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• *BRIEF REPORTS* •

Clinical evidence of growth hormone for patients undergoing abdominal surgery: Meta-analysis of randomized controlled trials

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Abstract

AIM: To assess the effectiveness and safety of perioperative growth hormone (GH) in patients undergoing abdominal surgery.

METHODS: We searched the following electronic databases: MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Chinese Bio-medicine Database. The search was undertaken in February 2003. No language restrictions were applied. Randomized controlled trials (RCT) comparing GH with placebo in patients undergoing abdominal surgery were extracted and evaluated. Methodological quality was evaluated using the Jadad scale.

RESULTS: Eighteen trials involving 646 patients were included. The combined results showed that GH had a positive effect on improving postoperative nitrogen balance (standardized mean difference [SMD] = 3.37, 95%CI [2.46, 4.27], $P<0.00001$), and decreasing the length of hospital stay (weighted mean difference [WMD] = -2.07, 95%CI [-3.03, -1.11], $P = 0.00002$), and reducing the duration of postoperative fatigue syndrome (SMD = -1.83, 95%CI [-2.37, -1.30], $P<0.00001$), but it could increase blood glucose levels (WMD = 0.91, 95%CI [0.56, 1.25], $P<0.00001$).

CONCLUSION: GH for patients undergoing abdominal surgery is effective and safe, if blood glucose can be controlled well. Further trials are required with a sufficient size to account for clinical heterogeneity and to measure other important outcomes such as infection, morbidity, mortality, fluid retention, immunomodulatory effects, and tumor recurrence.

Key words: Perioperative growth hormone; Abdominal surgery

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INTRODUCTION

Catabolism and negative nitrogen balance is a part of the metabolic reaction to major abdominal surgical trauma. It is a concern to surgeons because the catabolic response is correlated with the overall surgical morbidity rate, causing prolonged convalescence. Growth hormone (GH) has been shown to have anabolic effects and to reduce or even prevent nitrogen catabolism in patients undergoing abdominal surgery. The effect of GH has recently been studied by many researchers. In 1974 Wilmore *et al*.[1], suggested that adequate nutritional intake was necessary for GH to have nitrogen-saving effects. In 1986 the study by Phillips[2] demonstrated that GH stimulated hepatic production of somatomedin (insulin-like growth factor-I, IGF-I) whose action could promote diverse anabolic processes, such as synthesis of RNA, DNA, proteins or proteoglycans. However, the effects of GH on nonmetabolic clinical outcome remain unclear.

Meta-analysis has been gradually used in medicine to improve the statistical efficiency, to evaluate the disadvantages of formulated researches and hypothesis, and to reach reliable conclusions from the mixed assortment of potentially relevant studies to determine the most promising directions for future researches. We performed a meta-analysis of available studies to assess the effectiveness and safety, in order to improve our understanding of the clinical effects of perioperative GH treatment of patients undergoing abdominal surgery; clinical outcomes including nitrogen balance, length of hospital stay, blood glucose, and postoperative fatigue syndrome were measured. Other important outcomes, such as infection, morbidity, mortality, fluid retention, immunomodulatory effects and tumor recurrence, were also measured.

MATERIALS AND METHODS

Identification of trials

Our aim was to identify all relevant randomized controlled trials (RCT) that compared GH with placebo in patients undergoing abdominal surgery. A RCT was defined as a

trial in which patients were assigned prospectively to one of two interventions by random allocation. We used a multimethod to identify relevant studies for the present review. A computerized literature search of MEDLINE from 1966 to October 2002 was conducted using the following search terms: operation OR surgery OR postoperative OR perioperative AND GH AND RCT (publication type) or controlled clinical trials or clinical trials, randomized. In addition, we searched Embase (1980-2002), Cochrane Controlled Trials Register (Issue 1, 2003), and Chinese Biomedicine Database (1979-2002), reviewed our personal files, and contacted experts in the field. Bibliographies of all selected articles and review articles that included information on GH were reviewed for other relevant articles. This search strategy was done iteratively, until no new potential, randomized, controlled trial citations were found on review of the reference lists of retrieved articles.

