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Glucose and protein kinetics in patients undergoing colorectal surgery: perioperative amino acid versus hypocaloric dextrose infusion

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Abstract

Surgical injury provokes a stress response that leads to a catabolic state and, when prolonged, interferes with the postoperative recovery process. This study tests the impact of 2 nutrition support regimens on protein and glucose metabolism as part of an integrated approach in the perioperative period incorporating epidural analgesia in 18 nondiabetic patients undergoing colorectal surgery. To test the hypothesis that parenteral amino acid infusion (amino acid group, n = 9) maintains glucose homeostasis while maintaining normoglycemia and reduces proteolysis compared with infusion of dextrose alone (DEX group, n = 9), glucose and protein kinetics were measured before and on the second day after surgery using a stable isotope tracer technique. Postoperatively, the rate of appearance of glucose was higher ($P < .001$) and blood glucose increased more ($P < .001$) in the DEX group than in the amino acid group. The postoperative increase in the appearance of leucine from protein breakdown tended to be greater ($P = .077$) in the DEX group. We conclude that perioperative infusion of a nutrition support regimen delivering amino acids alone maintains blood glucose homeostasis and normoglycemia and tends to have a suppressive effect on protein breakdown compared with infusion of dextrose alone.

1. Introduction

Surgical injury provokes a stress response that leads to a catabolic state with hyperglycemia and increased oxidation of body protein [1]. If prolonged or aggravated by complications, these changes may affect the postoperative recovery process [2,3].

The stress response induces a state of insulin resistance that interferes with perioperative nutrition support [4]. The administration of intravenous dextrose covers at least the patient's energy expenditure to minimize the extent of negative nitrogen balance [5], but provokes undesired hyperglycemia [6]. Peripheral administration of amino acids in volunteers has been shown to stimulate protein synthesis and shifts nitrogen metabolism toward a positive protein balance [7,8], whereas endogenous glucose production increases or remains unchanged [9,10]. In patients after major surgery, amino acid infusion resulted in a small decrease in endogenous glucose production [8,11], indicating that amino acids resulting from the breakdown of tissue proteins were redirected toward synthetic and not only oxidative or gluconeogenic pathways. As a result, the circulating level of glucose remained within normal values, thus avoiding the possible negative effects associated with hyperglycemia on body organs and therefore reducing morbidity and mortality [8,12,13].

Both the peripheral and central nervous systems have been demonstrated to play a pivotal role in mediating the metabolic alterations [14]. Epidural blockade with local anesthetics not only provides optimal analgesia, but also facilitates glucose utilization [15] and blunts the loss of body protein [16], possibly by improving insulin sensitivity [17].

Department/institution to which the work is attributed: Department of Anesthesia, McGill University, Montreal.

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This study proposes a perioperative integrated approach of incorporating epidural analgesia and a 72-hour nutrition support initiated before surgery. It is hypothesized that peripheral infusion of amino acids alone compared with glucose alone over the 72-hour period would maintain glucose homeostasis by inhibiting the rise in endogenous glucose production and blood glucose concentration, as well as the rise in protein breakdown associated with surgical stress.

2. Materials and methods

2.1. Patients

2.1.1. Inclusion and exclusion criteria

The study protocol was approved by the research ethics board of the McGill University Health Centre, Montreal, Canada; and written informed consent was obtained from all patients. Inclusion criteria were age older than 18 years and colorectal surgery for nonmetastatic disease (including right, transverse, left or sigmoid hemicolectomy, subtotal or total colectomy and low anterior resection). Exclusion criteria were severe cardiac, hepatic, renal, or metabolic disorders (including diabetes mellitus); plasma albumin concentration less than 35 g L^{-1}; more than 10% weight loss over the preceding 3 months; anemia (hematocrit <30%); use of steroids; previous spine surgery limiting the use of an epidural catheter; and pregnancy. The 9 patients in the amino acid (AA) group were recruited prospectively between October 2005 and July 2006. The 9 patients in the dextrose (DEX) group were randomly retrieved from a previously published study population (n = 10) undergoing colorectal surgery [18]. The recruitment of this subset was similar to the AA group.

