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Randomized Control Trials

High dose amino acid administration achieves an anabolic response in type 2 diabetic patients that is independent of glycaemic control: A randomized clinical trial☆

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SUMMARY

Background & aims: Surgical stress provokes protein catabolism and hyperglycaemia that is enhanced in patients with type 2 diabetes (T2DM), and increases perioperative morbidity. This study hypothesized that perioperative administration of high dose intravenous (IV) amino acids (AA) will augment protein balance in T2DM patients receiving tight plasma glucose control via continuous IV insulin compared to standard plasma glucose control via subcutaneous (SC) insulin sliding scale.

Methods: Eighteen patients with well-controlled T2DM (HbA1C% < 7.1) undergoing colorectal surgery were assigned randomly to receive standard glucose control (6–10 mmol/l, SC insulin, $n = 9$) or tight glucose control (4–6 mmol/l, IV insulin, $n = 9$). Both groups received general anaesthesia and epidural analgesia. AA (1 ml/kg h Aminoven™ 10%, ~2.4 g/kg d) were infused via a peripheral vein for two 3-h periods: at the beginning of surgery and in the post-operative care unit. Whole-body protein and glucose kinetics were assessed by stable isotope tracers, L-[1-^{13}C]leucine and [6,6-$^{2}H_2$]glucose.

Results: Whole-body protein balance was positive after surgery in all patients. Since protein synthesis, breakdown and leucine oxidation were comparable in both groups, whole body protein balance was not different ($p = 0.605$). Tight glucose control suppressed endogenous glucose production (EGP, $p < 0.001$) and increased glucose clearance ($p < 0.001$) compared to standard glucose control during both study periods. No episode of hypoglycaemia occurred in either group.

Conclusion: High-dose perioperative AA administration under optimal anti-catabolic care with epidural analgesia was effective in achieving a positive protein balance in T2DM patients undergoing surgery that was independent of glycaemic control strategy. Continuous IV insulin maintained normoglycaemia by inhibiting EGP and increasing glucose clearance. Improved glucose control, without a pronounced increase in protein balance with the intravenous insulin regimen, suggests perioperative protein metabolism may be less sensitive to insulin than is glucose.

Abbreviations: AA, amino acids; EGP, endogenous glucose production; HbA1C%, glycated haemoglobin; IV, intravenous; SC, subcutaneous; T2DM, type 2 diabetes mellitus.

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1. Introduction

Type 2 diabetes has become an epidemic with the global prevalence of diabetes rising from 4.7% in 1980 to 8.5% in 2014 [1–3]. Alterations in macronutrient metabolism resulting from impaired insulin action are prominent features of T2DM [4,5]. Patients with T2DM have decreased anabolic capacity from insulin resistance of protein metabolism [6,7], making them susceptible to stress and consequently suffer from higher perioperative complication rates [4,8,9].

The stress response to surgical injury affects all patients by triggering neuroendocrine and inflammatory reactions that release catecholamines, cortisol, and pro-inflammatory cytokines leading to a catabolic state [5,10,11]. The resulting insulin resistance, "diabetes of injury" [12], is proportional to the magnitude of the surgical stress (i.e. open colorectal surgery versus laparoscopic cholecystectomy), and is highest during and immediately following surgery [13]. This response is magnified in T2DM as reflected in previous studies where protein catabolism after colorectal surgery is increased in patients with T2DM as compared to non-diabetic controls [14], resulting in significantly negative net protein balance. The inherent insulin resistance of T2DM exacerbates the insulin resistance due to surgery leading to greater hyperglycaemia from enhanced EGP and lower glucose clearance [12,15,16]. These metabolic alterations of protein catabolism and hyperglycaemia may contribute to prolonged postoperative convalescence and increased morbidity in patients with T2DM [17,18].

The obvious approach to counter-act these metabolic changes is insulin, which is a strong anabolic hormone. Intensive insulin therapy with a hyperinsulinaemic–euglycaemic clamp providing supraphysiologic insulin concentrations resulted in inhibition of proteolysis and pronounced plasma hypoaminoacidaemia during cardiac surgery [19]. Furthermore, protein balance remained negative in patients who received only glucose to maintain normoglycaemia [19,20]. It is possible that decreased plasma amino acid (AA) availability prevents an insulin-mediated increase in protein synthesis to achieve net protein balance. High dose intravenous AAs (equivalent to 2.8 g/kg d) during a hyperinsulinaemic–euglycaemic clamp were sufficient to increase AA availability as seen by a two to three fold increase of plasma AA concentrations, despite a decrease in proteolysis. This resulted in higher protein balance in these volunteers without diabetes [21]. Similarly, providing a perioperative nutrition support regimen including AA allowed an increase in insulin-stimulated protein synthesis to occur when sufficient amounts of insulin and AA were provided to non-diabetic and T2DM patients [22,23]. It is evident both insulin and AA need to be given for maximal anabolic benefit, however a hyperinsulinaemic–euglycaemic clamp is difficult to conduct in routine surgical settings since it requires intensive monitoring and specialized personnel [24].

