Full Length Research Paper

Effect of recombinant human growth hormone (rhGH) on treatment of geriatric thoracic and abdominal postoperative patients with acute respiratory failure

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The aim of this study was to explore the effect and ascertain the ideal dose of recombinant human growth hormone (rhGH) for the treatment of geriatric thoracic and abdominal postoperative patients with acute respiratory failure. Forty-five geriatric postoperative patients with acute respiratory failure were randomly divided into three groups (A, B and C). Patients in rhGH group A were given 4 IU rhGH by intramuscular injection twice a day continuously for 10 days. Patients in rhGH group B were given 4 IU rhGH by intramuscular injection once a day continuously for 10 days. Patients in control group C were admitted to the intensive care unit (ICU), but were not given rhGH. Other treatments were the same in the three groups. Comparisons were made among the groups regarding time of mechanical ventilation, average time in the ICU, success rate of one time pull out windpipe conduit, incidence rate of ventilator-associated pneumonia and case fatality rate, blood glucose content, and dosage of insulin per day from the beginning of the treatment until the 10th day. Compared with the control group, the parameters of recovery of respiratory function and fatality in the ICU of treatment groups A and B all showed statistically significant difference (P < 0.05). Although the blood glucose in group C showed no difference before and after treatment (P > 0.05), the blood glucose of rhGH group A became mildly elevated after treatment (P > 0.05) whereas that of group B showed the opposite effect (P < 0.05). Accordingly, the required dosage of insulin per day was much more than that before treatment (P < 0.05) in the controllable range. A daily rhGH dose of 4 IU for 10 days is safe for geriatric thoracic and abdominal postoperative patients with acute respiratory failure in the ICU. However, enhanced monitoring of blood glucose and intensive insulin therapy (IIT) should be conducted to prevent glycometabolic disturbance.

Key words: Respiratory insufficiency, ventilators, mechanical, recombinant human growth hormone (rhGH), aged patient.

INTRODUCTION

Recombinant human growth hormone (rhGH) has been greatly highlighted because of its anabolic effect. Its indication for clinical application has been steadily growing. At present, rhGH is widely used in large area burns, parenteral fistula, acute necrotizing pancreatitis, severe infection, dilated cardiomyopathy, Crohn's disease, lung cystic fibrosis in children, etc (Amorim et al., 2011; Castañeda et al., 2011; Hannon et al., 2011;

Noto et al., 2011; Souza and Collett-Solberg, 2011; Holmberg et al., 2007). Respiratory failure patients can also benefit from rhGH (Phung et al., 2010). Given its capability to raise blood glucose, the application of rhGH treatment for various indications, including the exact therapeutic doses and the best course of treatment, has been an intense topic of study and exploration by clinicians (Phung et al., 2010; Souza and Collett-Solberg, 2011; Jeevanandam et al., 1996).

In the current study, we compared the curative effect of two different doses of rhGH in elderly acute respiratory failure patients with mechanical ventilation recovering from

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chest abdominal surgery, to provide quantifiable basis for the intensive care unit (ICU) clinical applications.

DATA AND METHODS

Clinical data

Forty-five cases of acute respiratory failure after ICU chest abdominal surgery, 16 with chest surgery, and 29 with abdominal surgery were enrolled in this study from September 2008 to 2010. The patients were aged 60 to 75 years. Of the 45 patients, 24 had high blood pressure, 4 had coronary heart disease, 12 had chronic obstructive pulmonary disease (COPD), 4 had diabetes and 2 had malignant tumor. The basic cause of respiratory failure included pulmonary infection, pulmonary edema, atelectasis, and acute respiratory distress syndrome (ARDS), among others. All patients showed shortness of breath, cough, weakness, expectoration difficulties, and quickly increasing heart rate. In addition, percutaneous blood oxygen saturation was 75 to 89%, which is consistent with diagnosis standards for acute respiratory failure (Truwit et al., 2011).