2.1.2. Nutrition support

Individualized nutrition support was provided for each patient by determining resting energy expenditure (REE) by indirect calorimetry on the day before surgery after overnight fasting. Patients in the DEX group received a 10% dextrose solution to provide 50% of their REE. Patients in the AA group received a 10% amino acid solution without electrolytes (Travasol; Baxter, Montreal, Canada; composition as previously described [8]) to provide 20% of their REE. The rationale for infusing amino acids at 20% of REE was to limit nitrogen losses by compensating for the increased protein breakdown in colorectal patients after surgery in the absence of amino acids [15]. Both infusion rates are based on European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines for protein and glucose intakes [19,20]. Solutions were infused through a cannula inserted into a forearm vein. The infusion was started at 11:00 AM of the day before surgery, immediately after the preoperative study, and continued until 12:00 PM of the second day after surgery, immediately after the postoperative study. Both the anesthesiologist and the surgeon were aware of each patient's group assignment.

2.1.3. Anesthesia and perioperative care

Patients were operated on in the morning hours. All patients received an epidural catheter inserted between thoracic vertebral levels T8 to T11 before the induction of general anesthesia. Neuraxial blockade was established with 0.5% bupivacaine to achieve a bilateral sensory block from thoracic dermatome level 4 (T4) to sacral dermatome level 1 (S1) and maintained with a constant infusion of 0.25% bupivacaine during surgery. The sensory block was maintained postoperatively for at least 48 hours by continuous epidural infusion of 0.1% bupivacaine supplemented with 3 $\mu g\ mL^{-1}$ fentanyl. Pain levels were evaluated in all patients using an 11-point visual analog score (VAS) where 0 = no pain and 10 = excruciating pain every 4 hours after surgery. Pain relief was adjusted to achieve a visual analog score at rest of less than 3 and less than 5 during mobilization.

2.1.4. Experimental protocol

On the day before surgery, starting at 9:00 AM, patients underwent a 3-hour tracer kinetic study to characterize baseline glucose and protein metabolism after an overnight fasting and before administration of amino acids or dextrose, respectively (fasted state). The metabolic studies were repeated from 9:00 AM to 12:00 PM on the second postoperative day during dextrose or amino acid infusion, respectively (fed state). Plasma kinetics of glucose and leucine were determined by primed constant infusions of the tracers [6,6-$^2H_2$]glucose (99% enriched) and L-[1-^{13}C] leucine (99% enriched) (Cambridge Isotope Laboratories, Cambridge, MA) (Fig. 1). Sterile solutions of tracers were prepared in the hospital pharmacy, tested to be sterile and pyrogen-free, and kept at 4°C until administration.

Blood and expired air samples were collected to determine baseline enrichments. Priming doses of sodium bicarbonate ($NaH^{13}CO_3$) (0.08 mg kg^{-1}), [6,6-$^2H_2$]glucose (22 μmol kg^{-1}), and L-[1-^{13}C]leucine (4 μmol kg^{-1}) were injected and followed immediately by continuous infusions of L-[1-^{13}C]leucine (0.06 μmol kg^{-1} min^{-1}) and [6,6-$^2H_2$] glucose (0.11 μmol kg^{-1} min^{-1}) in the preoperative study. During the postoperative study, tracers were infused at higher rates to accommodate the increased pool dynamics in the fed state [8]. Specifically, [6,6-$^2H_2$]glucose was infused at 0.22 μmol kg^{-1} min^{-1} in the DEX group; and L[1-^{13}C] leucine was infused at 0.12 μmol kg^{-1} min^{-1} in the AA group. Four blood samples were collected at 30, 20, 10, and 0 minutes before the end of each study period to determine the protein and glucose metabolism.

