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The effect of ulinastatin on hyperglycemia in patients undergoing hepatectomy

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ARTICLE INFO

Article history:
Received 20 April 2014
Received in revised form
25 July 2014
Accepted 19 August 2014
Available online 23 August 2014

Keywords:
Perioperative period
Hyperglycemia
Ulinastatin
Inflammation
Insulin resistance

ABSTRACT

Background: To identify the effect of ulinastatin (UTI) administration on stress-induced hyperglycemia and acute insulin (INS) resistance experienced by patients undergoing partial hepatectomy.

Methods: Forty-six patients undergoing partial hepatectomy were assigned randomly to the control group (group C) or UTI treatment group (group U). Six cases underwent partial hepatectomy but were not eligible for inclusion. The patients in group U had an intravenous infusion of a total amount of 5000 IU/kg UTI before the induction of anesthesia and at the start of surgery. The patients in group C were given an identical volume of physiological saline in the same manner. Blood samples for the measurement of interleukin-6, cortisol, INS, and glucagon were obtained. Fasting plasma glucose concentration was measured immediately before skin incision (T1), 20 min after the liver lesion was removed (T2), at the end of surgery (T3), as well as on the first (T4) and second mornings after partial hepatectomy (T5). The insulin sensitivity index (ISI) was calculated at these time points.

Results: The fasting plasma glucose concentration in group U was significantly lower than that in group C at all time points except for T1. In group U, the insulin sensitivity index was higher, and the levels of interleukin-6, cortisol, and INS were lower than that in group C ($P < 0.05$).

Conclusions: The data suggest that UTI administration improves perioperative hyperglycemia by inhibiting the inflammatory reaction, as well as excessive release of inflammatory factors, and improves INS resistance.

1. Introduction

Dysglycemia during the perioperative period refers to any disorder in the stability of glucose levels in serum. This includes diabetes-induced hyperglycemia in previously diagnosed or undiagnosed patients; impaired glucose tolerance; impaired fasting glucose; stress-induced hyperglycemia in nondiabetic patients; and hypoglycemia. It is very common in patients undergoing major surgical procedures. However, hyperglycemia is the most common pattern of dysglycemia in clinical practice.

Considerable attention has been paid to hyperglycemia because it is an early warning sign of a poor prognosis [1,2]. Several measures have been taken to avoid hyperglycemia in patients undergoing major surgery. However, the treatment strategy of hyperglycemia is controversial. A moderate target for glycemic control has not been determined, and the benefits and risks of intense glucose control

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http://dx.doi.org/10.1016/j.jss.2014.08.027

by insulin (INS) in critically ill patients have been questioned [3,4].

Hyperglycemia refers to excess glucose in the blood, which means that glucose is not being metabolized appropriately. Hyperglycemia in major surgery usually involves hyperinsulinemia (i.e., cells are deconditioned to the INS stimulus and do not take up glucose very well). During such a condition, INS administration is not the best way to regulate the unstable level of glucose in blood because INS resistance occurs. Recent studies have indicated that perioperative hyperglycemia is, in general, related to the following conditions: preoperative metabolic condition; dysregulation of the neuroendocrine system; release of cytokines subsequent to the stress response; acute INS resistance; specific features of the surgical procedure, and perioperative management [5,6]. Therefore, theoretically, any intervention that regulates the neuroendocrine stress response and release of cytokines perioperatively can also modulate the consequent dysglycemia and mitigate perioperative hyperglycemia. Similar effects of propofol or opioids have been reported [7].

Hepatectomy is very different from other types of surgery. It involves very complicated occlusion and reopening of vessels, manipulation of the first and second hepatic portal vein, and the inferior vena cava. These procedures can contribute to ischemia–reperfusion injury to liver cells and the release of many inflammatory factors. These factors serve as a strong stress response that facilitates hyperglycemia during surgery.

Ulinastatin (UTI) is a broad-spectrum protease inhibitor. It is a type of glycoprotein separated and purified from human urine. It has been used widely in patients with acute inflammatory disorders such as acute pancreatitis, shock, systemic inflammatory reaction syndrome, and multiple organ dysfunction syndrome. *In vitro* experiments have demonstrated that UTI ameliorates ischemia–reperfusion injury by inhibiting neutrophil accumulation in the postischemic liver [8]. Recent *in vivo* and *in vitro* studies have also indicated that UTI administration can inhibit the additional expression of inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-2 and IL-8 (which play important parts in dysglycemia), impairment of the blood–brain barrier, as well as postoperative cognitive dysfunction [9–13]. Recent research has also suggested that UTI could be a useful marker of chronic inflammatory conditions in patients with type-1 or type-2 diabetes [14]. However, treatment of perioperative hyperglycemia by UTI administration has not been reported.