ICU treatment

Severe hypoxic respiratory failure is considered as the diagnostic criteria for patients with respiratory failure when arterial blood gas shows PaO_2 of < 8 kPa or $PaCO_2$ of > 6.65 kPa or at room air. Acute respiratory failure occurred in a day to 6 days post-operatively or directly during ICU treatment. Ventilator auxiliary acute respiratory failure occurred in a day to 6 days postoperatively or directly during the ICU treatment, in which the duration of ventilator-assisted breathing was more than 5 days. The primary diseases of the patients studied were brought under control. All patients received standard ICU cluster of management treatment, including the use of sensitive antibiotics, expectorants, bronchus relaxation, and ventilator (Zaydfudim et al., 2009; Miller et al., 2010; Rello et al., 2011). Parameters were adjusted accordingly, including water, electrolytes, acid-alkali balance, nutrition support, wound and drainage tube treatment, and intravenous or enteral nutrition support. The calorie intake standard was 125 kJ/D and the nitrogen intake was 0.25 g/kg/D. Vitamins and micronutrients were added. Blood glucose was monitored at regular intervals and intensive insulin therapy was carried out (Berghe, 2012; Liu et al., 2011; Mowery et al., 2012).

An artificial airway was built mainly by nasal endotracheal or oral tracheal intubation for individuals with extremely distinctive tracheas. The external breathing machine (PB840 or new bond e360) ventilation modes used were A/C (volume control or pressure control), synchronized intermittent mandatory ventilation (SIMV) + pressure support ventilation (PSV), PSV, 6 to 10 mg/kg tidal volume at a frequency of 12 to 20 times/min, Fi 0.2, 0.3 to 0.5, and positive end-expiratory pressure (PEEP) 3 to 10 cm H_2O. According to the patient's clinical manifestations and arterial blood-gas analysis results, breathing machine parameters were adjusted at timely intervals and gradually reduced before the machine was removed or went offline, drawing the tube as early as possible. The blood pressure of the patient with high blood pressure should be controlled at a reasonable level according to the Guidelines for Prevention and Treatment for Hypertension in China (2010) (Chinese Medical Association).

Grouping and index

The 45 patients were randomly divided into three groups (n = 15).

One treatment group received 4 IU rhGH (Saizen, Switzerland, Serono Products) (Bernd et al., 2010) once a day for 10 days through intramuscular injection. Another treatment group received 4 IU rhGH twice a day for 10 days through intramuscular injection. The third group served as control, wherein patients received ICU treatment at the same intervals and conditions but no rhGH treatment. The mechanical ventilation time, average time, decannulation rate, incidence of ventilator-associated pneumonia (VAP) and ICU mortality were recorded. After treatment day 10, blood glucose content and daily insulin dosage of patients were recorded.

Statistical analysis

Data were expressed as $\bar{x} \pm s$. Comparison among groups was conducted using F test. Count data were expressed as rates. Comparison between two variables was conducted using q test. All data were analyzed with Statistical Package for Social sciences (SPSS) 11.0 software. P < 0.05 represented statistical significance.

RESULTS

General data

The age, gender, infection site, and acute physiology and chronic health evaluation II (APACHE II) ICU scores had no significant difference among the three groups of patients (P > 0.05) (Table 1).

Mechanical ventilation curative effect and mortality

Compared with the control group, mechanical ventilation time, average time, decannulation rate, incidence of VAP and ICU mortality in treatment groups A and B showed statistically significant differences (Table 2).

Blood glucose and insulin dosage changes

No significant difference was found in blood glucose and insulin dosage changes before treatment among the three groups. After treatment, blood sugar in groups A and B increased. Compared with the control group, the differences in blood sugar and insulin dosage were significant (P < 0.05) (Table 3).

DISCUSSION

The number of patients requiring mechanical ventilation has been increasing annually as a direct result of population aging, major surgery, serious infections and change of anesthesia patterns, which increases the risk of respiratory failure (Ziberberg et al., 2008; Needam et al., 2005; Crimlisk et al., 2012). The ICU fatality ratio of patients with mechanical ventilation was 31% in Needam et al. (2004). Thirty-nine percent of ICU patients in the

Table 1. Comparison of general date in three groups of patients' admission ICU.

| Group | n | Gender | | Age | Pathogenesis | | | | Oxygenation index | APACHEII score |
		Male	Female		Pulmonary infection	Pneumonedema	Pulmonary atelectasis	Others		
Control	15	7	8	66±4	6	4	2	3	135.6±58.8	21.8±7.7
A	15	8*	7*	68±2*	7*	3*	2*	3*	137.2±56.3*	22.3±8*
B	15	9*	6*	67±3*	6*	4*	3*	2*	136.6±57.6*	21.4±8*

*Compared with the control group, P > 0.05.