Study selection and data extraction

The following selection criteria were used to identify published studies for inclusion in this analysis: study design - randomized clinical trial, population - hospitalized adult patients undergoing abdominal surgery, intervention - GH *vs* placebo initiated at the same time and with the same nutrition support, and outcome variables - at least one of the following primary outcome variables: nitrogen balance, length of hospital stay, blood glucose, postoperative fatigue syndrome, incidence of infection, morbidity, mortality, fluid retention, immunomodulatory effects, and tumor recurrence. Study selection and data abstraction were conducted independently by the two investigators.

Data analysis

The incidences of infection, tumor recurrence, fluid retention, morbidity, and mortality were treated as binary variables. Nitrogen balance, length of hospital stay, blood glucose, postoperative fatigue syndrome, and immunomodulatory effects were treated as continuous variables. Data analysis was performed using the random effect model with meta-analysis software (RevMan 4.2; Cochrane Collaboration, Oxford, UK). The continuous data outcomes were presented with 95% confidence intervals (CIs). When authors reported standard deviations, we used them directly. When standard deviations were not available, we computed them from the observed mean differences (either differences in changes or absolute readings) and the test statistics. When the test statistics were not available, given a *P* value, we computed the corresponding test statistics from tables for the normal distribution. We tested heterogeneity between trials with χ^2 tests, with $P<0.05$ indicating significant heterogeneity[3]. Methodological quality was evaluated using the Jadad scale[4].

RESULTS

From 460 articles screened, 38 were identified as RCT comparing GH with placebo and included for data extraction. Twenty studies were excluded, and the remaining 18 trials were included in the present meta-analysis[5-22]. Only one study[19] was in Chinese. Articles were excluded for the following reasons, namely the outcomes of interest were not recorded[23-37] and some articles repeated[38-42]. A total of 646 patients were enrolled in the included studies. The characteristics of studies included in meta-analysis comparing GH with placebo are presented in Table 1. Not all of the studies reported the outcome of interest, postoperative nitrogen balance was reported in 11 studies[5-15], length of hospital stay in 3 studies[17-19], postoperative fatigue syndrome in 3 studies[20-22], blood glucose in 6 studies[12-17].

The combined results showed that GH had a positive effect on improving the postoperative nitrogen balance (standardized mean difference [SMD] = 3.37, 95%CI [2.46, 4.27], $P<0.00001$) (Table 2A), and decreasing the length of hospital stay (weighted mean difference [WMD]=-2.07, 95%CI [-3.03, -1.11], $P = 0.00002$) (Table 2B), and reducing the duration of postoperative fatigue syndrome (SMD = -1.83, 95%CI [-2.37, -1.30], $P<0.00001$) (Table 2C), but it could increase blood glucose levels (WMD = 0.91, 95%CI [0.56, 1.25], $P<0.00001$) (Table 2D).

Table 1 Characteristics of studies included in meta-analysis comparing GH with placebo

Study	Year	Jadad score	Reference	Operation	GH
Lehner	1992	3	6	Major abdominal surgery	0.3 IU / kg / d for 5 d
López	1993	1	7	Major surgery of the digestive tract	0.2 IU / kg / d for 6 d
Wong	1995	2	8	Major abdominal surgery	0.2 IU / kg / d for 7 d
Tacke	1994	1	9	Major gastrointestinal surgery	0.3 IU / kg / d for 5 d
Saito	1992	3	10	Major abdominal operation	0.4 IU / kg / d for 6 d
Kolstad	2001	5	11	Laparoscopic cholecystectomy	13 IU / m^2 / d for 3 d
Jensen	1998	5	12	Ileoanal anastomosis with a J pouch	12 IU / d for 6 d
Ponting	1988	2	13	Major gastrointestinal surgery	0.1 mg / kg / d for 7 d
Hammarqvist	1992	1	14	Elective cholecystectomy	0.3 IU / kg / d for 3 d
Jiang	1989	4	15	Gastrectomy or colectomy	0.15 IU / kg / d for 7 d
Mjaaland	1991	3	16	Gastrointestinal surgery	24 IU / d for 5 d
Barle	2001	1	17	Laparoscopic cholecystectomy	12 IU / d for 5 d
Vara-Thorbeck 1	1993	3	18	Cholecystectomy	8 IU / d for 7 d
Barry 2	1998	4	19	Abdominal aortic aneurysm repair	0.3 IU / kg / d for 6 d
Liu	2001	5	20	Abdominal surgery	0.3 IU / kg / d for 5 d
Barry 1	1999	3	21	Abdominal aortic aneurysm repair	0.3 IU / kg / d for 6 d
Kissmeyer-Nielsen	1999	5	22	Ileoanal J-pouch surgery	12 IU / d for 6 d
Vara-Thorbeck 2	1996	3	23	Cholecystectomy	8 IU / d for 7 d