Blood samples were drawn during the last 10 minutes of the 2 study periods for the analysis of glucose, glucagon, insulin, and cortisol.

Indirect calorimetry (Vmax 29N; SensorMedics, Yorba Linda, CA) was performed for 15 minutes in the last hour of the pre- and postoperative tracer kinetic study periods. Whole-body oxygen consumption and carbon dioxide production were determined [21].

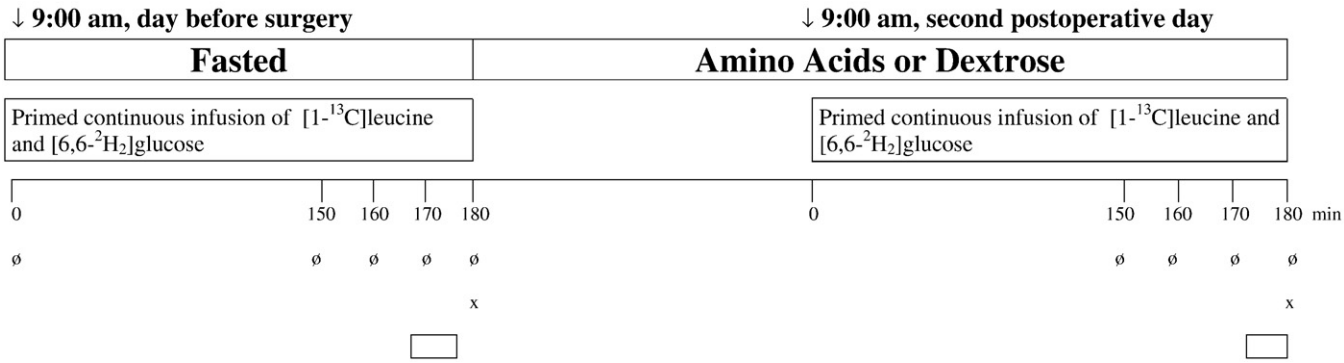

Fig. 1. Time course of the infusion of isotopes and collection of plasma and expired air samples (ø), indirect calorimetry (open rectangles), and collection of plasma for the determination of metabolic substrates and hormones (x) in the fasted state and during the infusion of amino acids and dextrose respectively.

2.2. Measurements

2.2.1. Isotopic enrichments

Isotopic enrichment of plasma [1-^{13}C]-ketoisocaproate (KIC), representing the intracellular leucine pool, was used as the basis for calculating both leucine flux and the appearance from breakdown of protein, as described [22,23]. The KIC enrichment was analyzed as its pentafluorobenzyl ester derivative using methane negative chemical ionization gas chromatography–mass spectrometry. Plasma [6,6-$^2H_2$] glucose enrichment was determined from its pentaacetate derivative by gas chromatography–mass spectrometry analysis under electron impact conditions [24].

2.2.2. Plasma metabolites and hormones

Plasma glucose was measured by an enzymatic colorimetric assay (GLU Glucose GOD-PAP; Roche Diagnostics, Indianapolis, IN) on automated clinical chemistry analyzers (Roche/Hitachi 904911: CAN 249 or Roche/Hitachi 912/917/MODULAR: CAN 525, Roche Diagnostics). Serum insulin was determined by a solid-phase, 2-site chemiluminescent immunometric assay (IMMULITE/IMMULITE 1000 Insulin; Diagnostic Products, Los Angeles, CA). Glucagon was determined by using a radioimmunoassay kit (Glucagon RIA KIT; Linco, St Charles, MO). Plasma cortisol was measured by an immunoassay (Unicell DXI 800; Beckman Coulter, Brea, CA).

2.2.3. Gaseous exchange

Average values of oxygen consumption and carbon dioxide production as well as the calculated respiratory quotient were determined by indirect calorimetry, accepting a coefficient of variation of less than 10% over 10 minutes [15,18].