Table 2. Comparison of mechanical ventilation curative effect and mortality among three groups.

Group	Mechanical ventilation time (day, Mean ± s)	Average ICU days (day, Mean ± s)	A decannulation rate [%(case)]	VAP incidence [%(case)]	ICU mortality [%(case)]
Control	9.8±3.6	12.4±3.2	46.7 (8/15)	40 (6/15)	20 (3/15)
A	6.8±2.5^{a1}	8.9±3.7^{b1}	80 (12/15)^{c1}	20 (3/15)^{d1}	6.7 (1/15)^{e1}
B	5.8±2.9^{a2}	8.6±3.4^{b2}	86.7 (13/15)^{c2}	20 (3/15)^{d2}	6.7 (1/15)^{e2}

Mechanical ventilation time: compared A and B group with the control, $^{a1}P< 0.05$ and $^{a2}P < 0.05$; Average ICU days: $^{b1}P < 0.05$ and $^{b2}P < 0.05$; a decannulation rate: $^{c1}P < 0.05$ and $^{c2}P < 0.05$; VAP incidence %: $^{d1}P < 0.05$ and $^{d2}P < 0.05$; ICU mortality: $^{e1}P < 0.05$ and $^{e2}P < 0.05$.

Table 3. Blood glucose, insulin dosage changes 10 days before and after rhGH treatment.

| Group | Blood glucose (mM) | | Insulin dosage (IU/d) | |
	Before treatment	After treatment	Before treatment	After treatment
Control	7.6±3.6	7.4±2.7	31.5±9.6	30.3±8.9
A	7.7±3.4	8.5±2.3^{a}	30.9±8.8	43.3±6.5^{c}
B	7.5±3.9	9.8±2.9^{b}	30.3±8.9	48.3±5.4^{dc}

Blood glucose change: compared A and control group, $^{a}P > 0.05$; compared B and control group, $^{b}P < 0.05$; insulin dosage changes: compared A and control group, $^{c}P < 0.05$; compared B and control group, $^{d}P < 0.05$; compared A and B group, $^{dc}P < 0.05$.

USA need long-term mechanical ventilation (> 96 h) (Esteban et al., 2008). In addition, the incidence of ventilator-associated pneumonia (VAP) has also increased (Berenholtz et al., 2011; Stonecypher, 2010). Age is the primary factor affecting the prognosis of patients requiring mechanical ventilation, given that the risk of death of 70-year-old patients is more than twice that of 40-year-olds (Esteban et al., 2008). Reducing the mechanical ventilation time of elderly patients with respiratory failure, associated complications, and ICU mortality is an important issue in critical care medicine. The elderly often have different levels of reduced lung function after abdominal and chest surgery.

Serious injuries, major surgery, and infection can elicit a stress-response state in the body with a high decomposition metabolism. A prolonged stress-response state can induce a negative nitrogen balance, decrease in immune function, systemic muscle consumption, and rehabilitation process hysteresis, eventually leading to multiple organ failure (Michie, 1997; Knox et al., 1996).

These conditions can easily accelerate into acute respiratory failure. Among these conditions, hypoalbuminemia and muscle function damage caused by negative nitrogen balance are the main reasons inhibiting the postoperative patient's respiratory function recovery. Thus, breathing auxiliary time is compulsorily extended.

Mechanical ventilation treatment is the most effective means to treat acute respiratory failure. However, long-term mechanical auxiliary treatment may increase ventilator-related complications, such as VAP. Risk factors for Ventilator-associated pneumonia (VAP) in RICU screening include intubation days, hypotension after intubation, cerebrovascular disease, and lower albumin (Crimlisk et al., 2012). Therefore, for elderly patients with acute respiratory failure after surgery, except for the early positive pathogeny cure, positive mechanical ventilation breath support and the creation of conditions that facilitate early tube removal are critical to successful treatment.

The rhGH is a synthetic metabolic hormone that can

weaken decomposition metabolism induced by injuries, stimulate protein synthesis, abate or even reverse negative nitrogen balance, correct hypoalbuminemia, promote the improvement of patient nutrition, accelerate wound healing, and promote whole body and breathing muscle function recovery (Bercu et al., 2001; Brearley et al., 2007). rhGH used in the treatment of mechanical ventilation can improve the nutritional status of patients and respiratory muscle strength, and shorten the duration of mechanical ventilation usage (Patel and Clayton, 2011).

