScience Pharmaceuticals Co. Ltd, Changchun, China.

Laboratory and nutritional condition measurements

Blood samples were drawn from each patient before operation to measure baseline values and on d 3 and 10 after operation to study the rhGH effect. Complete blood counts were estimated by the XE-2100 (Sysmex, Kobe, Japan). Plasma glucose, serum urea nitrogen, creatinine, bilirubin, alanine aminotransferase, alkaline phosphatase, total protein, albumin and electrolytes were estimated by an Olympus AU5400 Autoanalyser (Olympus, Tokyo, Japan). Serum fibronectin, prealbumin and transferrin were estimated by immunoturbidimetry and radioimmunoassay methods, respectively. Body weight were confirmed using qualified body weight scales before operation and on postoperative d 3 and 10.

Table 1 Baseline characteristics of patients (mean ± SD)

Variable	Placebo (n = 24)	rhGH (n = 24)	P
Age (yr)	58.50 ± 9.35	59.08 ± 10.93	0.789
Range	39-75	35-74	
Sex (female/male)	11/13	9/15	0.558
Weight (kg)	57.90 ± 8.42	56.19 ± 11.83	0.567
Height (cm)	162.42 ± 6.92	162.88 ± 7.16	0.823
Sepsis score	0.79 ± 0.98	0.67 ± 0.87	0.742
Operation position, n (%)			
Resection of stomach	6 (25)	5 (20.8)	0.297
Resection of colon	5 (20.8)	7 (29.2)	
Resection of rectum	12 (50)	9 (37.5)	
Others	1 (4.2)	3 (12.5)	

Nitrogen balance

Daily nitrogen input was assumed to be the nitrogen contents of PN and/or EN solution given. Daily nitrogen loss was assessed by collecting 24-h output and measuring the nitrogen content in feces, urine and gastric juice. Nitrogen loss through the surgical drains was also included. Daily nitrogen balance was calculated by subtracting daily nitrogen output from daily nitrogen input. Accumulated nitrogen balance was calculated by subtracting 7 d nitrogen output from 7 d nitrogen input. Nitrogen contents of samples were determined by the micro-Kjeldahl procedure[8].

Monitoring of adverse effects

All outcome and adverse effect parameters were monitored, especially GH-related adverse effects such as hyperglycemia, hypertension, edema, tetter, arthritis, and hand stiffness. Routine clinical evaluation included breath rate, pulse rate, temperatures and blood pressures. All infection, sepsis and deaths and their causes were recorded.

Statistical analysis

All data were assessed for normality of distribution and equality of variance. Student's t test and ANOVA were used to compare normally distributed data. Data are presented throughout as means and standard deviations (SD). Categorical data were compared using the Pearson χ^2 test or Fisher exact test. All data analysis was performed using the program SPSS 11.5 for Windows. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

There were no differences between the two groups in baseline characteristics (Table 1).

Daily and accumulated nitrogen balance

Changes in daily nitrogen balance are shown in Table 2. Patients given rhGH showed decreased nitrogen excretion and increased nitrogen retention compared with patients

Table 2 Daily and accumulated nitrogen balance after operation (g)

Time after operation	rhGH (n = 24)	Placebo (n = 24)	P
D 3	0.29 ± 3.31	-0.86 ± 5.81	0.405
D 4	0.87 ± 3.23	-2.43 ± 5.60	0.016
D 5	0.87 ± 3.85	-0.94 ± 5.93	0.217
D 6	1.71 ± 3.56	-1.03 ± 3.47	0.010
D 7	2.76 ± 2.91	-1.35 ± 3.13	< 0.001
D 8	2.69 ± 2.89	-1.08 ± 3.48	< 0.001
D 9	2.18 ± 4.27	-1.36 ± 6.16	0.025
Accumulated NB (7 d)	11.37 ± 16.82	-9.11 ± 17.52	0.0003

Data presented as mean ± SD. NB: Nitrogen balance.

given the placebo during the study period. Postoperatively, daily nitrogen balance in the rhGH group was increased significantly compared with the placebo group on d 4 and from d 6 to 9 ($P < 0.05$). On d 9, the accumulated nitrogen balance in the rhGH group was significantly improved compared with the placebo group.

Nutritional condition measurement

On d 1 before and d 3 after operation, there were no significant differences between the two groups in serum albumin, transferrin, prealbumin, fibronectin and total lymphocyte counts. On postoperative d 10, mean serum fibronectin levels were significantly higher in thr rhGH group than in the placebo group. While mean serum albumin, transferrin, prealbumin levels and total lymphocyte counts were not significantly different between the two groups (Table 3). The weight change was also not significantly different between the two groups.