2.2.4. Calculation of protein and glucose metabolism

Whole-body glucose and leucine kinetics were determined by conventional isotope dilution practice applying a 2-pool stochastic model during steady-state conditions during fasted and fed states [25].

When a physiologic and isotopic steady state exists, the rate of appearance (R_a) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (atom percentage excess [APE]) calculated by $R_a = (APE_{inf}/APE_{pl} - 1)*F$, where F is the infusion rate of labeled tracer, APE_{inf} is the tracer enrichment in the infusate, and APE_{pl} equals the tracer enrichment in plasma.

Under steady-state conditions, leucine flux (Q) is defined by the formula $Q = S + O = B + I$, where S is the rate at which leucine is incorporated into body protein, O is the rate of oxidation of leucine, B is the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown, and I is the rate of leucine intake including tracer (rate of infusion of L-[1-^{13}C]leucine [in micromoles per kilogram per hour]) and diet. Under conditions of a postabsorptive state, the essential amino acid leucine for protein synthesis and oxidation comes from a sole source, the breakdown of endogenous proteins; thus, flux is equal to breakdown. Plasma enrichment of [1-^{13}C]-KIC was used as the basis for calculating flux of leucine [26]. Net protein breakdown in the fed state was calculated by subtracting the exogenous leucine intake of the amino acid solution from the measured flux.

In the fasted state or when glucose intake is zero, glucose R_a equals the rate of its endogenous production. To determine endogenous glucose production during infusion of glucose, the exogenous infusion rate was subtracted from total R_a glucose, as previously described [15,18,21,27,28]. Glucose clearance, an index of the capacity for tissues to take up glucose, was calculated as the R_a of glucose divided by plasma glucose concentration [8,28].

2.3. Statistical analysis

Repeated-measures 2-way analysis of variance was used to assess if the change from fasting to fed state differed between treatment groups (amino acids vs dextrose). In the absence of a significant interaction (ie, the change from fasting to fed did not differ by treatment status), the effect of treatment was examined through the main effect of treatment from the analysis of variance. In the presence of a significant interaction (ie, the change from fasting to fed differed according to treatment status), the differences between

treatment groups were further explored by 2-sided, 2-sample Student test at each level of feeding. A significance level of $P < .05$ was used for all tests. Analyses were conducted using Intercooled STATA 9.0 (2005; StataCorp, College Station, TX).

3. Results

3.1. Patients

Patient characteristics were not different among groups (Table 1). Mean pain scores measured by visual analog scale at rest, at 12 and 24 hours after surgery, and during the study on the second postoperative day never exceeded the value of 5; and no patient complained about severe pain in either group.

3.2. Glucose and protein kinetics

In all studies, isotopic steady state of plasma [6,6-$^2H_2$] glucose and [1-^{13}C]KIC enrichment was achieved (coefficient of variation <5%). Preoperative glucose and protein kinetics measured in a fasted state were comparable in both groups (Table 2).

After surgery, R_a of glucose was higher in the DEX group than in the AA group ($P < .001$). The DEX infusion increased R_a of glucose by 46% compared with preoperative fasting, whereas the AA infusion did not affect R_a of glucose ($P < .001$). Postoperatively, endogenous glucose production decreased to a greater extent in the DEX group compared with the AA group ($P = .018$). The effect of type of feeding on glucose metabolism is reflected also in plasma glucose concentration that increased to a greater extent in the DEX group when compared with the AA group ($P < .001$) and therefore resulted in higher blood glucose levels (DEX group, 7.9 ± 1.4 mmol L^{-1}; AA group, 4.8 ± 0.8 mmol L^{-1}; $P < .001$). Glucose clearance was not affected.