Table 2 Random effect model of standardized mean difference (95%CI) in improving postoperative nitrogen balance (A) and in reducing the duration of postoperative fatigue syndrome (C) and weighted mean difference (95%CI) in decreasing the length of hospital stay (B) and in increasing blood glucose levels (D) with GH as compared with placebo

A

Study	Treatment *n*	Treatment Mean (SD)	Control *n*	Control Mean (SD)	Weight %	SMD (random) 95%CI
Ponting	6	1.80 (0.40)	5	-0.90 (0.70)	6.23	4.46 [1.85, 7.07]
Jiang	9	-7.10 (3.12)	9	-32.60 (4.20)	6.27	6.56 [3.97, 9.16]
Mjaaland	9	4.10 (1.10)	10	-3.10 (1.80)	8.36	4.55 [2.69, 6.41]
Hammarqvist	8	-2.32 (1.66)	9	-7.09 (0.71)	8.91	3.63 [1.94, 5.32]
Lehner	19	-4.30 (9.60)	21	-14.80 (3.30)	11.94	1.46 [0.76, 2.17]
Saito	18	-18.00 (3.30)	18	-185.00 (58.00)	10.60	3.98 [2.80, 5.15]
López	9	-7.30 (2.80)	9	-20.70 (4.10)	9.09	3.64 [2.00, 5.27]
Tacke	9	-10.00 (2.61)	10	-20.47 (3.86)	9.85	3.00 [1.60, 4.40]
Wong	8	3.00 (0.90)	7	-1.30 (0.75)	7.15	4.85 [2.59, 7.11]
Jenson	9	-47.00 (20.00)	10	-73.00 (20.00)	11.12	1.24 [0.24, 2.25]
Kolstad	11	-3.90 (0.40)	10	-5.70 (0.90)	10.49	2.53 [1.32, 3.73]
Total (95%CI)	115		118		100.00	3.37 [2.46, 4.27]

Test for heterogeneity: x^2 = 44.48, df = 10 (*P*<0.00001), I^2 = 77.5%. Test for overall effect: *Z* = 7.27 (*P*<0.00001).

B

Study	Treatment *n*	Treatment Mean (SD)	Control *n*	Control Mean (SD)	Weight %	WMD (fixed) 95%CI
Barry 2	8	13.00 (2.00)	10	17.00 (3.00)	17.05	-4.00 [-6.32, -1.68]
Liu	10	9.70 (1.80)	10	10.50 (1.30)	48.41	-0.80 [-2.18, 0.58]
Vara-Thorbeck 1	87	9.60 (3.60)	93	12.50 (7.10)	34.54	-2.90 [-4.53, -1.27]
Total (95%CI)	105		113		100.00	-2.07 [-3.03, -1.11]

Test for heterogeneity: x^2 = 6.93, df = 2 (*P*= 0.03), I^2 = 71.1%. Test for overall effect: *Z* = 4.24 (*P*<0.0001).