We hypothesized that UTI could ameliorate perioperative hyperglycemia. We obtained blood samples through central venous catheters that had been inserted via the right jugular vein after general anesthesia (GA) at several fixed time points or events during and after hepatectomy. Fasting plasma glucose (FPG), interleukin-6 (IL-6), cortisol (COR), INS, and glucagon (GLU) were measured in these blood samples. The insulin sensitivity index (ISI) was calculated to evaluate the benefit of UTI for controlling perioperative hyperglycemia.

2. Materials and methods

The study protocol was approved by the Ethics Committee of Guangdong General Hospital (Guangdong Academy of Medical Sciences) and registered in the Chinese Clinical Trial Registry (Registration number ChiCTR-TRC-13003829). Written informed consent was obtained from each patient.

Forty-six American Society of Anesthesiologists (ASA) I–II patients for laparotomy hepatectomy from October 2012–May 2013 were enrolled. The inclusion criteria were (i) Child–Pugh score $\leq$10 and (ii) no metastasis to other organs. The exclusion criteria were (i) abnormal findings on electrocardiography or chest radiographs; (ii) cardiac or pulmonary insufficiency; (iii) severe renal dysfunction; (iv) preoperative hemoglobin level $<$100 g/L; (vi) allergies; (vii) history of drug abuse; and (viii) infusion of glucose-containing liquid $<$8 h before surgery. Patients who had one of the following severe complications or events were also excluded as follows: (i) cardiovascular events; (ii) allergic shock; (iii) reoperation; (iv) hepatic failure; and (v) postoperative INS therapy. Patients were assigned randomly (by a computer-derived random number sequence) to two groups to intravenous infusion of 2500 IU/kg UTI (UTI treatment group or group U) or saline (control group or group C) at the beginning of anesthesia and surgery, respectively. Double-blind processing was carried out. That is, study drugs were dissolved in 20 mL physiological (0.9%) saline or only 0.9% saline with the same type of syringe, and markers were prepared according to the randomized groups by a person who did not take part in sample measurements or postoperative follow-up. The attending anesthesiologist and data collector were blinded to the infusion drug.

The general anesthetic method and perioperative management were standardized. Five-lead electrocardiography, noninvasive blood pressure, end-tidal PCo_2 ($EtCO_2$), heart rate (HR), and pulse oximetry (SpO_2) were recorded. A central venous catheter was placed in the right internal jugular vein for continuous monitoring of central venous pressure. An electroencephalography monitor version 4.3 (Narcotrend; MT MonitorTechnik GmbH, Bad Bramstedt, Germany) was connected to patients for assessing anesthetic depth. Atropine (0.01 mg/kg, intravenously) and midazolam (3 mg, intravenously) were administered to all patients 30 min before surgery. GA was induced with 1.0 mg/kg propofol and 4.0–5.5 ng/mL remifentanil by target-controlled infusion followed by injection with 0.6 mg/kg cisatracurium to facilitate tracheal intubation. GA was maintained with target-controlled infusion of remifentanil and sevoflurane inhalation in O_2 (50%–100%), and the depth of anesthesia with the Narcotrend index at 20–46 (stage D2–E1) was maintained. Intermittent positive-pressure ventilation with an adequate tidal volume to maintain an $EtCO_2$ of 36–40 mm Hg was maintained at a fresh gas flow of 2 L/min. Extra fentanyl and muscle-relaxation agents were infused intravenous according to need.

On the premise of a stable depth of anesthesia, fluctuation of mean arterial blood pressure (MAP) $<$20% or HR $<$30% to baseline was treated by adjusting the end-tidal concentration of sevoflurane and the infusion target of remifentanil or intravenous fluid speed. As adverse hemodynamic responses occurred (defined as fluctuation of MAP $>$20% or HR $>$30% to baseline), vasopressors (dopamine, norepinephrine, or glonoin) were infused to maintain hemodynamic stability followed by procedures to find out the pathogenesis of the events and initiate therapy. Bradycardia (HR $<$45 bpm) was treated by 0.01 mg/kg atropine. Hydroxyethyl starch solution (6%) (130/