The total R_a of leucine was not affected by the 72-hour feeding. However, there was a tendency toward a greater increase in R_a of endogenous leucine ($P = .077$) in the DEX group (30.1 ± 21.8 μmol kg^{-1} h^{-1}) compared with the AA group (12.8 ± 16.9 μmol kg^{-1} h^{-1}), suggesting a suppressive effect of amino acid infusion on protein breakdown in the AA group.

Table 1
Biometric and clinical data of patients

	AA	DEX
nr	9	9
Age, y	61 ± 21	62 ± 14
Weight, kg	66 ± 16	67 ± 18
BMI, kg m^{-2}	23.7 ± 4.3	23.8 ± 3.5
Sex, male/female	4/5	4/5
ASA, 1/2/3	0/8/1	0/9/0
Type of surgery		
Hemicolectomy/colectomy	6	4
Sigmoid resection	0	5
Anterior resection	3	0
Duration, min	166 ± 65	185 ± 61

Values are mean ± SD. ASA indicates American Society of Anesthesiologists classification; BMI, body mass index.

3.3. Plasma hormones

Before surgery, plasma insulin, cortisol, and glucagon concentrations were similar in both groups (Table 3). Postoperative plasma insulin was higher in the DEX group than in the AA group ($P = .01$). Dextrose infusion increased insulin to a greater extent than the amino acid infusion ($P = .039$). Neither cortisol nor glucagon concentrations were affected by infusion regimen. The homeostasis model assessment (HOMA) score did not differ before surgery, but increased postoperatively in the DEX group ($P = .002$).

3.4. Respiratory kinetics

Preoperative whole-body oxygen consumption was higher in the DEX group compared with the AA group ($P = .029$), as well as whole-body carbon dioxide production ($P = .008$), resulting in higher respiratory quotient for the DEX group ($P = .042$). The provision of nutrition did not affect any of the respiratory parameters.

4. Discussion

A 72-hour perioperative infusion of amino acids maintained blood glucose homeostasis while tending to suppress endogenous R_a of leucine (net protein breakdown) to a greater extent than the dextrose infusion. Perioperative nutrition support is still controversially discussed. On one hand, isocaloric and hypercaloric intravenous feeding not only requires a central venous line, but leads to hyperglycemia and even to higher morbidity in sufficiently nourished patients [29,30]. On the other hand, a surgery-induced catabolic state and associated loss of body protein need to be attenuated. A multimodal approach may be most effective. Epidural analgesia modulates the endocrine response, but does not in itself affect nutrient metabolism [22]. Provision of nutrition support is essential to facilitate the effects of epidural analgesia on protein and glucose metabolism [6,15]. This study aimed to differentiate the effects of dextrose and amino acid–based nutrition support regimens when infused over a 72-hour perioperative period in patients having epidural analgesia.

Intravenous provision of glucose induces hyperglycemia, which is associated with adverse clinical effects [31,32]. Furthermore, intravenous glucose does not stimulate whole-body protein synthesis [6]. Blood glucose concentration increases with the start of the operation and is related to the intensity of surgical injury [33]. These features are reflected in the higher levels of blood glucose as well as the stress hormones insulin and glucagon in the DEX group when compared with the AA group. Furthermore, patients of the DEX group developed a pronounced insulin resistance as

Table 2
Kinetics of leucine and glucose metabolism in the fasted and fed state

Variable	Amino acid group			Dextrose group			*P* values		
	Baseline	2 d after surgery	Difference	Baseline	2 d after surgery	Difference	Baseline	2 d after surgery	Difference
Endogenous R_a of glucose, μmol kg^{-1} min^{-1}	12.5 ± 2.4	11.4 ± 2.5	−1.1 ± 2.1	14.1 ± 2.1	9.3 ± 4.1	−4.8 ± 3.6	.165	.200	**.018**
R_a of glucose, μmol kg^{-1} min^{-1}	12.5 ± 2.4	11.4 ± 2.5	−1.1 ± 2.1	14.1 ± 2.1	20.6 ± 5.1	6.5 ± 4.2	.165	**<.001**	**<.001**
Glucose clearance, mL kg^{-1} min^{-1}	2.27 ± 0.51	2.40 ± 0.54	0.13 ± 0.26	2.63 ± 0.39	2.69 ± 0.78	0.06 ± 0.50	.216		.742
R_a of leucine, μmol kg^{-1} h^{-1}	117 ± 28	146 ± 31	29 ± 17	112 ± 18	142 ± 35	30 ± 22	.692		.897
Endogenous R_a of leucine, μmol kg^{-1} h^{-1}	117 ± 28	130 ± 29	13 ± 17	112 ± 18	142 ± 35	30 ± 22	.813		.077

