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Original article

The effect of perioperative glucose control on postoperative insulin resistance☆

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SUMMARY

Background & aims: Postoperative insulin resistance and the consequent hyperglycemia affects clinical outcome. Insulin sensitivity may be modulated by preoperative nutrition, adequate pain management and minimal invasive surgery. This study aims to disclose the impact of perioperative glucose control on postoperative insulin resistance.

Methods: Twenty patients scheduled for elective open hepatectomy were enrolled in this prospective, randomized study. In the treatment group ($n = 9$) insulin was administered intravenously to keep blood glucose between 6 and 8 mmol/l during surgery. The control group ($n = 8$) received insulin if blood glucose >14 mmol/l. Insulin sensitivity was measured by a hyperinsulinemic normoglycemic clamp (0.8 mU/kg/min), performed on all patients both on the day before surgery and immediately postoperatively. Plasma cortisol, insulin and C-peptide were measured.

Results: There was a significant difference in mean glucose value during surgery. In the control group 8.8 mmol/l (SD 1.5) vs. 6.9 mmol/l (SD 0.4) in the treated group, $p = 0.003$. In the control group insulin sensitivity decreased to 21.9% ± 16.2% of the preoperative value and in the insulin treated group to 46.8 ± 15.5%, $p < 0.005$. Insulin levels were significantly higher in the treatment group as well as consequently lower C-peptide levels.

Conclusions: This trial revealed a significant difference in postoperative insulin resistance in the group treated with insulin during surgery.

1. Introduction

Hyperglycemia is often observed in surgical and critically ill patients. The changes that are seen are similar to that of a patient with type 2 diabetes and are the result of a transient insulin resistance, characterized by enhanced hepatic gluconeogenesis and glycogenolysis and a compromised peripheral insulin-dependent glucose uptake.[1] Hyperglycemia is associated with an increased morbidity and mortality both in surgical and critically ill patients.

Perioperative hyperglycemia has been associated with a higher risk for morbidity such as infections, myocardial infarction, acute renal failure, and neurological damage.[2–4] The significance of hyperglycemia during critical illness and especially the relevance of normalizing glucose levels has been a hot topic since the studies from van den Berghe and colleagues,[5,6] where a significantly reduced risks of both morbidity and mortality in ICU-patients was shown when glucose was normalized with intensive insulin treatment. Post-hoc analysis of this latter study also showed that normoglycemia rather than the insulin dose given was responsible for these positive effects.[7] However, several later studies have not been able to reproduce these results[3,8,9] and the issue is still heavily debated. Studies in the perioperative period are less abundant.[10–12]

Whether controlling perioperative glucose levels have an effect on postoperative outcome is not entirely clear. Studies investigating this have mostly been focused on cardiac surgery with diabetic subjects.[8,13–16] From these studies it was suggested that poor perioperative metabolic control is associated with increased risk of postoperative complication such as wound infection and cardiac events. Even effects on mortality have been reported.[17]

Abbreviations: M, total glucose disposal, mg/kg/min; *M%*, difference between pre-and postoperative *M*-value expressed as percentage.

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Our thesis in this prospective study was that perioperative metabolic management in the form of normalizing glucose levels can be advantageous also in abdominal surgery. Postoperative insulin resistance was used as the outcome measure since we know that it is related to clinical outcome from other studies.[18,19] We hypothesized that controlling glucose level between 6 and 8 mmol/l during surgery may lower the degree of postoperative insulin resistance in comparison to a level >10 mmol/l. We investigated the effect in major open abdominal surgery.

2. Methods

2.1. Patients

Patients scheduled for elective partial hepatectomy due to neoplastic condition were enrolled in this randomized prospective study. Twenty patients studied per protocol were planned. Inclusion criteria were patients scheduled for open laparotomy, over 18 years of age and with no contraindications for epidural anaesthesia.

Patients with known diabetes mellitus or medication with corticosteroids were excluded. The study design was reviewed and approved by the regional ethics committee in Stockholm. The subjects were informed about the purpose and the nature of the study and written informed consent was given before inclusion.

2.2. Study design

Insulin sensitivity was measured by a normoglycemic hyperinsulinemic clamp, as described below, the day before surgery and immediately after surgery. Patients were randomized to perioperative insulin treatment (with a glucose target of 6–8 mmol/l) or to a control group. The control group was treated accordingly to current clinical practice. The day before scheduled operation, the patient arrived to the hospital at 1 pm, fasted for a minimum of 4 h. A normoglycemic hyperinsulinemic clamp was performed as described in detail below.