Adverse events

The main adverse effects seen during the study are summarized in Tables 4 and 5. Mean blood glucose levels were significantly higher in the rhGH group from d 3 to d 6 after operation (Table 4). Twenty-three patients in the rhGH group experienced hyperglycemia and 5 of these required insulin treatment (Table 5). Furthermore, 3 patients had other mild adverse events including 1 patient with edema, 1 with tetter and 1 with a fever. In the placebo group, 3 of 4 patients presenting hyperglycemia required insulin treatment. Concerning adverse events not related to the trial drug, 5 placebo-treated patients experienced mild electrolytes imbalance. There were no significant differences between the two groups in complete blood counts, liver and renal functions, body weights and the daily clinical parameters such as temperatures, blood pressures, and pulses.

Table 3 Nutritional condition measurement of two group patients

Test	D 1	D 3	D 10
Albumin (g/L)			
rhGH	40.85 ± 3.09	33.26 ± 3.82	35.16 ± 4.21
Placebo	41.19 ± 4.17	33.95 ± 3.68	35.57 ± 3.84
Transferrin (g/L)			
rhGH	2.41 ± 0.45	1.75 ± 0.44	2.15 ± 0.66
Placebo	2.51 ± 0.45	1.79 ± 0.42	2.11 ± 0.44
Prealbumin (mg/L)			
rhGH	133.90 ± 83.95	71.44 ± 46.54	105.51 ± 69.30
Placebo	164.03 ± 88.16	85.55 ± 57.87	109.99 ± 97.37
Fibronectin (mg/L)			
rhGH	97.40 ± 11.74	80.85 ± 8.13	104.77 ± 19.94[a]
Placebo	98.70 ± 20.17	83.69 ± 10.50	93.03 ± 16.03
TLC (10^9/L)			
rhGH	1.64 ± 0.60	1.03 ± 0.33	1.36 ± 0.54
Placebo	1.59 ± 0.52	1.15 ± 0.59	1.38 ± 0.46

Values are mean ± SD. TLC: Total lymphocyte count. [a]$P < 0.05$ *vs* placebo group.

DISCUSSION

Many attempts have been made to reverse the catabolic changes that occur in postoperative patients. Conventional nutrition support is unable to provide adequate nutritional supplements to increase or even maintain body proteins in hypercatabolic response conditions[9-11]. Recent studies indicated that rhGH had beneficial effects on stimulating body protein syntheses and producing nitrogen-spacing effects[6,12-14].

However, the impact of rhGH on body proteins and the change in blood glucose levels have not been previously investigated in patients receiving PN or EN following elective gastrointestinal surgeries[15-17]. In the present experiment, we observed the effect of rhGH on nitrogen balance, plasma proteins and blood glucose levels. The number of patients enrolled in the study is based on previous publications and the dosage of rhGH used is small considering its efficacy and safety[7,18,19]. rhGH treatment significantly increased the nitrogen retention of postoperative patients compared with the placebo group. Nitrogen balance began to improve from postoperative d 3 in the rhGH group, and 15 of 24 patients showed positive nitrogen balance on d 4. On d 9, 21 of 24 patients showed positive nitrogen balance in the rhGH group and the accumulated nitrogen balance was positive nitrogen balance, which was significantly different compared with the placebo group. Patients receiving only standard nutrition support were in a state of negative nitrogen balance during the whole period of the study. Our results demonstrated that administration of rhGH could result in significant anabolic effects on nitrogen balance and improve the efficiency of nutrition support.

In fact, changes of nitrogen balance may be associated with protein synthesis and breakdown[12,13,16]. The alteration in concentrations of plasma proteins reflects the metabolic responses to surgical traumas[20]. We found that serum fibronectin levels were higher in the rhGH group than in the control group after termination of treatment. This reflects a beneficial effect of rhGH on protein synthesis. However, serum transferrin, albumin, and prealbumin levels were not significantly different between the two groups. The potential reason might be that these protein levels are markedly affected by the acute-phase responses, thus they are not sufficiently sensitive and reliable in

Table 4 Comparison of blood glucose levels

Test	D 1	D 3	D 4	D 5	D 6	D 7	D 8	D 9
Glucose (mmol/L)								
rhGH	5.14 ± 0.64	6.71 ± 1.93[a]	7.17 ± 1.86[a]	8.28 ± 2.30[a]	7.68 ± 2.15[a]	7.29 ± 2.93	6.40 ± 2.00	6.20 ± 2.13
Placebo	5.26 ± 1.09	5.68 ± 1.33	5.81 ± 1.56	5.84 ± 1.48	5.95 ± 2.34	6.01 ± 2.64	5.66 ± 2.03	5.70 ± 1.89

Values are mean ± SD. [a]$P < 0.05$ *vs* placebo group.