C

Study	Treatment *n*	Treatment Mean (SD)	Control *n*	Control Mean (SD)	Weight %	SMD (fixed) 95%CI
Barry 1	7	1.60 (1.20)	10	4.90 (2.20)	21.23	-1.68 [-2.84, -0.52]
Kissmeyer-Nielsen	9	1.37 (0.55)	10	2.73 (2.00)	31.57	-0.86 [-1.82, 0.09]
Vara-Thorbeck 2	22	1.52 (0.43)	26	3.14 (0.75)	47.20	-2.55 [-3.33, -1.77]
Total (95%CI)	38		46		100.00	-1.83 [-2.37, -1.30]

Test for heterogeneity: x^2 = 7.32, df = 2 (*P* = 0.03), I^2 = 72.7%. Test for overall effect: *Z* = 6.72 (*P*<0.00001).

D

Study	Treatment *n*	Treatment Mean (SD)	Control *n*	Control Mean (SD)	Weight %	WMD (random) 95%CI
Barle	10	6.40 (1.00)	10	5.40 (0.50)	11.98	1.00 [0.31, 1.69]
Hammarqvist	8	5.60 (0.30)	9	4.80 (0.20)	20.69	0.80 [0.55, 1.05]
Jiang	9	6.17 (0.51)	9	6.06 (0.50)	16.26	0.11 [-0.36, 0.58]
Mjaaland	9	5.75 (0.43)	10	4.90 (0.30)	18.94	0.85 [0.51, 1.19]
Ponting	6	9.40 (0.70)	5	7.20 (0.50)	11.68	2.20 [1.49, 2.91]
Vara-Thorbeck 1	87	6.56 (1.02)	93	5.66 (0.71)	20.46	0.90 [0.64, 1.16]
Total (95%CI)	129		136		100.00	0.91 [0.56, 1.25]

Test for heterogeneity: x^2 = 23.97, df = 5 (*P* = 0.0002), I^2 = 79.1%. Test for overall effect: *Z* = 5.13 (*P*<0.00001).

DISCUSSION

The results must be interpreted with the difference in patients, dose or length of treatment, and unexplained heterogeneity. Clinical heterogeneity in the form of age, etiology and operation of patients points to the possibility of bias.

This meta-analysis did not show that GH had a positive effect on improving postoperative nitrogen balance. Eleven studies involving 233 patients were included. Although there was a heterogeneity (test for heterogeneity χ^2 = 44.48, df = 10, *P*<0.00001), the result was sure. Because all the 11 studies showed that GH had a positive effect on improving postoperative nitrogen balance with a statistical significance (minimum of SMD = 1.24, 95%CI [0.24, 2.25]). However, it seems that different doses had different effects, subgroup was not used. What attention should be paid to is that some studies only reported the cumulated nitrogen balance or the daily nitrogen balance. Further research should be done to assess the possible best dose.

To date, only three studies involving 218 patients, have examined whether treatment with GH could influence the length of hospital stay. The combined results showed that administration of GH could decrease the length of hospital stay. The results must be interpreted with caution due to the small size. Two of three trials[17,18] showed statistically and clinically significant differences in the length of hospital stay. So, further trials are required with a sufficient size to

account for clinical heterogeneity and length of hospital stay.

This meta-analysis showed that administration of GH could reduce the duration of postoperative fatigue syndrome after 1 mo. Three studies involving 84 patients were included. The evidence was not strong due to the small size and unexplained heterogeneity. It is also important to recognize that two[20,21] of the RCTs included in this review were not designed specifically to reduce postoperative fatigue and provided few or no theoretical rationales as to why the intervention under study might be expected to attenuate it. Attempts to assess fatigue objectively by measuring, for example, physical activity, time taken to return to normal routine, or involuntary or voluntary muscle force were problematic because they could be confounded by numerous factors including pain and anxiety. Much effort has therefore been devoted to developing short and easy-to-use questionnaires that could provide some quantification of a patient's subjective feeling of fatigue. Future research should ensure that an adequate measure of subjective fatigue is employed, possibly in tandem with important objective measures, such as time taken to return to work.