At the day of surgery the patient arrived to the operating theatre at 8 am after fasting since midnight. The patients received oxycodone (Oxycontin®) as premedication, intra- and postoperative analgesia was managed with a thoracic epidural catheter that was inserted at Th 6–9. After a test dose with Bupivacain epinephrine 5 mg/ml (3–5 ml) (Marcain adrenalin®, Astra Zeneca) and an epidural bolus dose of fentanyl (50 μg) (Fentanyl, Braun®), an epidural infusion containing Bupivacain 1 mg/ml, epinephrine 2 μg/ml and fentanyl 2 μg/ml (12–15 ml/h) was started. General anaesthesia was induced with Propofol-Lipuro (Braun®) and fentanyl and maintained with Sevoflurane (Sevoran, Abbott®). Atracurium (Hameln®) was used for muscle relaxation. All antibiotics given were diluted in sodium chloride or sterile water. All patients received a central venous catheter and an arterial catheter which were inserted after induction of anaesthesia. The blood samples for the study were taken from the arterial line. Continuous infusion of glucose 25 mg/ml, 1 ml/kg/h, started as soon as the central venous line was inserted, following the clinical routine at the hospital. Glucose was measured every 10 min using a bedside glucose monitor (Hemocue Glucose 201+®, HemocueAB, Ängelholm, Sweden). In addition, hourly plasma samples were obtained and stored at −80 °C for later plasma glucose analyses in the laboratory.

Before induction the patient was randomized, with a sealed, opaque envelope, either to the insulin treatment group or to the control group. When insulin treatment was required, the infusion (50 IU Actrapid® in 50 ml saline = 1 IU/ml) was started. Insulin was given either as a peripheral infusion or a central infusion as soon as the central catheter was inserted. An initial glucose level higher than 8 mmol/ml, or gradually increasing values higher than 7 mmol/l in two following samples, was considered an indication for insulin treatment. The infusion was started at 2 IU/h and then adjusted according to the current glucose level. In the control group glucose was targeted at 10–14 mmol/l. Insulin was only administered (by infusion or by intermittent boluses) when glucose levels exceeded 14 mmol/l.

After surgery the patient was transferred to the postoperative ward for observation over the next 12–24 h. The infusions stayed unchanged until the postoperative hyperinsulinemic normoglycemic clamp was performed. The postoperative clamp was started as soon as the epidural anaesthetic effect could be assessed and the patient appeared circulatory stable, i.e. 60–120 min after extubation.

Samples for plasma cortisol, insulin and C-peptide analyses were obtained at the start and the end of the clamping procedures and at the start of anaesthesia, at the start and at the end of the liver resection phase. These samples taken in pre-chilled EDTA tubes, centrifuged within 30 min (2700 rpm/min, 10 min in 4 °C, Universal 32 R Hettich Zentrifugen®, Andreas Hettich GmbH & Co. KG, Tuttlingen, Germany) and stored at −80 °C until analyses. Data for circulation, saturation, blood losses, blood transfusion, extension and time of surgery were collected. Also the rate of glucose-, norepinephrine- and insulin infusions was recorded. Crystalloids (Ringer-Acetate® 2 ml/kg) and colloids (Hydroxyethyl-starch, Voluven®, 2 ml/kg) were given as intraoperative fluid replacement. Blood loss during surgery was replaced with crystalloids, colloids and/or blood products.

2.3. Hyperinsulinemic normoglycemic clamp

Two peripheral vein catheters were inserted for infusions and blood sampling. Two plasma glucose values 10 and 5 min before the start of the clamp were used as a baseline mean value. During the clamp, plasma glucose was measured every 5 min. The clamp was initiated by a bolus of insulin (1.1 U/m^2) and then maintained by a constant insulin infusion (0.8 mU/kg/min) and a simultaneous variable infusion of glucose (200 mg/ml) to maintain normoglycemia. Albumin (400 mg) and potassium (32 mmol) were added to the insulin infusion. The goal level for steady state was set to ±0.5 mmol/ml of the baseline mean value. Total glucose disposal during hyperinsulinemic clamp is expressed as *M* (mg/kg/min). A high *M*-value represents a high insulin sensitivity. For safety reason, potassium was measured before and after the clamp using a venous blood sample analyzed on a blood-gas analyzer (ABL 800 Flex, Radiometer, Denmark). The clamp was repeated at the postoperative ward approximately 1 h after arrival. The preoperative glucose level was used as a target. For practical reasons arterial samples were drawn in the postoperative clamp. At the end of the 2 h clamp the insulin infusion was interrupted and thereafter the glucose infusion continued. After 30 min the infusion of glucose was stopped when a control sample showed normoglycemia.

The clamp was continued for 2 h. Steady state condition was assumed to be obtained after 60 min. Steady states for both the glucose infusion and glucose levels during the second hour were evaluated blinded by a person not involved in performing the clamps and unaware of the randomization. A period of at least 30 min with steady state for both glucose infusion and glucose levels was identified by this person and used for calculations. Clamps with no steady state during at least 30 min were excluded. This validation was done before any group calculation was performed. The amount of glucose given during the steady state period was used to calculate a mean *M*-value for whole body sensitivity to insulin (mg glucose/kg/min).