Table 5 Main adverse events

Event	rhGH group	Placebo group
Hyperglycemia	23[a]	4
Tetter	1	0
Sepsis	0	0
Infection	2	3
Death	0	0

[a]$P < 0.05$ *vs* placebo group.

nutritional assessment[21-23].

GH given during sepsis has been thought to impair immune function and result in hyperglycemia, which may explain why acute critically ill patients do not benefit from GH treatment[24,25]. However, GH can be administrated safely after acute inflammatory response stage for elective surgery patients, especially with a low dose and temporary duration of treatment. rhGH treatment was generally well tolerated with no serious adverse events in our trial. The mortality rate in the GH-treated group was zero, confirming its safety. These results are contrary to the increase in mortality among critically ill patients treated with GH reported in two large clinical trials by Takala *et al*[24]. We hypothesize that this discrepancy might be due to the difference in study patients. In our study, the patient populations were elective surgery subjects. Moreover, rhGH given during the response to stress leads to uncontrolled systemic inflammation in Takala's study. The main adverse events of the rhGH treatment were hyperglycemia. Insulin resistance caused by rhGH plays an important role in the rise of blood glucose. Other reasons may include nutritional support and systemic inflammation syndrome[26,27]. In our test, the hyperglycemia caused by rhGH administration was mild, for which low-dose rhGH and hypocaloric nutrition may be the reason. Furthermore, the hyperglycemia could be controlled easily by insulin. Considering the difference between critically ill patients and elective surgery patients, rhGH seems to be well tolerated after operation.

Our study included 14 cancer patients in the rhGH group, so the potential tumor-promoting effect of GH must be addressed. In animal models, whether rhGH administration promotes tumor recurrence is controversial[28-30]. Several authors even concluded that GH could promote host growth selectively and inhibit tumor metastasis[31,32]. Only two trials assessed the impact of GH on tumor recurrence in humans. Based on 2632 adverse events reports, the National Cooperative Growth Study analyzed the recurrence of brain tumors in patients receiving long-term GH replacement. It was concluded that there was no evidence of increased tumor recurrence[33]. Only one study investigated the impact of short-term treatment with three different doses of GH on long-term tumor recurrence in postoperative cancer patients[34]. Thirty-five percent of rhGH-treated patients showed tumor recurrences in comparison to 44% of patients given placebo. Based on the above two studies, we believe that when complete resection and appropriate antineoplastic treatment is administered, short-term GH treatment can be given safely to cancer patients.

In conclusion, our results indicate that postoperative rhGH treatment for 7 d improves nitrogen retention and protein conservation, enhances the efficiency of nutrition support in adult patients undergoing major abdominal surgeries. rhGH also is well tolerated without clinically significant adverse effects and the blood glucose level can be well controlled. A larger trial is required to measure clinical endpoints such as infection, morbidities, mortalities and tumor recurrences.

COMMENTS

Background

Administration of recombinant human growth hormone has been shown to significantly maintain the nitrogen balance in surgery patients receiving nutritional support. However, it is still uncertain whether short-term treatment of low-dose recombinant human growth hormone (rhGH) is effective as well and whether its effect on blood glucose will lead to higher risk.

Research frontiers

Conventional nutrition support is unable to provide adequate nutritional supplements to increase or even maintain body protein under hypercatabolic response conditions. Recent studies indicated that rhGH had beneficial effects on stimulating body protein and producing nitrogen-spacing effects.

Innovations and breakthroughs

The present study confirmed that administration of rhGH together with hypocaloric nutrition support produced nitrogen conservation and protein synthesis effects after elective abdominal surgery. In addition, the changes in blood glucose levels, especially the hyperglycemia caused by rhGH administration was slight and could be controlled in GH treatment period.

Applications

Our results indicate that postoperative rhGH treatment improves nitrogen retention and protein conservation, enhances the efficiency of nutrition support in adult patients undergoing major abdominal surgery. rhGH also is well tolerated without clinically significant adverse effects and the blood glucose level can be well controlled.

Peer review

The authors assess the role of a low dose of growth hormone in postoperative nitrogen balance in patients undergoing gastrointestinal operations who also received a "hypocaloric" feeding. They also discuss the adverse effects and potential disadvantage of rhGH administration and monitor the change of blood

glucose levels. The study demonstrates that the appropriate application of rhGH is well tolerated and of great benefit to postoperative patients.

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