This meta-analysis did not show that GH might increase blood glucose levels. Six studies involving 265 patients were included. Of the six, only the study of Jiang *et al*.[14], did not reach a statistical significance (SMD = 0.11, 95%CI [-0.36, 0.58]). Low-dose GH and hypocaloric nutrition may be the reason. Confirmation of the diabetogenic properties of GH was made after it was administered in excess to experimental animals and men. Transgenic animals, which over-expressed GH, developed insulin resistance, marked hyperinsulinemia, hyperglycemia, and hypertriglyceridemia in association with a number of molecular abnormalities[43,44]. Patients with acromegaly developed insulin resistance and hyperinsulinemia, while up to 40% became diabetic[45,46]. There is evidence that insulin resistance caused by GH plays an important role in the rise of blood glucose. In addition, GH could stimulate lipolysis with the release of glycerol and non-esterified fatty acids (NEFA). This provides a further mechanism for the diabetogenic properties of GH through the effect of NEFA to increase hepatic glucose output and decrease peripheral glucose oxidation according to the glucose-fatty acid cycle[47,48]. In fact, in the study of Berman *et al*.[23], the GH group had significantly elevated urine glucose levels throughout the study period, consistent with the demonstrated hyperglycemia and only moderately elevated insulin levels. Treatment with GH did result in hyperglycemia, and two patients were removed from the study. Hyperglycemia associated with GH administration could be treated easily by insulin, especially in long-term GH administration.

Only one RCT[36] conducted an analysis of a multicenter study with 104 patients undergoing major gastrointestinal surgery to assess the risk of long-term tumor recurrence after short-term (5 d) postoperative GH treatment. The study was a follow-up of a previous randomized study investigating the effect of three different doses of GH (0.075, 0.15, and 0.30 IU/kg/d) on the postoperative cumulative nitrogen balance in patients undergoing major surgery. Tumors recurred in 20 (35%) patients who were evaluated for and treated with GH (n = 57). This accounted for 4 of 17 (23%) patients given 0.075 IU/kg/d of GH, 9 of 20 (45%) given 0.15 IU/kg/d of GH, and 7 of 20 (35%) given 0.30 IU/kg/d. By comparison, tumors recurred in 8 of 18 (44%) of patients given placebo. The result of this study demonstrated that short-term treatment with GH for 5 d after major gastrointestinal surgery for adenocarcinoma did not increase the risk of tumor recurrence. But the group size was too small to further stratify the patients according to tumor type and tumor stage, so that no information was gained about the influence of GH dose in certain tumor stages.

Fluid retention is one of known side effects of GH administration. The sodium and fluid retaining impact of GH was demonstrated in humans almost 50 years ago by Ikkos *et al*.[49]. Underlying mechanisms of GH-induced fluid retention are as follows. GH could increase glomerular filtration rate mediated by insulin-like growth factor (IGF-I)[50-52], stimulate the renin-angiotensin-aldosterone system (RAAS)[53-57], reduce atrial natriuretic factors[58-61], and prostaglandins could play a role in GH-induced fluid retention[62]. In the study of Berman *et al*.[23], two GH patients were removed from the study for fluid retention. These patients were in the immediate postoperative period. However, whether the fluid retention was a result of surgery or GH administration could not be determined.

GH should not be given in acute inflammatory disease states. Findings by Takala *et al*.[63], pointed to the immunomodulatory effects of GH. These authors described higher hospital mortality in a Finish and an European study on critically ill non-cancer patients. It was proposed that the higher mortality was due to the application of GH at a later stage during the inflammatory disease process, leading to uncontrolled systemic inflammation. However, infection was not measured in these trials except one[17]. Only one RCT[18] reported the morbidity and mortality, so we could not draw a conclusion due to the small size. But there are still four studies[64-67] awaiting assessment in other languages or we cannot find the full text.

In conclusion, perioperative GH treatment of patients undergoing abdominal surgery can improve the postoperative nitrogen balance, and decrease the length of hospital stay, and reduce the duration of postoperative fatigue syndrome. But it might increase blood glucose levels. However, the evidence is not strong due to the difference in patients, dose or length of treatment, and unexplained heterogeneity. In order to examine the effectiveness and safety of perioperative GH treatment of patients undergoing abdominal surgery, further trials are required with a sufficient size to account for the clinical heterogeneity and to measure other important outcomes such as infection, morbidity, mortality, fluid retention, immunomodulatory effects, and tumor recurrence.

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