Various techniques are available to provide insulin to overcome insulin resistance. The continuous IV insulin infusion method, which titrates insulin infusion rate to plasma glucose targets, is routinely used in hospitals worldwide [25] for persistently elevated glucose levels in the critical care and perioperative setting [25]. To further enhance recovery after surgery, as validated by previous studies [22,26–28], epidural analgesia is able to minimize the postoperative catabolic response.

The perioperative period, with its close patient monitoring, gives a unique window of opportunity to administer nutritional interventions and insulin therapy to facilitate anabolism. Therefore, the present study was designed to determine whether high dose AA nutrition support with optimal anti-catabolic care including epidural analgesia would stimulate anabolism comparing two distinct perioperative glycaemic control techniques (standard glucose control with SC insulin sliding-scale vs tight control with continuous IV insulin therapy).

2. Materials and methods

2.1. Trial design

This was a single center, un-blinded, randomized controlled, parallel group clinical study conducted in St. Clara Hospital, Basel, Switzerland. After obtaining written informed consent patients were randomly assigned with sequentially numbered opaque sealed envelopes between two groups: standard plasma glucose control (target of 6–10 mmol/l, SC insulin sliding scale boluses (Humalog™, Insulin lispro, Eli Lilly Suisse)) or tight plasma glucose control (target 4–6 mmol/l, continuous IV insulin (Actrapid™, Novo Nordisk, Basel, Switzerland)). Both groups received high dose IV AA infusion during the study periods. The Ethics Committee of the city of Basel, Switzerland approved the study protocol in August 2009.

2.2. Participants

Eligible participants were patients aged >18 years with T2DM (controlled by diet, oral antihyperglycaemic medication, and/or insulin) that met the eligibility criteria: scheduled colorectal surgery (right, transverse, left, sigmoid, subtotal, total, and hemicolectomy, and low anterior resection) for non-metastatic-disease. Exclusion criteria were severe cardiac, hepatic, renal, or metabolic disorders, type 1 diabetes mellitus, >10% weight loss during the preceding 3 months, severe anaemia (haemoglobin < 80 g/L as defined by the World Health Organization), previous spinal surgery limiting the use of an epidural catheter, use of steroids, and pregnancy.

Patients admitted for elective colorectal surgery were recruited in St. Clara Hospital, Basel, Switzerland between December 2009 and November 2010 by the principal investigator. Eighteen patients were assessed for eligibility and none excluded for not meeting the exclusion criteria or refusal to participate and all participants' data were analysed for primary outcome (Fig. 1).

2.3. Anaesthesia and perioperative care

Patients underwent standardized bowel preparation before surgery and were permitted clear fluids until midnight and water until 5 am. General anaesthesia included IV thiopental, vecuronium, fentanyl, air in oxygen, and desflurane at end-tidal concentrations in order to maintain heart rate and blood pressure within 20% of preoperative values.

A thoracic epidural catheter was placed before induction of general anaesthesia. Neuronal blockade was maintained during surgery according to heart rate and blood pressure by repeated doses of bupivacaine 0.5% and by continuous infusion of bupivacaine 0.25% and fentanyl 4 μg/ml postoperatively. During and after surgery, 0.9% normal saline was infused at 2–4 ml/kg h. Postoperative pain levels were adjusted to obtain a numerical analogue score at rest of <4 (0 = no pain and 10 = worst pain imaginable).

2.4. Experimental protocol

Oral antihyperglycaemic medications were discontinued on the day of surgery. HbA1c was measured preoperatively to assess preoperative glycaemic control. Blood glucose concentration was monitored every 10–30 min (Ascensia CONTOUR Blood Glucose Meter, Bayer, Zurich, Switzerland) and adjusted with insulin according to the glycaemic control specifications of the patient's assigned study group. The perioperative blood glucose range from 4

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