Values are mean ± SD; n = 9 per group. Statistically significant *P* values in boldface.

reflected by an increased HOMA score postoperatively, whereas the AA group maintained their fasted level while receiving nutrition support.

When the DEX group is compared with a previous study in which nutrition support (dextrose 10%, 4 mg kg^{-1} min^{-1}) was given for just 3 hours on the second postoperative day, only a tendency for a higher endogenous R_a of glucose after 72-hour of infusion can be seen (R_a of glucose: 20.61 ± 5.11 [72 hours], 23.91 ± 3.25 [3 hours]; endogenous R_a of glucose: 9.28 ± 4.07 [72 hours], 2.2 ± 2.43 [3 hours]; glucose clearance: 2.69 ± 0.78 [72 hours], 2.47 ± 0.5 [3 hours]; R_a of leucine: 141.74 ± 34.55 [72 hours], 113.4 ± 27.9 [3 hours]) [15]. The difference for endogenous R_a of glucose might be explained with the higher caloric amount infused per minute. The net protein breakdown is not affected by the length of infusion. This correlates with previous studies because even high-caloric provision of carbohydrates failed to shift protein balance to a positive value [34].

When the AA group is compared with a previous study where amino acids (Travasol, 0.02 mL kg^{-1} min^{-1}; equivalent to 2.9 g kg^{-1} d^{-1}) were infused for 3 hours on the second postoperative day, no distinct difference can be detected (endogenous R_a of glucose: 11.41 ± 2.49 [72 hours], 10.3 ± 1.1 [3 hours]; R_a of leucine: 146.24 ± 30.55 [72 hours], 161.3 ± 14.7 [3 hours]; endogenous R_a of leucine: 130.1 ± 28.79 [72 hours], 108.5 ± 15.5 [3 hours]) [8]. Apparently, the longer perioperative infusion of amino acids does not provide any advantage either regarding net protein breakdown or in sparing of gluconeogenesis. However, one of the limitations of this study is the absence of protein synthesis measurement. Therefore, a possible positive effect on protein balance by amino acid infusion was not assessed even though an increased protein synthesis can be expected as previously shown with a provision of amino acids restricted to 3 hours postoperatively [8].

Amino acids originating from protein breakdown and nutrition can either be directed to gluconeogenesis or to oxidation, or be reincorporated into proteins. By suppressing gluconeogenesis from amino acids, higher levels of nitrogen are available for protein synthesis rather than for excretion as urea. In this study, endogenous R_a of glucose was decreased not only in the DEX group but also to a lesser extent in the AA group. The AA group not only benefits from glucose homeostasis but might also have saved amino acids from being used as gluconeogenic source. Furthermore, additional amino acids have been preserved as shown by a smaller endogenous R_a of leucine in the AA group when compared with the DEX group after 72-hour feeding. Therefore, when comparing the 2 study groups and assuming that leucine makes up for 8% of whole-body protein [28], 47 g of protein per day has been saved by infusing amino acids compared with dextrose.