GH absorption is generally slower. Plasma GH concentration reached its peak in 3 to 5 h after administration. Clearance half-life is generally 2 to 3 h. GH is cleared through the liver and kidneys. GH without metabolic excluded directly from the urine is extremely trace. In the blood circulation, almost all of the GH binds to high-affinity GH binding protein (hGHbp) to form a composite which make the half-life of GH in serum extended. The serum concentration of GH cannot be affected by different injection time in a day. However, the highest peak of GH concentration is usually accompanied by the slow-wave sleep. Therefore, injection is generally selected at night before bedtime.

Melarvie et al. (1995) studied the characteristics of the secretion of hGH in patients with severe infections and found that the average concentration of hGH at 24 h was lower than that of normal controls. The characteristics of pulsatile secretion still existed but the times reduced and the average concentrations and peak values were similar in the daytime and night time. The dominant feature of the nocturnal secretion presented in the normal human also disappeared. The hGH secretion in the normal human body is released in the manner of pulse or quantum. One time of pulse secretion can dramatically stimulate protein synthesis for several hours. Each hGH secretion time is very short and usually followed by a few hours of the refractory period. The axis of hypothalamic-pituitary growth hormone in the patient with severe infection is inhibited. The rhGH replacement therapy given to the patients with GH deficiency at night has a better effect. This is the result of the simulation of the dominant nocturnal secretion in the normal human. Therefore, doctors tend to give administration at night to the patients with severe infection. In addition, the increased incidence of elderly cardiovascular disease may be related to the relative lack of internal rhGH.

GH deficiency can lead to increasing the levels of blood plasma fiber pepsinogen and plasminogen activator inhibitor (PAI), vascular intimal thickening and the mural plaque formation, increasing the risk of myocardial infarction and stroke. Therefore, elderly patients given low doses of GH may be beneficial in the treatment of vascular disease. In theory, application of complementary treatment with small doses of GH to the elderly population in a large scale can significantly reduce the attacking risk of the cardiovascular disease. A large number of clinical studies have been performed by scientists from Europe and the United States and other countries to verify this theory. It is reasoned that the exact dose of rhGH and the required courses of treatment should be determined when rhGH is used for the treatment of the elderly, postoperative and even co-infected patients.

Our findings showed that in the surgery of elderly, critically ill patients with routine use of ventilator after abdominal and chest surgery, supplemental treatment with rhGH can increasingly promote earlier tube removal, shorten breathing machine treatment, and reduce the incidence of VAP and ICU mortality. At present, the optimal post-operative dose and treatment of rhGH for elderly patients with acute respiratory failure are unverified. In addition, the cost is higher and the application process can cause the possibility of high blood glucose or diabetes, thus ascertaining that the right dose and method of treatment is very important for successful postoperative care of elderly acute respiratory failure patients.

According to previous reports, high blood sugar in critical patients resulted when rhGH was used at 8 to 10 IU/d for 2 weeks. In two cases, the high blood sugar level was not controlled. High blood sugar was found to increase every 2 to 3 days on average and peak at 7 to 10 days. Therefore, given that high blood glucose hematic disease is difficult to control, the post-operative application of rhGH for critical patients should be carefully administered (Giglio et al., 2010; Garg et al., 1994). The current study studied elderly respiratory failure patients after abdomen and chest surgery administered with 4 or 8 IU/d rhGH for 10 days. The results were remarkably better than the control, confirming the curative effect of rhGH. ICU treatment was administered together with intensive insulin therapy scheme, in which blood sugar was strictly controlled. Consequently, the blood sugar levels achieved the best range (Liu et al., 2011).

We found that the initial blood sugar levels of the elderly postoperative respiratory failure patients studied were higher than normal. Different levels in blood sugar increase were observed during rhGH treatment. In the rhGH 8 IU/d treatment group, blood sugar levels increased at a statistically significant manner. Along with irritability, blood sugar increase after surgery can affect sugar transport to tissue cells. Although blood sugar levels were within the control range and serious complications did not happen in the study, blood glucose monitoring should be strengthened during rhGH treatment to prevent related complications, such as metabolic disorders, etc.

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