It has been shown consistently that epidural analgesia compared with intravenous opioid analgesia attenuates the

Table 3
Kinetics of hormones and metabolites and respiratory kinetics in the fasted and fed state

Variable	AA group			DEX group			*P* values		
	Baseline	2 d after surgery	Difference	Baseline	2 d after surgery	Difference	Baseline	2 d after surgery	Difference
Glucose, mmol L^{-1}	5.6 ± 0.7	4.8 ± 0.8	−0.8 ± 0.7	5.4 ± 0.6	7.9 ± 1.4	2.5 ± 1.4	0.498	**<.001**	**<.001**
Insulin, pmol L^{-1}	49 ± 19	52 ± 25	3 ± 29	64 ± 23	104 ± 48	40 ± 39	.139	**.010**	**.039**
Glucagon, pmol L^{-1}	22 ± 6	40 ± 18	18 ± 13	33 ± 19	32 ± 30	−1 ± 17	.102	.464	**.012**
Cortisol, nmol L^{-1}	301 ± 88	416 ± 264	115 ± 227	211 ± 99	448 ± 180	237 ± 192	.658		.236
Insulin-glucagon ratio	2.3 ± 0.7	1.5 ± 0.9	−0.8 ± 1	2.3 ± 0.9	4.8 ± 2.9	2.5 ± 2.4	.926	**.005**	**.002**
HOMA	1.67 ± 0.7	1.6 ± 0.83	0.07 ± 0.9	2.17 ± 0.94	5.18 ± 2.83	3.01 ± 2.32	.211	**.002**	**.002**
V_{O_2}, mL min^{-1}	167 ± 29	170 ± 37	3 ± 23	208 ± 35	203 ± 35	−5 ± 13	**.029**		.373
V_{CO_2}, mL min^{-1}	130 ± 24	134 ± 30	4 ± 14	167 ± 26	171 ± 26	4 ± 11	**.008**		>.999
RQ	0.78 ± 0.07	0.79 ± 0.06	0.012 ± 0.1	0.80 ± 0.02	0.85 ± 0.03	0.04 ± 0.02	**.042**		.351

Values are mean ± SD; n = 9 per group. RQ indicates respiratory quotient; VO_2, whole-body oxygen consumption; V_{CO_2}, whole-body carbon dioxide production. Statistically significant *P* values in boldface.

postoperative nitrogen loss in patients undergoing upper abdominal surgery [16,35,36]. In a previous study, epidural analgesia attenuated postoperative protein breakdown without affecting protein synthesis, resulting in patients being in negative protein balance [37]. When dextrose was infused, epidural analgesia compared with opioid administration induced a decrease in leucine oxidation during the second postoperative day; but protein balance remained negative in both groups, with no differences between the analgesic techniques, indicating that hypocaloric amounts of dextrose could not reverse negative postoperative protein balance [15]. However, a short-term, high-rate amino acid infusion provided such a strong anabolic effect that protein breakdown was inhibited and protein synthesis was stimulated, thus rendering protein balance positive, regardless of whether epidural analgesia or opioids were used [8]. The role of epidural analgesia appears to be paramount for glucose metabolism because plasma levels of counterregulatory hormones during surgery are blunted, resulting in improved insulin sensitivity [17] and glucose utilization [15,38].

It might be argued that the 2 groups in this study are not directly comparable because of the provision of different energy levels (20% of REE for the AA group and 50% for the DEX group, respectively). However, the study setting aimed to provide nutrition support as proposed by clinical guidelines and to isolate and compare the effect of these different substrates on glucose and protein metabolism.

The assessment of baseline values showed differences in respiratory kinetics between the 2 study subsets. However, the change from baseline to 2 days after surgery representing the main point of interest is comparable for both groups.

The present findings show that a perioperative infusion of amino acids maintains blood glucose homeostasis and tends to suppress endogenous R_a of leucine to a greater extent compared with dextrose infusion. This implies that the main metabolic derangements caused by surgery, hyperglycemia, insulin resistance, and loss of body protein were positively influenced by peripheral amino acid infusion and saved 47 g of lean body mass per day.

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